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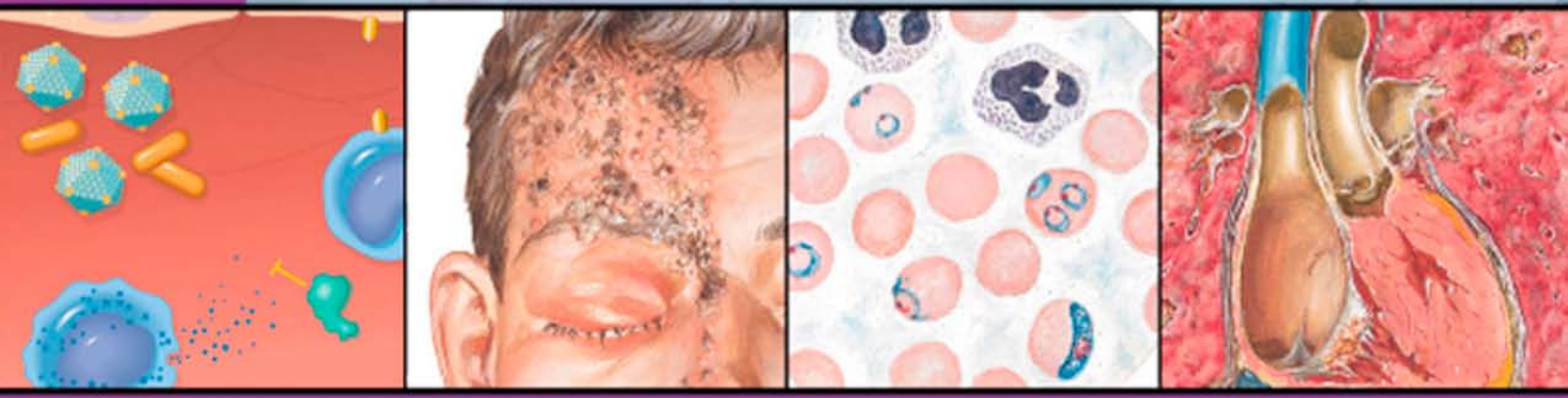

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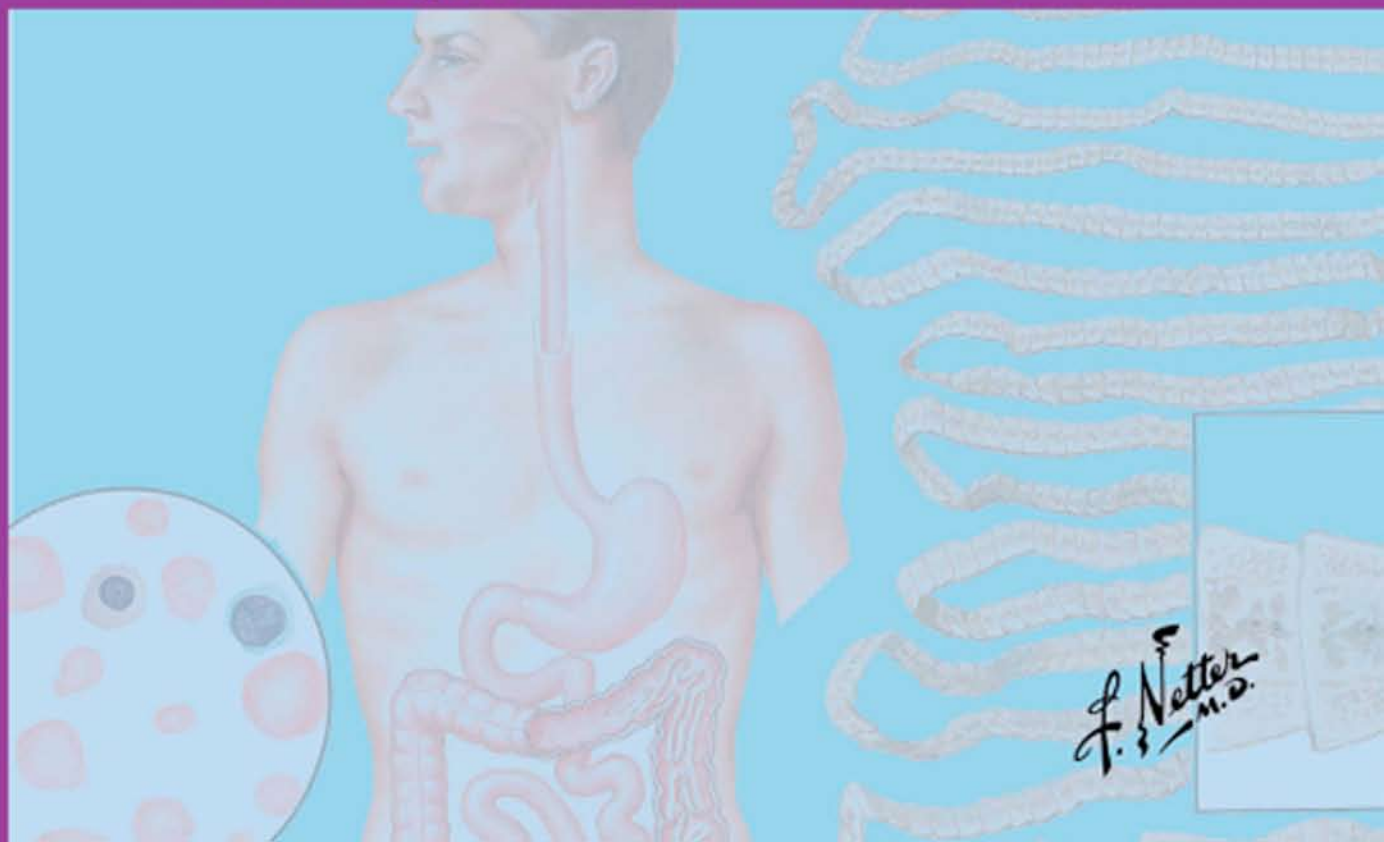

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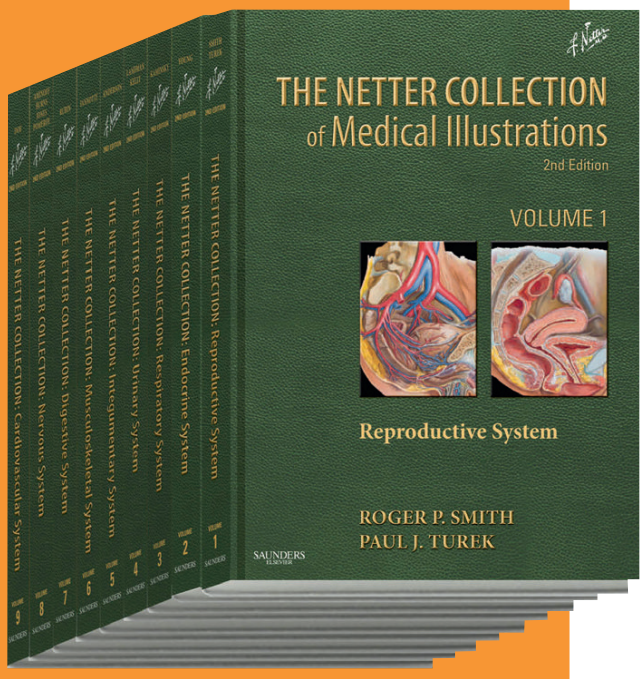

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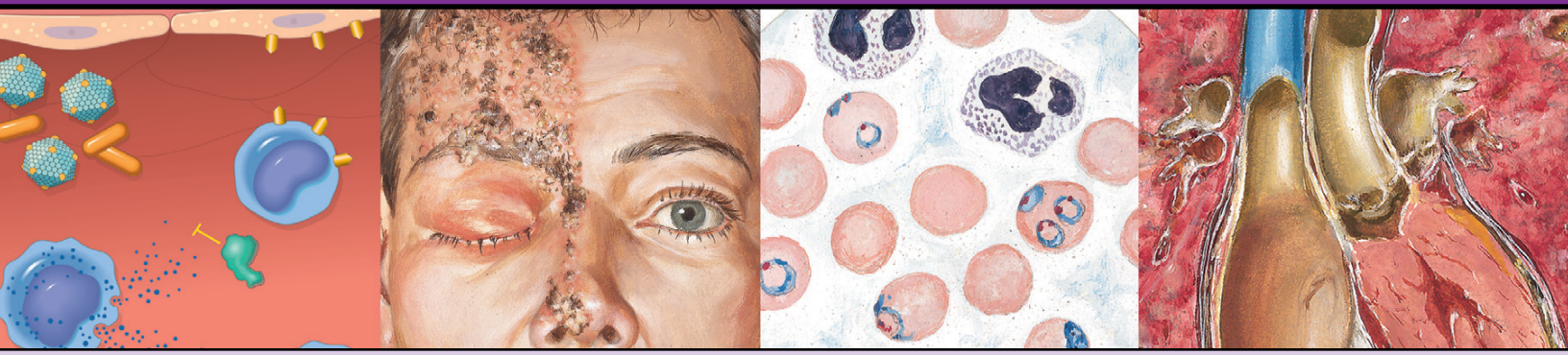

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About the Artists

Frank H. Netter, MD

Frank H. Netter was born in 1906 in New York City. He studied art at the Art Student's League and the National Academy of Design before entering medical school at New York University, where he received his MD degree in 1931. During his student years, Dr. Netter's notebook sketches attracted the attention of the medical faculty and other physicians, allowing him to augment his income by illustrating articles and textbooks. He continued illustrating as a sideline after establishing a surgical practice in 1933, but he ultimately opted to give up his practice in favor of a full-time commitment to art. After service in the U.S. Army during World War II, Dr. Netter began his long collaboration with the CIBA Pharmaceutical Company (now Novartis Pharmaceuticals). This 45-year partnership resulted in the production of the extraordinary collection of medical art so familiar to physicians and other medical professionals worldwide.

In 2005, Elsevier Inc. purchased the Netter Collection and all publications from Icon Learning Systems. There are now more than 50 publications featuring the art of Dr. Netter available through Elsevier Inc. (in the United States, www.us.elsevierhealth.com/Netter; and outside the United States, www.elsevierhealth.com).

Dr. Netter's works are among the finest examples of the use of illustration in the teaching of medical concepts. The 13-book *Netter Collection of Medical Illustrations*, which includes the greater part of the more than 20,000 paintings created by Dr. Netter, became and remains one of the most famous medical works ever published. *The Netter Atlas of Human Anatomy*, first published in 1989, presents the anatomic paintings from the Netter Collection. Now translated into 16 languages, it is the anatomy atlas of choice among medical and health profession students the world over.

The Netter illustrations are appreciated not only for their esthetic qualities but, more important, for their intellectual content. As Dr. Netter wrote in 1949, "… clarification of a subject is the aim and goal of illustration. No matter how beautifully painted, how delicately and subtly rendered a subject may be, it is of little value as a *medical illustration* if it does not serve to make clear some medical point." Dr. Netter's planning, conception, point of view, and approach are what inform his paintings and what makes them so intellectually valuable.

Frank H. Netter, MD, physician and artist, died in 1991.

Learn more about the physician-artist whose work has inspired the Netter Reference Collection at www.netterimages.com/artist/netter.htm.

Carlos Machado, MD

Carlos Machado was chosen by Novartis to be Dr. Netter's successor. He continues to be the main artist who contributes to the Netter Collection of medical illustrations.

Self-taught in medical illustration, cardiologist Carlos Machado has contributed meticulous updates to some of Dr. Netter's original plates and has created many paintings of his own in the style of Netter as an extension of the Netter Collection. Dr. Machado's photorealistic expertise and his keen insight into the physician-patient relationship inform his vivid and unforgettable visual style. His dedication to researching each topic and subject he paints places him among the premier medical illustrators at work today.

Learn more about his background and see more of his art at www.netterimages.com/artist/machado.htm.

About the Editors

Elaine C. Jong, MD, was born in New York City, graduated from Wellesley College with a BA in biological sciences, and later received her medical degree from the University of California–San Diego School of Medicine in La Jolla. After completing her residency in internal medicine at the University of Washington School of Medicine (UWSOM) Affiliated Hospitals in Seattle and a fellowship in infectious diseases at UWSOM, she joined the faculty in the Department of Medicine in the Division of Allergy and Infectious Diseases. She also served as a faculty member in the Division of Emergency Medicine and became Clinical Professor of Medicine in 1994. During her tenure at UWSOM, Dr. Jong founded and directed training clinics for the practice of refugee and international health, and travel and tropical medicine. She served as the director of the UW Hall Health Primary Care Center, incorporating the UW Student Health Service, and was the first medical director of the UW Campus Health Services, implementing programs for campus public health, occupational health, and employee health. Dr. Jong has a special interest in host defense mechanisms and has lectured and published widely on clinical topics in infectious diseases, travel and tropical medicine, and disease control and prevention. She is co-editor of *The Travel and Tropical Medicine Manual*, now in its fourth edition and recently translated into a Chinese language edition, and is also co-editor of *Travelers' Vaccines*, edition 2. She is a fellow of the Infectious Diseases Society of America, a past president of the clinical group of the American Society of Tropical Medicine and Hygiene, and the chair of the International Medical Advisory Board and co-director of the International Travel Medicine Education Program for the International Association for Medical Assistance to Travellers (IAMAT).

Dennis L. Stevens, PhD, MD, is chief of the Infectious Diseases Section and Director of Research and Development of the Veterans Affairs Medical Center in Boise, Idaho, and professor of medicine at the University of Washington's School of Medicine in Seattle. Dr. Stevens obtained a bachelor of arts degree in microbiology from the University of Montana, a doctoral degree in microbiology from Montana State University, and a medical degree from the University of Utah. He completed an internal medicine residency at the University of Utah and performed his fellowship in infectious diseases at Brooke Army Medical Center. Dr. Stevens' major research interests have been the pathogenesis of serious infections caused by toxin-producing gram-positive pathogens including *Clostridium perfringens*, *Clostridium sordellii*, group A *Streptococcus*, and methicillin-resistant *Staphylococcus aureus* (MRSA). Dr. Stevens recently received the Infectious Diseases Society of America Citation for his work on group A streptococcal infections and the William Altemeier Award from the Surgical Infections Society and was elected to membership in the Association of American Physicians. He has published more than 160 articles and 60 book chapters on serious invasive infections caused by gram-positive organisms and has been visiting professor at more than 70 national and 30 international institutions. He is a member of the Centers for Disease Control and Prevention Working Group on Invasive Streptococcal Infections and a consultant to the World Health Organization, and he has been an invited participant to the National Institutes of Health Workforce on severe group A streptococcal infection. He has testified twice before the U.S. Congress on the importance of basic science research in infectious diseases and on invasive group A streptococcal infections. Dr. Stevens is the current chairman of the Infectious Diseases Society of America's Guideline Committee for the Treatment of Skin and Skin Structure Infections.

Acknowledgments

Developing a new textbook of infectious diseases that would tap into the rich library of medical illustrations created by the late Dr. Frank Netter was a major undertaking not only for us but also for our dedicated colleagues who contributed ideas and chapters to this work. We thank everyone for devoting precious personal time to work on their contributions, and we acknowledge their expertise as well as their commitment to excellence.

We are grateful that Elyse O'Grady, editor, Netter Products, recognized our passion for the genius of Frank Netter and invited us to serve as editors for this new Netter series volume on infectious diseases. We thank Marybeth Thiel, senior developmental editor; Andrea Vosburgh, developmental editor; Cheryl Abbott, senior project manager; Cindy Thoms, project manager; and the superb staff in the editorial and production offices at Elsevier for their care and commitment in developing this new text.

We are indebted to John Martines at the University of Washington, whose communications with contributors and superb organizational skills were invaluable.

We would especially like to acknowledge our families: our spouses—Dr. Britt Litchford and Dr. Amy E. Bryant—whose encouragement and understanding throughout this project were essential to the completion of this book; our children—Brian and Steven Riggs, and Marisa (Stevens) Keith, and Katie Gibbons—who remind us that memorable stories and images are not forgotten; and finally our parents—Arthur and Peggy Jong, and John and Alma Stevens—who believed that education brings immeasurable benefits and is something that endures throughout one's life.

It is our hope that these illustrative Netter images, combined with evidence-based, cogent chapters, will provide valuable insights into the epidemiology, pathogenesis, diagnosis, and treatment of infections in all parts of the world.

Preface

As longtime colleagues in the Division of Allergy and Infectious Diseases at the School of Medicine, University of Washington, Seattle, we were honored and challenged by the unique opportunity to create a new textbook of infectious diseases, with the goal of using the beautiful medical artwork created by the late Dr. Frank Netter to teach and clarify important concepts in infectious diseases. Mindful of existing textbooks, such as Mandell's *Infectious Diseases*, that are considered authoritative as well as standards of excellence in the field, we set out to create a new resource with a strongly clinical orientation. The purpose of this book is to provide healthcare providers, both generalists and specialists, with up-to-date clinical approaches to the broad spectrum of infectious diseases from the perspective of how these various infections may affect patients as individuals, members of communities, and citizens of global society.

Reflecting the rapid accumulation of advances in the medical sciences, the infectious diseases specialty has many branches or subspecialties, and we were fortunate in recruiting section editors Patch Dellinger (Surgical Infections), Thomas File (Respiratory Infections), Jo Hoffman (Emerging Infectious Diseases), Jeanne Marrazzo (Sexually Transmitted Infections), and ChrisAnna Mink (Vaccine-Preventable Infections of Children and Adolescents) to join us for this ambitious project. A superb roster of talented contributing authors, recruited from our extended network of colleagues and friends, contributed their valuable time and expertise to writing concise, highly readable, and clinically relevant chapters. In each chapter, Dr. Netter's medical illustrations, in some cases revised to reflect new advances, are used to illustrate key points from the text, augmented by radiographic and photographic images, tables, and graphs. For some topics, new artwork was created by Carlos A.G. Machado, MD; John A. Craig, MD; James A. Perkins, MS, MFA; Tiffany S. DaVanzo, MA, CMI; and Anita Impagliazzo—talented medical artists carrying on Dr. Netter's mission of using art as an educational icon.

Although our academic interests, clinical activities, and teaching commitments have kept us on different paths within our large division in the past, we were drawn together to work on this book by our mutual admiration for the work of Dr. Frank Netter. His understanding of anatomy, physiology, pathogenesis, and clinical signs of disease are translated by his incredible artistic talent into visual images that are so powerful that they reduce complexities into simple concepts that remain embedded in our memories for decades. It is difficult to express the appreciation we have for how much his art contributed to our own enjoyment of medical education. We both had a strong desire to extend this experience to our peers, trainees, and students through the creation of a new up-to-date resource for learning about infectious diseases. We hope that we have succeeded in our goal and welcome your feedback, seeking further improvements for future editions.

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Edited by ChrisAnna M. Mink

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Introduction to Vaccine-Preventable Diseases in Children and Adolescents

1

ChrisAnna M. Mink

ABSTRACT

The development of immunizations is considered among the top 10 greatest health accomplishments of the twentieth century, and vaccines continue to contribute to improving the health of the world's population. In the United States, all of the diseases for which there are routinely administered vaccinations have been eradicated or have significantly decreased in incidence compared with the prevaccine era. Globally, the number of available vaccines and the number of immunized children have increased in both industrialized and developing nations. Although significant progress has been made in immunizing the global population, much work remains to be done for reaching the geographically and economically disenfranchised. Development of new vaccines and vaccine delivery systems as well as finding new uses for current vaccines are some of the most promising and exciting areas of healthcare research.

This section provides information about the vaccines currently available in the United States for routine immunization of children and adolescents. In addition, as there are frequent changes to the vaccine landscape, resources for finding current vaccine information have also been provided.

GEOGRAPHIC DISTRIBUTION

Worldwide, the percentage of children immunized with three doses of diphtheria, tetanus, and pertussis (DTP) and oral polio vaccines and a measles-containing vaccine is approaching 70%, which is nearly a threefold increase in the past 20 years. In 2007, the immunization rates for children in the United States were at their highest, with nearly 84% of children aged 19 to 35 months immunized for the 4:3:1:3:3 series (four diphtheria toxoid and tetanus toxoid with acellular pertussis vaccine [DTaP]; three polio; one measles, mumps, rubella vaccine [MMR]; three *Haemophilus influenzae* type b vaccine [Hib]; three hepatitis B). Although vaccines have proven safe and cost-effective (saving $5 to $16.50 for every dollar spent), many developing countries do not have adequate access to available or affordable vaccines.

GENERAL PRINCIPLES

Schedules

Synchronized immunization schedules for the United States are developed by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention (CDC), the American Academy of Pediatrics (AAP) Committee on Infectious Diseases *(Red Book)*, and the American Academy of Family Practitioners (AAFP) and are posted annually in January at www.cdc.gov/nip/recs/child-schedule.htm. Since 2007, two immunization schedules are posted for the pediatric age groups: one for children younger than 7 years of age and one for individuals 7 through 18 years of age. A separate schedule is available for immunizations for adults over the age of 18 years.

The World Health Organization (WHO) Expanded Program on Immunization (EPI) publishes immunization schedules for all of the countries in the world. These schedules are available at www.who.int/immunization_monitoring/en/globalsummary/scheduleselect.cfm.

Immunizations Received in Other Countries

Healthy individuals immunized in countries outside of the United States now living in the United States should receive vaccines according to the recommended schedule for healthy infants, children, and adolescents. Generally, only written documentation should be accepted as proof of previous vaccination. Written, dated, and appropriate records (e.g., correct age, dates, intervals, and number of doses) may be considered as valid, and immunizations may resume according to the U.S. schedule. If vaccination status is uncertain, the options include vaccinating or performing serologic testing for antibodies against the selected vaccine antigen, if testing is available.

TYPES OF IMMUNIZATIONS

The two major types of immunizations are active and passive.

Passive Immunization

Passive immunization refers to receipt of preparations of preformed antibodies, usually as immune globulin (IG). IG may be a general formulation or hyperimmune IG developed with high concentrations of antibodies against a specific disease, such as hepatitis B immune globulin (HBIG).

Administration of IG may be useful for (1) prophylactic immunization for a host who is not able to make antibodies, for example, an infant with congenital immunodeficiency, and (2) immediate preexposure or postexposure protection of individuals, especially when there is not sufficient time for the host to mount a protective antibody response, for example, in acute

exposure to hepatitis A in an infant too young to receive active immunization.

Active Immunization

With active immunization, a vaccine antigen is given to the host to elicit a protective immune response (e.g., antibodies or cellular immunity). The vaccine antigen may be composed of whole microorganisms, partial microorganisms, or a modified product (e.g., toxoid or purified component) of microorganisms. Whole organisms may be inactivated or live-attenuated. The elicited immune response usually mimics the response seen with natural infection, and ideally this occurs with no or minimal risks to the recipient.

VACCINE RECIPIENTS

Healthy Pediatric Populations

In the United States, all licensed vaccines have undergone review by the U.S. Food and Drug Administration (FDA) and have been proven safe and effective for the targeted population. Most of the routinely recommended pediatric vaccines are targeted for healthy children and adolescents (Figure 1-1). However, no vaccine is completely free of adverse events (AEs) or will provide 100% protection for every recipient.

Adolescents

Since 2005, several vaccines have become available for routine use in adolescents. These include tetanus toxoid with reduced-dose diphtheria toxoid and reduced-dose acellular pertussis vaccine (Tdap), human papilloma virus (HPV) vaccine, and meningococcal conjugate vaccines; all of these are discussed in detail in the chapters in this section. In addition, some existing vaccines for use in children, such as influenza and varicella vaccines, were given new recommendations for routine or "catch-up" indications in adolescents.

The AAP has recommended a routine health visit at 11 to 12 years, and this visit can be used to ensure that the adolescent has received all recommended immunizations as well as to afford the opportunity to provide anticipatory guidance for safe and healthy living for the teen years.

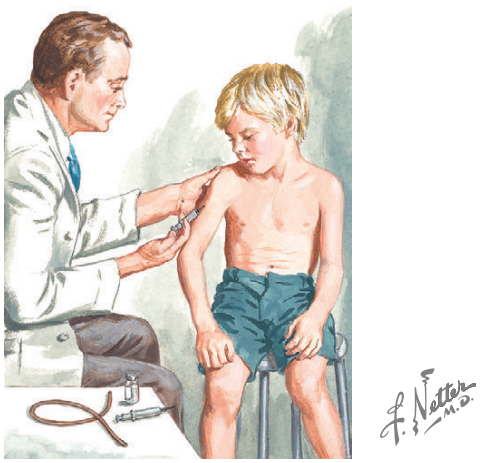

Figure 1-1 Vaccination.

Immunocompromised Children

A growing number of children and adolescents have congenital or acquired immune dysfunction and should not receive immunizations as routinely recommended. Special accommodations may be needed for immunizing these individuals, such as adjusting the schedule or possibly not administering some agents. However, there are no indications for giving decreased or partial doses of vaccines. The plan for vaccination of an immunocompromised child should be determined by the nature and degree of the immunosuppression, weighing the risks and benefits of vaccination with those of exposure to natural infection.

Preterm (<37 Weeks of Gestation) and Low–Birth-Weight (<2000 g) Infants

In general, medically stable premature and low–birth-weight infants may be immunized at the same dose, schedule, and postnatal age as full-term infants. One notable exception is the use of hepatitis B vaccine in infants who weigh less than 2000 g; details are provided in Chapter 15.

International Adoptees, Travelers, Immigrants, and Refugees

All routinely recommended vaccines should be up to date for age, as many families travel abroad without recognizing the possible exposures to vaccine-preventable diseases. In addition, traveling children and teens should receive vaccinations, as well as other preventative measures (e.g., malaria prophylaxis), targeted for their destination. There may be a need for an accelerated schedule—for example, early immunization with MMR for infants 6 to 12 months of age traveling to a measles-endemic area. Use of IG prophylaxis should be considered for some individuals susceptible to hepatitis A (e.g., infants not eligible for active vaccination). Current recommendations for travelers are posted at www.cdc.gov/travel and www.who.int.

ADVERSE EVENTS AND VACCINE INFORMATION

Adverse Events

Safety information about vaccines for healthcare providers and laypersons is available from several reliable resources including the AAP, CDC, FDA, and WHO. A select list of Internet resources for vaccine information is provided in Table 1-1. The vaccine manufacturer's package insert provides safety and tolerability data from the clinical trials for each specific vaccine.

As with any medication, no vaccine is completely free of AEs, and the known AEs should be discussed with vaccinees (non–minors) and/or parents or legal guardians. Most AEs observed after routine immunizations are local injection-site reactions such as erythema, edema, and pain and systemic reactions such as fever or irritability. Although the majority of AEs are mild

Table 1-1 Select Internet Resources for Vaccine Information

RESOURCE	FOR HEALTHCARE PROVIDERS	FOR LAY PERSONS
American Academy of Pediatrics (AAP)	www.aap.org	www.healthychildren.org/english/safety-prevention/immunizations/Pages/default.aspx
Centers for Disease Control and Prevention (CDC)	www.cdc.gov	
Vaccine page	www.cdc.gov/vaccines/pubs/ACIP-list.htm	www.cdc.gov/vaccines/vac-gen/default.htm
Mortality and Morbidity Weekly Report (MMWR)	www.cdc.gov/mmwr/preview/mmwrhtml/rr5102a1.htm	
U.S. Food and Drug Administration (FDA)	www.fda.gov/BiologicsBloodVaccines/Vaccines/default.htm	www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Consumers/default.htm
Vaccine Adverse Event Reporting System (VAERS)	http://vaers.hhs.gov/professionals/index	http://vaers.hhs.gov/
World Health Organization (WHO)	www.who.int	www.who.int/vaccine_safety/en

and self-limiting, some may be associated with transient impairment for the vaccinee, such as limited limb mobility because of pain.

Serious AEs, which may lead to permanent disability or life-threatening illness, are rarely observed after routine pediatric vaccinations. The occurrence of an AE after immunization proves not that the vaccine is the cause of the event but that there is a temporal relationship. If a serious AE occurs after administration of a vaccine (especially within 30 days of receipt), a complete evaluation for all plausible causes, including the role of the vaccine antigen, should be performed. All serious AEs and clinically significant AEs should be reported to the Vaccine Adverse Event Reporting System (VAERS) at http://vaers.hhs.gov, which is maintained by the CDC and FDA. Reporting AEs is valuable because it helps identify events that are infrequent or unexpected and not observed in the prelicensure clinical trials.

Informing Vaccine Recipients and Parents

Vaccine recipients and parents or legal guardians should be informed about the risks and benefits of vaccination and about the natural disease that the vaccine is designed to prevent. The latter is especially important in current times, when many individuals have not seen the natural diseases and their potential for causing serious complications, which vaccines have been successful in controlling or eradicating. Educating individuals about vaccine-preventable diseases is also important because there is increasing anti-vaccine sentiment, which is often based on inaccurate or limited data. Before choosing not to immunize their children, parents should have a full understanding of the potential risks of being unimmunized.

The National Childhood Vaccine Injury Act of 1986 requires that parents receive a Vaccine Information Statement (VIS) each time a child receives a vaccine covered under this legislation, regardless of the funding source used to purchase the vaccine. The VISs are available from the CDC at the National Immunization Program site at www.cdc.gov/VIS/default.htm. The vaccine manufacturer, lot number, and date of administration and that the VISs were provided should be documented.

ADDITIONAL RESOURCES

American Academy of Pediatrics (AAP): Vaccine information. In Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds: *Red Book: 2009 Report of the Committee on Infectious Diseases*, ed 28, Elk Grove Village, Ill, 2009, AAP, pp 1-104. *This resource provides a summary of the general principles of immunization, accommodations for compromised hosts, and current schedules.*

Atkinson W, Wolfe S, Hamborsky J, McIntyre L, eds: *Epidemiology and prevention of vaccine-preventable diseases*, ed 11, Washington DC, 2009, Public Health Foundation. Available at: www.cdc.gov/vaccines/pubs/pinkbook/default.htm. *This resource provides current information about epidemiology (primarily in the United States) and prevention of, including immunization against, vaccine-preventable diseases.*

Centers for Disease Control and Prevention (CDC): *2006 NIP annual report: a global commitment to lifelong protection through immunization*. Available at: www.cdc.gov/nip/webutil/about/annual-rpts/ar2006/2006annual-rpt.htm. *This report provides a summary of the rates of immunization for different age groups.*

Centers for Disease Control and Prevention (CDC): *Vaccines and immunizations: immunization schedules.* Available at: www.cdc.gov/vaccines/recs/schedules/default.htm. *This site has the annual U.S. schedules for immunizing different age groups.*

Kroger AT, Atkinson WL, Marcuse EK, et al: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP) 2006, *MMWR Recomm Rep* 55:1-48, 2006. *This resource provides general guidelines for immunizations.*

Mink C: Immunizations in pediatrics: a primary care approach. In Berkowitz CD, ed: *Pediatrics: a primary care approach*, Elk Grove Village, Ill, 2008, American Academy of Pediatrics. *This resource provides the basic principles for immunization of the pediatric age group.*

Diphtheria and Tetanus

Bruce D. Meade and Kristin E. Meade

2

ABSTRACT

Diphtheria and tetanus are bacterial diseases that are mediated by extremely potent toxins. Diphtheria is a communicable infection of the upper respiratory tract, skin, and rarely other mucous membranes caused by *Corynebacterium diphtheriae*, whereas tetanus is a neurointoxication resulting from anaerobic wound infections caused by *Clostridium tetani.* These diseases can be life-threatening, and early recognition and intervention are essential for effective management. Immunization against both diseases is usually performed with combination vaccines containing diphtheria and tetanus toxoids, which induce toxin-neutralizing antibodies that are protective. Suspected cases should be reported immediately to public health experts, as both diseases require treatment with specific antitoxin. Although these once-common diseases are now rare in the United States, ongoing vigilance is warranted because many individuals are susceptible and the diseases remain endemic in many regions of the world.

Diphtheria and tetanus are very different diseases in their clinical presentation. Nevertheless, the two diseases are commonly considered together because they share a common history, as well as key elements of pathogenesis and prevention. Potent toxins are central to the pathogenesis of diphtheria, a communicable, acute upper respiratory infection caused by *C. diphtheriae*, and tetanus, a neurointoxication resulting from a wound infection by *C. tetani.* Diphtheria toxin (DipT) and tetanus neurotoxin (TeNT) were among the earliest recognized bacterial toxins, and early immunology was stimulated by the discovery of protective, toxin-neutralizing serum antibodies. The science of vaccination was promoted by the revelation that DipT and TeNT can be chemically treated to produce toxoids, namely, molecules that have lost toxicity but retain their ability to induce protective antibodies. Today, tetanus and diphtheria toxoids are almost always coadministered in combination vaccines.

A basic knowledge of the toxins is essential for an understanding of pathogenesis. The specificity and toxicity are the result of the complex interactions between these toxins and host cells. DipT kills a variety of target cell types by disrupting protein synthesis. TeNT interacts only with neuronal cells and achieves toxicity through loss of inhibitory control of muscular activity.

For both diseases the key to prevention is to maintain adequate concentrations of toxin-neutralizing antibodies. As a result of successful immunization programs, diphtheria and tetanus are now rare in the United States and in other developed nations; therefore few healthcare professionals have directly observed a case. If diphtheria or tetanus is suspected, state and local health departments should be contacted for guidance. Diphtheria antitoxin (DAT) required for emergency treatment of diphtheria is available in the United States only from the Centers for Disease Control and Prevention (CDC).

DIPHTHERIA

Geographic Distribution and Magnitude of Disease Burden

C. diphtheriae is a species of aerobic, irregularly shaped, gram-positive rods, and humans are the only known reservoir. Strains are found in four biotypes known as *gravis*, *intermedius*, *mitis*, and *belfanti;* however, all four types can cause human disease. Spread occurs through contact with respiratory secretions or skin lesions. The genes responsible for DipT production are carried on a lysogenic bacteriophage. Strains of *C. diphtheriae* that do not carry the phage commonly colonize the human respiratory tract but cannot cause clinical diphtheria. Asymptomatic carriers of both toxigenic and nontoxigenic strains have been reported. Nontoxigenic strains are increasingly reported in several countries and have been associated with systemic disease in immunocompromised individuals. The bacteriophage can also be carried by *Corynebacterium ulcerans* or *Corynebacterium pseudotuberculosis*, and diphtheria-like illness has been observed in patients infected with *C. ulcerans.*

Before widespread vaccination, diphtheria was a leading cause of morbidity and mortality in the United States. In the pre-vaccine era, approximately 70% of diphtheria cases occurred in children younger than 15 years old. Disease was less common in infants younger than 6 months of age, presumably because of the protection provided by maternal antibodies acquired transplacentally. Asymptomatic infections were common. Clinical disease was less common in adults because most had immunity as a result of natural exposure. Immunity from exposure does not appear to be lifelong; however, immunity was maintained by frequent boosting through natural exposure.

In the United States, 57 cases of respiratory diphtheria have been reported to the CDC since 1980, and approximately 60% of these occurred in adults. In the states of the former Soviet Union, a large outbreak of diphtheria involving 157,000 cases and 5000 deaths, primarily in adults, occurred from 1987 to 1997. This outbreak was found to be associated with declines in the public health infrastructure and vaccination coverage rates and demonstrated the importance of maintaining high immunization coverage in all populations.

Through increased international efforts to improve vaccine coverage, there has been a steady decline in the number of reported cases worldwide. However, diphtheria remains endemic in countries with inadequate vaccination coverage. Travelers to those regions should ensure that they are up to date with diphtheria immunizations. Similarly, diphtheria should be

considered in the differential diagnosis for symptomatic individuals coming from those regions.

Risk Factors

Increased risk is directly associated with inadequate serum concentrations of DipT-neutralizing antibodies. Notably, immunity from vaccine or natural disease does not appear to be lifelong. In the United States, coverage with diphtheria booster immunization decreases with age, and studies have suggested that 40% to 70% of adults older than 40 years of age are susceptible. In the United States and Canada, circulation of toxigenic strains is uncommon, except in some areas within the northern plains region. Although the opportunity exists for introduction of toxigenic strains into the general population, outbreaks are rare when high immunization rates in infants and children are maintained.

Clinical Features

The initial diagnosis is based on the observation of classic clinical features. Two main types of infection can occur: a benign, self-limited, and nonspecific skin infection, and a respiratory form that can manifest as a localized nasal infection or a more serious pharyngeal or laryngeal disease. The incubation period ranges from 1 to 10 days but is typically less than 7 days. The respiratory disease begins gradually with nonspecific symptoms such as fatigue, sore throat, anorexia, and low-grade fever. Approximately 2 to 3 days after onset of symptoms, patients develop the classic pseudomembrane, which is an adherent gray membrane covering the tonsils, posterior pharynx, uvula, and/or posterior tongue that will bleed with attempts to remove it (Figure 2-1). As the disease progresses, patients may develop difficulty swallowing and a hoarse voice. In the most severe forms of respiratory diphtheria, extensive membrane formation and edema can result in airway obstruction; therefore patients should be monitored closely for respiratory compromise. Associated extensive cervical lymphadenopathy and soft-tissue swelling may cause the classic "bull-neck" appearance (Figure 2-2). Absorption of DipT into the bloodstream can cause serious systemic complications, notably myocarditis and neuropathies.

Diagnosis

Diphtheria is initially a clinical diagnosis, and laboratory confirmation requires isolation of toxigenic strains of *C. diphtheriae* from the site of infection. Proper culture requires special collection techniques and growth media; few laboratories have maintained expertise. Therefore in addition to discussion with the local laboratory, an experienced public health microbiology laboratory should be contacted for further guidance. For respiratory diphtheria, cultures should be obtained from the involved nasal or pharyngeal mucosa and should include both the pseudomembrane and the material beneath the membrane. Because there are asymptomatic carriers of nontoxigenic *C. diphtheriae*, confirmation also requires detection of DipT by one of four currently available tests: a cytotoxicity assay, the Elek test (a traditional but time-consuming in vitro immunoblotting test), and two newer and more rapid procedures—specifically, an enzyme-linked immunoassay and a polymerase chain reaction (PCR) test. PCR test results should be confirmed by one of the other methods that detects active toxin.

The differential diagnosis includes pharyngitis from more common causes, including bacterial pharyngitis caused by group A *Streptococcus* or *Arcanobacterium* and viral pharyngitis (e.g., caused by adenoviruses and enteroviruses); infectious mononucleosis from Epstein-Barr virus; and more unusual diseases such as acute necrotizing ulcerative gingivitis (Vincent's angina) and severe oropharyngeal candidiasis.

Clinical Management

Respiratory diphtheria mandates prompt treatment with antitoxin and antibiotics, supplemented with intensive supportive

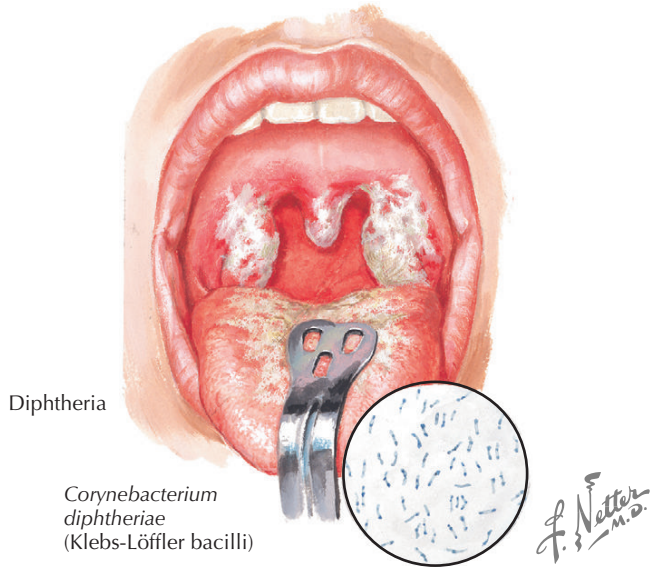

Figure 2-1 Pseudomembrane (diphtheria).

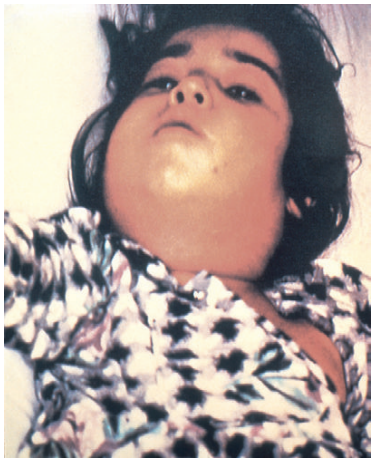

Figure 2-2 Classic bull-neck appearance. *(From Centers for Disease Control and Prevention, Public Health Image Library, 1995.)*

care. When diphtheria is suspected, treatment with equine antitoxin should begin before laboratory confirmation is obtained. No licensed product is available in the United States; however, DAT can be obtained from the CDC. The local or state public health departments should be contacted for public health investigations. Antitoxin only neutralizes circulating DipT and has no effect on intracellularly bound toxin, therefore early use is required to minimize the severity of the disease. Because the antitoxin is made from horse serum, it carries the risk of hypersensitivity reactions or serum sickness, and patients should be tested for sensitivity before administration. Individuals with hypersensitivity should receive the antitoxin according to the desensitization procedure provided by the CDC protocol, and only in settings equipped for treatment of anaphylaxis. Antibiotics are also an important aspect of therapy, but they do not replace the use of antitoxin. Although antibiotics have no effect on existing DipT, they will help to prevent further bacterial growth, slow toxin production, and decrease the risk of transmission. Antibiotic treatment consists of a 14-day course of either penicillin or erythromycin. Intravenous medications should be used initially but can be transitioned to oral medications as soon as the patient is able to tolerate oral therapy.

Supportive care involves careful respiratory and cardiac monitoring, as patients are at risk for airway obstruction as well as arrhythmia and cardiac compromise from myocarditis. Droplet precautions should be maintained for patients with suspected respiratory diphtheria until completion of antibiotic regimens and until two cultures, separated by at least 24 hours, are negative. Contact precautions are recommended for individuals with cutaneous diphtheria, and lesions should be covered. Treatment should include antibiotics and routine management for skin ulcers; DAT is rarely needed. Active diphtheria infection may not induce protective immunity, and all patients should receive an appropriate vaccination series after resolution of the acute illness.

Prognosis

Prognosis depends on the severity of the pharyngeal disease, the extent of respiratory compromise, the duration of disease before initiation of treatment, and the presence of myocarditis. Duration of illness depends on the severity of the disease and resulting complications and can range from a few days to several months. The case-fatality rate of respiratory diphtheria is 5% to 10%. Cutaneous diphtheria is rarely fatal.

TETANUS

Geographic Distribution and Magnitude of Disease Burden

C. tetani is a gram-positive, spore-forming, strict anaerobic bacterium that typically exhibits a terminal spore and can infect wounds. The spores are found in soil in nearly all areas of the world. Tetanus is typically associated with deep or penetrating wounds that create the anaerobic conditions that facilitate germination, growth of spores, and release of TeNT (often called *tetanospasmin*), the toxin responsible for the clinical manifestations of disease.

TeNT, one of the most toxic molecules known, achieves its toxicity through a series of complex steps that include a remarkable journey from the periphery to the central nervous system (Figure 2-3). TeNT binds to neuronal cells at the site of infection and then is transported centrally, where it interferes with release of inhibitory neurotransmitters. Once the inhibitory control is lost, motor neurons undergo sustained excitation leading to the muscular stiffness and spasms characteristic of tetanus.

In the United States the annual incidence of tetanus was 0.1 to 0.2 cases per million population over the last decade, down from 3.9 cases per million before widespread immunization. The decline can be attributed to immunization, as well as to hygienic improvements in wound management and childbirth practices. Cases have been reported in all age groups; however, the incidence rates tend to increase with increasing age—for example, 34% of the cases reported to the CDC from 2001 to 2007 were in individuals older than 65 years of age. During the same period, only 4% were in people younger than 15 years of age. The case fatality rate over the past decade has been about 10% to 15%; however, at least 75% of deaths occurred in individuals over 60 years old.

Worldwide, a steady increase in tetanus toxoid vaccinations has been associated with a decline in cases and deaths. However, tetanus remains a problem in parts of the world with low immunization coverage, with maternal and neonatal tetanus responsible for the great majority of deaths. Maternal tetanus is associated with inadequate vaccination and unhygienic obstetric practices. Neonatal tetanus results from infection of the umbilical stump, particularly in infants born to mothers with inadequate immunization. Over the past 20 years, the World Health Organization (WHO) has encouraged efforts to reduce maternal and neonatal tetanus; however, WHO estimates that there were approximately 180,000 neonatal deaths and 15,000 to 30,000 maternal deaths in 2002. Both maternal and neonatal tetanus are preventable via immunization of mothers, with neonatal protection resulting from transplacentally acquired TeNT-neutralizing antibodies.

Risk Factors

Mirroring the situation described earlier for diphtheria, higher risk is associated with inadequate concentrations of neutralizing antibodies, usually through a failure to stay up to date with recommended immunizations. Most cases of tetanus occur in individuals who lack TeNT-neutralizing antibodies and incur a wound that promotes the anaerobic growth of *C. tetani.* Conditions that encourage an anaerobic environment include co-infection with other bacteria, devitalization of tissue, or presence of a foreign body. Other risk factors include intravenous drug use and diabetes. Most nonneonatal cases occur after a penetrating injury; however, in about 30% of cases, the site of infection cannot be identified.

Clinical Features

Tetanus disease occurs in one of four clinical patterns: generalized, local, cephalic, or neonatal. The severity is influenced by the amount of toxin produced as well as the presence of preexisting, albeit not fully protective, concentrations of

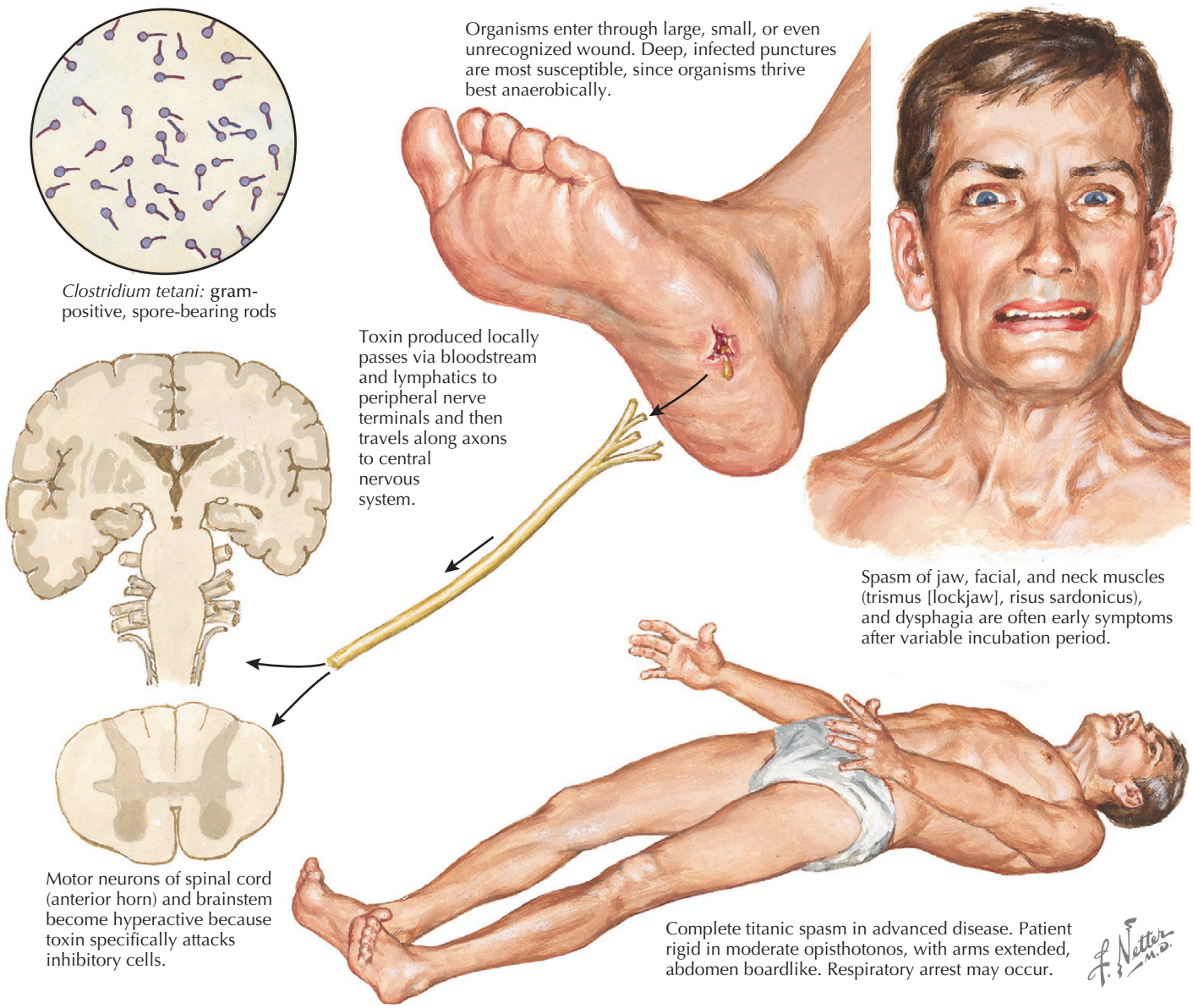

Figure 2-3 Generalized tetanus.

antibody. The incubation period from the time of inoculation is typically about 1 week but can be as rapid as 1 to 3 days or as long as many months. In general, rapid disease progression is associated with a more severe course. The most common and severe form of tetanus is generalized tetanus, characterized by diffuse tonic contraction of skeletal muscles as well as intermittent, painful muscular spasms (see Figure 2-3). The disease typically begins with localized muscle spasms, including trismus (lockjaw) or other cranial nerve involvement, which progress to include a stiff neck, opisthotonus (spasms and arching of the back), risus sardonicus (sustained muscle spasm of the face), a rigid abdomen, dysphagia, or apnea (caused by the contraction of the thoracic muscles and/or the glottal or pharyngeal muscles). Generalized tetanic spasms lead to a characteristic posture: clenching of the fists, arching of the back, flexion and abduction of the arms, and extension of the legs, often accompanied by apnea. Toxin damage to autonomic nerves also leads to autonomic instability, characterized early by irritability and restlessness, sweating, and tachycardia and later by labile blood pressures, cardiac arrhythmias, and fever.

Local tetanus is a rare clinical pattern characterized by muscle contraction in a single extremity or body region. Cephalic tetanus is similar but involves only the cranial nerves. Many cases progress to generalized tetanus and may represent an early stage of the disease. The facial nerve is the most commonly affected.

The fourth clinical pattern is neonatal tetanus. Disease onset is very rapid and generally occurs within the first 2 weeks of life. Symptoms are similar to those of generalized tetanus, including diffuse rigidity, muscle spasms, and trismus, leading to complications of apnea and the inability to suck. In addition, seizures have been observed in infants with tetanus.

Diagnosis

Tetanus is diagnosed solely on clinical grounds. Tetanus should be considered in the differential diagnosis of muscle spasms, particularly in patients with a history of an antecedent injury and inadequate immune status. The differential diagnosis includes drug-induced dystonias, dental infections, neuroleptic malignant syndrome, strychnine poisoning, and stiff person syndrome.

Clinical Management and Drug Treatment

Effective treatment of tetanus requires a multipronged approach, including neutralization of circulating toxin, reduction in toxin production, medical control of muscle spasms, management of autonomic instability, aggressive supportive care, and immunization. Neutralization of unbound, circulating antibody is achieved by the use of human tetanus immune globulin (TIG), a commercially available product licensed by the Food and Drug Administration (FDA). Prompt administration helps to minimize disease severity. Aggressive wound management and debridement, as well as antibiotic treatment with either penicillin or metronidazole, can reduce further TeNT production. Muscle spasms, in addition to being intensely painful, can be life-threatening when they lead to apnea. Limiting stimulation can minimize the frequency of spasms. Additional management includes the use of sedatives such as benzodiazepines or, in severe, refractory cases, neuromuscular blockade. Autonomic instability is often managed with magnesium sulfate, morphine, or beta-blockade. Supportive care is a vital part of the management of tetanus, as full recovery may take several weeks. Many patients require respiratory support, and early tracheostomy should be considered to avoid complications of prolonged intubation. Early enteral nutrition and prompt initiation of physical therapy may speed recovery. Tetanus disease does not confer lasting protective immunity, and all patients should immediately receive appropriate immunization.

Prognosis

The prognosis of people with tetanus is dependent on the availability of supportive care, as well as the age and underlying health of the patient. In general, the shorter the incubation period and the time to onset of spasms, the worse the prognosis. Recovery from tetanus requires regrowth of axonal nerve terminals, and therefore the duration of disease can be prolonged (typically 4 to 6 weeks). Because of the availability of supportive care, most patients in developed countries recover. In contrast, in developing countries the mortality rates range from 8% to 50% and 10% to 60% for nonneonatal and neonatal tetanus, respectively. Most adults and children who survive recover fully, but neonates may have varying degrees of neurologic damage, including intellectual deficits and cerebral palsy.

PREVENTION AND CONTROL OF DIPHTHERIA AND TETANUS

Vaccination with diphtheria and tetanus toxoids is the basis of prevention and control of these two diseases. Measurement of antitoxin antibodies is possible; however, interpretation of the antibody concentrations is complex and may not readily predict the protection status of the individual. More important than a specific antibody concentration, the key to protection is assurance of the appropriate series, including booster doses, of vaccinations.

In addition to routine vaccinations, tetanus immunizations have a role in management after potential exposure from an injury. Anyone with a clean, minor wound should receive a dose of a tetanus toxoid–containing vaccine if he or she has not had a booster dose in the past 10 years. For all other injuries, including but not limited to dirty, penetrating, or burn wounds, a dose of tetanus toxoid–containing vaccine should be given if the individual has not received a booster in the past 5 years, has received fewer than three vaccinations, or has unknown vaccination status. In addition, prophylactic administration of TIG is recommended for underimmunized patients with serious wounds.

Tetanus toxoid is available as a single antigen (TT) or in combination with pediatric or adult formulations of diphtheria toxoid (DT or Td, respectively) and whole-cell or acellular pertussis antigens (DTP, DTaP, and Tdap). The diphtheria toxoid component of childhood vaccines has a higher toxoid content (represented by capital *D*) and is designed to induce a good antibody response in immunologically naïve individuals younger than 7 years of age. For older and previously immunized individuals, a lower toxoid content vaccine (designated by lowercase *d*) is used because it induces a good antibody response while yielding fewer reactions. Products available vary by country and age, and national agencies should be consulted for the currently recommended products. In the United States the current recommendation is for an initial five-dose series in childhood, with doses at 2, 4, and 6 months, a fourth dose at 15 to 18 months, and a dose at 4 to 6 years of age. At least three doses of each toxoid are required for development of immunity, and additional doses are recommended to maintain this immunity. In the United States, booster doses of diphtheria and tetanus toxoid vaccines are recommended at age 10 to 12 years (combined with reduced dose acellular pertussis vaccines, Tdap) and then every 10 years to maintain protection. For individuals at least 10 years of age who are eligible to receive acellular pertussis vaccine, one dose of Tdap is recommended instead of Td. Anyone with uncertain vaccination history should be considered unvaccinated and receive the recommended age-appropriate series.

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Bordetella pertussis and Pertussis (Whooping Cough)

Sylvia H. Yeh and ChrisAnna M. Mink

3

ABSTRACT

Despite the availability of effective vaccines in most developed and developing countries, pertussis remains a significant cause of morbidity and mortality worldwide. Routine use of pertussis vaccines has shifted the burden of disease from middle childhood to young infants and older children, adolescents, and adults. The changing epidemiology dictates the need for new vaccines and new vaccine programs targeting these age groups.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

The World Health Organization (WHO) estimates that globally there are 20 to 40 million cases of pertussis annually, with over 90% occurring in developing nations. Annually, pertussis causes 400,000 deaths worldwide, with the majority occurring in young infants. Pertussis is endemic globally, with epidemic peaks every 3 to 5 years. This cycling has not been altered in the postvaccine era, likely because of an accumulation of susceptible individuals, in part a result of waning immunity. In general, the epidemiology of pertussis in countries that do not have a high uptake of pertussis vaccination in infants and children reflects that of the prevaccine era in the early twentieth century in the United States.

RISK FACTORS

Bordetella pertussis is strictly a human pathogen. It is the primary cause of clinical whooping cough and is readily transmitted by aerosolized droplets. The attack rate for susceptible individuals is estimated to be over 80%. In countries with high levels of pertussis vaccination (>80% coverage of young children) such as the United States, Japan, and Western European countries, the overall disease burden of pertussis has declined (Figure 3-1). However, the incidence of disease has increased in infants (especially those too young to have completed the primary immunization series) and in adolescents and adults (with waning immunity from vaccination or natural exposure). The Centers for Disease Control and Prevention (CDC) noted that during 2000 to 2006, 103,940 cases of pertussis were reported in the United States, and 27% of these cases occurred in persons aged 15 to 39 years. From 2000 to 2004, 19% of the reported cases of pertussis were in infants younger than 12 months of age. Infants have the greatest risk of morbidity and mortality with pertussis. Studies from industrialized countries have reported rates of hospitalization because of pertussis ranging from 17 (6- to 11-month-old infants) to 280 (0- to 5-month-old infants) per 100,000 population. In the United States, 145 of the 156 (93%) deaths reported from 2000 to 2006 were in infants younger than 12 months of age. A study of pertussis deaths in the 1990s revealed a higher than expected rate of death in Hispanic infants and infants born at less than 37 weeks of gestation. Data also suggest that administration of two to three doses of pertussis vaccine within the first 6 months of life is protective against severe disease.

CLINICAL FEATURES

After exposure to the bacteria, the average incubation period is 7 to 10 days, which is then followed by onset of symptoms. The clinical illness is divided into three stages: catarrhal, paroxysmal, and convalescent.

Catarrhal Stage

The catarrhal stage appears similar to the "common cold," with mild cough and coryza, and generally lasts 1 to 2 weeks. Fever is uncommon, and if present it is usually low grade. Unlike a common viral upper respiratory infection, which resolves quickly, in pertussis the cough gradually increases, and infected individuals are most contagious during this phase.

Paroxysmal Stage

In the paroxysmal stage the coughing persists and gradually increases in severity, resulting in the classic paroxysmal attacks. Whooping may be observed during the paroxysmal phase, which is characterized by the noise of the forced inspiratory effort after the coughing attacks (Figure 3-2). Posttussive emesis may be observed. This stage may last 6 to 12 weeks and is the period when complications are most likely to occur. The occurrence of complications is inversely related to age, with the youngest infants having the highest rate of complications. The most common complications include hospitalizations, apnea, pneumonia (primary and secondary), barotrauma events (e.g., subconjunctival hemorrhages, umbilical hernias, pneumothorax), and failure to thrive in infants who are unable to feed owing to coughing. Seizures, encephalopathy (likely related to generalized hypoxia), and death occur in less than 2% of patients and are generally seen in the youngest infants, although these events have been reported in adults. Pneumonia is the most common complication of pertussis (from either primary pertussis or secondary bacterial infection) and also the most common cause of pertussis-associated deaths. Infants younger than 4 months of age who died from pneumonia have been found to have histopathologic findings consistent with pulmonary hypertension.

Convalescent Stage

During the convalescent stage the cough continues to decrease gradually over several weeks to months. Sporadic coughing

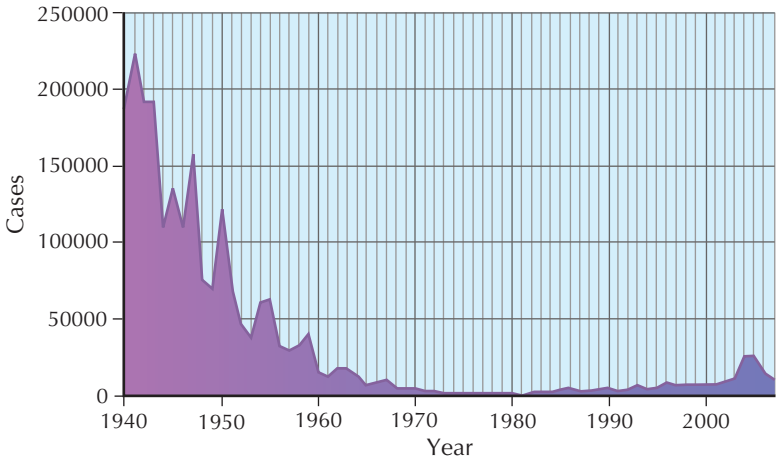

Figure 3-1 Epidemiology of pertussis in the United States, 1940 to 2007. *(From Centers for Disease Control and Prevention, Atkinson W, Wolfe S, Hamborsky J, McIntyre L, eds:* Epidemiology and prevention of vaccine-preventable diseases, *ed 11, Washington DC, 2009, Public Health Foundation.)*

Figure 3-2 Child coughing.

paroxysms may reappear with subsequent upper respiratory infections during convalescence.

Atypical Pertussis

Infants younger than 6 months of age and older children, adolescents, and adults are less likely to have the features of classic whooping cough. Young infants may have apnea as their only presenting feature, and a history of a coughing household member is often the diagnostic clue. Older children, teens, and adults may have chronic cough of varying severity as their primary sign. Persistent coughing has led to erroneous diagnoses such as asthma or reflux aspiration.

DIAGNOSTIC APPROACH

Clinical Diagnosis

Pertussis is a clinical diagnosis, and a high index of suspicion is essential in making the correct diagnosis. When the classic features of whooping cough are present, the diagnosis may be readily entertained. However, because the spectrum of illness is quite varied, pertussis may not be considered. The following case definitions for confirmed and probable cases of pertussis have been established by WHO and the CDC in conjunction with the Council of State and Territorial Epidemiologists:

- For endemic or sporadic cases, a clinical case is defined as an acute cough illness lasting at least 14 days accompanied by paroxysms of coughing, inspiratory whoop, or posttussive vomiting.
- In an outbreak or after household contact with a known case, a clinical case is defined as a cough illness for at least 14 days; presence of the typical pertussis-associated features is not required.

Laboratory Studies

BACTERIAL CULTURE

Growth of *B. pertussis* on specialized media (Bordet-Gengou or Regan-Lowe charcoal agar) is considered the gold standard, and although it is 100% specific, the sensitivity is variable and may be quite low. Factors that contribute to the poor sensitivity of culture include (1) inadequate nasopharyngeal (NP) sample, (2) samples obtained late in the illness, (3) prior antibiotic therapy, (4) previous pertussis immunizations, and (5) difficulty growing and identifying this fastidious organism in the clinical microbiology laboratory. Growth of *B. pertussis* may take 3 to 5 days, but generally microbiology laboratories will maintain the culture plates for 7 to 14 days.

DIRECT FLUORESCENT ANTIBODY

Direct fluorescent antibody (DFA) assay is also available for testing NP samples but is operator dependent and has variable sensitivity and specificity. Therefore in most settings the DFA assay is not a reliable test for laboratory confirmation of pertussis.

POLYMERASE CHAIN REACTION

Polymerase chain reaction (PCR) is an amplified molecular testing tool that often detects sequences in the pertussis toxin gene. In multiple trials evaluating NP samples, PCR has demonstrated higher sensitivity than culture, as well as a more rapid

turnaround time. The deficiencies of PCR include lack of standardization, limited availability, and the potential for contamination yielding false-positive results. Given the greater sensitivity and rapidity of PCR as compared with culture, PCR is gaining favor for diagnosing pertussis. Although many commercial laboratories offer PCR testing for *B. pertussis*, no Food and Drug Administration (FDA)–approved assays are currently available.

SEROLOGY

The most widely available serologic assay is an enzyme-linked immunosorbent assay (ELISA) for antibodies to purified antigens of *B. pertussis*. However, there is no established serologic correlate of immunity or serologic marker of acute infection. Currently, serologic testing is most informative when simultaneous testing of acute and convalescent serum samples is performed; however, fold-rise in titers may not be observed if the first sample is obtained late in the illness.

OTHER LABORATORY FINDINGS

During the paroxysmal stage, leukocytosis and lymphocytosis are the characteristic hematologic findings, although these may not be seen, especially in older individuals. The degree of leukocytosis can exceed 50,000 cells/mm^3, and the absolute lymphocyte count may exceed 10,000 cells/mm^3. The degree of lymphocytosis has been shown to correlate with the severity of illness. Hypoglycemia has been reported in young infants, which may be related to their inability to eat because of coughing or possibly secondary to toxins produced by the organism. Chest radiographs may be normal or may have subtle abnormalities such as peribronchial cuffing, perihilar infiltrates, or atelectasis. Pulmonary consolidation occurs in 20% of hospitalized patents.

CLINICAL MANAGEMENT

Supportive Care

Supportive care is the mainstay for management of *B. pertussis* infection in patients of all ages. Young infants are more likely to need hospitalization because of their risks for apnea, hypoxia, failure to thrive, and other complications. However, over 3% of pertussis-associated hospitalizations in the United States have been in adults older than 20 years of age. Infants with severe or frequent coughing paroxysms or apnea may require assisted ventilation. Some infants benefit from oxygen supplementation during coughing spells, feedings, and other exertions. Although there are no established criteria for hospitalization for infants, inability to maintain O_2 saturation during feeding and paroxysms warrants hospitalization.

Maintaining adequate hydration and caloric intake may be difficult for infants because of the paroxysms, which often prohibit them from eating and may cause increased caloric expenditure. Thus close attention to fluid and nutritional status is imperative. In addition, whenever possible, known triggers (e.g., exercise, cold temperatures) that cause coughing paroxysms in the child should be avoided.

Antibiotic Therapy

Antibiotic therapy should be initiated based on a high degree of clinical suspicion, even without laboratory confirmation. Antibiotic treatment is recommended for all infected individuals, regardless of their age or immunization status. The duration of symptoms before treatment seems to be an important factor for the impact of antibiotics. Early treatment (e.g., during the first 7 days of symptoms) may decrease the severity of symptoms, as well as decrease the risk of spread to other susceptible individuals. After 21 days of symptoms, antibiotics may still decrease spread to contacts but likely do little to alter the clinical course. Unfortunately, most patients do not come to medical attention until the paroxysmal phase, when there is likely to be less of an impact on the disease progression.

The antibiotics of choice are macrolide compounds, including erythromycin, clarithromycin, and azithromycin. Erythromycin should be taken for 14 days, and clarithromycin and azithromycin may be taken for 7 days. Oral erythromycin has been associated with infantile hypertrophic pyloric stenosis (IHPS) in infants younger than 1 month of age. It is not known if clarithromycin and azithromycin pose the same risks for IHPS. In infants younger than 1 month old, the risk of pertussis and its complications outweighs the risks of azithromycin therapy. Therefore the American Academy of Pediatrics (AAP) currently recommends azithromycin for infants younger than 1 month of age, though this is not an FDA-approved indication. Depending on the age of the individual, alternatives may include doxycycline, fluoroquinolones, and trimethoprim-sulfamethoxazole (TMP-SMX). Neither doxycycline nor the fluoroquinolones are recommended for use in young children owing to potential toxicities. Although it has excellent in vitro activity, TMP-SMX has not been systematically evaluated, and its clinical efficacy is largely unproven. TMP-SMX should not be used in the first 6 weeks of life because of the risks of bilirubin displacement and kernicterus. The β-lactam antibiotics have variable activity against *B. pertussis* and are not recommended.

Adjunctive Therapies

Treatment with agents such as antitussives, steroids, and aerosolized bronchodilators have not demonstrated efficacy or benefit for pertussis and are not routinely recommended. Initial studies of *B. pertussis* immunoglobulin (BPIG) showed an improvement in cough paroxysms. Further development of this product has not been pursued, and at this time BPIG is not available.

PROGNOSIS

As described earlier, infants have the greatest risk of morbidity and mortality, although complications from pertussis have also been reported in adolescents and adults. The prognosis of infants and children appears to be related to the occurrence and severity of complications. For adults, although the illness may be prolonged, recovery is usually complete.

PREVENTION AND CONTROL: VACCINES

The original vaccines for pertussis were killed whole-cell pertussis organisms, which were later available in combination with diphtheria toxoid and tetanus toxoid (DTwP). These vaccines were effective in reducing the overall burden of pertussis. However, reported temporal associations of adverse events led to a decrease in acceptance of these vaccines in many industrialized nations. Subsequently, pertussis vaccines that were more purified or composed of pertussis antigens (acellular pertussis vaccine [aP]) were developed. Currently, several aP vaccines in combination with diphtheria toxoid and tetanus toxoid (DTaP) are widely available for use in infants and young children. The aP vaccines have a reduced rate of adverse events compared with whole-cell pertussis vaccines. Durability of immunity following aP vaccines appears to be similar to that of whole-cell vaccines, but this still requires further investigation.

Throughout the world, pertussis vaccination generally begins around 2 months of age and consists of 3 to 5 doses by age 5 years. In the United States, DTaP is recommended for routine administration to infants at 2, 4, 6, and 12 to 15 months, with a booster dose at 4 to 6 years of age.

Because of the increasing recognition of pertussis in persons 10 years of age and older, who may expose young infants, vaccines targeted to the older age groups have been developed. Reduced-dose acellular pertussis (ap) vaccines combined with tetanus toxoid and reduced-dose diphtheria toxoid (Tdap) have been available for individuals 10 years of age and older in the United States since 2005. In the United States, Tdap is recommended for routine administration in early adolescents (11 to 12 years of age), and for one-time use to replace Td booster vaccination in older teens and adults. Use of Tdap instead of Td at 10-year intervals is under investigation. Tdap vaccines are also recommended for persons (e.g., pediatric healthcare workers; household contacts, and caregivers of young infants) who have contact with individuals at risk for severe pertussis. Strategies to implement routine vaccination of mothers and household contacts of newborn infants are being developed.

After pertussis exposure, DTaP vaccine should be administered as soon as possible for unimmunized children 7 years of age and younger with incomplete pertussis vaccine series or for those with four or fewer doses and for whom more than 3 years have elapsed since the last pertussis vaccine. Tdap should be administered to exposed individuals older than 10 years of age who are unimmunized. Tdap can be administered at intervals as short as 2 years after previous vaccines containing tetanus, diphtheria, or pertussis, during a community outbreak, or in persons with a high risk of complications with pertussis.

Universal immunization of infants and children with the whole-cell and acellular pertussis vaccines has been effective in reducing the disease burden of pertussis. However, with the shifting epidemiology, it has become apparent that new vaccines and delivery programs are necessary to control this human pathogen. Recently in many industrialized countries, routine immunization programs that included only vaccination of infants and children with DTwP or DTaP have been revised to include Tdap for adolescents and adults. However, the best strategy for protecting the youngest, most vulnerable infants is not yet known. The goals of expanding pertussis vaccinations to include individuals 10 years of age and older are not only to reduce infections in the older age groups, but ultimately, by decreasing pertussis circulation in the community, to provide protection for infants too young to be immunized.

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Haemophilus influenzae Type b

Sylvia H. Yeh

4

ABSTRACT

Haemophilus influenzae type b (Hib) was a leading cause of bacterial sepsis and meningitis in children before the widespread availability of conjugate vaccines in developed nations. However, in countries without vaccines, Hib continues to be a significant cause of morbidity and mortality in young children.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

Haemophilus influenzae is a pleomorphic, gram-negative coccobacillary human pathogen that can be transmitted person to person via respiratory droplets. It is the causative agent for a wide range of infections whose severity is related to the presence or lack of a bacterial capsule. Encapsulated (typable) strains of *H. influenzae* account for the vast majority of invasive disease, with *H. influenzae* type b (Hib) being the predominant serotype, especially in children younger than 5 years of age. Before widespread availability of conjugate vaccine in 1991, Hib was the leading cause of bacterial meningitis, occult bacteremia, epiglottitis, pneumonia, empyema, cellulitis, septic arthritis, and pericarditis. Invasive Hib infections occurred in 1 in 200 children in the United States during the first 5 years of life. This incidence has dramatically declined to approximately 1 per 100,000 over the past 15 years, reflecting the success of Hib conjugate immunization.

RISK FACTORS

Antibodies against the Hib polysaccharide capsule, polyribosylribitol phosphate (PRP), are protective against invasive disease. Young age is a primary risk factor, with infants 6 to 18 months of age having the greatest risk for invasive Hib disease because of their paucity of PRP antibodies. Infants younger than 6 months of age likely have some protection from passively acquired maternal antibodies. Underlying conditions such as human immunodeficiency virus (HIV), sickle cell anemia, functional asplenia, antibody or complement deficiency syndromes, and malignancy are also risk factors for Hib disease. Environmental exposures such as crowding, household size, daycare attendance, low family income, and low parental education level are also risk factors. Conversely, breastfeeding has been demonstrated to be protective against invasive Hib disease. In the prevaccine era, Hib invasive disease was rare in children over the age of 5 years, primarily related to antibody acquisition from natural exposure to the organism.

In adults, underlying conditions such as chronic obstructive pulmonary disease, smoking, HIV infection, alcoholism, pregnancy, and malignancy increase the risk of invasive Hib disease.

Significantly increased risk of invasive Hib disease has been reported in indigenous populations, including Australian Aboriginal children, Native Alaskan Eskimos, Native Americans, and Canadian First Nations children. These population differences likely relate to a variety of factors, including early exposure, crowding, microbiologic differences in the circulating strains, socioeconomic factors, and possibly genetics.

CLINICAL FEATURES

Although Hib can cause a variety of respiratory illnesses, in the prevaccine era it was notorious for causing significant invasive disease in infants and young children. Although these infections are now rare in immunized populations, practitioners should be familiar with their clinical manifestations because of possible resurgence of disease related to vaccine shortages and the potential for caring for unimmunized children from areas of the world without Hib vaccines. The following features are described as classically seen in the prevaccine era.

Cellulitis

Cellulitis is a somewhat unique manifestation of Hib disease seen in infants younger than 1 year of age. Hib cellulitis rarely occurs on the extremities, with most cases (74%) occurring at buccal, periorbital, or cervical areas. Facial cellulitis in infants often manifests with acute fever, with a unilateral area of induration, warmth, and tenderness, which may progress to have a violaceous hue. An aspirate of the point of maximal swelling will typically yield organisms. Facial cellulitis from Hib is often associated with bacteremia, and 10% to 20% of children will have a secondary focus, including meningitis.

Epiglottitis

Classically, epiglottitis from Hib occurs in older children, 2 to 7 years of age. In children younger than 2 years of age, Hib epiglottitis typically has a rapid onset and progression leading to severe blockage of the airway. Signs may begin with abrupt onset of high fever and drooling, with rapid progression to significant respiratory distress with children assuming a tripod position (sitting leaning forward, with mouth open and tongue and jaw protruding; Figure 4-1) to allow air entry. About 70% to 90% of patients with epiglottitis have positive blood cultures. The mortality rate is 5% to 10%, and death is usually related to abrupt airway obstruction. Children with tripoding should not have their oropharynx examined without the presence of personnel and capability for rapid intubation.

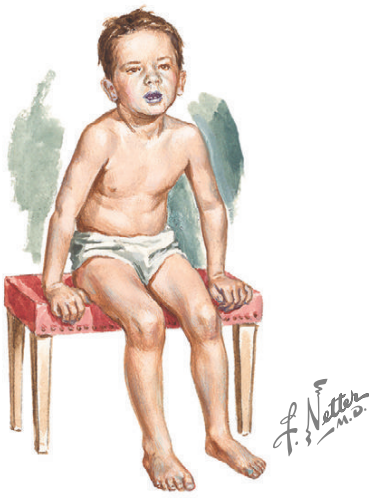

Figure 4-1 Tripod position assumed by child with epiglottitis.

Pneumonia

Hib pneumonia was common, often severe, and was frequently associated with empyema, pericarditis, and multilobe involvement. Hib pneumonia is usually preceded by an upper respiratory infection like a "common cold" with fever and cough and is clinically indistinguishable from pneumonia caused by other bacterial agents. Frequently a peripheral leukocytosis with a polymorphonuclear predominance is observed. Culture of blood, pleural fluid, tracheal aspirate, or lung aspirate may be positive in 75% to 90% of cases. The disease process is usually acute and not associated with long-term pulmonary dysfunction.

Septic Arthritis and Osteomyelitis

Hib was the leading cause of septic arthritis for children less than 2 years of age, and can be associated with contiguous osteomyelitis. Presenting signs include fever and limited limb use. Approximately 90% of septic arthritis cases involve a single large joint such as the knee, ankle, elbow, or hip. Long-term cartilage damage may result from Hib arthritic degeneration. Hib antigen detection is often positive from infected articular fluid.

Bacteremia and Sepsis

Hib was the second leading cause of occult bacteremia in febrile children 6 to 36 months of age. Unlike bacteremia with *Streptococcus pneumoniae* (the leading cause), which may spontaneously resolve, bacteremia with Hib is commonly associated with disseminated infections. Of children with occult Hib bacteremia, 30% to 50% had a focus (e.g., meningitis, pneumonia, or cellulitis).

Meningitis

Meningitis derives from high-grade bacteremia that seeds the cerebrospinal fluid (CSF) through the choroid plexus and eventually reaches the arachnoid villi to cause meningitis. There are no clinical features that differentiate Hib meningitis from meningitis from other bacterial causes (see Figure 37-1). Typically in bacterial meningitis the child demonstrates fever, irritability, and nuchal rigidity. Classical signs of involuntary flexion of the knees with passive flexion of the neck (Brudzinki's sign) and inability to extend a flexed leg (Kernig's sign) may be seen in older children and adults (see Figure 37-3). Altered mental status, vomiting, or seizures may also be presenting symptoms and signs. Hib meningitis can have a fulminant course with clinical sepsis, disseminated intravascular coagulation (DIC), and rapid neurologic deterioration leading to increased intracranial pressure, seizure, coma, and respiratory arrest. Approximately 10% to 20% of children with Hib meningitis will have additional foci of infection (e.g., cellulitis, arthritis, or pneumonia) with their concomitant bacteremia.

In fulminant meningitis, 80% of CSF Gram stain analyses will demonstrate the organism. However, the ability to identify the organisms on Gram stain is diminished with prior antibiotic administration. Although previous antibiotic administration may negatively affect the ability to isolate the organism from culture, it will not affect the overall CSF cell count differential, glucose, or protein, which have the usual abnormalities associated with bacterial meningitis. Peripheral blood may reveal anemia, leukocytosis, thrombocytosis, or thrombocytopenia.

DIAGNOSTIC APPROACH

Evaluation of a young child with fever should be directed by history, including vaccinations and risk factors for serious invasive disease (e.g., age or underlying condition), and physical findings. In young infants with fever without a specific source, complete blood count, urinalysis, and potentially a chest radiograph and lumbar puncture to assess for CSF pleocytosis should be considered, along with appropriate cultures of blood, urine, CSF, and any nidus on examination. The diagnosis of infections due to Hib is usually made by isolation of the organism by culture. Most invasive Hib disease is associated with bacteremia; therefore blood cultures should be performed if Hib is a consideration even for identified infectious sources (e.g., pneumonia or buccal cellulitis). Culture specimens should be processed quickly, as the organism is fastidious. Once *H. influenzae* has been isolated, it can be serotyped, usually in a public health laboratory facility.

Antigen detection for Hib capsule can be performed for infections in sterile spaces. This is useful when there has been previous antibiotic administration, which may sterilize cultures. Antigen detection in the CSF rarely yields false-positive results. However, cross-reactivity with antigens from *Escherichia coli*, *S. pneumoniae*, *Staphylococcus aureus*, or *Neisseria meningitidis* may lead to false-positive results in the serum or urine. Antigen detection may also be positive in the urine of children with Hib nasopharyngeal carriage or recent vaccination.

CLINICAL MANAGEMENT

General Management

Increasing rates of Hib resistant to multiple antimicrobial agents have been reported worldwide. Approximately 50% of Hib

isolates in the United States have evidence of plasmid-mediated β-lactamase production (greater for nontypable strains than type b). This β-lactamase production renders the organism resistant to ampicillin and amoxicillin. Use of β-lactamase inhibitors, such as found in amoxicillin-clavulanic acid, restores the antibiotic killing activity against such strains. Second-, third-, and fourth-generation cephalosporins are generally active against Hib including strains with β-lactamase production. Extended-spectrum macrolide antibiotics such as clarithromycin and azithromycin are also generally active against most strains of Hib, including those with β-lactamase resistance. Trimethoprim-sulfamethoxazole is active against Hib, but rates of resistance to this agent are increasing. Levofloxacin and other quinolones also have potent activity against Hib but are inappropriate for use in pediatric patients when there are safer alternative medications. The selection of antibiotic for treatment of Hib disease should be based on (1) suspected site of infection, (2) need for penetration of the blood-brain barrier and achievable bactericidal activity, (3) local antibiotic susceptibility of invasive isolates, and (4) duration needed for sterilization of both primary and secondary foci.

Invasive Disease

Pending determination of cause and susceptibility, the empiric treatment of suspected Hib meningitis should include a third-generation cephalosporin (cefotaxime or ceftriaxone) because of the ability of these agents to cross the blood-brain barrier and their resistance to β-lactamase activity. For other types of invasive Hib disease (pneumonia, septic arthritis, periorbital cellulitis), cefuroxime or a third-generation cephalosporin can be used for empiric therapy. Aminoglycosides are not recommended despite in vitro susceptibility.

Studies of pediatric patients with Hib meningitis suggest that adjunctive use of dexamethasone decreases the inflammatory response and may lessen the likelihood of hearing loss. The dose of dexamethasone is 0.6 mg/kg/day divided every 6 hours for a total of 4 days. Ideally, the first dose of dexamethasone should be administered just before or concurrently with the first antibiotic dose.

For abscesses, subdural empyema, pleural empyema, and pericardial effusions, percutaneous or surgical drainage is often necessary. In cases of septic arthritis, aspiration of infected joint fluid often is necessary for both diagnosis and reduction of intraarticular pressure. Repeated aspiration or placement of a surgical drain may also be necessary.

In addition, adjunctive and supportive therapies are important in the management of children with invasive Hib disease. For meningitis, careful evaluation and anticipation of potential complications, such as shock, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), seizures, subdural empyema, and evaluation for development of secondary foci are important. Fever may persist for prolonged periods in Hib meningitis, with approximately 10% of children remaining febrile for at least 10 days. For epiglottitis, airway management is critical, often dictating the need for intubation before the occurrence of airway obstruction.

Duration of therapy is determined by the site of infection, clinical response, and underlying host factors. For bacteremia, sepsis, and uncomplicated Hib meningitis, 10 days of antibiotics is generally sufficient. For cellulitis treatment, transition to oral antibiotics after a period of parenteral antibiotics can be made if there is a good clinical response. Similarly, for septic arthritis, pericarditis, empyema, and osteomyelitis, although they may require a longer duration of antibiotics (3 to 6 weeks), antibiotics may be switched from parenteral to oral administration after documentation of susceptibility, good therapeutic response, adequate antimicrobial blood levels, and ensured compliance.

PROGNOSIS

With the exception of meningitis and fulminant sepsis, patients with invasive Hib disease, if treated early with appropriate antibiotics, may recover with minimal to no long-term sequelae. However, even with prompt intensive care, mortality from Hib meningitis is approximately 5%. Complications occur early in the disease course and include seizure, cerebral edema, subdural effusions or empyema, SIADH, cortical infarction, cerebritis, intracerebral abscess, hydrocephalus, and rarely herniation. Routine imaging such as head computed tomography or magnetic resonance imaging is not necessary but can help clarify focal neurologic findings or complications that occur during the clinical course, especially subdural empyemas. Small sterile subdural effusions are common findings on imaging but are usually of no clinical significance.

Long-term sequelae occur in approximately 15% to 30% of meningitis survivors. These sequelae include sensorineural hearing loss, delay in language acquisition, developmental delay, gross motor abnormalities, vision impairment, and behavior abnormalities. A substantial proportion of these abnormalities may resolve over time, and therefore long-term monitoring is necessary. Evaluation of hearing during the initial hospitalization and follow-up if a hearing loss is detected are necessary to provide the earliest interventional services necessary should a hearing deficit become permanent.

PREVENTION AND CONTROL

Haemophilus influenzae *Type b Immunoprophylaxis*

The first vaccine developed for the prevention of invasive Hib was a purified Hib capsular PRP polysaccharide vaccine. However, polysaccharide vaccines are poorly immunogenic in young children, especially those younger than 18 months of age, owing to the polysaccharide's inability to induce T-cell dependent response. Linking a polysaccharide antigen to an immunogenic carrier protein allows for T-cell recognition, leading to inducible antibody responses and long-term protection in young infants.

Four Hib conjugate vaccines have been developed, but only three are widely used in the United States (Table 4-1). In general, it is ideal to complete the primary series with the same Hib conjugate vaccine; however, if this is not possible, the vaccines can be interchanged. In this instance three doses of the primary series are required. The booster dose at 12 to 15 months of age can be with any Hib conjugate vaccine, regardless of the type used in the primary series. Unimmunized children older

Table 4-1 *Haemophilus influenzae* Type b Conjugate Vaccines

Hib CONJUGATE	HbOC	PRP-OMP	PRP-T
Carrier protein	CRM197—diphtheria toxin mutant protein	*Neisseria meningitides* group B outer membrane protein	Tetanus toxoid
Trade name (manufacturer)	HibTITER (Wyeth-Lederle)	PedvaxHIB (Merck)	ActHIB (Sanofi Pasteur)
Dosing schedule in United States (age in months)	2, 4, 6, 12-15	2, 4, 12-18	2, 4, 6, 12-15
Available combinations (trade name)		PRP-OMP/HepB (Comvax)	DTaP/PRP-T (TriHIBit for ≥15 months of age only) DTaP/PRP-T/IPV (Pentace I for 2, 4, 6 months of age)

HbOC, Haemophilus b oligosaccharide conjugate; *Hib, Haemophilus influenzae* type b; *PRP-OMP,* Polyribosylribitol phosphate conjugated to outer membrane protein; *PRP-T,* Polyribosylribitol phosphate conjugated to tetanus toxoid.

than 59 months of age with underlying conditions that increase the individual risk of Hib disease should receive a single dose of Hib conjugate vaccine. For individuals who are younger than 59 months of age with HIV or immunoglobulin G2 (IgG2) subclass deficiency and who are unimmunized, two doses of vaccine given 4 to 8 weeks apart are suggested.

Chemoprophylaxis

Postexposure chemoprophylaxis is recommended for all household members if there is a contact younger than 4 years of age who has not received all Hib vaccinations appropriate for his or her age or if there is an immunocompromised child contact regardless of his or her immunization status. Prophylaxis should be initiated as soon as possible and ideally within 2 weeks of the onset of disease in the index case. Rifampin is the drug of choice for chemoprophylaxis in the dose of 20 mg/kg once daily (maximum daily dose of 600 mg) for 4 days. Other agents such as ampicillin, trimethoprim-sulfamethoxazole, erythromycin-sulfisoxazole, and cefaclor have been shown to be ineffective for chemoprophylaxis. Recommendations for treatment of contacts in daycare centers are controversial, but most experts recommend prophylaxis if two or more cases of Hib disease have occurred among attendees within 60 days.

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Pneumococcal Disease: Infections Caused by *Streptococcus pneumoniae*

5

R. Douglas Pratt

ABSTRACT

Worldwide, *Streptococcus pneumoniae* (pneumococcus) causes significant morbidity and mortality across all age groups. *S. pneumoniae* can be carried asymptomatically in the nasopharynx, and it can cause a wide range of diseases from upper respiratory infections including sinusitis and otitis media, lower respiratory infections (most commonly pneumonia), and invasive disease, including bacteremia and meningitis. Children younger than age 2 years, the elderly, and individuals with immunocompromise or anatomic or functional asplenia are most susceptible to invasive disease. Treatment is guided by severity of disease, site of infection, and susceptibility to antimicrobials. A 23-valent polysaccharide vaccine has been available in the United States for use in adults and high-risk children aged 2 years and older since 1983. A polysaccharide-protein conjugate vaccine with 7 serotypes, available in the United States and many other countries since 2000, has been highly effective in preventing invasive disease in infants and young children, as well as affording herd immunity. Conjugate vaccines formulated with additional serotypes of epidemiologic importance are now available in many countries.

GEOGRAPHIC DISTRIBUTION AND BURDEN OF DISEASE

The World Health Organization (WHO) estimates that more than 1.6 million people die annually of pneumococcal disease, of whom nearly 1 million are children younger than 5 years old; most deaths are caused by pneumonia.

Distribution of serotypes varies temporally and geographically. Outbreaks of pneumococcal disease caused by the same serotypes have been reported in institutional settings; however, epidemics in the general population are rare in developed countries.

In temperate regions, invasive pneumococcal disease (IPD), defined as an infection of a normally sterile body site, is more common during winter, possibly because of close proximity indoors and the spread of viral respiratory pathogens, which may facilitate pneumococcal invasiveness and transmissibility.

In developing countries, data about the burden of pneumococcal disease are limited. Using information from hospital-based studies and vaccine efficacy trials and inferring from disease patterns among native populations, the estimated burden of disease is high. Among African children younger than age 5 years, estimates of IPD rates range from 111 to over 500 per 100,000 per year.

In developed countries, the annual incidence of IPD has been estimated at 8 to 34 cases per 100,000 persons of all ages, and in excess of 50 cases per 100,000 elderly adults (>65 years of age). However, the true burden of disease caused by *S. pneumoniae* is likely much greater, as identification of the cause of bacterial pneumonia is difficult. Rates of IPD among young children have been reduced substantially in countries in which the conjugate vaccines are in widespread use. In the United States after introduction of the 7-valent conjugate vaccine, annual rates of IPD in children younger than 5 years of age have declined 77% from approximately 100 to 25 cases per 100,000.

S. pneumoniae is found in 25% to 50% of middle ear aspirates from children with acute otitis media (AOM). AOM is also the leading reason for prescribing antibiotics during childhood, and this use contributes substantially to increased antimicrobial resistance.

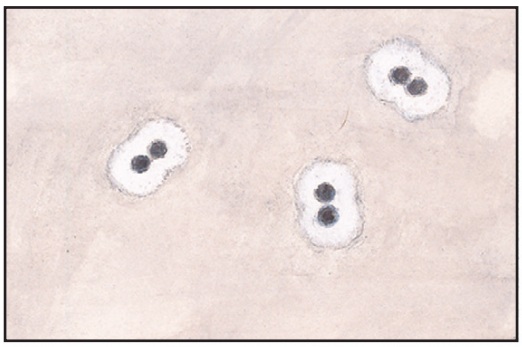
MICROBIOLOGY AND PATHOGENESIS

S. pneumoniae is a strictly human pathogen consisting of gram-positive, encapsulated, lancet-shaped bacteria occurring in pairs (called *diplococci*) and chains (Figure 5-1). At least 90 serotypes have been identified based on differences in the polysaccharide capsule, as observed with the quellung reaction (see Figure 5-1).

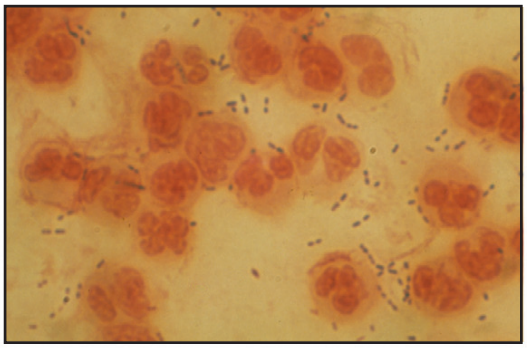
The polysaccharide capsule is considered the primary virulence factor of *S. pneumoniae*. Nonencapsulated strains are less likely to cause severe disease. The capsule contributes to pathogenesis by protecting the organism from phagocytosis. However, antibody binding to the capsule can facilitate phagocytosis and bacterial killing by polymorphonuclear leukocytes. Some pneumococcal proteins, including hyaluronate lyase, pneumolysin, neuraminidase, major autolysin, choline binding protein A, and pneumococcal surface protein A (PspA) have functions that also contribute to pathogenicity. These virulence proteins have been considered for development as vaccine antigen candidates.

RISK FACTORS

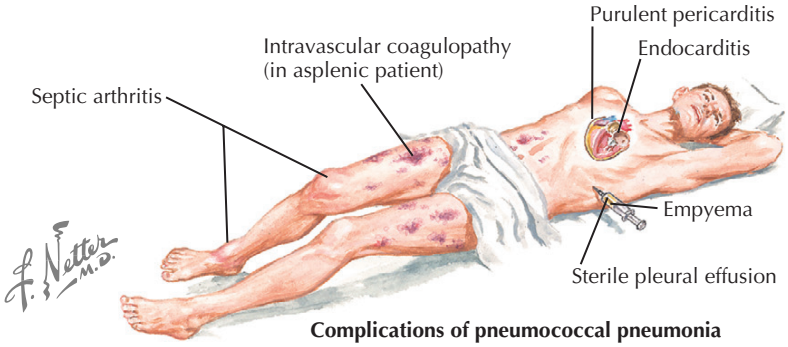
Children younger than age 2 years carry the highest burden of *S. pneumoniae* disease worldwide. Other groups at increased risk of invasive disease include the elderly, people with impaired immunity (e.g., humoral immunodeficiency, complement deficiency, human immunodeficiency virus [HIV] infection, and anatomic or functional asplenia [e.g., sickle cell



Quellung reaction. Swelling of bacterial capsule when exposed to antibody



Purulent sputum with pneumococci (Gram stain)



Complications of pneumococcal pneumonia

Figure 5-1 Pneumococcal disease.

disease]), cigarette smokers, those with cochlear implants and cerebrospinal fluid (CSF) leaks, and individuals with chronic diseases such as diabetes and heart, kidney, and lung disorders. IPD occurs at higher rates among certain ethnic groups; for example, Native Americans and Eskimos have rates of IPD that are several-fold higher than in the general population in the United States.

CLINICAL PRESENTATION

S. pneumoniae organisms are transmitted person to person via contact with infected respiratory droplets. Asymptomatic nasopharyngeal (NP) carriage is common in children 6 months to 5 years of age, and they are a source of transmission among close contacts by projecting droplets (>5 μm) across a short distance (1 meter).

Invasive Pneumococcal Disease

S. pneumoniae infection can manifest as fever and bacteremia without a focus or as an infection of any organ system, including AOM, sinusitis, conjunctivitis, periorbital cellulitis, soft-tissue infection, pyogenic arthritis, osteomyelitis, community-acquired pneumonia (CAP), empyema, endocarditis, peritonitis, sepsis, and meningitis (see Figure 5-1).

Onset of fever is typical for infections in all tissues and may be the only sign in young children with bacteremia. Otitis media typically causes pain in the ears. Pneumonia can cause fever, cough, pleuritic chest pain, and purulent or blood-tinged sputum.

Pneumococcal meningitis is characterized by high fever, headache, neck stiffness, and altered mental status. Other symptoms include nausea, vomiting, photophobia, and lethargy. Infants and young children may have nonspecific symptoms including irritability or poor feeding. In later stages, patients of any age may have seizures or focal neurologic findings or may be comatose.

The differential diagnosis for IPD includes other bacterial pathogens, such as *Haemophilus influenzae* type b (Hib), *Neisseria meningitidis*, and *Staphylococcus aureus*. In the United States and other areas using Hib vaccines, most cases of bacterial meningitis are caused by *S. pneumoniae and N. meningitidis*. Viral meningitis caused by enteroviruses can manifest like bacterial meningitis but is generally less severe.

Before the widespread use of the conjugate vaccine in the United States, *S. pneumoniae* was the most common bacterial cause of pneumonia in young children. Current bacterial causes of CAP in children include *S. pneumoniae*, *H. influenzae* (nontypeable), *Moraxella catarrhalis*, *Streptococcus pyogenes*, and *S. aureus* (including methicillin-resistant *S. aureus*

[MRSA]). However, respiratory viruses (e.g., respiratory syncytial virus [RSV], influenza, human metapneumovirus) cause most cases of pneumonia in children.

DIAGNOSTIC APPROACH

When *S. pneumoniae* is suspected as a cause of invasive disease, specimens should be obtained from the site(s) of infection for culture and Gram stain. Cultures provide highly specific diagnostic information, the ability to test for antibiotic susceptibility, and specimens for serotype-specific epidemiology. However, because pneumococci can colonize the upper respiratory tract, recovery of *S. pneumoniae* from the nasopharynx does not confirm it as the causative agent.

Most patients with IPD have leukocytosis (>12,000 cells/μL) and elevated markers of inflammation (e.g., C-reactive protein, erythrocyte sedimentation rate). Leukopenia may be seen with meningitis and other severe pneumococcal infections.

Diagnosing pneumococcal pneumonia can be challenging. Typical chest radiographs show consolidation of a segment, an entire lobe, or multiple lobes (see Figure 26-1). In hospitalized patients with pneumonia, blood cultures are positive in 10% of children and up to 25% of adults. Respiratory specimens, such as sputum (in adolescents and adults) and endotracheal or bronchoalveolar lavage samples, showing gram-positive diplococci and many polymorphonuclear neutrophils (PMNs) suggest a pneumococcal cause. Thoracentesis may be needed to drain pleural effusions or empyemas and to obtain specimens for culture.

In cases of fever without a focus and suspected IPD, blood should be obtained for culture. Depending on the signs and symptoms, specimens of CSF should be obtained for laboratory evaluation including cultures. Gram stain of the CSF sediment may reveal the characteristic gram-positive diplococci. The CSF will usually show a pleocytosis with a predominance of PMNs, though early in the disease lymphocytes may predominate. Typically, CSF protein is elevated and glucose is low relative to blood glucose levels.

A rapid in vitro diagnostic test based on the presence of pneumococcal capsular C polysaccharide in urine has been approved by the U.S. Food and Drug Administration (FDA) for diagnosing pneumococcal pneumonia in adults. The test is 70% to 80% sensitive and >90% specific when compared with conventional methods and is not affected by antibiotics. However, this test is not for use in children as it lacks specificity, probably because of higher rates of NP carriage. The rapid test is also FDA approved for detecting pneumococci in CSF of patients with meningitis. Polymerase chain reaction (PCR) assays may be useful in research but are not FDA approved for use in a clinical setting.

TREATMENT

Adjunctive and supportive treatment of IPD is similar to therapies used for Hib infections, as described in Chapter 4.

Pneumococcal infections are treated with antimicrobials to which the organism is susceptible. All cultures of *S. pneumoniae* from sterile body sites should be evaluated for antimicrobial susceptibilities, but in most cases empirical therapy should begin before susceptibilities are known.

The prevalence of *S. pneumoniae* strains that are not fully susceptible to penicillin varies by region (8% to 40%), but the proportion of such strains appears to be decreasing in the United States since introduction of the conjugate vaccine. Penicillin-resistant strains are defined as intermediately resistant (minimum inhibitory concentration [MIC] >0.1 to 1 mcg/mL) or highly resistant (MIC ≥2 mcg/mL). *S. pneumoniae* strains that are resistant to penicillin are often resistant to other antimicrobials, including cephalosporins and macrolides, and these multidrug-resistant strains have been identified throughout the world. *S. pneumoniae* strains resistant to vancomycin have not been identified in the United States; isolates that appear resistant are likely contaminated with other vancomycin-resistant bacteria.

Bacterial meningitis is treated with higher doses of antibiotics than used for other infections to ensure adequate drug levels in the CSF. The initial regimen for suspected pneumococcal meningitis in all ages should include vancomycin and ceftriaxone or cefotaxime until the antimicrobial susceptibilities are known. Meropenem may be an alternative. Corticosteroids have been used in the treatment of bacterial meningitis to reduce intracerebral inflammation; however, evidence of improved outcomes in children is equivocal. If used, corticosteroids should be given before or concurrently with the first dose of antimicrobials.

In CAP, the specific pathogen is usually not known and patients are treated presumptively with antimicrobials that are effective against *S. pneumoniae*, as well as other common bacterial pathogens. In children with mild to moderate CAP suggestive of bacterial infection, amoxicillin can be used for empirical treatment in an outpatient setting. If the clinical presentation is consistent with both bacterial and atypical pneumonia, a macrolide may be considered. For non–critically ill, hospitalized children, empirical treatment with intravenous ampicillin or a third-generation parenteral cephalosporin (e.g., cefotaxime, ceftriaxone) should be effective in most settings. If *S. aureus*, including MRSA, is suspected, vancomycin or clindamycin should be added. Duration of treatment is usually 10 days, though courses may be completed with oral antimicrobials in an improving patient. Longer courses may be required in a setting of persistent fever or pneumonia complicated by empyema or lung abscess.

Doxycycline in children younger than 8 years of age and fluoroquinolones in children who have not reached growth maturity are not appropriate because of potential toxicities and the availability of safer alternatives.

First-line treatment for uncomplicated AOM is amoxicillin (80 to 90 mg/kg/day). If initial therapy fails, antibiotics active against penicillin-nonsusceptible pneumococci and β-lactamase–producing *H. influenzae* and *M. catarrhalis* should be used (e.g., amoxicillin-clavulanic acid, second- and third-generation oral cephalosporins, and macrolides). In severe cases and when second-line therapy fails, parenteral ceftriaxone may be given and/or tympanocentesis may be used to drain infected fluid, obtain cultures, and guide therapy, as well as to provide pain relief (see Chapter 31).

PROGNOSIS

Early diagnosis and treatment with appropriate antimicrobials are keys to better clinical outcomes. For some infections, the clinical outcome may be worse in patients receiving discordant therapy (i.e., treatment with an antibiotic to which the strain is resistant).

Nearly all children with ear infections recover, although recurrent infections can lead to hearing loss and delayed language development. In children in industrialized nations, pneumococcal pneumonia may result in hospitalization, though the mortality rate is low. In children who have bacteremia without a focus, 10% will develop focal complications, 3% to 6% will develop meningitis, and about 1% will die. Of children younger than 5 years of age with pneumococcal meningitis, about 5% will die and 25% of survivors may have long-term problems such as hearing loss or learning disability. Sequelae in patients with meningitis are associated with the presence of coma and low CSF glucose level (<0.6 mmol/L).

The incidence of IPD and mortality resulting from bacterial infections in sickle cell disease has been declining. Probably this is a result of penicillin prophylaxis, new vaccines and vaccination strategies, and improved medical care.

PREVENTION

Good respiratory hygiene and active immunization are effective prevention strategies. Risk of IPD may be reduced by improvement in predisposing conditions such as diabetes and HIV, smoking cessation, and avoidance of crowded living conditions.

Immunoprophylaxis

The first vaccines developed against *S. pneumonia* were composed of polysaccharides extracted from common invasive serotypes. In the United States a tetravalent polysaccharide vaccine was licensed in 1946 but was discontinued in 1951 owing to the increasing use of penicillin. In 1977 a 14-valent polysaccharide vaccine became available; additional serotypes were added in 1983 to include 23 serotypes that are responsible for more than 90% of pneumococcal disease. The 23-valent vaccine (Pneumovax 23, Merck & Co.) is currently recommended in the United States by the Centers for Disease Control and Prevention (CDC) Advisory Committee on Immunization Practices (ACIP) for use in adults 65 years of age and older and in children age 2 years and older who have increased risk for infection.

Polysaccharide vaccines, including the pneumococcal vaccine, are not effective in children younger than 2 years of age. Polysaccharide antigens do not efficiently elicit T-cell help for antibody production. Protein-polysaccharide conjugate vaccines, manufactured by chemical linkage of bacterial polysaccharides to protein antigens such as diphtheria and tetanus toxoids, are better able to elicit T-cell help and induce protective immune responses, even in infants and young children. In clinical trials, a conjugate vaccine (Prevnar, Wyeth Pharmaceuticals) composed of seven serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F) accounting for approximately 80% of invasive disease in young children in the United States was proven highly effective in preventing invasive disease. Since licensure in the United States in 2000, high rates of vaccine coverage have resulted in a marked reduction in IPD in infants and small children, as well as adult and elderly populations, likely because of decreased transmission and herd immunity. In addition, the rates of antimicrobial resistance have fallen because the conjugate vaccine includes serotypes associated with high rates of resistance.

As disease caused by vaccine serotypes has diminished, some nonvaccine serotypes have emerged as important causes of disease in children, particularly serotype 19A. Two new conjugate vaccines formulated with additional serotypes, including serotypes important globally, became available in 2009 and 2010. A 13-valent vaccine (Prevnar 13) containing the seven original serotype plus serotypes 1, 3, 5, 6A, 7F, and 19A was licensed in the United States for use in children 6 weeks through 5 years of age; this vaccine is also available in other countries. A 10-valent conjugate vaccine containing additional serotypes 1, 5, and 7F is available in Europe, Canada, and elsewhere.

In the United States the protein-polysaccharide conjugate vaccine is recommended as a part of the routine immunization schedule for all infants at 2, 4, and 6 months of age, with a booster at 12 to 15 months of age. Additional dosing regimens are recommended for compromised hosts, as well as catch-up immunizations. The latest ACIP recommendations may be viewed at www.cdc.gov/ncidod/dbmd/diseaseinfo/streppneum_a.htm.

Investigational vaccines targeting proteins common to most pneumococci hold promise in providing broad protection against pneumococcal disease.

Chemoprophylaxis

Chemoprophylaxis is not routinely recommended for contacts of individuals with IPD or for travelers.

Penicillin chemoprophylaxis is recommended by the CDC for persons with functional or anatomic asplenia because of the high risk of severe infections. For children with sickle cell hemoglobinopathy, oral penicillin V (125 mg, twice daily) is recommended beginning before 4 months of age. The optimal duration of penicillin prophylaxis in these children has not been determined, but stopping at age 5 years in children who are fully vaccinated and who have been free of severe pneumococcal infections has not resulted in increased infections.

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Infections Caused by *Neisseria meningitidis*

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6

ABSTRACT

Neisseria meningitidis is both a commensal organism of the upper respiratory tract and a significant pathogen for humans. It causes devastating disease with significant morbidity and mortality worldwide. *N. meningitidis* can have various clinical presentations ranging from asymptomatic carriage or a mild upper respiratory illness to purulent meningitis and/or disseminated disease with fulminant sepsis. Strains with capsule types belonging to groups A, B, C, Y, W-135, and recently X are associated with invasive disease. The majority of patients infected with *N. meningitidis* are children, usually younger than 5 years old, adolescents, and young adults. Effective polysaccharide and polysaccharide conjugate vaccines are available for prevention of group A, C, Y, and W-135 disease. The group B polysaccharide is poorly immunogenic, and although outer membrane protein–based vaccines have been developed, they are primarily protective against the specific vaccine strain. New vaccines and treatments are under development.

GEOGRAPHIC DISTRIBUTION AND BURDEN OF DISEASE

N. meningitidis has a worldwide distribution, but there are distinct regional characteristics of the microbiology and epidemiology of disease. The Centers for Disease Control and Prevention (CDC) has reported the worldwide incidence of invasive meningococcal disease to be 0.5 to 5 per 100,000 population per year. In the United States the overall incidence is 0.5 to 1.5 per 100,000 population per year, primarily caused by serogroups B (23%), C (31%), and Y (35%). European countries have a wide range of disease incidence (0.2 to 14 cases per 100,000). The majority of these cases are caused by serogroup B, which has been especially true after introduction of meningococcal C conjugate (MCC) vaccines in some countries. An epidemic of group B meningococcal disease persisted for almost a decade in New Zealand (17.4 cases per 100,000 in 2001), but attack rates declined to 2.6 per 10,000 in 2007 in part because of the use of a specific outer membrane vesicle vaccine.

Before World War II, group A was the most common serogroup identified from disease isolates in industrialized countries. Now this serogroup is primarily associated with epidemic meningitis, especially in the sub-Saharan region in Africa known as the *meningitis belt*. Countries in this region experience recurrent epidemics every 5 to 10 years with incidence rates reaching 1000 per 100,000. Even in interepidemic years, group A disease rates can be as high as 25 per 100,000. Group A epidemics have also occurred in India, China, and Russia. Other areas of Africa have yearly rates of invasive group A disease higher than in industrialized nations. Travel to the Hajj pilgrimage has been a significant risk factor for exposure to group A meningococci.

Asymptomatic nasopharyngeal carriage of *N. meningitidis* is common and varies by age. Infants have a carriage rate of 1% to 2%, whereas adolescents and young adults have a carriage rate of 15% to 25%. Carriage of highly virulent strains occurs in less than 5% of the general population, even during outbreaks. Carriage isolates are often unencapsulated, or less virulent, than strains that cause invasive disease. Transmission of *N. meningitidis* is primarily through respiratory droplets. Invasive meningococcal disease is associated with recent acquisition of a new pathogenic strain rather than after extended colonization.

Studies of military recruits in the 1970s helped determine the infectivity and route of spread of the organism and established that preexisting antibodies that triggered complement-mediated killing of the bacteria provided protection against invasive disease.

The prevalence of bactericidal antibodies in the population increases with age and is inversely related to the rates of invasive disease. Infection rates are highest in children under age 5 years, especially 6 months to 1 year of age. A second period of increased risk is observed during adolescence and young adulthood. College freshman living in dormitories, and military recruits are at moderate risk, whereas and individuals with close or intimate contact with an index case are at 500 times increased risk of invasive disease. Individuals with terminal complement component deficiencies are at high risk of recurrent invasive meningococcal infections.

PATHOGENESIS

N. meningitides, a gram-negative diplococcus, is an obligate human pathogen. Endemic sporadic disease is caused by highly diverse strains, but most disease isolates can be grouped by genetic analysis of housekeeping genes (multilocus sequence typing [MLST]) into one of several hypervirulent lineages. In contrast, local outbreaks and sustained epidemics can be caused by a single strain type and are considered clonal.

Surface structures of the bacterium are important for strain characterization, disease pathogenesis, and immunity. Capsular polysaccharide type defines the serogroup of a strain. Strains expressing group A, B, C, Y, W-135, and more recently group X capsules are associated with invasive disease, whereas unencapsulated strains and strains of the remaining serogroups are usually associated with asymptomatic nasopharyngeal colonization. The polysaccharide capsule enhances efficient transmission and inhibits phagocytosis. Lipooligosaccharide (LOS) is an endotoxin that induces an inflammatory cascade that leads to the clinical features seen in septicemia, septic shock, and meningitis.

N. meningitidis has extensive mechanisms for the uptake and incorporation of deoxyribonucleic acid (DNA), a process known

as *horizontal exchange*, which allows the organism to adapt to the host and evade natural immunity. This process results in antigenic diversity of many surface proteins and occasionally capsule type switching. In addition, phase variation of surface structures such as opa and LOS also contribute to phenotypic diversity of the organism.

Genetic polymorphisms of the human host affect susceptibility to meningococcal infections and may affect disease outcomes. Genetic deficiencies of complement factors 5 to 9 (late complement component deficiency) are well recognized risk factors for recurrent or familial meningococcal disease. In addition, some case control studies have shown an association between meningococcal disease and polymorphisms of interleukin-1 receptor agonist (IL1RA), carcinoembryonic antigen cell adhesion molecules 3 and 6, surfactant proteins A and D, and factor H.

CLINICAL PRESENTATION

The spectrum of *N. meningitidis* infections can range from asymptomatic to fulminant septicemia and/or meningitis. The progression of invasive disease can be rapid, with circulatory collapse and death occurring within hours of presentation. In contrast, resolution of unsuspected culture-positive meningococcemia without treatment has been documented in adults and infants with fever and upper respiratory symptoms.

The hallmark features of meningococcal disease are fever and rash, classically a nonblanching petechial rash, which can progress to purpura associated with disseminated intravascular coagulation (DIC). The rash is not diagnostic; a macular or maculopapular rash can also be observed, and of note, rash is absent in almost one third of culture-proven disease in children. Approximately 11% to 15% of children presenting with petechiae have meningococcemia.

The most common presentation of invasive meningococcal disease is meningitis. Typical clinical findings of meningitis are the result of inflammation in the subarachnoid space and include fever, headache, meningismus, photophobia, and lethargy. Older children may also have positive Kernig's and Brudzinki's signs (see Figure 37-3). Infants may not have these classic symptoms of meningitis but usually demonstrate irritability, inconsolable crying, poor feeding, and lethargy. Meningococcal meningitis can occur with or without associated septicemia.

Septicemia accounts for 15% to 20% of invasive meningococcal disease and results from significant levels of bacteria and endotoxin in the bloodstream. The onset of disease is rapid, and clinical decline with significant morbidity or mortality can occur within 24 to 48 hours. Bacteremia and increased endotoxin production initiate an intravascular inflammatory cascade that causes endothelial damage resulting in DIC and multiorgan failure (Figure 6-1). The vascular damage initially results in petechiae and purpura and can ultimately lead to autoamputation of digits or entire limbs. The average duration from onset of symptoms to admission for patients with sepsis is 12 hours, which is less than half the time for patients with meningitis.

Other less common presentations of invasive disease include pneumonia, pyogenic arthritis, purulent pericarditis, osteomyelitis, and endophthalmitis. These clinical presentations are more often associated with serogroups Y or W-135 and are usually seen in older patients.

Chronic meningococcemia is a rare condition that manifests with recurrent intermittent fever, rash, and arthralgia or arthritis and may last for months. The presentation can be similar to that of many other viral, rheumatologic, or vasculitic conditions. *N. meningitidis* can be cultured from serum during acute episodes, and in the absence of appropriate treatment, some patients eventually progress to disseminated disease. The pathogenesis of chronic meningococcemia is not known; however, it is more commonly seen in patients with underlying terminal complement deficiency.

DIAGNOSTIC APPROACH

Invasive meningococcal disease should be considered in any patient with fever and signs or symptoms that are consistent with bacterial sepsis or meningitis. The initial evaluation includes cultures of blood and cerebrospinal fluid (CSF) and in some instances biopsies of skin lesions (see Figure 37-4). The CSF cell count, protein level, and glucose concentrations are usually abnormal, although normal CSF profiles have been reported. CSF should also be examined for gram-negative diplococci. Peripheral leukocytosis with a predominance of polymorphonuclear cells is typical, but leukopenia, thrombocytopenia, and anemia may be present. Coagulopathy and metabolic abnormalities, such as hyponatremia, hypoglycemia, and metabolic acidosis, can complicate the clinical management of patients with invasive disease.

Viable *N. meningitidis* can be obtained from 40% to 75% of blood and 90% of CSF cultures when obtained before the administration of antibiotics. The microbiologic evaluation should not delay therapy when invasive meningococcal disease is suspected; therefore in some circumstances antibiotics must be administered empirically before cultures can be obtained. Blood and CSF can be rapidly sterilized after antibiotic administration; however, organisms have been identified in skin lesions up to 12 hours after antibiotics have been given. *N. meningitidis* antigen testing of the CSF can be useful; however, cross-reaction occurs between serogroup B capsular antigen and *Escherichia coli* K1.

The differential diagnosis is influenced by the age and epidemiologic history of the patient and includes other causes of bacterial sepsis and meningitis including *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Staphylococcus aureus*, and gram-negative enteric pathogens, as well as rickettsial disease, Henoch-Schönlein purpura, and other noninfectious causes of vasculitis.

TREATMENT

Prompt initiation of parenteral antibiotics is the mainstay of treatment for invasive meningococcal disease. Third-generation cephalosporins, such as ceftriaxone and cefotaxime, are bactericidal, have excellent central nervous system penetration, and are most often used as initial therapy of meningitis until culture results and susceptibility profiles are determined. Most meningococcal isolates are susceptible to penicillin G (250,000 units/kg/day, maximum 12 million units/day, in four divided doses intravenously).

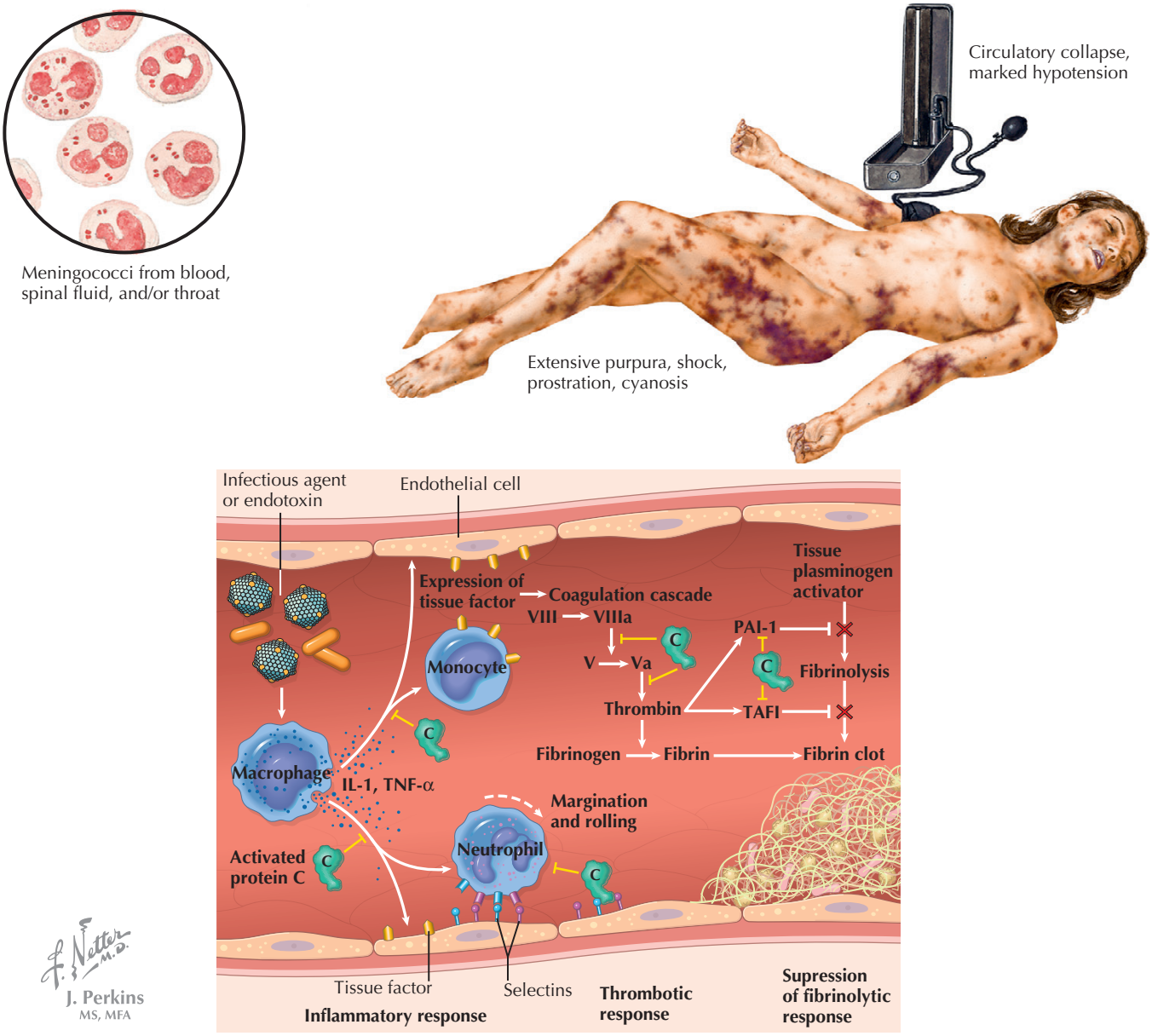

Figure 6-1 Disseminated intravascular coagulation (DIC).

Penicillin-resistant *N. meningitidis* strains have been described worldwide; however, the rate of penicillin resistance in the United States has remained low at approximately 3%. Ciprofloxacin-resistant isolates and clinical treatment and prophylaxis failures have been reported. Routine susceptibility testing is recommended for all *N. meningitidis* isolates from sterile body sites. The recommended duration of therapy for meningococcemia or meningitis is 7 to 10 days; however, there are reports of clinical and microbiologic resolution with shorter courses of therapy.

Emergent management of *N. meningitidis* infections involves fluid resuscitation, maintenance of blood pressure with pressor support, and early intubation if indicated to prevent circulatory collapse or increases in intracranial pressure. Adjuvant therapy with corticosteroids for patients with septic shock and meningitis has shown some benefit in adults and in pediatric patients with *H. influenzae* meningitis; however, there has been no proven benefit in meningococcal sepsis or meningitis. Activated protein C (APC), a component in the coagulation pathway, may be considered in adult patients with invasive meningococcal disease and severe sepsis who present early in their disease course. In pediatric patients, the risk and benefits of this therapy should be weighed, although it is generally not recommended.

PROGNOSIS

The overall mortality rate from meningococcemia is approximately 10% in the United States, with most cases of death

occurring in young infants and adolescents. Factors associated with poor outcome and high mortality rates include young age, absence of meningitis, presence of shock, clinical signs of ischemic damage, leukopenia, or thrombocytopenia. In less severe disease with prompt management, most patients have significant resolution of symptoms by the second day of illness and complete recovery within 1 week. After acute illness, <10% of patients develop postinfectious complications as a result of immune complex–induced inflammation such as arthritis, iritis, myocarditis, pericarditis, and vasculitis. These conditions usually manifest 4 or more days after onset of infection and can be managed with nonsteroidal antiinflammatory agents.

Sequelae from invasive meningococcal disease occur in up to 19% of patients and can include hearing loss, neurologic dysfunction or motor deficits, digit or limb amputation, and skin scarring.

PREVENTION AND CONTROL

Prevention of secondary cases of invasive meningococcal disease involves patient isolation, chemoprophylaxis of exposed individuals, and in some situations vaccination. Respiratory droplet precautions should be used until the patient has received 24 hours of appropriate antimicrobial therapy to eradicate carriage. Patients who are treated with antibiotics other than ceftriaxone or cefotaxime should receive chemoprophylaxis to eradicate nasopharyngeal colonization. Chemoprophylaxis is essential for close contacts because their attack rate is 500 to 800 times higher than in the general population. This includes all individuals who have been directly exposed to oral secretions from the index case, all child care or preschool contacts, and all individuals who slept in the same dwelling as the index case in the 7 days before onset of disease. Individuals who were seated next to the index case on a prolonged airplane flight (>8 hours) are also eligible for chemoprophylaxis. Routine prophylaxis is not given to medical personnel unless they had significant exposure to respiratory secretions. Ideally, chemoprophylaxis should be given within 24 hours after diagnosis in the index patient. Rifampin, ceftriaxone, ciprofloxacin, and azithromycin are effective chemoprophylactic medications. Rifampin or ceftriaxone can be used in younger children, but ciprofloxacin is recommended only for nonpregnant adults older than 18 years of age. Ciprofloxacin is not recommended in regions where resistant strains have been identified. In addition, vaccination of close contacts is recommended if the index case was caused by a serogroup included in current vaccines.

Vaccines are available for prevention of invasive disease caused by *N. meningitidis* groups A, C, Y, and W-135. The polysaccharide tetravalent meningococcal vaccine (MPSV4) was used for control of outbreaks and recommended for routine use in high-risk populations such as military recruits, individuals with terminal complement component deficiencies or asplenia, travelers to geographic regions with high rates of disease, and more recently college freshman living in dormitories. After the licensure of a tetravalent glycoconjugate meningococcal vaccine (MCV4) in the United States, routine immunization of all children 11 years of age and older was also recommended. MCV4 is preferred for both routine immunization of adolescents and immunization of all individuals 2 years of age and older who are at increased risk of invasive meningococcal disease. A booster dose of MCV4 is now recommended 3 to 5 years after the initial immunization for high-risk young children and routinely at 16 years of age for all adolescents who were initially immunized at 11 years of age.

Polysaccharide vaccines are not generally immunogenic in children younger than 2 years of age except group A meningococcal polysaccharide vaccine, which can be used in infants 6 months of age and older in a two-dose series during group A outbreaks. Polysaccharides do not induce memory, and immunity wanes after 3 to 5 years. Chemical conjugation of polysaccharides to a protein carrier creates T-cell–dependent antigens that are usually highly immunogenic in infant populations. Monovalent group C conjugate vaccines have been incorporated into routine infant immunization schedules in some countries where group C disease was common. These vaccines have been shown to decrease colonization and provide herd immunity.

Current management of epidemic group A disease in Africa uses a reactive vaccination strategy when disease rates exceed certain thresholds. This approach has been successful in treating outbreaks; however, it has not been useful in their prevention. Efforts are underway to develop and incorporate into widespread use a group A conjugate vaccine, with the goal of eliminating epidemic disease in Africa.

There are no vaccines currently licensed in the United States for the prevention of group B meningococcal disease. Vaccines using outer membrane vesicles depleted of LOS have been studied in the Netherlands, Cuba, Brazil, and Chile, and one was successfully implemented in New Zealand to address an epidemic caused by a group B strain. New vaccines that are designed to be broadly protective against the diverse strains associated with endemic disease are under development.

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Poliomyelitis (Polio) and Polioviruses

7

ChrisAnna M. Mink

ABSTRACT

In the early twentieth century, poliomyelitis was one of the most feared illnesses of humans, in part because it affected previously healthy individuals with little or no warning. Although the disease was once endemic worldwide, with the introduction and worldwide use of oral and injectable polio vaccines, the number of cases globally is numerable and the potential for eradication is real. In current times, acute flaccid paralysis (AFP) caused by other viral agents is the more commonly occurring paralytic illness. However, the polioviruses still circulate, and with disruption of proper sanitation or maintenance of vaccination within the population, infections can quickly reemerge.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

The polioviruses are single-stranded ribonucleic acid (RNA) viruses that are members of the *Enterovirus* genus in the Picornaviridae family and are ubiquitous throughout the world. Three serotypes (types 1, 2, and 3) of polioviruses are known, and humans are the only natural hosts, although replication in other primates can occur. Before introduction of immunization, type 1 infection was the most common.

Poliomyelitis has been described since the time of the Egyptians. Through the 1900s, polio remained endemic, although the majority of infections were inapparent. Most infections occurred in infants and were asymptomatic owing to protection from maternal antibodies; this permitted widespread immunity. Because polioviruses are primarily transmitted via the fecal-oral route, with improvement of sanitation in the United States, fewer infants were exposed. This resulted in the creation of a pool of susceptible individuals, and subsequently polio epidemics began to occur. In the first half of the twentieth century, polio occurred as a sporadic epidemic disease with outbreaks every few years without regular periodicity. The largest outbreak in the United States happened in 1952, when nearly 58,000 cases of polio occurred. In less developed countries, polio remained endemic into the latter half of the twentieth century, and with improved sanitation in these developing areas, epidemics began to occur similar to the pattern observed in the United States. With the introduction of polio vaccines in 1955, first the injectable vaccine and then an oral vaccine, dramatic reduction in the incidence of polio occurred. In the United States, the rate of paralytic polio fell from about 17.6 per 100,000 to 0.4 per 100,000 in the first 8 years after onset of vaccination. The last case of naturally occurring wild-type polio in the United States was reported in 1979. The Western hemisphere was certified free of wild-type polio in 1994. Globally, paralytic polio is on the verge of eradication with only four countries (Nigeria, India, Pakistan, and Afghanistan) reporting indigenous polio cases in 2007. However, because of many factors including war, government instability, economic depression, compromised vaccine efficacy, and opposition to polio vaccination, since 2007 a resurgence of infection has occurred (primarily in Africa and the Indian Subcontinent)—most notably an outbreak of nearly 400 cases in 15 countries in Africa.

RISK FACTORS

In the prevaccine era, virtually all infants were exposed to the polioviruses by the age of 6 months, though only a few developed paralytic disease. Risk factors for infection progressing to paralytic disease include young age, pregnancy, antibody deficiency states, male gender (prepuberty), strenuous exercise, and preceding limb injury within 4 weeks of infection. In adults, women have an increased risk of infection, perhaps because of more frequent exposure to young children, though they do not necessarily have an increased risk of paralysis.

CLINICAL FEATURES

Approximately 90% to 95% of infections are asymptomatic, with the ratio of clinically inapparent to apparent infections ranging from 60:1 to 1000:1. Clinically inapparent infections are defined as isolation of a poliovirus from stool or throat with concomitant fourfold rise in antibody titers.

The incubation period from contact with the virus to onset of symptoms of the prodromal illness is 9 to 12 days, with a range estimate of 5 to 35 days. During the incubation, the virus replicates in the lymphatic tissue of the intestinal tract, and an asymptomatic primary ("minor") viremia occurs, with systemic spread of the poliovirus. Polioviruses replicate within neurons, and the anterior horn cells of the spinal cord are most often involved. Rarely, posterior horn cells and dorsal root ganglia are also infected (Figure 7-1).

Abortive Poliomyelitis

In 4% to 8% of individuals, a second ("major") viremia occurs, causing a minor illness called *abortive poliomyelitis.* This illness may be clinically indistinguishable from other viral infections, with symptoms of fever, headache, sore throat, nausea, vomiting, and fatigue. These individuals usually recover completely within 5 to 10 days.

Nonparalytic Poliomyelitis

The central nervous system (CNS) is seeded during the major viremia in approximately 1% of infections, leading to aseptic

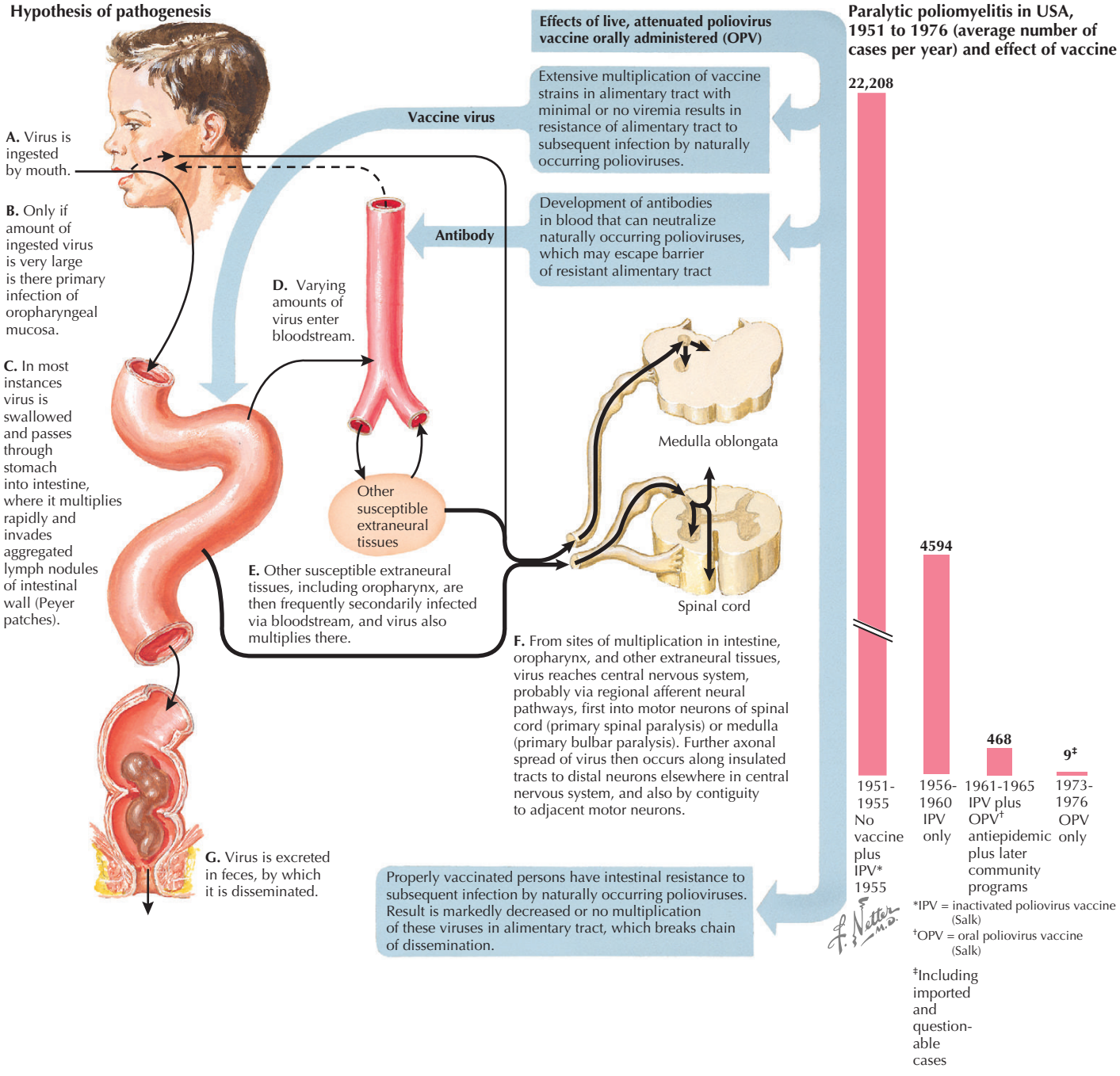

Figure 7-1 Poliomyelitis.

meningitis clinically similar to other nonpolio enteroviral meningitis. Although this illness is similar to abortive poliomyelitis, generally the symptoms are more severe, with meningeal irritation being the distinguishing feature.

Paralytic Poliomyelitis

Approximately 0.1% to 0.2% of infected, symptomatic individuals develop paralytic polio characterized by severe back, neck, and muscle pain with the development of muscle weakness, loss of reflexes, and paralysis. In children and rarely in adults, classic paralytic polio is a biphasic course with an initial minor illness (corresponding to abortive poliomyelitis), then a few days of presumed recovery, followed by an abrupt onset of a major illness characterized by symptoms of meningitis, fever, headache, neck stiffness, and cerebrospinal fluid (CSF) pleocytosis. The hallmark of paralytic polio is asymmetric paresis or paralysis. The maximal loss of functions is typically seen within 3 to 5 days of onset but may progress for up to 1 week. Legs are more often involved than arms, and proximal muscles of the extremities are more often involved than distal muscles (Figure 7-2). Sensory loss with polio is very rare. Spastic paralysis suggesting upper motor neuron disease may be observed with polioencephalitis, which may be seen in infants, but is rare.

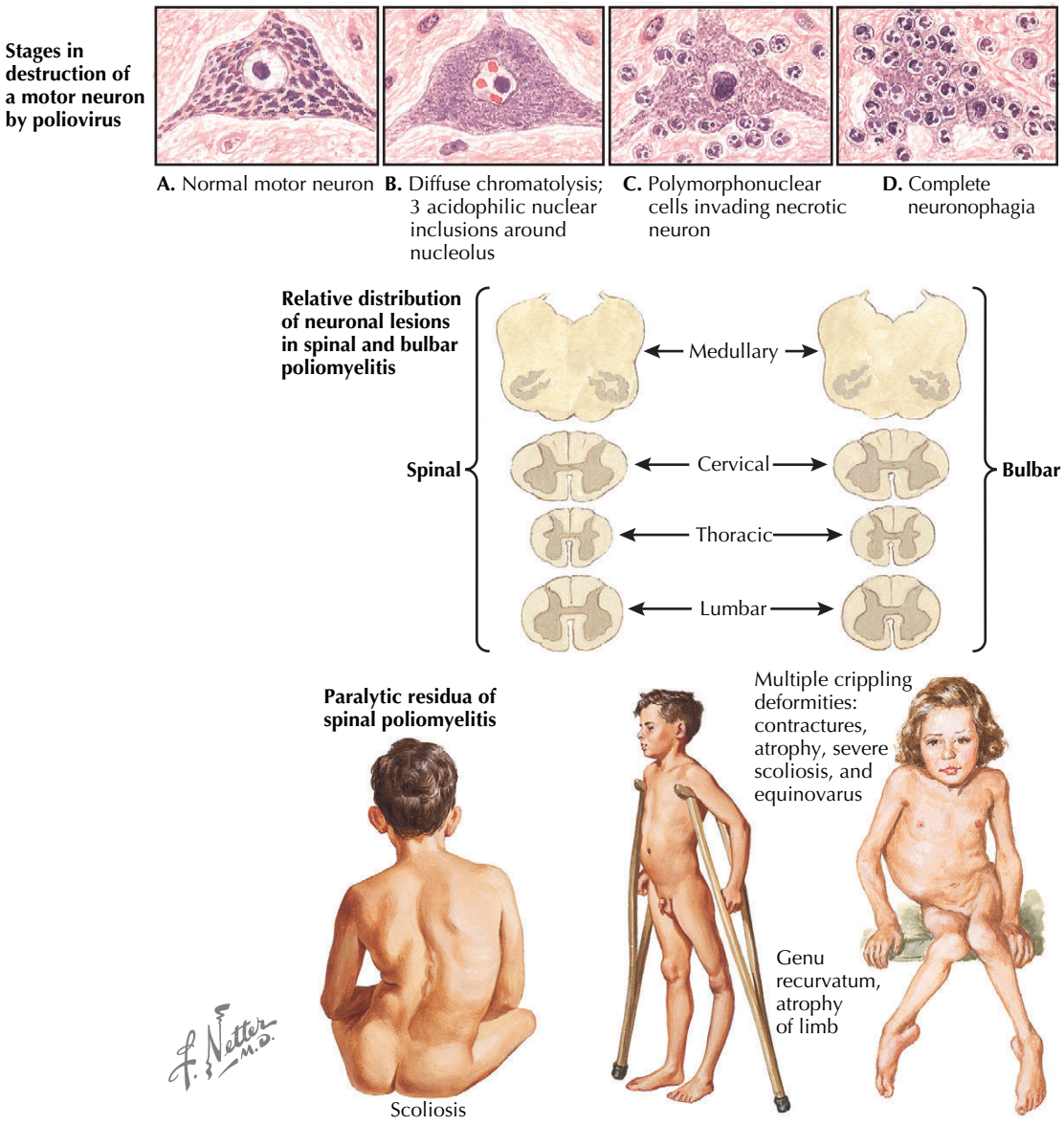

Figure 7-2 Poliomyelitis.

Bulbar Paralytic Poliomyelitis

During epidemics, bulbar paralytic polio accounts for 5% to 35% of cases. This entity results from paralysis of the muscle groups innervated by the cranial nerves, most commonly the ninth and tenth cranial nerves. The patient may have nasal speech, inability to swallow secretions, and dyspnea and often appears anxious or distraught, attributable to difficulty breathing and the associated hypoxia.

DIAGNOSTIC APPROACH

Clinical Findings

Suspicion for the diagnosis of polio is based on clinical presentation.

Acute Flaccid Paralysis

The World Health Organization (WHO) defines AFP as any case of flaccid paralysis with acute onset in a child younger than 15 years of age or clinically suspected polio at any age. AFP is the most common category of diagnoses that includes paralytic polio in the differential. Infectious agents are the leading identified cause of AFP, though other causes must also be considered, such as multiple sclerosis and spinal cord disorders (e.g., transverse myelitis and cord compression). For infectious agents, viruses are most common, including non–polio enteroviruses (especially enterovirus 71 and coxsackievirus A7), West Nile virus, and less likely herpesviruses. Other infectious considerations are Lyme disease, botulism, and diphtheria (especially for bulbar poliomyelitis). Guillain-Barré syndrome (GBS) can easily be confused with polio; however, it generally manifests as a

bilateral process with ascending paralysis with loss of sensory functions, as well as motor neuron dysfunction. In addition, with GBS the spinal fluid generally has elevated protein with minimal or no pleocytosis in the CSF. Identifying GBS is especially important, as management includes treatment with intravenous immunoglobulin or plasmapheresis.

Laboratory Findings

CSF findings with poliovirus infection are similar to those of other forms of viral meningoencephalitis, in that generally the pleocytosis is mild (20 to 300 cells/mm^3) with a lymphocyte predominance, though initially there may be a polymorphonuclear leukocyte predominance. The total protein may be normal or mildly elevated, and the CSF glucose is within the normal range. Other laboratory findings, such as the complete blood count and serum chemistry values, are usually normal or have nonspecific mild abnormalities.

Cultures of the nasopharynx and stool usually yield the infecting poliovirus during the acute illness, though patients may shed the virus for over 8 weeks after primary infection. In addition, after receipt of oral polio vaccine, viral shedding may persist for 6 weeks or longer. Isolation of polioviruses from the CSF is rare, including with paralytic polio.

In the absence of positive viral cultures, confirmation of polio infection may be obtained with serologic testing demonstrating a rise in antibody titers in paired acute and convalescent sera. Serum neutralizing antibodies develop about 1 week after infection and are lifelong. Immunity is type specific; however, serology cannot differentiate infection with wild-type or vaccine-type viral strains.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Supportive care is the mainstay of treatment for poliomyelitis. This may include pain management and physical therapy, as well as ventilation for patients who progress to respiratory failure. The role of antiviral therapy for polioviruses, as well as nonpoliovirus enterovirus infections, remains unclear. Pleconaril (an antiviral agent active against picornaviruses) has been evaluated in a limited number of clinical studies, yielding mixed results. At this time, no specific antiviral therapy is available.

PROGNOSIS

During the time of polio epidemics, about 50% mortality was observed in individuals with respiratory failure, with the overall mortality rate of around 5% to 10%. About two thirds of patients with AFP do not regain full strength.

In patients with a history of polio, new onset of functional deterioration after a prolonged period of stability (post-polio syndrome) may occur weeks to years later in 25% to 35% of survivors. Clinical presentation is characterized by muscle weakness, atrophy, and fatigue in the same muscles as involved in the original illness. Even without meeting criteria for post-polio syndrome, many polio survivors have long-term sequelae including muscle weakness, chronic pain, contractures, fatigue, depression, and other disorders associated with a lower quality of life.

PREVENTION AND CONTROL

Availability of vaccination against polio was heralded as one of the greatest successes of medical research in the twentieth century. In 1955, the inactivated polio vaccine (IPV) was introduced by Dr. Jonas Salk, followed by rapid decline in polio cases. In 1961 to 1962, the oral polio vaccine (OPV) was introduced by Dr. Albert Sabin and quickly replaced IPV because of the ease of administration and potential benefits of herd immunity through fecal shedding of the vaccine viruses. In most developing nations, OPV is still in use and has led to a remarkable decline in the global burden of polio infections.

In the United States and other industrialized nations, newer enhanced-potency IPV (eIPV) with increased antigen content has supplanted the use of OPV, in large part because of the occurrence of vaccine-associated paralytic polio (VAPP) with OPV. The risk of VAPP following OPV is approximately 1 in 2.5 to 4 million doses; in the latter half of the twentieth century, VAPP was observed more frequently than wild-type polio in the United States. This led to the switch of sequential vaccine regimen with two doses of eIPV followed by two doses of OPV from 1997 through 1999, and this was changed to an all-eIPV dosage regimen in 2000. IPV is generally safe and well tolerated by recipients, and it is contraindicated in individuals with previous adverse reaction to the vaccine or its components. Several combination vaccines for infants and children containing IPV are available and offer the benefit of fewer injections.

Currently, OPV is not routinely produced or used in the United States; however, an emergency stockpile of OPV is maintained in the event of a polio outbreak. OPV is recommended as the vaccine of choice during a mass vaccination campaign in the event of a polio outbreak. OPV should not be used in immunocompromised individuals, unvaccinated adults, or vaccinees with an immunocompromised household contact.

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Influenza

Sylvia H. Yeh

8

ABSTRACT

Influenza is a viral infection characterized by abrupt onset of fever, chills, myalgias, and respiratory symptoms such as cough, sore throat, and rhinitis. Influenza viruses, types A and B, cause annual epidemics worldwide leading to a substantial morbidity and mortality. Vaccination is the most cost-effective means of prevention. Antiviral therapy is available, but development of strain-specific resistance is becoming more common and requires continued global monitoring and vigilance.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Influenza infections occur in epidemics annually worldwide and are estimated to cause 3 to 5 million cases of serious illnesses and 250,000 to 500,000 deaths annually. In the United States, seasonal influenza accounts for approximately 226,000 hospitalizations and 36,000 deaths each year. Pandemic influenza is defined as the emergence and global spread of a new influenza A subtype to which the population has little or no immunity and that spreads rapidly from human to human. Pandemics may cause greater numbers of hospitalizations and deaths. During the 1918-1919 pandemic, an estimated 21 million deaths occurred globally. Generally, lower rates for morbidity and mortality were associated with 2009-2010 H1N1/09 pandemic, with approximately 14,500 deaths reported globally from April 2009 through January 2010.

In temperate regions, the disease is prominent during the winter months, with the peak usually occurring in January and February. In tropical areas, influenza viruses may circulate year round with one or two peaks of activity, usually associated with the regional rainy season. During pandemic influenza, the typical seasonality may not be observed because of sustained transmission among immune-naïve populations. The most recent pandemic started in spring 2009, spread globally, and had a second observed peak of cases in late October 2009. A similar pattern was observed in the 1918-1919 pandemic.

Three types of influenza viruses—A, B, and C—have been described; however, types A and B are the main causes of human disease. Influenza type C is associated with sporadic outbreaks of mild illnesses, primarily in children. Influenza viruses are single-stranded ribonucleic acid (RNA) viruses in the Orthomyxoviridae family, and are structurally similar but vary antigenically. Influenza A viruses are further classified based on antigenic variations on their surface proteins, hemagglutinin (HA) and neuraminidase (NA) (Figure 8-1). Recently the dominant circulating A strains have been H1N1, H3N2, and H1N2. Both influenza A and B viruses undergo rapid antigenic changes. Minor changes account for the yearly seasonal epidemics (antigenic drifts) wherein previous infections with influenza may provide some protection against disease. Novel antigenic changes (antigenic shifts) typically involve reassortment of antigens between human and nonhuman influenza viruses. These antigenic shifts can lead to pandemics, in which individuals are immune naïve and thus susceptible to more severe disease and widespread transmission. Humans may be infected with nonhuman influenza A strains, including swine and avian strains.

RISK FACTORS FOR ENDEMIC DISEASE

With seasonal influenza epidemics, children have the highest rates of infections (accounting for 6 to 15 per 1000 pediatric outpatient visits). In contrast, the highest risk for complications and hospitalizations is seen in persons 65 years of age and older, very young infants and children (younger than 2 years of age), and persons with chronic medical conditions. These conditions include congenital or acquired immunodeficiencies including human immunodeficiency virus (HIV) infection and receipt of immunosuppressive medications; chronic pulmonary, cardiac, renal, hepatic, neurologic or neuromuscular, hematologic, and metabolic diseases (including diabetes); and receipt of long-term aspirin therapy. Pregnant women and residents of long-term care facilities are also at increased risk of complications.

With pandemic influenza the rate of infections and complications may disproportionately affect healthy adults and others with no known risk factors.

CLINICAL FEATURES

Influenza viruses are readily spread person to person by infected respiratory droplets, and spread may also occur via fomites contaminated with infected droplets. Viral shedding may occur for 24 hours before onset of symptoms, continues for 5 to 10 days, and correlates directly with the degree of fever. Shedding may be longer in young children and immunocompromised individuals.

After exposure to the virus, the incubation period is 1 to 4 days, with a mean of 2 days. Influenza in older children and adults typically manifests with abrupt onset of fever, chills, myalgia, malaise, headache, and upper respiratory infection (URI) symptoms such as rhinorrhea, cough, and pharyngitis. Children may have only fever or may demonstrate URI symptoms indistinguishable from those of other viral respiratory infections. Conjunctival injection, abdominal pain, vomiting, and diarrhea are less commonly observed. Very young children and infants may have symptoms ranging in severity from nonspecific URI, to moderate respiratory illness, to a sepsis-like picture. Individuals who have preexisting immunity from previous natural infections or vaccination may have milder symptoms.

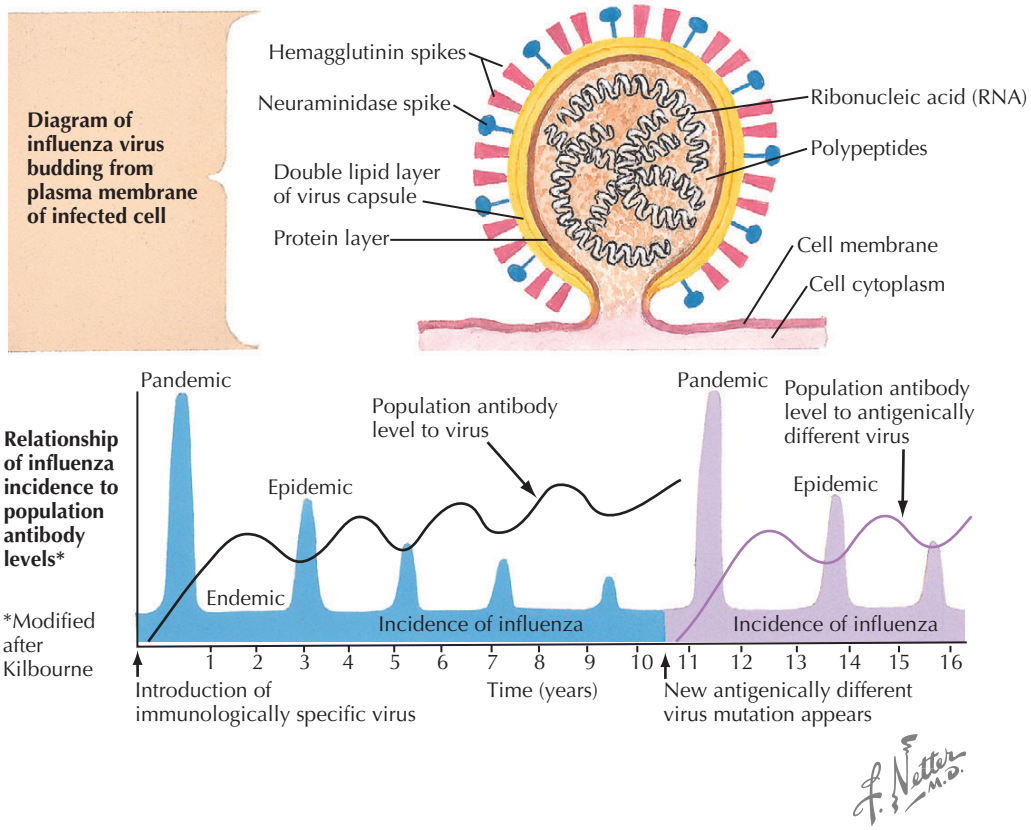

Figure 8-1 Influenza virus and epidemiology.

COMPLICATIONS

Although most influenza illnesses are self-limited, complications are not infrequent. Influenza virus may cause infection in any part of the respiratory tract, including otitis media, croup, bronchiolitis, and pneumonia (see Figure 30-2). Approximately 10% to 50% of children younger than 5 years of age develop viral bronchopneumonia with symptoms that are typically mild and resolve without treatment. Other complications caused by direct invasion of an organ by the influenza virus include myocarditis and encephalitis. Myositis is not an uncommon feature, more often seen after influenza B infection, at the time that respiratory symptoms are resolving. Patients may exhibit calf tenderness and refusal to walk. The myositis often self-resolves, though rarely rhabdomyolysis and renal failure can occur. Complications involving the central nervous system (CNS) range from febrile seizures to severe encephalopathy. Postinfluenza CNS events, presumably caused by the host response to the virus, include encephalopathy, Guillain-Barré syndrome, postinfluenza encephalitis, and transverse myelitis.

The most common complications are bacterial superinfection, which may occur anywhere along the respiratory tract, including otitis media, sinusitis, and secondary bacterial pneumonia. Bacterial sepsis may also be seen in association with influenza. Secondary bacterial infections typically cause a recrudescence of fever with associated localizing symptoms (e.g., ear pain for otitis media, cough or shortness of breath for pneumonia). The most common bacterial pathogens include *Staphylococcus aureus* (including methicillin-resistant *S. aureus*), *Streptococcus pneumoniae*, Group A streptococci, and *Haemophilus influenzae*. *S. aureus* is a prominent player for severe, progressive pneumonia as well as bacterial tracheitis and toxic shock syndrome in a setting of preceding influenza infection. Reye's syndrome (acute hepatic encephalopathy) and death may also occur.

In children, it is estimated that influenza accounts for 50 to 85 per 1000 medical office visits and 6 to 27 per 1000 emergency room visits each year in the United States. Also, a 10% to 30% increase in the number of prescribed antimicrobial agents has been reported. Hospitalization rates for young children rival those for the elderly, with 108 compared with 190 hospitalizations per 100,000 person-years in children younger than 5 years of age and persons older than 65 years of age, respectively.

DIAGNOSTIC APPROACH

During an influenza epidemic the diagnosis of influenza may be made clinically. However, the clinical presentation may be difficult to distinguish from that of infections from other respiratory pathogens, and laboratory identification of the causative agent can be useful. In addition, specific viral testing and identification may be important for epidemiologic reasons (e.g., public health surveillance), for consideration of empiric antiviral therapy, and for management of individuals at increased risk of complications.

Viral culture of nasopharyngeal secretions remains the gold standard for identification of influenza viruses. Rapid

culture-based tests are available, including shell vial techniques, in which small number of cells are inoculated and stained for detection of influenza antigens in a shorter period of time than traditional cell cultures. In addition, several rapid tests using either antigen detection or polymerase chain reaction (PCR) to identify influenza A and/or B viruses have become available. Use of these tests at the point of care may provide reassurance and limit the administration of unnecessary antibiotics and further diagnostic testing. However, the positive predictive value of these tests is highly dependent on the prevalence of influenza in the community; they are of limited value when the prevalence is less than 10%. In addition, the rapid tests may not be able to detect influenza viruses with significant antigenic changes, such as in a pandemic setting.

CLINICAL MANAGEMENT

For most individuals with influenza, the care is supportive, emphasizing patient comfort and fever control with antipyretics. Acetaminophen is the preferred antipyretic for most infants and young children. For most individuals, ibuprofen is also acceptable, but with assurance of good hydration. Aspirin is contraindicated for children with influenza because of the association with Reye's syndrome.

Specific antiinfluenza medications, including adamantanes and NA inhibitors, are available for treatment of influenza. These antivirals, when used within 48 hours of illness onset, may shorten the duration of symptoms. The NA inhibitors may reduce the risk of morbidity from influenza in certain hosts. Routine use for mild illnesses in immunocompetent hosts is not recommended but may be considered in persons at high risk for complications from influenza. Antiviral resistances have emerged, and treatment recommendations should be based on susceptibility data of circulating strains, as discussed later.

Adamantanes

Available drugs in the adamantane class are amantadine and rimantadine, which are active only against influenza A. These drugs target the M2 protein, which is present on influenza A but not B. When the adamantanes are used within 48 hours of symptom onset, the duration of fever, systemic symptoms, and viral shedding is shortened by 1 to 2 days. The most common adverse drug effects are insomnia, anxiety, nausea, and loss of appetite, and these are more commonly associated with amantadine than rimantadine. CNS side effects are infrequent but include agitation and an increase in seizure activity in persons with epilepsy; these are also more common with amantadine. This class of medications is not licensed for use in children younger than 1 year of age.

Neuraminidase Inhibitors

NA inhibitors inhibit the NA protein present on both influenza A and B, blocking the influenza virus from fusing with the host cell membrane. Two drugs in this class are available: oseltamivir, which is administered orally, and zanamivir, which is inhaled. Use of these medications within 24 to 48 hours of symptoms onset is associated with shortened duration of fever and constitutional symptoms but does not necessarily shorten viral shedding. Use of oseltamivir within 24 hours is associated with reduced risk of asthma exacerbations with influenza. The most common adverse effects from oseltamivir are nausea and vomiting. Reports of self-injurious behavior and delirium associated with oseltamivir have been determined to be more likely caused by influenza disease itself, but advising parents to monitor for abnormal behavior may be prudent. Bronchospasm has been reported with zanamivir administration, and therefore this drug should be used with caution in persons with asthma or pulmonary dysfunction.

PROGNOSIS

In most immunocompetent hosts, influenza is self-limited illness. However, in very young children and the elderly, rates of complications and death are higher than seen in other age groups. Hospitalization rates are much higher in very young children, with rates of 240 to 720 per 100,000 children per year in infants younger than 6 months of age compared with 20 per 100,000 children per year in children 2 to 5 years of age. Although death is rare, the rate is estimated at 0.4 per 100,000 children younger than 5 years of age per year. Data from 2003 to 2005 reveal that although children with underlying medical conditions are at greater risk of death, most (51%) pediatric deaths resulting from laboratory-confirmed influenza occurred in children with no known risk factors.

Individuals older than 65 years of age with underlying medical conditions have the highest rates of hospitalization, estimated at 560 per 100,000 persons per year (compared with 190 per 100,000 for persons older than 65 years of age who are healthy). Persons with immunodeficiency conditions, such as HIV, and pregnant women also have demonstrable increased risk of hospitalization and death compared with persons in similar age groups without these conditions.

PREVENTION AND CONTROL

Immunoprophylaxis

Two types of influenza vaccines are available for the prevention of influenza A and B: (1) inactivated vaccine (trivalent inactivated influenza vaccine [TIV]), given intramuscularly, and (2) live-attenuated influenza virus (LAIV), given intranasally. Each year, these vaccines are formulated to contain two influenza A and one influenza B strains; the specific strains included are based on the predicted likelihood of what strains will circulate in the hemisphere in the upcoming season. These predictions are based on patterns of global circulation and are determined by experts from the World Health Organization and from the U.S. Food and Drug Administration and Centers for Disease Control and Prevention (CDC) in the United States approximately 9 months ahead of the influenza season.

For both TIV and LAIV seasonal influenza vaccines, children 8 years of age and younger require two doses of vaccine, separated by 4 weeks, the first time that they are immunized. Generally, other inactivated and live vaccines may be coadministered with TIV and LAIV; however, no other live intranasal vaccines may be simultaneously administered with LAIV.

The viruses for both types of vaccines are propagated in chicken eggs and are contraindicated in persons with known severe allergic reaction (i.e., anaphylaxis, angioedema, hives, and allergic asthma) to chicken, egg proteins, or other components of the vaccines. TIV can be used in any persons 6 months of age and older. The efficacy of TIV is dependent on the age of the host, underlying host factors, and the antigenic match between the vaccine strain and the circulating strain. The efficacy of TIV varies from 60% to 95% against culture-confirmed influenza when the vaccine strain matches the circulating strain. LAIV is indicated for healthy persons 2 to 49 years of age. LAIV should not be administered to persons with reactive airway disease or asthma, known or suspected immunodeficiency, pregnant women, persons receiving salicylates, or persons with conditions considered to be high risk for severe influenza (for whom TIV is recommended). LAIV should be used with caution in persons with a history of Guillain-Barré syndrome within 6 weeks after a previous dose of influenza vaccination. The efficacy of LAIV is approximately 90% against culture-confirmed influenza cases when the vaccine strain matches the epidemic strain. In addition, available data suggest that LAIV may provide cross-protection against mismatched strains owing to antigenic drift.

If influenza vaccination supply is sufficient, all persons 6 months of age and older should be vaccinated each year. The specific groups designated by the CDC Advisory Committee for Immunization Practices (ACIP) to be targeted when vaccine supply is limited are listed in Box 8-1.

Chemoprophylaxis

In the event that annual influenza vaccination is not possible or is contraindicated, chemoprophylaxis with antiviral medication is second-line protection. Studies of antiviral chemoprophylaxis have demonstrated 20% to 40% reduction of secondary cases within households. However, chemoprophylaxis has potential drug toxicity as well as potential for development of antiviral resistance and should not be considered equivalent to vaccination. Chemoprophylaxis may be considered (1) for unimmunized individuals at high risk of complications from influenza or those who were vaccinated less than 2 weeks before high-risk exposure to influenza virus, (2) for unimmunized close contacts of high-risk persons, (3) for immunized high-risk children when the vaccine strain poorly matches the circulating strain, and (4) for control of an influenza outbreak in a close setting (such as an institution). Because of the emergence of resistance to the antivirals, recommendations regarding chemoprophylaxis need to be adjusted based on susceptibility of circulating strains. For the United States, these recommendations are available through the CDC (www.cdc.gov/flu/professionals/antivirals/index.htm).

Box 8-1 Centers for Disease Control and Prevention Advisory Committee on Immunization Practices Specific Groups for Influenza Vaccination, 2010

Pediatric Recommendations

All children aged 6 months to 18 years should be vaccinated annually.

Children and adolescents at higher risk for influenza complications should be a focus of vaccination efforts when vaccine supply is limited, including those who:

- are aged 6 months to 4 years (59 months)
- have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurologic or neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus)
- are immunosuppressed (including immunosuppression caused by medications or by human immunodeficiency virus)
- are receiving long-term aspirin therapy and therefore might be at risk for experiencing Reye's syndrome after influenza virus infection
- are residents of long-term care facilities
- will be pregnant during the influenza season

Adult Recommendations

Annual vaccination against influenza is recommended for any adult who wants to reduce the risk of becoming ill with influenza or of transmitting it to others.

Vaccination is recommended for all adults without contraindications in the following groups, because these persons either are at higher risk for influenza complications, or who are close contacts of persons at higher risk:

- persons age 50 years and older
- women who will be pregnant during the influenza season
- persons who have chronic pulmonary (including asthma), cardiovascular (except hypertension), renal, hepatic, cognitive, neurologic or neuromuscular, hematologic, or metabolic disorders (including diabetes mellitus)
- persons who have immunosuppression (including immunosuppression caused by medications or by human immunodeficiency virus)
- residents of nursing homes and other long-term care facilities
- healthcare personnel
- household contacts and caregivers of children age <5 years and adults age 50 years or older, with particular emphasis on vaccinating contacts of children age <6 months
- household contacts and caregivers of persons with medical conditions that put them at higher risk for severe complications from influenza

Adapted from Centers for Disease Control and Prevention (CDC): *Influenza prevention and control recommendations 2010-2011.* Available at: www.cdc.gov/flu/professionals/acip/specificpopulations.htm.

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Rotavirus Infection

S. Michael Marcy and Susan Partridge

9

ABSTRACT

Rotavirus infections are the most common cause of severe dehydrating gastroenteritis worldwide. In developing countries, virtually all children have been infected by age 2 to 3. Rotaviruses are double-stranded ribonucleic acid (RNA) viruses that belong to the family Reoviridae. The viral capsid is composed of three protein layers. Two structural proteins in the outer layer, VP4 and VP7, define the P (protease-sensitive) and G (glycoprotein) serotypes, respectively. Clinical presentation is characterized by varying severity of vomiting, diarrhea, and fever, either alone or in combination. Illness may be mild or asymptomatic, particularly in older children and adults. Infection is self-limited and treatment is supportive, directed at maintaining fluid and electrolyte balance and nutrition. Natural infection is generally protective against subsequent severe illness. Rotavirus immunization available in most industrialized countries has markedly reduced the rates of illness and death previously associated with rotavirus gastroenteritis. Two highly effective rotavirus vaccines are recommended for routine immunization in infancy.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

Rotavirus gastroenteritis is the most common cause of severe dehydrating diarrhea in infants and young children worldwide. Before the availability of rotavirus immunization almost all children acquired infection by age 3 years, irrespective of their geographic location or living conditions. In the United States, infection was responsible for a significant number of pediatric office and emergency department visits as well as hospitalizations. Although approximately 3,000,000 cases of rotavirus disease occurred annually in the United State among children younger than 5 years old, mortality rates were low, with 20 to 60 deaths annually. In developing countries where infections occur earlier in infancy and access to medical care is often limited, rotavirus gastroenteritis has been and remains a leading cause of mortality, with an estimated 600,000 childhood deaths per year, the majority in Asia and Africa.

RISK FACTORS

Transmission of infection is primarily fecal-oral, not only through person-to-person contact, but also via contact with contaminated environmental surfaces. Contamination of water and food is an uncommon source; the role of respiratory droplet transmission is uncertain. Rotavirus is shed in the stool of infected children not only during acute illness but also several days before and after. The high rate of transmission and prevalence of early childhood infection is likely potentiated by a combination of intense viral shedding during clinical disease (up to 10^{12} virions per gram of stool) together with a small oral infective dose (as few as 100 particles).

Risk factors for illness in infancy include use of formula rather than breastfeeding, low birth weight, residence in a household with one or more children younger than 2 years of age, attending a childcare facility, male gender, and young maternal age (Figure 9-1). Children and adults who are immunocompromised as a result of congenital or acquired immunodeficiency may also experience more severe or prolonged gastroenteritis.

CLINICAL FEATURES

Occurrence of rotavirus infection has been highly seasonal in temperate climates. Prior to the availability of rotavirus immunization, rotavirus activity in the United States, began in early winter in the Southwest and progressed northward and eastward, arriving in the New England states in the spring. Widespread use of rotavirus vaccine in infancy has resulted in a markedly diminished incidence of illness, although with little change in seasonality. The peak age of illness in developed countries is from 6 to 24 months. In developing countries most cases occur in the first year of life, which is probably a factor in the higher mortality in these areas.

Illness begins from 1 to 2 days after infection, most often with the abrupt onset of vomiting and fever, followed shortly by watery diarrhea (Figure 9-2). Any of these findings can occur alone or in combination; however, 95% of children have vomiting, diarrhea, or both. Vomiting is usually brief in duration, and diarrhea resolves in most cases after 3 to 7 days. Although a third of children manifest a fever of 39° C (102.2° F), most have a low-grade fever and up to 25% are afebrile at the time of onset of clinical disease.

Age is an important determinant of the clinical course. In the neonatal period, illness is usually asymptomatic or very mild, although rotavirus infection has been associated with necrotizing enterocolitis, particularly in preterm infants. Older infants and toddlers with their first infection manifest a broad spectrum of signs and symptoms, ranging from a single episode of watery diarrhea or emesis to fulminant gastroenteritis leading rapidly to electrolyte imbalance, hypovolemia, and shock. Although children with up to five rotavirus infections in the first 2 years of life have been described, illness occurring after the first infection is almost always mild to moderate. With rare exceptions, particularly among the elderly, adolescents and adults have asymptomatic infection or mild disease, probably as a result of protection derived from previous infection(s).

Rotavirus has been identified in the cerebrospinal fluid and in up to 90% of sera during the course of acute illness. Infection has been associated with seizures, encephalitis, meningitis, mild

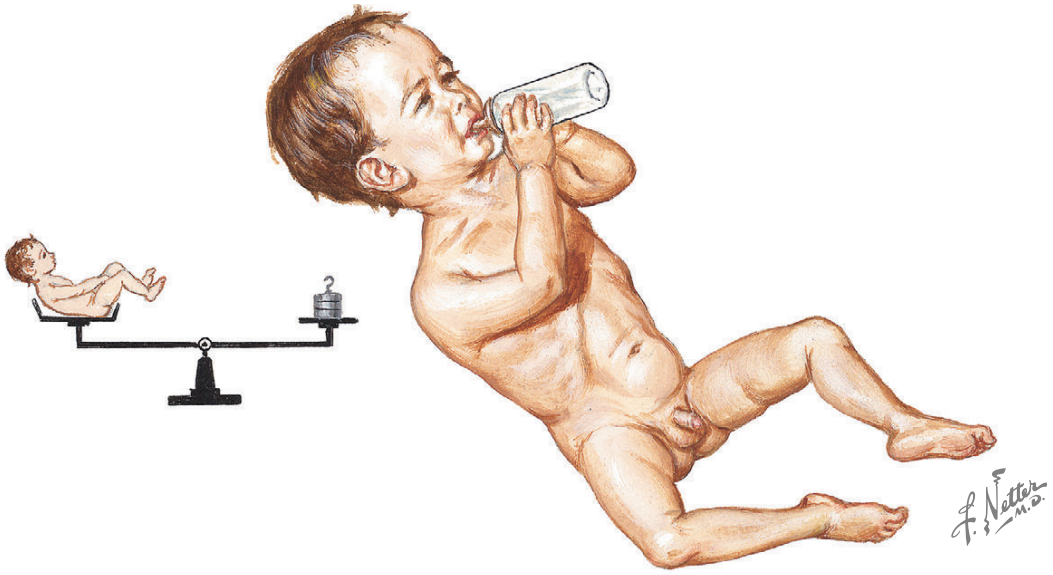

Figure 9-1 Low birth rate and used of formula rather than breast feeding are risk factors for rotavirus infection in infants. The bottle-fed boy shows signs of dehydration from rotavirus infection.

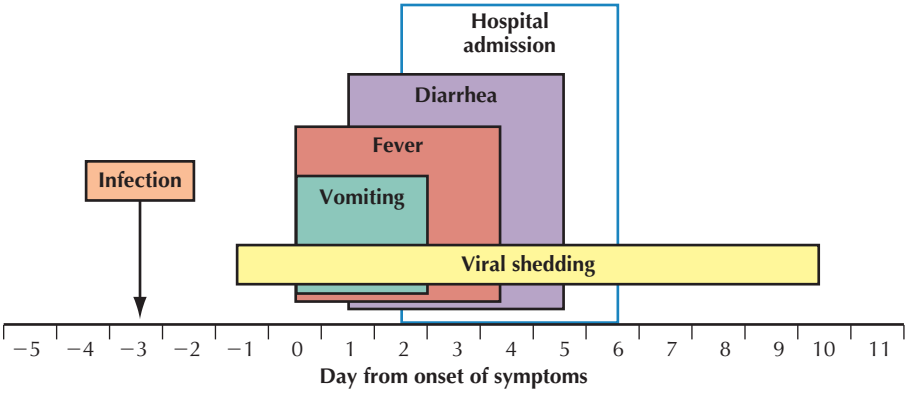

Figure 9-2 Clinical course of rotavirus infections. *(Data from Marshall G, Dennehy P, Matson DO, Staat MA:* Rotavirus: prevention and vaccination strategies to address burden of disease, *Thorofare, NJ, 2008, Vindico Medical Education.)*

elevation of liver enzymes, pancreatitis, myocarditis, myositis, and lower respiratory tract infection.

DIAGNOSIS

No clinical features distinguish rotavirus disease from that caused by many other gastrointestinal pathogens. Abrupt onset of vomiting, profuse watery diarrhea, and mild fever occurring in the winter or spring, depending on location, is highly suggestive of a rotaviral cause. Prolonged high fever and dysenteric or grossly bloody stools would mitigate against rotavirus infection as the cause.

Laboratory confirmation of rotavirus infection is not routinely necessary. When indicated, such as for a patient with a prolonged or atypical course of gastroenteritis or for inpatient cohorting, a number of confirmatory laboratory tests can be used. Enzyme-linked immunosorbent assay (ELISA) or latex agglutination tests are available in most clinical laboratories. Polymerase chain reaction (PCR) procedures may be available in larger hospital laboratories or academic centers.

CLINICAL MANAGEMENT

Treatment of rotavirus gastroenteritis is supportive, directed at restoration and maintenance of vascular volume, fluid, electrolyte, and caloric balance. Illness is self-limited; there is no antiviral therapy. In most cases, a few days of oral rehydration therapy (ORT) with appropriate electrolyte-carbohydrate solutions are sufficient. Severe dehydration, persistent vomiting, intractable watery diarrhea, or refusal of oral fluids may necessitate parenteral therapy. Breast-feeding should be continued or reinstituted as quickly as possible. In older infants and children, early refeeding with solids should be encouraged. Use of probiotics, specifically *Lactobacillus* GG (two capsules three times daily), has provided some benefit in shortening the course of illness.

PREVENTION AND CONTROL

Breastfeeding, hand washing, maintaining surface cleanliness (particularly in daycare centers), and diligently using contact precautions with hospitalized children are helpful in preventing rotavirus infection.

In the United States, two rotavirus vaccines (RotaTeq, Merck; Rotarix, Glaxo SmithKline) are recommended for routine infant immunization in the first 8 months of life. They are comparably effective and have resulted in an 80% reduction in rotavirus gastroenteritis of any severity and over 95% reduction against severe dehydrating gastroenteritis. In addition to providing direct protection in immunized infants, there is epidemiologic evidence that reduction in the community incidence of rotavirus has occurred, likely related to development of herd immunity.

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Measles

Alison Margaret Kesson

10

ABSTRACT

Measles is a highly contagious, acute febrile illness caused by rubeola virus, most commonly seen in young children. Measles is characterized by a coryzal prodrome, with cough, conjunctivitis, rhinorrhea, and fever, followed by an exanthem, a maculopapular rash. In addition, a pathognomonic enanthem, Koplik's spots (bluish spots on a red base), may be seen on the buccal mucosa. Most children recover completely, but serious complications involving the respiratory tract and central nervous system (CNS) may occur. In developing countries, measles continues to be a significant cause of morbidity and mortality, but these have been remarkably reduced in areas in which routine immunizations are used. Recently, however, growing antivaccine sentiment has led to decreased acceptance of measles vaccine by some, placing everyone at increased risk of natural infection and its complications.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

Measles occurs in every country in the world. In countries without vaccine programs, epidemics of measles occur every 2 to 5 years. Globally, measles causes 20 to 30 million infections with at least 1 million deaths annually. Countries in which vaccine is widely used have experienced a marked decrease in measles. However, in recent years purported risks associated with vaccination have led to decreased acceptance of measles vaccine among some segments of the population. This has led to an increase in unimmunized children and return of measles infections in some countries, including the United States. Since 2006, several outbreaks of measles have occurred in the United States and European countries with high immunization rates, many of which can be linked to an outbreak in unimmunized schoolchildren in Switzerland.

RISK FACTORS

Humans are the only known hosts for rubeola virus, the causative agent of measles. In general, measles is a more severe illness in adults, infants, and children younger than 5 years of age than in school-aged children. Individuals with compromised cellular immunity (congenital or acquired), malnutrition, and vitamin A deficiency are at risk for more severe illness.

CLINICAL FEATURES

Rubeola virus is a single-stranded ribonucleic acid (RNA) virus belonging to the family Paramyxoviridae. Infection is transmitted by direct contact with infected respiratory droplets and less commonly by airborne spread. It is one of the most communicable of the infectious diseases, with an attack rate over 80% for susceptible persons. Infected individuals are most contagious during the late prodromal phase, when cough and coryza are maximal.

The incubation period is 10 to 14 days from exposure to onset of symptoms. The virus invades endothelial and epithelial cells. After invasion of the respiratory epithelium, local viral multiplication and primary viremia with spread via leukocytes occurs. Next the prodromal phase begins, which generally lasts for 3 to 6 days and is thought to coincide with secondary viremia. About 2 to 3 days before the appearance of the rash, Koplik's spots (bluish-grey specks, at times described as appearing like coarse-size salt crystals, on an erythematous base) appear on the buccal mucosa, usually opposite the molars (Figure 10-1). Koplik's spots are pathognomonic of measles and may occur on any mucosal surface but may be overlooked without a careful examination.

The prodrome resembles a severe upper respiratory tract infection, with malaise, fever, and the classic "3 Cs" (conjunctivitis, cough, and coryza) of measles. Profuse nasal discharge and a brassy cough are usually maximal at day 5. A transient scarlatiniform or morbilliform rash lasting less than 24 hours may occur in this early phase.

The characteristic morbilliform rash (fine, red maculopapules) usually begins as blanching macules behind the ears and at the hairline (see Figure 10-1). It then spreads to involve the face and proceeds down the body to the extremities, and last to the palms and soles. The rash usually lasts 5 days, often becomes confluent, and then fades. A brownish discoloration of the skin may remain for 10 days after the disappearance of the rash. The skin may desquamate but this usually spares the hands and feet. In uncomplicated illness, the duration from late prodrome to resolution of fever and rash is 7 to 10 days. The rash may not develop in immunocompromised individuals, as the pathogenesis is thought to be hypersensitivity to the virus.

Other findings include generalized lymphadenopathy, splenomegaly, palpebral conjunctivitis, punctate keratitis, edema of the eyelids, and photophobia. Sore throat, myalgia, and headache are also common. Nonsuppurative acute appendicitis may also occur, which may be seen just before the rash.

COMPLICATIONS

The most common complications are respiratory tract infections, diarrhea, and CNS involvement. In infants, respiratory complications are more common; in older children, CNS complications are more common.

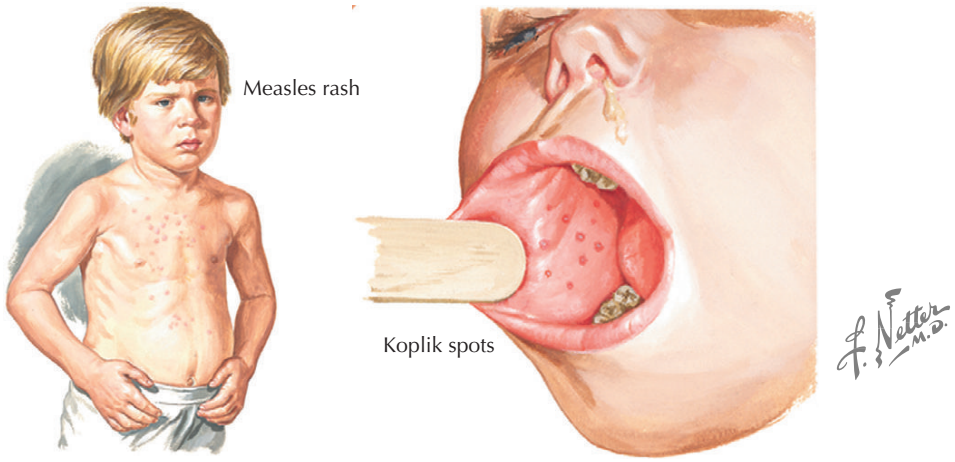

Figure 10-1 Clinical features of measles.

Respiratory Tract Infections

Invasion of any part of the respiratory tract is part of the measles virus infection. In addition, bacterial superinfection can occur in any area of the respiratory tract, including the middle ear. Otitis media, sometimes with spontaneous perforation of the tympanic membrane, can occur, as can laryngotracheobronchitis (croup) and bronchiolitis.

Pneumonia may be caused by direct viral invasion of the lungs or by bacterial superinfection. Radiographic evidence of pneumonia is common even with uncomplicated measles. Secondary bacterial pneumonia cannot be differentiated from measles pneumonia based on the pattern of x-ray changes. Bacterial pneumonia is commonly caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Staphylococcus aureus* and usually occurs 5 to 10 days after the onset of the rash. The patient usually has high fevers, purulent sputum, and leukocytosis at the time that the rash is resolving. Pneumonia is the most common cause of measles-associated deaths in infants. In developing countries the mortality rate with measles may approach 80%. Although pneumonia is less frequent in industrialized countries, it is still responsible for the majority of deaths in infants with measles.

In adults, measles virus pneumonia is more common than secondary bacterial pneumonia and manifests clinically as increasing respiratory distress and hypoxia in parallel with the rash. There may be evidence of prolonged viral replication with persistent high fever, prolonged Koplik's spots and rash, biochemical myositis, and hepatitis. This is a severe illness, but fatalities are rare.

Encephalitis

Cerebrospinal fluid (CSF) pleocytosis and electroencephalographic (EEG) abnormalities may occur in up to 50% of individuals with measles who have no overt CNS symptoms. Acute measles encephalitis occurs during the convalescent phase and is characterized by a resurgence of fever, headaches, and altered consciousness. The incidence of measles encephalitis is 1 in 1000 to 2000 cases; the condition ranges from mild to severe, and neurologic sequelae are common in survivors.

Acute postinfectious measles encephalomyelitis or acute disseminated encephalomyelitis (ADEM) may also be seen after measles. It is rare in children younger than 2 years of age but has an incidence of approximately 1 in 1000 in older children. It generally develops after the first week of rash and manifests with an abrupt onset of fever, headache, and seizures proceeding to obtundation and coma. The CSF may show a mild lymphocyte pleocytosis and elevated protein. Antibodies to myelin basic protein are present in the CSF. There is no evidence of measles virus antigens or RNA or intrathecal synthesis of measles antibodies, supporting an immunologic and not a virologic pathogenesis.

Subacute Sclerosing Panencephalitis

Subacute sclerosing panencephalitis (SSPE) is a chronic, degenerative CNS disorder attributed to persistent infection with a defective measles virus despite robust host immune responses. SSPE is a rare complication (approximately 1 in 300,000 cases) of measles, occurring predominantly in children in their first decade of life. The findings are of subtle deterioration in intellectual function and personality changes. Later manifestations include myoclonic jerks with characteristic EEG slow wave changes. Affected patients develop progressive intellectual deterioration, extrapyramidal dyskinesia with dystonic posturing, and often progressive visual loss. Onset is usually several years after the initial infection and progression is variable, with remissions, but it is usually fatal within 3 years. Patients with SSPE can be diagnosed by the very high titers of measles antibody in their serum and CSF.

Modified Measles

A mild form of measles has been observed in persons with some degree of passive immunity, such as infants who have

passively acquired maternal antibodies and some individuals who have received immune globulin (IG). The symptoms of modified measles are variable, and many classic features may be absent. The illness is usually mild and abbreviated, though the incubation period may be prolonged up to 21 days. Complications of measles and transmission to others are extremely rare.

Atypical Measles

Atypical measles has been described in persons who received formalin-inactivated measles vaccine and who years later developed wild measles infection. A prodrome of fever, cough, and dyspnea is followed by appearance of the rash, which, unlike in classical measles, begins peripherally and spreads centrally while sparing the face. The rash may be urticarial, maculopapular, hemorrhagic, vesicular, or a combination of these. The rash is accompanied by high fevers and edema of the extremities, and complications may occur. Despite the severity, the illness is often self-limited. Measles virus has not been isolated from these patients. The pathogenesis is thought to be related to hypersensitivity to the measles virus in a partially immune host. The killed measles virus vaccine was removed from the market in 1967.

Measles in Immunocompromised Hosts

Severe measles infection may occur in persons with deficient cellular immunity, such as those being treated for malignancy and those with acquired immunodeficiency syndrome (AIDS) or congenital immunodeficiencies. Often these individuals do not have a rash; however, there is a significant incidence of pneumonitis and encephalitis. A chronic form of encephalitis resembling SSPE often with concomitant pneumonia has also been reported.

Malnutrition leading to impaired cellular immunity, as well as intense exposure resulting from overcrowding appear to be factors contributing to severe measles infection in developing countries. In addition, vitamin A deficiency, which may occur with malnutrition, is also associated with more severe illness.

Measles during Pregnancy

Measles during pregnancy may be severe, mainly related to primary measles pneumonitis. During pregnancy, measles is associated with higher risk of miscarriage and premature delivery; however, is not known to cause congenital anomalies of the fetus.

Measles in Neonates

Congenital measles, in which the rash is present at birth or appears in the first 10 days of life, varies from mild to severe with mortality approaching 30%. Mortality is higher in premature infants and in infants who do not develop a rash. Postnatally acquired neonatal measles is rare, because generally infants are protected by transplacentally acquired antibodies as most mothers have measles antibodies (from immunization or natural infection). In the absence of maternal antibodies neonatal measles is often severe.

Other Abnormalities

Tuberculosis may be exacerbated or reactivated by measles infection but not measles vaccine; however, measles vaccine does suppress tuberculin skin sensitivity. This effect lasts approximately 4 to 6 weeks and is presumed to be secondary to suppressed cell-mediated immunity.

Transient biochemical hepatitis has been reported during acute measles in approximately 30% of cases and is more common in adults than children. Myositis with myalgia, elevated creatine phosphokinase, and hypocalcemia is observed in approximately a third of adults and adolescents.

Disseminated intravascular coagulation with measles virus infection of endothelium resulting in bleeding from epithelial and mucosal surfaces ("black measles") occurs rarely in countries with high vaccine coverage. Hemorrhagic measles is often severe and has a high mortality rate.

DIAGNOSTIC APPROACH

Clinical Findings

Classic measles with cough, coryza, conjunctivitis, Koplik's spots, and a maculopapular rash may be readily diagnosed clinically. Laboratory diagnosis may be useful for possible atypical measles, for unexplained pneumonia or encephalitis in immunocompromised patients, and in areas where clinicians may be unfamiliar with the clinical constellation of measles.

Diagnostic considerations for measles may vary with the geographic location of the patient and include dengue fever, Rocky Mountain spotted fever, and other *Rickettsia* infections; parvovirus B19; scarlet fever; *Mycoplasma pneumoniae;* Stevens-Johnson syndrome; adverse drug reactions; and rheumatologic disorders.

Laboratory Testing

Laboratory confirmation can be obtained by virus isolation, detection of measles antigen, RNA, or antibody measurement. Measles virus isolation is technically difficult and is not usually available in clinical laboratories. Viral culture is useful in patients with unexplained pneumonia or encephalitis and in immunodeficient patients in whom antibody responses may be minimal; however, culture may take 2 to 3 weeks. Measles antigen on cells from nasal exudates or urinary sediment may be detected using immunofluorescent antibodies, which can be done in a few hours. A sensitive reverse transcription–polymerase chain reaction (RT-PCR) method demonstrating viral RNA is available but primarily in reference laboratories.

Serology is the most commonly used laboratory method. Detection of measles IgM antibodies by enzyme-linked immunosorbent assay (ELISA) is diagnostic of acute infection; however, these antibodies are often not detectable until the rash appears. A fourfold rise in titers between acute and convalescent

sera can be measured using, neutralization, complement fixation (CF), or hemagglutination inhibition (HAI). Neutralization assays are technically difficult and generally not available; ELISA, CF, and HAI are more widely available. These tests are not overly sensitive but are specific. An individual's immune status can be determined by measuring measles IgG antibodies using an ELISA or HAI.

Diagnosis of SSPE is performed by demonstration of high measles HAI titers in serum and CSF in the presence of a compatible illness. More commonly, measles IgG demonstrated by ELISA in CSF is used to confirm this diagnosis.

TREATMENT

There is no recognized specific treatment for measles. The World Health Organization recommends treatment with vitamin A for all children with acute measles, regardless of their nutritional status or country of residence, to help decrease the severity of illness. Supportive therapy such as antipyretics and fluids is important.

Secondary bacterial infections need prompt treatment with appropriate antimicrobials; however, prophylactic antibiotics are of no known value. The measles virus is susceptible in vitro to ribavirin; however, ribavirin administered intravenously or by aerosol for treatment of measles is of unproven efficacy and has not been approved by the U.S. Food and Drug Administration.

PREVENTION

Before Exposure

Prevention is carried out by the administration of live-attenuated measles virus vaccine. Both killed and live virus vaccines have been developed; however, the killed vaccine was withdrawn in 1967 after the recognition of atypical measles (as described earlier). The vaccine routinely used currently is combined measles, mumps, rubella vaccine (MMR), which is given to healthy children 12 to 15 months of age, with a second dose of vaccine given later in childhood (generally at 4 to 6 years of age in the United States). The vaccine is not routinely given to infants younger than 12 months of age because the induction of immunity may be suppressed by residual maternal antibodies. Measles vaccine can be given to infants 6 to 12 months of age residing in or planning travel to areas with a high incidence of natural measles but should be routinely followed by additional doses after 12 months of age. Fever and a mild maculopapular rash can develop about 1 week after vaccination in 5% to 15% of children. The vaccine is usually not effective if the recipient has measles antibodies present, such as infants younger than 12 months of age or recent recipients of blood products. No deleterious side effects have been associated with recurrent measles vaccination. In the general population, 95% of properly immunized children respond serologically to the vaccine with persistent immunity for many years.

Live-attenuated measles vaccine is contraindicated in individuals with cell-mediated immunodeficiency; however, it is recommended for children with asymptomatic human immunodeficiency virus (HIV) infection, as the risk of vaccination is considered to be less than the risk of natural disease. Measles vaccine virus is grown in chick embryo tissue cultures and contains a negligible amount of egg protein. Persons with a history of anaphylactic reaction to eggs can safely be given measles vaccine, but it should be administered in a setting where any adverse reactions can be dealt with appropriately.

In 1998, Wakefield published a study of autistic children that raised the question of a connection between the MMR vaccine and autism. This study has subsequently been withdrawn by *The Lancet* and Dr. Wakefield reprimanded for falsification of data. In addition, no subsequent studies have identified a link between MMR vaccine and autism or other chronic illnesses.

After Exposure

IG can be given intramuscularly to prevent or ameliorate measles in susceptible individuals, when given within 6 days of exposure. IG is indicated for susceptible individuals with household or close contacts at high risk of complications (such as infants younger than 12 months of age, pregnant women, or immunocompromised persons) or for whom measles vaccine is contraindicated. Individuals who routinely receive intravenous IG (IVIG) do not need IG prophylaxis for measles if they received a dose of at least 400 mg/kg of IVIG within 3 weeks of exposure. After receipt of IG or IVIG, adjustment of the timing of subsequent active measles vaccination must be made (guidelines are published in the AAP *Red Book*).

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Mumps

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11

ABSTRACT

Mumps virus is the only known cause of epidemic parotitis. Mumps is an acute systemic viral infection, and the most significant clinical finding is a nonsuppurative inflammation of the salivary glands, most notably one or both parotid glands. In prepubertal children and most adults the illness is benign, and approximately one third of infections are subclinical. After puberty the disease is more likely to be severe, with more frequent occurrence of extrasalivary gland involvement, including orchitis, meningitis, encephalitis, and pancreatitis. Although a feared complication of orchitis, sterility is rarely observed. Treatment is supportive, and the primary means of prevention is with use of a live-attenuated mumps vaccine, which elicits an immune response in over 90% of recipients. In countries with widespread use of mumps vaccine, the occurrence of infection has decreased by nearly 99%.

GEOGRAPHIC DISTRIBUTION

Mumps virus is a member of the Paramyxoviridae family in the genus *Rubulavirus* and naturally infects only humans. Mumps is endemic throughout the world, with an estimated annual global incidence of 100 to 1000 per 100,000 of the population. In the prevaccine era, epidemics occurred every 2 to 5 years, the peak incidence was in late winter and early spring in temperate climates, and it occurred throughout the year in tropical climates. In areas with widespread use of mumps vaccine, this epidemiology is no longer seen.

RISK FACTORS

Absence of mumps-specific antibody is the primary risk factor for susceptibility to infection. Mumps is uncommon in infants younger than 1 year of age, presumably because of passive immunity from transplacentally acquired maternal antibodies. In the prevaccine era, mumps occurred most commonly in children 5 to 9 years of age, and more than 90% of children younger than 15 years of age had mumps. More recently in countries with universal immunization, outbreaks of mumps have been reported in closed populations of older children, adolescents, and young adults, such as secondary schools, colleges, universities, and military groups. These outbreaks have been attributed to waning vaccine-induced immunity.

CLINICAL FEATURES

The mumps virus is transmitted through infected respiratory secretions via direct contact, droplets, or fomites. The incubation period ranges from 12 to 25 days with a mean of 16 to 18 days. Mumps virus can be isolated from saliva 5 days before the onset of parotitis to 5 days after. Mumps is highly contagious, and peak infectivity occurs just before the onset of parotitis.

In symptomatic individuals, the prodrome includes low-grade fever, anorexia, malaise, and headaches. In primary infections, approximately 25% of patients initially have involvement of only one parotid gland; however, the second parotid gland usually enlarges within a few days. Patients commonly complain of earache, and parotid gland tenderness is noted on palpation. The parotid gland(s) may be painful and visibly enlarged. The ear of the affected side may be pushed upwards and outwards. The enlarged parotid gland may obscure the angle of the mandible and should not be confused with cervical adenopathy, which does not usually obscure this anatomic landmark. After the parotid swelling has peaked (at 3 to 5 days), the fever and tenderness rapidly resolve, and the parotid gland(s) return to normal size, usually within a week. Involvement of other salivary glands may occur, and involvement of submandibular glands may be confused with anterior cervical lymphadenitis. Involvement of sublingual glands is less common but may be associated with tongue swelling. The orifices of Stensen's and Wharton's ducts are often erythematous and edematous (Figure 11-1). Patients may complain of trismus and difficulty speaking and drinking. Acidic foods may induce parotid pain.

Natural infection was once considered to provide lifelong immunity, but more recent evidence suggests that reinfections can occur; these are usually milder and often lack the typical parotitis.

Central Nervous System Involvement

Central nervous system (CNS) involvement is the most common extrasalivary gland manifestation of mumps and is caused by the neurotropism of the mumps virus. This is significantly more prevalent in males than females for unexplained reasons. CNS manifestations range from asymptomatic cerebrospinal fluid (CSF) pleocytosis (seen in 50% of patients) to a very rare fulminant and potentially fatal encephalitis. Clinical meningitis occurs in 10% to 30% of cases and may occur before, during, after, or in the absence of parotitis. Typical clinical features include headache, vomiting, fever, and nuchal rigidity. The CSF may contain up to 2000 cells/mm^3, predominately lymphocytes, though a predominance of neutrophils may occur early in the disease. Protein levels are normal to mildly elevated, and glucose concentration may be low in up to 30% of patients (more commonly than in other viral meningitides). The CSF abnormalities may lead clinicians to consider bacterial meningitis in the differential diagnosis. Generally, mumps meningitis is benign, with complete recovery and an absence of any sequelae.

Encephalitis is a very rare and much more serious CNS manifestation of mumps. Signs of encephalitis include alteration

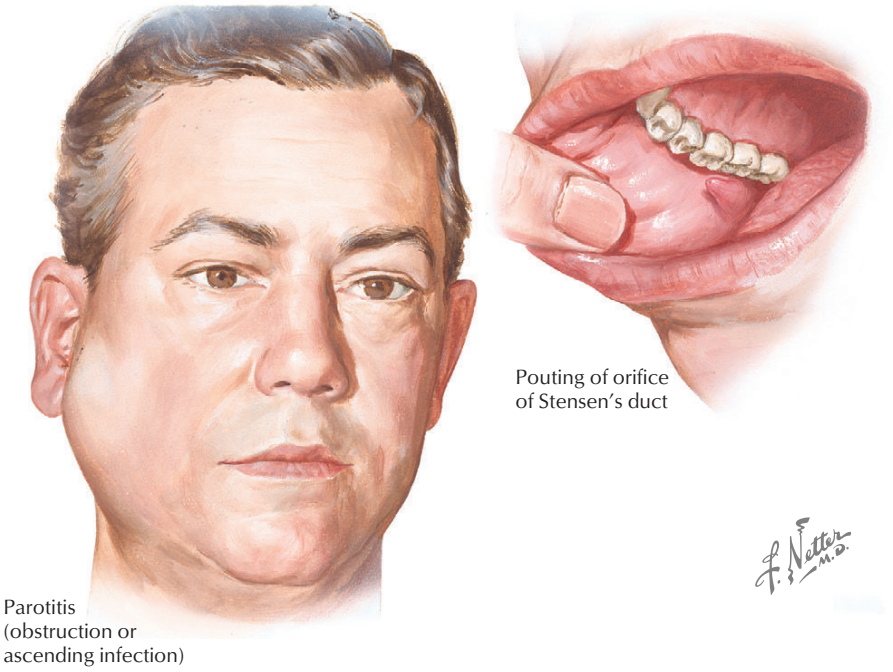

Figure 11-1 Mumps parotitis.

in the level of consciousness, convulsions, paresis, aphasia, and involuntary movements. Mumps encephalitis has a bimodal distribution of onset. There is an early group in which onset coincides with the presence of parotitis and a larger later group in which the condition develops 7 to 10 days after the onset of parotitis. Early-onset encephalitis represents direct damage to neurons as a result of viral invasion, whereas late-onset disease is considered to be a postinfectious process related to the host immune response. The CSF findings are similar to those of mumps meningitis. The neurologic manifestations usually resolve over a period of 1 to 2 weeks; however, a small minority of patients have significant neurologic sequelae, and death can occur. In countries without vaccination, mumps can be a significant cause of viral meningitis and encephalitis.

Cerebella ataxia, facial palsy, transverse myelitis, Guillain-Barré syndrome, and a poliomyelitis-like syndrome have rarely been associated with mumps. Aqueductal stenosis resulting in hydrocephalus has developed after CNS infection caused by mumps.

Epididymo-orchitis and Oophoritis

Epididymo-orchitis is the most common extrasalivary gland manifestation of mumps in adults but is rare before puberty. It develops in 20% to 30% of postpubertal males with mumps and is bilateral in about 15%. Most cases occur during the first week of parotitis, but it may precede parotitis or be the only manifestation of mumps. Physical examination reveals a warm, swollen, tender testicle and erythema of the scrotum accompanied by fever, headache, nausea, and vomiting. The testicular swelling usually resolves in 7 to 10 days, but residual tenderness may persist for several weeks. Mumps orchitis is often associated with significant anxiety and fear of sexual impotence or sterility; however, these complications rarely occur. Some degree of testicular atrophy occurs in about half of the patients with epididymo-orchitis months to years after the infection. In men with unilateral epididymo-orchitis, a slight cosmetic imbalance in testicular size may occur.

Oophoritis develops in about 5% of postpubertal women with mumps. Symptoms of fever, nausea, and lower abdominal pain are frequent. Rarely, reduced fertility and premature menopause have been reported as a consequence. Some postpubertal women with mumps complain of swelling and pain in their breasts consistent with mastitis.

Pancreatitis

Pancreatitis is an uncommon and severe complication of mumps that causes fever, nausea, vomiting, and severe epigastric pain. There is considerable controversy surrounding the relationship of mumps with juvenile diabetes mellitus. Although mumps virus has been shown to infect beta cells from pancreatic islets in vitro, no evidence of infection has been demonstrated in vivo. Many reports of temporal association of diabetes mellitus after mumps have been described, albeit occurring months to years after mumps infections.

Other Associated Conditions

Along with arthritis and arthralgia, myocarditis, and deafness, other rare associations with mumps infection include nephritis, hepatitis, thyroiditis, thrombocytopenia, and ocular complications (e.g., iritis, keratitis, and central retinal vein thrombosis).

ARTHRITIS AND ARTHRALGIA

Mumps may be associated with arthritis or arthralgia infrequently in adults and very rarely in children. Migratory polyarthritis is the most common manifestation, but monarticular arthritis and arthralgia have been reported. Both large and small

joints may be involved. Symptoms usually appear 10 to 14 days after the onset of parotitis and may last several weeks. Mumps virus has not been isolated from joint fluid, and no evidence of immune complex deposits has been detected, so the cause of the arthritis is uncertain. The process usually resolves spontaneously without any joint damage.

MYOCARDITIS

Electrocardiographic changes occur in up to 15% of patients with mumps, these being depressed ST segments, flattened or inverted T waves, and prolonged PR intervals. Clinical myocarditis is rare; however, deaths have been reported.

DEAFNESS

Sensorineural hearing loss caused by cochlear damage from the mumps virus can occur infrequently, with an incidence of 0.5 to 5 cases per 100,000 cases of mumps. Deafness may have an abrupt or gradual onset, is often unilateral, and may be transient or more commonly permanent. Vertigo is a common accompaniment.

Congenital Infection

An increase in fetal death and spontaneous abortion has been documented in pregnant women with mumps in the first trimester of pregnancy, but no significant increase in fetal loss has been noted with infections in the second or third trimesters. Mumps infection during pregnancy does not result in congenital abnormalities of the fetus. Mumps virus is excreted in breast milk. The incidence of perinatal mumps in infants of mothers with mumps is extremely rare, and the low incidence is thought to be a result of the protective effect of transplacental maternal antibodies.

DIAGNOSIS

Clinical Findings

Diagnosis of mumps is usually based on the history of exposure and physical examination findings of parotid swelling and tenderness accompanied by fever and malaise. However, a variety of other infectious and noninfectious causes of acute parotid swelling can be confused with mumps. Parainfluenza 3, coxsackieviruses, cytomegalovirus, and influenza A have all been associated with parotid swelling. Bilateral parotid swelling can also occur in human immunodeficiency virus (HIV) infection. Noninfectious causes of bilateral parotid swelling include medications, diabetes mellitus, malnutrition, uremia, and metabolic disorders. Acute bacterial infection of the parotid, as well as noninfectious causes such as tumors, cysts, and ductal obstruction, are usually associated with unilateral parotid swelling.

Laboratory Diagnosis

BLOOD ABNORMALITIES

Serum amylase is often elevated in mumps, indicating inflammation of the salivary glands or pancreas. The origin of the amylase can be determined by isoenzyme analysis or by determining pancreatic lipase. Amylase in the presence of parotitis may remain elevated for 2 to 3 weeks after resolution of symptoms.

The peripheral white blood cell and differential counts are usually normal; however, mild leukopenia with a relative lymphocytosis may be seen. In patients with evidence of meningitis, epididymo-orchitis, or pancreatitis, a leukocytosis with polymorphonuclear predominance may be noted.

SEROLOGY

Laboratory confirmation of a typical case of mumps is often unnecessary but may be useful in some settings. In areas with high vaccine coverage, the disease is uncommon, and clinicians may be less familiar with the manifestations. The diagnosis of mumps is confirmed with serology by detection of mumps immunoglobulin M (IgM) antibodies using enzyme-linked immunosorbent assay (ELISA). Alternatively, seroconversion from negative to positive or a fourfold rise in mumps IgG antibody titers between acute and convalescent sera, measured using complement fixation, hemagglutination inhibition, or neutralization assays, can confirm the diagnosis. Of note, hemagglutination inhibition tests can have significant cross-reactivity with other infectious agents, particularly with parainfluenza viruses.

VIROLOGY

Virus isolation is the definitive method to diagnose mumps. It is advisable to discuss viral cultures with the laboratory, especially in regions where mumps is rare, as cell cultures may not be readily available. The virus can be isolated from saliva and urine, as well as from CSF in patients with clinical meningitis. Mumps viral ribonucleic acid (RNA) can also be detected by reverse transcription–polymerase chain reaction (RT-PCR) from throat or CSF specimens.

CLINICAL MANAGEMENT

The treatment for mumps parotitis or orchitis is symptomatic and supportive. There is no specific antiviral therapy available.

PREVENTION AND CONTROL

Infection Control Precautions

Infected individuals should be considered contagious for 5 days after the onset of parotid swelling. Hospitalized patients with mumps should be maintained with droplet precautions for 5 days after onset of parotid swelling to prevent spread to susceptible individuals.

Vaccination

Active immunization with a live-attenuated mumps vaccine, usually administered as measles, mumps, and rubella (MMR) vaccine, elicits protective levels of mumps neutralizing antibodies in more than 90% of recipients after one dose. Significant adverse reactions to vaccination are rare, but parotitis, orchitis,

and fever have been reported. Aseptic meningitis occurs in less than 0.3% of vaccine recipients. Individuals with known anaphylactic reactions to neomycin or gelatin should receive mumps-containing vaccines in a setting that can manage such reactions and only after consultation with an allergist. A desensitization protocol may be used before vaccination if required. Individuals with egg allergies are at very low risk of anaphylactic reactions, as mumps vaccines are produced in chicken embryo cells, which contain little ovalbumin.

Routine vaccination is recommended for children at 12 to 15 months of age, after loss of transplacentally acquired maternal antibodies. Most Western countries also recommend a second vaccination with MMR vaccine at 4 to 12 years of age, primarily to prevent measles. This has also resulted in decreasing the risk of mumps vaccination failure. From 2002 to 2007, mumps outbreaks were reported in both the United States and United Kingdom, predominantly involving young adults. A significant minority of affected individuals had received two MMR vaccinations, indicating that vaccine-induced immunity to mumps may wane with time, leaving populations susceptible to outbreaks.

Because it is a live-attenuated viral vaccine, mumps vaccine should not be administered to pregnant women, individuals who have received immunoglobulin or a blood product in the preceding 3 months, patients receiving immunosuppressive therapy or who have congenital or acquired immunodeficiency, patients with advanced malignancy, or individuals with an intercurrent febrile illness. Individuals with HIV infection who are not severely immunocompromised may be immunized with mumps or combined MMR vaccines.

Mumps vaccine given to an immune-susceptible individual postexposure has not been shown to be protective but will provide protection for subsequent exposures. Passive protection for exposed susceptible persons has been provided using mumps immunoglobulin, but this is no longer commercially available in the United States.

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Rubella

Alison Margaret Kesson

12

ABSTRACT

Rubella virus is a positive single-stranded ribonucleic acid (RNA) virus belonging to the family Togaviridae and is the only member of the genus *Rubivirus*. Rubella (German measles) is an acute viral infection that can affect people in all age groups. When acquired postnatally, it is characterized by a generalized maculopapular rash, low-grade fever, and lymphadenopathy and resembles a mild case of rubeola (measles). Many infections with rubella are very mild or even subclinical; however, it may cause arthritis, especially in adolescent and adult females. When infection occurs in the developing fetus, it has the potential to cause severe infection with resultant birth defects (congenital rubella syndrome [CRS]). No specific antiviral treatment is available for rubella, and control is primarily through use of a live-viral vaccine administered during childhood.

GEOGRAPHIC DISTRIBUTION

In the prevaccine era, rubella occurred globally, with minor epidemics every 6 to 9 years. Large-scale epidemics occurred at intervals of up to 30 years; the most recent major pandemic in the western world occurred in 1964. Since 1969, with availability of rubella vaccine, no major epidemics have occurred in countries with widespread use of the vaccine. The World Health Organization (WHO) estimates that there are over 100,000 cases of CRS annually, with most cases occurring in developing nations in which rubella vaccination is not routinely used.

PATHOGENESIS

Transmission of rubella virus is by droplets that are shed from respiratory secretions of infected persons. Incubation for rubella appears to be related to the size of the inoculum and ranges from 12 to 23 days with an average of 18 days. Initial infection of the nasopharyngeal epithelium is followed by lymphatic spread to the regional lymph nodes and transient viremia. Maximal viremia and viruria occur 10 to 17 days after infection. The rash usually appears 16 to 18 days after infection, with antibody production being detected at the time of clearance of the viremia. Maximal viral transmission occurs from 5 days before through 6 days after the onset of the rash.

Few data assessing the pathologic findings in postnatal rubella are available. In contrast, extensive pathologic studies have been performed for CRS, though most were completed before the availability of contemporary molecular techniques. Defects caused by CRS result from both specific cell damage and a decrease in the number of cells.

Infants with congenital rubella infection shed large quantities of the virus from body secretions for many months or years after birth, and they may transmit infection to susceptible contacts. Persons who are vaccinated against rubella may transiently excrete rubella virus from the pharynx, but they do not transmit the rubella to others, likely because the quantity of virus shed is small.

Rubella infection confers lifelong protection in most people. However, despite persistence of specific immunity to rubella virus, reinfection can occur. The majority of reinfections are asymptomatic. Rubella reinfection months to years after rubella vaccination has been observed and is more common among vaccinees than individuals who have experienced natural infection. This may be because of lower concentrations of antibodies in persons with vaccine-induced immunity than in those with natural immunity. Rubella reinfection during pregnancy has been documented to cause CRS in the fetus; however, this is an extremely rare event.

RISK FACTORS

The age of an infected individual is an important determinant of severity of rubella, with children being more likely to have milder disease than adults. In contrast, the fetus is at high risk of development of serious sequelae if infected early in pregnancy.

Rubella is only moderately contagious when compared with measles. Before the introduction of the rubella vaccine, only 80% to 90% of adults were immune to rubella compared with 98% who were immune to measles. This allowed for a significant number of susceptible adults and thus the frequent occurrence of CRS. After introduction of the rubella vaccine, a significant decrease in the population of susceptible adults and the number of CRS cases has been observed.

CLINICAL FEATURES

Postnatal Rubella

Generally, postnatal rubella is a mild illness and the major clinical manifestations are lymphadenopathy, which may last several weeks, and rash. The lymph nodes most commonly involved include the posterior auricular, posterior cervical, and suboccipital chains. Splenomegaly can occur rarely. Sometimes called "3-day measles," clinically the disease may resemble a mild case of measles (rubeola). The rash of rubella begins on the face and moves down the body and is maculopapular, but unlike measles is not confluent and may desquamate during convalescence (Figure 12-1). The rash may be absent in some cases, but the presence and distribution of lymphadenopathy may suggest the diagnosis. An enanthem consisting of petechial lesions of the soft palate (Forschheimer spots) has been described with rubella, but this is not diagnostic. The rash may be accompanied by mild coryza and conjunctivitis and usually lasts 3 to 5 days. Fever is

present but rarely lasts beyond the first day of rash. Arthritis and arthralgia have been reported in as many as one third of adult women with rubella but is much less common in children and in men. The arthritis tends to involve fingers, wrists, and knees and may be slow to resolve, lasting up to 1 month, but rarely becomes chronic.

In addition to measles, other diagnostic considerations include scarlet fever, roseola, parvovirus B19 infection, infectious mononucleosis, toxoplasmosis, some enteroviral infections, Kawasaki disease, rheumatologic disorders, and allergic reactions.

The majority of postnatal rubella cases resolve without problems. Hemorrhagic manifestations are an uncommon complication of rubella and may be secondary to thrombocytopenia and vascular damage. Thrombocytopenia, which is more common in children than in adults, may last from weeks to months and may cause serious problems if bleeding occurs in vital areas (e.g., brain, kidney, or eye). Thrombocytopenic purpura has also been reported.

Encephalitis and postinfectious encephalopathy are extremely rare complications of rubella. Central nervous system involvement is more frequent in adults than in children, and most survivors have no sequelae. The neurologic symptoms appear abruptly from day 1 to 6 after the rash and include headache, vomiting, lethargy, nuchal rigidity, and generalized seizures often accompanied by encephalographic abnormalities. Cerebrospinal fluid is characterized by pleocytosis, mildly elevated protein, and normal glucose concentrations.

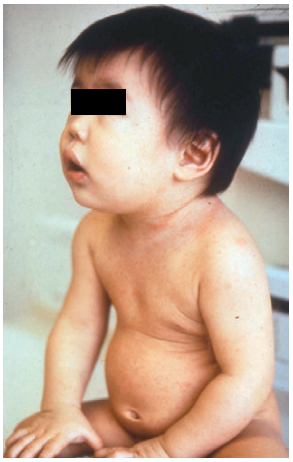

Figure 12-1 Child with rubella rash. *(Courtesy Centers for Disease Control and Prevention Public Health Image Library.)*

Congenital Rubella Syndrome

The connection between maternal rubella infection and some birth defects was first described in 1941 by Gregg. Congenital rubella infection can cause fetal death, premature delivery, and an array of congenital defects. In general, the younger the fetus when infected, the more severe the injuries observed. Infection during the first 2 months of gestation has a 65% to 85% chance of affecting the fetus with an outcome of multiple congenital defects, spontaneous abortion, or both. Rubella during the third month of gestation has been associated with a 30% to 35% chance of developing a single defect, such as deafness or congenital heart disease. Infection in the fourth month carries a 10% risk of a single congenital defect, and this risk continues until 20 weeks of gestation.

Specific signs and symptoms of CRS can be classified as either temporary (e.g., low birth weight), permanent (e.g., deafness), or developmental (e.g., myopia) (Table 12-1). The most common manifestations are growth retardation, deafness, cataracts or glaucoma, congenital heart disease, and intellectual handicap. The characteristic rash occurs in about 5% of cases and results from dermal erythropoiesis; this has been called "blueberry muffin syndrome" (Figure 12-2). CRS should not be considered a static disease. Delayed manifestations include progressive encephalopathy (which resembles subacute sclerosing panencephalitis of measles), deafness, and endocrinopathies. The development of insulin-dependent diabetes mellitus in late childhood has been observed in approximately 20% of individuals with CRS. Autoimmune thyroid dysfunction has also been described.

DIAGNOSIS

Because of the features and nonspecific nature of the illness, both congenital and postnatal rubella infection can often be difficult to diagnose clinically. Virus isolation from the throat,

Table 12-1 Features of Congenital Rubella

PERMANENT	TRANSIENT	DEVELOPMENTAL
Hearing loss	Low birth weight	Hearing loss
Cataract and microphthalmia	Thrombocytopenic purpura	Myopia
Retinopathy	Hepatosplenomegaly	Intellectual handicap
Patent ductus arteriosus	Jaundice	Pulmonary stenosis
Pulmonary stenosis	Hepatitis	Central language disorders
Intellectual handicap	Pneumonitis	Diabetes mellitus
Behavioral disorders	Lymphadenopathy	Thyroid disorders
Central language disorders		Seizures
Cryptorchidism		Behavioral disorders
Inguinal hernia		
Diabetes mellitus		
Thyroid disorders		

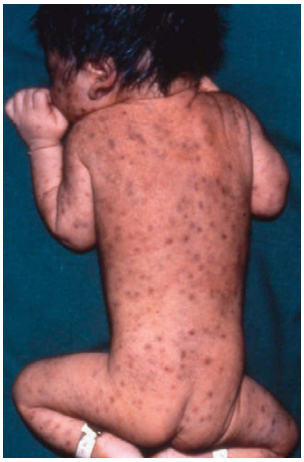

Figure 12-2 Congenital rubella syndrome and "blueberry muffin" rash.

urine, synovial fluid, or other secretions is diagnostic. In utero diagnosis of congenital rubella infection has been made by isolation of the virus from amniotic fluid. However, viral culture may take several weeks, making diagnosis retrospective. If viral culture is considered, it is advisable to discuss this with the laboratory before obtaining the samples, as tissue culture cells may not routinely be available. More recently, molecular methods such as reverse transcription–polymerase chain reaction (RT-PCR) are preferred to virus isolation, as they are rapid and more sensitive.

Laboratory diagnosis of postnatal rubella is usually made serologically by detection of antibodies using hemagglutination inhibition (HAI) assay, which is considered to be the assay standard. More recently, latex agglutination or enzyme-linked immunosorbent assay (ELISA) techniques, which detect either rubella immunoglobulin G (IgG) or IgM antibodies, have become available and are technically easier to perform. Acute postnatal infection may be diagnosed by demonstration of rubella IgM or a fourfold or greater increase in rubella IgG antibody titer between acute and convalescent serum specimens. Positive rubella IgM antibody tests are diagnostic of recent primary postnatal infection, but they can also rarely have positive results in patients who have reinfection with rubella virus.

A demonstration of rubella IgG is evidence of immunity to rubella. The true protective level of rubella IgG antibodies against reinfection has not been determined. Thus revaccination before pregnancy for women of childbearing age with low rubella IgG titers (less than 40 international units per milliliter) is commonly recommended.

For CRS in a newborn infant, serologic diagnosis can be made with serial testing showing a rise in the titer of rubella IgG rather than the expected fall with passively acquired maternal antibodies. The detection of rubella IgM antibodies in newborn infant serum is diagnostic of congenital infection, as this antibody does not cross the placenta. Congenital rubella infection can also be diagnosed by placental biopsy at 12 weeks with demonstration of rubella antigen or detection of RNA by in situ hybridization or PCR. It may also be diagnosed by the presence of specific IgM in fetal blood, but this is usually not detectable until at least 22 weeks of gestation.

TREATMENT

No specific therapy for rubella is available, and because postnatal rubella is a mild illness, treatment is usually not indicated. Individuals with arthralgia or arthritis may need symptomatic treatment with rest and nonsteroidal antiinflammatory agents. No treatment is available for infants with CRS.

PREVENTION AND CONTROL

Infection Control

Hospitalized patients with rubella should be maintained with procedures for droplet precautions to prevent the spread of infection to susceptible individuals. Individuals with postnatal rubella should be excluded from activities until 7 days after the onset of rash. Infants with CRS should be considered infectious until they are at least 1 year of age or have demonstrated two negative viral cultures after 3 months of age.

Vaccination

Active immunization for rubella is with a live-attenuated vaccine either as the trivalent measles, mumps, and rubella (MMR) vaccine or, in some countries, as a monovalent rubella vaccine. The rationale for the use of the vaccine is to prevent congenital rubella by control of postnatal rubella. This approach has been very successful, and universal immunization of populations against rubella has led to a significant decrease in the incidence of CRS. Immunization with rubella vaccine may cause a mild transient viremia. Although uncommon, the main complications of vaccination are fever, lymphadenopathy, arthritis, and arthralgia. Seroconversion after rubella vaccination is approximately 95%, and booster injections of rubella vaccine are not routinely indicated but may be advised for women of childbearing age who have less than 40 international units per milliliter of IgG antibodies. No cases of CRS have been attributed to rubella vaccination; however, vaccination during pregnancy is contraindicated. If a pregnant woman is inadvertently vaccinated with rubella vaccine, termination of pregnancy is usually not recommended because of the very low theoretical risk of CRS.

Administration of immunoglobulin after a known rubella contact is not advocated for prevention or modification of rubella in susceptible pregnant women, as there is no evidence that it protects the fetus against congenital infection.

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Varicella-Zoster Virus Infections

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13

ABSTRACT

Varicella-zoster virus (VZV) causes primary varicella, a common childhood illness called *chickenpox*. This virus establishes latency and may reactivate later in life causing herpes zoster, commonly called *shingles*. Although both varicella and zoster usually resolve without event, significant complications may develop, even in healthy individuals. In the United States, widespread use of a VZV vaccine in children has diminished the burden of disease; however, worldwide VZV infections remain a significant cause of morbidity and mortality.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

VZV is a member of the Herpesviridae family, and initial infection (varicella) is commonly called *chickenpox*. Varicella is present worldwide and is common in areas without routine vaccination. Seasonal epidemics occur with peaks in late winter and spring. In the United States, before the introduction of routine vaccination in 1996, approximately 4 million cases of chickenpox occurred each year. Most individuals were infected by adolescence, and the peak age of onset was 4 to 5 years of age. Attack rates are lower in tropical areas, where a greater proportion of adolescents and adults are susceptible.

After chickenpox the virus remains latent in the dorsal root ganglia and can reactivate, causing herpes zoster, commonly referred to as *shingles*. Herpes zoster is infrequent in children, but persons older than 60 years of age have an incidence of 7.2 to 11.8 cases per 1000 population per year, increasing with advancing age.

RISK FACTORS

VZV is highly transmissible, with attack rates of nearly 90% among susceptible household contacts but only 10% to 30% among susceptible persons with casual contact (e.g., classroom or hospitals). Individuals with impaired immunity are at increased risk for severe disseminated disease caused by VZV, including complications of pneumonitis and hepatitis, which rarely may lead to hepatic failure. Adolescents and adults, pregnant women, and neonates born within 2 days before or 4 days after onset of maternal varicella are also at risk for progressive disease.

CLINICAL FEATURES

Varicella (Chickenpox)

The incubation period for primary VZV infection ranges from 10 to 21 days. Once infected, persons are contagious (via respiratory droplets and direct contact) for 1 to 2 days before the onset of rash until all lesions have crusted (usually 5 to 7 days). For 24 to 48 hours before the rash, constitutional symptoms such as fever, malaise, anorexia, headache, and mild abdominal pain may be present. Cutaneous lesions develop first on the scalp, face, or trunk and then spread to the lower portions of the body. Lesions start as erythematous macules, which then develop into clear fluid–filled vesicles, often described as resembling "dewdrops on a rose petal" (Figure 13-1). These lesions are usually pruritic. After 24 to 48 hours the fluid becomes cloudy, and eventually the lesions crust over. Lesions develop at different intervals such that at any one time, lesions at multiple stages are present. In unimmunized children, primary infection produces fewer than 300 lesions.

Primary varicella infection tends to be more severe in children infected from a household contact (likely because of more intense exposure), as well as in adolescents and adults. Individuals with underlying skin conditions such as eczema, trauma, and sunburn may have higher concentration of lesions at the afflicted sites.

Although primary varicella usually resolves without event, healthy children rarely develop complications. Bacterial superinfection (commonly with *Staphylococcus aureus* or *Streptococcus pyogenes*) is the most common cause of morbidity in healthy children. These children may have impetigo-like lesions, cellulitis, lymphadenitis, subcutaneous abscesses, bacteremia, osteomyelitis, or necrotizing fasciitis. Neurologic complications such as meningoencephalitis or cerebellar ataxia are typically immune mediated, and generally resolve without treatment. Meningoencephalitis is associated with rapid recovery, whereas cerebellar ataxia may take weeks to resolve. Other rare complications include hepatitis, Reye's syndrome, thrombocytopenia, nephritis, and arthritis.

Herpes Zoster (Shingles)

Herpes zoster manifests with an eruption of vesicular lesions in a sensory dermatomal distribution (Figure 13-2). Lesions may erupt over a course of 3 to 7 days, with complete resolution of the rash usually within 2 weeks. The rash is pruritic and may be associated with local pain and hyperesthesia. Zoster is unusual in childhood, but when present the extent of the lesions is limited, with minimal neuropathic symptoms. Risks for developing zoster during childhood include having primary varicella infection in the first year of life and immunocompromising conditions, especially those affecting cellular immunity (e.g., acquired immunodeficiency syndrome, chemotherapy, or prolonged high-dose steroids). In compromised hosts, zoster may disseminate, with lesions occurring outside of the dermatome and involvement of internal organs. Other complications of zoster depend on the dermatome affected.

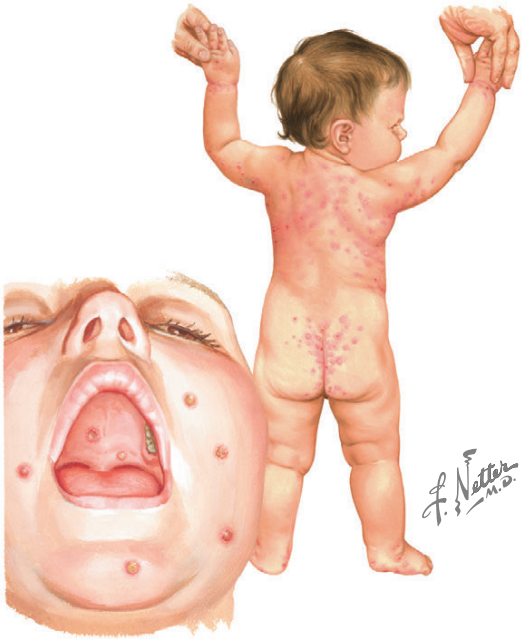


Figure 13-1 Child with chickenpox.

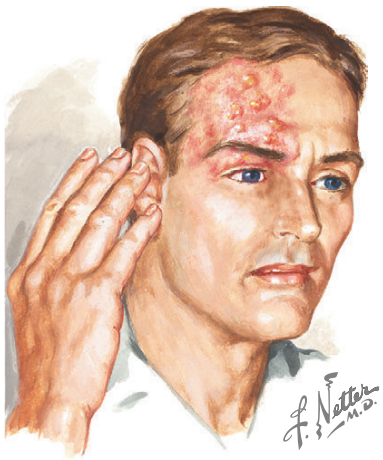


Figure 13-2 Zoster in ophthalamic branch.

Some unique manifestations of herpes zoster occur when the reactivated virus involves nerves of the head and neck. Ramsay-Hunt syndrome occurs when VZV reactivates in the geniculate ganglion and consists of unilateral facial palsy, pain and vesicles in the auditory canal, and lost of taste in the anterior two thirds of the tongue. When zoster involves the ophthalmologic branch of the facial nerve (herpes zoster ophthalmicus) sight-threatening keratitis may develop, necessitating emergent ophthalmologic consultation. Zoster involving the maxillary or mandibular branch of the trigeminal nerve may cause intraoral lesions affecting the palate, tonsillar fossa, tongue, and floor of the mouth.

Pain preceding the rash, acute neuritis, and postherpetic neuralgia are more common with zoster in adults than in children. Approximately 80% to 85% of persons over 50 years of age with zoster will develop postherpetic neuralgia. The pain can be quite debilitating and may last for weeks to months. Early antiviral treatment can ameliorate the severity and duration.

Disease in High-Risk Hosts

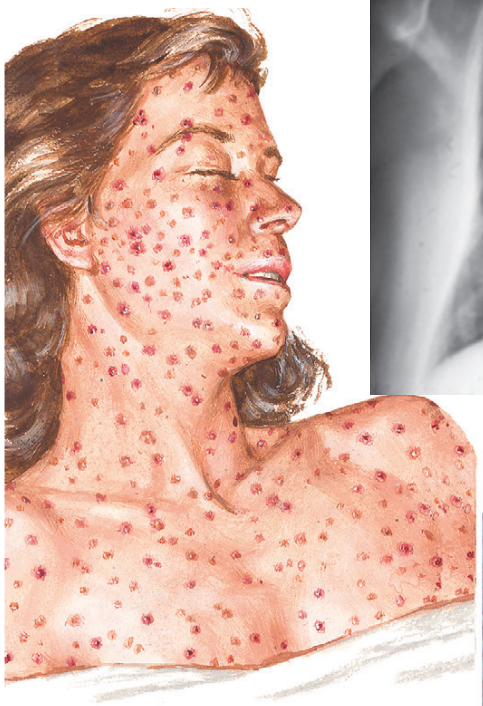
In children with underlying immunodeficiency (congenital or acquired), with hematologic malignancy, or receiving chemotherapy, primary varicella without antiviral therapy is often progressive, manifesting with an extended period of new lesion eruptions, pneumonitis, hepatitis, encephalitis, and/or disseminated intravascular coagulation (DIC) (Figure 13-3). The mortality rate of untreated primary varicella in these hosts ranges from 7% to 17%. Presentations of potentially life-threatening varicella include respiratory symptoms, hemorrhage into a vesicular lesion (indicative of potential DIC), or severe abdominal or back pain.

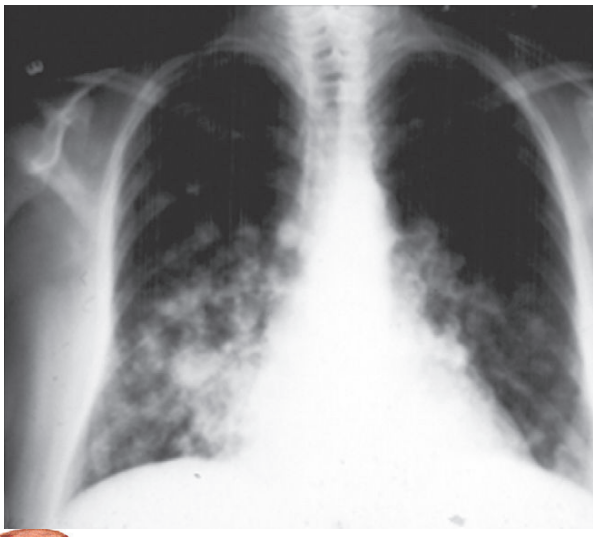
Adolescents and adults are at increased risk for having complicated primary varicella despite being otherwise healthy. In this population the most common complication is varicella pneumonia, which may manifest with cough, pleuritic chest pain, and hemoptysis, with or without cyanosis. This occurs on average 3 days (range of 1 to 6 days) after the onset of the rash. Resolution usually occurs within 24 to 72 hours without antiviral treatment, but varicella pneumonia can progress to respiratory failure.

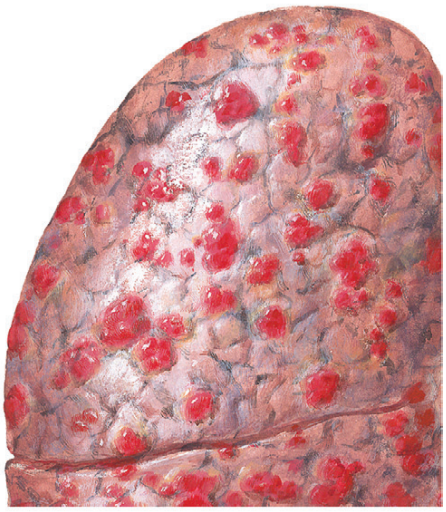
Nonimmune pregnant women are at high risk for adverse outcomes with primary varicella, with pneumonia being the major cause of morbidity and mortality. In addition, severe sequelae to the fetus including spontaneous abortion, fetal demise, or premature delivery can occur. Rarely (less than 2% of cases), maternal varicella can lead to congenital varicella syndrome, the severity of which is dependent on the gestational age at the time of infection. Infection during the first 20 weeks of gestation carries the highest risk of severe embryopathy. Congenital varicella can affect the skin (cutaneous defects, cicatricial scars, hypopigmentation, bullous lesions), the extremities (hypoplastic limb, muscular atrophy and denervation, joint abnormality, absent or malformed digits), eye (chorioretinitis, microphthalmia, anisocoria), the central nervous system (CNS) (intrauterine encephalitis with cortical atrophy, seizures, mental retardation), or other organs (e.g., hydronephrosis or hydroureter and esophageal dilatation or reflux).

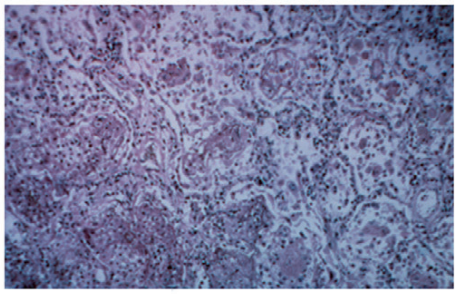
Varicella may also be severe for the neonate born within 2 days before or 4 days after the onset of maternal varicella, with a mortality rate of 30% if untreated. This is a result of the lack of transfer of maternal antibodies with the primary viremia. Neonates born 5 days after the onset of maternal varicella are not at increased risk for severe disease, as maternal antibodies have had the opportunity to cross the placenta.

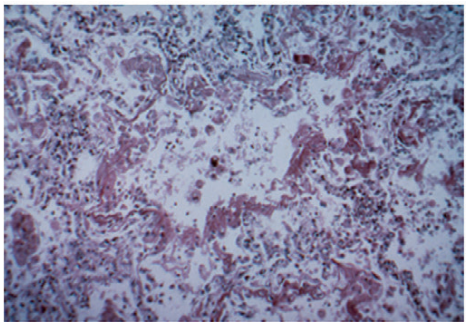
Herpes zoster in immunocompromised hosts can lead to severe dermatomal infection, extension beyond the dermatome, and dissemination. Pneumonia, hepatitis, encephalitis, and DIC may result from hematogenous spread of reactivated virus. Severely immunocompromised hosts such as those with human immunodeficiency virus infection may have chronic or relapsing cutaneous disease, retinitis, and CNS infections with or without skin findings.


Hemorrhagic chickenpox


Varicella pneumonia. Nodular infiltrates in both lower lobes


Pleural hemorrhagic pocks


Pulmonary histology, low power. Alveoli filled with fibrin, fluid, and cellular exudate.


High power: Mononuclear infiltrate in interstitium and fibrin lining alveoli.

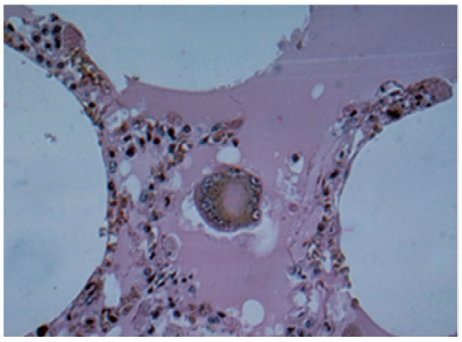

Multinucleated giant cell with much fluid in alveolus.

Figure 13-3 Varicella pneumonia.

DIAGNOSTIC APPROACH

In healthy individuals, primary varicella and zoster are clinical diagnoses. In atypical presentations or in patients with other possible causes of vesicular lesions, laboratory confirmation may be necessary to facilitate initiating appropriate therapy. Vesicular fluid or lesions can be tested for VZV by polymerase chain reaction, direct fluorescent antibody (DFA), or tissue culture. DFA is the most commonly available test and offers better sensitivity than a Tzanck smear. Serologic tests for VZV-specific antibodies are often not useful in the acute phase, because immune globulin M (IgM) anti-VZV antibodies are inconsistently present. If present, IgM anti-VZV antibodies indicate current or recent infection. Acute and convalescent serum specimens may demonstrate a rise in IgG VZV antibodies and may improve sensitivity.

Complete blood count and liver function tests may be indicated when disseminated disease is suspected; however, lymphocytosis and mild hepatic enzymatic elevations are common in uncomplicated disease. When neurologic complications exist, mild cerebrospinal pleocytosis (<100 cells/mm^3) with moderate protein elevation (<200 mg/mL) may be present. Patients with uncomplicated zoster may also have cerebrospinal fluid pleocytosis.

CLINICAL MANAGEMENT

For most healthy children, symptomatic therapy for chickenpox and herpes zoster is all that is required. Antiviral therapy is recommended for adolescents, adults, immunocompromised hosts, and individuals with disseminated disease but is not

routinely recommended for healthy children. The optimal timing of therapy is within the first 72 hours of the onset of the rash. Acyclovir is the most commonly used medication, and the prodrug valacyclovir may be used when oral administration is an option (Table 13-1).

Aspirin should not be used during varicella infections owing to the risk of Reye's syndrome. Symptomatic relief of fever with acetaminophen may be undertaken with careful attention to dosage. Ibuprofen use has been associated with increased rates of necrotizing fasciitis in isolated reports, and therefore this drug should be used cautiously. After weighing risks and benefits, antihistamines and topical calamine lotion may be used for pruritus treatment. Should bacterial superinfection develop, antibiotics that include coverage for group A *Streptococcus* and *S. aureus* (including methicillin-resistant *S. aureus)* based on local epidemiology and sensitivity patterns should be instituted.

For zoster in all age groups, acyclovir reduces the development of new lesions from over 1 week to less than 3 days. In adults, acyclovir treatment may also reduce the likelihood of developing acute neuritis.

PROGNOSIS

For healthy children with primary varicella, the prognosis is good with complete recovery. Although most lesions heal without scarring, many children have one or two scars, typically on the face, as these earlier lesions may involve deeper layers of the skin. For adolescents, adults, pregnant women, and immunocompromised hosts, there is greater risk of morbidity and mortality, but this may be reduced with prompt antiviral therapy.

After herpes zoster, most children do not incur long-term sequelae. Adults, however, may experience postherpetic neuralgia, which may be debilitating and may require treatment targeting pain control.

PREVENTION AND CONTROL

Individuals with varicella should be considered contagious until all lesions are crusted. Hospitalized patients should be maintained with airborne precautions. Children should be excluded from school or daycare. Persons with zoster do not need to be isolated if the lesions can be covered. Healthcare workers without evidence of immunity who have been exposed to varicella should not be in the hospital setting from days 8 to 21 after exposure or for 28 days if they received VariZIG.

Active Immunoprophylaxis: Vaccination

Currently in the United States a live-attenuated varicella vaccine (Varivax, Merck & Co., Inc.) is recommended for use in all children; a two-dose regimen is used, with vaccine given at 12 to 15 months and 4 to 6 years of age. After licensure in 1995, widespread vaccination at 12 to 15 months of age led to a dramatic decline in primary varicella. However, from 2001 to 2005, breakthrough cases of chickenpox began to occur, peaking in children aged 7 to 10 years. Although most of these cases were mild, typically with fewer than 50 lesions, they posed a risk to the children and their susceptible contacts. Therefore in 2007 the addition of the second dose of vaccine at 4 to 6 years of age was recommended, after postlicensure data suggested a reduction of breakthrough disease in this preadolescent age group.

Because it is a live virus, VZV vaccine is contraindicated in persons with altered immunity and in pregnant women. Varicella vaccines should not be given to persons on high-dose immunosuppressive therapy including systemic steroids (≥2 mg of prednisone per kilogram or total ≥20 mg of prednisone per day or equivalent for ≥2 weeks). In 2009, no combination varicella-containing vaccines were available in the United States. A combination varicella with measles, mumps, and rubella

Table 13-1 Recommendations and Doses of Acyclovir for Varicella

RECOMMENDATION	DOSAGE	TIMING
Indicated: • Malignancy, bone marrow, or organ transplant, high-dose steroid therapy • Congenital T-lymphocyte immunodeficiency • HIV infection • Neonatal varicella (maternal varicella within 5 days after or 2 days before delivery) • Associated pneumonia or encephalitis	Intravenous acyclovir: • <1 year old: 30 mg/kg/day divided q8h, infusion to run over 1 hour • ≥1 year old: 1.5 g/m^2/day divided q8h, infusion to run over 1 hour	Initiate as soon as possible after initial lesions Treat for 7 days or until 48 hours after no new lesions
Optional: • Chronic mucocutaneous disorders • Chronic diseases that may be exacerbated by acute VZV infection* • Healthy persons >12 years of age or secondary household contacts	Oral acyclovir†: • 80 mg/kg/day divided into four doses (max 800 mg/dose)	Initiate within 24 hours after initial lesions appear Treat for 5 days

HIV, Human immunodeficiency virus.
*These conditions may include cystic fibrosis, other pulmonary disorders, diabetes mellitus, disorders requiring chronic salicylate therapy or intermittent corticosteroid therapy.
†Valacyclovir may be used.

Box 13-1 Situations for Consideration of Postexposure Antibody Prophylaxis

Candidates for VariZIG with Significant Exposure
- Susceptible immunocompromised children
- Susceptible pregnant women
- Newborn infant whose mother had onset of chicken pox within 5 days before delivery or within 48 hours after delivery
- Hospitalized preterm infant (≥28 weeks gestation) of mother without evidence of varicella immunity
- Hospitalized preterm infant (<28 weeks gestation or ≤1000 g birth weight), regardless of maternal immunity status

Situations Qualifying for Significant Exposure
- Residing in the same household
- Face-to-face indoor play lasting at minimum 5 minutes (some experts use 1 hour)
- Hospital varicella exposure: same 2- to 4-person bedroom or adjacent beds in a large ward
- Hospital zoster exposure: intimate contact (e.g., touching or hugging) a person considered to be contagious

vaccine is available in the European Union and is being evaluated for licensure in the United States.

In 2006, Zostavax (Merck & Co., Inc.) was licensed for adults 60 years of age and older to reduce the risk of zoster and expressly to prevent postherpetic neuralgia (67% efficacy in preventing postherpetic neuralgia and 73% efficacy in preventing postherpetic pain lasting more than 6 months). Zostavax differs from Varivax in that it contains up to a 14 times greater amount of live-attenuated VZV. Zostavax is contraindicated in persons with primary or acquired immunodeficiency.

Postexposure Prophylaxis

VACCINATION

VZV vaccine can be given to susceptible individuals after exposure to varicella, if not otherwise contraindicated. Postexposure vaccination should be given within 3 days but can be given up to 5 days after exposure and may reduce the likelihood of disease or its severity.

PASSIVE IMMUNOPROPHYLAXIS

VariZIG, an investigational high-titer VZV immune globulin, is available in the United States through a new drug expanded access program. High-risk individuals for whom VariZIG should be considered are listed in Box 13-1. VariZIG should be administered within 96 hours of the exposure. If VariZIG is not available, intravenous immune globulin (IVIG) may be given to high-risk individuals postexposure, though the amount of varicella-specific antibody in different preparations of IVIG varies. Although no longer available, varicella-zoster immune globulin protected against development of primary varicella or attenuated the course, when given within 48 hours of exposure.

CHEMOPROPHYLAXIS

Prophylactic use of acyclovir given within 7 days after exposure may help prevent or attenuate varicella disease for susceptible immunocompromised individuals when active or passive immunization is not possible.

EVIDENCE

Coffin SE, Hodinka RL: Utility of direct immunofluorescence and virus culture for detection of varicella-zoster virus in skin lesions, *J Clin Microbiol* 33:2792-2795, 1995. *This reference provides comparative data for the DFA and culture of VZV.*

Kuter B, Matthews H, Shinefield H, et al: Ten-year follow-up of healthy children who received one or two dose injections of varicella vaccine, *Pediatr Infect Dis J* 23:132-137, 2004. *This reference provides data about the postlicensure follow-up of clinical trial participants for varicella vaccine and incidence of breakthrough varicella.*

ADDITIONAL RESOURCES

American Academy of Pediatrics (AAP): Varicella-zoster infections. In Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds: *Red Book: 2009 Report of the Committee on Infectious Diseases*, ed 28, Elk Grove Village, Ill, 2009, AAP, pp 714-727. *This resource provides an overview of the diagnosis, treatment, and prevention of VZV infections.*

Arvin A: Varicella-zoster virus. In Long SS, Pickering LK, Prober CG, eds: *Principles and practice of pediatric infectious diseases*, ed 3, Philadelphia, 2008, Churchill Livingstone, pp 1021-1029. *This resource provides a review of the virology, diagnosis, and treatment of VZV infections.*

Harpaz R, Ortega-Sanchez IR, Seward JF; Advisory Committee on Immunization Practices (ACIP) Centers for Disease Control and Prevention (CDC): Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm Rep* 57:1-29, 2008. *This resource provides recommendations for the prevention of herpes zoster.*

Marin M, Güris D, Chaves SS, et al; Advisory Committee on Immunization Practices, Centers for Disease Control and Prevention (CDC): Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm Rep* 56:1-39, 2007. *This resource provides recommendations for the prevention of varicella infections.*

Hepatitis A Infection and Prevention

Dean A. Blumberg

14

ABSTRACT

Hepatitis A infection is one of the most commonly reported vaccine-preventable diseases in the United States. Clinical illness, characterized by fever, malaise, jaundice, and nausea, caused by hepatitis A virus (HAV) is similar to hepatitis caused by other viral pathogens. Although most cases of hepatitis A are self-limited, fulminant hepatitis resulting in death may occur. Widespread routine childhood vaccination against hepatitis A has resulted in an impressive decrease in hepatitis A infections, with a notable diminishment of previous racial or ethnic and geographic disparities.

ETIOLOGY

Hepatitis A infection is caused by HAV, a ribonucleic acid (RNA) virus in the genus *Hepatovirus* within the family Picornaviridae. HAV is an icosahedral-shaped nonenveloped virus that replicates in the cytoplasm. The genome consists of single-stranded RNA that encodes information for 11 individual proteins. There are four closely related genotypes of human HAV strains but only one major serotype.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Approximately 1.5 million clinical cases of hepatitis A occur each year worldwide, and the prevalence of antibodies (indicating previous infection) in the population can vary from 15% to almost 100% in some countries. Nordic countries show the lowest prevalence of infection, approximately 15%. In other parts of Europe, Australia, Japan, and the United States, the seroprevalence of antibodies to HAV is 30% to 70% in adults. In developing areas of the world, most adults show serologic evidence of past infection (see Figure 67-1).

In the United States the incidence of hepatitis A has reached historic lows since the late 1990s, when hepatitis A vaccines became more widely used. However, hepatitis A remains one of the most frequently reported vaccine-preventable diseases in the United States, with about 22,700 cases representing 38% of all hepatitis cases (5-year average from all routes of transmission) reported annually. In general, the incidence of hepatitis A in the United States has been cyclic, with nationwide increases occurring every 10 to 15 years. The last peak occurred in 1995, with the decline in rates likely attributable to wider routine use of hepatitis A vaccines (Figure 14-1). Historically, higher rates of hepatitis A have occurred in the western United States, but this geographic variation is no longer present.

RISK FACTORS FOR INFECTION

HAV is most commonly contracted via ingestion. After a brief viremia, the primary site of replication is the liver, and the virus is shed into the bile with subsequent passage to the intestines and feces. The highest concentration of virus in the stool, and thus the period of greatest infectivity, occurs during the 2 weeks before onset of symptoms. Infected stools result in transmission to others, through either ingestion of contaminated water or food or person-to-person contact. An outbreak of hepatitis A infection can be caused by a combination of these factors—for example, contaminated food may infect restaurant patrons and employees, who then are the source for further transmission into their larger communities.

Children are most at risk for infection. They are at increased risk for acquiring infection from fecal oral pathogens, including HAV, because they have limited proficiency with personal hygiene and toileting habits and because of their propensity to explore the environment with their mouths. Because most infected children have asymptomatic or unrecognized infection, they can play a major role in community outbreaks.

Epidemics may occur locally or nationwide, often related to food-borne outbreaks. With more frequent international travel and global food production, hepatitis A can readily spread beyond the regions of known high endemicity to any area of the world. In communities with high rates of hepatitis A, most people are infected before reaching young adulthood. In the United States, communities with high rates of infection include Alaskan Native, American Indian, and selected Hispanic, migrant, and religious communities, although in recent times these elevated rates are less pronounced, likely because of widespread vaccination (Figure 14-2). In communities with low rates of hepatitis A, most infections occur in school-age children, adolescents, and young adults.

HAV may also be transmitted through sexual contact and in rare instances through transfusion of blood products collected from donors during the viremic period. Adults most at risk for infection with hepatitis A include household and sexual contacts of infected individuals, men who have sex with men, individuals in personal contact with a child who attends a daycare center, illicit drug users, and individuals traveling to countries where hepatitis A is common. In the United States,

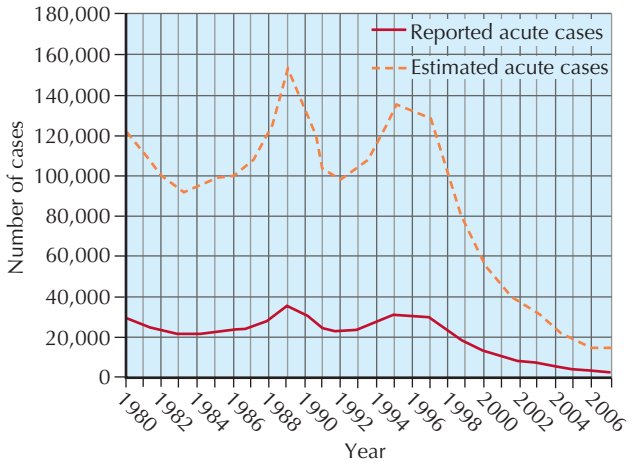


Figure 14-1 Incidence of hepatitis A by year, United States, 1980 to 2007. *(Data from Centers for Disease Control and Prevention. Available at: www.cdc.gov/hepatitis/HAV/StatisticsHAV.htm#section3. Accessed February 6, 2010.)*

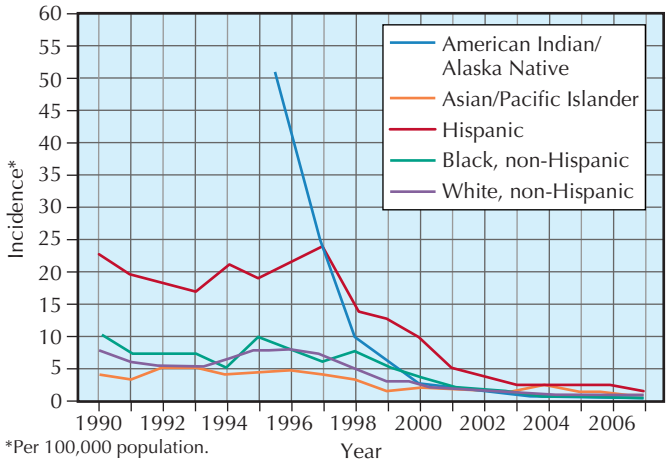


Figure 14-2 Incidence of acute hepatitis A by race or ethnicity and year, United States, 1990 to 2007. *(Data from Centers for Disease Control and Prevention. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/ss5803a1.htm. Accessed February 6, 2010.)*

85% of travel-related cases are associated with travel to Central and South America. Of note, a specific risk factor cannot be determined for more than half of all individuals who acquire hepatitis A infection.

CLINICAL FEATURES

HAV can cause symptomatic or asymptomatic infection. The necessary infectious dose is not known but presumably is 10 to 100 viral particles. Clinical features usually appear after an average incubation period of 28 days, with a range of 15 to 50 days. Symptomatic infection is characterized by a relatively acute onset of symptoms that may include jaundice, weakness, fatigue, myalgia, anorexia, nausea, abdominal pain, fever, clay-colored stools, and/or dark-colored urine. Pruritus is less common. Diarrhea is common in young children (60%) but infrequent in adults. Physical findings can include jaundice, abdominal tenderness, hepatomegaly, or splenomegaly (Figure 14-3).

Symptoms and severity of illness correlate inversely with age. In children younger than 6 years of age, 70% of infections are asymptomatic, and less than 10% of patients will have jaundice. Older children and adults usually develop symptoms. Generally, more than 75% of infected adults are symptomatic, with 50% to 85% exhibiting jaundice.

COMPLICATIONS

No chronic or long-term infection is associated with hepatitis A; however, prolonged or relapsing symptoms for up to 9 months occur in approximately 10% of infected individuals. Infrequent complications of hepatitis A include pancreatitis, triggering autoimmune hepatitis, and cholestatic hepatitis, which is characterized by fever, pruritus, and prolonged elevated bilirubin that can persist for months.

HAV is a rare but important cause of fulminant hepatitis, manifested by increasingly severe jaundice, and deterioration in liver function. This may result in hepatic encephalopathy and coagulopathy, particularly in older adults and individuals with chronic liver disease.

DIAGNOSTIC APPROACH

Clinically, infection with HAV may be indistinguishable from other causes of hepatitis. Hepatitis A can be differentiated from other types of viral hepatitis only through laboratory testing. Serologic testing detects immunoglobulin M antibody to HAV (IgM anti-HAV) starting 5 to 10 days before symptom onset, and these antibodies may be detectable for up to 6 months after infection. Immunoglobulin G antibody to HAV (IgG anti-HAV) also appears early in the course of infection and is detectable for life, denoting immunity to hepatitis A infection.

Other laboratory abnormalities include elevated liver enzymes. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), and γ-glutamyltranspeptidase (GGT) concentrations are elevated before symptom onset, and bilirubin elevation follows. ALT and AST elevations usually range from 200 to 5000 international units per liter and peak at 3 to 10 days after onset of symptoms, though these findings are not specific for HAV infection. Generally with HAV infection, elevated liver function test findings return to normal by 2 to 3 months after the onset of illness. Patients with acute HAV infection usually have a mild lymphocytosis, and occasional atypical mononuclear cells may be seen.

Although polymerase chain reaction (PCR) testing of serum and stool for HAV is a promising diagnostic tool, such tests are not standardized and are not widely available. Liver biopsy is generally not indicated for HAV infection. However, when performed, typical pathology of viral hepatitis is observed, including hepatocellular necrosis, inflammatory cell infiltration, and regeneration of hepatocytes.

Other diagnostic considerations for HAV infection include other viral agents, most commonly hepatitis B and C, but also

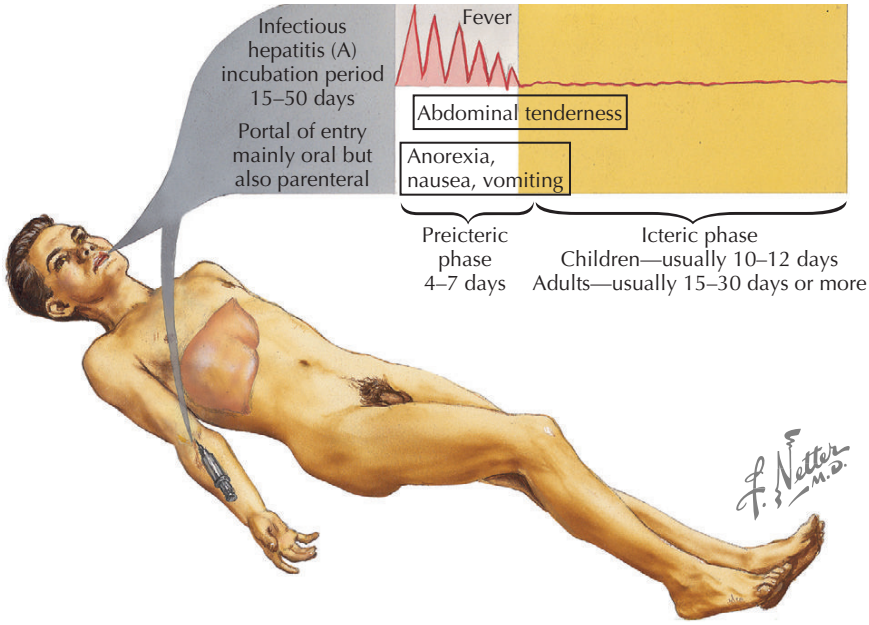


Figure 14-3 Clinical course of hepatitis A.

Epstein-Barr virus (EBV), cytomegalovirus (CMV) and other enteroviruses, and bacterial infections (e.g., leptospirosis). Toxic hepatitis caused by prescribed medications that are metabolized by the liver (e.g., isoniazid, acetaminophen), alcohol, illicit drugs or poisons (e.g., carbon tetrachloride), and nonspecific injury (e.g., ischemia or shock) may also be considered.

CLINICAL MANAGEMENT

There is no specific antiviral treatment for patients with hepatitis A. Supportive care is the mainstay of treatment. Alcohol avoidance is recommended during the acute stage. No other dietary restrictions are recommended. Patients are encouraged to monitor their energy level and increase activities judiciously. Medications that might cause liver damage or are metabolized hepatically should be used with caution (Figure 14-4). Patients with prolonged jaundice and cholestatic hepatitis may benefit from a short course of rapidly tapered corticosteroids, resulting in improved symptoms and resolution of disease.

In general, most individuals infected with HAV can be managed as outpatients. Because nausea and vomiting may lead to inadequate fluid intake, patients should be monitored for dehydration. If dehydration occurs, intravenous fluid administration and hospitalization may be necessary. Infected individuals with signs or symptoms of acute liver failure require management in an intensive care setting for appropriate monitoring of liver function, as well as supportive care. Liver transplantation may be considered for patients with fulminant hepatic failure.

PROGNOSIS

Most infected individuals recover within 2 months. Hepatitis A does not cause chronic infection. Relapsing hepatitis, in which exacerbations may occur weeks or months after apparent recovery, occur in 10% to 15% of cases. Fulminant hepatitis is rare but may result in death. The overall case fatality rate of hepatitis A is 0.8% in the United States, and it rises to 2.6% in adults 60 years of age and older. In the United States, more than 70% of deaths from hepatitis A occur in individuals 50 years of age and older.

PREVENTION AND CONTROL

Hepatitis A vaccine provides the best protection against hepatitis A infection, but other important preventative measures include improved sanitation and meticulous personal hygiene practices, such as good hand washing and proper food-handling techniques.

Hepatitis A Vaccines

The first hepatitis A vaccine was licensed in the United States in 1995. Vaccine guidelines have evolved over the years from target-group recommendations (i.e., vaccine for specific ages, communities, and groups with risk factors) to the current recommendations for routine childhood vaccination.

The hepatitis A vaccines currently available in the United States are prepared from purified, cell culture–grown HAV that is formalin-inactivated and are licensed for intramuscular use in persons 1 year of age and older. HAV vaccines are highly immunogenic, resulting in excellent efficacy (≥94% efficacy starting 2 weeks after one dose and >99% 1 month after the second dose). There are two monovalent formulations, one for children 18 years of age or younger and one for adults, available from two manufacturers (Havrix from GlaxoSmithKline and Vaqta from Merck & Co.). These vaccines are given in a two-dose series consisting of an initial dose with a second dose 6 to 18 months later. The duration of protection after vaccination is not known but, based on surveillance data, is predicted to be at least 10 years. Adverse events after immunization are generally mild local reactions and self-limited. Hepatitis A vaccines are contraindicated in those with a severe allergic reaction to a previous dose of hepatitis A vaccine or known allergy to any of the vaccine components.

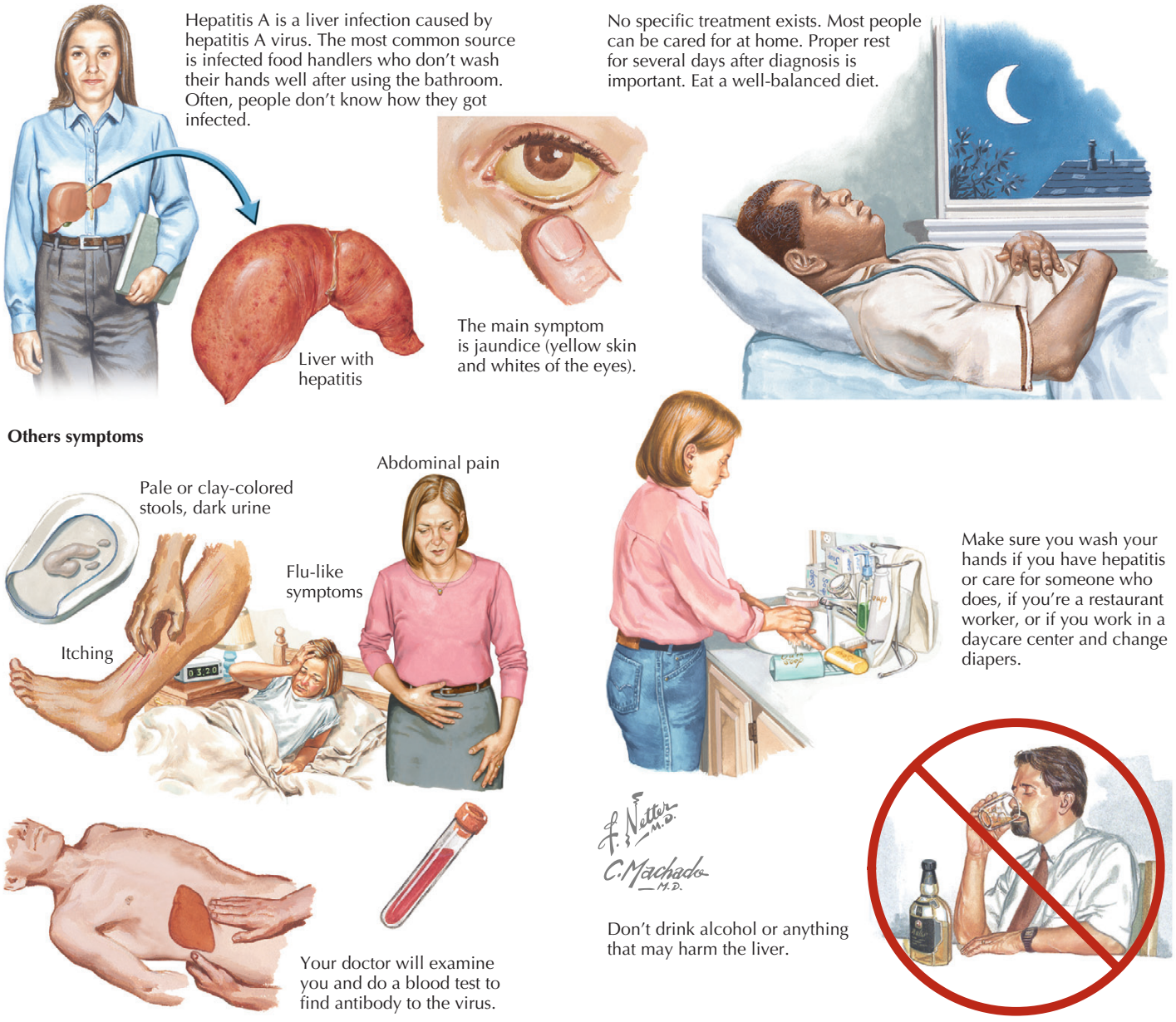


Figure 14-4 Management of hepatitis A.

Hepatitis A vaccine is also available in combination with hepatitis B vaccine. The combined hepatitis A–hepatitis B vaccine is licensed in the United States for those 18 years of age and older and is administered as either a three- or four-dose series.

Hepatitis A Vaccine Recommendations

Since 2005 in the United States, routine childhood vaccination has been recommended beginning at 1 year (12 to 23 months) of age. Vaccination is also recommended for unvaccinated individuals 1 year of age and older who are traveling to a hepatitis A–endemic area, all individuals 1 year of age and older during an outbreak, men who have sex with men, illicit drug users, those with occupational exposure, individuals receiving clotting factor concentrates, those with chronic liver disease, and anyone wishing to be immunized.

Hepatitis A vaccine is preferred for preexposure protection in all populations unless contraindicated and for postexposure prophylaxis for most individuals aged 1 through 40 years.

Preexposure Prophylaxis with Immune Globulin

Intramuscular immune globulin (IG) confers >85% protection against HAV infection if administered before or within 2 weeks of HAV exposure. Preexposure prophylaxis with IG should be provided to susceptible individuals traveling to an area with an increased rate of hepatitis A and in whom use of HAV vaccine is not permissible. Administration of hepatitis A vaccine is

generally recommended; however, there are situations in which prophylaxis with IG instead of, or in addition to, the hepatitis A vaccine is appropriate. Older adults, immunocompromised persons, and persons with chronic liver disease or another chronic medical condition may not have a brisk immune response to hepatitis A vaccine. If these individuals are planning to depart in less than 2 weeks, they should receive IG in addition to hepatitis A vaccine (simultaneously, at separate anatomic sites). In addition, travelers with a contraindication to hepatitis A vaccine should receive a single dose of IG. The dose depends on the anticipated length of exposure: 0.02 mL/kg provides protection for up to 3 months; if the travel period exceeds 2 months, 0.06 mL/kg should be administered (this dose must be repeated if the travel period exceeds 5 months). Because hepatitis A vaccine is not licensed for children younger than 12 months of age, an appropriate dose of IG is recommended for this age group.

EVIDENCE

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Daniels D, Grytdal S, Wasley A; Centers for Disease Control and Prevention (CDC): Surveillance for acute viral hepatitis—United States, 2007, *MMWR Surveill Summ* 58:1-27, 2009. *This reference provides the most recent data about viral hepatitis, including hepatitis A in the United States.*

Fiore AE: Hepatitis A transmitted by food, *Clin Infect Dis* 38:705-715, 2004. *This reference provides data about food-borne hepatitis A infections.*

Postexposure Prophylaxis

Postexposure prophylaxis should be given to persons who have recently been exposed to hepatitis A if they have not been previously vaccinated. They should receive either hepatitis A vaccine or IG (0.02 mL/kg) as soon as possible, within 2 weeks of exposure. Hepatitis A vaccine is preferred if they are healthy and 12 months to 40 years of age. For persons over 40 years of age, IG is preferred because of the lack of hepatitis A vaccine efficacy data for older age groups in this situation and the possibility of a more severe clinical course of hepatitis A in older adults. For children younger than 12 months old, immunocompromised persons, persons with chronic liver disease, and those with a vaccine contraindication, IG should be used.

ADDITIONAL RESOURCES

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Hepatitis B Infection

Dean A. Blumberg

15

ABSTRACT

Globally, hepatitis B infection is one of the most common communicable diseases. Acute hepatitis B may be asymptomatic or cause clinical illness similar to infections caused by other hepatotropic viruses (hepatitis A to E). Most acute infections resolve without sequelae; however, progression to chronic infection may occur. The risk for developing chronic infection is inversely related to age at the time of acquisition of infection. The main morbidity and mortality from hepatitis B occur secondary to chronic hepatitis B infection, which may result in cirrhosis or hepatocellular carcinoma. Treatment of acute hepatitis B infection is primarily supportive. Children and adolescents with chronic hepatitis B infection should undergo routine monitoring for disease progression and to determine appropriate treatment initiation. Treatment includes antiviral agents and interferon and is usually managed by pediatric liver specialists. Hepatitis B is preventable with vaccination, which is universally recommended for infants in most industrialized nations as well as in many developing areas.

ETIOLOGY

Hepatitis B virus is a member of the Hepadnaviridae family. The virus contains partially double-stranded deoxyribonucleic acid (DNA) and hepatitis B core antigen (HBcAg), surrounded by hepatitis B surface antigen (HBsAg). Humans are the only known host, and people with chronic hepatitis B infection are the primary reservoir.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Worldwide, more than 350 million individuals are infected with hepatitis B virus, and 5% of the world's population has chronic hepatitis B infection. The highest prevalence of hepatitis B occurs in Asia (particularly in China and Taiwan), Africa, the Amazon basin, Greenland, and North America among Native North Americans in Canada and Alaska. The Centers for Disease Control and Prevention (CDC) estimate that over 1 million U.S. residents have chronic hepatitis B infection, with 2000 to 4000 deaths annually. Since 1990 the incidence of hepatitis B infection has declined in all age groups in the United States, with the largest decline (approximately 98%) occurring in children younger than 15 years of age, largely attributable to use of hepatitis B vaccination.

RISK FACTORS FOR INFECTION

Hepatitis B is transmitted parenterally (e.g., by needlestick or sharing of needles), perinatally, sexually, and less commonly horizontally. The virus is present in all body fluids, except stool, but only salvia, semen, and serum have been proven infectious. Infants are most often infected from exposure to blood during the birth process to an infected mother. Horizontal transmission is less well defined but appears to occur rarely in households where one or more members have chronic infection. Other risk factors for infection include high-risk sexual activity (e.g., multiple partners or traumatic contact), injection drug use (IDU), and men who have sex with men. In adolescents 12 to 21 years of age, high-risk sexual activity and IDU are the most commonly identified risk factors; additional factors are homelessness and being a runaway. Even after intensive investigation, up to 40% of patients with acute hepatitis B infection have no identifiable risk factors.

Many international adoptees are from geographic areas with high prevalence of hepatitis B infection. Because children may have few or no symptoms with hepatitis B infection, all internationally adopted children should be screened.

CLINICAL FEATURES

Acute Infection

The incubation period is generally 3 months but ranges from 6 weeks to 6 months. The clinical features of acute hepatitis B infection depend partly on age. The manifestations of infection range from asymptomatic, mild nonspecific symptoms (i.e., flulike illness), clinical hepatitis with jaundice, to fulminant hepatitis, which may lead to hepatic failure and death. Acquisition of horizontal infection at a younger age usually results in milder illness or may even be asymptomatic, whereas older children and adults are more likely to be symptomatic. Acute hepatitis B is usually asymptomatic in children younger than 1 year of age (<1% develop symptoms). About 10% of children 1 to 4 years of age will be symptomatic, and this increases to about 40% for older children and adults.

Clinical illness from hepatitis B is similar to hepatic infection caused by other hepatotropic viral pathogens. Onset is generally insidious with nonspecific signs and symptoms such as nausea, vomiting, abdominal pain, fever, malaise, headache, and decreased appetite (Figure 15-1). Dark urine appears before the onset of jaundice. Jaundice is generally present for 1 to 3 weeks and is associated with abdominal pain and hepatomegaly. Light or gray stools may be present. Recovery is gradual, and fatigue and malaise usually resolve within a few weeks or months.

In pediatric age groups, extrahepatic manifestations may include glomerular nephritis, serum sickness, arthralgias and arthritis, and rashes such as urticaria and papular acrodermatitis (Gianotti-Crosti).

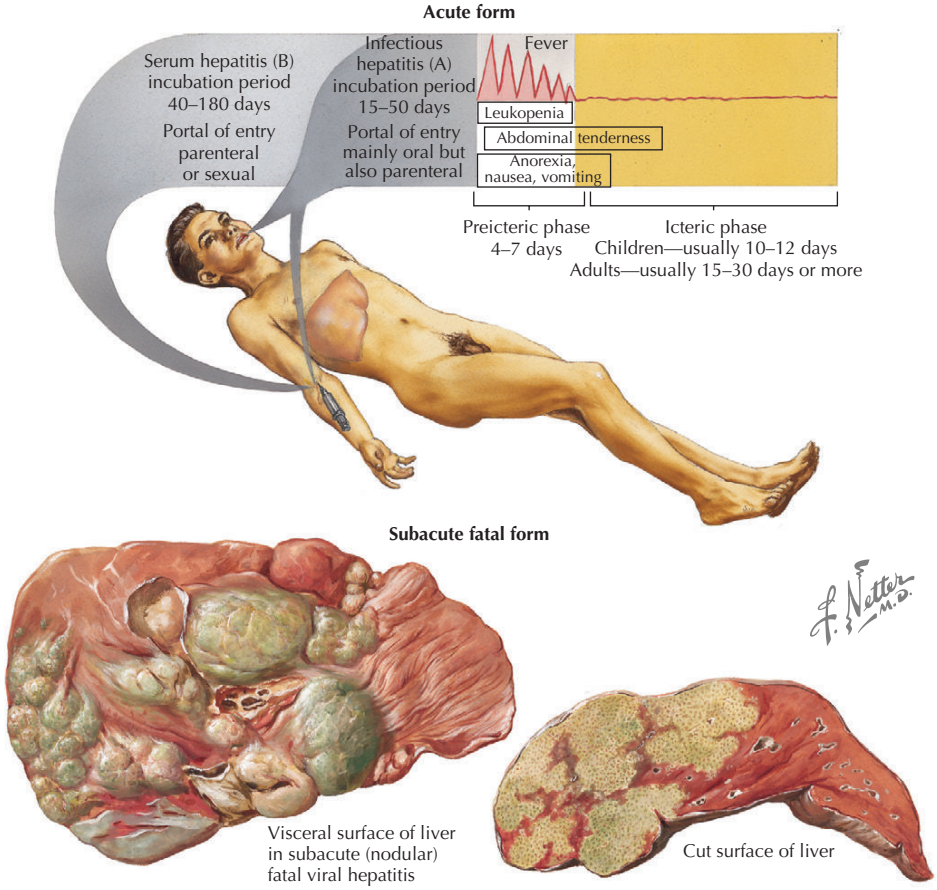

Figure 15-1 Hepatitis B clinical presentation.

Chronic Infection

Chronic hepatitis is defined as persistence of HBsAg in serum for at least 6 months *or* the presence of HBsAg in a person negative for immunoglobulin M (IgM) antibodies to HBcAg.

Chronic infection may cause no symptoms or may result in chronic active hepatitis and cirrhosis (Figure 15-2). Individuals with chronic active hepatitis often have fever, abdominal pain, and malaise. Advanced disease may lead to spider nevi, ascites, coagulopathy, and esophageal varices. About 25% of patients with chronic infection eventually die from complications related to hepatitis B infection. Hepatitis B also causes up to 80% of hepatocellular carcinomas.

DIAGNOSTIC APPROACH

Patients with acute hepatitis B infection have elevated transaminases and bilirubin. Definitive diagnosis of hepatitis B infection is most commonly confirmed by use of several serologic assays. HBsAg may be detected during acute or chronic infection. Antibody to HBsAg (anti-HBs) is detected during the recovery period of acute infection, but may also be seen in those chronically infected. Antibody to hepatitis core antigen (anti-HBcAg) may denote past infection; anti-HBcAg IgM usually represents recent acute infection, although false-positive assay results may occur. The presence of hepatitis E antigen (HBeAg) is a marker of increased infectivity in those with acute or chronic infection; antibody to HBeAg (anti-HBe) may be detected after acute or chronic infection. Hepatitis B vaccination elicits only anti-HBs antibodies.

Polymerase chain reaction (PCR) assays are available to detect and quantify hepatitis B DNA, which may be useful for monitoring disease progression.

DIFFERENTIAL DIAGNOSIS

The diagnostic considerations vary with age, vaccination history, and exposures, such as travel, sexual activity, and known infectious contacts. The most common diagnostic considerations include hepatitis caused by other viral agents, especially hepatitis A and C, and D and E (if there is a history of travel to endemic regions) (see Chapter 67). Other viral considerations include cytomegalovirus, herpes simplex virus, Epstein-Barr virus, and yellow fever. Bacterial causes for hepatitis are less common but may include sepsis, leptospirosis, Lyme disease, and syphilis. Noninfectious considerations include Wilson's disease, malignancies, toxins, illicit drugs, and ingestions (accidental or intentional).

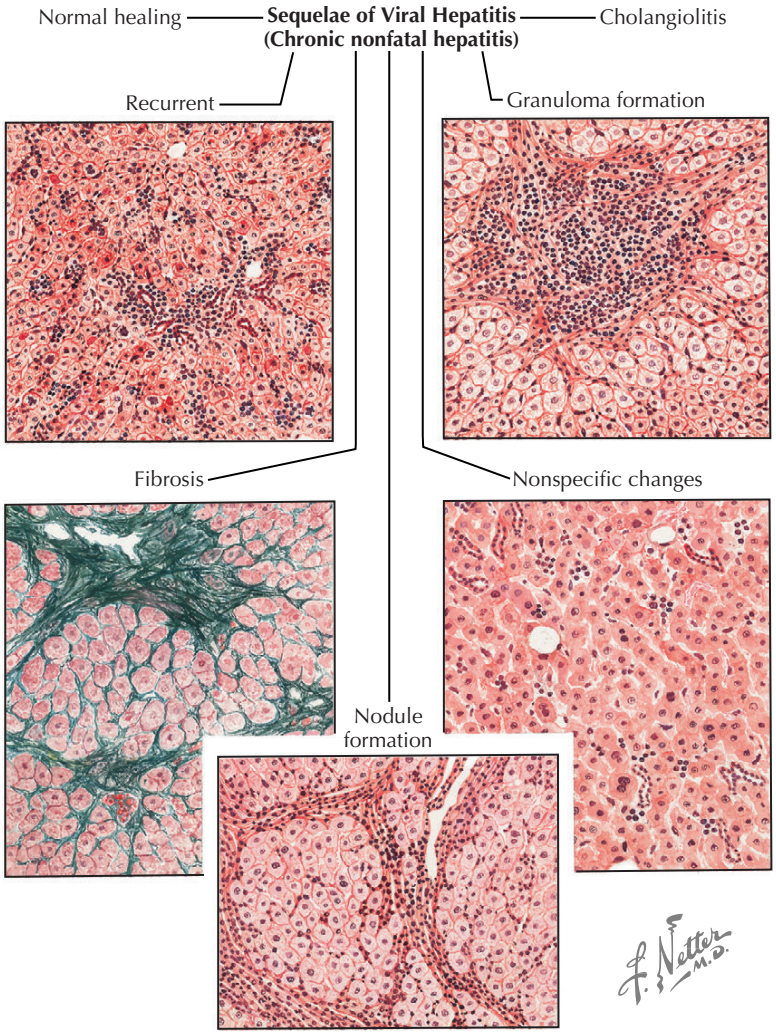

Figure 15-2 Chronic hepatitis B sequelae.

CLINICAL MANAGEMENT

Acute Infection

Treatment is primarily supportive for acute infection, with particular attention to hydration, nutrition, and patient comfort. Antiviral therapy (lamivudine or telbivudine) may be considered for fulminant hepatitis B and with entecavir for protracted and severe acute hepatitis B (Figure 15-3).

Chronic Infection

For children identified to have chronic hepatitis B infection, obtaining baseline alanine aminotransferase (ALT), alpha fetoprotein, HBeAg, anti-HBe, and viral load; performing liver ultrasound; and assessing the family history for liver disease are recommended. If the ALT is normal, alpha fetoprotein is <10 ng/mL, and family history is negative, then periodic follow-up blood tests are recommended (ALT and alpha fetoprotein every 6 months; HBeAg and anti-HBe every 12 months). The development of anti-HBe antibody is a good prognostic sign and may occur before resolution of HBsAg. Hepatic ultrasound should be considered for those at high risk, and liver biopsy considered to assess the disease stage. Patients with elevated ALT or alpha fetoprotein or positive family history of liver disease should have consultation with a pediatric liver specialist.

In patients in all age groups, co-infection should be assessed by checking human immunodeficiency virus (HIV) serology, antibodies to hepatitis A, and hepatitis C virus and hepatitis D virus antibody (if the patient is from an endemic area or has a history of IDU). To prevent further hepatic injury, patients should be vaccinated against hepatitis A if they are nonimmune. Heavy alcohol use, as well as use of medications that are metabolized by the hepatic system, should be avoided.

Indications for treatment are based on disease progression, viral load, and liver biopsy results. Treatment is generally initiated and monitored by specialists in the field. For chronic hepatitis B infection, immunomodulators and antiviral therapy may be administered. Medications approved by the U.S. Food and Drug Administration (FDA) for use in adults include interferons (interferon α-2b and pegylated interferon α-2a) and antiviral agents, including lamivudine, adefovir, entecavir, telbivudine, and tenofovir. Both interferon preparations and lamivudine are approved for treatment of chronic hepatitis B infection in children; however, interferon therapy results in significant adverse effects. The antiviral agents specifically inhibit hepatitis B viral DNA polymerase,

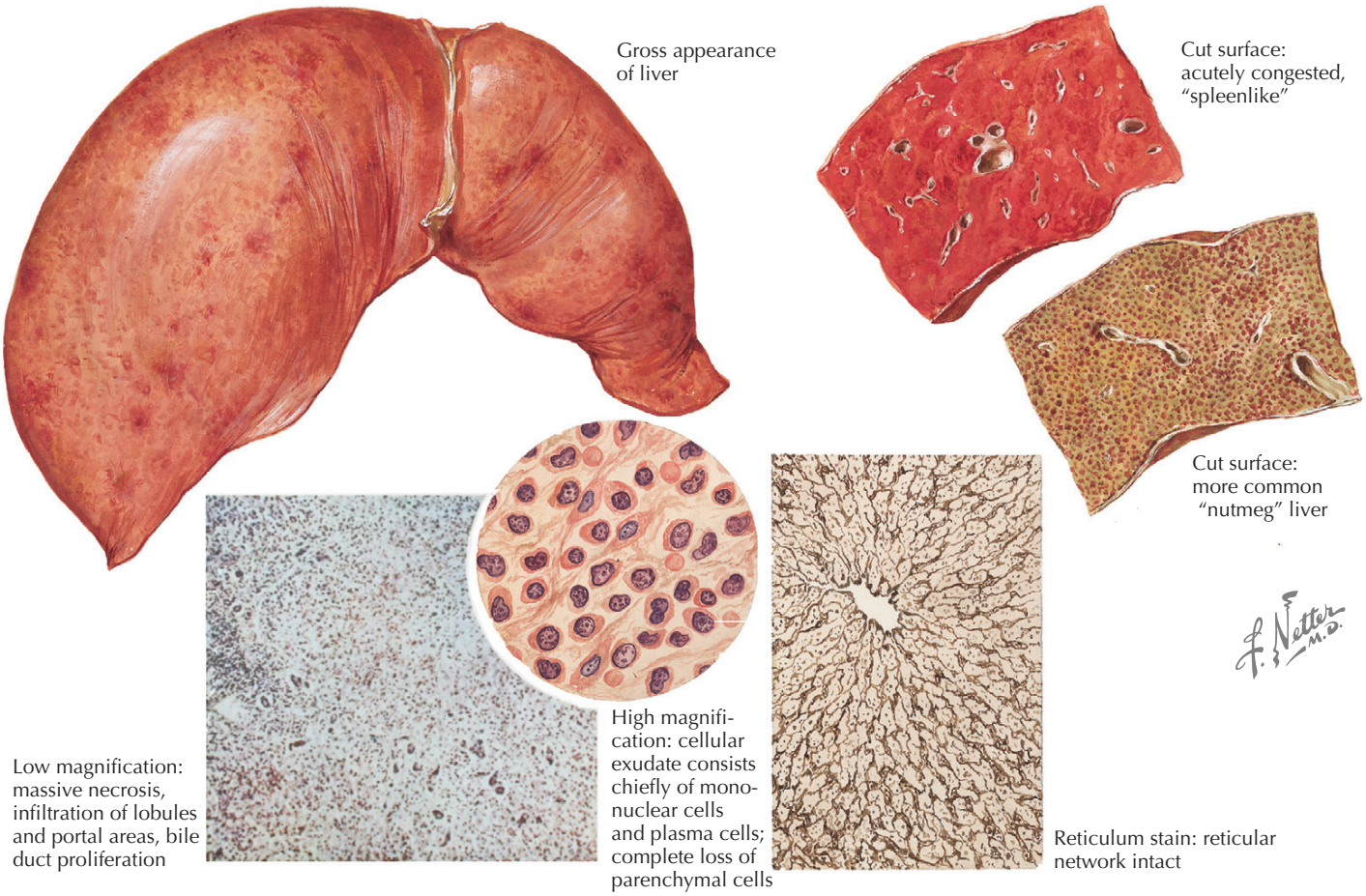

Figure 15-3 Pathology of fulminant hepatitis B infection.

but antiviral resistance has been described. Combination therapy is often used to improve responses and minimize resistance issues. Treatment is generally for prolonged time periods (months to years). The optimal regimen for children remains unknown, and investigational trials are underway.

PROGNOSIS

Acute Infection

Hospitalization rates for acute hepatitis B infection range from 25% to 35%, with the higher rate occurring among older patients. Case fatality rates are generally <2%. Recovery without sequelae occurs in 90% to 95% of infants with horizontal transmission, and 80% to 85% of adults. Fulminant hepatitis may occur in 1% to 2% of infants and 1% of adults. Co-infection with hepatitis D may result in a more severe clinical course of acute hepatitis B.

Chronic Infection

Age of infection is inversely correlated with the risk of chronic infection. The risk of developing chronic infection is 90% among newborns infected perinatally, 50% for children infected at 1 year of age, 20% for children infected at 1 to 4 years of age, and 5% to 7% for older children and adults. Chronic infection may lead to cirrhosis and hepatocellular carcinoma, both of which occur more commonly in those infected as infants compared with adults. Serious complications occur in 15% to 40% of individuals with chronic hepatitis B infection. Patients with chronic hepatitis B infection are susceptible to superinfection with hepatitis D virus, which increases the risks of development of cirrhosis and of mortality.

PREVENTION AND CONTROL

Nonvaccine Measures

Blood and body fluids from patients with acute or chronic hepatitis B infection are infectious, and appropriate measures should be implemented to prevent transmission to other people. Standard precautions should be followed for hospitalized patients. Hepatitis B–infected individuals should not share items that may be contaminated with blood, such as toothbrushes or razors, or donate blood, sperm, or organs.

Screening for Hepatitis B Infection

Foreign-born individuals, including international adoptees, immigrants, and refugees from areas with high prevalence

of hepatitis B infection (>2%), should be screened for infection. Serologic testing may also be considered for other high-risk groups, but testing should not delay initiation of immunizations.

To prevent perinatal hepatitis B transmission, all pregnant women should be tested for HBsAg at an early prenatal visit. Testing should be repeated in late pregnancy if clinical hepatitis develops, an exposure occurs, or other risk factors are present (e.g., IDU). If no prenatal testing is performed or the results are not available, the mother should be tested at the time of delivery. Management of infants based on the mother's hepatitis B status is shown in Table 15-1.

Passive Immunoprophylaxis

Hepatitis B immune globulin (HBIG) is prepared from hyperimmunized donors whose plasma has high concentrations of anti-HBs. HBIG may be used to provide short-term protection in specific postexposure settings. Indications include perinatal exposure of infants to mother with unknown status or known hepatitis B infection, travelers with inadequate time to receive the vaccine series, and specific, discrete exposures to HBsAg-positive or unknown-status individuals.

Active Vaccination to Prevent Infection

Hepatitis B vaccination is available for preexposure and postexposure prophylaxis and provides long-term protection. Hepatitis B vaccines are produced recombinantly in yeast cell systems. The vaccines contain noninfectious HBsAg (10 to 40 mcg of HBsAg protein per milliliter), a small amount of yeast protein, and aluminum hydroxide as an adjuvant. Pediatric formulations contain trace or no thimerosal. Administration is via the intramuscular route. Adverse effects are generally mild and mainly

Table 15-1 Hepatitis B Immunoprophylaxis Administration Based on Infant Birth Weight and Mother's Hepatitis B Status

MATERNAL HBSAG STATUS	INFANT BIRTH WEIGHT ≥2000 g	INFANT BIRTH WEIGHT <2000 g
HBsAg positive	Hepatitis B vaccine + HBIG (within 12 hours of birth) Continue vaccine series beginning at 1-2 mo of age Check anti-HBs and HBsAg after completion of vaccine series HBsAg-negative infants with anti-HBs levels ≥10 mIU/mL are protected and need no further interventions HBsAg-negative infants with anti-HBs levels ≤10 mIU/mL should be reimmunized with three doses at 2-mo intervals and then retested HBsAg-positive infants need follow-up and monitoring for chronic liver disease	Hepatitis B vaccine + HBIG (within 12 hours of birth) Continue vaccine series beginning at 1-2 mo of age Immunize with four doses of vaccine; do not count the birth dose as part of the series Check anti-HBs and HBsAg after completion of vaccine series HBsAg-negative infants with anti-HBs levels ≥10 mIU/mL are protected and need no further interventions HBsAg-negative infants with anti-HBs levels ≤10 mIU/mL should be reimmunized with three doses at 2-mo intervals and then retested HBsAg-positive infants need follow-up and monitoring for chronic liver disease
HBsAg unknown	Test the mother for HBsAg immediately on admission for delivery Hepatitis B vaccine within 12 hours of birth HBIG within 7 days if mother tests positive for HBsAg; if mother's status remains unknown, some experts recommend HBIG within 7 days Continue vaccine series beginning at 1-2 mo of age, based on mother's HBsAg status	Test the mother for HBsAg immediately on admission for delivery Hepatitis B vaccine within 12 hours of birth HBIG within 7 days if mother tests positive for HBsAg; if mother's status remains unknown, some experts recommend HBIG within 7 days Continue vaccine series beginning at 1-2 mo of age, based on mother's HBsAg status Immunize with four doses of vaccine; do not count the birth dose as part of the series
HBsAg negative	Hepatitis B vaccine at birth, before hospital discharge Continue vaccine series beginning at 1-2 mo of age Follow-up HBsAg and anti-HBs not needed	Hepatitis B vaccine dose 1 at 30 days of chronologic age if medically stable, or at hospital discharge if <30 days Continue vaccine series beginning at 1-2 mo of age Follow-up HBsAg and anti-HBs not needed

Adapted from Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds: *Red Book: 2009 Report of the Committee on Infectious Diseases,* ed 28, Elk Grove Village, Ill, 2009, AAP.
HBsAg, Hepatitis B surface antigen; *HBIG,* hepatitis B immune globulin; *anti-HBs,* antibody to HBsAg.

consist of local tenderness and low-grade fever. After a vaccine series, more than 95% seroconversion is achieved, which results in >90% efficacy. Studies are ongoing to determine length of immunity, but it is at least 20 years.

Two hepatitis B single antigen vaccines are available in the United States: Recombivax from Merck & Co. and Engerix-B from GlaxoSmithKline. Both vaccines come in doses for pediatric (5 to 10 mcg/0.5 mL) and adult (10 to 40 mcg/1.0 mL) populations. High-dose vaccines are available for adult hemodialysis and immunocompromised patients. Both vaccines are given in a three-dose series (at 0, 1 to 2, and 6 months) and are generally interchangeable. A fourth dose may be given if a birth dose was administered. The birth dose must be a single antigen formulation.

In the United States and most industrialized nations, as well as many developing countries, routine immunizations are started at birth and completed during infancy. Hepatitis B vaccines are also recommended for all unvaccinated individuals, especially those at increased risk of exposure to hepatitis B, including travelers to countries where hepatitis B infection is endemic. Healthcare workers should have documented hepatitis B immunization because of the increased risk of percutaneous exposure in healthcare settings. All close contacts of individuals with chronic hepatitis B infection should receive hepatitis B vaccinations.

Hepatitis B vaccine is also available as a component of combination vaccines. For the vaccination of infants and children, a diphtheria-tetanus–acellular pertussis–hepatitis B–inactivated polio vaccine (DTaP-HBV-IPV, Pediarix, GlaxoSmithKline) is available and may be administered for the first three doses of the infant vaccine series. Hepatitis B vaccine combined with *Haemophilus influenzae* type B conjugate vaccine (Hib-HBV, ComVax, Merck & Co.) may be administered at 2, 4, and 12 months of age. For adults (18 years of age and older), a combination hepatitis B–hepatitis A vaccine (HBV-HAV, TwinRix, GlaxoSmithKline) is available. The primary schedule for HBV-HAV vaccine is administration at 0, 1, and 6 months; alternatively, a four-dose schedule, given on days 0, 7, and 21 to 30, followed by a booster dose at 12 months, may be used.

"Catch-up" immunization for hepatitis B may be performed at any age for unimmunized individuals. At their routinely scheduled health maintenance visit, previously unvaccinated 11- to 12-year-old children should receive hepatitis B vaccine administered in a three-dose series at 0, 1, and 6 months if pediatric formulations are used. Alternatively, use of two 10 mcg doses of Recombivax, administered at 0 and 4 to 6 months, is FDA approved for those 11 to 15 years of age.

Booster doses of hepatitis B vaccine beyond the initial series are generally not recommended. The long incubation period of hepatitis B theoretically allows for the development of a protective anamnestic immune response after exposure.

Postexposure Prophylaxis

Postexposure prophylaxis may be administered to unvaccinated individuals after an identified percutaneous or sexual exposure to hepatitis B virus. The regimen includes prompt initiation and completion of the appropriate doses of the hepatitis B vaccine series for those previously unimmunized, as well as prompt (ideally within 24 hours) administration of HBIG.

EVIDENCE

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Human Papillomavirus Infections and Prevention

Dean A. Blumberg

16

ABSTRACT

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide, causing warts and also anogenital cancers, most notably cervical cancer. Worldwide, it is the second most common cause of cancer mortality in women. In the United States and several other industrialized nations, vaccination to prevent HPV infection is now routinely recommended for girls and young women to prevent morbidity and mortality from cervical and other cancers. HPV vaccination may also be performed to prevent genital warts in males, as well as females, 9 to 26 years of age.

ETIOLOGY

Papillomaviruses affect a wide variety of animals, though they are highly species specific. HPV is a deoxyribonucleic acid (DNA) virus that infects only humans. There are over 100 types of HPV, of which approximately 40 have been identified to cause clinical infections. HPV types may be grouped according to clinical site and consequences of infection: cutaneous (mostly asymptomatic), plantar warts, common and flat warts, external genital warts, and genital mucosal cancer–associated types.

Low-risk types usually cause warts. HPV types 6 and 11 are the low-risk types that cause more than 90% of genital warts. Other low-risk types that cause genital warts include types 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108. Types classified as high risk cause low-grade and high-grade genital lesions and may progress to cause cervical and other anogenital cancers, as well as head and neck cancers. High-risk types 16 and 18 cause the majority of cervical and other cancers. Other high risk types include types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

HPV infections occur worldwide and are the most common sexually transmitted infection. Globally, approximately 500,000 cases of cervical cancer are caused by HPV every year, representing about 10% of all cancers of women. Cervical cancer is the leading cause of cancer mortality in women in many developing countries, and it is the second most common cause of cancer mortality in women worldwide.

In the United States approximately 20 million people are infected with HPV, with more than 6 million new infections occurring every year. HPV affects >1% of the general population and causes nearly all anogenital warts. HPV causes approximately 10,000 cases of cervical cancer, resulting in about 4000 deaths, every year. Invasive cervical cancer incidence and mortality rates are higher in black women compared with white women (approximately a 6:1 ratio). Direct medical costs related to HPV disease, detection, and management are nearly $4 billion annually, second in cost only to human immunodeficiency virus (HIV) among sexually transmitted infections.

RISK FACTORS FOR INFECTION

HPV causes cutaneous and mucosal epithelial infection. Primary HPV infection occurs in the basal layer of the epidermis. Minor trauma of the epidermis allows HPV to access the basal layer, where replication initially occurs. Viral replication leads to virion production. Virions are released from the epidermis, which leads to further infections.

Naturally thin mucosal layers, such as occur in the cervix or anus, are particularly susceptible to infection (Figure 16-1). Infection may result from an infectious contact or autoinoculation. Minor trauma is often not clinically apparent and may result from normal sexual intercourse or other skin-to-skin contact activities.

There are several factors that increase risk for HPV infection. Sexual behavior influences infection, with increasing risk for HPV infection noted for individuals with young age at sexual initiation, increasing number of sex partners, increasing number of partner's sex partners, and young age (less than 25 years). Sexual activity leads to anogenital HPV transmission. In the United States, more than 50% of men and women acquire HPV infection within 5 years of initiation of sexual activity. Men who have sex with men are at increased risk for infection and for developing anogenital cancer. Other factors that have been less consistently found to be associated with increased risk for HPV infection include smoking, diet, hormonal contraceptives, inconsistent condom use, uncircumcised male partner, and history of genital herpes simplex virus infection.

CLINICAL FEATURES

HPV infections may be classified as asymptomatic (generally mucosal), subclinical, or clinical (apparent, usually seen on the skin). Clinically apparent infections usually result in warts rather than malignancies. Most HPV infections are asymptomatic, and many associated lesions are self-limited. However, the concerns with HPV infections, most notably anogenital and head and neck lesions, are the risks to progress to cancer. Of note, it appears that HPV infection alone does not cause malignant transformation of the infected tissue, but cofactors (e.g. tobacco use, ultraviolet radiation, pregnancy, folate deficiency, and immune suppression) are important contributors for developing malignancy.

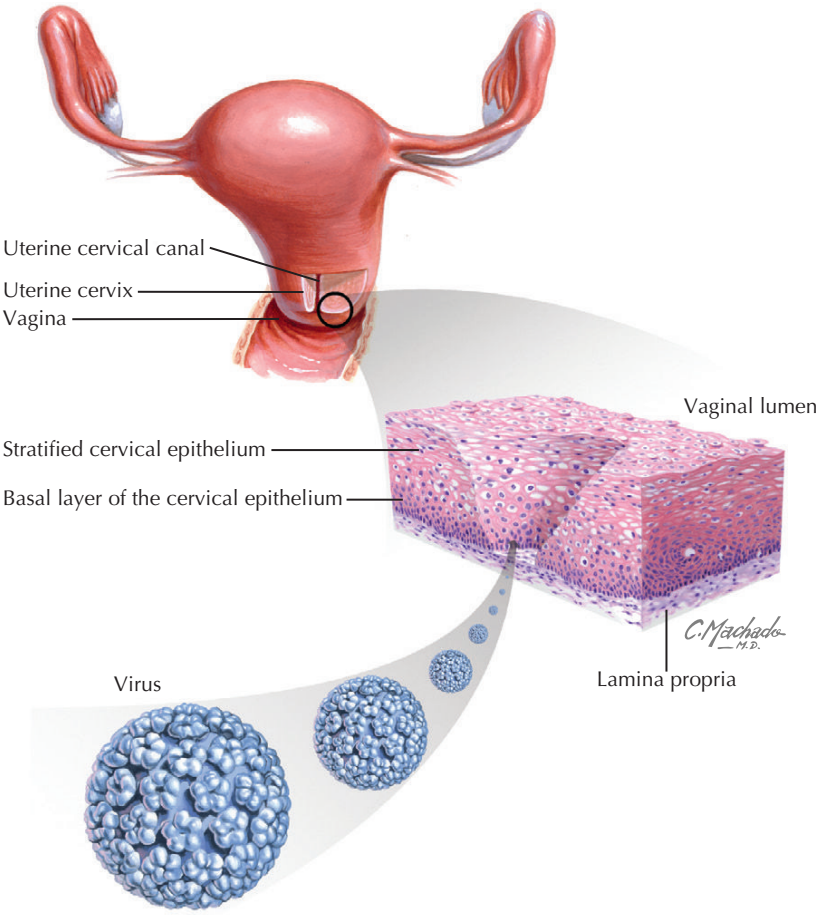

Figure 16-1 Human papillomavirus cervical infection. The area that is circled on the uterine cervix is depicted by the enlarged cross-section of the cervical epithelium where the virus proliferates.

Warts

Almost all genital warts are caused by HPV (see Figure 57-1). Plantar warts and common and flat warts are also caused by HPV.

If mothers have genital warts or asymptomatic genital HPV infection, newborns may be exposed to the virus during the birth process. Aspiration of genital secretions may result in respiratory tract infection and subsequent recurrent respiratory papillomatosis. Approximately 3000 cases of recurrent respiratory papillomatosis occur every year in the United States. Because extensive warts may result in airway obstruction, aggressive surgical therapy may be needed, sometimes necessitating several procedures every year.

Cancers

All cervical cancers are caused by HPV. HPV also causes approximately 50% of vaginal, vulvar, and penile cancers; 90% of anal cancers; and 20% to 30% of oropharyngeal cancers.

DIAGNOSTIC APPROACH

Please see discussion in Chapter 57.

CLINICAL MANAGEMENT

There is no specific antiviral therapy available for HPV infections. Generally, treatment is directed toward HPV-associated conditions such as warts or cervical dysplasia.

Management of Warts

For treatment of warts, reduction of symptoms is usually the primary goal. No single therapeutic approach has proven beneficial for all warts. Medications used for HPV cutaneous infections are applied topically and may be associated with pain or adverse local reactions of the skin and should not be used on mucosal surfaces. Treatment of anogenital warts may be painful; often multiple treatments are required. Recurrence is common (75% recur within 6 months).

Two broad categories of medications are effective in treating HPV disease. The first category is the immune response modifiers (i.e., imiquimod and interferon-α), and the second category is the cytotoxic agents (e.g., podofilox, podophyllin, 5-fluorouracil, salicylic acid, trichloroacetic acid [TCA], and bichloroacetic acid [BCA]). Surgical treatment may also be considered for some lesions, especially those that are extensive. Recurrence after complete surgical removal is less common than after medical treatment.

Further discussion of the specific treatment of warts is included in Chapter 57.

Prevention of Progression to Cervical Cancer

Periodic Papanicolaou tests (Pap tests or smears) are recommended for women to detect low-grade and high-grade lesions that are associated with HPV infection, which may progress to cervical cancers. With the initiation of routine screening with Pap smears in the 1940s, detection and removal of these lesions has resulted in a 70% reduction in cervical cancer mortality in the United States, though the rate of new infections has remained fairly constant.

PROGNOSIS

More than 95% of HPV infections are transient. High-risk HPV types that cause persistent infection (detectable for more than 6 to 12 months) are the most important predictor of high-grade cervical cancer precursors. Persistent active infection causes continued cellular proliferation leading to inhibition of cellular differentiation and the development of premalignant and malignant lesions.

The risk of persistent HPV infection is increased by smoking, immune compromise, older age, other sexually transmitted infections, viral load, and infection with multiple HPV types. Folate deficiency also increases the risk of malignant transformation.

Initial cervical infection may result in cervical intraepithelial neoplasia (CIN) I, denoting a condyloma or mild dysplasia. Persistent infection may cause progression to CIN II (moderate dysplasia), which may then progress to CIN III (severe dysplasia or carcinoma in situ). CIN III is the immediate precursor to invasive cervical cancer. Progression from initial infection to CIN III takes approximately 1 to 5 years, whereas further progression from CIN III to invasive cervical cancer usually occurs over several more years, even decades. This prolonged interval before invasive cervical cancer occurs provides the opportunity for effective screening and treatment measures to prevent invasive cervical cancer.

PREVENTION AND CONTROL

Nonvaccine Measures to Prevent Infection

Abstinence from sexual activity or lifetime mutual monogamy may prevent genital infection. Consistent male condom use results in an approximately 70% reduction in female HPV infection. Because HPV may infect areas outside of those covered by a condom, condom use does not fully protect against infection of other external anogenital areas.

Vaccination to Prevent Infection

HPV vaccines consist of viruslike particles: empty viral shells composed of recombinant L1 that contain no infectious genetic material. L1 is the major structural HPV protein, accounting for approximately 85% of the viral capsid. L1 is expressed in a heterologous system (yeast), and the recombinant proteins self-assemble into viruslike particles that mimic the structure of natural virions. Immunity to HPV is predominantly type-specific, and L1 proteins host the virion immunodominant neutralization epitopes. The vaccines induce neutralizing antibodies that prevent HPV cell entry.

HPV vaccines are administered prophylactically. The aim is to reduce HPV infection and subsequently reduce HPV-associated morbidity and mortality. Timing of vaccination is important. Ideally individuals should be vaccinated before sexual debut, suggesting that younger age at vaccination should result in the greatest benefit. Current HPV vaccines are not intended for treatment of established HPV infection.

HPV type 16 accounts for 53% of cervical cancers, and HPV type 18 accounts for an additional 17% of cervical cancers. Therefore vaccines contain HPV types 16 and 18 viruslike particles in order to address 70% of cervical cancers in the United States. Worldwide, the proportion of cervical cancers caused by high-risk HPV types varies; however, HPV types 16 and 18 cause a majority of cervical cancers in every geographic region.

Currently, two HPV vaccines are licensed by the Food and Drug Administration in the United States. HPV4 (Gardasil, Merck & Co.) is a quadrivalent vaccine that contains types 6 and 11 viruslike particles in addition to types 16 and 18, with an aluminum-based adjuvant. HPV4 vaccine is licensed for prevention of cervical, vaginal, vulvar, and anal cancers; associated precancerous lesions and genital warts in females 9 to 26 years of age, and also for the prevention of genital warts, anal cancer, and associated precancerous lesions in males 9 to 26 years of age. It is administered intramuscularly (IM) in a three-dose series, at times 0, 2 months, and 6 months.

HPV2 (Cervarix, GlaxoSmithKline) is a bivalent vaccine containing types 16 and 18 viruslike particles, licensed for females 10 to 25 years of age for the prevention of cervical neoplasia and cancer due to types 16 and 18. HPV2 differs from HPV4 not only in the HPV types included in the vaccine, but also in that HPV2 contains a novel adjuvant, aluminum hydroxide and monophosphoryl lipid A. HPV2 is administered in a three-dose series, at times 0, 1, and 6 months.

Both HPV vaccines are generally well tolerated, though both were associated with local reactions (pain, swelling, erythema) in the majority of recipients in clinical trials. These adverse events are generally mild to moderate and self-limited. Systemic events, such as fever (temperature >99.5° F), fatigue, and headache, occurred in more than 10% of vaccinees. Because syncope may occur, observation for at least 15 minutes after vaccination is recommended to prevent injury from falling.

Both HPV vaccines are highly immunogenic; however, there is no serologic correlate of protection against infection. Both vaccines have demonstrated >90% protection against acquisition of HPV vaccine types and subsequent precancerous cervical lesions caused by these types. HPV4 vaccine also prevents >95% of genital warts and >75% of anal cancer and associated precancerous lesions caused by HPV types included in the vaccine.

The Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention recommends administering either HPV vaccine on a schedule of 0, 1 to 2 months, and 6 months for females aged 9 to 26 years. Routine

immunization is recommended for all girls at 11 to 12 years of age, with catch-up immunization at 13 to 26 years of age. Ideally for maximal benefit, vaccination should occur before onset of sexual activity. However, sexually active girls and women are likely to benefit from vaccination, as they are not likely infected with all HPV types included in the vaccines.

In 2009, the ACIP made a recommendation for permissive use of HPV4 vaccine for males aged 9 through 26 years to reduce their likelihood of acquiring genital warts. Similar to use in females, HPV4 would be most effective when administered to males before exposure to HPV through sexual contact. A stronger recommendation for vaccination of males was not made because it was not considered to be cost beneficial in this group.

HPV vaccination is recommended for individuals with an equivocal or abnormal Pap test result, positive HPV test result, or genital warts, as past infection is not likely with all HPV types included in the vaccines; therefore vaccination should provide protection against some HPV types. Individuals who are immunosuppressed may not have as robust of an immune response as immunocompetent subjects but may still benefit from vaccination. Lactating women may be vaccinated, as the HPV vaccines are inactivated with no known or theoretical adverse events expected. HPV vaccines can be administered at the same visit with other inactivated and live-viral vaccines, including tetanus-diphtheria–acellular pertussis vaccine (Tdap), tetanus-diphtheria vaccine (Td), and meningococcal conjugate vaccine (MCV), which are also recommended at the 11- to 12-year-old health maintenance visit.

HPV vaccines should not be administered during pregnancy. The vaccine series should be delayed until after pregnancy. If a vaccine dose is administered during pregnancy, there is no indication for intervention.

Precautions and contraindications for HPV vaccine administration include moderate or severe illness (defer until clinical improvement) and a history of immediate hypersensitivity or severe allergic reaction to yeast or to any vaccine component.

Currently studies are underway to assess possible therapeutic use of HPV vaccines alone or adjunctly with medications.

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Kahn JA: HPV vaccination for the prevention of cervical intraepithelial neoplasia, *N Engl J Med* 361:271-278, 2009. *This reference provides a discussion of the clinical trials for therapy and prevention of HPV infections.*

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Gearhart PS, Randall TC, Buckley RM: *Human papillomavirus.* Updated March 2010. Available at: http://emedicine.medscape.com/article/219110-overview. Accessed June 28, 2010. *This resource provides an updated review of the diagnosis, management, and prevention of HPV infections.*

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Edited by Dennis L. Stevens

SECTION
II

Skin and Soft-Tissue Infections

17 *Introduction to Skin and Soft-Tissue Infections*
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Introduction to Skin and Soft-Tissue Infections

Dennis L. Stevens

17

ABSTRACT

Skin and soft-tissue infections are among the most common human afflictions, and descriptions from the last few centuries suggest that many of these have the same clinical presentations today as historically described. Regardless of the cause, location, or chronicity, the cardinal manifestations of inflammation (heat, swelling, erythema, and tenderness or pain) are invariably present. Infections of the skin and/or subcutaneous tissues are highly diverse in respect to cause, location, incidence, systemic manifestations, severity, and complications. They may occur as single or recurrent episodes. Many cases are mild or self-limited, but some progress to cause scarring, loss of digits or limbs, or even death. Though skin and soft-tissue infections are common, the causes are diverse, and therefore the clinician faces an immense challenge in establishing a specific diagnosis and prescribing definitive treatment. Important considerations in evaluating patients are the following:

- The patient's symptoms
- The general appearance of the infected site
- Historical clues such as contact with insects or animals, especially involving bites, travel to specific geographic areas, occupation, use of a hot tub, or having a home aquarium
- The immune status of the host
- Chronicity
- Anatomic distribution

Anatomic considerations are paramount to the correct diagnosis. In general, vesicular lesions (herpes simplex) and crusted lesions are the most superficial and may be either impetigo (*Staphylococcus aureus* or group A *Streptococcus*) or dermatomycosis caused by a variety of fungi. Erysipelas is also superficial, caused by group A *Streptococcus* and characterized by brilliant red color, well-demarcated edges, and pain. None of these superficial infections is associated with scarring. Localized soft-tissue infections (folliculitis, furuncles, carbuncles, and abscesses) involve the epidermis and dermis and are usually purulent in nature and caused by *S. aureus*, including methicillin-resistant *S. aureus* (MRSA). Cellulitis is caused by a variety of streptococci and affects the subcutaneous tissues and is characteristically a pinkish erythema with less distinct borders than erysipelas. Necrotizing infections invariably involve the fascia (necrotizing fasciitis) or muscle (gas gangrene and clostridial myonecrosis). In general, these necrotizing infections may ultimately involve all the layers of the soft tissue, particularly if there is a delay in recognition and treatment.

If the diagnosis cannot be established based on the history, symptoms, and signs, then needle aspiration, biopsy, or surgical exploration may be necessary to obtain specimens for appropriate staining and culture. This is extremely important in those patients with systemic signs of infection or those with historical or observational evidence of rapid progression. With the emergence of antimicrobial resistance among many of these microbes, treatment (particularly for severe infections) should be based on the results of Gram stain and cultures and antimicrobial susceptibility.

EPIDEMIOLOGY

Although the exact incidence of these infections in the general population is unknown, they are among the most common infections occurring in all age groups. Some skin and soft-tissue infections are age related—for example, impetigo is more common in children, and erysipelas is more common in older adults. Infections of the skin and soft tissues can be caused by bacteria (including rickettsiae), fungi, viruses, parasites, and spirochetes. There are hundreds of possible causative agents, with two common species of gram-positive cocci being the predominant causes of skin and soft-tissue infections—*S. aureus* and *Streptococcus pyogenes*—although other streptococci, such as groups B, C, and G streptococci, are being recognized more commonly. Staphylococcal skin infections are most commonly associated with infections that begin in hair follicles and cause a variety of infections ranging from folliculitis, furuncles, carbuncles, and subcutaneous abscesses. Staphylococcal infections usually have a focal central collection of pus with surrounding erythema. Some practitioners have advocated referring to these types of infections as *purulent cellulitis.* It is unclear if the surrounding erythema is indeed cellulitis (infection in the skin) or merely sympathetic inflammation. In contrast, streptococci more commonly cause erysipelas or cellulitis. Both cause a diffuse erythematous infection not associated with purulent drainage. Thus, streptococcal infections should be called *nonpurulent cellulitis.* It should be noted that staphylococcus and group A *Streptococcus* can both cause impetigo, which is superficial infection of the keratin layer of the skin associated with crusting lesions that occasionally weep golden brown fluid. In the past, many terms have been used to describe rapidly destructive lesions of the skin and soft tissues, and such nomenclature has not been helpful to the clinician. Gas gangrene and necrotizing fasciitis are examples of such devastating infection. Whereas gas gangrene is generally also referred to as *clostridial myonecrosis*, in fact most cases involve all the layers of the soft tissue including muscle, fascia, subcutaneous tissue, and skin. Similarly, necrotizing fasciitis can be caused by mixed aerobic and anaerobic bacteria (polymicrobial) or monomicrobial. The latter type is most commonly caused by group A *Streptococcus*, but cases involving *Aeromonas hydrophila* and *Vibrio vulnificus* have also been

described. As with gas gangrene, necrotizing fasciitis commonly destroys not only fascia but also muscle, subcutaneous tissue, and skin. Thus rightfully these should both be reclassified as simply necrotizing soft-tissue infections. Because these necrotizing soft-tissue infections are rapidly progressive and cause extensive mortality and morbidity, an aggressive approach to diagnosis and treatment is mandatory.

Skin and soft-tissue infections caused by newly recognized or previously rarely encountered microbes are continually being described in immunocompromised patients, especially those with acquired immunodeficiency syndrome (AIDS).

Several noninfectious diseases can mimic infection of the soft tissues—for example, contact dermatitis, pyoderma gangrenosum, gout, psoriatic arthritis with distal dactylitis, Reiter's syndrome, relapsing polychondritis, or mixed cryoglobulinemia secondary to immune complex disease from chronic hepatitis C or B virus infection. All may manifest with erythematous rashes, with or without fever.

PATHOGENESIS

The integument is an organ that reacts to noxious, infectious, external and internal stimuli in a limited number of ways. It is therefore not surprising that infection can be mimicked by the noninfectious inflammatory conditions listed previously. The rich plexus of capillaries beneath the dermal papillae provides nutrition to the stratum germinativum and the dermatocytes, which are bound together by tight junctions and form the barrier to microbial invasion. Once microbes have penetrated this barrier through a hair follicle, cut, or bite, the dermal plexus of capillaries delivers the components of the host's defense—oxygen, complement, immunoglobulins, macrophages, lymphocytes, and granulocytes—to the site of infection. At some locations, factors such as pressure, thrombosis, or drugs may reduce or stop blood flow, resulting in inadequate oxygenation. If tissue perfusion is moderately attenuated, tissues may remain viable, but the threshold for progression of infection may be lowered. Predisposing conditions in this category include the following:

- Peripheral vascular disease affecting large arteries
- Diabetes mellitus causing microvascular disease
- Chronic venous stasis causing postcapillary obstruction

Necrosis of the skin and deeper tissue may occur if there is severe hypoxia. The following are two examples:

- Pressure necrosis resulting in decubitus ulcers
- Compartment syndromes resulting in hypoxia and then necrosis in muscles confined within tight fascial bundles

When the host is physiologically, structurally, and immunologically normal, only certain pathogens such as *S. aureus* and group A streptococci are able to cause disease by virtue of their potent virulence factors, such as toxins, capsules, or dermonecrotic enzymes. This statement is supported by the observation that normal skin, although constantly exposed to many indigenous and exogenous microbes, rarely becomes infected. In contrast, patients who have compromised skin integrity (e.g., patients with burns), vascular defects (e.g., those who have diabetes mellitus or pressure ulceration), or immunologic deficits may become infected with either virulent organisms (e.g., staphylococci or streptococci) or microbes that are usually saprophytic, such as *Pseudomonas aeruginosa*, *Escherichia coli*, enterococci, or *Fusarium* species.

PREVENTION

Avoidance of cuts, scratches, and other forms of trauma that disrupt the natural barrier function of the skin helps to prevent skin and soft-tissue infections. For example, stopping shaving may prevent recurrent folliculitis in the beard area (sycosis barbae). Prompt cleansing, debridement, and disinfection of such lesions are important for preventing infection, particularly in the case of bite wounds. Treatment of eczema reduces the risk of secondary bacterial infection.

Prevention of recurrent folliculitis or furunculosis is difficult to achieve, but there has been some success using intranasal applications of bacitracin or mupirocin ointment. Hexachlorophene or chlorhexidine soaps may be tried to eliminate or reduce staphylococcal carriage in adults. Prophylaxis with systemic antibiotics is of doubtful efficacy and can result in the emergence of resistant strains; it should be tried only for severe cases. Finally, recurrent bacterial cellulitis of the lower extremities can often be prevented by topical antifungal treatment for dermatophyte infections such as tinea pedis because even minor or inapparent superficial fungal infection can serve as a portal of entry for gram-positive cocci.

Impetigo

Dennis L. Stevens

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ABSTRACT

Impetigo is a common crusted and superficial infection of the skin that occurs in individuals throughout the world. From the historical perspective, impetigo has occurred most frequently among economically disadvantaged children in tropical or subtropical regions, but it is also prevalent in northern climates during the summer months. Its peak incidence is in children aged 2 to 5 years, though older children and adults, including the homeless and migrant farm workers, may also be affected. There is no sex predilection, all races are susceptible, and impetigo is nearly always caused by beta-hemolytic streptococci and/or *Staphylococcus aureus*. In recent times impetigo caused by *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), have become problematic.

GEOGRAPHIC DISTRIBUTION

Impetigo occurs in all regions of the world but is most common in children in the tropics. In temperate areas, impetigo has been described in Native American children living on Indian reservations and in children in poor economic conditions in cities. In adults, impetigo has recently been described in the homeless, migrant farm workers, and travelers returning from tropical vacations.

RISK FACTORS

Studies of streptococcal impetigo performed at the Red Lake Indian Reservation in the 1960s demonstrated that personal hygiene, humidity, and geographic location influence the incidence of disease. Predisposing factors also include minor trauma, abrasions, and insect bites. Skin colonization of unbroken skin with particular streptococcal strains such as M-type 49 precedes the development of impetiginous lesions by an average of 10 days. Inoculation or colonization of surface organisms into the skin by abrasions, minor trauma, or insect bites then ensues. Over the course of 2 to 3 weeks, proliferation of streptococcal strains results in the classic crusted lesions with yellow serosanguineous drainage. At this stage streptococci may be transferred from the skin and/or impetigo lesions to the upper respiratory tract. In contrast, in patients with staphylococcal impetigo, nasal colonization usually precedes cutaneous disease.

CLINICAL FEATURES

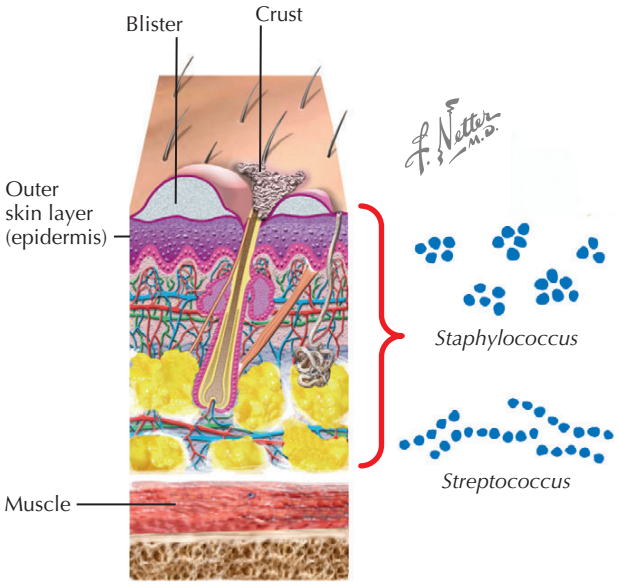
The cutaneous distribution of impetigo is largely on exposed areas of the body, most often the face and extremities (Figure 18-1). Interiginous areas are spared. Individual lesions are well localized, but multiple cutaneous lesions may develop and may be either bullous or nonbullous in appearance. The former appear initially as superficial vesicles that rapidly enlarge to form flaccid bullae filled with clear yellow fluid, which later becomes darker, more turbid, and often purulent. Bullae may rupture, leaving a thin brown crust resembling lacquer. The lesions of nonbullous impetigo begin as papules that rapidly evolve into vesicles surrounded by an area of erythema and then into pustules that gradually enlarge and then break down over a period of 4 to 6 days to form characteristic thick-crusted cutaneous lesions. Impetiginous lesions heal slowly and leave depigmented areas but do not form scars. A deeply ulcerated form of impetigo is known as *ecthyma*. Regional lymphadenitis may occur, but systemic symptoms are usually absent.

The appearance of impetiginous lesions provides some clues regarding the etiology. For example, bullous impetigo is usually caused by strains of *S. aureus* that produce a toxin causing cleavage in the superficial skin layer. In the past, nonbullous lesions were usually caused by streptococci. Now, 50% of cases are caused by staphylococci alone or in combination with streptococci. Streptococci isolated from lesions are primarily group A, but occasionally other serogroups such as C and G are responsible.

DIAGNOSTIC APPROACH

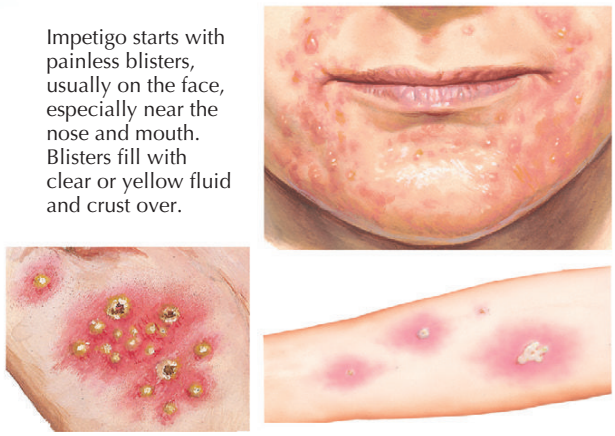
Impetigo is most commonly diagnosed based on the characteristic dry, crusted skin lesions that weep golden-colored fluid. Gram stain of vesicular fluid or exudates beneath the crusts reveals gram-positive cocci resembling *S. aureus* or group A *Streptococcus* (GAS). Cultures are invariably positive for one or the other or both. Cultures are more important than ever based on the evolving resistance of *S. aureus* (MRSA) and high-level resistance in specific geographic areas of GAS to erythromycin. The anti–streptolysin O response is weak in patients with streptococcal impetigo, presumably because skin lipids suppress streptolysin O response but anti-DNase B levels are consistently elevated.

Although assays of streptococcal antibodies are of limited value in diagnosis and management of impetigo, they provide helpful supporting evidence of recent streptococcal infection in patients suspected of having poststreptococcal glomerulonephritis. It must be emphasized that the greatest consequence of impetigo caused by GAS is not the impetiginous lesion, but the postinfection sequela, poststreptococcal glomerulonephritis. In times past, there was a strong association between specific strains of GAS that caused impetigo and the development of poststreptococcal glomerulonephritis. In the last 20 years, the incidence of this complication has markedly declined to less than 1 case per 100,000 population. This is likely related to the rarity of the classic M-49 strain (Red Lake strain) in modern times compared with the 1950s era.



Bacteria called *Staphylococcus* (staph) and *Streptococcus* (strep) cause impetigo. They normally live on the skin surface but can go deeper and cause infection.

Impetigo starts with painless blisters, usually on the face, especially near the nose and mouth. Blisters fill with clear or yellow fluid and crust over.



Your doctor makes a diagnosis from the look of the blisters and sores.

Figure 18-1 Managing impetigo.

CLINICAL MANAGEMENT

In the past, therapy directed primarily at group A streptococci (e.g., penicillin) was successful, both in healing the lesions and decreasing recurrences of nonbullous impetigo for at least several weeks. Because *S. aureus* currently accounts for most cases of bullous impetigo as well as a substantial portion of nonbullous infection, penicillinase-resistant penicillins or first-generation cephalosporins are preferred, although impetigo caused by MRSA is increasing in frequency. Erythromycin has been a mainstay of pyoderma therapy, but its utility may be lessened in areas where erythromycin-resistant strains of *S. aureus*, or more recently *Streptococcus pyogenes*, are prevalent. Topical therapy with mupirocin is equivalent to oral systemic antimicrobials and may be used when lesions are limited in number. It is expensive, however, and resistance not only has developed but is in part related to the general usage of mupirocin in the community. Recently, retapamulin ointment was approved by the Food and Drug Administration (FDA) for treatment of impetigo caused by both GAS and *S. aureus*. Bullous impetigo caused by MRSA poses a difficult problem for clinicians. Although empiric treatment with dicloxacillin, amoxicillin-clavulanate, or an oral cephalosporin may be the easiest choice, patients should be observed carefully for evidence of clinical failure as a result of MRSA. If this occurs, trimethoprim-sulfamethoxazole or clindamycin may be effective, though resistance to both agents has been described. Occasionally in patients with extensive impetigo caused by MRSA, parenteral antibiotics such as vancomycin, daptomycin, or linezolid would be reasonable choices based on susceptibility testing. All these agents have been approved by the FDA for complicated skin and soft-tissue infections; however, no clinical trials have been performed with these agents for impetigo per se.

PROGNOSIS

Impetiginous lesions resolve spontaneously with or without antibiotics and do not leave a scar because the infection occurs in the outer keratin layer of skin. Antibiotic treatment topically or orally speeds the rate of resolution. Suppurative complications of streptococcal impetigo are uncommon, and for as yet unexplained reasons, rheumatic fever has never occurred after streptococcal impetigo. On the other hand, cutaneous infections with nephritogenic strains of GAS are the major antecedent of poststreptococcal glomerulonephritis in many areas of the world. No conclusive data indicate that treatment of streptococcal pyoderma prevents nephritis.

PREVENTION AND CONTROL

General body hygiene is important in preventing impetigo. In addition, minor skin trauma and abrasions in children should be quickly cleansed with soap and water and appropriately covered with sterile dressings. Antibiotic ointment probably aids in prevention of impetigo because it is useful in shortening the course of established impetigo, yet such studies have not been performed. Topical or oral antibiotics are also important as an epidemiologic intervention to eradicating nephritogenic strains from the community and for reducing transmission within families and daycare settings.

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Erysipelas and Cellulitis

Dennis L. Stevens

19

ABSTRACT

Pathologically, *cellulitis* is defined as a diffuse area of soft-tissue infection characterized by leukocytic infiltration of the dermis, capillary dilatation, and proliferation of bacteria. Clinically, cellulitis is recognized as an acute infection of the skin characterized by localized pain, pinkish erythema, swelling, heat, and a diffuse, indistinct border. Erysipelas is similar to cellulitis but characteristically has fiery red erythema and a distinct border. Cellulitis can be caused by microbes colonizing the skin or by bacteria introduced through animal contact, including bites from dogs, cats, and humans. In the last case, causative microbes are normal inhabitants of the oral flora of the specific animal. Endogenous flora of the human skin that most commonly cause cellulitis are streptococcal species such as groups A, B, C, and G streptococci. Cultures of cellulitic skin are generally positive in bite wound cases but positive in only approximately 25% of cases in which the infection is caused by endogenous flora. This is likely because the streptococci produce a variety of readily diffusible protein toxins that mediate the inflammatory reaction. Thus, relatively few microbes may actually be present in the skin. Clearly, better diagnostic reagents are needed to improve the management of patients with cellulitis.

DISEASE BURDEN, EPIDEMIOLOGY, AND MICROBIOLOGY

The epidemiology of cellulitis is poorly defined. It is not a reportable disease, and establishment of a specific causative diagnosis may be difficult, as described previously. Currently, there are nearly 1 million hospital admissions for skin and soft-tissue infections (SSTIs) in the United States annually, and this figure has increased 29% since 2000. Figures for outpatient cases are not available. Cellulitis is clearly among the more common diagnoses within the category of SSTIs that necessitate hospitalization. Recent clinical trials suggest that cellulitis represents about 30% of complicated SSTIs; however, this figure is likely an underrepresentation, because these trials generally exclude patients who do not have a specific microbe isolated. In addition, such trials enhance the representation of localized abscesses and carbuncles owing to the ease of obtaining culture-positive material. Thus, these trials uniformly suggest that *Staphylococcus aureus* is the most common cause of "culturable" SSTI. Cellulitis and erysipelas are most commonly caused by *Streptococcus pyogenes* and occasionally by streptococci of groups B, C, and G. Establishment of the correct disease burden of cellulitis will require prospective population-based studies and more sensitive microbial detection methods (Figure 19-1).

PATHOGENESIS AND RISK FACTORS

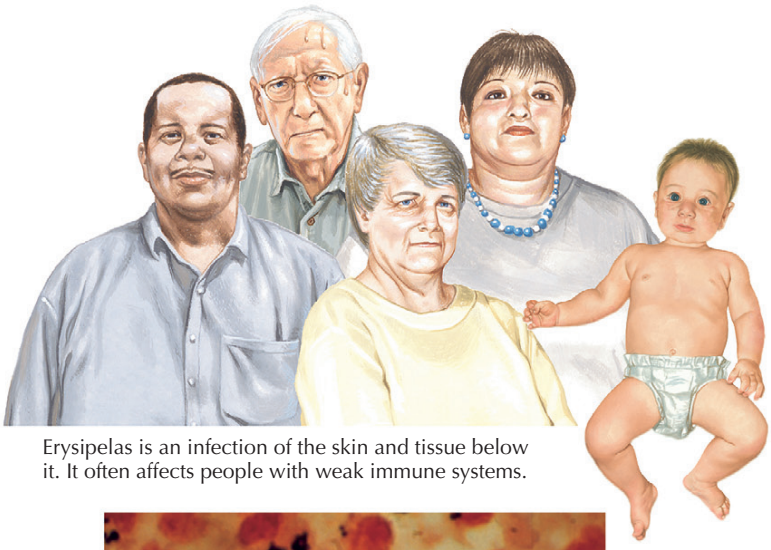
Intact, healthy skin in nonimmunocompromised hosts is a nearly perfect barrier to infection. Thus, cellulitis occurs only when one or more risk factors are present. Minute breaks in the skin barrier are most commonly caused by abrasions; insect bites; burns; splinters; dermatophyte infections; particularly of the toe webs; animal or human bites; or surgery. In addition, certain conditions appear to predispose to infection without providing a portal of entry, including chronic venous insufficiency and lymphedema (Table 19-1). Thus, cellulitis and erysipelas caused by streptococci are much more common in patients with stasis dermatitis from venous insufficiency and chronic lymphedema from elephantiasis, radical mastectomy, or prostatectomy with regional node dissection.

Virtually nothing is known regarding the host response and microbe virulence factors responsible for pathogenesis. Clearly all the cardinal manifestations of acute inflammation are present in diffuse spreading cellulitis. Because cytokines such as tumor necrosis factor (TNF) and interleukin-1 (IL-1) are important acute response cytokines in general, they likely play an important role in mediating the pain, redness, and heat so characteristic of cellulitis and erysipelas. In addition, diffusion of a number of extracellular toxins from a nidus of infection to surrounding tissues undoubtedly also contributes to these signs and symptoms of disease.

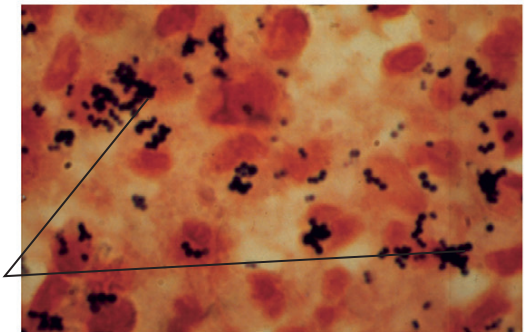
CLINICAL FEATURES

Erysipelas

Erysipelas may be a specific variant of cellulitis but can be distinguished by its precise margin and bright color (Figure 19-2). Erysipelas involves the outer layer of the epidermis, whereas cellulitis extends into the subcutaneous tissues, which probably explains the more diffuse margins and pinkish color of cellulitis. Erysipelas is characterized by the abrupt onset of fiery red swelling of the face or extremities. Erysipelas is most common in elderly adults, and the severity of systemic toxicity can vary from region to region. Distinctive features are well-defined margins, particularly along the nasolabial fold, rapid progression, and intense pain. Flaccid superficial bullae may develop during the second to third day of the illness, but extension to deeper soft tissues is rare. Desquamation of the involved skin occurs after 5 to 10 days. Whereas most studies suggest that erysipelas has become less common and less severe now than in the past based on hospitalization records, a recent study from Belgium demonstrated an increase from 1.88 cases per 1000 population to



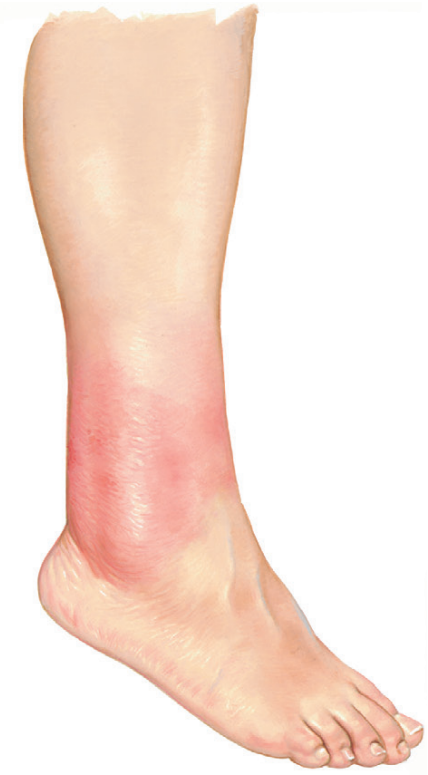
Erysipelas is an infection of the skin and tissue below it. It often affects people with weak immune systems.



Bacteria

The infection is caused by a kind of bacteria called group A streptococci.

F. Netter M.D.
C. Machado M.D.

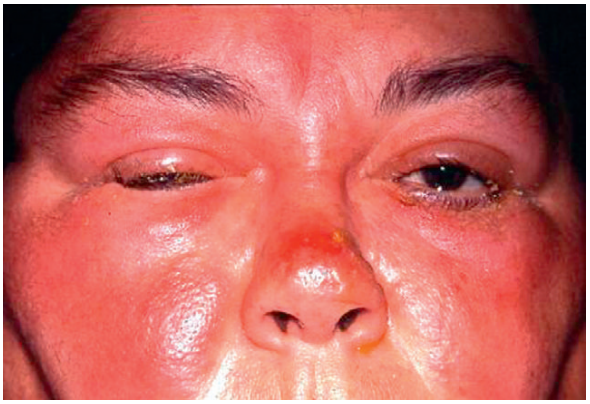


The leg is usually affected. The skin becomes red and swollen, feels tender and hot, and can have blisters. Other symptoms are fever, chills, headache, tiredness, loss of appetite, abdominal pain, and swollen glands.

Figure 19-1 Erysipelas.

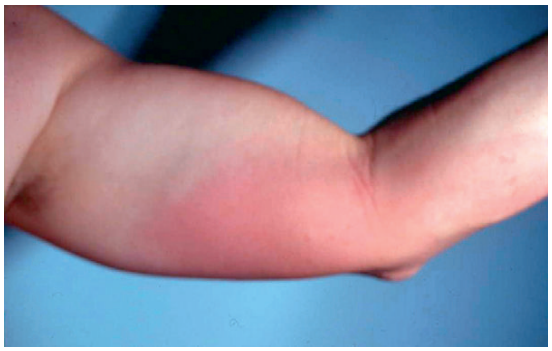
Table 19-1 Cellulitis Associated with Specific Exposures or Underlying Medical Conditions

RISK FACTORS	LIKELY CAUSATIVE AGENT
Cat bite	*Pasteurella multocida*
Dog bite	*P. multocida*, *Capnocytophaga canimorsus* (DF-2), *Staphylococcus intermedius*
Human bite	*Streptococcus pyogenes*, *Eikenella corrodens*, *Staphylococcus aureus*, *Fusobacterium*, *Peptostreptococcus*, *Prevotella*, *Porphyromonas*
Tick bite + erythema chronicum migrans	*Borrelia burgdorferi*
Hot tub exposure	*Pseudomonas aeruginosa*
Diabetes mellitus	Group B streptococci
Periorbital cellulitis (children)	*Haemophilus influenzae*
Saphenous vein donor site	Groups C and G streptococci
Fresh water laceration	*Aeromonas hydrophila*
Sea water exposure, cirrhosis, raw oysters	*Vibrio vulnificus*
Chronic stasis dermatitis	Groups A, C, and G streptococci
Lymphedema	Groups A, C, and G streptococci
Cat scratch	*Bartonella henselae*, *Bartonella quintana*
Tilapia fish	*Streptococcus iniae*
Fishmongering, bone rendering	*Erysipelothrix rhusiopathiae*
Fishtank exposure	*Mycobacterium marinum*
Compromised host + ecthyma gangrenosum	*P. aeruginosa*
Compromised host	*Stenotrophomonas hydrophila*



Note the bright red salmon color of the skin and the well demarcated edge along the nasolabial fold. Erysipelas is a superficial infection and scarring is rare. Infection can occur on the face or lower extremity.

Figure 19-2 Erysipelas.



Note the pinkish color and less distinct edge of the infection. This is subcutaneous infection and is usually caused by streptococci, including groups A, B, C, and G (non-purulent cellulitis). There is usually not a portal of entry. If a purulent center is present, the surrounding erythema is referred to as a purulent cellulitis and the cause is most commonly *S. aureus*.

Figure 19-3 Cellulitis.

2.49 cases per 1000 population between 1994 and 2004. Erysipelas is most commonly caused by *S. pyogenes* and less commonly by group C or group G *Streptococcus.* The erythema, pain, tenderness, and swelling of erysipelas are likely caused by potent streptococcal toxins and/or by the host responses to these toxins. Thus cultures may be negative owing to the relatively low number of microbes that is sufficient to cause infection. Occasionally, bullous lesions and throat cultures are positive for group A streptococci even when skin cultures are negative. A rare form of erysipelas is caused by *Campylobacter jejuni* and *Campylobacter fetus* in patients with agammaglobulinemia and occasionally in patients with acquired immunodeficiency syndrome (AIDS). Surgical debridement is rarely necessary, and treatment with penicillin is effective. Swelling may progress for a time despite appropriate treatment, even while fever, pain, and the intense red color are diminishing. A hemorrhagic form of erysipelas caused by group A streptococci has been described in six patients who developed purpura, bullae, and petechiae despite antibiotics but who responded to a combination of antibiotics and corticosteroids.

Cellulitis

The term *cellulitis* is commonly used by physicians, but is not well defined in the literature. Pathologically, it is a diffuse area of soft-tissue inflammation associated with leukocytic infiltration of the dermis, capillary dilatation, and proliferation of bacteria. Clinically, cellulitis is recognized as an acute inflammatory condition of the skin characterized by localized pain, erythema, swelling, and heat. The area of erythema is a paler pink than the flaming red of erysipelas and has indistinct margins (Figure 19-3).

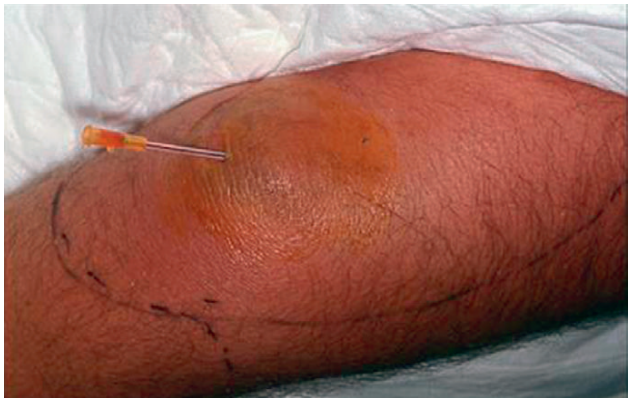
Cellulitis is most commonly caused by indigenous flora such as *S. pyogenes* followed by groups B, C, and G streptococci, which colonize the skin and appendages. Bacteria may gain access to the epidermis through cracks in the skin, abrasions, cuts, burns, insect bites, surgical incisions, and intravenous catheters. The erythema surrounding a central localized infection such as a furuncle, carbuncle, or abscess caused by *S. aureus* is in reality likely just an inflammatory reaction to the focal infection but is sometimes said to be cellulitis. Drainage of these

abscesses involves opening the central part of the lesion, and usually the incision is not extended into the surrounding erythema. Cultures of the purulent center are invariably positive for staphylococcal species (Figure 19-4), but cultures of the areas of centripetal erythema are usually negative. The genesis of these localized staphylococcal abscesses is usually secondary to folliculitis or a foreign body (e.g., a splinter, prosthetic device, or intravascular catheter) or surgical procedures. In contrast, streptococcal cellulitis may begin spontaneously with no defined portal of entry and is a more rapidly spreading diffuse process, commony associated with lymphangitis and fever.

Recurrent Cellulitis and Erysipelas

Recurrent streptococcal cellulitis of the lower extremities may be caused by group A, C, or G streptococci in association with skin lesions such as chronic venous stasis, saphenous venectomy for coronary artery bypass surgery, and lymphedema. Recently a retrospective study demonstrated that a recurrence of cellulitis or erysipelas occurred in 47% of 171 patients and was positively associated with chronic edema of the affected leg. Streptococci also cause recurrent cellulitis or erysipelas in patients with chronic lymphedema resulting from irradiation, lymph node dissection (breast and prostatic cancer), Milroy's disease, or elephantiasis. Finally, among 47 patients with an average of 4.1 recurrent episodes of erysipelas, cutaneous barrier disruption was found in 81% and was usually intertrigo (60%).

In a recent study, patients with at least three recurrences of erysipelas of the upper extremity after radical mastectomy for breast cancer were treated with 2.4 million units of benzathine penicillin given intramuscularly every 2 weeks. The mean erysipelas-free period was 2.7 years. The estimated recurrence rate at 1 year was 26%. Thus there was a therapeutic benefit, but recurrences did occur despite parenteral prophylaxis. A second study investigating recurrences after an initial episode of erysipelas identified a recurrence rate of around 8% of patients despite a variety of antibiotic prophylactic treatments. Noncompliance and inappropriate antibiotics were the major cause of failure.



The focus of infection in this elbow is the olecranon bursa and the organism is methicillin-resistant *S. aureus*.

Figure 19-4 Purulent cellulitis.

DIAGNOSIS

The cause of cellulitis and erysipelas can be suspected on the basis of the epidemiologic data supplied earlier. If there is drainage, an open wound, or an obvious portal of entry, Gram stain and culture can often provide a definitive diagnosis. In the absence of these findings, the bacterial cause of cellulitis may be difficult to establish. Even with needle aspiration from the leading edge or punch biopsy of the cellulitis itself, cultures are positive in only 20% of cases. This suggests that relatively low numbers of bacteria may cause cellulitis and that the expanding area of erythema within the skin may be the direct result of extracellular toxins or the soluble mediators of inflammation elicited by the host.

DIFFERENTIAL DIAGNOSIS

Staphylococcal infections of deeper tissues may also cause superficial redness, warmth, and swelling of the skin, even though the skin itself is not infected. Examples include olecranon bursitis, septic arthritis, osteomyelitis, and staphylococcal parotitis. Acute gout can also be associated with red, hot, and tender skin overlying the affected joint and can therefore mimic cellulitis. Other deep infections of the head and neck, such as anaerobic infections, actinomycosis, and tooth abscesses can also be confused with cellulitis. Deep infections such as staphylococcal or streptococcal myositis, necrotizing fasciitis, or gas gangrene may resemble cellulitis initially, but in these severe infections marked evidence of systemic toxicity is usually present. The brown recluse spider bite resembles acute infection soon after the bite but rapidly progresses to localized tissue destruction and central necrosis from the action of its dermonecrotic toxins. These infections may resemble pyoderma gangrenosum or may become secondarily infected with skin organisms. Finally, cutaneous allergic reactions to soaps, topical agents, insect bites, and so on can have the appearance of cellulitis and of course may serve as a portal of entry for indigenous flora and become secondarily infected.

MANAGEMENT AND ANTIBIOTIC TREATMENT

In contrast to staphylococcal cutaneous abscesses, surgical debridement of streptococcal cellulitis is rarely necessary, and treatment with penicillin is effective. Swelling may progress for 24 to 36 hours despite appropriate treatment. However, fever, pain, and the intense red color diminish. Commonly, the red to pink color of cellulitis becomes more of a reddish blue color after 24 hours of appropriate antibiotic treatment. Thus these findings are indicative of a good response to treatment. In contrast, patients who manifest continued swelling, increased pain, and persistent fever and have evidence of systemic toxicity such as rising serum creatinine, leukocytosis, tachycardia, or hypotension should be emergently evaluated for deeper infection such as septic joint, necrotizing fasciitis, or gas gangrene.

Empirical Choices of Antibiotics for the Treatment of Cellulitis

Because many different microbes can cause cellulitis, the choice of initial empirical antibiotic therapy depends on the risk factors,

exposures, and clinical features described earlier. Once cultures and sensitivities are available, the choice is easier and more specific. The physician must first decide whether the patient's illness is severe enough to require parenteral treatment, either in the hospital or on an outpatient basis.

Presumed Streptococcal or Staphylococcal Cellulitis Requiring Hospitalization

For presumed streptococcal or staphylococcal cellulitis, nafcillin, cephalothin, cefuroxime, vancomycin, or erythromycin is a good choice. Cefazolin and ceftriaxone have less activity against *S. aureus* than cephalothin, although clinical trials have shown a high degree of efficacy. Ceftriaxone is a useful choice for outpatient treatment because it can be given once daily. Similarly, teicoplanin and vancomycin have excellent activity against *S. pyogenes* and *S. aureus*, but teicoplanin, unlike vancomycin, may be given once daily by intravenous or intramuscular injection. Because of the virtual epidemic of methicillin-resistant *S. aureus* (MRSA) infections worldwide, severe soft-tissue infections in patients who are toxic, in those who have been recently hospitalized, or in those who previously received antibiotics should be treated with agents that have high-level activity against these strains. Reasonable choice would be vancomycin, tigecycline, linezolid, daptomycin, teicoplanin, or telavancin. Appropriate cultures and sensitivities as well as local antibiograms are thus crucial for treatment rationale.

Empirical Choices of Antibiotics for Outpatient Treatment of Cellulitis

For patients with less severe infections, treatment with an oral antibiotic such as dicloxacillin, cefuroxime axetil, cefpodoxime, erythromycin, clarithromycin, or azithromycin is effective.

For known group A, B, C, or G streptococcal infections, penicillin or erythromycin should be used orally or parenterally. For serious group A streptococcal infections such as necrotizing fasciitis or streptococcal toxic shock syndrome, clindamycin is more efficacious than penicillin. This is probably because in this type of infection, in which there are large numbers of bacteria, streptococci are in a stationary growth phase and do not express a full complement of penicillin-binding proteins. In contrast, the activity of clindamycin is not affected by inoculum size or growth phase. In addition, clindamycin suppresses the synthesis of many streptococcal exotoxins and surface proteins. In situations in which MRSA coverage is necessary, clindamycin has been used effectively in children, although clindamycin resistance is increasingly becoming problematic. Though trimethoprim and tetracycline have been used for oral treatment of minor MRSA infections after incision and drainage, these antibiotics do not have predictable in vitro activity against streptococci. Thus if empirical treatment demands coverage for both MRSA and streptococci, Septra plus penicillin or an oral cephalosporin may be necessary. Linezolid had excellent activity against both and is an oral agent, but the expense is a major consideration.

Treatment of Cellulitis Caused by Unusual Microbes

For cellulitis associated with *Eikenella corrodens*, useful antibiotics are penicillin, ceftriaxone, sulfamethoxazole-trimethoprim, tetracyclines, and fluoroquinolones. Interestingly, this organism is resistant to oxacillin, cefazolin, clindamycin, and erythromycin. Cellulitis associated with cat bites may fail to respond to treatment with oral cephalosporins, erythromycins, and dicloxacillin. Reasons for failure include resistance of *Pasteurella multocida* to oxacillin and dicloxacillin and the inadequate serum and tissue levels attained with older oral cephalosporins and erythromycins. *P. multocida* is resistant to dicloxacillin and nafcillin but sensitive to all other β-lactam antimicrobials as well as quinolones, tetracycline, and erythromycin. Ampicillin-clavulanate, ampicillin-sulbactam, and cefoxitin are good choices for treating animal or human bite infections. *Aeromonas hydrophila* is sensitive to aminoglycosides, fluoroquinolones, chloramphenicol, trimethoprim-sulfamethoxazole (co-trimoxazole), and third-generation cephalosporins but is resistant to ampicillin. Rifampin (rifampicin) plus ethambutol has been an effective treatment for *Mycobacterium marinum*, although no comprehensive studies have been carried out. In addition, some strains of *M. marinum* are also susceptible to tetracycline or trimethoprim-sulfamethoxazole. The gram-positive aerobic rod *Erysipelothrix rhusiopathiae*, which causes cellulitis in bone renderers and fishmongers, remains susceptible to erythromycin, clindamycin, tetracycline, and cephalosporins but is resistant to sulfonamides and chloramphenicol.

Soft-tissue infections caused by *Pseudomonas aeruginosa* are seen most often in compromised hosts, burn patients, or those with hot tub exposure. In addition, *P. aeruginosa* may be introduced into the deep tissues by stepping on a nail, a scenario referred to as the "sweaty tennis shoe syndrome." Treatment includes surgical inspection and drainage, particularly if the injury also involves bone or the joint capsule. Choices for empirical treatment of *P. aeruginosa* SSTIs pending antimicrobial susceptibility data include aminoglycosides, third-generation cephalosporins such as ceftazidime, cefoperazone, or cefotaxime, semisynthetic penicillins such as piperacillin-tazobactam, penem compounds, and fluoroquinolones. (The quinolones are not approved for use in children younger than 13 years of age.)

Recently, *Stenotrophomonas maltophilia* has emerged as an important cause of nosocomial cellulitis in patients who have cancer. The bacterium has been isolated from incubators, nebulizers, humidifiers, and tap water in hospitals. The cellulitis may be related to intravenous catheters and in some circumstances may be metastatic via the bloodstream. Trimethoprim-sulfamethoxazole or ticarcillin–clavulanic acid with or without ciprofloxacin is a reasonable treatment choice, although cultures and sensitivities are important because of the high prevalence of antibiotic-resistant organisms in the healthcare environment.

Further information regarding the diagnosis and treatment of common and uncommon skin and soft-tissue infections, including those in compromised hosts, can be found in "Practice Guidelines for Diagnosis and Management of Skin and Soft-Tissue Infections." See Additional Resources.

EVIDENCE

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ADDITIONAL RESOURCES

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Folliculitis, Furuncles, and Carbuncles

Dennis L. Stevens

20

ABSTRACT

Localized purulent infections of the skin are extremely common in all parts to the world in all age groups and in both sexes. *Staphylococcus aureus* is the single most common cause of these infections; most are minor, requiring local treatment such as drainage—unless systemic effects are evident, in which case surgical incision and drainage as well as appropriate antibiotics are necessary. In the past a wide variety of antibiotics were effective against these bacteria, but over the last 5 to 6 years there has been a virtual explosion of skin and soft-tissue infections caused by methicillin-resistant *S. aureus* (MRSA). MRSA infections pose two major problems for the clinician: first, resistance to all β-lactam antibiotics including cephalosporins, and second, an apparent increase in severity.

DISEASE BURDEN

S. aureus is once again reemerging as a major threat to human health and well-being the world over. Folliculitis, furuncles, and carbuncles have plagued *Homo sapiens* throughout their evolution. *S. aureus* too has evolved and adapted to a wide variety of human conditions and medical innovations. After the introduction of antibiotics, *S. aureus* developed resistance to penicillin in the 1940s, and in the 1950s it emerged as an important cause of serious nosocomial infections. With the development and widespread use of chloramphenicol and tetracycline in the 1960s, a wide variety of superinfections with antibiotic-resistant *S. aureus* strains occurred. The timely discovery of β-lactamase–resistant cephalosporins and later the semi-synthetic β-lactam antibiotics (methicillin, oxacillin, and nafcillin) provided effective treatments for the next 10 to 15 years. Still, as early as the 1970s, sporadic reports of MRSA began to appear. Epidemics of MRSA were reported in some unique facilities with extremely ill patients and with intense antibiotic usage. Over the subsequent 20 to 30 years, the widespread emergence of MRSA infections has been observed in certain regions of Europe, throughout the United States, as well as in Japan and the Western Pacific. Until very recently these MRSA strains have largely been associated with hospital-acquired infections (HA-MRSA). Only recently have reports of true community-acquired MRSA (CA-MRSA) infections begun to emerge. Empiric treatment of some of these cases with conventional antibiotic agents was inadequate and resulted in disastrous outcomes before it was determined that the causative agent was MRSA. CA-MRSA has been named the USA300 strain.

PATHOGENESIS OF CUTANEOUS INFECTION AND THE GENETICS OF MRSA STRAINS

Staphylococci colonize the skin and nasal mucosa of approximately 20% of the population. Proliferation of these bacteria within the epidermis or dermis can occur after minor trauma that carries the microbes to deeper structures. Thus a sliver can carry staphylococci into the dermis and result in a felon or subcutaneous abscess (Figure 20-1). In addition, alteration of the barrier function of intact skin after water immersion, thumb sucking, or a hang nail can result in paronychia (Figure 20-2). Similarly, obstruction of hair follicles can result in development of folliculitis, furuncles, and carbuncles in the skin (see Figure 20-1) or in the anterior nares (Figure 20-3).

The earliest tissue response in staphylococcal infection is acute inflammation with a vigorous exudation of polymorphonuclear leukocytes. Vascular thrombosis and tissue necrosis quickly lead to abscess formation. As a result of the development of a fibrin meshwork and later fibroblast proliferation, these abscesses become walled-off zones of loculated infection and tissue destruction, with dying leukocytes and viable bacteria at the center. Fibrosis and scarring are often prominent in healing. CA-MRSA strains appear to have the ability to cause necrosis of not only soft-tissue structures but also lung tissue. Although the precise toxin responsible is debated, the histopathology suggests disruption of vascular integrity, reduced tissue perfusion, and subsequent tissue necrosis.

There is now clear genetic-based evidence that CA-MRSA strains are distinct from HA-MRSA. In fact, Daum and colleagues (2004) demonstrated that there are at least four different types of *mecA* (methicillin resistance) gene cassettes. Interestingly, types I, II, and III are associated with strains causing HA-MRSA infections, whereas type IV distinguishes CA-MRSA strains. The type IV *mecA* gene cassette is much smaller (23 kD) compared with types I, II, and III, which are 95, 80, and 55 kD, respectively. It has been postulated that if smaller gene cassette size is in fact associated with greater likelihood of transfer of antibiotic resistance to sensitive strains, then many strains of *S. aureus* in the community could acquire *mecA* gene cassette type IV, and the prevalence of CA-MRSA infections would increase dramatically. Indeed, this phenomenon has come to fruition, and recent estimates document that 59% of staphylococcal isolates causing skin and soft-tissue infections in the outpatient setting are in fact CA-MRSA. Whereas most of the infections associated with CA-MRSA are folliculitis, furuncles, carbuncles,

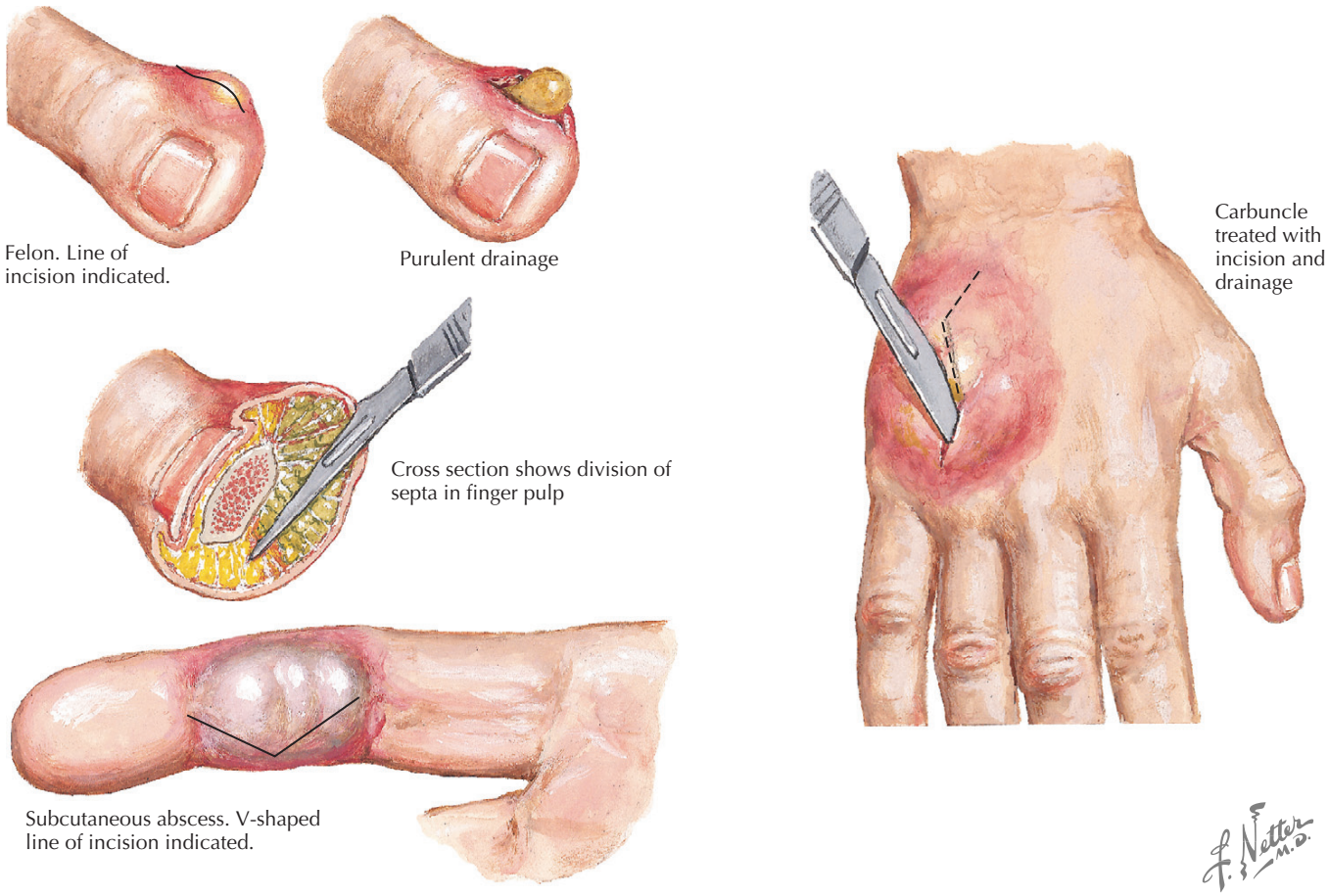


Figure 20-1 Cellulitis and epidermal access.

and cutaneous abscesses, more severe infections have been described including necrotizing fasciitis and hemorrhagic necrotizing pneumonia. In each case, these novel syndromes have been the result of *S. aureus* strains acquiring mobile genetic elements, usually bacteriophages carrying genes coding for certain virulence factors, with subsequent incorporation of specific toxin genes, including the Panton-Valentine leukocidin (PVL) gene into the CA-MRSA genome. Though there is clearly an association between CA-MRSA strains, severity of infection, and presence of the PVL gene, Hamilton and colleagues (2007) showed no correlation between severity of human diseases and the level of PVL production in various CA-MRSA clinical strains. Additional studies to identify the role of virulent extracellular toxins of *S. aureus* in human diseases is warranted. Whereas PVL toxin has gotten much attention, clearly alpha-hemolysin and fibronectin binding proteins, among others, are well recognized virulence factors in a variety of *S. aureus* infections.

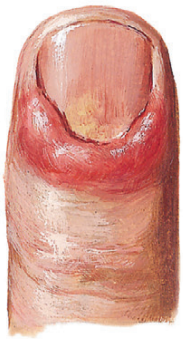
RISK FACTORS

The importance of the granulocyte in host defense is supported by the enhanced susceptibility to staphylococcal infections seen in patients with neutropenia or various disorders of neutrophil function, such as chronic granulomatous disease, Chediak-Higashi syndrome, and various disorders of neutrophil chemotaxis. Although it has been suggested that diabetic patients are especially prone to boils and carbuncles, few data support this concept. In contrast, it is well established that patients with Job's syndrome, who have high levels of serum immunoglobulin E (IgE) antibody and often a congenital defect of the STAT3 signaling pathway, are strongly predisposed to these focal *S. aureus* infections. However, the most important factors predisposing to staphylococcal infections are not immunologic defects but mechanical defects. Minute skin abrasions, other minor trauma, and puncture wounds from slivers, to mention a few, provide the portal of entry in most staphylococcal skin infections.

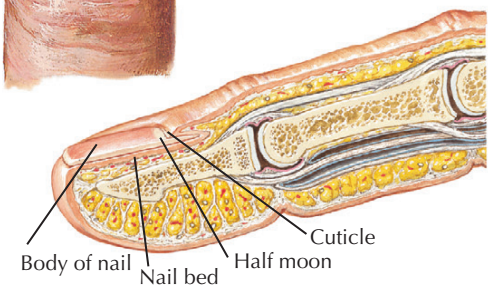
CLINICAL FEATURES OF FOLLICULITIS, FURUNCLES, AND CARBUNCLES

Evolution of Folliculitis to Furuncles, Carbuncles, and Abscesses

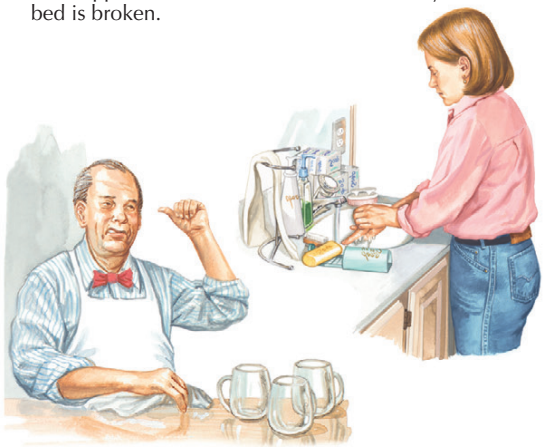
Pustules or abscesses can develop when microorganisms that permanently or transiently reside on skin surfaces are introduced into deeper tissues after even minor skin trauma, as described earlier. Pathogens can also seed the skin hematogenously after bacteremia secondary to a variety of infections including endocarditis or by contiguous spread from infectious foci in the lung or gastrointestinal tract. Most commonly, small



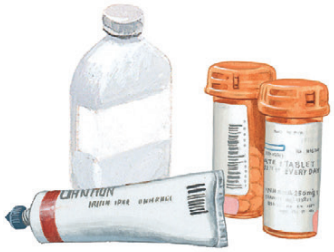
Paronychia is a very common infection of the skin around fingernails, caused by bacteria or fungi. The skin becomes red and swollen, and the area may have pus.



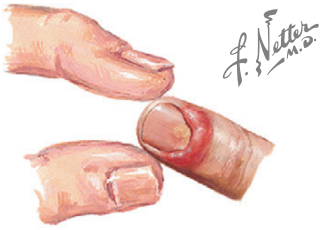
The nail body lies on top of the nail bed. An infection can happen when the seal between the body and bed is broken.



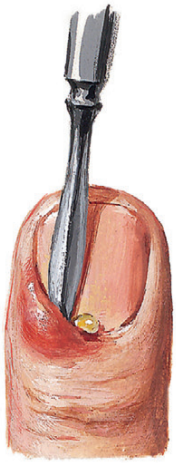
You may be more prone to developing the infection if your hands are often wet (such as dishwashers and bartenders). Biting nails or hangnails, thumb sucking, penetrating injuries (e.g., from splinters), and exposure to harsh chemicals, acrylic nails, or nail glue can lead to infection.



Treatment can be simply soaking in water with liquid antibacterial soap. Your doctor may prescribe a topical antibiotic cream or lotion (if bacteria are the cause) or an antifungal medicine given by mouth (if a fungus is the cause).



Your doctor will diagnose paronychia by examining your fingernails.



Your doctor may need to drain the pus.

Wear vinyl gloves to prevent contact with irritating substances, such as water, soap, detergent, scouring pads, and chemicals.

Figure 20-2 Managing paronychia.

Figure 20-3 Furuncle of nasal mucosa.

focal abscesses develop in the superficial layers of the skin, where hair follicles serve as the portal of entry. Such lesions are called *folliculitis*. *S. aureus* accounts for most of these infections, but many different bacterial species can cause localized folliculitis on occasion.

Folliculitis can progress to form subcutaneous abscesses, called *furuncles* or *boils*, which usually drain and resolve spontaneously but may progress to form a large, exquisitely painful group of contiguous furuncles, called a *carbuncle*. Felons are subcutaneous abscesses that develop on the pulp of digits (see Figure 20-1) and paronychia develops between the nail bed and the overlying skin of a digit (see Figure 20-2).

Recurrent Furunculosis

The greatest predisposing factor for developing recurrent furunculosis has been the colonization of the anterior nares with

S. aureus. Small abscesses or furuncles can develop around hair follicles of the anterior nares as well (see Figure 20-3). Thus, touching the nose or nasal secretions and then rubbing or scratching the skin results in autoinoculation and abscess formation. Interpersonal contact with contaminated fingers may result in spread of *S. aureus* carriage or infection to others, especially in situations where there is close physical contact. CA-MRSA strains that harbor PVL have been associated with epidemics of these types of infections among prisoners, athletes, and children in daycare centers. Breaking the cycle can be useful to prevent recurrences; however, it is first important to document nasal colonization by appropriate culture techniques. Topical application of intranasal mupirocin or bacitracin ointment for the first 5 days of each month has been shown to decrease colonization and reduce the frequency of recurrent infection by about 50%. Treatment of recurrent furunculosis may require surgical incision and drainage as well as antistaphylococcal antibiotics such as oral dicloxacillin or parenteral nafcillin for methicillin-sensitive *S. aureus* (MSSA) or alternative treatments for MRSA as described later.

Diffuse Folliculitis

Diffuse folliculitis occurs in two distinct settings. The first, "hot tub folliculitis," is caused by *Pseudomonas aeruginosa* bacteria, which can flourish in water maintained at a temperature of 98.6° to 104° F (37° to 40° C) that is insufficiently chlorinated. The infection is usually self-limited, although serious complications of bacteremia and shock have occasionally been reported.

The second form of diffuse folliculitis, "swimmer's itch," occurs when the skin is exposed to bodies of fresh water contaminated with avian schistosomes. Warm water temperatures and alkaline pH provide a suitable habitat for snails, which are the intermediate hosts between birds and humans. Free-swimming parasitic larvae called *cercariae*, shed by the snails into freshwater lakes and rivers, readily penetrate human hair follicles or pores, but quickly die. This triggers a brisk allergic reaction, causing intense itching, erythema, and sometimes a papular rash. The infestation is self-limited, secondary infection is uncommon, and oral antihistamines and topical corticosteroid cream usually relieve the symptoms promptly.

DIAGNOSTIC APPROACH

In evaluating patients with focal cutaneous infections, *S. aureus* is clearly the most common microbe causing such infections. However, the empiric treatment of staphylococcal infections has become increasingly complex owing to the rapid increase in the prevalence of both CA-MRSA and HA-MRSA strains. The clinical decisions regarding diagnostic tests, selection of empiric antibiotic therapy, route of antibiotic administration, and surgical intervention must be based on the seriousness of the infection, the trends in staphylococcal resistance patterns (i.e., percentage of strains that are MRSA) in the specific geographic area, and the established risk factors for MRSA infection in a given patient. More than ever, making a correct diagnosis and obtaining good culture material for bacterial isolation and antibiotic susceptibility testing are crucial for rational antibiotic selection, as switching from the initial empiric therapy may be warranted by the results of susceptibility testing on the culture isolate. Should a CA-MRSA strain be isolated, careful follow-up, monitoring of the patient's clinical course, and changing therapy promptly according to the antibiotic susceptibility pattern may be necessary to ensure good outcomes.

TREATMENT

Treatment of Minor Staphylococcal Infections

Minor staphylococcal infections of the skin, such as folliculitis, furunculosis, paronychia, and styes, generally respond well to the topical application of warm soaks. Larger focal infections, such as carbuncles or deep abscesses (particularly those over 5 cm in diameter), often require incision and drainage (see Figure 20-1). Concomitant antibiotic treatment is indicated in the following situations:

- When the infection is associated with systemic signs of infection (e.g., fever or tachycardia)
- When lesions are large, numerous, or recurrent
- When surgical drainage alone has failed
- If patients have underlying medical problems (e.g., valvular heart disease or implanted prosthetic devices)
- When the nose or face is involved

Cloxacillin (Cloxapen) or dicloxacillin (Dynapen) in an oral dose of 250 to 500 mg every 6 hours is generally sufficient for MSSA. Alternatives would be an oral cephalosporin, erythromycin, clindamycin, or one of the newer macrolides. A recent randomized trial compared antibiotics (trimethoprim-sulfamethoxazole [TMP-SMX]) with placebo in pediatric patients with MRSA skin abscesses after incision and drainage and found no difference in outcome, though those treated with antibiotics had fewer new lesions.

Treatment of Major Staphylococcal Infections with No Risk Factors for MRSA

For serious staphylococcal skin infections, such as large abscesses with fever, deep-wound sepsis, or necrotizing fasciitis, parenteral antibiotics are mandatory. Oxacillin (Bactocill) or nafcillin in a dose of 1 to 2 g every 4 hours and parenteral cephalosporins, such as cephalothin, cefuroxime axetil (Ceftin), or cefuroxime sodium (Zinacef), are excellent alternatives.

Treatment of Serious Staphylococcal Infections with a High Likelihood of MRSA

Empiric treatment of severe staphylococcal soft-tissue infections should be with an agent that has proven efficacy against MRSA, at least until antibiotic susceptibilities are available. Constitutive resistance to erythromycin is common among HA-MRSA strains and in certain geographic regions. Inducible clindamycin resistance is increasing in prevalence in both CA-MRSA and HA-MRSA strains. In addition, the use of ciprofloxacin (Cipro, Proquin XR) and even the newer quinolones is limited by the emergence of resistance. Interestingly, TMP-SMX (Bactrim, Septra) remains active against both MSSA and MRSA strains. Anecdotally, TMP-SMX also is commonly used to treat MRSA-complicated skin and skin-structure

infections. In situations where streptococcal infections cannot be excluded, cephalexin, penicillin, or clindamycin should be administered.

Vancomycin has been traditionally used as the workhorse antibiotic to treat all MRSA infections; however, numerous problems have emerged. With the increased use of vancomycin, strains of *S. aureus* have appeared that are resistant to vancomycin with minimum inhibitory concentrations (MICs) of >16 mcg/mL (vancomycin-resistant *S. aureus* [VRSA]). Although these organisms are uncommon in the United States, vigorous control measures are required to prevent them from joining vancomycin-resistant enterococci (VRE) as major nosocomial pathogens. Vancomycin-intermediate *S. aureus* (VISA) with MICs of 2 to 4 mcg/mL and heteroresistant strains with MICs of 4 to 16 mcg/mL have also appeared. Heteroresistance can be detected only in broth culture in the presence of a very large inoculum (10^7 colony-forming units [CFUs] per milliliter). There also is mounting evidence that over the course of 3 to 4 decades of vancomycin use, MICs have gradually increased, even in sensitive strains. This development has relevance to the treatment of skin and soft-tissue infections, because tissue levels of vancomycin may reach only 2 to 4 mcg/mL owing to limited tissue penetration of this antibiotic. In the past, MRSA strains commonly had MICs of 0.1 to 0.5 mcg/mL, values considerably below achievable tissue levels of vancomycin (Vancocin). As suggested, at the present time and in the future, we may encounter strains with MICs of 1 to 2 mcg/mL, which may account for the greater failure rate of vancomycin in the treatment of a variety of infections including those involving the skin and soft tissue.

New Antibiotics to Treat MRSA Infections of Skin and Soft Tissue

Recent clinical trials have documented the efficacy of linezolid (Zyvox), daptomycin (Cubicin), quinupristin-dalfopristin (Synercid), tigecycline (Tygacil), and telavancin in the treatment of skin and soft-tissue infections. One other antibiotic—teicoplanin—has excellent activity against MRSA, has proven activity in skin and soft-tissue infections, and is available in other countries, but not the United States.

Linezolid inhibits protein synthesis, but, unlike the other antibiotics in this class, it prevents the initiation of the formation of the complex of transfer ribonucleic acid (tRNA), messenger ribonucleic acid (mRNA), and ribosome. As a result, cross-resistance to other types of protein synthesis inhibitors is not possible. Linezolid has been approved in the United States for skin and soft-tissue infections as well as nosocomial and community-acquired pneumonias (CAPs) caused by MRSA, and evidence is accumulating that, like clindamycin, linezolid is a potent suppressor of toxin production by *Staphylococcus* strains. Because of this characteristic, linezolid may be a more suitable agent to use in patients with staphylococcal toxic shock syndrome (TSS) or necrotizing fasciitis caused by PVL-producing strains. In vitro, linezolid and daptomycin have shown excellent activity against VISA and VRSA.

Daptomycin and tigecycline have been approved for treatment of skin and soft-tissue infections, including MRSA, in the United States. Daptomycin's mechanism of action involves the formation of pores in the cell membranes of bacteria with rapid loss of intracellular potassium. Tigecycline is a minocycline derivative that inhibits protein synthesis.

Quinupristin-dalfopristin is a semi-synthetic derivative of pristinamycin that is at least as active as vancomycin against MRSA and may be a useful alternative when resistance phenotypes for erythromycin, ciprofloxacin, rifampicin, or gentamicin are detected. However, its administration has been associated with a high incidence of phlebitis and myopathy. As a result, its use requires a central line placement.

Telavancin and dalbavancin are semi-synthetic lipoglycopeptide antibiotics that contain a heptapeptide core enabling them to inhibit cell wall synthesis by interfering with cross-linking. In addition, telavancin and dalbavancin affect the integrity of bacterial cell membranes, increasing membrane permeability. Both drugs have activity against VISA strains but have poor activity against VRSA. Telavancin requires daily administration, but dalbavancin has an extremely long half-life (147 to 258 hours) and is given by intravenous (IV) injection of a 1-g dose and, 7 days later, 500 mg intravenously. Currently, additional phase III clinical trials comparing vancomycin with dalbavancin are underway, and its consideration by the U.S. Food and Drug Administration (FDA) has been delayed. Oritavancin is a third lipoglycopeptide and Phase III clinical trials are underway. These newer agents are promising alternatives for treatment of patients with complicated skin and skin structure infections (cSSSIs) when vancomycin cannot be used.

Iclaprim is a folic acid antagonist with fourfold to tenfold higher activity against staphylococci than TMP-SMX. Ceftobiprole has excellent activity against MRSA isolates, even though it is a cephalosporin. Phase III clinical trials for ceftobiprole and iclaprim have been completed, and the results of those trials are currently being evaluated by the FDA.

PREVENTION AND CONTROL

Epidemiologic control of staphylococcal infections requires the ongoing surveillance and reporting of infections. The dramatic increase in the prevalence of MRSA in community and hospital environments is proof of the difficulty of controlling the spread of these microbes. Contact precautions should be followed in the management of patients with active infections of skin or wounds. There has been a movement among infection-control practitioners to culture the nares of all patients admitted to hospitals in an effort to define patients at risk for MRSA infection. However, the detection and treatment of these nasal carriers is labor-intensive, and decreased infection rates may not be achieved, particularly if hospital personnel include nasal or rectal carriers with recurrent furunculosis. Topical treatment with germicidal soaps, povidone-iodine solution, or antibiotic ointments has been advocated, but long-term results have been disappointing. Topical mupirocin 2% ointment (Bactroban, Centany) can reduce the MRSA carrier rate, but, because recolonization is common, mupirocin is not recommended for extended use in long-term care facilities. A placebo-controlled trial of nasal mupirocin (Bactroban) in 34 patients who were *S. aureus* carriers found that a monthly course of nasal mupirocin reduced the incidence of nasal colonization and skin infections for at least 1 year. However, because resistance to mupirocin and

recolonization after therapy can occur, indiscriminate use of mupirocin should be avoided. Orally administered antibiotics, including rifampin (Rifadin, Rimactane), TMP-SMX, and ciprofloxacin have failed to live up to initially promising findings.

Bacterial interference, which attempts to replace epidemiologically virulent strains of staphylococci with strains that have been deliberately attenuated to be less virulent, has generally been abandoned, in part because infections have been caused by these supposedly less virulent strains. Attempts to develop staphylococcal vaccines are continuing. In a recent clinical trial in dialysis patients, a staphylococcal surface carbohydrate conjugated to *Pseudomonas* exotoxin A significantly reduced the incidence of bacteremia, although the protective antibodies lasted only 8 months.

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SUMMARY

The MRSA epidemic has evolved rapidly, and new data are needed regarding the efficacy of older antibiotic agents, such as tetracycline, clindamycin, and TMP-SMX in the treatment of MRSA infections. Because of the high prevalence of MRSA in hospitals and in the community, we are probably at the tipping point where practitioners should select antibiotic agents with proven efficacy in clinical trials for the treatment of MRSA infections. This recommendation can be stated with more confidence in seriously ill patients. As a result, a practitioner should select one of the newer antibiotic agents discussed in this chapter to treat a seriously ill patient. Because of the increased expense of those agents, it is more important than ever to make a correct microbial diagnosis and obtain antibiotic susceptibilities on clinical isolates. Based on antibiotic susceptibility testing, it may then be possible to step down to an older, and cheaper, antibiotic to complete the course of therapy.

ADDITIONAL RESOURCE

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Life-Threatening Skin and Soft-Tissue Infections

Dennis L. Stevens and Amy E. Bryant

21

ABSTRACT

This chapter discusses those soft-tissue infections that are truly life-threatening. As such, early clinical recognition is the most important aspect of clinical management. Staphylococcal and streptococcal toxic shock syndromes (referred to here as *StaphTSS* and *StrepTSS*, respectively) have similar clinical features once established, yet the prognosis and management are quite different.

Necrotizing soft-tissue infections occur in three distinct settings. The first, necrotizing fasciitis (NF) type I, occurs when mucosal barriers are breached such that mixed aerobic and anaerobic microbes are leaked into the deep soft tissues, resulting in rapidly progressive necrotizing infections. These infections are usually associated with gas-producing microbes. Surgical inspection of suspicious lesions is paramount, and if necrosis is found, adequate debridement is absolutely necessary.

The second, type II NF, is usually monomicrobic; group A *Streptococcus* is clearly most common, though *Vibrio vulnificus*, *Aeromonas hydrophila*, and methicillin-resistant *Staphylococcus aureus* (MRSA) may also cause extensive soft-tissue necrosis. Surgical intervention is also of major importance and provides a definitive etiologic diagnosis as well. These infections are usually not characterized by gas in the tissue.

The third type of necrotizing soft-tissue infection is gas gangrene (also known as *clostridial myonecrosis*). This infection is always associated with gas in the tissue and, like other forms of necrotizing soft-tissue infection, is rapidly progressive. Causative organisms include *Clostridium perfringens*, *Clostridium histolyticum*, *Clostridium septicum*, *Clostridium novyi*, and *Clostridium sordellii*. All these species are agents of gas gangrene after penetrating trauma; however, the more aerotolerant *C. septicum* can also cause spontaneous gas gangrene in patients with adenocarcinoma of the colon or neutropenia. *C. sordellii* and *C. novyi* have been associated with gas gangrene after skin injection of black tar heroin. *C. sordellii* has also recently been associated with a toxic shock–like syndrome in women after abortion or childbirth.

DISEASE BURDEN

Life-threatening skin and soft-tissue infections are relatively uncommon, and comprehensive epidemiology has been performed only for invasive group A streptococcal infections including NF. The incidence is approximately 3.5 cases per 100,000 population per year in the United States. Of these, approximately 50% are NF or myonecrosis, of which half are associated with TSS. Before the 1900s the incidence of malignant scarlet fever was as high as 25 cases per 100,000 population, but it has dramatically declined both in frequency and severity since the advent of antibiotics. Gas gangrene reached epidemic proportions during the Civil War and World Wars I and II; however, antibiotics, rapid transport to evacuation hospitals, and immediate vascular reconstruction have contributed its declining incidence among active duty military personnel. Mixed aerobic and anaerobic infections are most common in diabetic patients but may also occur after a variety of surgical procedures, such as cholecystectomy, colonic surgery, and gynecologic procedures. Although relatively uncommon, these infections can be devastating and often affect otherwise healthy individuals.

STAPHYLOCOCCAL TOXIC SHOCK SYNDROME

StaphTSS was first reported in 1978; by 1990, more than 3300 cases had been reported in the United States, 90% of which occurred during menstruation in women who were using tampons. A specific toxin, staphylococcal toxic shock syndrome toxin-1 (TSST-1), was implicated in these cases. The incidence of StaphTSS declined precipitously after superabsorbable tampons were withdrawn from the market. Currently, fewer than 100 cases of StaphTSS occur each year, and most of these nonmenstrual cases are nosocomially acquired, often as a result of postoperative staphylococcal wound infections when packing material has been used (e.g., rhinoplasty). It is interesting to note that these cases are associated with strains that produce staphylococcal enterotoxin B (SEB).

Clinical Presentation and Diagnostic Approach

StaphTSS is a multisystem disease with diverse clinical manifestations (Figure 21-1). A characteristic sunburn-type rash is present in 90% of patients; it is most prominent on the face and trunk and in intertriginous areas. It blanches with digital pressure and is often confused with a drug rash (Figure 21-2, *right*). Other early signs of StaphTSS include fever, confusion, nausea, vomiting, diarrhea, tachycardia, and hypotension. Sudden onset and skin rash are the best clues to the diagnosis.

Laboratory tests are helpful to confirm the diagnosis. Leukocytosis with a left shift and thrombocytopenia (<100,000 platelets/mm^3) are common findings. Urinalysis may show mild pyuria and, occasionally, microscopic hematuria. Blood urea nitrogen and creatinine levels are elevated in more than 50% of patients. Serum bilirubin and hepatic enzyme levels are raised in about half of patients. Serum creatine kinase levels are high in more than one third of patients, and myoglobinuria has developed in some patients. Elevated serum amylase levels are also

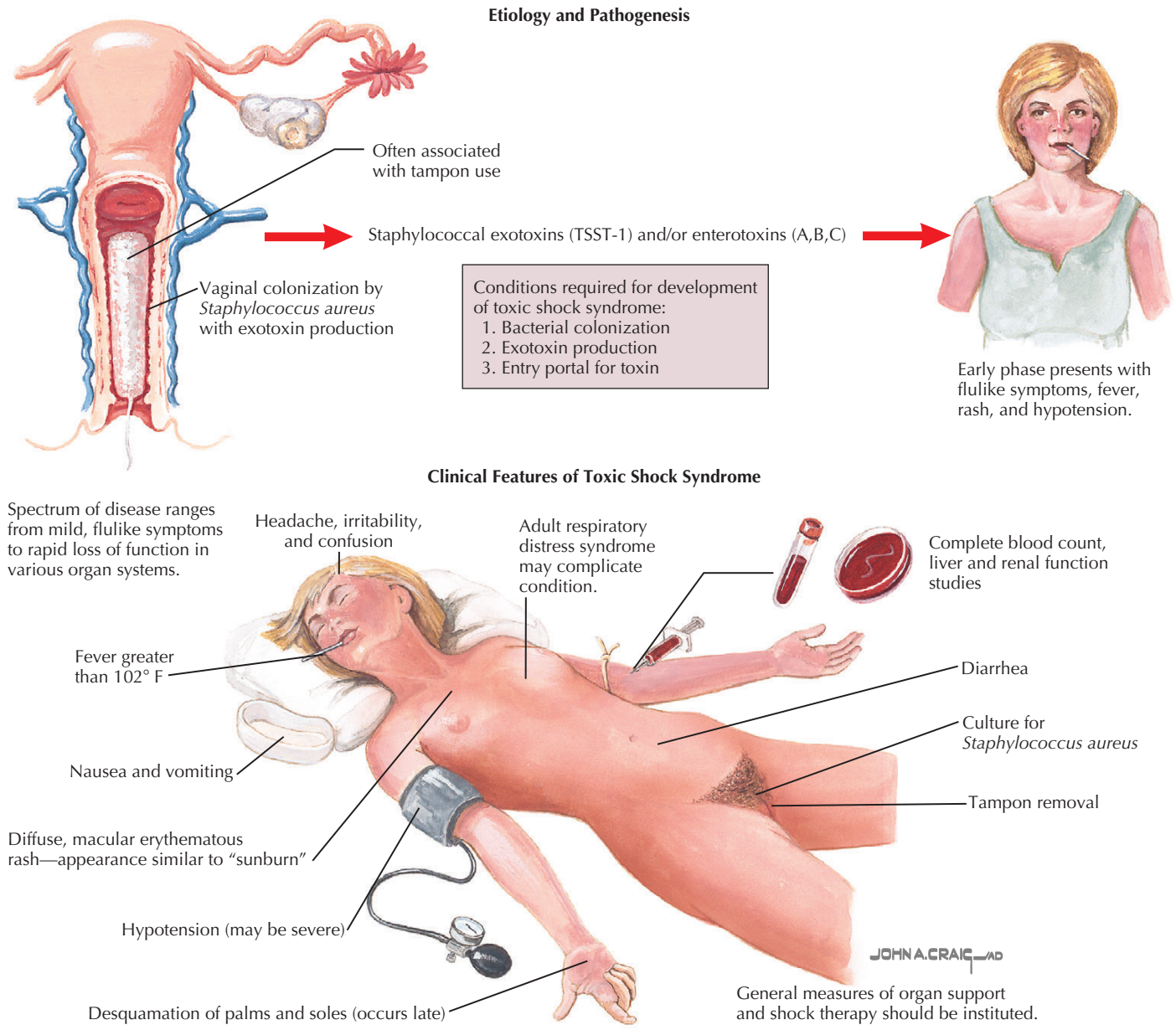


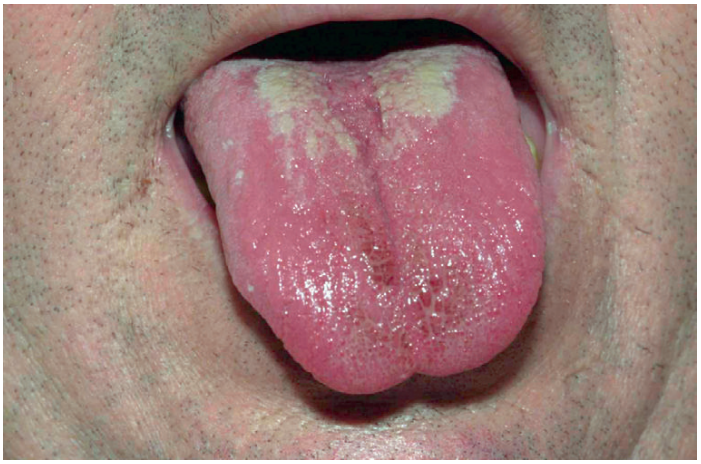
Figure 21-1 Staphylococcal toxic shock syndrome.

found but may be related to the azotemia rather than to clinically evident pancreatitis. Unexplained marked hypocalcemia is often observed. The drop in serum calcium level is out of proportion to the degree of hypoalbuminuria noted in some patients and may be caused by elevated serum calcitonin levels.

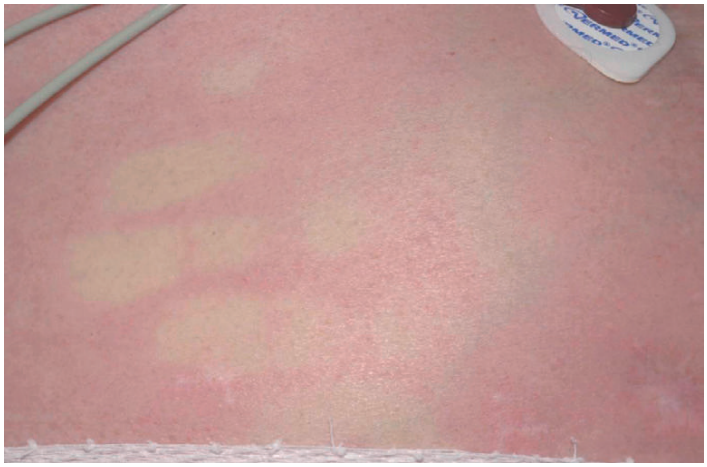
Blood cultures are negative in most cases, but a positive blood culture should not exclude the diagnosis. The original Centers for Disease Control and Prevention (CDC) definition of StaphTSS excluded patients with bacteremia, but it has been shown that some strains that cause bacteremia produce either TSST-1 or SEB. Thus some patients with bacteremia may have more complicated septic shock caused by the presence of these toxin genes. Group A streptococci can produce a severe form of TSS that resembles StaphTSS, except for the paucity of cutaneous manifestations and a marked difference in mortality (see the discussion of StrepTSS later and Table 21-1).

Treatment

The management of StaphTSS demands immediate treatment of hypotension and shock with vigorous fluid replacement (and supplemental catecholamines if needed), attention to the site of *S. aureus* colonization or infection (e.g., removal of packing material, drainage of any abscess), and systemic antimicrobial therapy with an antistaphylococcal agent. Because this infection is commonly associated with a diffuse capillary leak syndrome, administration of 10 to 12 L of normal saline may also be necessary. If the albumin drops below 1.5 g/dL, replacement with



Desquamation of the tongue with a strawberry appearance.



The diffuse sunburn-type rash of toxic shock syndrome blanches under digital pressure.

Figure 21-2 Staphylococcal toxic shock syndrome.

Table 21-1 Staphylococcal versus Streptococcal Toxic Shock Syndrome

FEATURE	STAPHYLOCOCCAL	STREPTOCOCCAL
Age	15-35	0-80
Severe pain	Rare	Common
Hypotension	100%	100%
Rash	Very common	Less common
Renal failure	Common	Common
Bacteremia	Low	60%
Tissue necrosis	Rare	Common
Risk factors	Tampons, packing	Trauma, varicella
Thrombocytopenia	Common	Common
Mortality	<3%	30%-70%

colloid rather than crystalloid should be considered. One retrospective analysis of 45 patients suggested that glucocorticoids may assist in recovery, but more data are needed before this can be recommended for all patients with StaphTSS. With proper management and support, most patients recover in 1 to 2 weeks; mortality is less than 5%.

STREPTOCOCCAL TOXIC SHOCK SYNDROME

Like StaphTSS, StrepTSS is a toxin-mediated disease. Though multiple exotoxins have been implicated in experimental studies, streptococcal pyrogenic exotoxin type A (SPEA) has been linked epidemiologically. The increased incidence of invasive streptococcal infections may also be linked to the global spread of toxigenic strains of streptococci, particularly M-types 1 and 3, containing the gene for SPEA. Like the staphylococcal toxins TSST-1 and SEB, SPEA enters the circulation and functions as a superantigen, stimulating both lymphocytes and macrophages to produce cytokines that mediate the shock syndrome.

People of all ages are vulnerable to StrepTSS; about half of the patients have diabetes or alcoholism. When a primary focus is identified, it is most often a necrotizing soft-tissue infection; respiratory infections are the next most common focus.

Clinical Presentation and Diagnostic Approach

The onset of StrepTSS can be subtle with fever, chills, nausea, vomiting, and diarrhea for 12 to 36 hours before the sudden onset of hypotension that occurs in all patients and is often severe. Other clinical features include a generalized erythematous rash (10% of cases), which desquamates 7 to 10 days into the illness, acute respiratory distress syndrome (60% of cases), renal failure (80% of cases) and soft-tissue necrosis, such as NF or myonecrosis (see Table 21-1). In patients with NF or myonecrosis, the initial complaint is often severe, unrelenting pain out of proportion to the clinical findings (see the discussion of necrotizing fasciitis, later). In many such cases, infection begins at the site of antecedent trauma that does not break the skin (e.g., muscle strain, bruise). Without a portal of bacterial entry to provide clinical clues, the diagnosis is often missed or delayed, causing mortality in these "cryptic" infections to approach 85%. Further, experimental evidence suggests that administration of nonsteroidal antiinflammatory agents may predispose to worse outcomes in these infections. Laboratory evidence of multiorgan involvement typically can be found and characteristically includes evidence of renal impairment, hepatic abnormalities, and laboratory evidence of disseminated intravascular coagulation, though clinical evidence of coagulopathy is rarely present.

Treatment

Even after aggressive treatment, including antibiotics, circulatory and respiratory support, and appropriate surgical debridement, mortality rates range from 30% to 70% (see the discussion of streptococcal necrotizing fasciitis, later, for antibiotic treatment and use of intravenous immunoglobulin [IGIV]).

SCARLET FEVER

The incidence of scarlet fever has declined sharply in the antibiotic era. When it does occur, it most commonly accompanies acute streptococcal pharyngitis. The initial symptoms are fever and sore throat. Within 1 to 5 days the characteristic fine, red, sandpaper-like eruptions appear on the skin, often beginning on the chest and rapidly spreading to other parts of the body. Although the tongue and buccal mucosa are classically involved, the perioral area may be spared, thus accounting for the typical circumoral pallor. The rash is caused by hyperemia and capillary damage produced by erythrogenic (scarlatina) toxins. In areas of trauma, such as the antecubital fossae, punctate hemorrhages (Pastia sign) may occur. Nausea and vomiting may be present, and fever and prostration may be severe. Desquamation of skin and mucous membranes is prominent during healing; one characteristic feature is the strawberry tongue (see Figure 21-2, *left*). Therapy is the same as that for the underlying streptococcal infection.

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Epidemics of staphylococcal scalded skin syndrome (SSSS) have been reported among children, usually in neonatal intensive care units, but sporadic cases have also been described among the elderly. A particular strain of *S. aureus* belonging to phage group II is responsible, and these strains produce an extracellular toxin called *exfolatin* that degrades the intercellular desmosomes, which provide tight binding between adjacent epithelial cells. Thus, flaccid fluid-filled bullae develop. The shear plane is very superficial and does not result in scarring, though considerable fluid can extravasate if lesions are extensive. The propensity of skin to slough is demonstrated by a positive Nikolsky sign, which is elicited by placing a thumb on skin and applying lateral pressure. Despite fluid loss, infection usually remains superficial and skin slippage can occur at sites remote from the primary source of infection. Thus the mortality is low.

This disease must be distinguished from toxic epidermal necrolysis (TEN) which also results in skin sloughing and is associated with a positive Nikolsky sign. TEN is more common in adults, is usually associated with drug reactions, and carries a higher mortality rate; the cleavage plane in TEN is much deeper at the stratum germinativum layer. Thus a skin biopsy or frozen section readily distinguishes SSSS from TEN. Figure 21-3 illustrates the evolution of SSSS in an elderly adult. Note the flaccid bullae.

NECROTIZING FASCIITIS

NF is a surgical diagnosis demonstrating friable deep fascia and accumulation of inflammatory fluid that resembles dishwater. Although this is a very specific surgical diagnosis, it is quite apparent that NF is also associated with necrosis of skin, subcutaneous tissue, fascia, and in some cases, muscle. Thus a better term might be *necrotizing soft-tissue infection*.

Under the current definition, NF encompasses two microbiologic entities. Type I disease is caused by mixed anaerobes (e.g., *Clostridium*, *Bacteroides*, *Prevotella*, and *Peptostreptococcus* organisms), streptococci, and enteric gram-negative bacilli (e.g., *Escherichia coli*, *Klebsiella*, and *Proteus* organisms). Infection most often complicates deep wounds, including those resulting from surgical procedures involving the gastrointestinal tract or genitourinary systems. Predisposing factors include a compromised vascular supply, either generalized or diabetes related. Type II NF (hemolytic streptococcal gangrene, "flesh-eating disease") is most commonly caused by *Streptococcus pyogenes* and may occur at the site of a cut, burn, or insect bite. It may also follow surgical wounds or childbirth or may occur spontaneously at sites of antecedent trauma that does not break the skin.

Disease Burden

NF per se is not a reportable disease, and few data exist regarding its prevalence. However, the widespread publicity given to streptococcal NF has fueled popular concern about invasive group A streptococcal infections. The CDC estimates that 10,000 to 15,000 cases of invasive group A streptococcal infections occur each year in the United States; of these, NF occurs in 5% to 10% of patients and carries a case-fatality rate of about 30%. In patients with StrepTSS, a mortality rate as high as 70% to 85% is the norm. Group A streptococcal NF is usually community acquired and sporadic in nature, and many patients have predisposing conditions such as varicella infection, trauma, diabetes, and immunosuppressive disorders. Most group A streptococci that cause invasive disease produce one or more pyrogenic (formerly erythrogenic) toxins, but the genetic heterogeneity of causative strains does not support a clonal basis for the resurgence of invasive streptococcal infections.

Clinical Presentation and Approach to the Diagnosis

Patients with NF generally have a history of the rapid onset of severe pain in a limb, along with malaise, chills, and fever. The affected area is red, hot, shiny, swollen, and exquisitely tender. Late findings of NF are a blue-black discoloration indicative of superficial necrosis near the center, blistering or bullae formation, and edema that extends beyond the margins of skin erythema. Crepitus may be palpable or audible in patients with NF resulting from gas-forming organisms such as *Clostridium* species or mixed aerobic and anaerobic bacteria. The margins of erythema may progress visibly over a matter of hours.

Approximately 50% of patients with NF caused by group A streptococci do not manifest the classic cutaneous manifestations described earlier; these patients may have only fever, chills, and severe pain. In roughly half of these patients, NF begins at the site of cutaneous penetrating trauma such as burns, insect bites, splinters, abrasions, chickenpox vesicles, or surgical incisions. In the remaining cases, infection begins at the site of nonpenetrating deep trauma such as hematoma, ankle sprain,

Figure 22-4 Diagnosis of tinea pedis.

the leading edge of the skin change may help establish the diagnosis. Treatment is similar to that for tinea corporis.

Tinea Manus and Tinea Pedis

Tinea manus affects the palmar and interdigital areas of the hand. The palmar surface is diffusely dry, scaly, and erythematous. The infection may be acquired by direct contact with an infected person or animal, by contact with the soil, or through autoinoculation. It is commonly associated with tinea pedis and occurs in the hand used to excoriate the feet, resulting in the "two feet–one hand syndrome." The typical causative organisms are the same as those for tinea pedis and tinea cruris: *T. rubrum* (most common), *T. mentagrophytes*, and *Epidermophyton floccosum*.

Tinea pedis, or athlete's foot, has four common presentations (Figure 22-4). The interdigital form is the most common. It begins as scaling, erosion, and erythema of the interdigital and subdigital skin of the feet. The infection may spread to the adjacent sole or instep. When it involves the dorsal aspect, it is considered tinea corporis. Occlusion and bacterial co-infection produce the pruritus, malodor, and interdigital maceration. A second form, usually caused by *T. rubrum*, has a moccasin-like distribution in which the plantar skin becomes scaly, with hyperkeratosis and erythema limited to the thick skin, the soles, and the lateral and medial aspects of the feet. The third is the vesiculobullous type, typically caused by *T. mentagrophytes*, characterized by the development of vesicles, pustules, and sometimes bullae on the thin skin of the sole or periplantar areas. The fourth is the acute ulcerative type, typically an exacerbation of

interdigital tinea pedis. It is characterized by ulcers and erosions in the web spaces and commonly secondarily infected with bacteria (gram-negative organisms). The differential diagnosis includes contact dermatitis, eczema, and psoriasis. KOH microscopy and culture can help with differentiation.

Treatment involves application of topical antifungal cream or allylamine terbinafine to infected areas and web spaces. Infrequently, oral antifungals should be considered in individuals with refractory infections, those with diabetes, immunocompromised patients, and those with moccasin tinea pedis. Commonly used antifungal regimens include terbinafine (250 mg daily), griseofulvin (250 to 500 mg twice daily), and itraconazole (200 mg daily). The addition of a systemic or topical antibiotic for streptococcal coverage is warranted in cases in which cellulitis is suspected. Reinfection is common, especially if onychomycosis is present, and should be treated appropriately. Furthermore, footwear should be disinfected in patients with tinea pedis. Adjunctive therapy includes powders and wearing absorbent socks and nonocclusive shoes.

Tinea Cruris

Tinea cruris, frequently called *jock itch*, affects the inner aspects of the upper thighs and crural folds, with possible extension to the buttocks and abdomen. The scrotum is generally spared, unlike in candidiasis, in which it is commonly affected. Like most other dermatophyte infections, it is more common in tropical environments where ambient temperature and humidity are high. This dermatophytosis is more common in men than in women because the scrotum encourages a warm and moist environment. The predisposing factors include obesity, excessive perspiration, and the presence of a warm, moist environment. It is frequently associated with tinea pedis, because clothing gets contaminated when it passes over the feet before coming into contact with the skin on the groin area. The symptoms include burning and pruritus that commonly begin unilaterally in the crural fold. The disease can progress to become bilateral and symmetrical. Characteristic lesions are sharply demarcated with a raised scaly erythematous advancing border that may contain pustules and vesicles (Figure 22-5).

The duration of infection depends on the causative organism. *E. floccosum*, *T. rubrum*, and *T. mentagrophytes* are the most common causative agents. The anthropophilic species *T. rubrum* tends to produce more chronic infections, whereas the zoophilic form, *T. mentagrophytes*, commonly causes acute diseases. *E. floccosum* is frequently associated with the "epidemics" seen in dormitory or locker-room outbreaks. Other conditions that may mimic tinea cruris include candidal intertrigo, erythrasma, mechanical intertrigo, psoriasis, and seborrheic dermatitis.

Tinea cruris typically responds well to topical antifungal treatment. Adjunctive treatment can include a low-dose corticosteroid. Systemic antifungal therapy may be considered for refractory tinea cruris. Prevention of recurrent disease is important. Preventative measures include avoiding prolonged exposure to moisture, keeping the affected area dry, wearing loose clothing, drying thoroughly after bathing, washing contaminated clothing and linens, and using topical powders. Also important is the evaluation and treatment of tinea pedis.

Tinea Unguium

Tinea unguium, a dermatophyte infection of the nail, is a subset of onychomycosis and accounts for 40% to 50% of nail dystrophies, which also may be caused by nondermatophyte molds and yeast. It is characterized by thickened, discolored, broken, and dystrophic nails. It can be caused by all dermatophytes, but the most common causative pathogens are *T. rubrum*, *T. mentagrophytes*, and *E. floccosum*. Risk factors for developing this infection include diabetes, presence of tinea pedis, aging, and poorly fitting shoes. The differential diagnosis includes yellow nail syndrome, psoriasis, lichen planus, trauma, nail-bed tumor, atopic dermatitis, and contact dermatitis.

Tinea unguium can be challenging to manage because of prolonged therapy (3 to 4 months for fingernail infections and 4 to 6 months for toenail infections), potential systemic medication side effects, difficulty of eradication, and frequent recurrence of toenail disease. This diagnosis can be made using periodic acid–Schiff staining with histologic examination of the clipped, distal free edge of the nail and attached subungual debris. Topical agents have low efficacy except in the treatment of white superficial onychomycosis or distal lateral subungual onychomycosis. Systemic antifungal therapy is generally required. It is helpful to confirm the diagnosis of tinea unguium when long-term systemic therapy is being considered, because treatment can be long and expensive and there are potential side effects of therapy.

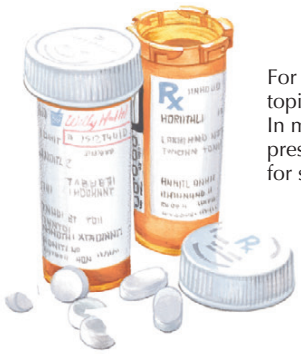
Tinea Versicolor

Tinea versicolor is a common superficial infection caused by an overgrowth of a group of yeast species in the genus *Malassezia*. Within this classification of yeasts, *Malassezia globosa* and *M. furfur* are the predominant species isolated in tinea versicolor. The yeast normally lives in the pores of the skin. Certain factors that can trigger conversion from the saprophytic yeast (spore) form to the mycelia or filamentous (hyphal) form that is associated with clinical disease include hot and humid environments, Cushing disease, a genetic predisposition, immunosuppression, and malnutrition.

It can occur in either sex, most commonly affecting teenagers and young adults aged 15 to 24 years, when the sebaceous glands are more active. Affected individuals frequently have abnormal skin pigmentation that can be either hypopigmented or hyperpigmented with fine scales involving the "seborrheic areas" of the body, most notably the trunk. Although most patients are asymptomatic, some may report distress from the uneven skin color, scaling, and sometimes pruritus. Patients often report that the involved skin fails to tan in the summer. This is because the yeast produces azelaic acid, which inhibits pigment transfer to keratinocytes, leading to accentuated demarcation of the uninfected skin.

The clinical suspicion can be confirmed by KOH microscopic examination of scales scraped from lesions, which classically demonstrates both hyphae and spores in a pattern that is often described as "spaghetti and meatballs." A Wood lamp may also be used; the affected skin will produces a pale white-yellow fluorescence. The differential diagnosis includes seborrheic dermatitis, pityriasis rosea, eczema, and tinea corporis.

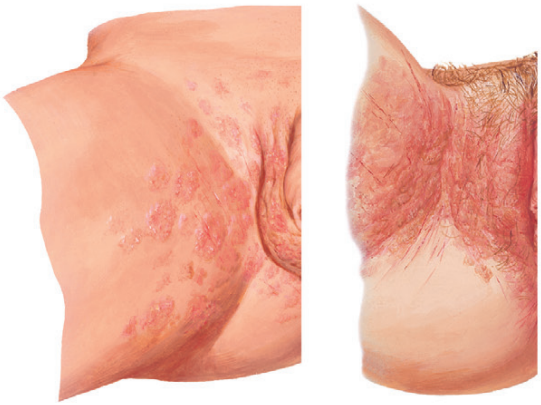
Tinea cruris is commonly called jock itch. It is a fungal infection of the groin and upper thighs and usually affects males. Females and non-athletes can also get it.



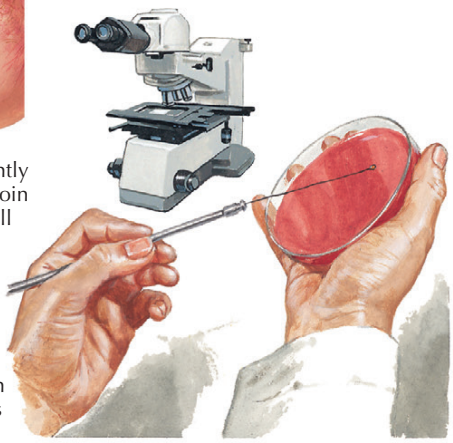
For very mild cases, only over-the-counter topical antifungal cream may be needed. In most cases, however, your doctor will prescribe a special antifungal cream or, for severe cases, medicine taken by mouth.

Wear loose-fitting, clean cotton underwear, especially when participating in physical activities. Boxer shorts are preferred.

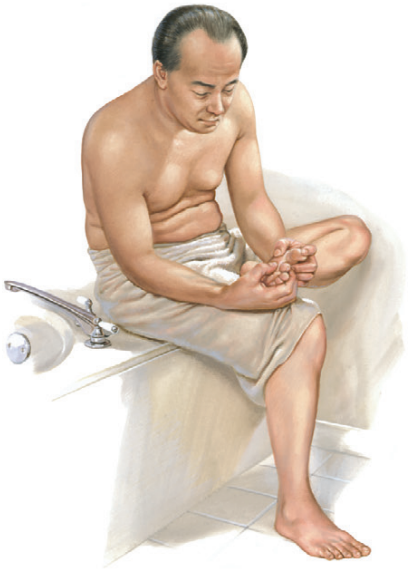
Male Female



The skin in the groin and upper thighs becomes slightly raised, red to brown, and itches. Both sides of the groin may show patches, scaling with sharp edges, or small blisters. The rash is contagious as long as you have redness and scaling.



Your doctor usually only needs to examine you to make a diagnosis. Sometimes, your doctor may take a small sample of the infected skin and culture it (put it in a dish and let it grow). The culture is then studied under a microscope to see whether a fungus is present and what kind it is.



Always wash your hands after touching or scratching your feet or groin area.

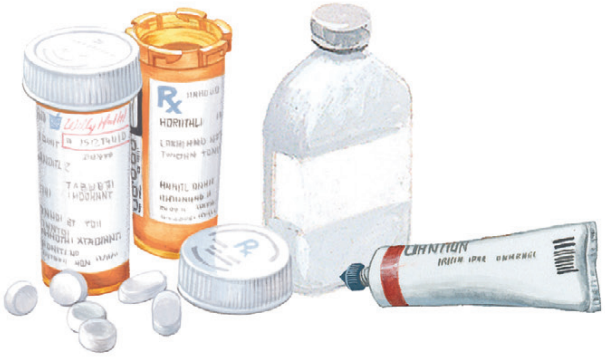
Figure 22-5 Managing tinea cruris.

A number of treatment choices are available, both topical and oral (Figure 22-6). Most of these are very effective. However, recurrence is common. Selenium sulfide lotion may be applied daily for 10 to 15 minutes and washed off well, for 2 weeks. In resistant cases, overnight application can be helpful. Topical azole antifungals can be applied twice daily for 2 to 3 weeks. Prophylactic therapy with weekly application of any of the topical agents may help reduce the high rate of recurrence. For recalcitrant or extensive disease and with patients in whom compliance is an issue, oral therapy is sometimes used. Monotherapy with ketoconazole 200 mg or 400 mg orally (PO) daily for 5 days achieves cure rates greater than 90% to 95% at 4 weeks. Patients should be informed that this yeast is part of the normal skin flora and is therefore not considered contagious. The skin color alterations typically resolve within 1 to 2 months after treatment has been initiated and will not leave permanent scars or pigmentary changes.

Cutaneous Candidiasis

Candidiasis is an infection that is most frequently caused by the yeast *Candida albicans*, but other species with increasing frequency can cause human disease. *Candida* species are part of the normal inhabitants of the gastrointestinal tract but rarely colonize the skin unless there is a break in the integument. *Candida* species are dimorphic fungi that exist in both hyphal and yeast forms. Any factor that adversely affects the immune system may predispose a person to candidiasis, including pregnancy, the neonatal period, immunologic or endocrine dysfunction, debilitated states, corticosteroids, and immunosuppressive agents.

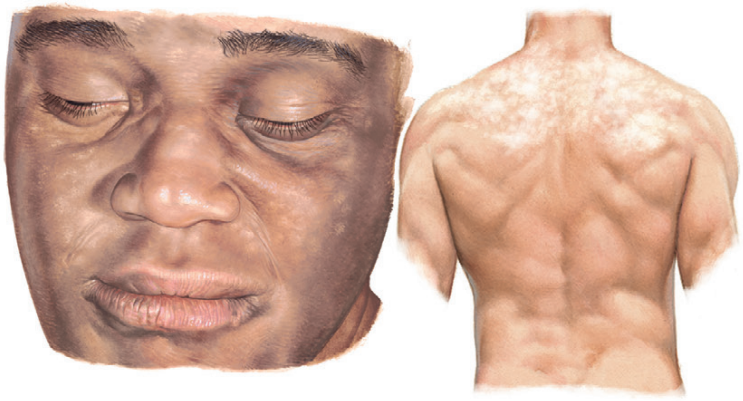
Tinea versicolor is a rash caused by fungus that usually lives on the skin. Teenagers and young adults can get it, more often in warmer weather, because fungus grows easily in heat and humidity. Unlike similar infections, tinea versicolor won't be passed among people.



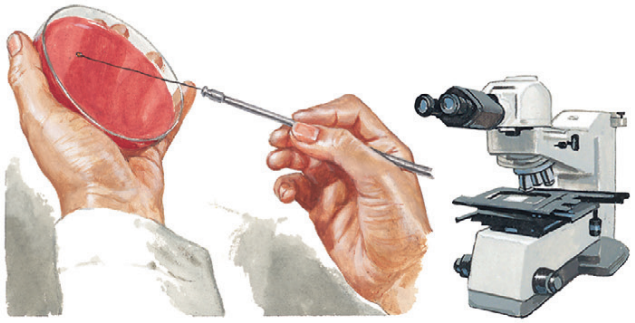
Your doctor may prescribe a cream, lotion, or pills to treat the rash. Treatment may last up to 1 month, but your skin may take several months to return to normal. So don't be discouraged if it doesn't look normal after a few weeks.

Sunlight may help your rash, but ask your doctor whether being in the sun is good for you, and if so, how long you should stay in the sun. Using sunscreen is also important.

Don't scratch at the rash. If the itching really bothers you, talk to your doctor about medicine to help relieve it.



The rash occurs on the upper arms, chest, back, and neck and sometimes the face. The rash can be various colors and has small, white-to-pink or tan-to-dark spots with sharp edges and scales.



Your doctor makes a diagnosis by seeing the usual appearance of the rash on the skin. Your doctor may take a small scraping of a patch for study with a microscope if the diagnosis isn't clear.

Figure 22-6 Managing tinea versicolor.

Humidity, heat, and friction between skin surfaces are environmental factors that also may play a role.

Superficial candidiasis frequently manifests with pruritic lesions that may begin as vesicles, pustules, or erythematous plaques and eventually lead to maceration and fissuring, leaving behind a denuded, erythematous base. Often there are red satellite pustules surrounding the primary area. The usual sites for cutaneous *Candida* infection include the mouth (thrush), intertriginous areas (*Candida* intertrigo), perineal region (*Candida* diaper dermatitis), periungual area (paronychial candidiasis), and genital region.

KOH microscopy of scrapings from lesions will usually reveal yeast and hyphae consistent with candidiasis. Material may be sent on Sabouraud dextrose agar for confirmatory fungal culture. Treatment involves the use of the appropriate topical and/or oral antifungal agent. Heat, humidity, and tight fitting clothing should be avoided. Moist or occluded areas must be "dried out." Underlying diseases such as diabetes should be identified and controlled. Numerous effective topical agents are currently available. Nystatin is commonly used. Topical azole antifungal therapy applied once or twice daily for approximately 2 weeks is also quite effective.

DIAGNOSTIC METHODS

Potassium Hydroxide Microscopy

This single most important test for the diagnosis of dermatophyte infection is direct visualization of hyphae under the microscope. The scale can be obtained from the active border of the lesion, loose hairs from the affected area, or, in the case

of nail involvement, subungual debris. The small fragments of scale are placed on a microscope slide and gently separated, and a coverslip is applied. A few drops of 10% to 20% KOH can be added to the edge of the coverslip and allowed to run under via capillary action. For hair or nail samples, gently warm the slide. The wet-mount preparation is then examined under a microscope.

Wood Lamp Examination

The Wood lamp is limited in its usefulness, as most dermatophytes currently seen in the United States do not fluoresce. Some strains of *M. canis* and *Microsporum equinum* seen in tinea capitis exhibit blue-green fluorescence when stimulated by certain wavelengths of ultraviolent light. Erythrasma, a noninflammatory, pale brown, scaly eruption of the groin, axillae, and toe webs caused by the bacterium *Corynebacterium minutissimum*, fluoresces a brilliant coral red, whereas tinea cruris and cutaneous candidiasis do not fluoresce. Fungal infections of the skin do not fluoresce, except for tinea versicolor, which produces a pale white-yellow fluorescence.

Fungal Culture

Definitive diagnosis usually relies on culture. Plucked hair or skin scrapings may be cultured. It is helpful to confirm the diagnosis of tinea unguium when long-term systemic therapy is being considered.

Skin or Nail Biopsy

Skin or nail biopsy is useful when the diagnosis is difficult to establish, the condition is refractory to treatment, or KOH microscopy is negative in a patient with dystrophic nails.

EVIDENCE

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Herpes Simplex Virus Infection

John D. Kriesel and Christopher M. Hull

23

ABSTRACT

Herpes simplex viruses (HSVs) are double-stranded deoxyribonucleic acid (DNA) viruses that cause lifelong infection and frequent reinfections or reactivations. There are two types of HSV: HSV-1, the cause of human cold sores, and HSV-2, the usual cause of genital herpes. Each virus type has different clinical manifestations, means of transmission, and epidemiologies. The development of type-specific serologic assays has allowed for differentiation between the two strains of viruses. These sensitive and specific serologic assays have expanded knowledge about the geographic distribution, burden of disease, and risk factors for HSV-1 and HSV-2. Understanding of these diseases is growing, and there have been advances in both the treatment and the prevention of HSV infections with antiviral medications.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

HSVs are common and ubiquitous worldwide pathogens. There are two identified strains of HSVs: HSV-1 and HSV-2. The most common clinical presentation of HSV-1 infection is herpes labialis, commonly known as *cold sores* or *fever blisters*. Herpes labialis occurs in approximately 20% to 40% of the general population and manifests as recurrent vesicular herpetic lesions on the lips or around the mouth. Serologic studies show that approximately 60% of the adult population in the United States is infected with HSV-1, although many infected persons are asymptomatic (i.e., do not have recognized herpes labialis).

HSV-2 is the primary cause of genital herpes, which manifests as recurrent genital vesicular and ulcerative lesions. Genital herpes is one of the most common sexually transmitted infections worldwide. The seroprevalence of HSV-2 infection varies widely within the U.S. adult population, but overall it is approximately 20%. This translates to some 60 million infected persons in this country, about half of whom have recognized genital herpes disease.

RISK FACTORS FOR INFECTION AND DISEASE

Most HSV-1 reactivations are mild, although uncomfortable and cosmetically disfiguring. In persons with an underlying immunosuppressing disease, active facial and intraoral HSV-1 infection can be persistent and may spread to cause major morbidity. The same is true for HSV-2 infections. Patients with acquired immunodeficiency syndrome (AIDS), for instance, sometimes experience continuous genital or perirectal ulcerations because of persistent replication of HSV-2.

Primary orofacial infection with HSV-1 is predominantly acquired during childhood and is often asymptomatic. Age, socioeconomic status, and geographic location affect the frequency of HSV-1 infection. Women are somewhat more susceptible to genital herpes than men. Other risk factors for HSV-2 infection include a high number of lifetime sexual partners, a history of sexually transmitted diseases, and early age of first intercourse.

CLINICAL FEATURES

Primary infection with HSV occurs via inoculation of the oral or genital mucosa. The virus must contact mucosal surfaces or abraded or eroded skin, where it replicates and initiates infection. HSV-1 is spread primarily via direct contact with contaminated secretions or saliva. HSV-2 is usually spread via sexual contact from infected genital skin or secretions. The spectrum of primary infection is variable, ranging from asymptomatic infection to fulminant gingivostomatitis or genital infection, often with associated constitutional symptoms including fever, malaise, headache, and myalgia. More important, the virus has the ability to ascend through sensory nerve axons to establish chronic, lifelong, latent infection within the trigeminal, geniculate, vagal, and sacral ganglia (Figure 23-1). These ganglia contain the sensory neuron cell bodies. HSV-1 and HSV-2 do not integrate into the human genome, but rather are maintained in an episomal (or extrachromosomal) state within the sensory neuron nucleus.

On reactivation of HSV from its latent state, the virus descends along sensory neurons to reinvade cutaneous tissues, where it appears as vesicles and ulcers. Oral HSV outbreaks are often preceded by a prodrome consisting of localized burning, tenderness, tingling, and paresthesia at the site of reactivation. Other associated symptoms may include headache, fever, malaise, lymphadenopathy, and fatigue. Genital herpes outbreaks are also commonly preceded by prodromal symptoms including dysesthesias and muscle cramping.

Herpes Labialis

Recurrent HSV-1 lesions usually develop on the lower lip but can also be found on the upper lip, nose, cheek, chin, and eyelid (Figure 23-2). The resultant epithelial cell death and inflammatory response leads to the characteristic vesicular (sometimes even pustular) and ulceronecrotic lesions. The lesions of herpes labialis tend to occur on the outer third of the lips, and the lower lip is more frequently involved than the upper lip. Lesions on the nose, chin, or cheeks account for less than 10% of cases. Lesions are most often single; "secondary lesions," those appearing one or more days after the first sore, develop in one fifth of cases. From episode to episode, lesions commonly cross the

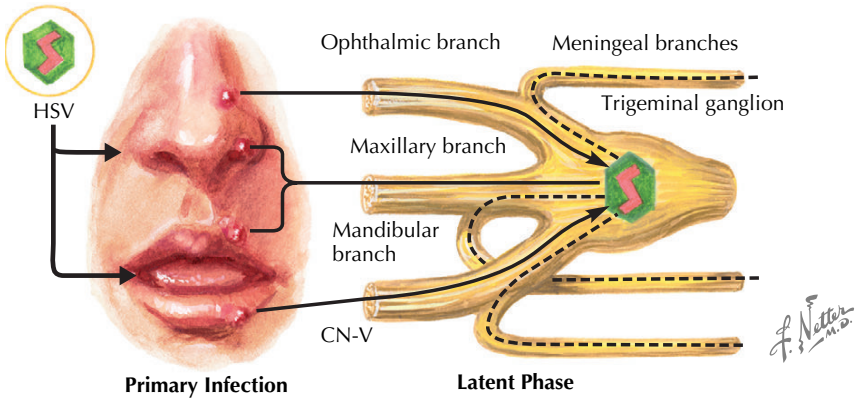

Figure 23-1 Herpes simplex.

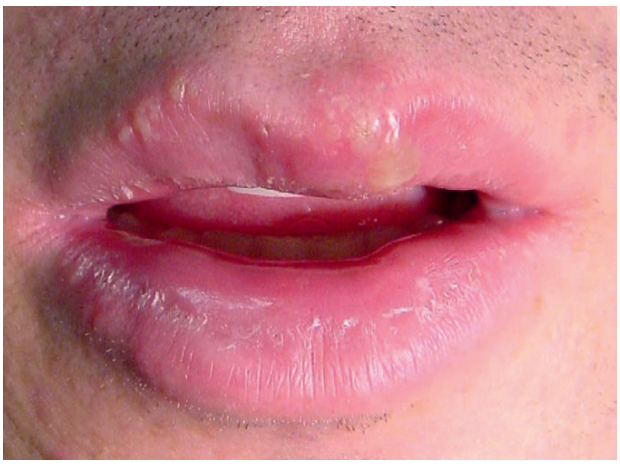

Figure 23-2 Herpes labialis. *(Courtesy Salt Lake City/County STD Clinic.)*

midline of the face or move from one lip to the other if the patient experiences frequent episodes; in patients with infrequent recurrences, the lesion location generally remains the same. The healing time for herpes labialis lesions is variable, with the majority healed within 7 or 8 days. Most patients will have one to three outbreaks per year, but roughly 10% will have more frequent recurrences (more than six lesions per year).

The severity of recurrent herpes labialis is variable, ranging from prodromal symptoms without the development of any signs to extensive disease of both lips and cheeks after severe sunburn. Lesions that do not progress beyond the papule stage have been called "aborted" lesions. Aborted genital outbreaks also occur commonly, especially with early antiviral treatment. Episodes in which there is complete destruction of the epithelium, manifested by development of the vesicle, ulcer, and/or crust stages, have been called "classical" lesions. Aborted lesions are the outcome of incipient episodes in about 25% of cases. Of these lesions, roughly half are limited to prodromal symptoms, with or without erythema, and the others progress to the papule stage before resolving. Although the former have been termed "false" prodromes because of failure of the episode to progress, they are associated with a 60% rate of HSV excretion in the oral cavity and thus appear to be caused by reactivation of the virus. The classic herpes virus lesion progresses through distinct and identifiable stages from a prodrome (localized tingling or burning at the site of herpes reactivation), erythema, papule (edema), vesicle, ulcer, crust (soft debris then hard eschar), and healed (loss of crust).

Well-documented stimuli that appear to induce HSV-1 recurrences in humans include ultraviolet exposure (sunburn) of the lips, febrile illness, and menstruation. Some medical procedures also induce herpes labialis, including surgical manipulation of the trigeminal nerve (to treat trigeminal neuralgia), hyperthermia, laser-assisted in situ keratomileusis (LASIK), and epidural morphine. The mechanisms by which trigger factors induce reactivation of HSV-1 are not completely understood, but they seem to relate to interferon effectors in the skin and/or ganglion.

Genital Herpes

Primary genital herpes is most often caused by HSV-2 infection, although up to 50% of primary genital outbreaks may be caused by HSV-1, presumably transmitted by oral-genital contact. A patient's first genital herpes outbreak is typically more severe than subsequent recurrences. Patients with primary genital herpes should understand that they are very likely to experience one or more genital herpes recurrences in the next few months.

Recurrent genital herpes lesions need not follow a definite primary outbreak; for unknown reasons, some previously HSV-2–infected patients simply begin to have recurrent genital herpes lesions. In men, genital herpes lesions are often vesicular (blisters with clear fluid) or pustular. They are usually painful and most often occur on the shaft of the penis but also are common on the pubis, groin, thigh, buttocks, and scrotum. In women, genital herpes lesions are more likely to manifest as a small ulcer or fissure on the vulva or perineum (Figure 23-3). Women may also experience genital herpes outbreaks on the pubis, groin, buttocks, or lower back. Homosexual men are more likely than heterosexual men to have perirectal genital herpes outbreaks. Primary genital herpes may manifest as proctitis in the homosexual population.

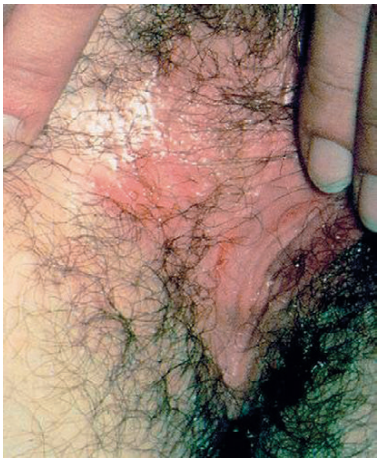

Figure 23-3 Genital herpes. This is a typical genital herpes recurrence with erythema in the labial folds of a young woman. Genital recurrences are usually painful and may present manifest as bumps, fissures, or vesicles. *(Courtesy Salt Lake City/County STD Clinic.)*

Genital herpes outbreaks are often heralded by a prodrome. Prodromal symptoms include itching, burning, dysuria, and other abnormal sensations in the genital area. Some genital herpes patients may have buttock or leg pain, occasionally mimicking sciatica, as a prodromal symptom. Occasionally, typical genital herpes prodromal symptoms are not followed by a visible outbreak. These "aborted" genital herpes episodes are more common when antiviral treatment is started promptly.

The frequency of genital herpes outbreaks is highly variable, ranging from one every few years to almost monthly. HSV-2 infection that is completely asymptomatic is not uncommon. Triggering factors are difficult to identify, because the outbreaks occur randomly. Some patients believe that stress, vigorous sex, lack of sleep, or sun exposure leads to outbreaks. Most lesions heal in 1 to 2 weeks. Genital herpes lesions can be very severe and persistent in immunocompromised individuals, including those with AIDS.

Asymptomatic Shedding and Unrecognized Infection

Infectious HSV is shed from the genital or oral mucosa on about 2% to 3% of days. Shedding of HSV DNA at these sites is much more common, occurring on 25% to 40% of days. Studies show that only 10% to 25% of persons with HSV-2 antibodies identify themselves as having genital herpes disease. It follows that most genital herpes transmissions occur either from persons without recognized disease or during periods when the transmitting partner did not have a recognized outbreak.

Other Manifestations of Herpes Simplex Virus Infection

HSV infections can occur elsewhere and can present manifest with life-threatening infection in some cases. *Eczema herpeticum* (also referred to as *Kaposi's varicelliform eruption*) is a term used for disseminated cutaneous infection by HSV in patients with other chronic dermatologic conditions, including atopic dermatitis. Herpes gladiatorum is a unique cutaneous infection with HSV seen in individuals who wrestle. Transmission of virus occurs from infected individuals to susceptible persons during contact. Lesions usually develop on the lateral neck, face, and forearms, areas in direct contact with the face of the infected wrestling partner. *Herpetic whitlow* refers to infection of the digits, often the index finger. Whitlow caused by HSV-1 was more common before the widespread use of protective gloves in dental and medical personnel. Most cases of herpetic whitlow now are caused by HSV-2 infection, presumably acquired from sexual activity.

Erythema multiforme (EM) is an acute, self-limited, cutaneous eruption characterized by the development of dusky erythematous macules. These are often referred to as "targetoid" because of their central dusky or purple zone and outer erythematous rim. Occasionally these are associated with central vesiculation or ulceration. The lesions of EM are commonly found on the hands, forearms, and oral mucosa. The development of EM is most commonly precipitated by HSV infection. Preceding herpes labialis will be seen in approximately 50% of subjects with EM. The herpes labialis lesions may develop before, simultaneously, or after the lesions of EM. The pathogenesis of HSV-associated EM is unclear but is likely related to an HSV-specific host response. HSV-encoded proteins and HSV DNA can be identified within lesional skin of EM, and virally encoded antigens have been detected on keratinocytes.

HSV-1 may also infect and reactivate in the cornea. There are about 25,000 new cases of ocular herpes per year in the United States with a total case burden of about 400,000. These cases are particularly problematic in that ocular recurrences are difficult to prevent, treatment is not entirely satisfactory, and frequent ocular reactivations can overwhelm the natural antiinflammatory capacity of the cornea, leading to blindness.

Herpes encephalitis can be caused by either HSV-1 or HSV-2, although HSV-1 predominates. This disease is rare and may be insidious or rapid in onset, often heralded by personality changes or mood swings. Virtually all patients proven to have HSV encephalitis have fever. Mollaret's (aseptic) meningitis is a related condition caused by recurrent HSV-2 reactivation from the sacral ganglia into the spinal cord and meninges, often without accompanying genital lesions. Neonatal herpes is a rare but particularly feared complication of genital HSV infection. These cases are usually caused by HSV-2 passed to the child either during gestation or, more commonly, at the time of delivery.

DIAGNOSTIC APPROACH

There are a number of laboratory tests that can be used to confirm the diagnosis of HSV. Isolation and culture of the virus remains useful for the diagnosis of cutaneous disease. The virus can be isolated and cultured from infected tissue or fluid (vesicles, ulcerations, cornea, throat, and other sites). Cultures are most sensitive while lesions are in the vesicular or pustular stages. If possible, the lesion to be tested (vesicle or pustule) should be unroofed or carefully broken with a sterile needle.

The resulting fluid should be collected on a Dacron swab, placed in viral transport medium, and sent to the laboratory, where it is placed in the appropriate cell culture system. The sensitivity of HSV cultures rapidly declines as the lesions ulcerate and crust. Typing of viral isolates to differentiate between HSV-1 and HSV-2 is strongly recommended, as this affects the patient's treatment and prognosis.

Polymerase chain reaction (PCR) now often allows the etiologic causative diagnosis of genital ulcers, papules, vesicles, and erosions. Collection of the specimen is identical to that described above earlier for HSV culture. PCR for HSV DNA is considerably more sensitive than viral culture, particularly when the lesions being tested are a few days old, crusted over, or healing. HSV PCR is offered by many reference laboratories. HSV PCR should also permit distinction between HSV-1 and HSV-2, an important consideration for prognosis and counseling.

HSV antibody tests have been developed to take advantage of antigenic differences between HSV-1 and HSV-2. The type-specific enzyme-linked immunosorbent assay (ELISA) test is based on differences in the HSV envelope glycoprotein G between HSV-1 and HSV-2. This relatively simple serologic assay has sensitivity and specificity exceeding 90%, similar to the more difficult and expensive Western blot method. It is crucial to be sure one is ordering a type-specific assay when performing a herpes serology. The older non–type-specific assays frequently lead to confusion, because they cannot distinguish between HSV-1 and HSV-2. The following are the current U.S. Food and Drug Administration–approved, type-specific assays: Western immunoblot, HerpeSelect HSV-1 and HSV-2 ELISA (Focus Diagnostics, Cypress, California), HerpeSelect HSV-1 and HSV-2 immunoblot (Focus Diagnostics), BioKit HSV-2 Rapid Assay (Biokit USA, Lexington, Massachusetts), and Captia HSV-1 and HSV-2 (Trinity Biotech, Wicklow, Ireland).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for herpes labialis should include folliculitis, aphthous stomatitis, oral candidiasis, medication-induced stomatitis, pharyngitis, Stevens-Johnson syndrome, and hand, foot, and mouth disease (Coxsackie coxsackievirus infection). Intraoral lesions of HSV, clusters of tiny (1 to 3 mm) vesicles and ulcers, develop exclusively on the gingivae and anterior hard palate in immunocompetent patients, are difficult to see, and are less symptomatic than their cutaneous counterpart. Recurrent HSV lesions seldom appear on the soft palate or posterior pharynx. Aphthous stomatitis, or "canker sores," are common intraoral ulcerations of unknown cause. In contrast to intraoral HSV lesions, aphthous ulcers are located on the tongue or buccal mucous membranes and are generally larger, more painful, single lesions.

Discrete genital or anal ulcers in sexually active young adults in most parts of the United States are genital herpes until proven otherwise. Chancroid, syphilis, and lymphogranuloma venereum can also cause genital ulcerative lesions. Primary syphilis may be distinguished from other ulcers by the presence of a indurated, nonpurulent ulcer (that may be painful). In Salt Lake City, syphilis chancres are relatively rare and occur mainly in homosexual men. Other ulcer characteristics are not helpful in distinguishing infectious causes. Furunculosis, often caused by *Staphylococcus aureus*, can also appear similar to genital herpes. Shaving the genital area appears to predispose to furunculosis, which can be diagnosed by a Gram stain of the lesion exudate and/or a negative HSV culture. Diagnostic testing of suspicious genital lesions, including recurring bumps and fissures, is critical to prevent a missed diagnosis of genital herpes.

TREATMENT

Major progress has been made in recent years in the understanding of HSV infections and the development of safe and effective antiviral drugs. Acyclovir is the prototype antiviral medication and functions as a nucleoside analogue that competitively inhibits viral DNA polymerase. Acyclovir must first be phosphorylated by the herpes-specific thymidine kinase and then phosphorylated two more times by host cell enzymes to the active form. The active drug then competes for binding of the viral DNA polymerase in virus-infected cells. This limits replication and further spread of the virus but does not prevent death of the infected cells. Acyclovir is available in topical, oral, and intravenous formulations. Valacyclovir is the l-valyl ester prodrug of acyclovir. After oral absorption, it is metabolized to acyclovir and has the same mechanism of action and safety profile as acyclovir. The oral bioavailability of valacyclovir is threefold to fivefold higher than that of acyclovir. Famciclovir is the prodrug of penciclovir. Penciclovir (Denavir) is available only in a topical formulation because of poor oral bioavailability. Famciclovir, like valacyclovir, has a higher oral bioavailability and is metabolized to famciclovir after oral absorption. Famciclovir and penciclovir have a mechanism of action similar to that of acyclovir and valacyclovir and inhibit viral DNA polymerase. Table 23-1 gives specific treatment recommendations.

Table 23-1 Treatment Recommendations for Herpes Simplex Virus Infections

INFECTION	RECOMMENDED TREATMENT
Herpes labialis (recurrence)	VACV 2 g PO bid × 1 day FACV 1.5 g PO × 1 dose
Genital herpes (first episode)	ACV 400 mg tid × 10 days FACV 250 mg tid × 10 days VACV 1 g PO bid × 10 days
Genital herpes (recurrence)	ACV 400 mg tid × 5 days VACV 500 mg bid × 3 days FACV 1 g bid × 1 day
Genital herpes (suppression)	ACV 400 mg bid VACV 500-1000 mg once daily FACV 250 mg bid
Neonatal herpes	ACV 10 mg/kg IV q8h × 10-21 days
Immunocompromised	ACV 400 mg 3 to 5 times per day × 7-14 days or 5 mg/kg IV q8h × 7 days VACV 1 g bid × 7-14 days FACV 500 mg bid × 7-14 days

ACV, Acyclovir; *bid,* twice per day; *FACV,* famciclovir; *IV,* intravenously; *PO,* by mouth; *tid,* three times per day; *VACV,* valacyclovir.

Herpes Labialis

Episodic or prophylactic treatment with antiviral drug therapy is the current standard of care for recurrent herpes labialis infections. A variety of topical over-the-counter (OTC) preparations are available, but in the majority of cases the mechanism of action is not clear and rigorous clinical trials to define efficacy have not been performed. Abreva (10% docosanol cream) has been the most intensively studied product and is approved for OTC sale in the United States. Two controlled human studies showed some positive effect of treatment.

Studies of acyclovir ointment in immunocompetent subjects have provided little or no evidence of efficacy. However, acyclovir ointment was effective for herpes labialis in immunocompromised patients and was approved for this indication in the United States. Acyclovir was shown to penetrate human skin more effectively from cream than ointment formulation. Accordingly, data supporting the efficacy of acyclovir cream have been more readily obtained than for the ointment. Acyclovir 5% cream is applied topically to the affected area five times per day for 5 days. Penciclovir 1% cream is an alternative topical treatment that is applied topically to the affected area every 2 hours for 4 days.

In most instances, oral antiviral therapy for herpes labialis is preferred because of the limited efficacy of topical treatments. Acyclovir, valacyclovir, and famciclovir have all been used for episodic treatment of herpes labialis. With early initiation of therapy, acyclovir, valacyclovir, and famciclovir reduce lesion healing time, viral shedding, and pain. High-dose, short-course therapy with valacyclovir and famciclovir have become the most commonly used treatments for episodic herpes labialis. Valacyclovir is given at a dosage of 2 g twice a day for 1 day, and famciclovir is given as a single 1500-mg dose at the earliest signs of herpes labialis recurrence.

Three previous exploratory studies have investigated the effect of topical corticosteroids on the severity of recurrent herpes labialis. In these studies, the addition of a topical corticosteroid to an antiviral compound reduced lesion size and increased the number of aborted lesions. In all three studies, the antiviral-corticosteroid combinations were well tolerated, and there were no increased adverse events attributable to topical corticosteroids. The expanded clinical activity demonstrated in these studies (more rapid healing and increased aborted lesions) constitutes an improvement compared with what is seen with antiviral medications alone (more rapid healing), and supports the concept that corticosteroids are a valuable new therapeutic modality in this disease. Larger controlled studies are needed to expand and confirm these findings.

Prophylactic oral antiviral therapy for certain herpes labialis recurrences may be an effective and appropriate management strategy for selected patients. Patients who may benefit from this approach include individuals with frequent recurrences (more than six per year), patients with a history of HSV-associated EM, individuals anticipating intense sun exposure, patients undergoing certain surgical procedures, immunocompromised patients, and wrestlers with a history of herpes gladiatorum (Table 23-2).

Table 23-2 Prophylaxis of Herpes Simplex Infections

CONDITION OR STIMULUS	TREATMENT	COMMENTS
Ultraviolet radiation	ACV 400 mg bid	Start at least 1 day before ultraviolet exposure and continue for 7 days.
Facial resurfacing: laser resurfacing, chemical peels, dermabrasion	ACV 400 mg bid VACV 500 mg daily, bid FACV 250 mg bid	Start 1-2 days before procedure and continue for 7 days or until reepithelialization.
Recurrent erythema multiforme	ACV 400 mg bid	Suppressive therapy needed. Episodic therapy does not appear to be helpful.
Frequent herpes labialis recurrences (six or more per year)	ACV 400 mg bid VACV 500 mg daily	May also be considered in patients with less frequent outbreaks whose appearance is very important or those who experience severe anxiety with outbreaks.
Herpes gladiatorum	VACV 500-1000 mg daily	Any wrestler with a history of herpes labialis or gladiatorum should be considered for suppressive therapy during periods of training and competition.
Ocular herpes	ACV 400 mg bid	Important to consider in individuals with a history of recurrent ocular HSV and in patients undergoing ocular procedures. Prevents only about 50% of outbreaks.
Genital herpes	ACV 400 mg bid VACV 500-1000 mg daily FACV 250 mg bid	Highly effective for the prevention of HSV-2 outbreaks. If using VACV, start with 1000 mg daily and then may dose reduce after 1 year.

ACV, Acyclovir; *bid,* twice per day; *FACV,* famciclovir; *HSV,* herpes simplex virus; *VACV,* valacyclovir.

Genital Herpes

For some patients genital herpes is considered to be nothing more than a nuisance that occurs uncommonly. For these patients episodic treatment or no treatment at all may be appropriate. However, for other patients, particularly those with very frequent or very severe outbreaks, genital herpes is a stressful and difficult disease. There is an undeserved stigma attached to genital herpes—an infection borne by nearly 20% of the adult population—and most patients require reassurance and appropriate counseling. Patients with genital herpes caused by HSV-1 usually experience fewer outbreaks per year than those with HSV-2 genital herpes (one versus three to four per year). Therefore viral typing of genital herpes lesions is important and should be performed whenever possible. For patients with frequent outbreaks, defined by the Centers for Disease Control and Prevention (CDC) as six or more per year, or those with actual or perceived severe genital herpes, prophylactic antiviral therapy is appropriate.

Episodic treatment of genital herpes outbreaks decreases the duration of the outbreaks by about one third. The duration of live viral shedding is similarly decreased. Initiation of therapy immediately on recognition of the outbreak is recommended, to maximize the effect of antiviral therapy. Patients are sometimes disappointed by the limited efficacy of this treatment strategy, but by the time antiviral therapy is taken and absorbed, in most instances, HSV has already reactivated within the sensory neuron, traveled down the axon, and infected the innervated skin, creating a visible lesion. Antiviral medications act by preventing further viral replication; they cannot by themselves affect the natural inflammation already set in motion by the existing viral infection.

The current CDC-recommended regimens for episodic treatment of genital herpes outbreaks include acyclovir 400 mg three times per day for 5 days, acyclovir 800 mg twice a day for 5 days, acyclovir 800 mg twice a day for 2 days, famciclovir 125 mg twice a day for 5 days, famciclovir 1000 mg twice a day for one day, valacyclovir 500 mg twice a day for 3 days, and valacyclovir 1000 mg daily for 5 days. The cost of generically available acyclovir versus the more expensive valacyclovir and famciclovir regimens often figures into the decision about which antiviral to prescribe. On the other hand, the ease and convenience of the less frequent valacyclovir and famciclovir regimens favor compliance in patients who can afford them.

Prophylactic therapy with daily antivirals is remarkably effective, preventing 95% of HSV-2–induced lesions (see Table 23-2). The cost and inconvenience of daily therapy should be weighed against the expected effects of prophylaxis.

Shorter courses of antiviral medications have also been studied and proven to be effective for the treatment of genital herpes. These studies have been patient-initiated to maximize the effect of antiviral treatment. In addition to the CDC-recommended 3-day valacyclovir course, acyclovir 800 mg three times a day for 2 days is effective. This high-dose regimen resulted in aborted lesions in 27% of the patients without decreasing the time to next recurrence. A shorter-course (2-day) treatment with famciclovir 500 to 250 mg twice a day was recently shown to be as effective as a full 5-day treatment course. For those interested in the specific results of clinical trials, Cernik and colleagues (2008) have provided an excellent evidence-based review of therapies for genital and labial herpes.

PROGNOSIS

Herpes simplex infections cannot be cured with existing antiviral medications. Many patients, including those with herpes labialis and genital herpes, find that outbreaks become less common over time. Rates of genital herpes recurrences generally decline by about three outbreaks per year but remain high in some individuals. Patients with genital herpes caused by HSV-1 infection usually have far fewer outbreaks than those with disease caused by HSV-2. Fortunately, neither oral nor genital herpes recurrences typically cause scarring or anesthesia at the site of the outbreaks.

PREVENTION AND CONTROL

Attempts to vaccinate against herpes simplex infections have generally been unsuccessful. During the 1990s, one genital herpes vaccine candidate failed to protect its recipients while another showed promise, but only among women who were uninfected with HSV-1. A promising HSV-2 subunit vaccine was recently studied in more than 7000 young women. Unfortunately, it failed to prevent both acquisition of HSV-2 infection and genital diseased caused by HSV-2.

Unlike many other sexually transmitted diseases (e.g., gonorrhea, chlamydia), genital herpes infections are not reported to the CDC. Therefore the usual epidemiologic method of finding, contacting, testing, and treating partners is not employed for genital herpes patients. Nevertheless, recent serologic data show that HSV-2 infections are decreasing gradually over time in the United States.

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Nontuberculous Mycobacterial Skin Infections

Luis G. Tulloch

24

ABSTRACT

Nontuberculous mycobacteria (NTM), also known as *mycobacteria other than tuberculosis* (MOTT) and *anonymous* or *atypical mycobacteria*, are increasingly recognized instigators of dermatologic disease. In 1932 Pinner coined the phrase *atypical mycobacteria* and in 1938 and 1948, respectively, Freeman and MacCallum reported the earliest cases of nontuberculous mycobacterial skin infections. In 1959 Runyon classified NTM into four groups: three slowly growing groups, subclassified according to the pigment that their colonies produce on Lowenstein-Jensen agar, and one rapidly growing group (Table 24-1). The first major outbreaks of Buruli ulcer (BU) and fish tank granuloma (FTG) were reported in the 1940s through 1960s. Additionally, cases of rarer NTM causing skin infections, primarily in the setting of cosmetic or surgical procedures, appeared in the later part of the century. Reports of NTM skin infections continue to rise, in part because of increased recognition, but also because of the acquired immunodeficiency syndrome (AIDS) epidemic and the advent of immunosuppressive therapy.

GEOGRAPHIC DISTRIBUTION AND CLINICAL CHARACTERISTICS

Mycobacterium marinum

Mycobacterium marinum is the cause of FTG, an entity previously known as *swimming pool granuloma* because the first major reported outbreak occurred in 1961 in swimmers in Colorado.

FTG is rare, occurring in less than 1 per 100,000 persons annually. The majority of the reported cases have occurred in industrialized countries, but the disease is probably underreported in developing regions. *M. marinum* is ubiquitous in freshwater and saltwater environments, particularly in relatively still or stagnant water, such as aquariums and nonchlorinated swimming pools. Inoculation of the mycobacteria usually occurs through breaks in the skin of persons who come in contact with aquariums or nonchlorinated water, including, aquarium owners, fishmongers, and swimmers. Occasionally patients report having come into contact with marine crustaceans or mollusks. Only a minority of patients (<10%) deny any of these exposures.

M. marinum infection is characterized by the appearance of one or more skin lesions; these lesions are localized to the upper extremities in 90% or more of the reported cases. They usually develop in the fingers, hands, wrists, elbows, and knees because these body parts are the most prone to injury. Typically, these lesions develop 2 to 6 weeks after inoculation. In a series reporting 63 cases of *M. marinum* skin and other soft-tissue infections in France, the median time between inoculation and the appearance of lesions was 16 days, but the range was 0 to 292 days. The lesions may or may not be painful and usually appear as nodules or verrucous plaques with a central ulceration, although they may also appear as abscesses or sporotrichoid lesions (Figure 24-1). Infection is usually limited to the skin, but tenosynovitis and osteomyelitis have been reported in up to 29% of cases. Disseminated infection is rare and usually occurs only in immunocompromised patients.

Mycobacterium ulcerans

Mycobacterium ulcerans is the species of mycobacterium that causes BU, also known as *Bairnsdale ulcer*, *Daintree ulcer*, *Mossman ulcer*, and *Searl ulcer*. BU is the third most common mycobacterium-borne illness after tuberculosis and leprosy. About 7000 people develop BU annually. Sir Albert Cook, a British medical missionary working in Kampala, Uganda, was the first to describe the clinical syndrome in 1897. Then in 1961 Dodge and Lunn coined the term *Buruli ulcer* because the majority of their observations about the disease were derived from patients in Buruli County, Uganda (currently the Nakasongola District). In 1948 MacCallum isolated *M. ulcerans* from patients in Bairnsdale, Australia.

BU has been reported in at least 30 countries, primarily in subtropical and tropical regions of Africa, Asia, Australia, and Latin America. In Africa most of the cases occur in Benin, Ghana, and the Ivory Coast. In Asia and Latin America the highest incidence rates occur in Papua New Guinea and French Guyana, respectively. In Australia the southern regions, New South Wales and Victoria, carry the majority of that country's disease burden. West Africa has by far the majority of the cases, with approximately 2000 new cases per year. The other regions usually report anywhere from one to dozens of new cases annually. The cases of BU reported in Canada and England have occurred in tourists who recently returned from an endemic region. BU usually affects people aged 15 years or younger and people aged 75 years or older; 75% of those affected are children under the age of 15. The preponderance of studies report no differences in gender. In addition, patients with human immunodeficiency virus (HIV) infection and patients without prior bacille Calmette-Guérin (BCG) vaccination are at higher risk of acquiring this particular disease. BU is rarely contagious, but the mode of transmission to humans has not been completely determined. The leading hypothesis is that inoculation of *M. ulcerans* occurs through breaks in recently contaminated skin. Early epidemiologic studies concluded that BU is predominant near swamplands. In Benin, Johnson (2005) reported that the prevalence of BU in the Gnizounmé arrondissement decreased from 32.6 per 1000 persons to 0.6 per 1000 persons as the distance from the Couffo River increased from 1 to 10 km. It was

Table 24-1 Runyon's Classification of Nontuberculous Mycobacteria

GROUP	GROWTH RATE	COLONY PIGMENT	ORGANISM(S)
I	2-3 weeks	Photochromogen	*Mycobacterium kansasii, Mycobacterium marinum*
II	2-3 weeks	Scotochromogen	*Mycobacterium gordonae, Mycobacterium scrofulaceum, Mycobacterium szulgai*
III	2-3 weeks	Nonchromogen	*Mycobacterium avium-intracellulare, Mycobacterium haemophilum, Mycobacterium malmoense, Mycobacterium simiae, Mycobacterium ulcerans, Mycobacterium xenopi*
IV	3-5 days	N/A	*Mycobacterium abscessus, Mycobacterium chelonae, Mycobacterium fortuitum*

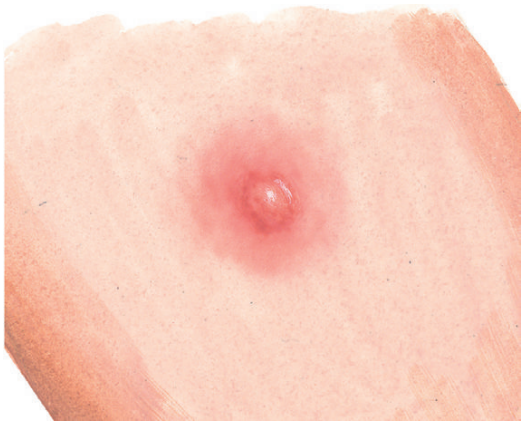

Nodular lesion with central ulceration.

Figure 24-1 Fish tank granuloma.

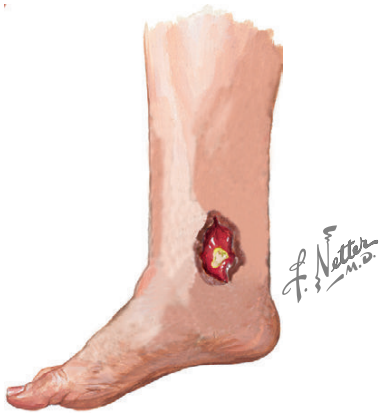


Figure 24-2 Major Buruli ulcer overlying a patient's medial malleolus.

thought that persons closer to the Couffo River are more likely to use it as an unprotected source of water. In addition, more recent data have associated BU with waterway projects and certain water-dwelling species of the Hemiptera order.

The clinical presentation of BU depends primarily on the interplay between the host's immune response and the genotype and phenotype of the particular strain. Typically, lesions appear 8 to 12 weeks after inoculation. Disease may appear anywhere in the body, but approximately 80% of lesions occur in the legs. Portaels (2009) reports that children 15 years of age or younger usually develop lesions in the head, neck, and trunk. Most lesions are painless. BU may be separated into localized and disseminated disease. Localized disease may start as a nodule or a papule. The nodular type is most commonly encountered in Africa, and the nodule usually measures 2 to 4 centimeters in diameter. The papular type, most commonly seen in Australia, typically manifests as an erythematous lesion smaller than a centimeter. These early lesions may become ulcers. The ulcers are classically described as being "pristine": painless and symmetrical, consisting of an oily, yellowish-whitish base of necrotic material surrounded by hyperpigmented, undermined edges. The ulcers may be minor (≤2 cm) or major (>2 cm) (Figure 24-2). Minor ulcers heal spontaneously, result in minimal scarring, and do not cause bone or joint disease. Major ulcers may also heal spontaneously but usually result in scars and contractures. In addition, up to 10% may be complicated by contiguous

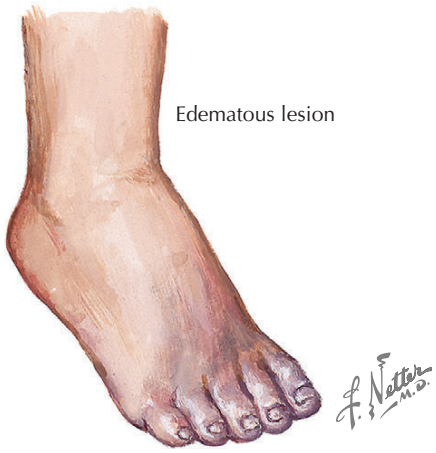


Figure 24-3 Different types of disseminated Buruli ulcer.

or metastatic osteomyelitis. Disseminated BU may appear as a clearly demarcated plaque of papery, hyperpigmented or hypopigmented skin measuring up to 15 centimeters in diameter. Disseminated BU may also manifest as a nonpitting, edematous lesion circumscribed by vague margins that may measure 5 cm in diameter or involve an entire extremity or a large portion of the head, neck, or trunk (Figure 24-3). Both types of

disseminated BU may result in contiguous or metastatic osteomyelitis by spreading through the bloodstream or lymphatic vessels.

Rapidly Growing Mycobacteria

The rapidly growing mycobacteria (RGM)—*Mycobacterium abscessus*, *Mycobacterium chelonae*, and *Mycobacterium fortuitum*—are increasingly recognized causes of skin infections. The RGM make up Runyon's group IV: They produce colonies on subculture in 7 days or less.

Their geographic distribution has not been completely described; RGM-borne cutaneous disease has been reported throughout the world. The American Thoracic Society (ATS), Infectious Diseases Society of America (IDSA), and several case reports imply that like *M. marinum*, RGM may be ubiquitous, perhaps particularly in water, and may be transmitted to the host through breaks in colonized or contaminated skin. RGM are primarily implicated in a broad spectrum of cosmetic and surgical procedures, including breast, cardiothoracic, and dermatologic surgery; mesotherapy; pedicures; and tattooing.

The discriminating clinical characteristic of RGM skin lesions is their appearance 1 to 2 weeks after exposure. These lesions may be asymptomatic or pruritic, tender, or both. They are primarily abscesses, nodules, papules, or plaques; the nodules, papules, or plaques may be erythematous or violaceous in color, and some may be scaling or draining purulent material (Figure 24-4). In most case reports, the lesions are restricted to a small region of skin, but in some cases the lesions coalesce and affect large swathes of skin. There are no case reports delineating the natural history of RGM-borne disease, nor are there any data regarding clinical presentation among immunocompromised patients.

DIAGNOSTIC APPROACH

The most important step in establishing the diagnosis is to consider NTM skin infections as a possible cause. In many cases diagnosis has been delayed by months because of insufficient clinical suspicion. In the case of BU, the diagnosis should be considered during the initial visit with the patient because the disease has a characteristic geographic distribution and clinical course, and because prompt treatment is necessary to prevent serious physical disability. Culture specimens can be obtained relatively easily by swabbing underneath the undermined edge of an ulcerated lesion. Nodular, papular, and edematous forms of disease are more difficult to diagnose, and it is reasonable to target more common causes in the initial work-up. In contrast, there is no characteristic geographic distribution to aid in the diagnosis of FTG or RGM skin infections, and apart from a history of swimming, ownership of an aquarium, or recent cosmetic or surgical procedures, the clinical presentation of FTG and RGM disease is usually nonspecific. Therefore patients with localized disease, in particular nodular or papular disease, may be managed by initially treating empirically against more common causes and then biopsying the lesion if there is no response to treatment. Patients with an abscess, an ulcer, or disseminated disease and a history that suggests possible NTM skin infection should be cultured for NTM in addition to undergoing the standard battery of stains and cultures (Figure 24-5).

Once collected, clinical specimens should undergo acid-fast bacillus (AFB) staining and be cultured in broth and solid mediums (Figure 24-6). Most NTM grow well at 28° to 37° C except for *M. marinum* and *M. ulcerans*, which grow best at 25° to 30° C and 28° to 30° C, respectively. Species-level identification of NTM is necessary, because it guides treatment. Growth rate is still used to distinguish RGM (growth in ≤7 days) from slowly growing mycobacteria (growth in >7 days) (see Table 24-1). Production of pigment is no longer used to identify NTM. Biochemical testing and polymerase chain reaction (PCR) have replaced this modality.

M. marinum requires susceptibility testing only if the infection fails empirical therapy. In contrast, RGM require routine susceptibility testing against the macrolides, amikacin, tobramycin, cefoxitin, imipenem, doxycycline, and the quinolones.

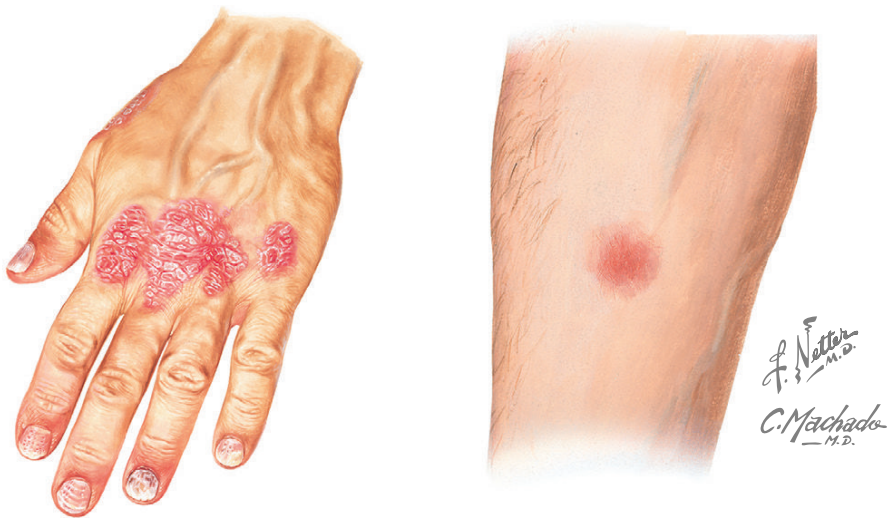


Figure 24-4 Different presentations of rapidly growing mycobacterial skin infections.

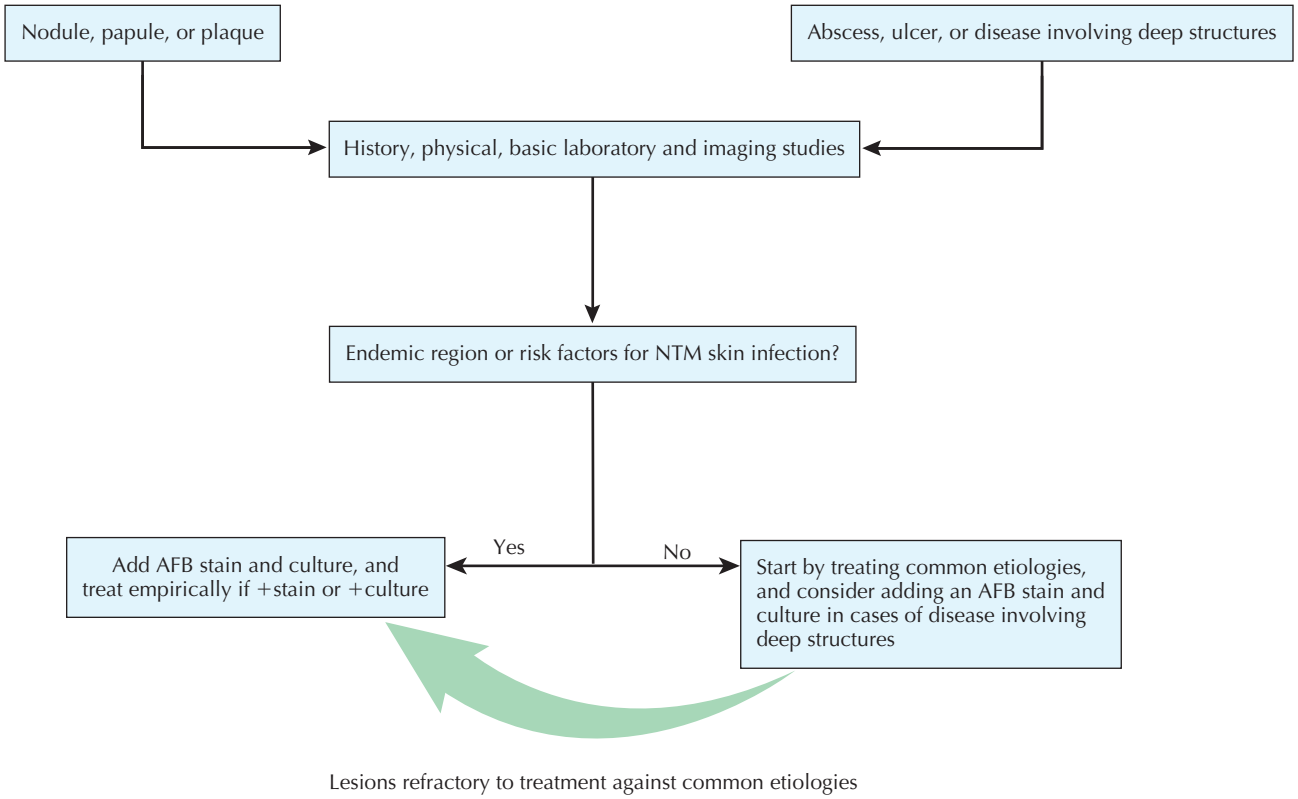


Figure 24-5 Diagnostic approach to mycobacterial skin infections. Based on a reasonable approach to diagnosis; there are no large randomized controlled trials or major society guidelines to guide these recommendations. *AFB*, Acid-fast bacillus; *NTM*, nontuberculous mycobacteria.

Because *M. ulcerans* is difficult to culture, there are very few studies on its susceptibility pattern and thus no recommendations to guide susceptibility testing.

CLINICAL MANAGEMENT AND DRUG TREATMENT

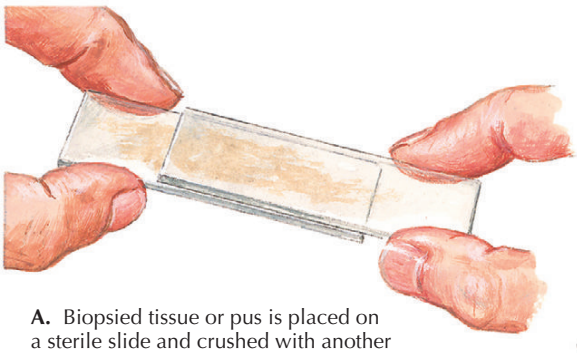
Mycobacterium marinum

According to the ATS and IDSA Statement on Diagnosis and Treatment of NTM (2007), by in vitro susceptibility testing, *M. marinum* is susceptible to trimethoprim-sulfamethoxazole (TMP-SMX), rifampin, rifabutin, ethambutol, and clarithromycin; susceptible or intermediately susceptible to doxycycline and minocycline; intermediately susceptible to streptomycin; and resistant to isoniazid and pyrazinamide.

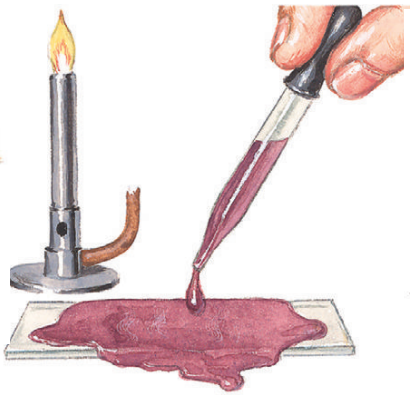
In some cases the lesions heal spontaneously in 24 to 36 months, but therapy is generally recommended to hasten the healing process. There are no randomized controlled trials to guide antibiotic therapy. Some case series report successful treatment of minimally invasive disease with tetracycline alone, particularly doxycycline or minocycline. Nonetheless, most of the larger series and the major society guidelines recommend pharmacotherapy with at least two agents. The combination of rifampin plus clarithromycin or ethambutol has been employed successfully in many case reports. The ATS and IDSA guidelines recommend a combination of clarithromycin plus ethambutol to treat skin infections and the addition of rifampin to treat tenosynovitis or osteomyelitis (Table 24-2). Duration of therapy varies among the case reports, but the general consensus is to treat for 1 to 2 months after the disappearance of skin lesions. Thus duration of therapy is usually 3 to 6 months. Surgical debridement is necessary if the infection involves deep or delicate structures or if it is refractory to antibiotic therapy.

Mycobacterium ulcerans

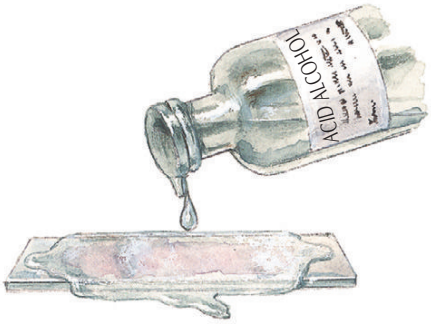
Localized BU may heal spontaneously. Nonetheless, most cases of BU—in particular, major ulcers and disseminated types of the disease—result in physical disability. Historically, treatment has consisted primarily of surgical resection and primary closure or skin grafting. Recently there has been increasing interest in using antimycobacterial drugs either as primary therapy to treat localized disease or in addition to surgical management to minimize the size of the surgical resection and rates of relapse. In 2004 the World Health Organization (WHO) published a series of recommendations regarding the diagnosis and treatment of BU: disease limited to the soft tissues may be treated with 4 to 8 weeks of oral rifampin and intramuscular streptomycin and surgical resection if necessary. A recent randomized controlled trial



A. Biopsied tissue or pus is placed on a sterile slide and crushed with another slide; slides are drawn apart to make smears.

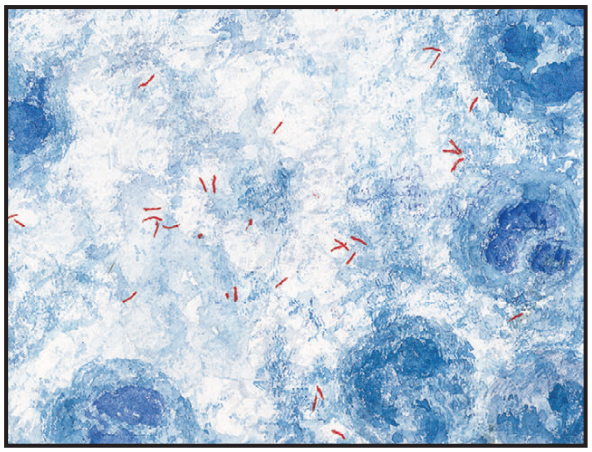


B. Slide is flooded with carbolfuchsin and then heated.



C. Slide is rinsed with water, decolorized with acid alcohol, and rinsed again.

D. Slide is counterstained with methylene blue or malachite green for 30 seconds, rinsed again, and dried.



E. Slide of specimen is stained with carbolfuchsin (Ziehl-Neelsen method as above) and viewed under oil immersion, showing acid-fast bacilli (*M. tuberculosis*) as bright red rods.

Figure 24-6 Preparing acid-fast bacillus slides.

concluded that early (<6 months), relatively localized (<10 cm) disease may be treated with 4 weeks of oral rifampicin and intramuscular streptomycin followed by 4 weeks of oral rifampicin and clarithromycin (Nienhaus, 2010). Osteomyelitis and septic arthritis require surgical resection in addition to a 9-week course of perioperative antibiotics (see Table 24-2).

Rapidly Growing Mycobacteria

Recommended antibiotic therapy against RGM is based on in vitro susceptibility studies and case reports. RGM are universally susceptible to clarithromycin, though resistance can emerge, particularly in infections caused by *M. abscessus*. In addition, *M. abscessus* is susceptible to amikacin in 90% of cases, *M. chelonae* is susceptible to tobramycin, and *M. fortuitum* is typically susceptible to amikacin, imipenem, ciprofloxacin, and the sulfonamides.

As stated in the previous section, the specific species of RGM should be identified because this guides treatment. With regard to *M. abscessus*, the ATS and IDSA recommend treatment with 4 to 6 months of an oral macrolide accompanied by at least 2 weeks of one or two parenteral agents, usually amikacin plus cefoxitin or imipenem. The cefoxitin or imipenem can be discontinued after 2 weeks if the patient's condition is improving (see Table 24-2). Duration of treatment depends on the depth of the infection and on the patient's response to treatment. In a recent Korean case report (Kwon, 2009), a patient with *M. abscessus* infection associated with acupuncture was successfully treated with clarithromycin, but most case reports use the recommended regimen. In contrast, the recommended treatment against localized *M. chelonae* and *M. fortuitum* skin disease consists of 6 months of an oral macrolide. In most cases clarithromycin is used. "Serious" cutaneous disease or osteomyelitis should be treated with at least two agents. There is no recommendation on the route (see Table 24-2). In addition, surgery should be considered if the patient has abscesses, disease involving deep or delicate structures, or disease that is refractory to antibiotic therapy. Lastly, the removal of foreign

Table 24-2 Recommended Empirical Treatment* of Nontuberculous Mycobacterial Infections

NONTUBERCULOUS MYCOBACTERIA	FIRST-LINE ANTIBIOTICS, ROUTE, AND DURATION	SURGICAL MANAGEMENT	SOURCE
Mycobacterium marinum	Clarithromycin or azithromycin PO + ethambutol PO ± rifampin IV or PO (if tenosynovitis, osteomyelitis, or septic arthritis) × 4-8 wk after resolution of symptoms	If infection is complicated by an abscess, osteomyelitis, or septic arthritis, or is refractory to pharmacologic therapy	ATS, IDSA (2007)
Mycobacterium ulcerans, soft tissue only	Rifampin PO + streptomycin IM × 4-8 wk or rifampin PO + streptomycin IM × 4 wk; then rifampin PO + clarithromycin PO × 4 wk	If infection is refractory to pharmacologic therapy	WHO (2004)
M. ulcerans, osteomyelitis or septic arthritis	Rifampin PO + streptomycin IM × 1 wk preoperatively then × 8 wk postoperatively	Always	WHO (2004)
Mycobacterium abscessus	Clarithromycin or azithromycin PO + amikacin IV + cefoxitin or imipenem IV × 2 wk; then discontinue the cefoxitin or imipenem if the patient is improving and continue the rest × 4-6 months	If infection is complicated by an abscess, osteomyelitis, or septic arthritis, or is refractory to pharmacologic therapy. In addition, any foreign bodies associated with the infection need to be resected.	ATS, IDSA (2007)
Mycobacterium chelonae, Mycobacterium fortuitum, soft tissue only	Clarithromycin† PO × 4-6 months		
M. chelonae, M. fortuitum, osteomyelitis or septic arthritis	Clarithromycin† + second agent (*M. chelonae,* tobramycin; *M. fortuitum,* amikacin, imipenem, quinolones, or sulfonamides) × 6 months		

ATS, American Thoracic Society; *IDSA,* Infectious Diseases Society of America; *IM,* intramuscularly; *IV,* intravenously; *PO,* orally; *WHO,* World Health Organization.
*Final treatment should be guided by susceptibility testing results.
†*In vitro*, only 80% of *M. fortuitum* isolates are susceptible to clarithromycin.

bodies associated with the infection is necessary for complete recovery.

PROGNOSIS

In immunocompetent patients, most skin lesions caused by *M. marinum* and RGM heal spontaneously, but it may take 24 to 36 months or up to a year, respectively. Immunocompromised patients always require treatment to clear their infections. As stated previously, if left untreated BU may result in physical disability and social stigmatization in up to 20% of patients. The large scars and contractures, in particular those overlaying the joints, restrict mobility and thus the patient's capacity to work.

PREVENTION

In the case of BU, recommended prevention strategies include wearing long-sleeved shirts and trousers, using protected water sources, and thoroughly cleaning any wound with soap and water. In addition, the BCG vaccine may grant immunity for 6 months to a year, and it has been demonstrated to prevent BU-associated osteomyelitis in children. A vaccine against BU is many years away. FTG may be prevented by avoiding aquariums and nonchlorinated pools or at least by wearing gloves when working with aquariums or marine creatures. Prevention of RGM consists primarily of sterilizing surgical and cosmetic instruments before use.

EVIDENCE

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SECTION III

Edited by Thomas M. File, Jr.

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Introduction to Respiratory Tract Infections

25

Thomas M. File, Jr.

Respiratory tract infections are the most common type of infection managed by healthcare providers, and they are of great consequence because of cost, mortality, emergence of antibiotic-resistant pathogens, and potential for epidemic dissemination.

Acute respiratory tract infections are the greatest single cause of death in children worldwide. Whereas community-acquired pneumonia is the eighth leading cause of death and the most common cause of death caused by infectious disease in the United States, nosocomial pneumonia is the leading cause of death from infections acquired in the hospital. A recent reclassification of nosocomial pneumonia has added a subclass of healthcare-associated pneumonia (HCAP), which includes pneumonia in a person who was hospitalized in the preceding 90 days, received intravenous (IV) antibiotic therapy in the past 30 days, or lived in a long-term care facility in the previous 90 days.

Indicators of overall burden of respiratory infections suggest that the morbidity and mortality rates attributed to these diseases are increasing, as are the proportion of hospitalizations attributed to these infections. Many factors, such as the emergence of acquired immunodeficiency syndrome (AIDS), the increased association of underlying conditions (e.g., diabetes and heart or lung disease), the reemergence of tuberculosis, the emergence of new pathogens (e.g., community-acquired methicillin-resistant *Staphylococcus aureus* [CA-MRSA], H5N1 influenza A, and 2009 H1N1 influenza A), and increased antibiotic resistance, probably contribute to this increase.

Respiratory tract infections are also the cause of most antibiotic use. Approximately three quarters of all outpatient antimicrobial use is for respiratory infections—especially for acute bacterial sinusitis for adults and acute bacterial otitis for children. Although many respiratory infections require antimicrobial therapy for optimal management, most outpatient respiratory infections (e.g., acute bronchitis, nasal pharyngitis, cold, nonspecific upper respiratory tract infection [URI]) are caused by respiratory viruses for which antibiotic use is not warranted. Overuse of antibiotics for both community- and hospital-acquired respiratory infections is a source of great antibiotic abuse and increases the likelihood of further hindering the already high level of antibiotic resistance. The emergence of CA-MRSA in the community and multidrug-resistant gram-negative pathogens (e.g., *Acinetobacter*, *Pseudomonas*) in the hospital setting further challenges our ability to successfully treat these infections. Most recently the emergence of the pandemic of H1N1 influenza A has illustrated the importance of viral infections as well as bacterial causes of these infections (see Section IX: Emerging Infectious Diseases and Pandemics). The pathogenic mechanisms for secondary bacterial pneumonia in patients with influenza is of major importance because these co-infections are frequently associated with high mortality.

There is a great need for rapid diagnostic tests that will identify specific pathogens among the diverse groups of bacteria, viruses, fungi, and atypical pathogens that can cause pneumonia. The lack of these tests certainly also contributes to excessive antibiotic use.

Critical to the appropriate management of respiratory tract infections is an understanding of the pathogenesis, microbiology, diagnosis, and treatment of these diseases. This section reviews the current concepts of respiratory tract infections, including both upper and lower tract infections, in light of recent information and published guidelines. It provides a useful source of essential information for healthcare providers with the goal of achieving optimal care of patients.

Community-Acquired Pneumonia, Bacterial

26

Thomas M. File, Jr.

ABSTRACT

Community-acquired pneumonia (CAP) is defined as an acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community and has not had recent hospitalization or association with other healthcare facilities such as nursing homes, dialysis centers, and outpatient clinics. CAP is a common and potentially serious illness, particularly in elderly patients and those with significant comorbidities. CAP may be caused by myriad pathogens, but bacteria are the most common causes. Bacteria have traditionally been divided into two groups: typical and atypical agents. Typical organisms include *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Staphylococcus aureus*, group A streptococci, *Moraxella catarrhalis*, anaerobes, and aerobic gram-negative bacteria. Atypical organisms include *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydophila* (also known as *Chlamydia*) *pneumoniae*, and *Chlamydophila psittaci*. This chapter will focus on the general approach to CAP in adults, with a concentration primarily on typical bacterial causes. Other chapters focus specifically on pneumonia caused by aspiration, viruses, or atypical organisms.

DISEASE BURDEN

CAP is associated with significant morbidity and mortality and considerable costs of care. In the United States, CAP is the most frequent cause of death resulting from infectious diseases and is the eighth leading cause of death overall. The mortality rate of patients treated on an outpatient basis is <1%; for those who require admission to the hospital, it averages 12% but increases to 30% to 40% for those with severe CAP who require admission to the intensive care unit (ICU). The overall rate of CAP ranges from 8 to 15 per 1000 persons per year; the highest rates are at the extremes of age. More cases occur during the winter months. The economic cost exceeds $17 billion a year.

PATHOGENESIS AND RISK FACTORS

The primary route of pathogens into the lungs is by microaspiration of upper airway contents. Although the respiratory tract is constantly exposed to particulate material, the lower airways are usually sterile because of the pulmonary defense mechanisms, which include the anatomy of the nasal passages, the cough reflex, the ciliary respiratory epithelium, and humeral and cellular factors (e.g., immunoglobulins, complement, macrophages, and neutrophils). CAP occurs when there is a defect in host defenses, exposure to a particularly virulent microorganism, or an overwhelming inoculum. Other routes for pathogens to the lung are hematogenous spread, direct spread from a contiguous focus, and macroaspiration. There are several predisposing conditions (Box 26-1).

Once bacteria reach the lungs, they can cause an inflammatory response that results in disease. This is best studied with *S. pneumoniae*, which in the absence of opsonizing antibodies, rapidly multiplies in the alveolar spaces, leading to local hyperemia, edema, and mobilization of neutrophils. The filling of alveoli with bacteria, red cells, and fluid leads to significant increase in weight of the lung in this early phase of consolidation (Figure 26-1). Subsequently this leads to advanced consolidation with increased neutrophils, pulmonary cells, and fibrin.

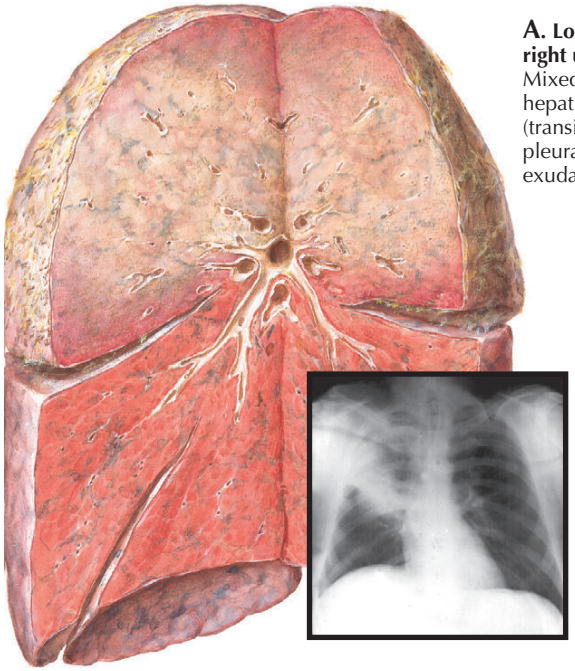
MICROBIOLOGY

Although numerous pathogens have been associated as a cause of CAP, a limited range of key pathogens cause the majority of cases (Table 26-1). The predominant pathogen continues to be *S. pneumoniae* (pneumococcus), which accounts for approximately two thirds of all cases of bacteremic pneumonia. Other causative agents include (but are not limited to) *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*, *Legionella* species, enteric gram-negative bacteria (Enterobacteriaceae), *Pseudomonas aeruginosa*, *S. aureus*, anaerobes (aspiration pneumonia), and respiratory viruses (influenza, adenovirus, respiratory syncytial virus, parainfluenza, coronavirus). *S. aureus* (Figure 26-2) and gram-negative bacilli (such as *Klebsiella* species; Figure 26-3) are less frequently isolated and are the cause in selected patients (e.g., patients with severe CAP requiring intensive care admission or those who have recently received antimicrobial therapy or have pulmonary comorbidities). The frequency of other causes—for example, *Mycobacterium tuberculosis*, *C. psittaci* (psittacosis), *Coxiella burnettii* (Q fever), *Francisella tularensis* (tularemia), and endemic fungi (histoplasmosis, coccidioidomycosis, blastomycosis)—varies with epidemiologic setting.

Recently, a community-associated methicillin-resistant *S. aureus* (CA-MRSA) strain has emerged as a cause of severe CAP associated with hemorrhagic and necrotizing complications and usually following influenza infection. CA-MRSA is more virulent than the traditional nosocomial MRSA strains, and strains of CA-MRSA tend to be more susceptible to antimicrobial agents than hospital-acquired MRSA strains. The majority of CA-MRSA strains contain a novel type IV staphylococcal cassette chromosome (SCC*mec*) gene and also carry the Panton-Valentine leukocidin (PVL) genes, which produce toxins that create lytic pores in cell membranes of neutrophils, inducing release of chemotactic factors that promote inflammation and tissue destruction. Such patients often have necrotizing pneumonia and abscesses (see Figure 26-2). Although PVL toxins may be a highly linked epidemiologic marker for CA-MRSA strains, it remains unclear whether PVL is the major virulence determinant of CA-MRSA.

Box 26-1 Predisposing Conditions of Community-Acquired Pneumonia

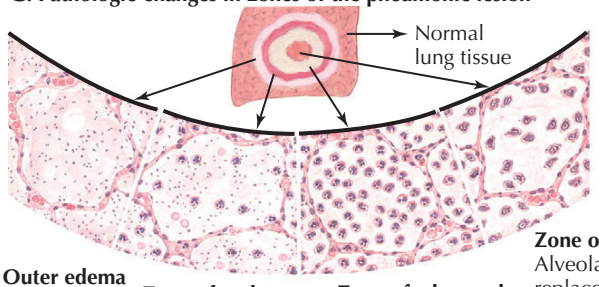
- Alterations in the level of consciousness, which predispose to both macroaspiration of stomach contents (because of stroke, seizures, drug intoxication, anesthesia, and alcohol abuse) and microaspiration of upper airway secretions during sleep
- Smoking
- Alcohol consumption
- Toxic inhalations
- Pulmonary edema
- Uremia
- Malnutrition
- Administration of immunosuppressive agents (solid organ or stem cell transplant recipients or patients receiving chemotherapy)
- Mechanical obstruction of a bronchus
- Being elderly (there is a marked increase in the rate of pneumonia in persons ≥65 years)
- Cystic fibrosis
- Bronchiectasis
- Chronic obstructive pulmonary disease (COPD)
- Previous episode of pneumonia or chronic bronchitis
- Uncontrolled comorbidities (e.g., congestive heart failure, diabetes)



A. Lobar pneumonia; right upper lobe. Mixed red and gray hepatization (transition stage); pleural fibrinous exudate

B. Right upper lobe and segment of right lower lobe pneumonia

C. Pathologic changes in zones of the pneumonic lesion



Outer edema zone Alveoli filled with edema fluid containing pneumococci

Zone of early consolidation Polymorphonuclear and some red cell exudation

Zone of advanced consolidation Intense polymorphonuclear outpouring; pneumococci phagocytized and destroyed

Zone of resolution Alveolar macrophages replace leukocytes

Figure 26-1 Pneumococcal pneumonia.

Antimicrobial resistance, especially the emergence of multidrug-resistant *S. pneumoniae*, has escalated worldwide over the last two decades. Risk factors for drug-resistant *S. pneumoniae* include very young age (<2 years) and old age (>65 years); β-lactam, macrolide, or fluoroquinolone therapy within the previous 3 months; alcoholism; medical comorbidities; immunosuppressive illness or therapy; and exposure to a child in a daycare center. Available data suggest that a clinically relevant level of penicillin resistance is a minimum inhibitory concentration (MIC) of ≥4 mcg/mL. At this breakpoint the rate of penicillin resistance for pneumonia for most locations in North America is ≤10%

Table 26-1 Most Common Causes of Community-Acquired Pneumonia

AMBULATORY PATIENTS	HOSPITALIZED (NON-ICU)	SEVERE (ICU)
Streptococcus pneumoniae	*S. pneumoniae*	*S. pneumoniae*
Mycoplasma pneumoniae	*M. pneumoniae*	*Staphylococcus aureus*
Haemophilus influenzae	*C. pneumoniae*	*Legionella* species
Chlamydophila pneumoniae	*H. influenzae*	Gram-negative bacilli
Respiratory viruses*	*Legionella* species	*H. influenzae*
	Aspiration	
	Respiratory viruses*	

Adapted from Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults, *Clin Infect Dis* 44(suppl 2):S27-S72, 2007; based on collective data from recent studies.

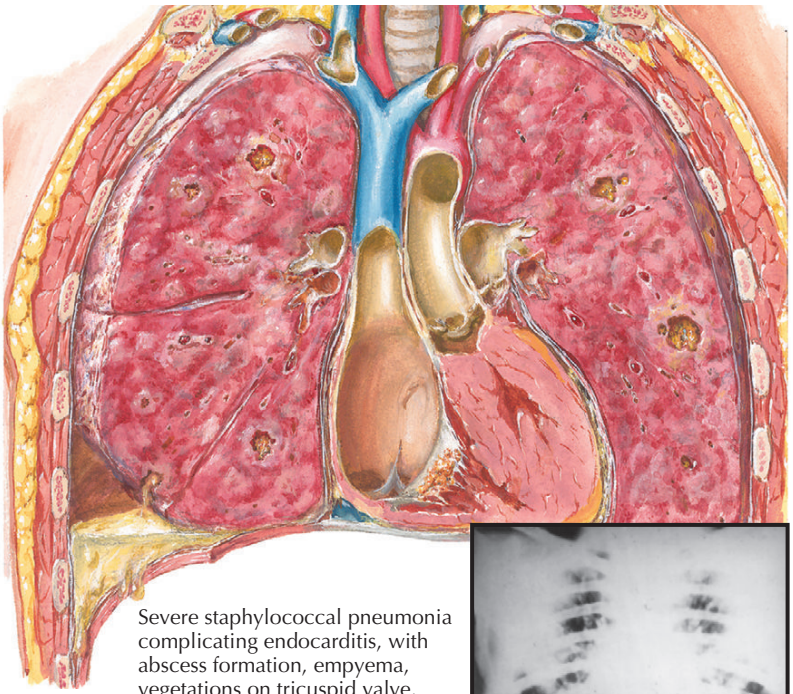
ICU, Intensive care unit.

*Influenza A and B, adenovirus, respiratory syncytial virus, parainfluenza.

CLINICAL FEATURES

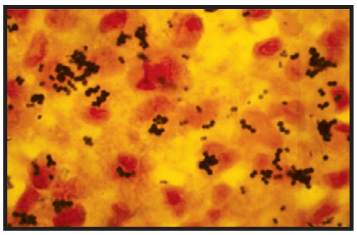
Symptoms and signs of CAP include cough (either productive or nonproductive), pleuritic chest pain, shortness of breath, temperature higher than 38° C, and crackles on auscultation. Mucopurulent sputum production is more frequently found in association with bacterial pneumonia, whereas scant or watery sputum production is more suggestive of an atypical pathogen. Although there are classic descriptions of certain types of sputum production and particular pathogens (e.g., pneumococcal pneumonia and rust-colored sputum), these clinical descriptions usually do not help with initial clinical decision making regarding treatment because the clinical presentations of the specific pathogens are variable. Gastrointestinal symptoms (nausea, vomiting, diarrhea) and mental status changes may accompany respiratory manifestations.

On physical examination the majority of patients are febrile, although this finding is frequently absent in older patients. Increased respiratory rate is frequently noted, and this may be



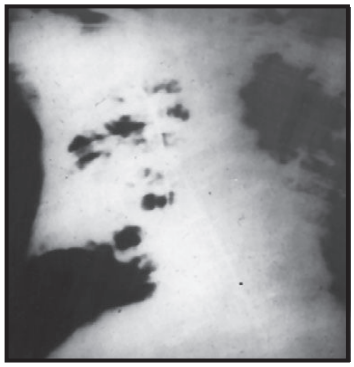
Severe staphylococcal pneumonia complicating endocarditis, with abscess formation, empyema, vegetations on tricuspid valve, and emboli in branches of pulmonary artery

Coagulase test. *Tube on left* shows plasma clot; *tube on right* is control



Staphylococcal and polymorphonuclear leukocytes in sputum (Gram stain)

Early staphylococcal pneumonia



Late staphylococcal pneumonia with abscesses and pneumothorax

Figure 26-2 Staphylococcal pneumonia.

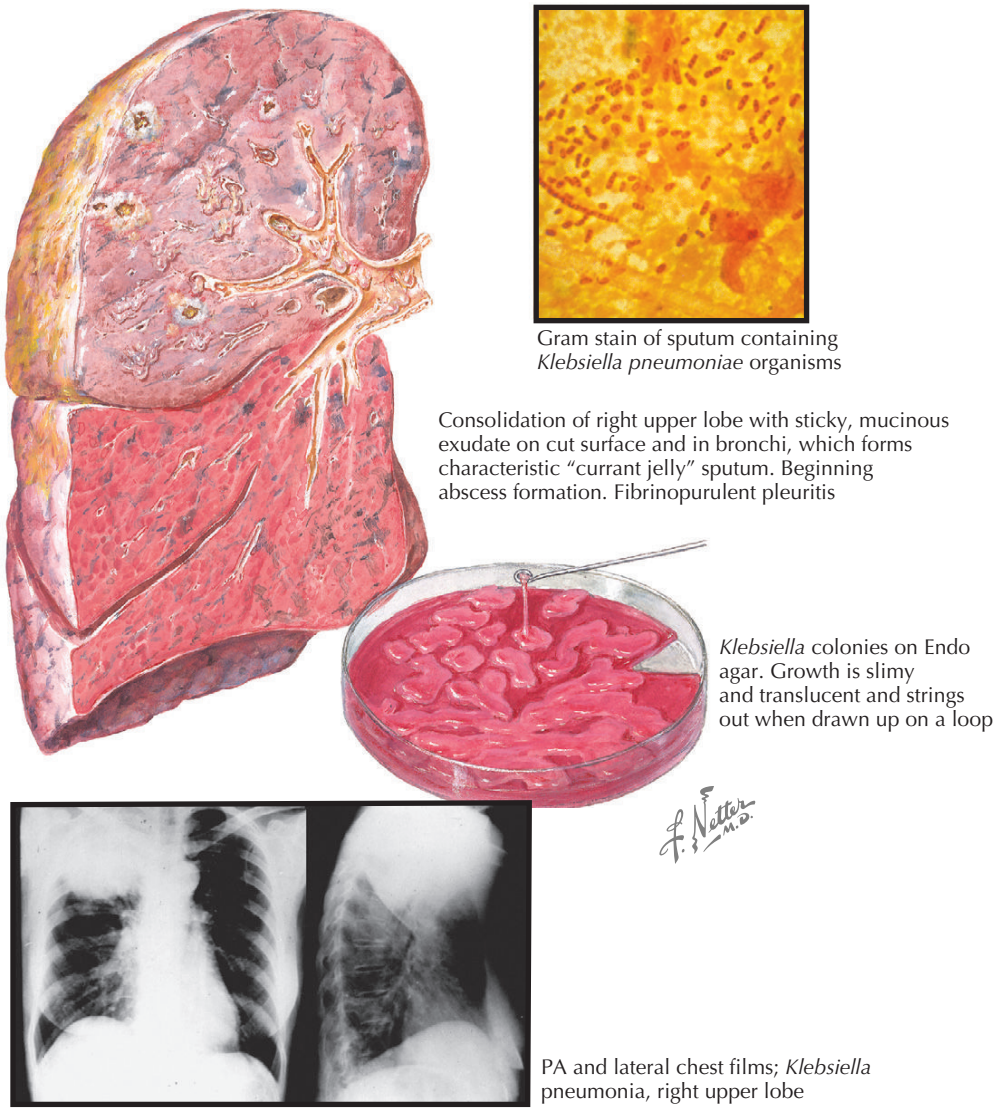


Figure 26-3 *Klebsiella* (Friedländer's) pneumonia.

the most sensitive sign in elderly patients; tachycardia is also common. Chest examination reveals audible rales in most patients, and approximately one third have evidence of consolidation. However, no clear constellation of symptoms and signs has been found to accurately predict whether or not the patient has pneumonia.

The major blood test abnormality is leukocytosis (typically 15,000 to 30,000 per mm^3) with a leftward shift. Leukopenia can occur and generally is associated with a poor prognosis.

DIAGNOSTIC APPROACH

Adult patients who are immunocompetent should be evaluated for pneumonia if they demonstrate signs including cough, sputum production, labored breathing (including altered breath sounds and rales), and/or fever. These symptoms (especially cough) are nonspecific and may also be present in patients with other diseases that should be considered in the differential diagnosis (Box 26-2, Figure 26-4).

The presence of an infiltrate on plain chest radiograph is considered the gold standard for diagnosing pneumonia when clinical features are supportive. Radiologists cannot reliably differentiate bacterial from nonbacterial pneumonia on the basis of the radiographic appearance. Computed tomography (CT) scans are significantly more sensitive in detecting pulmonary infiltrates in patients hospitalized with CAP, but the clinical significance of this finding is unclear.

Determining Severity of Illness and Site of Care

Site of care in patients with CAP affects the overall cost of treatment, the intensity of diagnostic testing, and the empirical antimicrobial(s). A general consensus is that the majority of patients can be safely treated as outpatients. However, selected patients should be hospitalized based on the requirements of care (e.g., need for close observation, respiratory support, intravenous antibiotics, or other concerns). The advantages of not

Box 26-2 Differential Diagnosis of Cough and Fever

Infectious
Upper Respiratory Tract
Acute or chronic sinusitis
Lower Respiratory Tract
Acute or chronic bronchitis
Acute exacerbation of chronic obstructive pulmonary disease
Bronchiectasis
Tuberculosis

Noninfectious
Pulmonary embolism or infarction
Pulmonary neoplasm
Radiation pneumonitis
Interstitial lung disease
Sarcoidosis
Collagen vascular disease
Drug-induced pulmonary disease
Hypersensitivity pneumonitis
Granulomatous vasculitis
Eosinophilic pneumonitis

admitting patients for treatment of CAP include decreased cost, patient preference, and avoidance of iatrogenic complications in the hospital. For elderly patients, particularly, a reduction in time in a hospital bed can facilitate better convalescence. Hospitalization should be considered when (1) patients have preexisting conditions that may compromise the safety of home care, (2) patients have hypoxemia, (3) patients are unable to take oral medications, or (4) psychosocial factors can potentially influence effective treatment (such as an unstable home environment or psychiatric disorders that may hinder adherence to therapy). Mortality prediction tools can also help guide clinicians in determining the requirement of hospitalization.

The pneumonia prediction rule, developed over 10 years ago, offers important insights into the risk of mortality. This technique uses a combination of demographic variables, comorbidities, physical observations, and laboratory and radiographic variables to assign patients to one of five classes. Those belonging to pneumonia severity index (PSI) class 1 or 2 have a low risk of mortality (<1%) and can be treated as outpatients. Those in PSI class 3 have a slightly higher risk of mortality (<5%) and may require a brief observational stay in a hospital. Those in PSI class 4 or 5 have the highest mortality risk (8% to 40%) and will require hospitalization; those in PSI class 5 should be admitted to an ICU. Though the PORT prediction rule is effective in determining mortality risk, it is not the most practical approach in the clinical setting as it is partly based on laboratory evaluations that can be time-consuming.

The CURB-65 rule uses only five aspects in making a clinical determination—confusion, urea concentration, respiratory rate, blood pressure, and age. Those meeting two or more of these criteria should be considered for hospitalization. However, this method requires a blood sample and laboratory analysis for urea concentration. In response to this, the CRB-65 was designed. It omitted the blood urea measurement and was practical for office-based settings. In CRB-65, a score of 0 equates to home treatment, a score of 1 to hospital-supervised treatment, and a score of 2 or more to hospitalization.

Recommendations regarding admission to the ICU are provided by the Infectious Diseases Society of America (IDSA)/American Thoracic Society (ATS) guidelines for management of CAP. According to the IDSA/ATS guidelines, direct admission to the ICU is essential for patients with septic shock requiring vasopressor or for patients with acute respiratory failure requiring intubation and mechanical ventilation. ICU admission should also be considered for patients who have three or more of the following: confusion or disorientation, uremia (blood urea nitrogen ≥20 mg/dL), respiratory rate ≥30 breaths/min, hypotension requiring aggressive fluid resuscitation, Pao_2/Fio_2 ratio ≤250, multilobar infiltrates, leukopenia (white blood count <4000 cells/mm^3), thrombocytopenia (platelet count <100,000 cells/mm^3), or hypothermia (core temperature <36° C).

Determining Causative Diagnosis

The utility of diagnostic studies to determine the causative agents of CAP is controversial because of the lack of rapid, easily performed, accurate, cost-effective methods that allow immediate results for the majority of patients at the point of service (i.e., the initial evaluation by a clinician in an office or acute care setting). Nevertheless, there is good rationale for establishing a causative diagnosis (i.e., to permit antibiotic selection that permits optimal selection of agents against a specific pathogen, to limit the consequences of antibiotic misuse, and to identify pathogens of potential epidemiologic significance such as *Legionella* or tuberculosis [TB]).

Routine microbiologic tests are not recommended by most of the recent guidelines for patients managed in the community. However, if a patient has purulent sputum, it is reasonable to send a sample to the laboratory for Gram stain and culture on the basis that the information may be of value for directing specific therapy if the patient's condition is failing to respond to initial empirical therapy.

Investigations that are variably recommended for patients requiring admission include blood cultures, Gram stain and culture, and thoracentesis if there is significant pleural fluid present. Approximately 11% of patients with CAP will have positive blood cultures, more commonly associated with severe illness. Because false-positive blood cultures may be more common than pathogen-positive blood cultures from patients admitted to a general ward, they may have limited benefit for such patients and are considered "optional" in recent guidelines. In more severely ill patients requiring ICU admission, blood cultures may increase the likelihood of finding a pathogen not covered by customary antimicrobial therapy and are recommended for all such patients. The value of performing a sputum Gram stain and culture is limited by the facts that many patients cannot produce a good specimen and the validity of the Gram stain is related directly to the experience of the interpreter; however, when stringent criteria are applied, the specificity for pneumococcal pneumonia can approach 90%. Sputum culture for other pathogens (e.g., *Legionella* species, fungus, virus, *Mycobacterium* species) should be obtained based on epidemiologic considerations. *M. tuberculosis* should be considered when

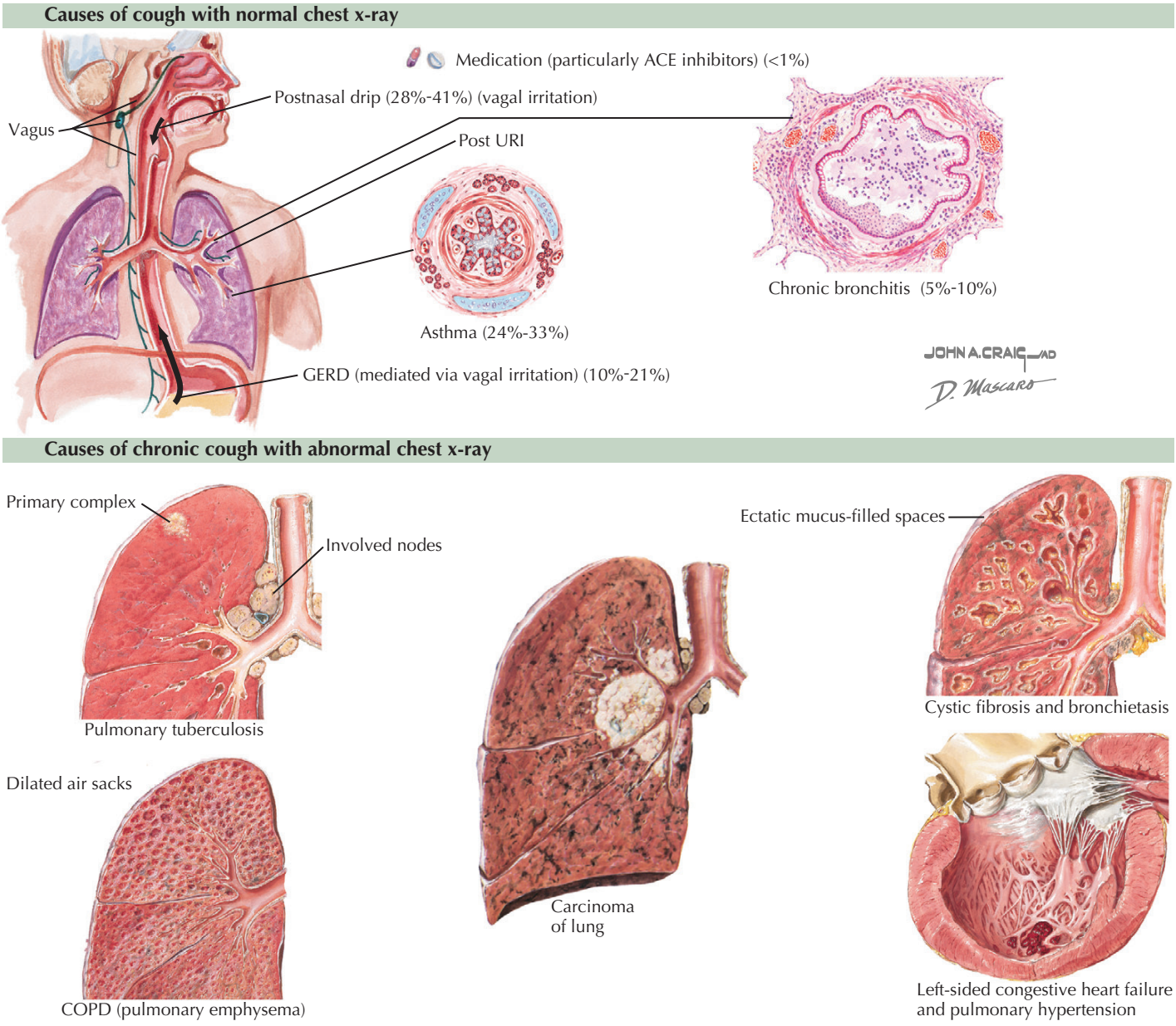


Figure 26-4 Causes of chronic cough.

patients are from endemic areas, when the chest radiograph shows an upper lobe cavitary infiltrate, when patients have had prolonged symptoms of cough (often with weight loss and night sweats), when patients are homeless, or when they have a history of exposure to TB.

Because the early administration of therapy is important for the outcome of CAP, an attempt to obtain expectorated sputum should never delay prompt initiation of antimicrobial therapy.

Other tests considered helpful for patients admitted to the hospital include the urinary antigen assays for *Legionella* and *S. pneumoniae* and a direct stain (i.e., acid-fast) for detection of mycobacterial infections in patients with epidemiologic risks for TB. Many rapid diagnostic tests such as nucleic acid amplification tests (i.e., polymerase chain reaction [PCR]) assays are early in development and not commonly available, but offer promise for rapid diagnosis and will likely become increasingly utilized in the future. Serologic tests are generally not helpful in the early management of CAP because the determination of acute and convalescent titers is required before the cause can be ascribed to a specific pathogen. Percutaneous transthoracic needle aspiration (PTNA) or other invasive testing (including bronchoscopy and biopsy) is not routinely recommended for the evaluation of patients but may be valuable in immunocompromised hosts, suspected TB in the absence of productive cough, selected cases of chronic pneumonia, pneumonia associated with suspected neoplasm or foreign body, suspected *Pneumocystis carinii* pneumonia, some cases in which intubation is required, and suspected conditions that require lung biopsy.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Empirical Antimicrobial Therapy

Until there are better rapid diagnostic methods, the majority of patients will be treated empirically. Although some authorities propose a syndromic approach to therapy (counting on the predictability of a cause based on the presenting clinical manifestations), most data indicate that the presenting clinical features are not specific enough to reliably predict the cause of CAP. Therefore unless there is a specific epidemiologic factor (e.g., influenza epidemic), the empirical approach to initial therapy is usually based on the likelihood that one of the key pathogens is responsible for disease. Recently published guidelines from North America give specific recommendations for empirical therapy for CAP (Table 26-2).

For outpatients, empirical therapy with a macrolide, doxycycline, antipneumococcal fluoroquinolone (e.g., levofloxacin, gemifloxacin, moxifloxacin), or the combination of a β-lactam plus macrolide are recommended treatment options based on risk factors of recent antimicrobial use and comorbidities. For general inpatient treatment, combination therapy with a β-lactam such as cefotaxime, ceftriaxone, ertapenem, or ampicillin-sulbactam plus azithromycin or monotherapy with a respiratory fluoroquinolone is recommended. For patients with severe CAP requiring ICU admission, recommendations are given based on risks for *Pseudomonas* and/or CA-MRSA. *Pseudomonas* is an uncommon cause of CAP but should be considered with the following risk factors: history of bronchiectasis or advanced chronic obstructive pulmonary disease with frequent use of antimicrobials or steroids. If CA-MRSA is a consideration, linezolid or vancomycin should be added to the regimen. Although methicillin-resistant strains of *S. aureus* are still the minority, the excess mortality of inappropriate antibiotic therapy would suggest that empirical coverage should be considered when CA-MRSA is a concern. The best indicator of *S. aureus* is the presence of gram-positive cocci in clusters in a tracheal aspirate or adequate sputum sample (see Figure 26-2). Clinical risk factors for *S. aureus* CAP include end-stage renal disease, intravenous drug abuse, prior influenza, and prior antibiotics (especially fluoroquinolones).

Pathogen-Directed Therapy

Treatment options are obviously simplified if the causative agent is established or strongly suspected (Box 26-3). Diagnostic procedures that provide identification of a specific cause within 24 to 72 hours can still be useful for guiding continued therapy. If,

Table 26-2 Epidemiologic Conditions and/or Risk Factors Related to Specific Pathogens in Community-Acquired Pneumonia

CONDITION	COMMONLY ENCOUNTERED PATHOGEN(S)
Alcoholism	*Streptococcus pneumoniae,* oral anaerobes, *Klebsiella pneumoniae, Acinetobacter* species, *Mycobacterium tuberculosis*
COPD and/or smoking	*Haemophilus influenzae, Pseudomonas aeruginosa, Legionella* species, *S. pneumoniae, Moraxella catarrhalis, Chlamydophila pneumoniae*
Aspiration	Gram-negative enterics, oral anaerobes
Lung abscess	CA-MRSA, oral anaerobes, endemic fungal pneumonia, *M. tuberculosis,* atypical mycobacteria
Exposure to bat or bird droppings	*Histoplasma capsulatum*
Exposure to birds	*Chlamydia (Chlamydophila) psittaci* (if poultry—avian influenza)
Exposure to rabbits	*Francisella tularensis*
Exposure to farm animals or parturient cats	*Coxiella burnettii* (Q fever)
HIV (early)	*S. pneumoniae, H. influenzae, M. tuberculosis*
HIV (late)	Above plus *Pneumocystis jiroveci, Cryptococcus, Histoplasmosis, Aspergillus,* atypical mycobacteria (especially *Mycobacterium kansasii*), *P. aeruginosa, H. influenzae*
Hotel or cruise ship stay in previous 2 weeks	*Legionella*
Travel to or residence in southwestern United States	*Coccidioides* species, hantavirus
Travel to or residence in Southeast and East Asia	*Burkholderia pseudomallei,* avian influenza, SARS
Influenza active in community	Influenza, *S. pneumoniae, Staphylococcus aureus, H. influenzae*
Cough >2 weeks with whoop or posttussive vomiting	*Bordetella pertussis*
Structural lung disease (e.g., bronchiectasis)	*P. aeruginosa, Burkholderia cepacia, S. aureus*
Injection drug use	*S. aureus,* anaerobes, *M. tuberculosis, S. pneumoniae*
Endobronchial obstruction	Anaerobes, *S. pneumoniae, H. influenzae, S. aureus*
In context of bioterrorism	*Bacillus anthracis* (anthrax), *Yersinia pestis* (plague), *F. tularensis* (tularemia)

Adapted from Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults, *Clin Infect Dis* 44(suppl 2):S27-S72, 2007.
COPD, Chronic obstructive pulmonary disease; *CA-MRSA,* community-associated methicillin-resistant *Staphylococcus aureus; HIV,* human immunodeficiency virus; *SARS,* severe acute respiratory syndrome.

Box 26-3 Recommended Empirical Antibiotics for Community-Acquired Pneumonia

Outpatient Treatment

1. Previously healthy and no use of antimicrobials within the previous 3 months:
   - A macrolide
   - Doxycycline
2. Presence of comorbidities or use of antimicrobials within the previous 3 months (in which case an alternative from a different class should be selected):
   - Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, levofloxacin [750 mg])
   - β-Lactam *plus* a macrolide
3. In regions with a high rate (>25%) of high-level (minimum inhibitory concentration [MIC] ≥16 mcg/mL) macrolide-resistant *Streptococcus pneumoniae,* consider use of alternative agents listed above in 2 for patients without comorbidities.

Inpatients, Non–Intensive Care Unit Treatment

- Respiratory fluoroquinolone
- β-Lactam *plus* a macrolide

Inpatients, Intensive Care Unit Treatment

- A β-lactam (cefotaxime, ceftriaxone, ampicillin-sulbactam) *plus* either azithromycin *or* a respiratory fluoroquinolone (for patients allergic to penicillin, a respiratory fluoroquinolone and aztreonam are recommended).

Special Concerns

1. If *Pseudomonas* is a consideration (risk factors include bronchiectasis and chronic obstructive pulmonary disease with frequent antimicrobial or steroid use):
   - An antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, meropenem) *plus* either ciprofloxacin or levofloxacin (750-mg dose)
   - The above β-lactam *plus* an aminoglycoside and azithromycin
   - The above β-lactam *plus* an aminoglycoside and an antipneumococcal fluoroquinolone (for patients allergic to penicillin, substitute aztreonam for above β-lactam)
2. If community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) is a consideration, add linezolid or vancomycin.

Adapted from Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults, *Clin Infect Dis* 44(suppl 2):S27-S72, 2007.

for example, an appropriate culture reveals the isolation of penicillin-susceptible *S. pneumoniae*, therapy can be specified by selecting a narrow-spectrum agent (such as penicillin or amoxicillin). This will hopefully reduce the selective pressure for resistance. This information is often available at the time of switch from parenteral to oral therapy and may be used to direct specific antimicrobial choices.

Duration of Therapy

Patients should be treated for a minimum of 5 days as long as they have been afebrile for 48 to 72 hours and are clinically stable relative to baseline status. A longer duration of therapy is recommended for patients with bacteremic *S. aureus* pneumonia because of the risks for associated endocarditis and deep-seated infection; patients with extrapulmonary infection (especially meningitis); patients with *P. aeruginosa* pneumonia; and patients with infection caused by less common pathogens. Potential benefits of therapy shorter than 10 days include improvement of patient compliance and reduction of microbial resistance, cost, and adverse events such as *Clostridium difficile* infections.

PROGNOSIS

In most patients fever is reduced within 3 to 4 days of therapy; however, cough and fatigue will often persist for several weeks even in patients with mild disease. Symptoms can be expected to last longer in more seriously ill patients. Such information should be imparted to patients for better awareness of their illness and anticipated clinical course.

Up to 15% of patients may not respond appropriately to initial antibiotic therapy. Nonresponse can be defined as absence or delay in achieving clinical stability within several days or actual clinical deterioration. A number of possibilities, both infectious and noninfectious, should be considered (Table 26-3). A systematic assessment of patients should take these considerations into account. The most common causes of treatment failure are lack of or delayed response by the host despite appropriate antibiotics and infection with an organism that is not covered by the initial antibiotic regimen. Antibiotic changes in this time period should be considered only for patients with deterioration or in whom new culture data or epidemiologic clues suggest alternative causes.

PREVENTION

Vaccines targeting pneumococcal disease and influenza are a mainstay for preventing CAP. Pneumococcal polysaccharide vaccine and inactivated or live-attenuated influenza vaccine should be considered for all patients according to recent recommendations from the Centers for Disease Control and Prevention (CDC). Chemoprophylaxis (i.e., oseltamivir or zanamivir), can be used as an adjunct to influenza vaccination. Clinicians should also intervene to modify some of the associated risk factors for pneumonia in adults. Because smoking is a significant risk factor for CAP, smoking cessation should be attempted; this is particularly important and relevant when patients are hospitalized for pneumonia. In addition, stabilization of underlying conditions (e.g., congestive heart failure, diabetes) and promotion of appropriate nutrition may help to reduce the risk of CAP and thereby promote longer and healthier lives.

Table 26-3 Recommended Antimicrobial Therapy for Specific Pathogens[a]

ORGANISM	PREFERRED ANTIMICROBIAL(S)	ALTERNATIVE ANTIMICROBIAL(S)
Streptococcus pneumoniae, penicillin nonresistant (MIC <2 mcg/mL)	Penicillin G; amoxicillin	Macrolide; cephalosporins (oral—cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren; parenteral—cefuroxime, ceftriaxone, cefotaxime); clindamycin; doxycycline; respiratory fluoroquinolone[b]
S. pneumoniae, penicillin resistant (MIC ≥2 mcg/mL)	Agents based on susceptibility, including cefotaxime, ceftriaxone, fluoroquinolone	Vancomycin, linezolid, high-dose amoxicillin (3 g/day with penicillin MIC ≤4 mcg/mL)
Haemophilus influenzae	Non–β-lactamase producing: amoxicillin β-lactamase producing: second- or third-generation cephalosporin; amoxicillin-clavulanate	Fluoroquinolone; doxycycline; azithromycin[c]; clarithromycin[d]
Mycoplasma pneumoniae or Chlamydophila pneumoniae	Macrolide; a tetracycline	Fluoroquinolone
Legionella species	Fluoroquinolone; azithromycin	Doxycycline
Chlamydia psittaci	A tetracycline	Macrolide
Coxiella burnettii	A tetracycline	Macrolide
Francisella tularensis	Doxycycline	Gentamicin, streptomycin
Yersinia pestis	Streptomycin, gentamicin	Doxycycline, fluoroquinolone
Anthrax (inhalation)	Ciprofloxacin, levofloxacin, doxycycline (usually with second agent)	Other fluoroquinolones; β-lactam, if susceptible; rifampin; clindamycin; chloramphenicol
Enterobacteriaceae	Third-generation cephalosporin; carbapenem[d] (drug of choice if extended-spectrum β-lactamase producer)	β-lactam or β-lactamase inhibitor[e]; fluoroquinolone
Pseudomonas aeruginosa	Antipseudomonal β-lactam[f] *plus* ciprofloxacin or levofloxacin[g] or aminoglycoside	Aminoglycoside *plus* (ciprofloxacin or levofloxacin[g])
Burkholderia pseudomallei	Carbapenem, ceftazidime	Fluoroquinolone, TMP-SMX
Acinetobacter species	Carbapenem	Cephalosporin-aminoglycoside, ampicillin-sulbactam, colistin
Staphylococcus aureus:		
Methicillin susceptible	Antistaphylococcal penicillin[h]	Cefazolin; clindamycin
Methicillin resistant	Vancomycin or linezolid	TMP-SMX
Bordetella pertussis	Macrolide	TMP-SMX
Anaerobe (aspiration)	β-lactam or β-lactamase inhibitor[e]; clindamycin	Carbapenem
Influenza	Oseltamivir or zanamivir	
Mycobacterium tuberculosis	Isoniazid *plus* rifampin *plus* ethambutol *plus* pyrazinamide	Refer to American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America guidelines for specific recommendations
Coccidioides species	Uncomplicated infection in normal host—no therapy generally recommended; For therapy—itraconazole, fluconazole	Amphotericin B
Histoplasmosis	Itraconazole	Amphotericin B
Blastomycosis	Itraconazole	Amphotericin B

Adapted from Mandell LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults, *Clin Infect Dis* 44(suppl 2):S27-S72, 2007.
MIC, Minimum inhibitory concentration; *TMP-SMX,* trimethoprim-sulfamethoxazole.
[a]Choices should be modified based on susceptibility test results and advice from local specialists. Refer to local references for appropriate doses.
[b]Levofloxacin, moxifloxacin, gemifloxacin (not a first-line choice for penicillin-susceptible strains); ciprofloxacin is appropriate for *Legionella* and most gram-negative bacilli (including *H. influenzae*).
[c]Azithromycin more active in vitro than clarithromycin for *H. influenzae.*
[d]Imipenem-cilastatin, meropenem, ertapenem.
[e]Piperacillin-tazobactam for gram-negative bacilli; ticarcillin-clavulanate; ampicillin-sulbactam or amoxicillin-clavulanate.
[f]Ticarcillin, piperacillin, ceftazidime; cefepime, aztreonam, imipenem, meropenem.
[g]750 mg qd.
[h]Nafcillin, oxacillin, flucloxacillin.

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Hospital-Acquired Pneumonia

Lee E. Morrow and Marin H. Kollef

27

ABSTRACT

Hospital-acquired pneumonia (HAP) is a new infection of the lung parenchyma that develops more than 48 hours after hospital admission. Epidemiologic data suggest that HAP occurs in up to 1% of patients, prolongs hospital stay by 7 to 9 days, and represents the most common hospital-acquired infection leading to death. The morbidity and mortality attributed to HAP are significantly increased if infection is caused by multidrug-resistant pathogens. The subset of HAP occurring more than 48 hours after initiation of mechanical ventilation is termed *ventilator-associated pneumonia* (VAP). Risk factors for HAP and VAP are diverse and include both patient-specific and treatment-associated elements. Clinical defining criteria for pneumonia require a new or worsening infiltrate on chest radiography in conjunction with typical clinical and laboratory findings. Although microbiologic confirmation is ideal, the optimal diagnostic strategy is hotly debated. Recent trends in the microbial resistance rates for pathogens causing HAP have led to significant changes in the recommendations for empirical therapy, with an increased reliance on broad-spectrum therapy followed by culture-based deescalation. Empirical treatment decisions must also take into consideration local microbiologic data, host-specific risk factors, and the severity of the patient's acute illness. Limited new antibiotic development and high attributable mortality rates highlight the importance of evidence-based HAP prevention strategies.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

In the United States, pneumonia accounts for 13% to 18% of all hospital-acquired infections and is the leading cause of death from nosocomial infection. Although most cases of HAP arise outside the intensive care unit (ICU), HAP rates are highest in ICU patients—particularly those who are mechanically ventilated. These patients account for up to 25% of all nosocomial infections and for more than half of all antibiotics prescribed. HAP prolongs lengths of stay by an average of 7 to 9 days and increases costs by an estimated $40,000 per occurrence.

The precise incidence of VAP is difficult to establish, mostly because there are no universally accepted defining criteria at present. Furthermore, the most commonly used standards for VAP rely on clinical criteria that often overlap with other sites of infection and multiple noninfectious pneumonia mimics. It is likely that VAP incidence varies significantly among institutions based on differences in geography, the populations receiving treatment, and local standards of care for diagnosis and therapy.

Both HAP and VAP share similarities with but are distinct from healthcare-associated pneumonia (HCAP). HCAP is pneumonia in a person who was previously hospitalized in the preceding 90 days, received intravenous (IV) antibiotic therapy or chemotherapy in the past 30 days, lived in a long-term care facility in the previous 90 days, received wound care during the last month, or underwent hemodialysis. Like many HAP and VAP patients, all HCAP patients are at increased risk of infection with resistant pathogens. However, the diagnosis of HCAP does not consider either the patient's location at the time of onset or the severity of illness.

RISK FACTORS

HAP—like any other pneumonia—results when microbes penetrate the normally sterile lower respiratory tract, overwhelm local host defenses, and establish infection. Although pathogens are most often introduced in aspirated oropharyngeal secretions, they may enter the lung hematogenously in patients with bacteremia. Intubated patients develop VAP as a direct consequence of the endotracheal tube acting as a foreign body that bypasses key barriers to infection. VAP ultimately results from varying degrees of aspiration of secretions pooled above the endotracheal tube cuff and/or direct inoculation from the biofilm that forms on the endotracheal tube surface.

Some of the risk factors that predispose patients to develop HAP are patient specific and include male sex, advanced age, chronic underlying disease (especially pulmonary disease), immunosuppression, obesity or malnutrition, altered level of consciousness, smoking, and alcohol or drug abuse. Other risk factors are treatment related, including intubation, enteral feedings, recent surgery, entry to the ICU, and recent antibiotic exposure (Figure 27-1).

Although causative agents include a wide variety of bacterial pathogens and may be polymicrobial, anaerobes are uncommon in HAP. Fungi and viruses are also infrequently implicated in immunocompetent patients. The bacteria that most frequently cause HAP are stratified into those causing early- and late-onset disease. Early-onset HAP occurs on hospital days 3 to 7 and is often caused by community-acquired organisms such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. In contrast, late-onset HAP occurs beyond hospital day 7 and is more frequently caused by hospital-acquired gram-negative bacilli and *Staphylococcus aureus* (including methicillin-resistant strains). HAP caused by *S. aureus* is more common in patients with head trauma, diabetes, or admission to an ICU. The distribution of organisms causing HAP varies by hospital, patient population, and previous antibiotic exposure history—and evolves over time, highlighting the need for regularly updated local surveillance data.

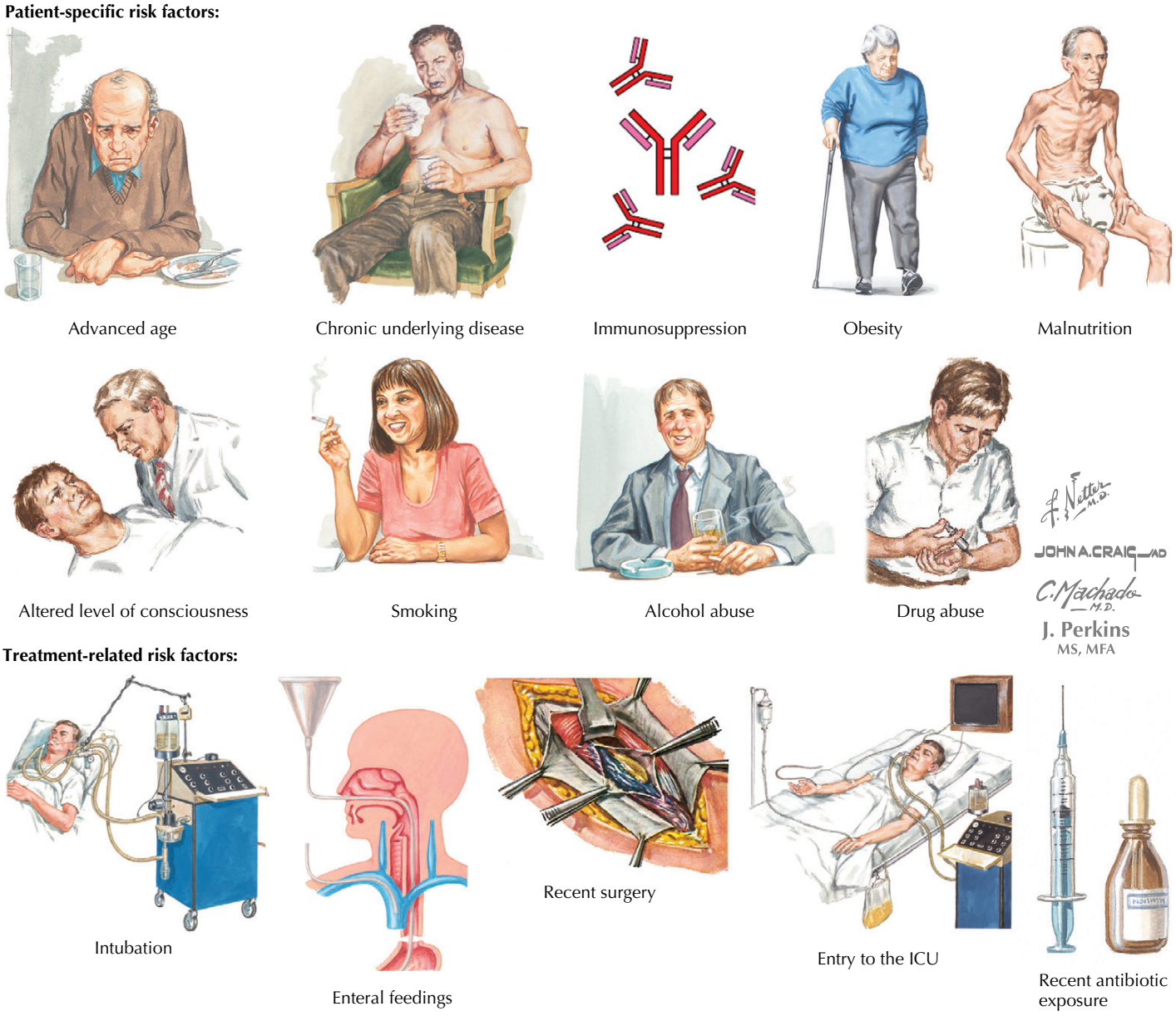


Figure 27-1 Risk factors for the development of hospital-acquired pneumonia.

CLINICAL FEATURES

The presenting signs and symptoms of HAP are nonspecific and vary in intensity based on the severity of the infection and the patient's underlying pulmonary reserve. The most common signs and symptoms include fever, cough, increasing sputum or purulent sputum production, dyspnea, and pleuritic chest pain. Pneumonia should also be considered in patients who have an increase in their oxygen requirements, respiratory rate, or work of breathing. The presentation of HAP in the elderly population may be more subtle, with a predominance of vague complaints. Geriatric patients are less likely to have significant fever but are more likely to have altered mental status. Evaluation of the patient with VAP is particularly challenging, as patients are unable to provide any history and innumerable ICU-associated conditions are easily confused with pneumonia.

Physical examination findings of HAP are similarly nonspecific and fall along a spectrum of severity that is associated with the physiologic effects of infection on the patient. Initially insignificant abnormalities may progress to cyanosis and respiratory distress in severe cases. As with any respiratory infection, the most common findings of HAP include hyperthermia, tachycardia, and tachypnea. Findings of consolidation—crepitations, bronchial breath sounds, tactile fremitus, dullness to percussion, reduced motion of the thorax, and egophony—may all be present. However, many of these findings will be absent or difficult to elicit in critically ill or mechanically ventilated patients.

Given the nondescript nature of many findings associated with HAP, alternative causes of fever or clinical deterioration must be evaluated in hospitalized patients (Figure 27-2). Possible considerations include central venous catheter infections, urinary tract infections, *Clostridium difficile* colitis, aspiration

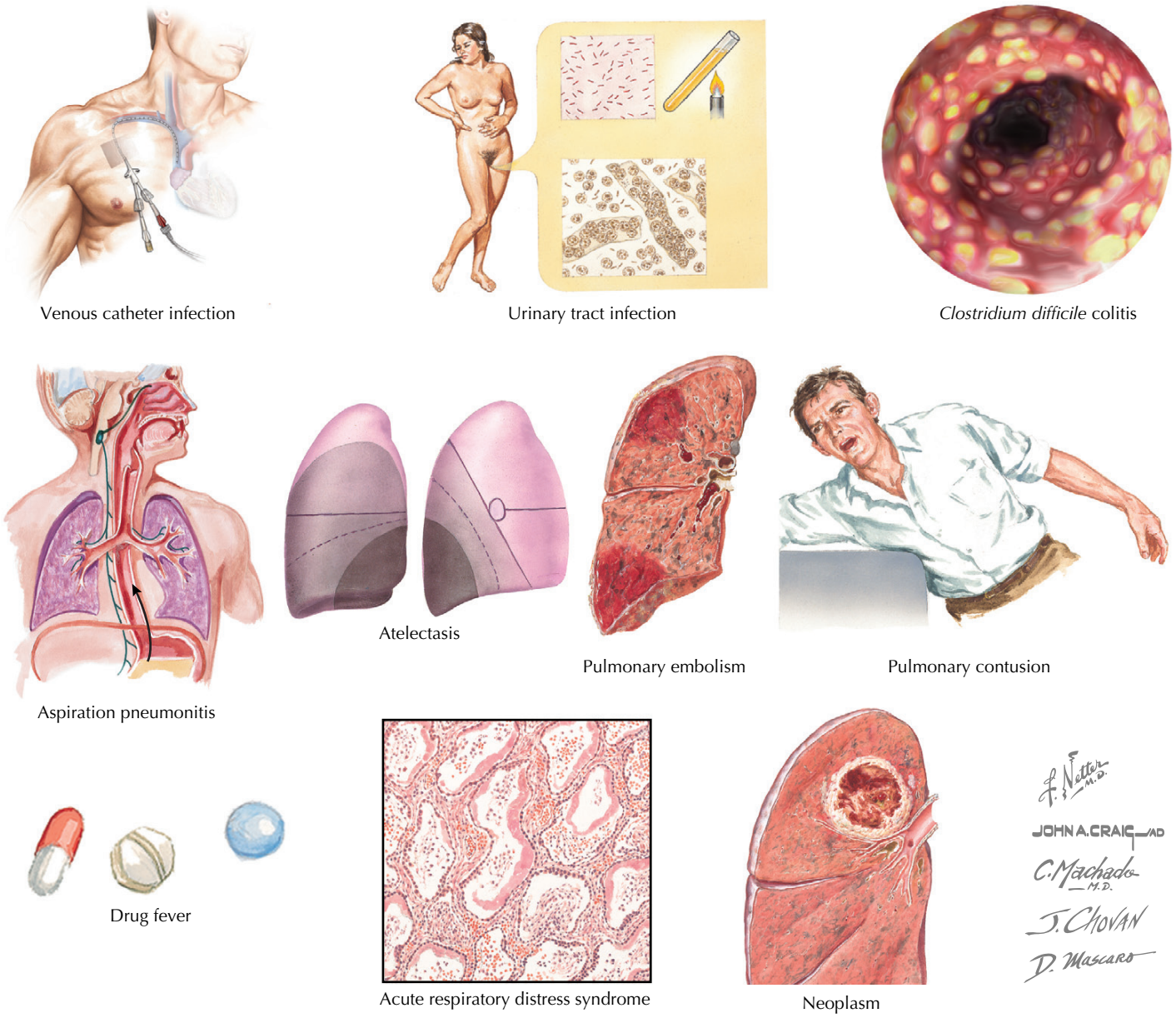


Figure 27-2 Differential diagnosis of hospital-acquired pneumonia.

pneumonitis, atelectasis, pulmonary embolism, pulmonary contusion, drug fever, acute respiratory distress syndrome, and neoplasms. Each of these entities has clinical characteristics that overlap with HAP and merits a high level of suspicion.

DIAGNOSTIC APPROACH

The clinical diagnosis of HAP requires a new or progressive infiltrate on the chest radiograph in conjunction with appropriate clinical and laboratory findings (fever, rales, leukocytosis, and sputum expectoration). Various combinations of these factors have consistently proven to be sensitive but nonspecific, ultimately leading to overdiagnosis of pneumonia with resulting unnecessary antibiotic prescription. Objective scoring systems that systematically combine such clinical parameters have been validated in patients with VAP and are often modified for use in patients with HAP. The most widely used tool, the clinical pulmonary infection score (CPIS), assigns varying point values based on the severity of derangement in body temperature, leukocyte count, sputum consistency, oxygenation measures, radiographic abnormalities, and culture results (Table 27-1). The total CPIS score ranges from 0 to 12 points: scores higher than 6 correlate significantly with bronchoscopically confirmed VAP.

Radiographic demonstration of a new or progressive infiltrate is required for the diagnosis of HAP but is nonspecific and must be accompanied by other evidence supporting active infection. When possible, microbiologic evidence of infection should be aggressively pursued in order to exclude noninfectious causes of an abnormal chest radiograph such as congestive heart failure,

Table 27-1 Clinical Pulmonary Infection Score (CPIS)*

DIAGNOSTIC CRITERION	VALUE	POINTS
Temperature (° C)	36.5 to 38.4	0
	38.5 to 39.0	1
	<36.5 or >39.0	2
White blood cells (per mm^3)	4000 to 11,000	0
	<4000 or >11,000	1
	≥500 bands	1
Tracheal secretions	Secretions suctioned <14 times per 24 hours	0
	Secretions suctioned >14 times per 24 hours	1
	Purulent secretions	1
Pao_2/Fio_2 (mmHg)	>240 or ARDS	0
	<240 and no ARDS	2
Chest radiograph findings	No infiltrate	0
	Diffuse or patchy infiltrate	1
	Localized infiltrate	2
Tracheal aspirate culture and Gram stain (semiquantitative: 0/+/++/+++)	No or rare pathogenic bacteria (0/+)	0
	Pathogenic bacteria cultured (++/+++)	1
	Pathogenic bacteria on Gram stain	1

From Pugin J, Auckenthaler R, Mili N, et al: Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and non-bronchoscopic "blind" bronchoalveolar lavage fluid, *Am Rev Respir Dis* 143:1121-1129, 1991.
ARDS, Acute respiratory distress syndrome.
*A total CPIS ≥6 points is consistent with the diagnosis of ventilator-associated pneumonia.

pulmonary infarction, aspiration pneumonitis, vasculitis, and alveolar hemorrhage (Figure 27-3). Although posteroanterior and lateral radiographs are usually adequate, computed tomography scans are useful in assessing pneumonia-related complications such as empyema or lung abscess. False-negative chest radiographs are very uncommon but may be seen in patients with neutropenia, acquired immunodeficiency syndrome, tuberculosis, or profound dehydration.

Laboratory studies are used to confirm the diagnosis of pneumonia, to establish a causative pathogen, and to assess severity of illness. Appropriate testing includes a complete blood count (CBC), two sets of blood cultures drawn from independent sites (including one set through any lines that have been in place for more than 24 hours), and sputum for Gram stain with culture and sensitivity testing. The CBC gauges the leukocyte response to infection and gives information regarding anemia that may further impair oxygen delivery. Positive blood cultures serve two purposes: they identify a causative pathogen in up to 20% of cases, and they identify a subset of patients with increased mortality. A Gram stain that is timely, properly prepared, and correctly interpreted is useful for guiding the empirical therapeutic regimen. Any sputum sample showing leukocytes without organisms should raise suspicion for atypical organisms such as *Legionella*, mycobacteria, or viruses.

Arterial blood gas sampling is indicated in all critically ill patients and in those with pulse oximetry saturations less than 92% while breathing room air. Additional tests to assess concurrent end-organ dysfunction include measurements of electrolytes and serum glucose, hepatic function tests, assessment of renal parameters, and measurement of lactic acid. The role of nonspecific inflammatory markers such as procalcitonin and sedimentation rates is not well defined. Diagnostic thoracentesis must be promptly performed to exclude empyema in all patients with significant parapneumonic effusions. Serum immunoglobulins and human immunodeficiency virus testing should be offered to younger patients who develop HAP. Because these patients may rapidly decompensate, a focused yet comprehensive diagnostic regimen is mandatory (Figure 27-4).

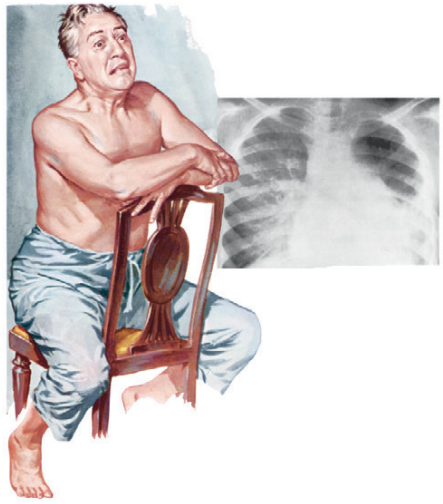
Intubated patients with suspected VAP are unique in that the endotracheal tube provides convenient, immediate access to uncontaminated tracheal specimens. All such patients should have endotracheal aspirates sent for Gram stain and quantitative cultures. Quantitative endotracheal aspirates (QEAs) containing 10^5 or more organisms per milliliter correlate with diagnostic thresholds by more invasive techniques such as bronchoalveolar lavage (BAL) or protected specimen brush (PSB) sampling. Incorporating QEA with clinical diagnostic criteria improves diagnostic certainty beyond clinical criteria alone and leads to outcomes similar to those seen with more invasive strategies (BAL or PSB). The added expense and inherent risks of BAL or PSB are justified in patients with severe initial illness, patients not responding to initial therapy, and those suspected to have infections caused by unusual pathogens.

CLINICAL MANAGEMENT AND DRUG TREATMENT

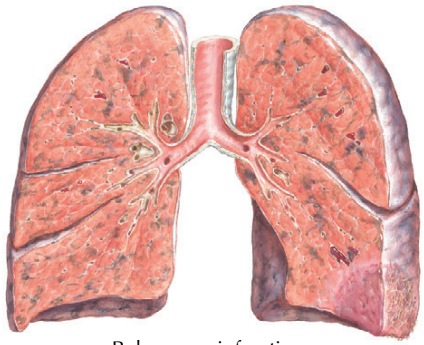
A key initial decision in managing patients with HAP is whether their severity of illness merits transfer to the ICU. Indications for ICU monitoring and supportive care include hemodynamic instability, impending respiratory failure, and alteration in mental status that may lead to inability to maintain a patent airway. Other factors that justify more rigorous monitoring include advanced age, limited physiologic reserve because of comorbid chronic illnesses, need for intensive nursing care, evidence of new end organ injury, and rapid rate of clinical worsening.

Regardless of the site of care, the patient's oxygen saturations should be closely monitored and supplemental oxygen administered as needed to maintain values at or above 92%. Adequate pulmonary toilet and regular reassessment of the patient's ability to maintain a patent airway are critical. Clinicians must also ensure adequate nutrition, hydration, and deep venous thrombosis prophylaxis. In complicated cases, early consultation with an infectious disease or pulmonary specialist is prudent.

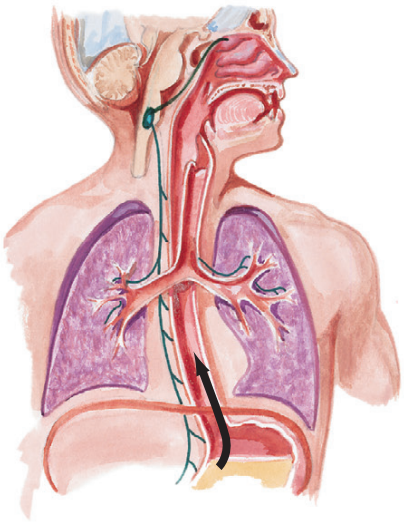
Because the causative pathogen is typically unknown at the time of HAP diagnosis, initial antibiotic therapy is empirical. Both delayed initiation of antibiotic therapy and/or inadequate empirical therapy are associated with increased morbidity, mortality, and hospital costs. Accordingly, it is recommended that IV antibiotics with an appropriate spectrum of activity be initiated as soon as possible after the diagnosis of HAP has been established. Although sputum and blood cultures should ideally



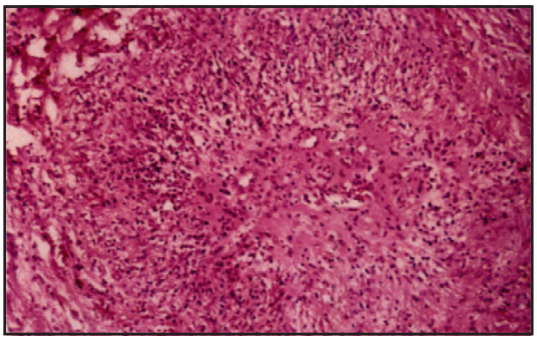
Congestive heart failure



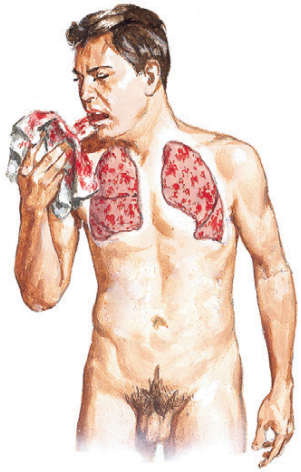
Pulmonary infarction



Aspiration pneumonitis



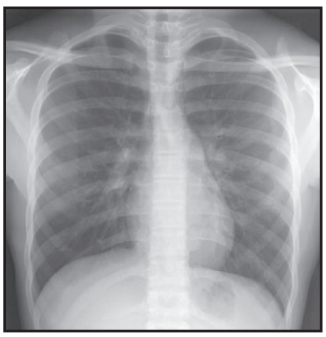
Vasculitis



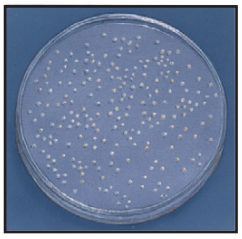
Alveolar hemorrhage

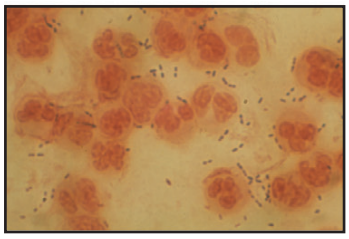
F. Netter M.D.
D. Mascaro
JOHN A. CRAIG AD

Figure 27-3 Noninfectious causes of an abnormal chest radiograph.

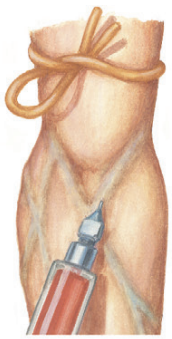


Chest radiographs

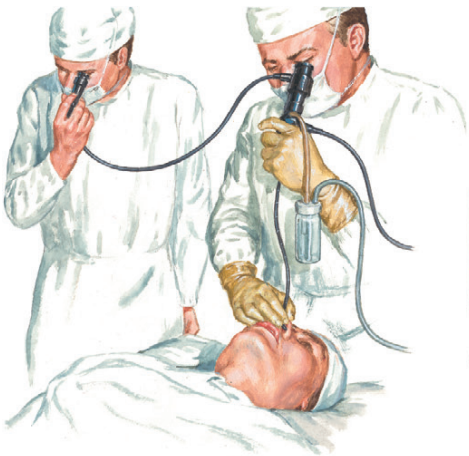




Sputum culture and Gram stain

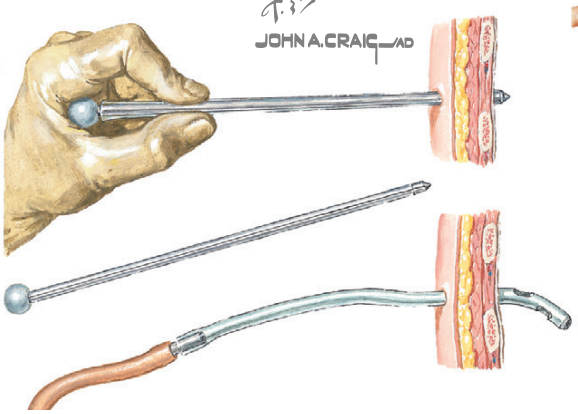


Laboratory evaluations

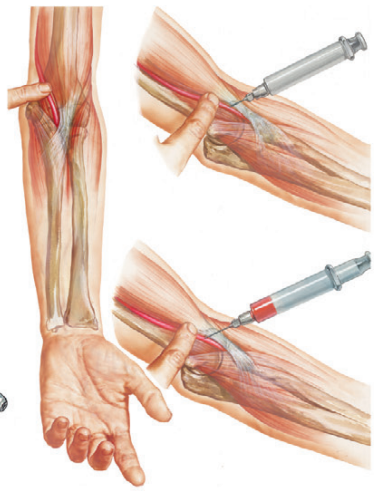


Bronchoscopic evaluation

F. Netter M.D.
JOHN A. CRAIG AD



Thoracentesis



Arterial blood gases

Figure 27-4 Comprehensive testing for suspected hospital-acquired pneumonia.

be obtained before antibiotic therapy is initiated, treatment should not be delayed in order to pursue diagnostic measures. Patient-specific risk factors, severity of illness, and local antimicrobial resistance patterns must be considered when initial therapies are being selected. Additional influencing factors include frequency of administration, need for adjustment of doses in patients with renal or hepatic failure, risk of drug interactions, drug allergies, and cost.

The current strategy endorsed by the American Thoracic Society (ATS) and Infectious Disease Society of America (IDSA) is to select empirical HAP therapy based on each patient's risk of infection with a multidrug-resistant pathogen (Tables 27-2 and 27-3). The ATS-IDSA–defined risk factors for multidrug-resistant pathogens include antibiotic therapy in the preceding 90 days, current hospitalization of 5 days or more, high frequency of antimicrobial resistance in the community or specific hospital unit, and immunosuppressive disease or therapy (Figure 27-5). The guidelines recommend that patients without risk factors for resistant pathogens be treated with IV monotherapy using ceftriaxone, a respiratory fluoroquinolone, ampicillin-sulbactam, or ertapenem. In patients with risk factors for resistant organisms, the guidelines recommend double coverage for gram-negative organisms (an antipseudomonal carbapenem, antipseudomonal cephalosporin, or antipseudomonal β-lactam and β-lactamase inhibitor in combination with an antipseudomonal fluoroquinolone or an aminoglycoside) with consideration of an agent having anti-MRSA activity (linezolid or vancomycin). Optimal administration of these antibiotics includes adequate doses administered at proper intervals with particular attention to adjustments for renal and/or hepatic insufficiency.

Adoption of routine empirical broad spectrum therapy requires a concurrent commitment to culture-based deescalation of the initial antibiotic prescription. This strategy mandates aggressive sampling of respiratory tract specimens followed by frequent communication with the microbiology laboratory. Once the pathogen has been identified and the in vitro susceptibility demonstrated, the onus falls on the clinician to stop

Table 27-2 American Thoracic Society and Infectious Disease Society of America Recommended Empirical Antibiotic Therapies for Hospital-Acquired Pneumonia

POTENTIAL PATHOGENS	RECOMMENDED ANTIBIOTIC AGENTS*
No Known Risk Factors for Multidrug-Resistant Pathogens	
Antibiotic-sensitive gram-negative bacilli (GNB) *Enterobacter* species *Escherichia coli* *Klebsiella pneumoniae* *Proteus* species *Serratia marcescens* *Haemophilus influenzae* Methicillin-sensitive *Staphylococcus aureus* (MRSA) *Streptococcus pneumoniae*	Ampicillin-sulbactam *or* Ceftriaxone *or* Ciprofloxacin, levofloxacin, or moxifloxacin *or* Ertapenem
Known Risk Factors for Multidrug-Resistant Pathogens	
Pathogens listed above and *Acinetobacter* species Extended-spectrum β-lactamase–producing GNB *Legionella pneumophila* MRSA† *Pseudomonas aeruginosa*	Antipseudomonal β-lactam or β-lactamase inhibitor *or* Antipseudomonal carbapenem *or* Antipseudomonal cephalosporin **PLUS** Aminoglycoside *or* Antipseudomonal fluoroquinolone **PLUS** Anti-MRSA therapy

*See Table 27-3 for appropriate dosage of recommended antibiotic agents.
†If *Legionella* is suspected, the antibiotic regimen should include a macrolide (e.g., azithromycin) or a fluoroquinolone (e.g., ciprofloxacin or levofloxacin).

Table 27-3 Appropriate Dosage Regimens of American Thoracic Society and Infectious Disease Society of America Recommended Antimicrobial Therapies

ANTIBIOTIC	RECOMMENDED DOSAGE*
No Known Risk Factors for Multidrug-Resistant Pathogens	
Ampicillin-sulbactam	1.5-3 g every 6 hours
Ceftriaxone	1-2 g daily
Ciprofloxacin	400 mg every 8-12 hours
Ertapenem	1 g daily
Levofloxacin	750 mg daily
Moxifloxacin	400 mg daily
Known Risk Factors for Multidrug Resistant Pathogens	
Antipseudomonal β-Lactam and β-Lactamase Inhibitor	
Piperacillin-tazobactam	4.5 g every 6 hours
Antipseudomonal Carbapenem	
Imipenem	500 mg every 6 hours or 1 g every 8 hours
Meropenem	1 g every 8 hours
Antipseudomonal Cephalosporin	
Cefepime	1-2 g every 8-12 hours
Ceftazidime	2 g every 8 hours
Aminoglycoside	
Gentamicin	7 mg/kg daily†
Tobramycin	7 mg/kg daily†
Amikacin	20 mg/kg daily†
Antipseudomonal Fluoroquinolone	
Ciprofloxacin	400 mg every 8 hours
Levofloxacin	750 mg daily
Anti-MRSA therapy	
Linezolid	600 mg every 12 hours
Vancomycin	15 mg/kg every 12 hours†

MRSA, Methicillin-resistant *Staphylococcus aureus.*
*Recommended dosages assume normal renal and hepatic function.
†Recommended trough levels: gentamicin <1 mcg/mL; tobramycin <1 mcg/mL; amikacin 4-5 mcg/mL; and vancomycin 15-20 mcg/mL.

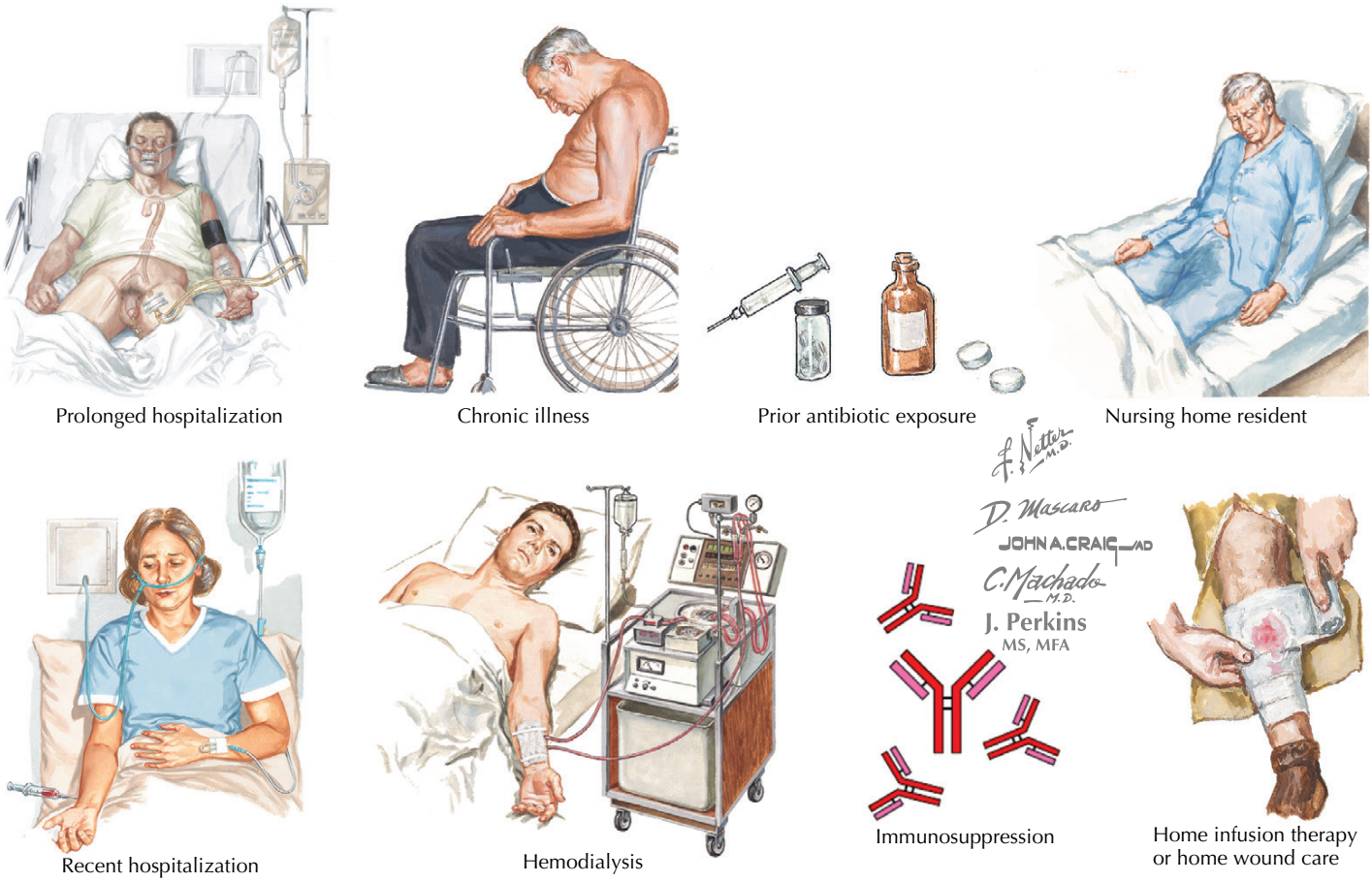


Figure 27-5 Risk factors for infection with an antibiotic-resistant organism.

therapies that are ineffective or redundant. Adjuvant therapies such as granulocyte colony-stimulating factors, activated protein C, and steroids are of unproven benefit in patients with HAP and should not be routinely used.

Assessment of the clinical response to initial therapy requires ongoing monitoring of the patient's temperature, sputum volume and characteristic, radiographic findings, oxygenation parameters, white blood cell count, and other pertinent laboratory results. The course of HAP is variable, but clinical response should be apparent 72 hours after initiation of antibiotic therapy. Failure to improve or clinical deterioration may be caused by isolation of the wrong organism, inadequate antibiotic administration, an incorrect diagnosis of pneumonia, or development of a pneumonia-related complication. In such instances a comprehensive workup should immediately be initiated. Repeat microbiologic sampling is essential, and persistent negative cultures should prompt consideration of noninfectious pulmonary processes. Detailed radiographs—including some combination of lateral decubitus films, ultrasound, and computed tomography scans—are necessary to exclude local complications such as cavitation, abscess formation, and empyema (Figure 27-6).

The proper duration of therapy for HAP is unknown, but practitioners commonly provide 10 to 14 days of therapy. It is likely that shorter courses of antibiotics may be given in patients without risk factors for resistance who are not severely ill, are infected with a susceptible organism, and have a rapid response to treatment. More prolonged courses are often necessary in patients with isolation of a resistant pathogen, those with critical illness or immunosuppression at the time of diagnosis, and those with complications such as bacteremia or empyema.

As previously discussed, the CPIS was designed as a tool to aid in the diagnosis of VAP. However, serial CPIS values may also be helpful in identifying patients with a low likelihood of having true pneumonia. It has been shown that patients with radiographic findings of HAP but persistently low CPIS scores (less than 6) can safely be taken off antibiotic therapy at 72 hours. These data further support the recent trend toward shorter courses of antibiotic therapy.

PROGNOSIS

Despite high absolute mortality rates in HAP patients, the mortality that is directly attributable to HAP is controversial. Crude mortality rates as high as 70% have been reported in patients with HAP, but many of these critically ill patients die from their underlying disease and not because of their pneumonia. Case-control studies estimate that HAP increases mortality by 33% to 50% while VAP increases mortality 2- to 10-fold. Variables associated with increased mortality in nosocomial pneumonia include serious illness at the time of diagnosis (increased

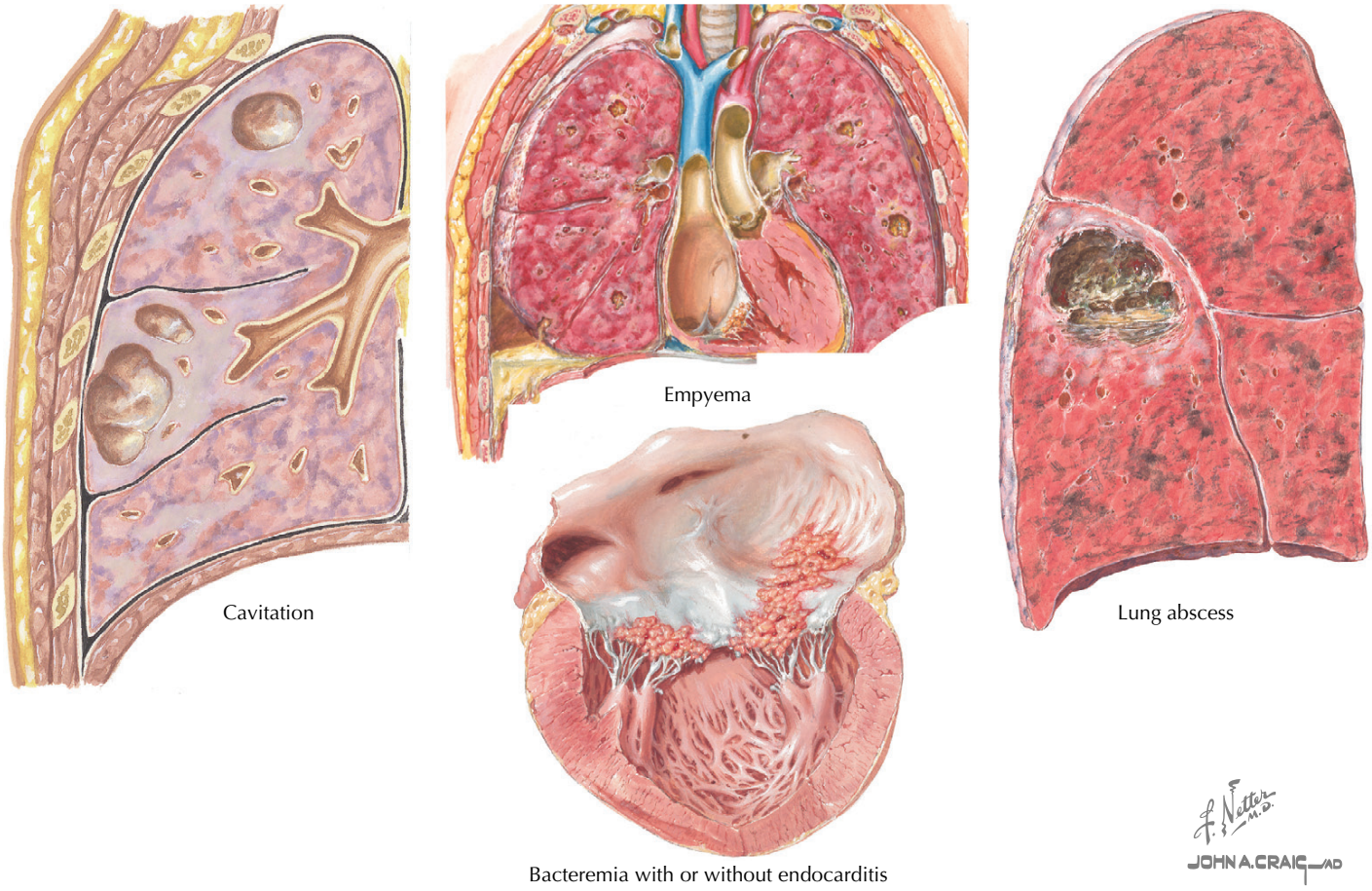


Figure 27-6 Complications of hospital-acquired pneumonia.

APACHE score, shock, coma, respiratory failure, acute respiratory distress syndrome); bacteremia; severe underlying comorbid disease; infection caused by an organism associated with multidrug resistance (*Pseudomonas aeruginosa*, *Acinetobacter* species); radiographic infiltrates that are multilobar, cavitating, or rapidly progressive; and ineffective empirical therapy.

PREVENTION AND CONTROL

Although the most effective HAP prevention strategies are widely available, relatively inexpensive, noninvasive, and practical, they are also underused. Prevention measures should target education, improved compliance with basic infection control recommendations, and risk reduction related to medications and invasive devices.

The principal method for preventing HAP is routine, effective hand hygiene (i.e., use of alcohol-based hand rubs or hand washing with soap and hot water), as transmission of pathogens occurs mainly via healthcare workers' contaminated hands. Although this strategy has little expense and is universally available, the average rate of appropriate hand hygiene is only 40%. Established barriers to compliance with hand hygiene include inadequate knowledge, perceived lack of time for appropriate hygiene, staff prioritization of patient care over hand washing, skin irritation, and lack of institutional support for education and monitoring efforts. Patients known to be colonized or infected with a resistant pathogen should consistently be isolated, and appropriate precautions should be exercised during patient-care encounters.

HAP-specific prevention strategies focus on reducing risk factors for aerodigestive tract colonization and aspiration, particularly in intubated patients. Simple and inexpensive measures such as minimizing the use of sedatives and maintaining the patient in a semiupright position (head of bed at greater than 30 degrees from horizontal) reduce aspiration and decrease the risk of HAP. Indiscriminate antibiotic use must be avoided, as it may result in mucosal colonization with nosocomial pathogens including antibiotic-resistant strains. Cytotoxic drugs and immunosuppressive agents should be used judiciously, given that they impair the host response to infection. Postoperative patients and those with chronic obstructive pulmonary disease should regularly perform bedside incentive spirometry and ambulate as much as feasible.

Selective digestive decontamination of the digestive tract is a HAP-prevention strategy that involves administration of combinations of antibiotics to the oropharynx and stomach with or without systemic antibiotics. A similar strategy involves regular rinsing of the oral cavity with chlorhexidine. Conflicting results regarding efficacy in prevention of HAP, lack of mortality benefit, contrasting results in different subpopulations, and

concerns over long-term selection of multidrug-resistant pathogens currently limit the use of these practices.

Because HAP is 20 times more likely to occur in ventilated patients, intubation and mechanical ventilation should be avoided when possible and discontinued as soon as feasible. In intubated patients, meticulous attention should be given to the ventilator circuit, endotracheal tube, and suction apparatus. Orotracheal and orogastric tubes are preferred to nasotracheal and nasogastric tubes, as they are associated with reduced rates of sinusitis and clinically diagnosed VAP. Ventilator circuits should be changed whenever visibly soiled; more frequent changes are not associated with reduced VAP rates. Heat-moisture exchangers are used to eliminate condensate accumulation, but the data on attributable VAP reduction are conflicting. Secretion management using closed suctioning systems is recommended to minimize interruptions of the ventilator circuit. Drainage of subglottic secretions and silver-coated endotracheal tubes are novel VAP-prevention strategies that attempt to reduce or sterilize biofilms. These devices have significant acquisition costs, but they appear to be cost-effective in patients receiving more than 72 hours of mechanical ventilation. Regardless of the tube employed, adequate endotracheal cuff pressures must be maintained.

Better short- and long-term prevention strategies are clearly needed in order to ensure each patient's well-being during hospitalization and after discharge. The importance of such interventions cannot be overemphasized, given the current healthcare milieu of a rapidly growing elderly population with increasing numbers of comorbid illnesses, intense pressure to shorten hospital length of stay, reduced funding for infection control programs, increasing antimicrobial resistance, and a lack of emphasis on antibiotic research and development.

EVIDENCE

Aarts MAW, Brun-Buisson C, Cook DJ, et al: Antibiotic management of suspected nosocomial ICU-acquired infection: does prolonged empiric therapy improve outcomes? *Intensive Care Med* 33:1369-1378, 2007. *This prospective cohort study found that empirical antibiotics were started four times more often than infection was confirmed, were frequently continued despite the lack of evidence for infection, and failed to improve clinical outcomes.*

Chastre J, Wolff M, Fagon JY, et al: Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial, *JAMA* 290:2588-2598, 2003. *A critically important clinical trial comparing the clinical outcomes of patients treated with shorter courses of antibiotic therapy with those receiving treatment for a more conventional duration.*

Fridkin SK, Gaynes RP: Antimicrobial resistance in intensive care units, *Clin Chest Med* 20:303-316, 1999. *This systematic review outlines aspects of the ICU environment that predispose to infection caused by resistant pathogens and summarizes information on the rates of resistance for the most common pathogens leading to nosocomial infection.*

Gasink LB, Lautenbach E: Prevention and treatment of healthcare acquired infections, *Med Clin North Am* 92:295-313, 2008. *The authors provide an overview of infection control measures in general, with specific recommendations related to prevention of hospital-acquired pneumonia.*

Kollef MH, Shorr A, Tabak YP, et al: Epidemiology and outcomes of health-care–associated pneumonia: results from a large US database of culture-positive pneumonia, *Chest* 128:3854-3862, 2005. *This retrospective study clearly demonstrated that the distribution of pathogens causing hospital-acquired and ventilator-associated pneumonia is distinct from that seen with community-acquired pneumonia. The observed trend of increased multidrug-resistant pathogens causing infections in patients with nosocomial pneumonia was associated with worse clinical outcomes.*

Luna CM, Blanzaco D, Niederman MS, et al: Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome, *Crit Care Med* 31:676-682, 2003. *This prospective study established the utility of the clinical pulmonary infection score as a predictor of poor outcomes in patients being treated for ventilator-associated pneumonia.*

Singh N, Rogers P, Atwood CW, et al: Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription, *Am J Respir Crit Care Med* 162:505-511, 2000. *This clinical trial demonstrated that the clinical pulmonary infection score could safely be used to minimize unnecessary antibiotic use in ICU patients with infiltrates of uncertain cause.*

ADDITIONAL RESOURCES

Guidelines for preventing healthcare-related pneumonia 2003: Recommendation of CDC and the Healthcare Infection Control Practices Advisor Committee. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/rr5303a1.htm. Accessed January 14, 2009.

Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. Available at: www.thoracic.org/statements/resources/mtpi/guide1-29.pdf Accessed January 26, 2011.

Horan TC, Andrus M, Dudeck MA: *CDC/NHSN surveillance definition for health care-associated infection and criteria for specific types of infection in the acute care setting.* Available at: www.cdc.gov/ncidod/dhqp/pdf/nnis/NosInfDefinitions.pdf. Accessed January 14, 2009.

National Healthcare Safety Network (NHSN) system report. Data summary for 2007 through 2007, issued November 2008. Available at: www.cdc.gov/ncidod/dhqp/pdf/nhsn/2008NHSNReport.pdf. Accessed January 14, 2009.

Atypical Pneumonia

Thomas M. File, Jr.

28

ABSTRACT

The term *atypical pneumonia* was first used more than 50 years ago to describe cases of pneumonia caused by an unknown agent(s) and that appeared clinically different from pneumococcal pneumonia. Although the original distinction between atypical and typical pneumonia arose from the perception that the clinical presentation of patients was different, recent studies have shown that there is excessive overlap with clinical manifestations from specific causes, which does not permit empirical therapeutic decisions to be made solely on this basis. Thus the scientific and clinical merit of the designation *atypical pneumonia* is controversial, and many authorities have suggested that the term *atypical* be discontinued. However, the term remains popular among clinicians and investigators and prevalent in recent literature regardless of its clinical value. Moreover, options for appropriate antimicrobial therapy for the most common causes are similar, which is considered justification by some for lumping these together.

Atypical pneumonia was initially characterized by constitutional symptoms, often with upper and lower respiratory tract symptoms and signs, a protracted course with gradual resolution, a lack of typical findings of consolidation on chest radiograph, failure to isolate a pathogen on routine bacteriologic methods, and a lack of response to penicillin therapy. In the 1940s an agent that was believed to be the principal cause was identified as *Mycoplasma pneumoniae*. Subsequently other pathogens have been linked with atypical pneumonia because of similar clinical presentation, including a variety of respiratory viruses, *Chlamydia psittaci*, *Coxiella burnettii*, and *Chlamydophila* (also known as *Chlamydia*) *pneumoniae*. Less common causative agents associated with atypical pneumonia include *Francisella tularensis* and *Yersinia pestis* (plague), although these agents are often associated with a more acute clinical syndrome. Finally, pneumonia caused by *Legionella* species, albeit often more characteristic of pyogenic pneumonia, is also included because it is not isolated using routine microbiologic methods.

BURDEN OF DISEASE

M. pneumoniae, *C. pneumoniae*, and *Legionella pneumophila* are the most common causes of atypical pneumonia (Figures 28-1 and 28-2). The results of recent studies indicate that they cause from 15% to as much as 50% (in selected outpatient populations) of cases of community-acquired pneumonia (CAP). However, these pathogens (with the exception of *L. pneumophila*) are not identified often in clinical practice because there is not a specific, rapid, or standardized test for their detection. The other causes of atypical pneumonia occur with much less frequency.

PATHOGENESIS

M. pneumoniae infections are ubiquitous and can affect people in all age groups. *M. pneumoniae* are extracellular pathogens that adhere to the respiratory epithelium by means of specialized protein attachments. They are unique among bacteria because they do not have a cell wall; this property renders the organism resistant to β-lactam antimicrobial agents. *M. pneumoniae* are transmitted from person to person by respiratory droplets with a usual incubation period of several weeks. It is estimated that only 3% to 10% of infected persons develop pneumonia. Many of the pathogenic features of infection are believed to be immune mediated rather than induced directly by bacteria (antibodies produced against the glycolipid antigens of *M. pneumoniae* may cross-react with human red cells and brain cells).

C. pneumoniae are very small bacteria (once considered viruses) that are obligate intracellular parasites and are unique among bacteria for their developmental cycle, forming infectious forms (elementary bodies) and noninfectious forms (reticulate bodies). Infections are often acquired early in life, and the bacteria may remain in a latent form afterward. Reinfections or recrudescent processes, both referred to as *recurrent infection*, may occur throughout one's lifetime. Most adults who are hospitalized with *C. pneumoniae* pneumonia have recurrent infection.

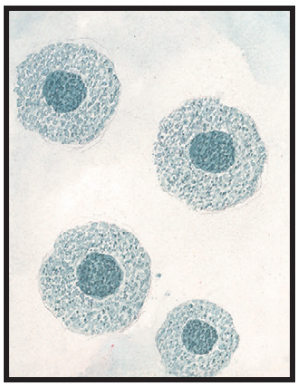
Legionella species are small bacilli that have special growth requirements in the laboratory. They do not stain with common reagents but can be seen in tissues stained with Dieterle's silver stain (see Figure 28-2) They are intracellular organisms that are engulfed by alveolar macrophages via phagocytosis. More than 49 different *Legionella* species have been identified. The most common to infect humans is *L. pneumophila*, which contains 16 different serogroups (serogroup 1 causes most cases of infection in North America).

Legionella organisms produce virulence factors that enhance intracellular survival and growth within the macrophages; chemokines and cytokines released by the infected macrophages trigger an inflammatory response that is often severe and can lead to a rigorous influx of neutrophils within the alveoli (see Figure 28-2). *Legionella* is not spread person to person but usually by exposure to water. Outbreaks may be associated with infected water sources. The incubation period is 10 days.

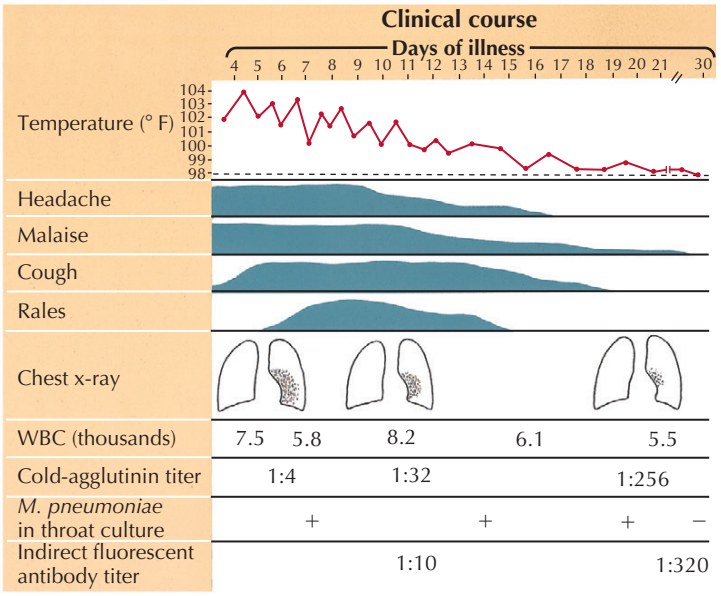
CLINICAL FEATURES

Although the diagnosis of these specific pathogens is difficult to establish on clinical manifestations alone, there are several generalizations that may be helpful to the clinician in considering these infections.

PA chest x-ray film: patchy perihilar infiltrates chiefly in left lung



Colonies of mycoplasma growing on agar and stained, showing "fried egg" appearance caused by penetration of agar by the growth in central area of each colony



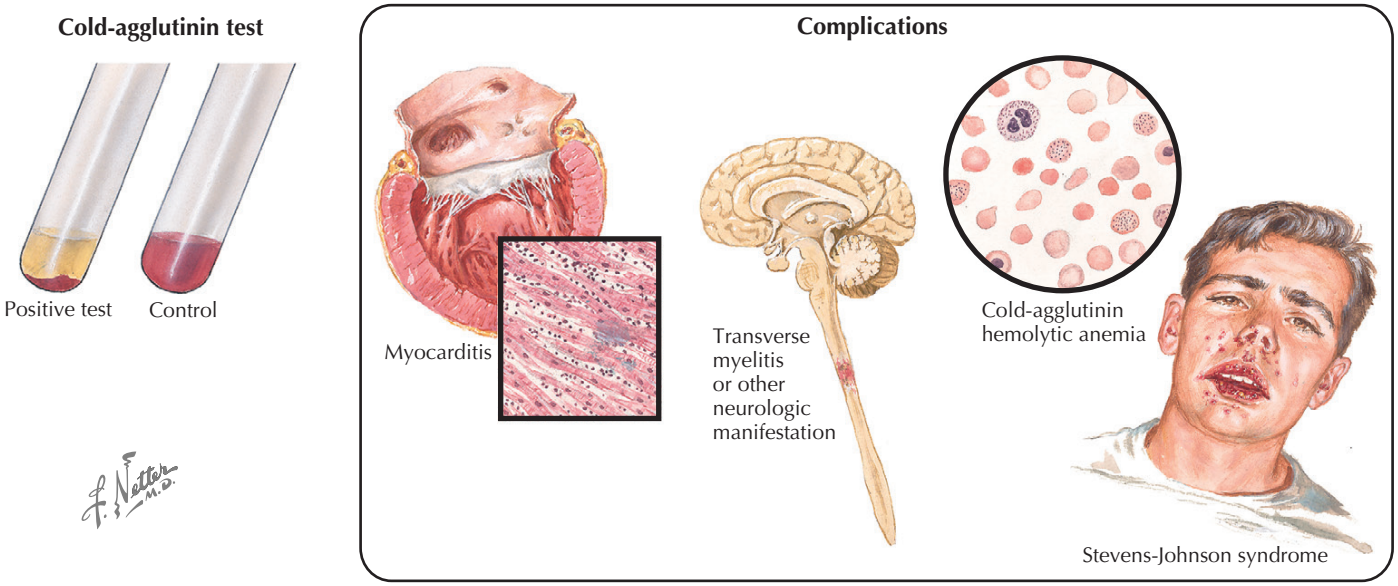


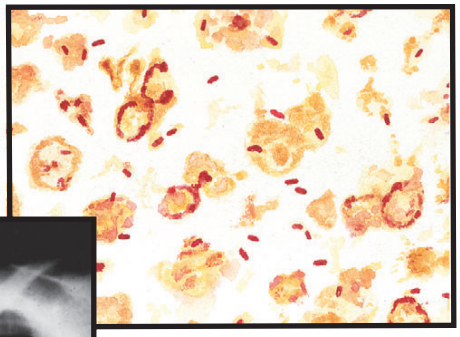
Figure 28-1 Mycoplasmal (Eaton agent) pneumonia (primary atypical pneumonia).

Mycoplasma pneumoniae

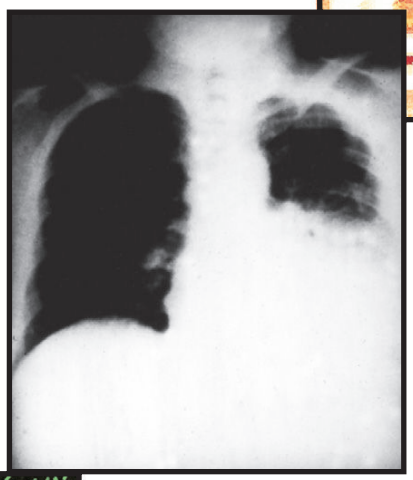
Although commonly perceived as a cause of CAP, predominantly in young healthy patients, the incidence of *M. pneumoniae* pneumonia increases with age, highlighting the importance of this pathogen in the elderly as well. The onset is usually insidious over several days to a week. Constitutional symptoms including headache (usually worse with cough), malaise, myalgias, and sore throat are frequently present. Cough is typically initially dry, may be paroxysmal, is frequently worse at night, and may become productive of mucopurulent sputum. Sinus and ear pain are occasionally reported. *M. pneumoniae* pneumonia is often associated with extrapulmonary manifestations including rash, neurologic involvement (i.e., aseptic meningitis, meningoencephalitis, cerebral ataxia, Guillain-Barré syndrome, and transverse myelitis), hemolytic anemia (associated with cold agglutinins), myopericarditis, polyarthritis, and pancreatitis.

The physical findings are often minimal, seemingly disproportionate to the patient's complaints. Auscultation of the lungs usually reveals variable scattered rales or wheezes. Bullous myringitis, first described in volunteer subjects infected with *M. pneumoniae*, has been infrequent in naturally occurring infection and is not a diagnostic sign. Chest radiograph findings are variable. Most common is peribronchial pneumonia. Dermatologic manifestations may range from a mild maculopapular or vesicular rash to Stevens-Johnson syndrome (see Figure 28-1).

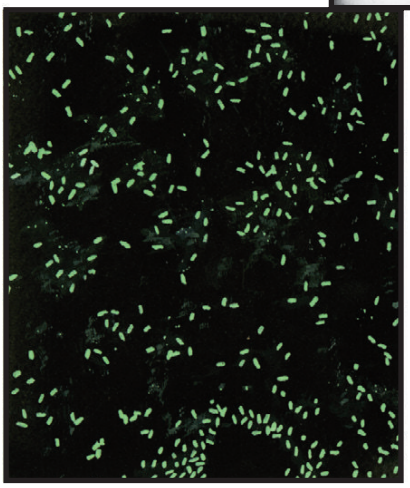
The course of *M. pneumoniae* pneumonia is usually mild and self-limiting. However, significant pulmonary complications may occur and include pleural effusion, pneumatocele, lung abscess, pneumothorax, bronchiectasis, chronic interstitial fibrosis, respiratory distress syndrome, and bronchiolitis obliterans.



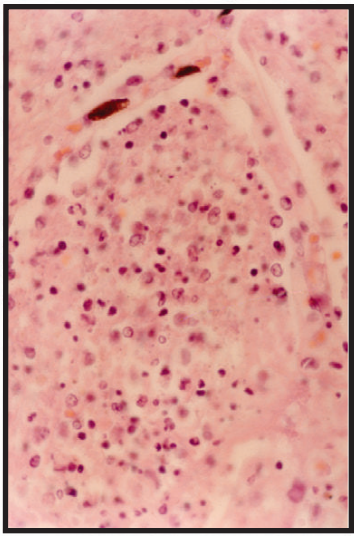
Small, blunt, pleomorphic intracellular and extracellular bacilli in lung of patient with Legionnaires' disease as shown by Dieterle silver impregnation stain, x 1500



Chest x-ray film on fifth day of illness of 58-year-old man with serologically confirmed Legionnaires' disease. Left lower lobe consolidation the only involvement. Clinical improvement within 2 to 3 days of initiation of treatment with erythromycin. Radiologic changes did not completely disappear for 2 months.



Legionella spp. identified by specific fluorescent antibody stain



Histologic section of lung (H&E stain) from fatal case of Legionnaires' disease. Extensive intraalveolar exudate present, containing many large macrophages.

Figure 28-2 Legionnaires' disease.

Chlamydophila pneumoniae

Pneumonia caused by *C. pneumoniae* may be sporadic or epidemic. The clinical manifestations of *C. pneumoniae* pneumonia remain somewhat unclear because of the lack of a gold standard of diagnosis and the contributing effect of co-pathogens. The onset is usually insidious. Infections often manifest initially with sore throat, hoarseness, and headache as important nonclassic pneumonic findings. Cough is prominent but unproductive and may last, if not treated early and effectively, for weeks or even months. Clinical characteristics, however, are generally not predictive of *C. pneumoniae* as a cause. Chest radiographs of patients with *C. pneumoniae* pneumonia tend to show less extensive opacifications in relation to clinical findings than other processes.

The clinical characteristics associated with primary infection may be difficult to distinguish from those of reinfection because of the confounding effect of comorbid conditions on age. However, patients with primary infection are usually younger and tend to have higher fever. For older patients with reinfection, the presence of comorbid illness and the requirement for supplemental oxygen therapy are often the reason for hospital admission.

Legionella pneumophila

Legionellosis is primarily associated with two clinically distinct syndromes: Legionnaires' disease, a potentially fatal form of pneumonia, and Pontiac fever, a self-limited, nonpneumonic illness. Many of the clinical features of Legionnaires' disease are

more typical of pyogenic (bacterial) pneumonias than the previously described atypical pneumonia. However, as Legionnaires' disease has become increasingly recognized, less severely ill patients are seen earlier in the course of disease, and thus clinical manifestations of unusual severity once considered to be distinctive Legionnaires' disease are now known to be less specific.

The onset is often acute, with high fever, myalgias, anorexia, and headache. Temperature often exceeds 40° C. Gastrointestinal symptoms are prominent, especially diarrhea, which occurs in 20% to 40% of cases. Relative bradycardia, which had been purported to be a common finding in earlier studies, has been overemphasized as a diagnostic finding. Hyponatremia and elevated lactate dehydrogenase (LDH) levels are common abnormal laboratory findings.

Other Causes of Atypical Pneumonia: Coxiella burnetii *(Q fever), Psittacosis, Tularemia, Plague*

Several of the less common causes of the atypical pneumonia syndrome are infections transmitted from animals to humans. In such cases epidemiologic clues may be very important; and although specific manifestations cannot be considered diagnostic of a specific cause, there are general findings that are characteristic of these diseases (Table 28-1).

DIAGNOSTIC APPROACH

Laboratory tests used for the diagnosis of the causative agents associated with atypical pneumonia are listed in Table 28-2. Serologic tests are the most common tests for diagnosis of *M. pneumoniae* and *C. pneumoniae* but are of limited value in the clinical evaluation of a patient given the requirement for measurement during acute and convalescent specimens. Recently nucleic acid amplification tests (most commonly polymerase chain reaction, PCR) have been developed, but at the time of this writing none are approved by the U.S. Food and Drug Administration (FDA) or available in the United States. A rapid urinary antigen test is available for *L. pneumophila* serogroup 1.

ANTIMICROBIAL THERAPY

Antimicrobial agents generally considered effective for the atypical pathogens are included in Tables 28-1, 28-3, and 28-4. Because most cases of atypical pneumonia are treated empirically, clinicians must also consider the possibility of other standard pathogens (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*) when deciding on antimicrobial therapy.

Therapy for *Mycoplasma* and *Chlamydia* has been the subject of some conjecture. A common view is that it really does not matter whether antibiotics are given for most of these infections because the mortality is low, these infections are often self-limiting, there may be ambiguity of diagnosis (especially for *C. pneumoniae*), co-pathogens may have confounding effects, and antimicrobial efficacy is questioned. However, there are data indicating that treatment (especially for *M. pneumoniae*) reduces the morbidity of pneumonia and shortens the duration of symptoms.

There is little debate concerning the need for therapy for *Legionella* pneumonia. Delay in instituting appropriate antimicrobial therapy for *Legionella* pneumonia significantly increases mortality. Therefore empirical anti-*Legionella* therapy should be included in the treatment of severe CAP. Erythromycin had initially been accepted as the treatment of choice for Legionnaires' disease; however, intracellular models as well as animal models of *Legionella* infection indicate that the systemic fluoroquinolones and the newer macrolides (especially azithromycin) show superior activity compared with erythromycin. These newer agents have better pharmacokinetic properties: better bioavailability, longer half-life (resulting in fewer doses per day), better intracellular penetration into macrophages, and better tolerability. On the basis of greater activity in intracellular models and several observational studies, the quinolones may produce a superior clinical response compared with macrolides.

Table 28-1 Common Characteristics and Therapy for the Other Atypical Pneumonias

PATHOGEN	EPIDEMIOLOGIC OR UNDERLYING CONDITION	CLINICAL FEATURES	RECOMMENDED THERAPY
Chlamydophila (Chlamydia) psittaci	Exposure to birds	Headache, myalgia prominent, liver involvement, Horder's spots (macular rash)	Tetracycline, doxycycline, macrolide
Coxiella burnettii (Q fever)	Exposure to farm animals (especially parturient)	Headache prominent, liver involvement	Tetracycline, doxycycline; macrolides
Francisella tularensis (tularemia)	Exposure to rabbits	Headache, chest pain prominent; hilar adenopathy	Streptomycin or gentamicin considered as drug of choice; doxycycline effective for most cases (especially if not severe)
Yersinia pestis (pneumonic plague)	Exposure to infected animals (rodents, cats, squirrels, chipmunks, prairie dogs)	For inhalation, acute onset with rapidly severe pneumonia; blood tinged sputum	Streptomycin, gentamicin; tetracycline, doxycycline

Table 28-2 Diagnostic Studies for Pathogens Associated with Atypical Pneumonia

PATHOGEN	RAPID TEST	STANDARD CULTURE OR MICROBIOLOGIC TEST(S)	SEROLOGY, OTHER TESTS
Mycoplasma pneumoniae	PCR[a] [95][b]	Throat or NP swab [90] (requires 7-10 days for preliminary growth)	ELISA, CF[c] [75-80] (IgM may be present after 1 week but can persist 2-12 months) Diagnostic criteria: • Definite: fourfold titer rise • Possible: IgG ≥1:64 (CF); IgM ≥1:16 (ELISA) • Cold agglutinin [50] (less than 50% specificity; takes several weeks to develop)
Chlamydophila pneumoniae	PCR[a] [80-90]	Throat or NP swab[d] [50-90]	MIF[c] (IgM may take up to 4-6 weeks to appear in primary infection) Diagnostic criteria: • Definite: fourfold titer rise • Possible: IgG ≥1:512; IgM ≥1:32
Legionella pneumophila	Urine antigen[e] [60-70] PCR[a], DFA[f] [25-75]	Sputum, bronchoscopy [75-99] (selective media required, 2-6 days)	IFA[c] [40-75] Diagnostic criteria: • Definite: fourfold titer rise • Possible: IgG or IgM ≥1:512 (titer of 1:256 has positive predictive value of only 15%)
Chlamydia psittaci	PCR[a]	Usually not done (considered laboratory hazard)	CF (presumptive IgG >1:32) MIF for IgM
Coxiella burnettii	PCR[a]	Usually not done (considered laboratory hazard)	ELISA, IFA, CF
Francisella tularensis		Culture (selective media)	ELISA preferred Passive hemagglutination
Yersinia pestis	Gram stain, morphology, gram-negative coccobacillus exhibiting bipolar staining ("safety pin"); PCR	Culture	Serology available

CF, Complement fixation; *DFA,* direct fluorescence antibody; *ELISA,* enzyme-linked immunosorbent assay; *IFA,* indirect fluorescence antibody; *IgG,* immunoglobulin G; *IgM,* immunoglobulin M; *MIF,* microimmunofluorescence; *NP,* nasopharyngeal; *PCR,* polymerase chain reaction.
[a]Available in selected laboratories; reagents are not cleared by the U.S. Food and Drug Administration.
[b][ ] = % sensitivity of test.
[c]Rarely done; requires specialized culture techniques.
[d]Paired sera generally required.
[e]Only for *L. pneumophila* serogroup 1 (approximately 60% to 70% of cases); can be positive for months.
[f]DFA; primarily for *L. pneumophila* serogroup 1; some false-positive results with other species; technically demanding.

The addition of rifampin to erythromycin has been suggested for patients who are severely ill; however, there is no convincing laboratory data to show that adding rifampin to fluoroquinolones or the more active macrolide therapy improves bacterial killing. Doxycycline has also been shown to be effective in limited, well-documented cases. Recommendations for initial parenteral therapy are listed in Table 28-4. Oral therapy for less serious cases or for step-down from intravenous therapy includes the oral macrolides and fluoroquinolones as well as doxycycline.

The duration of therapy for optimal response of *C. pneumoniae* and *M. pneumoniae* has not been well established. In initial descriptions of *C. pneumoniae* pneumonia, observers found that respiratory symptoms frequently recurred or persisted after short courses (5 to 10 days) of erythromycin or tetracycline. In recent recommendations the usual duration of therapy for *C. pneumoniae* or *M. pneumoniae* using more recently approved agents has been 7 to 10 days (shorter for azithromycin because of the longer half-life); however, recent studies (mostly with the fluoroquinolones) have suggested that a minimum of 5 days may be adequate for immunocompetent patients if the patient has had a good clinical response within 48 to 72 hours. Similarly, the usual duration of therapy for Legionnaires' disease in immunocompetent adults has been 7 to 14 days; one recent study showed good efficacy of 750 mg per day of levofloxacin for 5 days. For therapy of immunocompromised patients or more severe disease, longer duration is recommended.

Therapy for the other atypical pneumonias is included in Table 28-1. The tetracyclines are generally considered the drugs of choice for *C. psittaci*, with the macrolides as appropriate alternatives (similar duration as for *C. pneumoniae*). The newer fluoroquinolones are active in vitro and in animal models, but their efficacy for human infection is unknown. For *C. burnettii* the tetracyclines and macrolides are both considered effective

Table 28-3 Recommended Antimicrobial Therapy for *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* (Adult Doses*)

ANTIMICROBIAL	DOSE	DURATION (DAYS)
Erythromycin†	500 mg qid	10-14
Clarithromycin (Biaxin)	500 mg bid	7-10
Azithromycin (Zithromax)†	500 mg initially then 250 mg qd (alternative 500 mg qd)	5 (3)
Dirithromycin (Dynabac)	500 mg qd	10-14
Telithromycin (Ketek)	800 mg qd	7
Tetracycline	500 mg qid	10-14
Doxycycline†	100 mg bid	7-10
Levofloxacin (Levaquin)†	500 mg qd	7-14
	750 mg qd	5 (data are limited)
Moxifloxacin (Avelox)†	400 mg qd	7-14
Gemifloxacin (Factive)	320 mg qd	5-7 days

bid, Twice per day; *qd,* once per day; *qid,* four times per day.
*Oral except where noted.
†Also can be administered intravenously in equivalent dose.

Table 28-4 Parenteral Therapy for Serious *Legionella* Infections*

PREFERRED ANTIMICROBIAL	ALTERNATIVE ANTIMICROBIAL
Fluoroquinolone	Erythromycin 1 g IV q6h ± rifampin†‡
Levofloxacin (Levaquin) 750 mg IV q24h (750 mg qd for 5 days possible for immunocompetent patients)	
Moxifloxacin (Avelox) 400 mg IV q24h	Doxycycline (Vibramycin) 100 mg IV q12h± rifampin
Azithromycin (Zithromax) 500 mg IV q24h	

IV, Intravenously; *qd,* once daily.
*Requiring hospitalization or in immunocompromised patients; can change to oral when clinically stable and can take orally.
†300-600 mg IV every 12 hours.
‡Not approved by U.S. Food and Drug Administration for this indication.

(usually for 10 days). In one small prospective study, doxycycline was slightly more effective than erythromycin, but most cases were benign and self-limiting. Combination therapy (e.g., doxycycline plus ciprofloxacin or rifampin) has been used for Q fever endocarditis. No prospective controlled clinical trials have defined optimal antimicrobial therapy for *F. tularensis*. The traditional choice of therapy for pneumonic tularemia is streptomycin (1 g every 12 hours if patient is severely ill or 500 mg every 12 hours in milder disease) or gentamicin (3 to 5 mg/kg/day) for 7 to 14 days. Doxycycline (100 mg intravenously or by mouth twice daily) has often been used with good success, particularly in less severe pneumonia, and is easier to administer.

PREVENTION

Because the source of *Legionella* is often the water supply, prevention of nosocomial legionellosis is possible by disinfection of the water source. Methods include use of copper-silver ionization units, superheating of the water to a temperature of 70° C (158° F) and flushing distal outlets, and treatment of the water supply with chloride dioxide.

EVIDENCE

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Aspiration Pneumonia

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ABSTRACT

Aspiration is defined as abnormal entry of fluid or particulate matter into the lower airways. *Aspiration pneumonia* refers to the pulmonary sequelae of aspiration. Aspiration is common, but aspiration pneumonia is relatively infrequent and usually occurs in patients who have the complication as a result of aspirating large amounts or an aspirate containing toxic materials or particulate matter that is not easily cleared.

FREQUENCY AND DISEASE BURDEN

Aspiration may account for a substantial number of cases of community-acquired and nosocomial pneumonia. Many bacteria that are common causative agents of pneumonia reach the lower airways either by inhalation or aspiration of upper airway secretions. The distinction is often hard to make and may not be important in terms of clinical care. For communication purposes, *aspiration pneumonia* generally refers to the pulmonary sequelae that occur in association with large-volume aspiration in patients who often have limited ability for pulmonary clearance by cough reflex or glottic closure. There are three syndromes under the umbrella of aspiration pneumonia that are very distinctive in terms of pathophysiology, clinical presentation, and management (Table 29-1).

FACTORS THAT PREDISPOSE TO ASPIRATION OR ASPIRATION PNEUMONIA

Conditions that are associated with high rates of aspiration and aspiration pneumonia include (1) reduced consciousness with the result of decreased cough reflex; (2) dysphagia resulting from neurologic deficits or esophageal pathology; and (3) mechanical disruption of the integrity of the upper airways as with tracheotomy, endotracheal intubation, nasogastric feeding, protracted vomiting, and drowning. For practical application of these observations, the diagnosis of aspiration and its pulmonary complications is based on observed aspiration or presumed aspiration as determined by typical clinical findings in a host who is prone to aspiration as defined earlier.

BACTERIAL INFECTION

Bacterial infection is the most common form of aspiration pneumonia. It is classically caused by bacteria that normally colonize the upper airways or stomach. The usual pathogens are anaerobic bacteria that compromise the dominant flora of the upper airways, primarily the gingival crevice, and include *Prevotella melanogenica*, *Fusobacterium nucleatum*, *Peptostreptococcus*, and multiple aerobic and microaerophilic streptococci such as *Streptococcus milleri*. Most of these organisms have relatively low virulence potential and consequently are usually associated with aspiration of relatively large volume.

Clinical Features

The clinical features are typically seen in patients who are prone to aspiration as a result of reduced consciousness (e.g., anesthesia, seizure disorder, alcoholism, head trauma) or dysphagia. The initial clinical event is pneumonitis that involves a dependent pulmonary segment as determined by the position of the patient at the time of aspiration. If aspiration occurs in the upright position, the favored lung segments are lower lobes, the right more often than the left because of the more direct takeoff of the right mainstem bronchus. If aspiration occurs in the recumbent position, the favored segments are the posterior segments of an upper lobe or superior segment of a lower lobe. The clinical signs and symptoms are those that are common with pneumonia: fever, cough, sputum, and dyspnea. The initial event may be relatively acute and simulate other forms of community-acquired pneumonia (CAP), or it may be a much more subtle process with presentation later in the disease course with chronic cough, low-grade fever, pleurisy, sputum that is often putrid, and weight loss. These symptoms and sometimes the x-ray examination may suggest tuberculosis.

Diagnostic Studies

Patients with bacterial infections associated with aspiration will usually have x-ray changes indicating infection in the dependent pulmonary segments as noted earlier. After 1 week or longer with infections involving anaerobes, there is often cavitation, the classic "primary lung abscess," often in an alcoholic patient. The presence of putrid sputum is diagnostic of anaerobic infections, but the recovery of these organisms to document this bacteriologic pattern is challenging; sputum should not be cultured anaerobically owing to universal contamination by anaerobes as sputum traverses the upper airways. Therefore the bacterial diagnosis requires procedures that are rarely done, such as transtracheal aspiration, transthoracic needle aspiration, or bronchoscopy with quantitative cultures. Some patients will have empyema, which is an appropriate source for anaerobic culture. In most cases the constellation of typical clinical features in an aspiration-prone patient combined with putrid sputum provides the clinician with the necessary information for diagnosis and treatment.

Treatment

The antibiotic agents of choice for anaerobic bacterial infections of the lung are clindamycin, any β-lactam–β-lactamase

Table 29-1 Aspiration Syndromes

	BACTERIAL INFECTION	CHEMICAL PNEUMONITIS	MECHANICAL OBSTRUCTION
Inoculum	Bacteria from oral or gastric secretions	Classically gastric acid, pH <2.7, and large volume	Fluids (drowning) or particulate matter
Clinical features	Pneumonia; often involves anaerobic bacteria and/or empyema Nosocomial cases usually involve aerobic GNB	Acute, fulminant pneumonia, often with observed aspiration, cyanosis, acute dyspnea with: (1) rapid recovery, (2) ARDS, or (3) pulmonary superinfection	Fluids: spontaneous clearance, suction response or drowning Solids: obstruction with symptoms depending on level of obstruction
Diagnosis	Imaging: usually radiograph showing infiltrate in dependent segment with or without abscess or empyema Culture: may need uncontaminated specimen	Imaging: infiltrate in dependent pulmonary segment with or without ARDS Aspirate pH is useless because of rapid neutralization	Imaging: obstruction may show drowning pattern (fluids) or atelectasis with or without distal pneumonia (particulate)
Treatment	Antibiotics directed against: • Community-acquired cases: anaerobes • Nosocomial: GNB and possibly MRSA	Support	Fluid: aspiration of inoculum Particulate material: bronchoscopy and extraction of foreign body

ARDS, Acute respiratory distress syndrome; *GNB,* gram-negative bacilli; *MRSA,* methicillin-resistant *Staphylococcus aureus.*

inhibitor (such as amoxicillin-clavulanate, ampicillin-sulbactam, piperacillin-tazobactam), or a carbapenem (ertapenem, imipenem, or meropenem). Note that the coverage needs to include aerobic and microaerophilic streptococci, which are common companions to the anaerobes. Metronidazole, which is excellent against anaerobic bacteria, is inadequate on the basis of a 50% failure rate, presumably resulting from a lack of activity against the aerobic streptococci. The standard regimens used for CAP are generally suboptimal, including doxycycline, cephalosporins, and fluoroquinolones. Nevertheless, data to support this clinical impression are sparse. Abscesses rarely require drainage, because most drain by communication with the bronchus. The duration of antibiotic therapy depends on the features of the infection; pneumonitis can be treated for 7 to 10 days like CAP, but patients with lung abscess need much longer courses and are usually treated until the infiltrate is cleared or there is only a small, stable residual lesion. Most of this can be done with oral agents on an outpatient basis, but earlier discontinuation may result in a relapse. Patients who have empyema need to have adequate drainage, which often poses a therapeutic challenge owing to the tendency of these infections to form loculated collections requiring tube repositioning and/or open thoracotomy.

Patients with nosocomial pneumonia or ventilator-associated pneumonia caused by aspiration may have anaerobes in the aspirate or at the infected site, but these are generally not considered as important as the gram-negative bacteria such as coliforms or *Pseudomonas aeruginosa* and methicillin-resistant *Staphylococcus aureus* (MRSA)—the leading pathogens of hospital-acquired and ventilator-associated pneumonia. Here the antibiotics need to be directed against the aerobic component of the infection, and agents can be selected on the basis of the dominant isolates with aerobic cultures of respiratory secretions.

Prognosis

The prognosis with anaerobic infections including pneumonitis, abscess, and/or empyema is good. The overall mortality of patients with primary lung abscess is less than 5%, and death is usually restricted to patients with serious underlying disease such as carcinoma. Patients with empyema need adequate drainage, which usually results in long hospitalization and repeated attempts at tube placement, thoracotomy, and decortication. It should be emphasized that the cause, management, and prognosis of the compromised host with pneumonitis, lung abscess, or empyema are very different; this applies to organ transplant recipients and patients with advanced acquired immunodeficiency syndrome (AIDS), those undergoing cancer chemotherapy, and those with lymphomas.

CHEMICAL PNEUMONITIS

Chemical pneumonitis refers to aspiration of substances that are toxic to the lower airways, usually gastric acid as originally described by Mendelson in 1946 as a complication of gastric acid aspiration during obstetric anesthesia. This is sometimes referred to as *Mendelson syndrome*.

The original description by Mendelson still serves today. Sixty-one obstetric patients aspirated stomach contents, and this was followed rapidly by acute respiratory distress, often complicated by wheezing and cyanosis. Chest x-ray films showed infiltrates that were usually located in one or both lower lobes. The patients were seriously ill but often made rapid recovery within 36 hours, and there was x-ray resolution by 7 days with no specific therapy.

The subsequent experience with this syndrome has been somewhat different, probably because the host is not the young, previously healthy obstetric patient, but often elderly and with

multiple comorbidities. The course is now described in three patterns: (1) acute syndrome with rapid recovery; (2) progressive disease with acute respiratory distress syndrome (ARDS) and often death or prolonged morbidity requiring long-term supportive care; or (3) improvement followed by pulmonary superinfection, often with "hospital flora," including *S. aureus* and/or gram-negative bacilli.

Pathophysiology

There have been multiple studies of Mendelson syndrome using experimental animals with intratracheal installation of acid. This work shows that the pH must be less than 2.5 and the inoculum is usually 1 to 4 mL/kg, which translates to at least 25 mL in adult humans. This is required to produce the full syndrome, but the finding also suggests that lesser volumes or somewhat higher pHs may result in less severe disease than the classic syndromes such as pneumonitis, which is more benign in presentation and course. More recent studies in animals suggest that gastric acid and small gastric particles of food act synergistically to produce this classic syndrome. Other toxins that cause lung injury include hydrocarbon base fuel (fire eater's pneumonia) and mineral oil (lipoid pneumonia).

Clinical Features

The classic syndrome includes abrupt onset of severe dyspnea, low-grade fever, cyanosis, rales, hypoxemia, and infiltrates involving one or both lower lobes. Bacteriologic study findings are generally negative but might be very deceptive owing to common pathogens that are found in upper airways and contaminate expectorated sputum. However, the insult is chemical, and bacteria cannot survive in the pH that causes the lung injury. That said, it should be noted that bacterial superinfection is a potentially important complication later in the course.

Treatment

This is a chemical pneumonia that is sometimes compared to a "flash burn" of the lung, in which all destruction takes place within minutes or even seconds. There is no need to attempt to neutralize the gastric acid because this is done by the rapid inflammatory response. The main purpose of treatment is supportive care, but most patients are given antibiotics because infection is difficult to rule out. Corticosteroids have been tested extensively in experimental animals and patients with variable results. The acid-injured lung is infection prone, so the clinician needs to be aware of this possibility with new fever, progressive infiltrates, or other indicators of infection. The most common pathogens are the organisms that cause nosocomial pneumonia, primarily aerobic gram-negative bacilli and *S. aureus*. In general, recommendations for management are those for ARDS and management of any pulmonary superinfection. As noted, antibiotics are commonly given because it is often impossible to exclude bacterial infection and they are clearly indicated with evidence of bacterial infection. The other component of treatment that is important to emphasize is to take measures to prevent any future episodes of aspiration.

Prognosis

All of Mendelson's patients survived, but these were young, healthy women; the more recent experience indicates mortality rates of 20% to 30% or higher, presumably because of a much different population of patients in terms of comorbidities and age. There are the three clinical patterns as noted earlier: some patients improve rapidly and may have x-ray clearance within 3 to 4 days, some have progressive disease with ARDS, and some improve and then deteriorate because of a pulmonary superinfection. One large series showed about one third of patients in each category. There is another group of patients that is poorly defined but possibly important to recognize. These are patients who have smaller inocula and focal pneumonia that resolves but may leave a residual scar that is seen on later imaging. These episodes are not clinically important except in the context of preventing further aspiration events. Some of these patients may show up later with otherwise unexplained focal pulmonary fibrosis caused by "mini-Mendelson" syndrome. (Note that there is no proof of this concept.)

MECHANICAL OBSTRUCTION

Aspiration pneumonia may result in airway obstruction by fluid (drowning) or segmented obstruction from particulate matter. Studies in animals show that intratracheal infusion of nontoxic fluids in limited quantities causes only a transient, self-limited course of hypoxemia that clears rapidly, but in some cases it will trigger pulmonary edema. The experience with small amounts of nontoxic fluids is common, usually uneventful, and quickly self-limited. The older literature includes an investigator who placed barium on the tongues of elderly men who were asleep with open mouths. Radiographs the next day showed barium in the lungs, but it was an insignificant event. However, a large amount that cannot be cleared will manifest as drowning, reflecting the inability to eliminate the inoculum. Also relatively common is aspiration of particulate matter, in which the pulmonary consequences with lack of spontaneous clearance depend on the size of the object relative to the diameter of the airway. This is most common in children 1 to 3 years old during the oral stage of development, and the most common solid particles are, in rank order, peanuts, other vegetable particles, inorganic material, and teeth. With large airway obstruction there is acute hypoxemia, sudden respiratory distress, cyanosis, aphonia, and death. This may simulate an acute myocardial infarction during a meal at a restaurant and is consequently sometimes called the "café coronary syndrome." The suggested treatment is the Heimlich maneuver, which requires firm and rapid pressure applied to the upper abdomen in an effort to dislodge the obstruction. With smaller particles there may be obstruction of a bronchus, resulting in atelectasis and downstream pneumonia. Partial obstruction may result in recurrent pneumonitis involving the same pulmonary segment. These infections often involve anaerobic bacteria from the upper airways. The treatment suggested for obstruction at lower levels is usually bronchoscopy with removal of a foreign body. When there is complicating infection, the requirement is for antibiotics, but there is the accompanying need for removal of the obstruction.

PREVENTION

The patient who is aspiration prone needs to be managed in a fashion that will reduce the probability of this event. As noted, common predisposing conditions include any event that compromises consciousness, neurologic disorders that cause dysphagia, esophageal disorders, and medical interventions that compromise the integrity of the airways and their protective mechanisms including cough and glottic closure. Particularly important in the aspiration-prone patient is elevation of the head of the bed and particular care with endoscopy and intubation.

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ADDITIONAL RESOURCES

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Bartlett JG: Anaerobic bacterial pneumonitis, *Am Rev Respir Dis* 119:19, 1979. *A review of "anaerobic bacterial pneumonitis." The bacteriology was based on transtracheal aspiration, and the clinical presentation was similar to that of CAP caused by* Streptococcus pneumoniae *or other common pulmonary pathogens.*

Bartlett JG, Gorbach SL: The triple threat of aspiration pneumonia, *Chest* 68:560, 1975. *The authors review the three distinctive consequences of aspiration: bacterial infection, chemical pneumonitis, and obstruction.*

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Viral Respiratory Infections

Michael J. Tan

30

ABSTRACT

Viruses are an important but underrecognized cause of pneumonias. The exact percentage of all pneumonias caused by viral infection is unknown, but viruses are probably responsible for 25% of cases. The most common respiratory viruses are influenza, respiratory syncytial virus (RSV), adenovirus, and parainfluenza virus. Patients with severe chronic lung disease, chronic medical conditions, immunosuppression, and the elderly are groups most susceptible to viral pneumonia. With the exception of influenza, treatment is largely supportive.

INFLUENZA VIRUS

Influenza viruses are enveloped, single-stranded ribonucleic acid (RNA) viruses of the family Orthomyxoviridae. The viruses are classified as type A, B, or C and subtyped based on differences in the surface hemagglutinin (H) and neuraminidase (N) glycoproteins. Influenza A is the leading cause of influenza in adults in the United States and is responsible for 90% of all epidemic influenza. Prevention, diagnosis, and treatment are important, as secondary bacterial pneumonia can be severe and is not uncommon.

In the United States, influenza virus has no geographic predilection. It is spread by respiratory secretions from individuals who are actively shedding the virus. Incubation is approximately 1 to 5 days. Epidemics occur annually during the winter months. It is associated with 10,000 to 40,000 excess deaths. Eighty percent of these deaths are in patients older than 65. Patients with chronic lung diseases such as chronic obstructive pulmonary disease and emphysema, congestive heart failure, hemoglobinopathies, and immunosuppression are at risk for severe disease (Figure 30-1; Box 30-1).

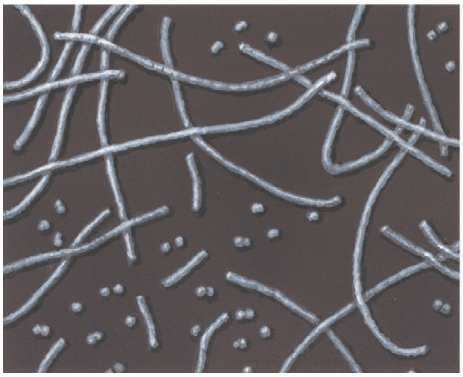
Clinical manifestations include an acute febrile respiratory illness with cough, sore throat, headache, malaise, and myalgias. Symptoms are usually self-limited, with the major symptoms improving after 3 to 5 days. Complications can include secondary bacterial infections caused by *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, or gram-negative pathogens. These secondary infections are often suggested by initial improvement followed by clinical worsening (Figure 30-2). Diagnosis of influenza is suggested by the symptoms listed earlier, usually with the presence of influenza in the community. Confirmation can be made with several available rapid diagnostic kits that detect viral nucleoproteins or viral neuraminidase. Rapid diagnostic tests for influenza have high specificity (>90%) but have low to moderate sensitivity (20%-70%) compared with other influenza tests. These and other virus and viral antigen detection methods may also be helpful in nonepidemic months (Table 30-1).

Treatment is largely supportive with management of symptoms with antipyretics and analgesics. The neuraminidase inhibitors zanamivir and oseltamivir are effective against influenza A and B. The tricyclic amines, amantadine and rimantadine, are classically active against only influenza A. However, widespread resistance of influenza A (H3N2) and 2009 pandemic H1N1 to amantadine and rimantadine has been seen. Presently, therefore only neuraminidase inhibitors should be used if influenza is suspected. Resistance to neuraminidase inhibitors of the 2011 predominant strains is rare (<1%). The neuraminidase inhibitors are also effective for chemoprophylaxis. The current antiviral recommendations are readily available from the Centers for Disease Control and Prevention website on seasonal influenza, www.cdc.gov/flu.

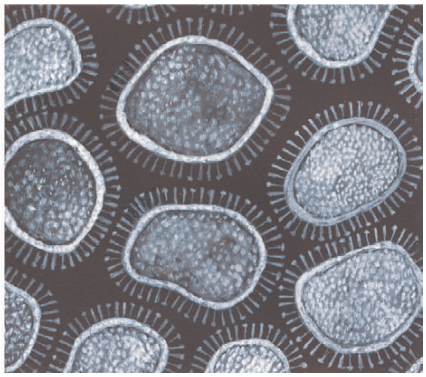
The most effective means of prevention is with annual influenza vaccination. Two vaccines are currently available: the intranasal attenuated live virus and the intramuscular inactivated split virus. Both vaccines usually contain the three virus strains that are projected to be responsible for the annual epidemic. The attenuated live virus is reserved for healthy individuals. Close contacts of immunosuppressed individuals should avoid contacts with immunosuppressed patients for 7 days after vaccination with the live virus vaccine. Recommendations now suggest relative safety of health care workers receiving live virus vaccine, even if they are caring for immunesuppressed individuals. Those workers taking care of hematopoietic stem cell transplant patients, however, should avoid live virus vaccine. Efficacy is similar for both vaccines. The optimal time for vaccination is usually late October through November, as the season usually occurs late December through March. Vaccination is usually effective from about 2 weeks to 4 to 6 months postvaccination. However, recent data suggest vaccination efficacy is maintained late in the season and into the summer; vaccination should be given at earliest availability and should not be delayed until later in the season.

AVIAN INFLUENZA AND PANDEMIC INFLUENZA

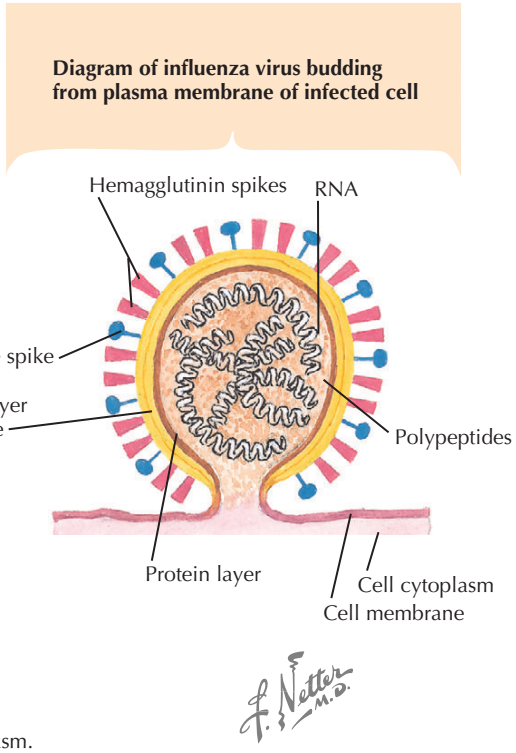
Two influenza entities that have come to be of significant public concern in recent years are the avian and pandemic influenza. Avian influenza is caused by influenza viruses that naturally occur in wild birds. Typically they are transmitted between birds, and occasionally from birds to humans. Person-to-person transmission is currently rare and uncommon. Low pathogenic avian influenza is common in birds and not a significant mortality risk, but highly pathogenic influenza, specifically H5N1, can be deadly to domesticated birds. Because there is little human immunity and little human vaccine availability, these strains can also be deadly to humans. Patients at risk for avian influenza usually have significant contact with infected poultry. H5N1 has

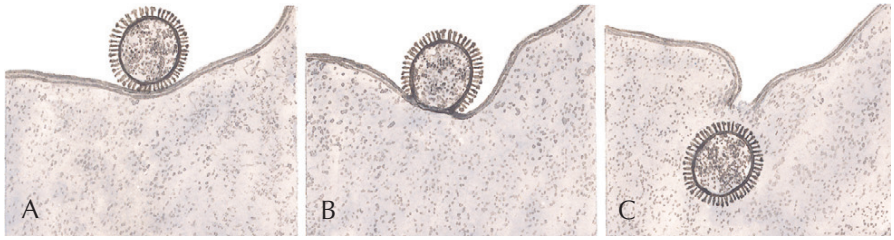


Electron microscopic appearance of influenza A_2 virus; filaments and spherical forms (× 10,000)



Virus viewed in section at much higher magnification (×300,000)





Influenza virus invasion of chorioallantoic membrane cell of chick embryo. **A.** Attachment to cell membrane. **B.** Fusion of viral envelope with cell membrane. **C.** Penetration into cell cytoplasm.

Figure 30-1 Influenza virus and its epidemiology.

Box 30-1 Groups at High Risk for Complicated Influenza

- Persons older than 65 years of age
- Nursing home residents
- Adults and children with chronic cardiopulmonary disease
- Immunocompromised adults with diabetes mellitus, renal failure, human immunodeficiency virus, and other immunosuppressive diseases
- Patients receiving chronic corticosteroids or other immunosuppressive medications
- Pregnant women who will be in the second and third trimester of pregnancy during influenza season

Table 30-1 Diagnostic Tests for Viral Infections

Respiratory syncytial virus infection	Tracheal aspirate or bronchial alveolar lavage for viral culture, antigen testing by ELISA and fluorescein conjugate monoclonal or polyclonal antibody, RT-PCR
Parainfluenza	Nasal and bronchial secretions for viral culture and immunofluorescent assays, RT-PCR Serum for complement fixation and hemagglutination
Influenza	Respiratory secretions for viral cultures and immunofluorescent and ELISA assays, RT-PCR
Adenovirus infection	Respiratory secretions for viral culture, complement fixation, hemagglutination inhibition, and neutralization

ELISA, Enzyme-linked immunosorbent assay; *RT-PCR*, reverse transcription–polymerase chain reaction.

been resistant to tricyclic amines. Neuraminidase inhibitors have been suggested for prophylaxis and treatment if outbreaks occur; however, emerging resistance has the potential to limit efficacy.

Pandemic flu refers to a global influenza outbreak resulting from a highly virulent influenza to which humans have little natural immunity. This may result from introduction of an immunologically specific virus or development of an antigenically different mutation to which human hosts have little defense (see Figure 8-1). It occurs rarely rather than seasonally. This type of influenza is spread easily from person to person and may result in rapid global spread, a lack of treatment or medical supplies, overwhelmed healthcare systems, and economic and social disruption. The 2009 H1N1 influenza pandemic was the fourth pandemic in the past century. Notably, the most adversely affected demographic differed from seasonal influenza in that the greatest percentage of complications were observed in adolescents and young adults. For both H5N1 and pandemic influenza, isolation and quarantine may be needed to limit the spread

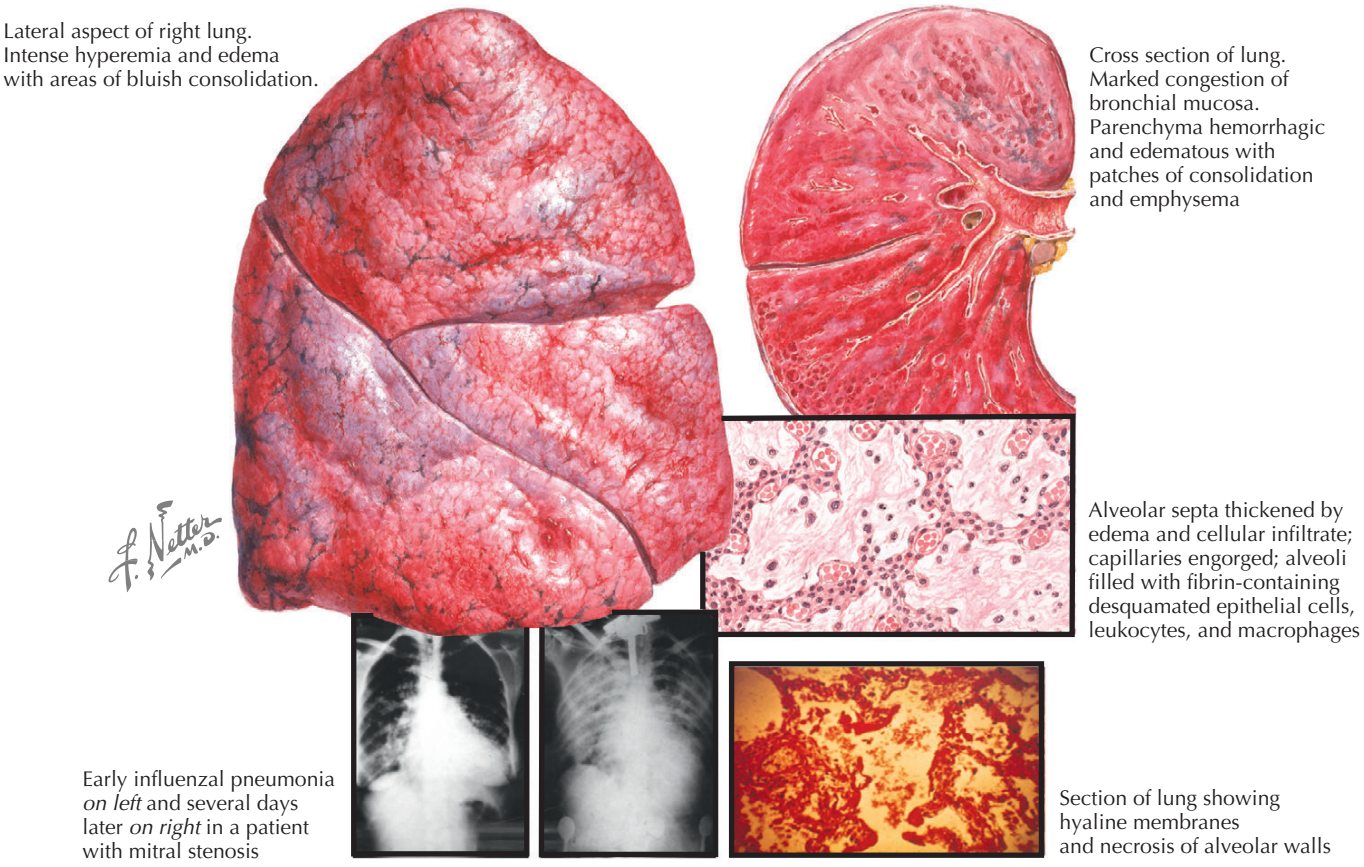


Figure 30-2 Influenza pneumonia.

of the infection. In response to concerns regarding pandemics, governments have been stockpiling antiviral medications for treatment and prophylaxis; resistance patterns, however, cannot be guaranteed.

RESPIRATORY SYNCYTIAL VIRUS

RSV is an enveloped, single-stranded RNA virus of the Paramyxoviridae family. Although paramyxoviruses (including RSV, parainfluenza, and measles) can cause respiratory tract infections in children and adults, RSV is the most common cause of lower respiratory tract infections in infants and children. It is responsible for 25% of hospitalizations of children with pneumonia and 40% to 50% of hospitalizations of children with bronchiolitis. Premature infants and children with bronchopulmonary dysplasia, congenital heart disease, and immunodeficiency are at greatest risk. There is no geographic predilection for infection. With the presence of pneumonia, the death rate is reported to range from 11% to 78%.

Infection occurs by inoculation of ocular, nasal, or oral mucosa after contact with fomites or infected secretions. The virus may persist on environmental surfaces for several hours. Good hand hygiene and contact precautions are the most effective means of prevention.

Asymptomatic infections with RSV are uncommon. Nasal congestion, sinusitis, otitis media, coryza, and pharyngitis are typical presentations in children. Lower respiratory tract infections may also be seen and include tracheobronchitis, bronchiolitis, and pneumonia. Infections in the elderly and immunocompromised more often tend to involve the lower respiratory tract. Patients often have fever, nonproductive cough, anorexia, and dyspnea. Physical examination may reveal wheezing and crackles. In adults, radiographs may exhibit bilateral interstitial or patchy infiltrates with occasional lobar consolidation. Radiographs in children may demonstrate bronchial wall thickening and hyperinflation.

Diagnosis is made by examination of respiratory secretions. Viral culture is considered the gold standard, but results may require several days. Identification of RSV antigen by immunofluorescence is faster and fairly sensitive. Polymerase chain reaction (PCR) assays are available but not yet licensed, and acute and convalescent serologies may also be performed, but these are usually helpful only for retrospective diagnosis (see Table 30-1).

Ribavirin is the only effective antiviral agent for RSV, but its use in children is controversial; and the benefit of ribavirin therapy for healthy or immunocompromised adults has not been established. Ribavirin has not been shown to be effective prophylaxis for RSV. Currently there is no vaccination available.

PARAINFLUENZA VIRUS

Parainfluenza virus is a common paramyxovirus that infects most persons during childhood. Immunity, however, is transient, and reinfection manifests as mild upper respiratory tract

infection. Different serotypes may lead to different presentations. Parainfluenza viruses are responsible for croup, bronchitis, pharyngitis, and pneumonia in children. Adults generally get mild upper respiratory infection. Immunocompromised hosts may have severe pneumonia, and outbreaks have been reported in extended care facilities. Symptoms of parainfluenza pneumonia may include fever, cough, coryza, dyspnea, crackles, or wheezes. Chest radiographs may not demonstrate any abnormality. Focal or diffuse interstitial infiltrates may be seen.

Virus may be detected by culture, but growth is often slow, and immunofluorescence or antigen detection assays may be more rapidly performed on nasal or bronchial secretions. PCR assays are also available, and some can concurrently test for other respiratory viruses as well (see Table 30-1).

Treatment is largely supportive. Ribavirin has been used, but there are few data to support its use. There are no currently available vaccines.

HUMAN METAPNEUMOVIRUS

Human metapneumovirus (hMPV) is another paramyxovirus that is relatively recently described as causing human disease. These viruses are found worldwide and cause disease similar to that caused by other paramyxoviruses, with cough, nasal congestion, rhinorrhea, dyspnea, hoarseness, and wheezing. Transmission is through contact with infected respiratory secretions. hMPV generally causes a self-limited mild upper respiratory tract infection in children and adults. It has been implicated in causing bronchiolitis, asthma exacerbation, and pneumonia in older adults. It is a recognized cause of severe respiratory tract infection in hematopoietic cell and lung transplant patients. It is difficult to isolate on culture. PCR may be performed in research laboratories. There is no effective treatment, although it is susceptible in vitro to ribavirin. Treatment is supportive. No vaccine is currently available.

ADENOVIRUS

Adenovirus is a nonenveloped deoxyribonucleic acid (DNA) virus associated with pharyngitis, bronchiolitis, and pneumonia. Most infections with adenovirus are mild or asymptomatic; however, severe pneumonia is possible and has been reported in communal living situations. There is no geographic predilection for the virus. Immunocompromised patients may be more susceptible to pneumonia. Disseminated infection in immunocompromised or transplant patients may lead to pulmonary or central nervous system disease.

Common clinical manifestations include fever, cough, malaise, hoarseness, and sore throat. Occasionally cervical lymphadenopathy and conjunctivitis can be seen. Chest radiographic studies may demonstrate patchy lower lobe infiltrates or diffuse interstitial infiltrates. No defining characteristics allow differentiation from other community-acquired pneumonias, however. Diagnosis can be made by culturing virus from respiratory secretions. PCR assay on tissue or blood or complement fixation can also be performed. Immunofluorescence can be performed as a rapid test on throat swabs, nasopharyngeal washes, or sputum samples (see Table 30-1).

There is no effective antiviral treatment known for adenovirus at this time. Treatment remains largely supportive. Ribavirin has in vitro activity against adenovirus and has been used anecdotally. Cidofovir has also been used for adenovirus pneumonia, but nephrotoxicity limits its use. There is no currently available vaccine for adenovirus.

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): *Seasonal influenza (flu)*. Available at: www.cdc.gov/flu. Accessed February 12, 2009. *Gives up-to-date information regarding the current patterns of seasonal influenza, resistance patterns, and methods of prevention. This site also contains links to nonseasonal influenza sites.*

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Mandel LA, Wunderink RG, Anzueto A, et al: Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults, *Clin Infect Dis* 33:S27-S72, 2007. *The most recent guidelines from the Infectious Diseases Society of America detailing appropriate management and treatment of community-acquired pneumonia.*

U.S. Department of Health and Human Services: Flu.gov website. Available at: www.pandemicflu.gov. Accessed February 12, 2009. *This site gives up-to-date information for the tracking and spread of pandemic influenza. It details efforts to prevent the spread of pandemic influenza and clarifies the differences between seasonal influenza and pandemic influenza.*

Sinus Infections

Anthony W. Chow

31

ABSTRACT

Sinusitis is defined as an inflammation of the mucosal lining of the paranasal sinuses and can be caused by various factors including allergy, environmental irritants, and infection by viruses, bacteria, or fungi. It is also commonly referred to as *rhinosinusitis*, because there is almost always coexisting inflammation in the nasal mucosa. Sinusitis can be classified based on duration of symptoms into acute, subacute, and chronic. Acute sinusitis lasts up to 4 weeks and is usually caused by a viral or bacterial infection. Chronic sinusitis lasts more than 12 weeks and may result from a wide range of allergic and nonallergic causes. Subacute sinusitis lasts 4 to 12 weeks and usually represents a transition between acute and chronic sinusitis. Other patterns include recurrent acute sinusitis, defined as the occurrence of four or more episodes of acute sinusitis within 1 year, each lasting at least 7 days; and acute exacerbation of chronic sinusitis, defined as the presence of signs and symptoms of chronic sinusitis that worsen but return to baseline after treatment.

Sinusitis can also be categorized according to the mode of infection and underlying conditions, such as nosocomial sinusitis associated with nasotracheal intubation, odontogenic sinusitis, and sinusitis in severely immunocompromised hosts. From a clinical and management standpoint, the most important goal is to distinguish a bacterial infection from viral or allergic causes in acute sinusitis and to identify structural or fungal causes in chronic sinusitis. Distinguishing bacterial infection is critical for appropriate antimicrobial therapy, whereas structural or fungal causes may necessitate surgical intervention for diagnosis and treatment.

ANATOMIC CONSIDERATIONS

The paranasal sinuses (maxillary, ethmoid, frontal, and sphenoid) are air-filled cavities lined by pseudostratified, ciliated columnar epithelium. They are interconnected through small tubular openings, the sinus ostia, which drain into different regions of the nasal cavity (Figure 31-1). The frontal, anterior ethmoid, and maxillary sinuses open into the middle meatus, whereas the posterior ethmoid and sphenoid sinuses open into the superior meatus. The osteomeatal complex, an area between the middle and inferior nasal turbinates representing the confluence of drainage from the paranasal sinuses, is a particularly important anatomic site because of its potential for mucosal thickening and impaired drainage leading to sinus infection even without mechanical obstruction of the ostia.

The maxillary sinuses, either alone or in combination with the ethmoid or frontal sinuses, are the most frequent site of infection. The ostium of the maxillary sinus lies at an obtuse angle toward the roof (see Figure 31-1), so the maxillary sinus does not empty well in the erect posture but drains best when the patient is lying on the side opposite the affected sinus. The floor of the maxillary sinus directly adjoins the maxillary bone in which the apices of the first, second, and third molar teeth reside; hence, extraction or root infection of these teeth is a frequent cause of maxillary (odontogenic) sinusitis. Furthermore, because the superior alveolar nerves (branches of the maxillary nerve) supply both the molar teeth and the mucous membranes of the sinus, maxillary sinusitis may frequently manifest as a toothache.

The frontal sinus is not a frequent site of infection but may be a focus for spread of infection into the orbit or the brain (Figure 31-2). The frontal sinus is supplied by the supraorbital branch of the ophthalmic division of the trigeminal nerve. Thus headache is a prominent symptom of frontal sinusitis.

The ethmoid sinuses are composed of multiple air cells that are separated by thin bony partitions, and each air cell drains by an independent ostium. The ethmoid sinuses are separated from the orbit by a paper-thin orbital plate. Perforation of the plate allows direct spread of infection into the retro-orbital space. Ethmoid sinusitis can also spread to the superior sagittal vein or the cavernous venous sinus (see Figure 31-2).

The sphenoid sinus occupies the body of the sphenoid bone in proximity to the pituitary gland above; the optic nerve and optic chiasm in front; and the internal carotids, the cavernous sinuses, and the temporal lobes of the brain on each side (see Figure 31-2). Therefore sphenoid sinusitis can spread locally to cause cavernous sinus thrombosis, meningitis, temporal lobe abscess, and orbital fissure syndromes. The superior orbital fissure syndrome, characterized by orbital pain, exophthalmos, and ophthalmoplegia, is caused by involvement of the abducens, oculomotor, and trochlear nerves and the ophthalmic division of the trigeminal nerve as they pass through the orbital fissure.

The paranasal sinuses are generally considered to be sterile, although transient colonization from the upper respiratory tract may occur. A patent osteomeatal complex and normal mucociliary clearance function are the key defense mechanisms of the paranasal sinuses.

EPIDEMIOLOGY AND RISK FACTORS

According to the 2006 National Health Interview Survey, approximately 24 million cases of sinusitis are diagnosed each year, representing 14% of all adults 18 years of age or older. Children younger than age 15 and adults 25 to 64 years old are the most frequently affected. It is the fifth leading cause for antimicrobial prescriptions in office practice. Total direct costs for treating sinusitis are estimated at $3 billion per year, not to mention significant indirect costs such as days lost from work, decreased productivity, and impaired quality of life.

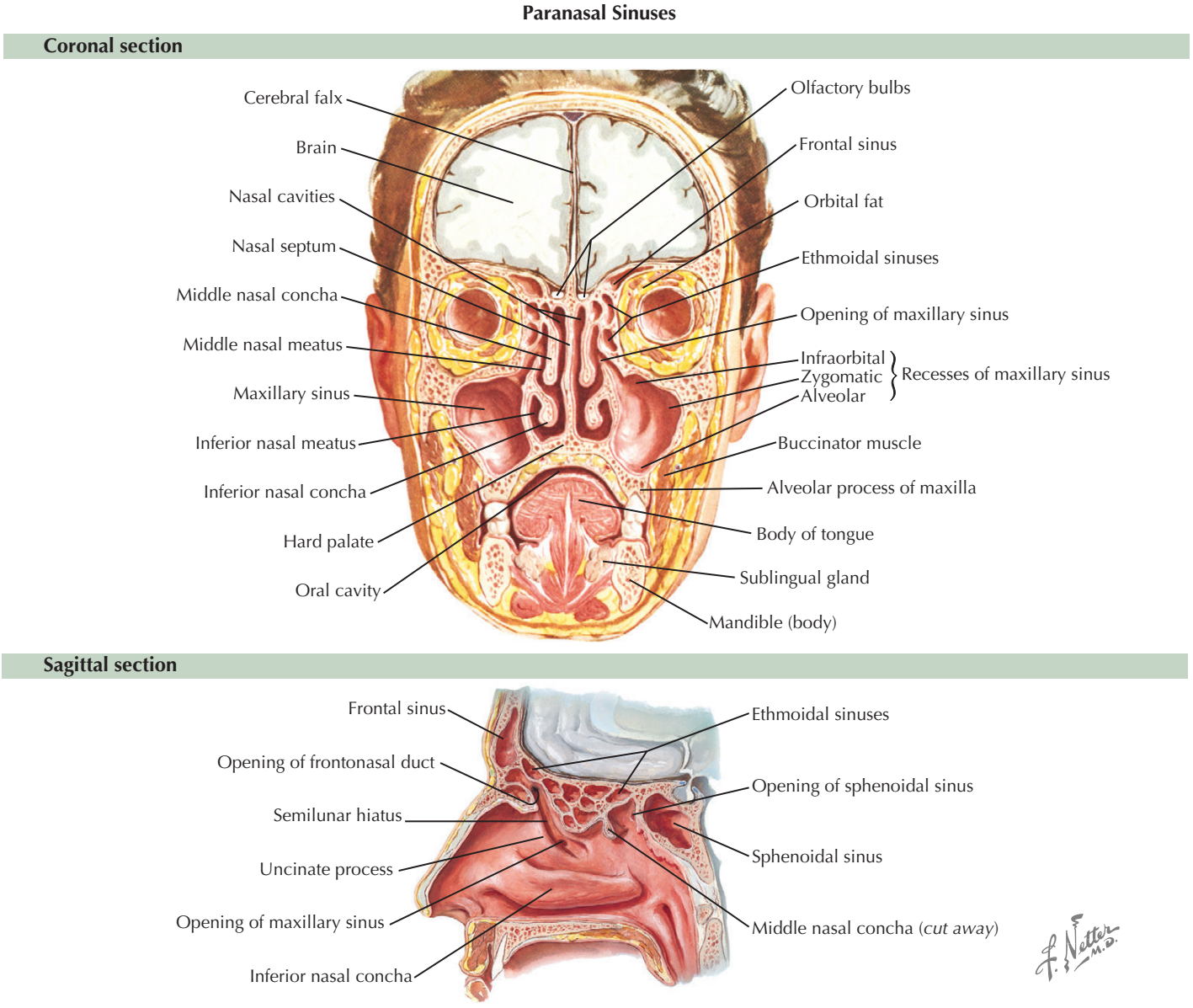


Figure 31-1 Anatomic relationships of the paranasal sinuses.

Several risk factors predispose to acute or chronic sinusitis (Box 31-1). The most common cause of acute sinusitis is a viral upper respiratory infection or the common cold. Adults typically develop two to three colds per year, and children have six to eight episodes per year. However, only up to 2% of adults and 6% to 13% of children with viral upper respiratory infections develop a secondary bacterial infection of the sinuses. Nose blowing that generates excessive positive intranasal pressures and propels contaminated fluid from the nasal cavity into the paranasal sinuses may be an important predisposing mechanism.

A strong association exists among allergic rhinitis, asthma, and recurrent sinusitis in both children and adults. It has been suggested that allergic rhinitis may be a predisposing factor for acute maxillary sinusitis in 25% to 30% of patients, and as many as 60% to 80% of patients with chronic sinusitis. The observation that asthma, allergic rhinitis, and rhinosinusitis frequently coexist raises the possibility that these conditions are manifestations of an inflammatory process within an integrated and contiguous upper and lower airway (the integrated airway hypothesis). This concept is supported by the finding that the upper and lower airways share many similarities in epithelial histology, physiology, and immunologic responses as well as susceptibility to various allergic and nonallergic inciting factors.

Mild and selective immune deficiencies have been frequently demonstrated in children and adults with recurrent or persistent symptoms of sinus disease. One study found that 52% of patients had selective immunoglobulin (Ig) deficiencies (IgG2, IgG4 subclass, or IgA) or poor responsiveness to some polysaccharide antigens. In addition, chronic or recurrent sinusitis is an important source of morbidity in patients with cystic fibrosis and patients infected with human immunodeficiency virus (HIV).

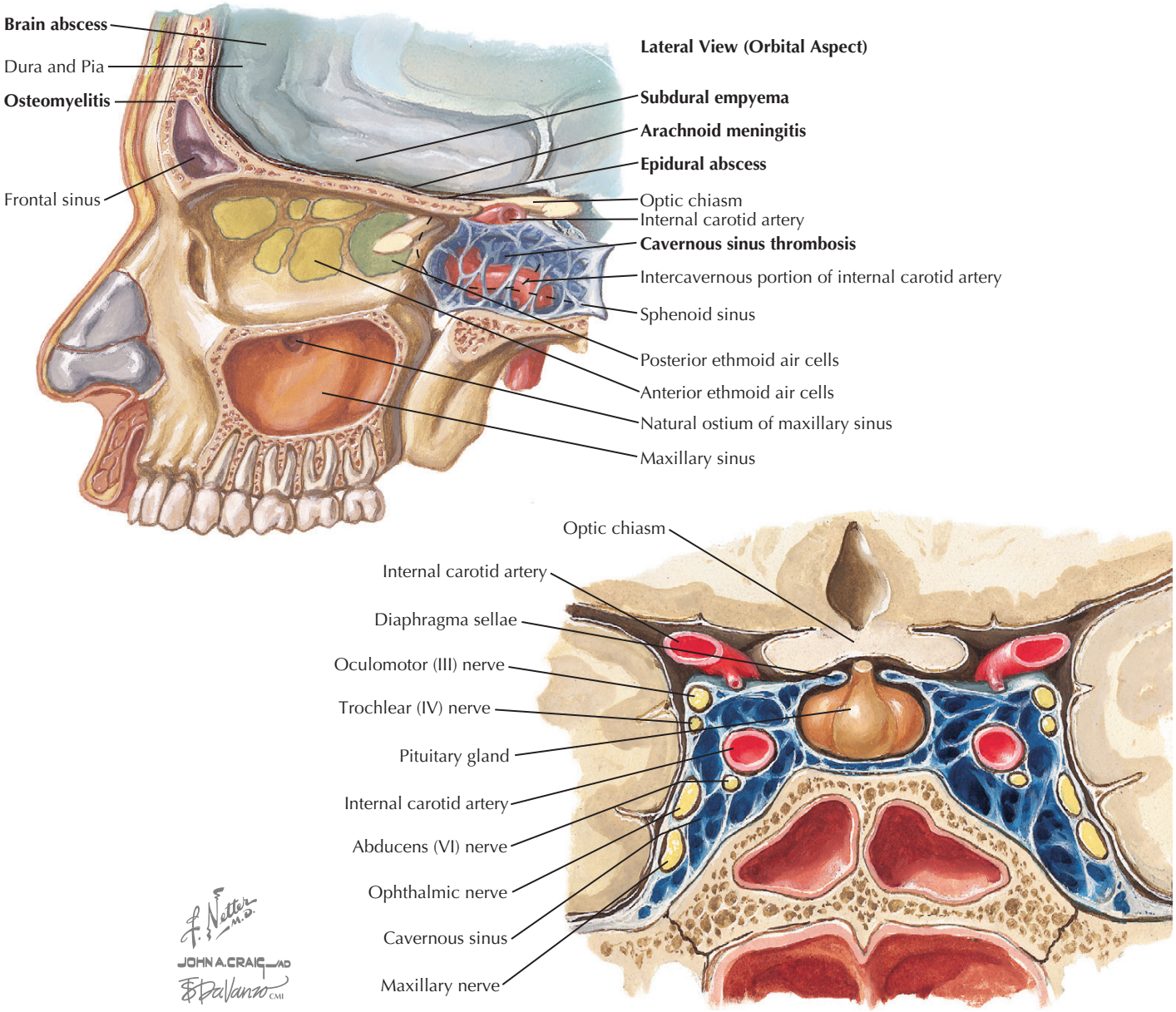


Figure 31-2 Proximity of the paranasal sinuses to the orbit and intracranial structures; cavernous sinuses.

Certain actions, such as sustaining head trauma, swimming, diving, cocaine sniffing, and nasotracheal or nasogastric intubation, may repeatedly traumatize the nasal mucosa and facilitate microbial invasion of the paranasal sinuses. Dental extraction and periapical infections of the maxillary molar teeth are particularly important causes of odontogenic sinusitis.

MICROBIOLOGY

Sinus puncture and aspiration is the gold standard for establishing the microbial cause of sinusitis. Although acute sinusitis is primarily caused by respiratory viruses such as rhinoviruses, influenza A, parainfluenza, respiratory syncytial virus, and adenoviruses, direct isolation of these viruses from antral aspirates has been relatively uncommon. In acute bacterial sinusitis, *Streptococcus pneumoniae* and nonencapsulated *Haemophilus influenzae* are the causative agents in 70% of adults, whereas the addition of *Moraxella catarrhalis* accounts for 80% of cases in children (Table 31-1). In contrast, the normal upper respiratory flora typically includes coagulase-negative staphylococci, *Corynebacterium* species, and *Staphylococcus aureus*. *S. aureus* together with viridans streptococci and *S. pneumoniae* are the predominant isolates in acute sphenoid sinusitis. Anaerobes are uncommonly isolated in acute sinusitis but are the predominant flora in chronic sinusitis. The isolation of anaerobes during acute sinusitis suggests an odontogenic source. Approximately 25% of patients with the clinical diagnosis of acute community-acquired sinusitis will have sterile cultures from antral aspirates. Nosocomial sinusitis secondary to prolonged nasotracheal intubation

Box 31-1 Predisposing Factors for Sinusitis

Impaired Mucociliary Function
Viral upper respiratory tract infection
Allergic rhinitis
Irritants from cold or dry air
Chemicals or drugs (rhinitis medicamentosa)
Human immunodeficiency virus infection
Cystic fibrosis
Ciliary dysmotility syndrome

Obstruction of Sinus Ostia
Viral upper respiratory tract infection
Allergic rhinitis
Anatomic abnormalities (e.g., nasal polyps, deviated nasal septum, choanal atresia, foreign body, tumors)

Immune Defects
Common variable immunodeficiency
Selective immunoglobulin deficiency (immunoglobulin A [IgA], IgG subclasses)
Acquired immunodeficiency syndrome
Wegener's granulomatosis
Diabetes mellitus

Direct Microbial Invasion of the Sinuses
Odontogenic infection
Nasotracheal or nasogastric intubation
Head trauma
Swimming or diving
Cocaine sniffing

is commonly a polymicrobial infection caused by gram-negative bacteria, *S. aureus*, and anaerobes.

Up to 40% of *H. influenzae*, 80% of *M. catarrhalis*, and 30% of respiratory tract anaerobes produce β-lactamase. Over 25% of *S. pneumoniae* is now resistant to trimethoprim-sulfamethoxazole (TMP-SMX). Macrolide-resistant *H. influenzae* and *S. pneumoniae* are also isolated with increasing frequency.

The microbiology of chronic sinusitis is more closely linked to underlying comorbid diseases and differs considerably from that of acute sinusitis. In patients with cystic fibrosis, *Pseudomonas aeruginosa* and nontypable *H. influenzae* are the most frequent pathogens. Sinusitis in patients with HIV infection is often caused by gram-negative bacilli and unusual pathogens such as *Aspergillus* species and cytomegalovirus. In debilitated and severely immunocompromised hosts, such as those with uncontrolled diabetes mellitus, advanced HIV infection, or chemotherapy-induced neutropenia, invasive fungal infection with *Aspergillus*, *Mucor*, *Pseudallescheria boydii*, *Fusarium*, and other saprophytic fungi may occur. In chronic sinusitis associated with nasal polyposis or allergic fungal rhinosinusitis, hypersensitivity to and colonization by *Aspergillus* and other saprophytic fungi in the paranasal sinuses can often be demonstrated. In addition, there is an increased prevalence of nasal colonization by enterotoxin-producing *S. aureus* in patients with chronic sinusitis associated with nasal polyposis. Such patients typically demonstrate local production of enterotoxin-specific IgE antibodies and coexisting aspirin sensitivity or asthma.

Table 31-1 Microbial Causes of Acute and Chronic Sinusitis Determined by Antral Sinus Aspirate or Sinus Surgery Specimens

MICROBIAL AGENT	*Prevalence Mean (Range)* ADULTS (%)	CHILDREN (%)
Acute Sinusitis		
Streptococcus pneumoniae	20-43	36-37
Haemophilus influenzae	6-35	23-25
Moraxella catarrhalis	2-10	19-25
Streptococcus pyogenes	1-7	2
Staphylococcus aureus	0-8	8-10
Gram-negative bacilli (includes Enterobacteriaceae species, *Pseudomonas aeruginosa*)	0-24	2
Anaerobes *(Bacteroides, Fusobacterium, Peptostreptococcus, Veillonella)*	0-12	0-4
Respiratory viruses (rhinovirus, influenza, parainfluenza, adenovirus)	3-15	0-2
Chronic Sinusitis		
Aerobes	29-43	20
Streptococcus species	9-14	6
Staphylococcus species	5-14	6
Haemophilus influenzae	1-6	3-5
Anaerobes	57-88	80
Peptostreptococcus species	25-38	23-73
Bacteroides species	14-27	27-29
Fusobacterium species	3-4	5-16

Data from Chow AW: Acute sinusitis: current status of etiologies, diagnosis, and treatment, Curr Clin Top Infect Dis *21:31-63, 2001; Gwaltney JM Jr: Acute community-acquired sinusitis*, Clin Infect Dis *23:1209-1225, 1996; Wald ER: Microbiology of acute and chronic sinusitis in children*, J Allergy Clin Immunol *90:452-460, 1992; Noye KA, Brodovsky D, Coyle S, et al: Classification, diagnosis and treatment of sinusitis: Evidence-based clinical practice guidelines*, Can J Infect Dis *9(suppl B):3B-24B, 1998; Brooke I: The role anaerobic bacteria in sinusitis*, Anaerobe *12:5-12, 2006; and Brook I, Foote PA, Hausfeld JN: Increase in the frequency of recovery of methicillin-resistant* Staphylococcus aureus *in acute and chronic maxillary sinusitis*, J Med Microbial *57:1015-1017, 2008.*

CLINICAL FEATURES

Acute Sinusitis

Acute sinusitis is often difficult to distinguish from the common cold or allergic (vasomotor) rhinitis. The presence of at least two major symptoms or one major and two or more minor symptoms may distinguish acute sinusitis (whether viral or bacterial) from rhinitis (Table 31-2). Three hallmarks that suggest a bacterial sinusitis rather than a viral infection are: (1) persistence (i.e., more than 10 days), (2) severity, and (3) worsening of respiratory symptoms. The probability of identifying a bacterial infection by sinus aspiration is approximately 60% for patients with symptoms persisting beyond 10 days. There is often a "double sickening" or biphasic course with worsening symptoms after initial improvement. The presence of purulent postnasal discharge, maxillary toothache, facial pain, or unilateral maxillary sinus tenderness further increases the likelihood of a bacterial infection. Hyposmia, jaw pain with mastication, nasal congestion, and a recent history of upper respiratory tract infection are other manifestations. The combination of these clinical findings greatly enhances the diagnostic probability. In children, the most common manifestations of bacterial sinusitis are cough (80%), nasal discharge (76%), and fever (63%). Parents of preschoolers often report malodorous breath. Headache, facial pain, and swelling are rare.

In ethmoid sinusitis, edema of the eyelids and excessive tearing may be a prominent feature. Retroorbital pain and proptosis indicate extension of infection into the orbit. Anterior rhinoscopy may reveal hyperemic and edematous nasal turbinates, often with purulent discharge from the middle meatus. Severe intractable headache is dominant in sphenoid sinusitis and can mimic ophthalmic migraine or trigeminal neuralgia. Neurologic deficit with hypoesthesia or hyperesthesia of the ophthalmic or maxillary dermatomes of the trigeminal nerve may be detected in one third of the patients.

In nosocomial sinusitis secondary to prolonged nasotracheal or nasogastric intubation, the clinical features may be relatively silent apart from unexplained fever. The presence of purulent rhinorrhea or a middle ear effusion may be the only physical finding. A high index of suspicion is required for early diagnosis.

Table 31-2 Diagnostic Criteria of Sinusitis*

MAJOR SYMPTOMS	MINOR SYMPTOMS
Purulent anterior nasal discharge	Headache
Purulent or discolored posterior nasal discharge	Ear pain, pressure, or fullness
Nasal congestion or obstruction	Halitosis
Facial congestion or fullness	Dental pain
Facial pain or pressure	Cough
Hyposmia or anosmia	Fever (for subacute or chronic sinusitis)
Fever (for acute sinusitis only)	Fatigue

Modified from Meltzer EO, Hamilos DL, Hadley JA, et al: Rhinosinusitis: establishing definitions for clinical research and patient care, J Allergy Clin Immunol *114:S155-S212, 2004.*

*A diagnosis of sinusitis is probable in the presence of at least two major symptoms or one major and two or more minor symptoms.

Subacute and Chronic Sinusitis

Chronic sinusitis may mimic asthma, allergic rhinitis, or chronic bronchitis. Pain or tenderness on palpation may be present over the affected sinuses. Fever is uncommon. Physical findings may be subtle. Fatigue, general malaise, and an ill-defined feeling of unwellness and irritability can be more prominent than local symptoms of nasal congestion, facial pain, or postnasal drip. More recently, several multidisciplinary expert panels have established four cardinal findings as the diagnostic criteria for chronic sinusitis: (1) anterior and/or posterior mucopurulent drainage; (2) nasal obstruction; (3) facial pain, pressure, or fullness; and (4) decreased sense of smell (hyposmia or anosmia). The presence of at least two of these signs or symptoms together with objective demonstration of mucosal inflammation is required to make a firm diagnosis. In addition, chronic sinusitis may manifest in three distinctive clinical syndromes: (1) chronic sinusitis with nasal polyposis, (2) allergic fungal rhinosinusitis, and (3) chronic sinusitis without nasal polyposis. The most common presentation is chronic sinusitis without nasal polyposis (60% to 65% of cases), followed by chronic sinusitis with nasal polyposis (20% to 33%), and allergic fungal rhinosinusitis (6% to 12%).

Chronic sinusitis without nasal polyposis is a heterogeneous entity that includes patients with allergic and nonallergic causes, structural abnormalities, and/or immunodeficiency. The sinus mucus typically shows abundant eosinophils and neutrophils but lacks evidence of fungal hyphae. Chronic sinusitis with polyposis is clinically more distinctive because of the presence of bilateral nasal polyps in the middle meatus or the sinus cavities. These polyps are typically infiltrated with eosinophils, and the nasal secretions demonstrate high levels of histamine and Th2 cytokines including interleukin 5 (IL-5) and IL-13. There is a high association with aspirin sensitivity and asthma, and colonization with enterotoxin-producing *S. aureus* with evidence of IgE-mediated hypersensitivity to these superantigens. Allergic fungal sinusitis is characterized by abundant "allergic mucin" associated with sinus opacification, the presence of degranulating eosinophils, and fungal hyphae. IgE-mediated hypersensitivity to one or more colonizing fungi can usually be demonstrated.

DIAGNOSTIC APPROACH

In primary care the diagnosis of acute bacterial sinusitis is mainly based on the history and physical examination. Routine sinus radiography is unnecessary, and sinus puncture is seldom performed owing to its invasiveness and poor patient acceptance. Transillumination has limited value because it lacks sensitivity and does not distinguish bacterial from viral sinusitis.

Imaging Studies

Imaging studies are essential for patients with suspected orbital or intracranial complications, in recurrent or chronic sinusitis, and for those whose condition does not improve despite appropriate medical therapy.

SINUS RADIOGRAPHY

Plain sinus radiographs are now largely superseded by computed tomography (CT) for evaluating the sinonasal cavity. It may be indicated in elderly patients or young children who cannot tolerate a coronal CT examination. A single Waters (occipitomental) view should suffice to visualize the maxillary and frontal sinuses. The Caldwell (occipitofrontal) and lateral views are used for evaluating the ethmoid and sphenoid sinuses, respectively. Radiographic findings in acute sinusitis include thickened mucosa (>6 mm), air-fluid level, or complete opacification of the involved sinuses and are predictive for bacterial infection in 75% of cases as determined by sinus puncture, although its sensitivity is low (60%). It is more helpful for excluding sinus disease when clinical manifestations are unclear (specificity 80%).

Ultrasonography

The accuracy of ultrasonography for demonstrating retained fluid or thickened mucosa of affected sinuses is highly operator dependent, and false-positive examination findings are common. Despite a sensitivity of approximately 70%, its specificity is low, and it is also technically difficult to perform in young children. Therefore routine use of ultrasonography is not recommended except for individuals in whom radiography or CT scanning is not feasible (such as in obtunded and critically ill patients with suspected nosocomial sinusitis).

Computed Tomography

A coronal CT scan is the most cost-efficient approach for the diagnosis of acute sinusitis compared with standard sinus radiographs and other imaging methods. Compared with plain radiographs, CT provides greater definition of the sinus cavity and its contents and offers better visualization of the ethmoid and sphenoid sinuses. Contrast-enhanced CT is invaluable for assessing orbital or intracranial complications (Figure 31-3) and can clarify anatomic variations that may play an important role in recurrent or chronic sinusitis. However, although CT is very sensitive for detecting sinus abnormalities, it lacks specificity for bacterial infection, because abnormalities can be demonstrated in over 80% of patients with the common cold. Therefore CT abnormalities should be interpreted only in the context of additional clinical information.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is used rarely because of its cost and limitations in assessing cortical bone. Although MRI provides better visualization of soft tissues than CT, it is best reserved for the investigation of intracranial suppurative complications and for the delineation of the anatomic relationships between the intraorbital and extraorbital compartments.

Sinus Cultures

SINUS PUNCTURE AND QUANTITATIVE CULTURES

Surface cultures of the nasal vestibule or the nasopharynx are unreliable for microbiologic diagnosis of sinusitis owing to regular contamination by the resident microflora. Although culture of aspirates from sinus puncture remains the gold standard, this procedure is poorly accepted by patients and impractical in most primary care situations. In addition, the microbial cause of acute bacterial sinusitis is well characterized and relatively predictable in most immunocompetent persons, and antimicrobial therapy is usually initiated empirically without microbiologic confirmation. Therefore sinus puncture is reserved primarily for situations in which empirical therapy has failed, patients who are immunocompromised, and patients who are suspected to have serious complications.

ENDOSCOPICALLY DIRECTED MIDDLE MEATAL CULTURES

Several meta-analyses have evaluated the accuracy of endoscopically directed middle meatal cultures compared with sinus puncture in acute bacterial sinusitis. The accuracy rates have ranged from 76% to 78% in both adults and children. If the analysis is restricted to isolation of main pathogenic bacteria in acute bacterial sinusitis (i.e., *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*), the accuracy rate improves to 87%. Therefore endoscopically directed middle meatal cultures may become an acceptable method for the microbiologic diagnosis of acute maxillary bacterial sinusitis.

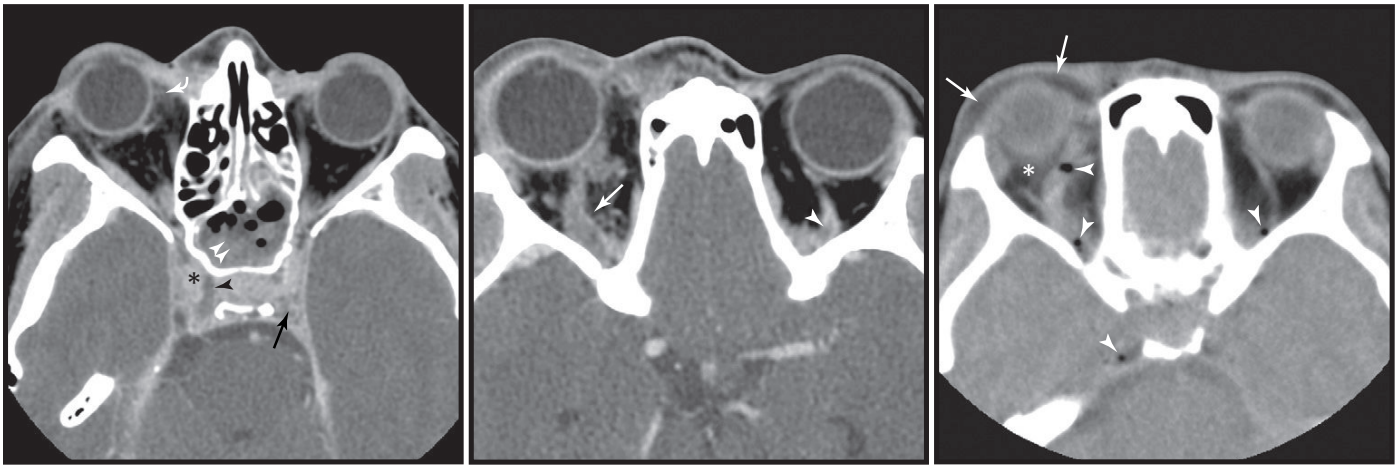
Other Investigations

Mucosal biopsy and histopathologic studies may be indicated in patients with recurrent or chronic sinusitis to rule out malignancy or invasive fungal infections. Skin testing with environmental or seasonal allergens such as pollens, dust mites, animal danders, and saprophytic fungi is warranted to rule out allergy. An IgE-mediated immediate hypersensitivity response is elicited if a wheal and flare reaction is observed within 20 minutes. Serum immunoassays for allergen-specific IgE antibodies may be useful in some cases, particularly *Aspergillus*-precipitating antibodies for patients with suspected allergic fungal sinusitis. Overall, the sensitivity of immunoassays ranges from 70% to 75% compared with skin testing. Studies for immune function in patients with chronic or recurrent sinusitis may include total quantitative immunoglobulins (IgG, IgA, IgM, and IgG subclasses), preimmunization and postimmunization specific antibody responses to tetanus toxoid and pneumococcal vaccine, and T-cell subset analysis.

CLINICAL MANAGEMENT AND DRUG TREATMENT

The goals of management of sinusitis are (1) to optimize symptomatic relief and facilitate drainage of congested sinuses, (2) to eradicate infection and restore sinus function, (3) to prevent recurrence and complications, and (4) to reduce antibiotic overuse in ill-defined upper respiratory tract infections and minimize the development of antibiotic resistance. Various management options exist (Box 31-2). Because acute sinusitis is most commonly caused by respiratory viruses that spontaneously resolve after 7 to 10 days, supportive and symptomatic management should suffice. Antimicrobial therapy is reserved

Contrast-Enhanced CT of the Orbits



Inspissated material with gas bubbles in the sphenoid sinus (*white arrowheads*), fat stranding reflecting right intraorbital edema (*curved arrow*), lack of normal enhancement in the right cavernous sinus (*arrowhead*) around the right cavernous carotid artery (*), and heterogeneous enhancement in the left cavernous sinus caused by partial thrombosis (*arrow*).

Expansion of thrombosed right superior ophthalmic vein (*arrow*) with a nonocclusive filling defect representing partial thrombosis of the left superior ophthalmic vein (*arrowhead*).

Repeat post-contrast CT several days later shows increased edema in the right preseptal (*arrows*) and retro-orbital fat (*). Gas is visible now in the right and left superior ophthalmic veins and in the right cavernous sinus (*arrowheads*).

Figure 31-3 Computed tomographic findings in cavernous sinus thrombosis secondary to acute sphenoid sinusitis. *(Reproduced with permission from Hurley MC, Heran MKS: Imaging studies for head and neck infections,* Infect Dis Clin North Am *21:305-353, 2007.)*

Box 31-2 Management Options for Sinusitis

Supportive and symptomatic
- Intranasal glucocorticosteroids
- Sinus irrigation
- Humidification and hydration
- Analgesics and antipyretics
- Decongestants (topical and systemic)
- Mucolytic agents

Antimicrobial (oral or parenteral)

Surgical (functional endoscopic sinus surgery [FESS])
- Correct intranasal, ostial, or other abnormalities
  - Turbinectomy
  - Septal surgery
  - Polypectomy
  - Adenoidectomy
  - Tonsillectomy
- Promote drainage
  - Intranasal antrostomy
  - Ethmoidotomy
  - Frontal sinus trephination
- Remove diseased tissue
  - Caldwell-Luc operation
  - Ethmoidectomy
  - Frontal sinus obliteration
  - Sphenoidectomy

for those with severe, persistent, or worsening symptoms despite 7 to 10 days of "watchful waiting" with symptomatic management. Surgical treatment is considered when medical management has failed or complications are suspected.

Supportive and Symptomatic Management

INTRANASAL CORTICOSTEROIDS

Topical corticosteroid nasal sprays reduce inflammation and edema in the nasal mucosa and may be beneficial as adjunctive therapy for acute bacterial sinusitis in both adults and children. Several recent double-blind, placebo-controlled, randomized trials found that the use of intranasal glucocorticoids (mometasone, fluticasone, flunisolide, or beclomethasone) alone or as adjuvant therapy to antibiotics increased the rate of symptom response compared with placebo. Adverse effects were minimal. Intranasal steroids may also benefit patients with chronic or recurrent sinusitis. In contrast to topical steroids, no controlled clinical trials of systematic corticosteroids for acute sinusitis have been published.

SINUS IRRIGATION

Saline irrigation of the nasal cavity has been found in several randomized controlled trials to improve clinical symptom scores and radiographic findings in patients with chronic sinusitis.

Hypertonic and physiological saline appear equally effective for sinus irrigation in children and adults.

DECONGESTANTS AND MUCOLYTIC AGENTS

Nasal and oral decongestants are α-adrenergic agonists that shrink the erectile vascular tissue of the nasal turbinates and theoretically may help to relieve osteomeatal and nasal obstruction. However, there is conflicting evidence as to whether these agents functionally improve aeration of the sinuses. Furthermore, prolonged use of nasal decongestants beyond 3 or 4 days can cause rebound vasodilatation (rhinitis medicamentosa).

Despite the lack of demonstrated effectiveness, mucolytic agents (e.g., guaifenesin) are frequently prescribed in conjunction with oral or nasal decongestants. These agents thin nasal secretions and theoretically may promote drainage. There is currently insufficient evidence to recommend either nasal decongestants or mucolytic agents as adjunctive therapy in acute or chronic sinusitis.

ANTIHISTAMINES

The role of oral antihistamines as adjunctive treatment of acute sinusitis without coexisting allergic rhinitis remains to be determined. There are theoretic concerns that antihistamines might impede mucociliary clearance by drying the mucous membrane and thickening nasal secretions.

MISCELLANEOUS MEASURES

The symptomatic value of hydration, warm facial packs, steam baths, antipyretics, and analgesics (acetaminophen or nonsteroidal antiinflammatories) for comfort and pain relief is self-evident. However, the potential benefit of heated humidification, zinc lozenges, or *Echinacea* preparations remains unclear.

Antimicrobial Therapy

Even though only 0.5% to 2% of patients with acute sinusitis develop a bacterial infection, over 80% are prescribed an antibiotic. This misuse of antimicrobial therapy not only exposes patients to unnecessary adverse effects and results in escalating healthcare costs, it is also the major driving force for the emergence of antibiotic resistance among respiratory pathogens. Therefore the appropriateness and efficacy of antimicrobial therapy in acute bacterial sinusitis have been critically evaluated in various double-blind, placebo-controlled, randomized clinical trials.

META-ANALYSES OF PLACEBO-CONTROLLED RANDOMIZED TRIALS

No fewer than five systematic reviews or meta-analyses of antimicrobial therapy for acute bacterial rhinosinusitis have been published since 2005. A total of 3872 patients were enrolled in 20 double-blind, placebo-controlled, randomized trials. All five meta-analyses of these placebo-controlled trials came to the same conclusions despite slightly different inclusion or exclusion criteria and outcome measures: (1) antimicrobial therapy is associated with a higher rate of cure or symptom improvement than placebo, and (2) although the differences are statistically significant, the benefits are only marginal and at the expense of an 8% increase in adverse effects. Overall, 11 to 15 patients with acute sinusitis would need to be treated with antibiotics before one additional patient would benefit. The high rate of spontaneous resolution (approximately 70%) in the control patients supports the strategy of "watchful waiting" with symptomatic management in patients with acute bacterial sinusitis. Thus only severely ill patients (high fever with temperature ≥39° C, periorbital edema, purulent nasal discharge, facial pain, or headache), those with suspected orbital or intracranial complications, and those whose symptoms persist or worsen after 7 to 10 days of symptomatic management should be considered candidates for empirical antimicrobial therapy.

EMPIRICAL ANTIMICROBIAL REGIMENS

For acute bacterial sinusitis in adults, antibiotic therapy is primarily directed against *H. influenzae* and *S. pneumoniae*, whereas in children, *M. catarrhalis* should also be covered. Amoxicillin-clavulanate is preferred over amoxicillin alone based on the increasing prevalence of β-lactamase–producing respiratory pathogens in acute bacterial sinusitis, particularly *H. influenzae* (25% to 35%) and *M. catarrhalis* (90%). A 10- to 14-day course of therapy is recommended. Doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended for adults with type-1 penicillin hypersensitivity. In children, levofloxacin (for type-1 penicillin hypersensitivity) or combination of an oral third generation cephalosporin (cefixime or cefpodoxime) plus clindamycin (for non–type-1 penicillin hypersensitivity) may be used. Trimethoprim-sulfamethoxazole (TMP-SMX) is no longer recommended for initial empirical therapy of acute bacterial sinusitis because of high rates of resistance among both *S. pneumonia* and *H. influenza* (30% to 40%). Similarly, newer macrolides (azithromycin or clarithromycin) are no longer recommended because of high rates of resistance among *S. pneumonia* (30%). Second- and third-generation oral cephalosporins are not recommended as monotherapy of acute bacterial sinusitis because of variable rates of resistance among *S. pneumonia*e. Combination of a third-generation oral cephalosporin (cefixime or cefpodoxime) plus clindamycin is recommended for patients from geographic regions with high endemic rates of penicillin-nonsusceptible *S. pneumonia*. The respiratory fluoroquinolones (levofloxacin or moxifloxacin) or a parenteral third-generation cephalosporin (cefotaxime or ceftriaxone) should be reserved for patients who have severe symptoms, who are immunocompromised, or whose condition has not responded to first-line agents despite 3 to 5 days of empirical first-line therapy. In patients with odontogenic sinusitis, treatment should be directed at mixed anaerobes and streptococci, and penicillin or clindamycin is a suitable agent (Table 31-3).

TREATMENT OF PENICILLIN-NONSUSCEPTIBLE *S. PNEUMONIAE*

An increasing rate (15% to 25%) of intermediate or highly penicillin-resistant *S. pneumoniae* isolates resulting from altered β-lactam target sites has been reported from various regions in

the United States and Canada. High-dose amoxicillin regimens (1 g/125 mg three times daily) remains effective for intermediate-resistant strains. High-level penicillin resistance among *S. pneumoniae* is rare, but patients can be treated with cefotaxime or ceftriaxone.

TREATMENT FAILURE

Patients in whom symptoms persist or worsen despite a 3- to 5-day course of first-line antibiotic therapy should receive an additional course of high-dose amoxicillin-clavulanate or with respiratory fluoroquinolones. If this regimen fails, imaging studies should be performed and a sinus aspirate obtained, and further antimicrobial therapy should be guided by culture and susceptibility data. Patients with subacute or recurrent symptoms that fail to respond to the earlier-described approach should be investigated for structural abnormalities by sinus endoscopy and for comorbid conditions such as cystic fibrosis, Churg-Strauss vasculitis, Wegener's granulomatosis, or immunodeficiency syndromes. Repeated antral lavage in addition to antibiotics may be required before consideration of a surgical approach (Figure 31-4).

FUNGAL SINUSITIS

Antimicrobial therapy for fungal sinusitis is required only if the disease is invasive or the patient is severely immunocompromised and the risk of progression is high. Noninvasive disease usually responds to surgical debridement alone. Most immunocompromised patients with invasive fungal infection will require a combination of surgery and high-dose intravenous amphotericin B. Voriconazole is more effective than amphotericin B in invasive aspergillosis and *P. boydii* infections and may be the agent of choice for these conditions.

SUBACUTE AND CHRONIC SINUSITIS

Antibiotic therapy alone is of questionable value in chronic sinusitis. Medical treatment options should begin with topical intranasal steroids and saline irrigations. Surgical procedures to correct sinus abnormalities, relieve obstruction of the osteomeatal complex, and improve drainage are often required. In choosing an antibiotic for chronic sinusitis, the initial coverage should include *S. aureus* and β-lactamase–producing organisms, including anaerobic species. Clindamycin may be added if

Table 31-3 Empirical Antimicrobial Regimens for Acute and Chronic Bacterial Sinusitis

STRATIFICATION	FIRST LINE (DAILY DOSE)*†	SECOND LINE (DAILY DOSE)*†
Acute Sinusitis in Adults		
Initial empirical therapy	Amoxicillin-clavulanate (500 mg/125 mg tid, or 875 mg/125 mg q12h)	Amoxicillin-clavulanate (2000 mg/125 mg bid) Doxycycline (200 mg qd on day 1, then 100 mg qd)
β-Lactam allergy	Doxycycline (200 mg qd on day 1, then 100 mg qd)	Levofloxacin (500 mg qd) Moxifloxacin (400 mg qd)
Failed initial therapy	Amoxicillin-clavulanate (2000 mg/125 mg bid) Levofloxacin (500 mg qd) Moxifloxacin (400 mg qd)	Ceftriaxone (1-2 g IV q24h) Cefotaxime (2 g IV q6h)
Hospitalized patients	Levofloxacin (500 mg qd) Moxifloxacin (400 mg qd)	Ceftriaxone (1-2 g IV q12-24h) Cefotaxime (2 g IV q6h)
Chronic Sinusitis in Adults		
Empiric therapy	Amoxicillin-clavulanate (500 mg/125 mg bid × 3 weeks) plus clindamycin (450 mg tid × 3 weeks)	Levofloxacin (500 mg qd × 3 weeks) Moxifloxacin (400 mg qd × 3 weeks)
Acute Sinusitis in Children		
Initial empirical therapy	Amoxicillin-clavulanate (45 mg/kg/day bid)	Amoxicillin-clavulanate (90 mg/kg/day bid
β-Lactam allergy	Levofloxacin (10-20 mg/kg/day q12-24h) (type I hypersensitivity)	Cefixime (8 mg/kg/day bid) or cefpodoxime (10 mg/kg/day bid), each plus clindamycin (30-40 mg/kg/day tid) (non-type I hypersensitivity)
Failed initial therapy	Amoxicillin-clavanate (90 mg/kg/day bid)	Cefixime (8 mg/kg/day bid) or cefpodoxime (10 mg/kg/day bid), each plus clindamycin (30-40 mg/kg/day tid)
Hospitalized patients	Ceftriaxone (50 mg/kg/day IV q12h) Cefotaxime (100-200 mg/kg/day IV q6h)	Levofloxacin (10-20 mg/kg/day IV q12-24h)
Chronic Sinusitis in Children		
Empiric therapy	Amoxicillin-clavulanate (45 mg/kg/day bid × 3 weeks) plus clindamycin (30 mg/kg/day qid × 3 weeks)	Levofloxacin (10-20 mg/kg/day qd × 3 weeks)

IV, Intravenously.
*Oral dose, unless specified otherwise.
†Duration of therapy usually 10 to 14 days, unless specified otherwise.

anaerobic organisms are suspected. Subsequent antimicrobial selection (including antifungal agents) should be guided by sinus puncture and culture results. Many of the second-line antibiotics used for acute bacterial sinusitis are also effective in chronic sinusitis, but the course of treatment is generally prolonged to 4 to 6 weeks.

Surgical Management

The indications for surgical treatment include refractory sinusitis caused by osteomeatal obstruction, invasive fungal infections, and orbital or intracranial complications. Traditional open sinus procedures have been largely replaced by functional endoscopic sinus surgery (FESS), which facilitates drainage by removing any soft tissue causing obstruction of the ostia and allows improved access to the ethmoid and sphenoid sinuses. Approximately 80% to 90% of patients undergoing FESS experience significant improvement in sinusitis symptoms and function, and complication rates are low (less than 1%).

COMPLICATIONS

Suppurative complications of acute and chronic sinusitis is relatively rare in the postantibiotic era. Extension of infection from the maxillary or ethmoid sinuses into the adjacent structures may result in osteomyelitis of the facial bones, including prolapse of the orbital antral wall with retroorbital cellulitis, proptosis, and ophthalmoplegia. Direct intracranial extension from the maxillary sinus is rare, except in rhinocerebral mucormycosis. Frontal sinusitis may lead to osteomyelitis of the frontal bones (Pott's puffy tumor) or thrombosis of the superior sagittal sinus. Intracranial extension of infection from the ethmoid or sphenoid sinusitis may result in cavernous sinus thrombosis, epidural or subdural empyema, meningitis, and brain abscess (see Figure 31-2). The diagnosis and management of these life-threatening complications require an aggressive and multidisciplinary approach.

PREVENTION AND CONTROL

Apart from pneumococcal and *H. influenzae* vaccines, there are currently no effective preventive measures for acute or chronic sinusitis. Efforts should be directed to early and aggressive treatment of acute sinusitis, surgical correction of anatomic deformities of the sinus ostia, promotion of good dental hygiene, and effective control of underlying allergic manifestations.

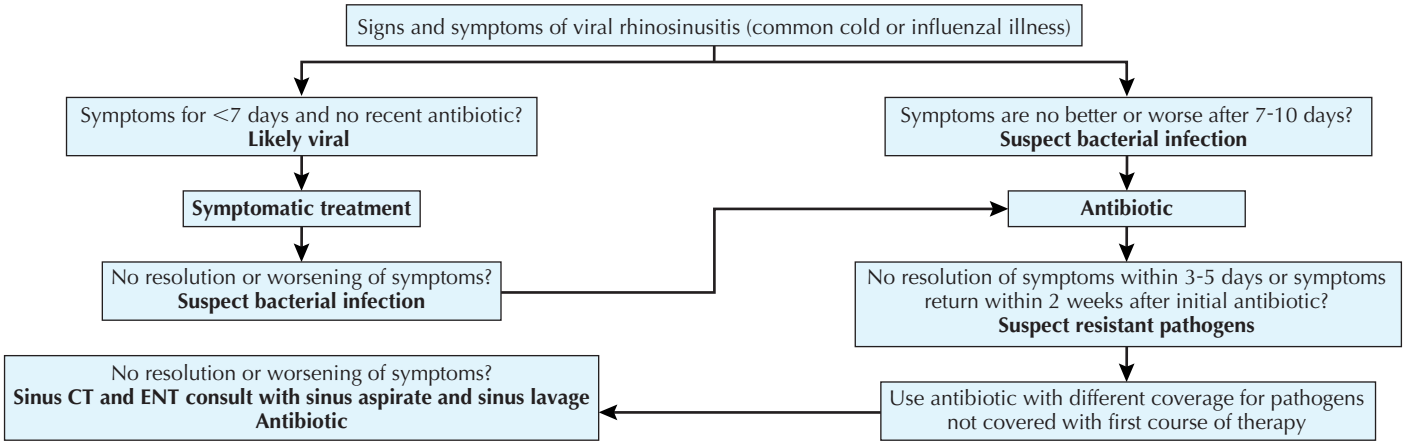


Figure 31-4 Algorithm for the management of acute sinusitis. *(Modified from Brooks I, Gooch WM 3rd, Jenkins SG, et al: Medical management of acute bacterial sinusitis: recommendations of a clinical advisory committee on pediatric and adult sinusitis,* Ann Otol Rhinol Laryngol *182(suppl):2-20, 2000.)*

EVIDENCE

Ahovuo-Saloranta A, Borisenko OV, Kovanen N, et al: Antibiotics for acute maxillary sinusitis, *Cochrane Database Syst Rev* 2:CD000243, 2008. *This Cochrane meta-analysis reviewed the effect of antimicrobial therapy for uncomplicated acute sinusitis from 51 randomized controlled trials, including six placebo-controlled studies involving 631 participants in a primary care setting. Only a small treatment effect was demonstrated compared with placebo, and 80% of participants treated without antibiotics improved within 2 weeks.*

Falagas ME, Giannopoulou KP, Vardakas KZ, et al: Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials, *Lancet Infect Dis* 8:543-552, 2008. *This meta-analysis assessed data on the therapeutic role of antibiotics for acute sinusitis compared with placebo from 17 double-blind randomized controlled trials, including three involving children. The authors concluded that use of antibiotics for acute sinusitis confers a small therapeutic benefit over placebo with a corresponding rise in the risk of adverse events.*

Harvey R, Hannan SA, Badia L, Scadding G: Nasal saline irrigations for the symptoms of chronic rhinosinusitis, *Cochrane Database Syst Rev* 3:CD006394, 2007. *This Cochrane meta-analysis reviewed the effectiveness and safety of topical saline for the treatment of chronic sinusitis from eight randomized controlled trials. The authors concluded that the beneficial effects of topical saline outweigh the relatively minor adverse effects and support its use as a treatment adjunct for the symptoms of chronic sinusitis.*

Karageorgopoulos DE, Giannopoulou KP, Grammatikos AP, et al: Fluoroquinolones compared with β-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials, *CMAJ* 178:845-854, 2008. *This meta-analysis evaluated the effectiveness and safety of newer fluoroquinolones compared with β-lactams for the treatment of acute bacterial sinusitis from eight randomized controlled trials. The authors concluded that the newer fluoroquinolones cannot be endorsed as first-line therapy because they conferred no benefit over β-lactam antibiotics.*

Rosenfeld RM, Singer M, Jones S: Systematic review of antimicrobial therapy in patients with acute rhinosinusitis, *Otolaryngol Head Neck Surg* 137:S32-S45, 2007. *This systematic review of 13 double-blind randomized controlled trials of antimicrobial therapy for adult rhinosinusitis concluded that seven patients must be treated with antibiotics to achieve one additional positive outcome above and beyond spontaneous resolution at 7 to 12 days.*

Young J, De Sutter A, Merenstein D, et al: Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data, *Lancet* 371:908-914, 2008. *This meta-analysis assessed the overall effect of antibiotic treatment versus placebo from individual patient data of adults with acute rhinosinusitis enrolled in 11 double-blind randomized controlled trials. The authors concluded that 15 patients would have to be given antibiotics before an additional patient was cured above and beyond spontaneous resolution at 14 days.*

Zalmanovici A, Yaphe J: Steroids for acute sinusitis, *Cochrane Database Syst Rev* 4:CD005149, 2007. *This Cochrane meta-analysis assessed the effectiveness and safety of topical steroids for the treatment of acute sinusitis in four double-blind, placebo-controlled, randomized trials. The authors concluded that intranasal corticosteroids are useful as monotherapy or adjuvant therapy with antibiotics for acute sinusitis with modest but clinically important benefits and relatively minor adverse effects.*

ADDITIONAL RESOURCES

Chow AW, ed: *Infections of the head and neck. Infectious Disease Clinics of North America*, vol 21, no 2, Philadelphia, 2007, WB Saunders, pp 1-599. *This volume, devoted to the diagnosis and treatment of infections of the head and neck, including acute and chronic sinusitis as well as life-threatening complications, highlights the multidisciplinary nature of these infections. The indigenous microflora and innate immunity in the head and neck region and recent advances in microbiologic, radiographic, and molecular investigations are reviewed, and the principles of antimicrobial therapy based on suspected source, likely pathogens, and predicted susceptibility or resistance patterns are presented.*

Rosenfeld RM, Andes D, Bhattacharyya N, et al: Clinical practice guideline: adult sinusitis, *Otolaryngol Head Neck Surg* 137:S1-S31, 2007. *This clinical practice guideline developed by the American Academy of Otolaryngology–Head and Neck Surgery in conjunction with a multidisciplinary panel provides an evidence-based framework for the management of acute rhinosinusitis in adults. The guideline aims to improve diagnostic accuracy, reduce inappropriate antibiotic use and radiographic imaging, and promote appropriate use of ancillary tests including nasal endoscopy, CT, and testing for allergy and immune function.*

Acute Otitis Media

Blaise L. Congeni

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ABSTRACT

Acute otitis media (AOM) is the most common bacterial infection seen in pediatric patients, and treatment of AOM is the most common reason children receive antibiotics. AOM follows eustachian tube dysfunction, which is most often seen with a viral upper respiratory infection. Consequently, those organisms that are part of the normal flora of the nasopharynx are the major pathogens responsible for AOM. Although the cause has remained relatively constant over the last few decades, changes secondary to immunization and antibiotic pressure may now be occurring. Accurate diagnosis is essential for appropriate management. Of all the features associated with AOM, establishing appropriate therapy has recently undergone the greatest change and yet is associated with the most significant controversy. Most notably, many experts have advocated that a substantial proportion of patients might appropriately be observed and not treated with antibiotics. Only physicians who understand the natural pathogenesis and changing etiology along with the elements of appropriate diagnosis can formulate a comprehensive approach to the treatment of pediatric patients with this infection. Moreover, going forward, it seems clear that a consensus can be reached only when treatment recommendations are validated with supporting studies that have demonstrated rigorous adherence to entry criteria concerning diagnosis and patient selection.

MAGNITUDE OF THE PROBLEM, RISK FACTORS, PATHOGENESIS, AND ETIOLOGY

Virtually all children experience at least one middle ear infection during the first decade of life. AOM, however, is not limited to pediatric patients, and the disease seen in adults is similar to that seen in pediatrics with regard to pathogenesis, etiology, and treatment. Not only is AOM being diagnosed more frequently, it now accounts for approximately one quarter of all office visits. AOM is not only the most common reason children visit a physician, it is also the second most common reason for a surgical procedure in the pediatric population, behind only circumcision. The persistent effusion seen in the middle ear after an episode of AOM is responsible for significant hearing loss and delay in development of language skills.

Recurrent and persistent disease is also more commonly seen now. There are several risk factors for acute and recurrent otitis media (Box 32-1). By age 3, approximately one third of children will have been identified as otitis prone, one third as having no trouble with otitis media, and one third as occasionally infected. Those with recurrent disease contribute greatly to antibiotic usage and development of antibiotic resistance.

Anatomic, physiologic, and immunologic factors all contribute to this epidemiology. Furthermore, the eustachian tube is shorter and more horizontally positioned in children (Figure 32-1). This makes it easier for nasopharyngeal flora to gain access to the middle ear.

Eustachian tube malfunction is generally the final step that leads to nasopharyngeal organisms gaining access to the middle ear. Mucosal edema, which can lead to obstruction of the eustachian tube, impairs drainage of secretions of the middle ear. Bacteria that then gain access to the middle ear can readily multiply. Respiratory syncytial virus, parainfluenza virus, and influenza virus are the viruses most commonly responsible for causing impairment of eustachian tube function. Less commonly, other factors play a pivotal role in the development of AOM, including allergy, genetic factors (Native American or Eskimos), or immunologic factors. The role of daycare centers in the epidemiology of AOM and recurrent disease is a significant issue as well. Daycare attendance in the United States has increased substantially, and currently half of U.S. children attend a daycare center regularly. The larger the number of children in attendance at the center, the greater the likelihood of exposure to a wide variety of viral pathogens. This can obviously lead to the increase in diagnosis of AOM seen in such children (Figure 32-2).

The cause of AOM naturally reflects the pathophysiology. *Streptococcus pneumoniae*, nontypable *Haemophilus influenzae*, and *Moraxella catarrhalis* are the leading pathogens. Whereas viruses play a pivotal role in predisposing the host, middle ear taps of children with AOM rarely yield a viral pathogen alone.

Since 2000, universal immunization of all infants with conjugated pneumococcal vaccine 7-valent (PCV-7) has been recommended. Since the introduction of this vaccination, several changes in the epidemiology of AOM have been seen. There have been several benefits, although the reduction in AOM overall has been modest compared with the reduction in invasive disease caused by *S. pneumoniae*. Because the seven serotypes contained in the PCV-7 vaccine were more likely drug-resistant strains of *S. pneumoniae* (DRSP), fewer infections are caused by DRSP. Replacement of these vaccine types with infections with nontypable *H. influenzae* or nonvaccine strains of *S. pneumoniae* has been reported.

CLINICAL FEATURES AND DIAGNOSIS

Ear pain is the most specific finding associated with AOM. This finding occurs in approximately two thirds of patients; however, it is less often seen in younger patients. This may relate to an inability to adequately verbalize this manifestation. In general, symptoms in younger patients tend to be less specific, as is the

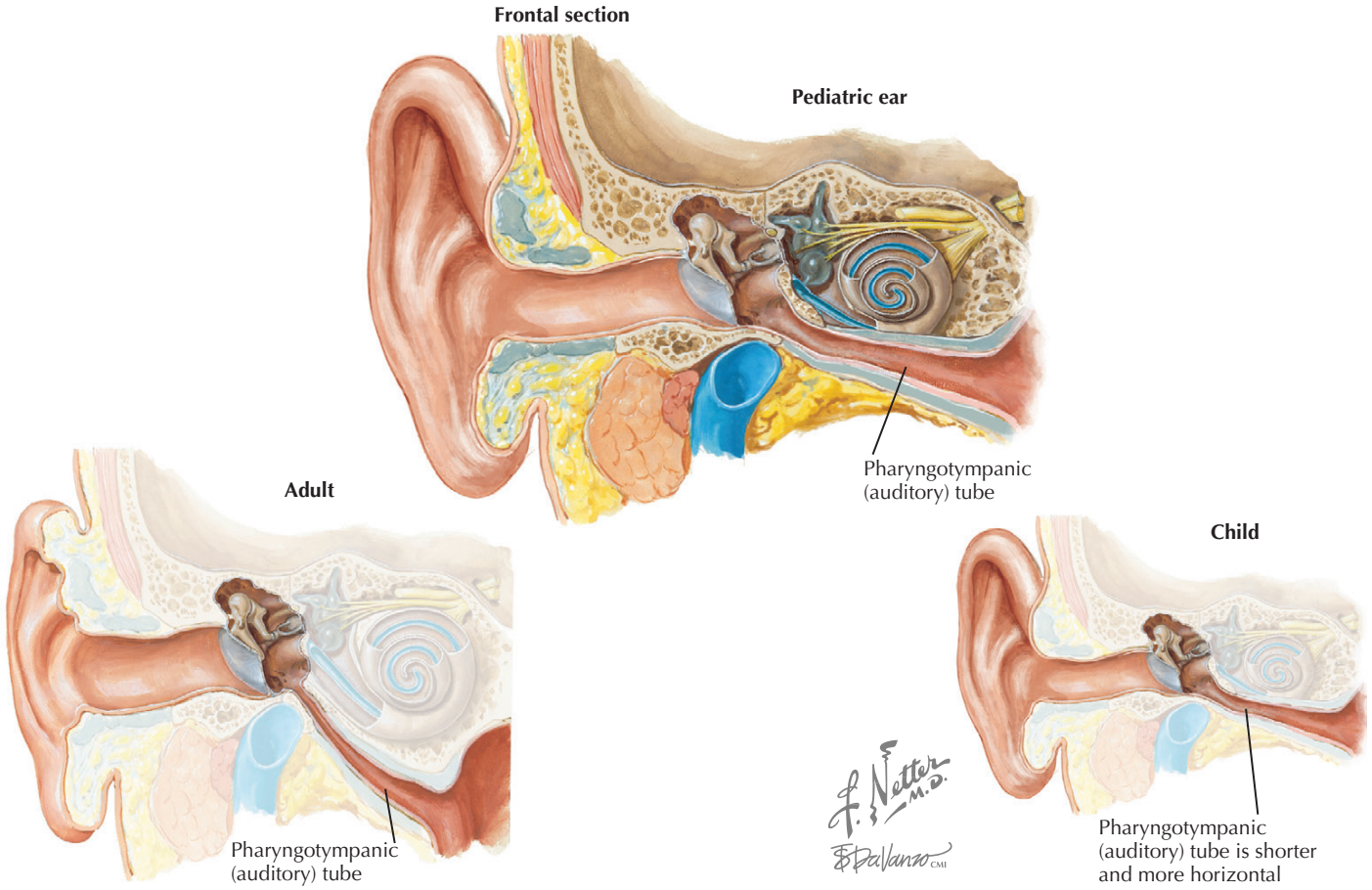


Figure 32-1 Eustachian tube.

Box 32-1 Major Risk Factors for Acute and Recurrent Otitis Media

- Onset of otitis media in infancy
- Male gender
- Sibling with recurrent acute otitis media
- Bottle feeding only
- Parents who smoke at home
- Daycare attendance
- Craniofacial anomalies

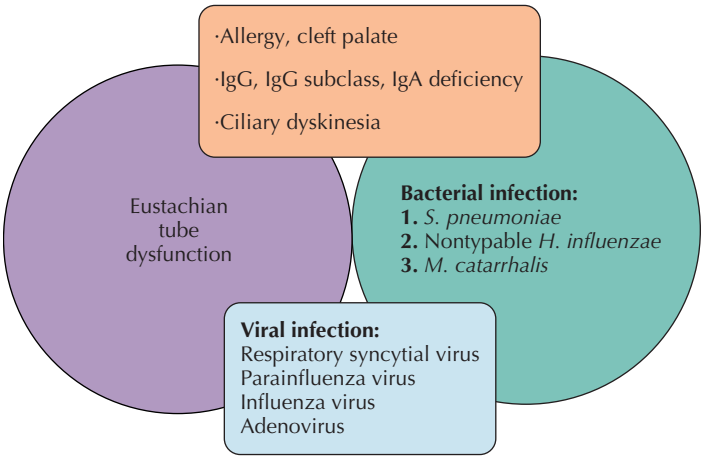
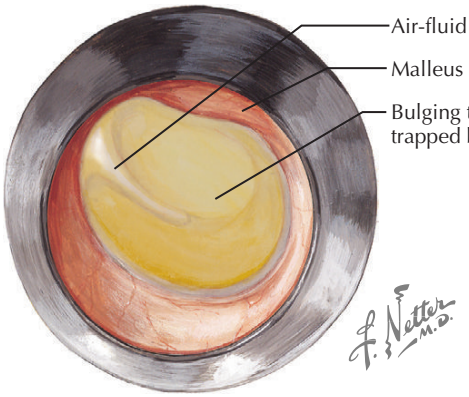


Figure 32-2 Pathogenesis of otitis media.

case in other pediatric infections. Patients younger than 1 year old are asymptomatic about half of the time. Likewise, otorrhea is a highly specific but infrequently occurring finding and is often associated with sudden relief of pain. Less specific symptoms include coryza, irritability, poor feeding, sleep disturbance, fever, hearing loss, "tugging" at the ears, and difficulty with balance.

The initial presentation is helpful in predicting the causative organism. Disease caused by *S. pneumoniae* or *S. pyogenes* is more likely to manifest suddenly, with high fever and severe otalgia. Spontaneous resolution is also less likely, and complications are more likely to occur with infection with these organisms. On the other hand, *B. catarrhalis* is associated with the greatest likelihood of spontaneous resolution and the mildest disease. Disease caused by *H. influenzae* falls between these two extremes.

Making the diagnosis of AOM can be challenging. The diagnosis is almost invariably confirmed in clinical practice by physical examination alone (Figure 32-3). Although the symptoms are often nonspecific, the patient may be very uncooperative,



Otoscopic view demonstrating clinical appearance of otitis media

Figure 32-3 Tympanic membranes.

and adequately restraining such a patient is essential. Even with adequate restraint, additional difficulties with examination may arise. The canals may be occluded with cerumen, and removal is difficult. Moreover, the practitioner must have appropriate equipment, which means adequate illumination and a proper seal with the speculum on the otoscope. Disposable specula are not as satisfactory in producing an adequate seal. Only when all these conditions are satisfied is an adequate inspection and attempt at insufflation (pneumatic otoscopy) possible.

Generally speaking, there are two parts to establishing the diagnosis of AOM: evidence of middle ear effusion and abnormalities of the tympanic membrane that indicate inflammation. Both must be present for diagnosis to be confirmed. Presence of a middle ear effusion is established by any of the following: opacification not caused by scarring, an air-fluid level, or the absence of mobility. The last finding can be demonstrated by pneumatic otoscopy, tympanogram, or acoustic reflectometry. Bulging or fullness of the tympanic membrane associated with discoloration confirms the presence of inflammation. Fullness or bulging has the highest predictive value for establishing the presence of a middle ear effusion.

The American Academy of Pediatrics (AAP) recommendations for diagnosis and management further require a history of an acute onset in order to confirm the diagnosis. However, confirming an abrupt onset can be problematic. An abrupt onset of otorrhea or otalgia may be more specific to this diagnosis, but these do not occur with sufficient regularity to make them very useful. Fever and/or irritability are frequently seen, but these symptoms occur with viral upper respiratory infections, and therefore establishing onset of disease with regard to these symptoms is usually difficult at best and so adds little in establishing the diagnosis.

Much of the difficulty associated with establishing the diagnosis of AOM results from the fact that a middle ear effusion that is not purulent can be seen as part of a viral upper respiratory infection. Such an effusion is referred to as *otitis media with effusion* (OME). This can also occur before AOM or after therapy for AOM. Antibiotic therapy is of no benefit for the patient with OME, and distinguishing OME from AOM can be especially challenging.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Several important concepts need to be considered when deciding on the appropriate management of the patient with AOM. The most important concept that drives the entire discussion is that AOM is so often self-limited. With or without appropriate antibiotic treatment, patients generally improve. This is referred to as the "Pollyanna phenomenon." This greatly complicates the interpretation of studies that look to compare different antibiotic regimens. When a clinical endpoint is used (e.g., physical examination of the ear), significant differences are not seen even when a placebo-treated group is included, unless very large numbers of subjects are included. Demonstrating sterilization of the middle ear by using a repeat ear tap is therefore a preferred method of studying treatment options for patients with otitis media. These issues need to be kept in mind when studies are evaluated.

The other major issue that must be conceded early on is that it is likely that many of the studies regarding AOM may be flawed. Studies that rely only on physical examination findings for establishing the diagnosis must begin with a stringent definition of AOM. Confirmation of the diagnosis, skill on the part of the enrolling physician, and the presence of sufficient patients at risk for failure (such as those younger than 2 years of age) are also essential. Developing recommendations from flawed studies is particularly problematic with AOM because spontaneous resolution is so common. Finally, the goal or goals of antibiotic therapy must be clearly understood. Complications such as mastoiditis or cholesteatoma are rare, even when antibiotic therapy is initially withheld, as long as patients are followed closely and appropriate therapy is offered if symptoms do not improve (i.e., "watchful waiting"). Younger patients, however, being at greater risk for complications and failure, will generally demonstrate a greater benefit from antibiotic therapy. Other outcomes, such as duration of pain, must also be considered when considering withholding of antibiotics. In other words, the assumption that antibiotic therapy results in more rapid resolution of pain, as some studies suggest, might shift the equation toward antibiotic therapy for some physicians.

Short- and long-term prognoses are good with or without antibiotic therapy. Having said that, studies that have included a placebo group consistently demonstrate lower failure rates in the group treated with antibiotics. In most patients treated with antibiotics, recurrent disease is caused by new pathogens or new serotypes of the same pathogen. The major severe complications include mastoiditis, facial palsy, otorrhea, brain abscess, cholesteatoma, and epidural abscess. All of these complications have dramatically decreased in the antibiotic era, and no convincing data have emerged to suggest that that has changed even with more children having antibiotics withheld ("watchful waiting").

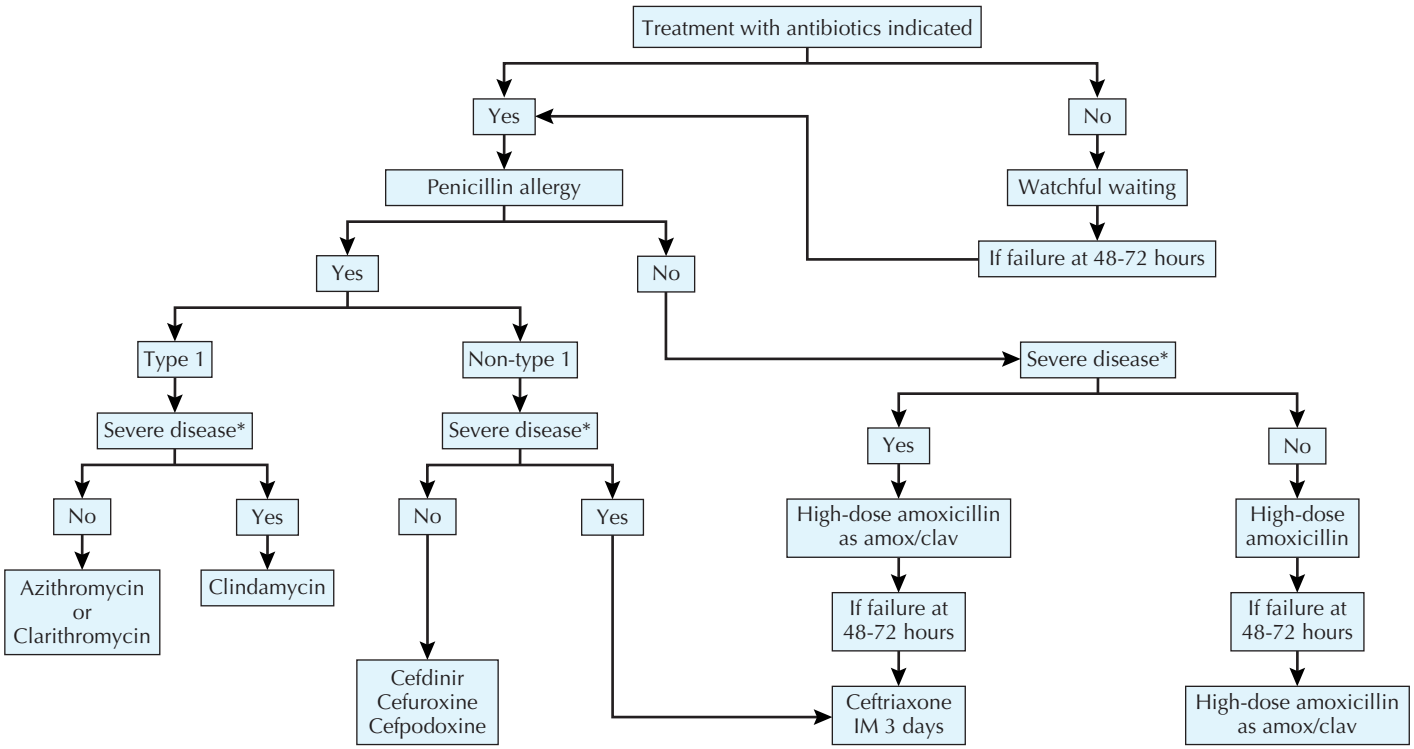
Antibiotic Therapy

Amoxicillin (80 to 90 mg/kg/day) has generally been the mainstay of treatment for patients with AOM. Advantages include low cost, acceptable taste, and the safety of a β-lactam. Currently in the United States approximately 10% or more of *S. pneumoniae* isolates are resistant to amoxicillin owing to alteration of penicillin-binding proteins. One third of the *H. influenzae* and virtually all of the *B. catarrhalis* strains are resistant because of production of β-lactamase. In patients with severe disease, a high likelihood of resistant organisms, failure of treatment with amoxicillin previously, or a history of amoxicillin allergy, alternative agents are considered.

In patients with severe disease, temperature greater than 39° C, or severe otalgia or in patients needing therapy for β-lactamase–producing strains, high-dose amoxicillin-clavulanate (80 to 90 mg/kg of amoxicillin per day in two doses) is generally preferred. If, as noted previously, *H. influenzae* is in fact becoming more prevalent with widespread use of the pneumococcal vaccine, earlier use of a β-lactamase stable agent such as amoxicillin-clavulanate might make good sense. For patients with non–type 1 allergies to penicillins, cephalosporins including cefuroxime, cefpodoxime, or cefdinir may be used. Injectable ceftriaxone may also be useful for patients in whom these regimens fail. For patients with a type 1 history of allergy to a penicillin, azithromycin, clarithromycin may be used. The use of a sulfonamide, frequently along with erythromycin, may be used in this circumstance as well. Clindamycin may be used if the offending pathogen is known to be *S. pneumoniae* (Figure 32-4).

Using regimens that provide appropriate pharmacokinetic and pharmacodynamic parameters is greatly preferred. This means selecting appropriate agents and using appropriate doses for the offending pathogen. β-Lactam antibiotics that achieve levels greater than the minimum inhibitory concentration for over 40% of the dosage interval are more likely associated with a bacteriologic cure. Virtually all patients who experience an early bacteriologic cure improve more rapidly and are much less likely to experience a relapse.

Most patients with AOM are treated with a 10-day course of treatment, excluding parenteral therapy. Although compelling evidence is not available, most experts recommend the standard 10-day course for patients younger than 6 years of age, patients



*Severe disease is defined by temperature ≥39° C and/or severe otalgia.

Figure 32-4 Acute otitis media treatment algorithm. *(Data from American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media: diagnosis and management of acute otitis media,* Pediatrics *113:1451-1465, 2004.)*

with severe disease, and patients with immunologic disorders. Other patients can probably be treated with 5 to 7 days of treatment.

Observation without the Use of Antimicrobial Agents

Because the benefit of antibiotic therapy appears to be modest, recent recommendations have offered options and strategies that do not initially employ antibiotic therapy. The guidelines developed by the AAP and American Academy of Family Practice look at three characteristics of patients with AOM that are useful in establishing a strategy for treatment. These include age of the patient, severity of the disease, and certainty of the diagnosis. It is important to understand that a consensus does not yet exist as to how robust the evidence is for using this approach. A consensus also does not exist relative to what the stated goal is in treating patients with AOM. If the goal is to reduce antibiotic use in the general population, some would argue that this can best be accomplished by reducing antibiotic use in patients with viral disease. If modest clinical improvement with regard to pain is the goal of the practitioner, the benefit of antibiotic therapy might be seen in a different light, and withholding of antibiotics would be a less attractive option. These recommendations make it clear that medications to reduce pain (analgesics) should be offered if pain is present. It is also clear in the recommendations that the observation or "watchful waiting" option is appropriate only when follow-up can be ensured so that antibiotics can be offered if symptoms persist or worsen beyond 48 to 72 hours.

The decision to withhold antibiotic therapy should be reserved for patients otherwise healthy, 6 months to 2 years of age, with nonsevere illness and uncertain diagnosis and for children older than 2 years of age without severe symptoms or with uncertain diagnosis.

Special Considerations

Because the conjugate pneumococcal vaccine has been widely used since 2000, some investigators have reported an increase in AOM caused by *H. influenzae* along with a decrease in otitis media secondary to *S. pneumoniae*. This may lead some to consider use of a β-lactamase stable drug as an earlier option. In addition since 2000, concern for emergence of *S. pneumoniae* serotypes not included in the vaccine have increased. Recently, serotype 19A, a multidrug-resistant strain of *S. pneumoniae*, has emerged. Serotype 19A should be considered as a potential pathogen in patients in whom conventional therapy has repeatedly failed. Tympanocentesis to confirm 19A as the caused should be considered. Currently no licensed drug is available for use in pediatric patients, including injectable ceftriaxone, that would reliably treat them. Hence, confirmation that serotype 19A is, in fact, the pathogen must be undertaken.

PREVENTION

Several strategies should be considered in the pediatric patient with recurrent AOM. The first step is developing reliable data with regard to the frequency of the problem. If intervention is necessary, modifying environmental or host risk factors is generally the appropriate starting place. Encouraging breastfeeding, reducing pacifier use, and reducing parental smoking in the home may all provide some benefit. However, the most significant intervention probably will occur if out-of-home daycare or child care is used. Studies have consistently demonstrated benefit to moving the child to a care center with fewer children. When parents cannot make alternative arrangements, they should be advised that some benefits may actually occur as a result of attendance at an out-of-home center for child care.

After environmental risk factors have been evaluated, several medical interventions should be considered in the otitis-prone child. Appropriate immunization has minimal risk and the potential for significant benefit. Currently all children 6 months to 18 years of age should be immunized with an influenza vaccine annually. This has been shown to reduce subsequent episodes of AOM. Universal immunization with the conjugate pneumococcal vaccine is also expected to provide some benefit to the otitis-prone patient. Chemoprophylaxis is also a consideration in some of these patients. Amoxicillin, 40 mg/kg/day in one or two doses, is the regimen generally used. The benefit for prevention of otitis media is generally felt to be modest and carries the risk of increasing antibiotic resistance. Use of second-line therapies for breakthrough disease would likely be recommended.

A comprehensive discussion of the role of surgical options for such patients is beyond the scope of this presentation. Placement of tympanostomy tubes has the greatest benefit in patients with recurrent AOM associated with persistent middle ear effusion. Adenoidectomy has also been of modest benefit. The rationale revolves around the idea that swollen adenoids may harbor bacteria that can gain access to the middle ear from that location.

EVIDENCE

Craig WA, Andes D: Pharmacokinetics and pharmacodynamics of antibiotics in otitis media, *Pediatr Infect Dis J* 15:255-259, 1996. *This review presents the evidence and basis for making decisions regarding antibiotic selection for AOM. The pharmacokinetic-pharmacodynamic model is used to establish the basis for drug selection.*

Pichichero ME, Casey JR: Emergence of a multiresistant serotype 19A pneumococcal strain not included in the 7-valent conjugate vaccine as an otopathogen in children, *JAMA* 298:1772-1778, 2007. *These authors review the presentation and approach to the patient with AOM secondary to* S. pneumoniae *serotype 19A.*

ADDITIONAL RESOURCES

American Academy of Pediatrics Subcommittee on Management of Acute Otitis Media: diagnosis and management of acute otitis media, *Pediatrics* 113:1451-1465, 2004. *This is the definitive review for recommendations regarding AOM. The committee presents the evidence for the views expressed.*

Wald ER: Acute otitis media: more trouble with the evidence, *Pediatr Infect Dis J* 22:103-104, 2003. *This is an editorial detailing problems with the evidence that led to the recommendations of the AAP and AAFP.*

Wald ER: To treat or not to treat, *Pediatrics* 115:1087-1089, 2005. *This is an editorial that details an alternative view on reasons to treat or withhold antibiotics in patients with AOM.*

Pharyngitis

John R. Bower

33

ABSTRACT

"Sore throat" or pharyngitis is one of the most frequent complaints of patients in the acute care setting, accounting for nearly 7 million pediatric and 6 million adult visits each year. On the surface, pharyngitis would appear to pose few challenges to the clinician; the site of infection is both visible and accessible for inspection and culture, and the majority of pharyngeal pathogens are self-limiting respiratory viruses. Unfortunately, the diagnosis and management of acute pharyngitis is complicated by the 10% to 30% of cases caused by bacterial pathogens, particularly group A beta-hemolytic streptococci (GAS). Concerns over the risk of suppurative and nonsuppurative complications associated with GAS pharyngitis have fueled the widespread practice of empirical antimicrobial therapy. However, the consequences of antimicrobial overuse, measured by cost, adverse events, and bacterial resistance, have refocused attention on the need for targeted therapy based on an appreciation of the epidemiology and diverse clinical presentations of acute pharyngitis.

EPIDEMIOLOGY

Viral Causes of Pharyngitis

Acute pharyngitis is most often caused by a virus. Depending on the season and the patient's age, 70% to 90% of acute episodes are viral and involve a wide array of common viruses (Table 33-1). By far, the most common virus associated with pharyngitis is the common cold agent, rhinovirus. Outbreaks of rhinovirus usually begin in September, with the start of school. The virus efficiently passes from children to adults. A second peak of rhinovirus activity appears in the spring.

Adenovirus ranks second among viral causes of pharyngitis in both children and adults. During late winter and early spring approximately 20% of pharyngitis cases may involve adenovirus, especially in children younger than 5 years of age. Young adults, including military recruits, constitute another high-incidence group. Childhood infections typically involve serotypes 1, 2, 5, and 6, whereas adults are susceptible to serotypes 3, 4, and 7. A unique form of adenoviral infection is pharyngoconjunctival fever, which usually occurs in children; exposure to contaminated swimming pools may be associated with community outbreaks of the disease.

Enteroviruses are a common cause of pharyngitis in the late summer and fall months. Group A coxsackieviruses are most often associated with herpangina, whereas coxsackievirus A16 and enterovirus 71 are the primary agents of hand, foot, and mouth disease. Group B coxsackieviruses and echoviruses are responsible for nonspecific febrile illnesses, pharyngitis, and aseptic meningitis.

Herpes simplex virus (HSV) has long been recognized as a cause of pharyngitis in children and has also been reported in young adults. Among college students with sore throat, HSV is the third most commonly identified viral pathogen, responsible for up to 6% of cases, and is predominantly type 1. Rare cases of necrotizing tonsillitis caused by HSV have also been observed.

Bacterial Causes of Pharyngitis

GAS is not only the most common bacterial pathogen, but also the most likely to result in complications of pharyngitis. In children, GAS causes 10% to 30% of cases of pharyngitis, with children aged 5 to 15 years at greatest risk for infection and complications. In adults, GAS accounts for 5% to 10% cases. Winter months are associated with an increase in GAS pharyngitis in people of all ages, but especially in children when it can be found in up to 50% of cases.

Although less common than GAS, other bacterial causes of pharyngitis should be considered. Groups C and G streptococci are the most common non–group A streptococci associated with pharyngitis, accounting for 2% to 6% of cases in children and young adults. The true incidence of groups C and G streptococci is unclear owing to the frequency of normal colonization. In college students, group C *Streptococcus* has been identified in 26% of students with pharyngitis compared with 11% of controls, supporting its role as a pathogen but underscoring the frequency of normal colonization. Of importance, there is no evidence that pharyngitis caused by non–group A streptococci poses a concern with regard to acute rheumatic fever (ARF). Rare reports linking group C streptococcus to poststreptococcal glomerulonephritis have not been validated. *Arcanobacterium haemolyticum* is found in less than 3% of cases of pharyngitis, although a higher incidence has been observed in adolescents and young adults.

Neisseria gonorrhoeae should be considered in individuals with pharyngitis and a history of orogenital sex with a partner at risk for gonorrhea. Rates of *N. gonorrhoeae* pharyngitis vary according to a patient's risk factors and community prevalence but are generally highest in adolescents and young adults. The isolation of *N. gonorrhoeae* from a prepubescent child must always raise suspicion for sexual abuse; however, care should be taken to verify *N. gonorrhoeae* because nonpathogenic *Neisseria* species are frequently present as normal flora in the oropharynx.

Although found as normal flora, the anaerobe *Fusobacterium necrophorum* is associated with a variety of head and neck infections and potentially life-threatening septic complications. In patients with pharyngitis, *F. necrophorum* appears more commonly among 16- to 20-year-olds, with a reported age range of 13 to 57 years.

The atypical agents, *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*, are commonly associated with lower

Table 33-1 Microbial Causes of Pharyngitis by Type of Pathogen

Bacterial	Group A streptococci
	Groups C, G streptococci
	Neisseria gonorrheae
	Arcanobacterium haemolyticum
	Fusobacterium necrophorum
	Corynebacterium diphtheriae
Viral	Rhinovirus
	Coronavirus
	Adenovirus
	Parainfluenza virus types 1, 2, and 3
	Influenza A and B virus
	Coxsackievirus
	Herpes simplex virus
	Epstein-Barr virus
	Cytomegalovirus
	Human immunodeficiency virus
Atypical agents	*Mycoplasma pneumoniae*
	Chlamydophila pneumoniae

Data from Bisno AL, Gerber MA, Gwaltney JM Jr, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis, Clin Infect Dis *35:113-125, 2002.*

Table 33-2 Clinical and Epidemiologic Characteristics of Group A Beta-Hemolytic Streptococcal Pharyngitis

Features suggestive of group A *Streptococcus* as causative agent	Sudden onset
	Sore throat
	Fever
	Headache
	Nausea, vomiting, and abdominal pain
	Inflammation of pharynx and tonsils
	Patchy discrete tonsils
	Tender, enlarged anterior cervical nodes
	Patient aged 5-15 years
	Presentation in winter or early spring
	History of exposure
Features suggestive of viral cause	Conjunctivitis
	Coryza
	Cough
	Diarrhea

Data from Bisno AL, Gerber MA, Gwaltney JM Jr, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis, Clin Infect Dis *35:113-125, 2002.*

respiratory tract infections and suspected to be the primary cause of mild pharyngitis in up to 17% of patients with sore throat and a co-pathogen in an additional 14%.

Historically, *Corynebacterium diphtheriae* has been one of the most important causes of tonsillar disease. Vaccination for diphtheria has virtually eliminated the organism in the United States; however, the disease remains endemic in many developing countries, with outbreaks also reported among the New Independent States of the former Soviet Union, the Russian Federation, and most recently Haiti.

Noninfectious Causes of Pharyngitis

Noninfectious diseases may produce inflammation of the posterior pharynx. Among these processes are Stevens-Johnson syndrome; toxic shock syndrome; Kawasaki disease; Behçet's syndrome; aphthous stomatitis; and periodic fever, pharyngitis, adenopathy, and aphthous stomatitis syndrome (PFAPA). PFAPA usually occurs in children younger than 5 years of age and is frequently misdiagnosed as recurrent tonsillitis.

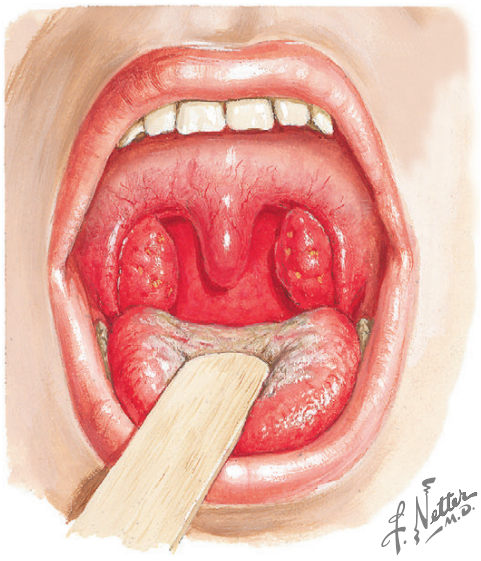


Figure 33-1 Streptococcal pharyngitis.

DIAGNOSIS

Clinical Manifestations

The principal challenge in managing pharyngitis is distinguishing viral from bacterial causes, particularly GAS. Pharyngitis is broadly defined as mucous membrane inflammation either localized to the posterior pharynx or contiguous with the adjacent membranes of the posterior nares or larynx. Differences in the extent of pharyngeal inflammation and in accompanying signs and symptoms help distinguish between GAS and viruses (Table 33-2). Patients with GAS most often demonstrate sudden onset of sore throat, marked pain with swallowing, and fever (Figure 33-1). Other signs and symptoms indicative of GAS include headache, nausea, vomiting, and the absence of cough and coryza. Findings that favor viral pathogens include conjunctivitis, punctate ulcerative tonsillar lesions, and stomatitis (Figure 33-2). Certain strains of GAS can trigger scarlet fever by elaborating an erythrogenic toxin that induces a bright, fine, maculopapular rash. Starting over the neck, the rash extends to the trunk and extremities and is particularly prominent over flexural creases and the perineum. After several days the rash fades and is followed by a fine desquamation as seen with sunburn. The lingual papillae become quite prominent, producing the characteristic "strawberry tongue" appearance.

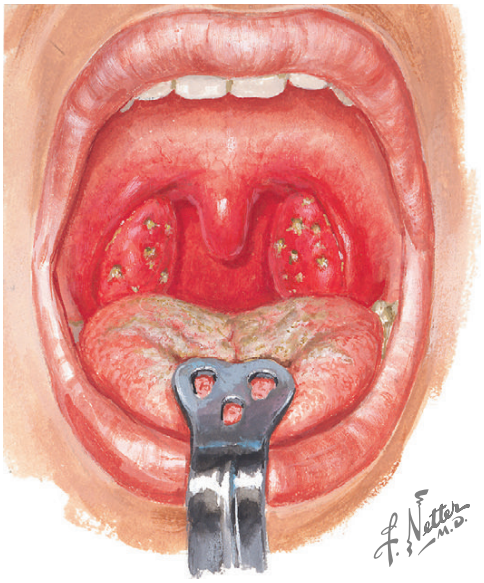


Figure 33-2 Viral pharyngitis. More discrete punctuate pattern versus the strep pharyngitis.

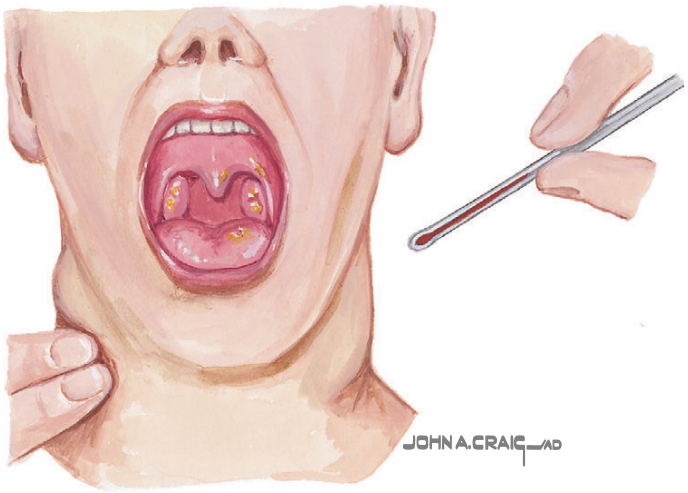


Figure 33-3 Epstein-Barr virus pharyngitis.

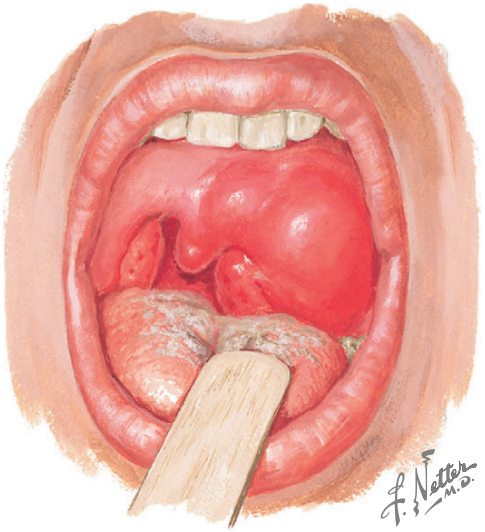


Figure 33-4 Peritonsillar abscess.

Unfortunately, even with strict clinical criteria GAS can be predicted with only 50% accuracy. GAS may also be present in the absence of marked pharyngeal inflammation. The role of GAS in patients with mild pharyngitis is uncertain. Although it is clear that GAS can result in mild or even clinically inapparent infection, based on rises in anti–streptolysin O, it appears that the majority of patients with mild respiratory symptoms are at low risk for ARF and likely represent a GAS carrier state.

The clinical diagnosis of GAS pharyngitis is hampered by the presence of other pathogens that elicit similar signs. Groups C and G streptococci and *A. haemolyticum* cause exudative pharyngitis, adenopathy, and fever that are clinically indistinguishable from GAS. Strains of *A. haemolyticum* even induce a scarlatiniform rash similar to scarlet fever. Viruses may also mimic the clinical findings of GAS pharyngitis. Adenoviral pharyngitis causes tonsillar exudate, adenopathy, and fever over half of the time, mostly in children. More readily distinguished from GAS is adenoviral pharyngoconjunctival fever, which usually manifests as a unilateral follicular conjunctivitis, though it progresses to the other eye one fourth of the time. Epstein-Barr virus (EBV) manifests with acute onset of sore throat, fever, and cervical lymphadenopathy, and in one half of cases the pharyngitis is exudative (Figure 33-3). Occasionally, palatal petechiae appear, making EBV even more difficult to distinguish from GAS pharyngitis. Splenomegaly (present in 50% of patients), generalized lymphadenopathy, and periorbital edema, when present, provide clinical evidence in favor of EBV. HSV pharyngitis may manifest with fever, exudative pharyngitis, and cervical lymphadenopathy. In college students diagnosed with HSV pharyngitis, only one third demonstrated lesions typical of HSV. Herpetic gingivostomatitis is common in young children and causes vesicular lesions involving the lips, gingiva, and tongue; however, very early in the course patients may have lesions limited to the posterior pharynx.

Clinically milder forms of pharyngitis, lacking exudate and marked edema, are usually caused by viruses. Enteroviruses frequently cause mild pharyngitis as part of a nonspecific febrile illness. More characteristic of enteroviruses is herpangina, which manifests with fever and discrete vesicular lesions involving the soft palate, tonsils, and surrounding posterior pharynx. Lesions are generally localized to the proximal portion of the oral cavity. Hand, foot, and mouth disease characteristically appears with vesicular lesions over the palms and/or soles, but they may be limited to the mouth and throat. Influenza A and B are characterized by the abrupt onset of fever, sore throat, myalgia, malaise, and dry cough. The rapid onset of cough and constitutional signs and symptoms, coinciding with known influenza activity in the community, is usually sufficient to suggest influenza.

Complications

Peritonsillar abscess, or quinsy, is the most frequent suppurative complication associated with pharyngitis (Figure 33-4). It occurs

most often in adolescents and young adults and is rare in younger children. Organisms associated with peritonsillar abscesses include GAS and anaerobes, often present as mixed infection. Patients appear unwell with dysphagia, muffled "hot potato voice," and fetid breath. The soft palate is displaced on the affected side with accompanying deviation of the uvula. Lateral pharyngeal abscesses may occur secondary to pharyngitis or peritonsillar abscess. Patients often have swelling over the lateral aspect of the neck and restriction in neck movement. Asymmetry of the posterior pharyngeal wall may be present, but its absence does not exclude the diagnosis. Pharyngeal infections with *F. necrophorum* may extend locally to cause deep neck infection, septic thrombophlebitis, and potentially life-threatening septic embolization (Lemierre syndrome).

Serious nonsuppurative complications are most always a result of GAS and include ARF and poststreptococcal glomerulonephritis (Figure 33-5). ARF occurs most commonly in children 5 to 14 years of age and is rare in children under 3 and in adults over 40 years of age. Despite a marked decline in the prevalence of ARF, sporadic outbreaks continue to appear. Poststreptococcal glomerulonephritis occurs most often in children and typically appears 10 days after infection and occurs only with nephritogenic strains of GAS.

Laboratory Diagnosis

Pivotal to the care of patients with pharyngitis is the accurate identification of infection caused by GAS. Whereas patients infected with other bacterial pathogens, such as non–group A streptococci, may benefit from antimicrobial therapy, they do not merit widespread screening or empirical antimicrobial treatment strategies. The problem is that GAS pharyngitis cannot be diagnosed by clinical evidence alone. Even experienced physicians are accurate only 50% of the time when examining patients with exudative pharyngitis. Despite this limitation, clinical judgment retains an important role in pharyngitis diagnosis and management. Clinical scoring tools, such as the modified Centor score, have proven useful in identifying patients at low risk for GAS (Table 33-3). Patients with clinical scores of 0 to 1 are at low risk for GAS and require no further testing and no antimicrobial treatment. More complicated is the approach to patients who are at less low risk for GAS, such as those with clinical scores ≥2. Patients with modified Centor scores of ≥2 are positive for GAS in only 15% to 50% of patients. Reliance on clinical scoring tools alone can result in up to 40% of patients receiving an unnecessary antimicrobial. In an effort to further aid clinicians in improving GAS diagnosis, several guidelines for the diagnosis and management of pharyngitis have been advanced. Inherent to these pharyngitis guidelines is a basic diagnostic and management strategy that still relies on clinical judgment in avoiding the errors of overtreatment and undertreatment.

The basic diagnostic and management strategy used for patients with sore throat begins with the clinician establishing whether the presentation is consistent with uncomplicated acute pharyngitis and then judging whether the patient is at low or higher risk for GAS based on history and physical examination (Figure 33-6). This risk assessment for GAS may use a clinical score or rely on a general pattern of clinical and epidemiologic findings (see Tables 33-2, 33-3, and 33-4). Patients judged at low risk for GAS can be managed with symptomatic care and require no further evaluation.

Patients judged at higher risk for GAS require laboratory testing to confirm or exclude the presence of GAS, specifically the throat culture and rapid antigen detection test (RADT) (Figure 33-7). Because of the high specificity of RADTs, culture and antigen detection are equivalent in confirming GAS. Less certain is the role of RADTs in excluding GAS infection. Sensitivity among RADTs varies from 66% to 95%, leading to the general recommendation that negative RADT results should be confirmed by throat culture. Even RADTs using optical immunoassay, which offer the potential for improved sensitivity, vary widely in reported sensitivity (75% to 95%). Consequently, recommendations that waive the need to confirm a negative RADT result by throat culture should be based on an individual laboratory's internal validation of RADT sensitivity.

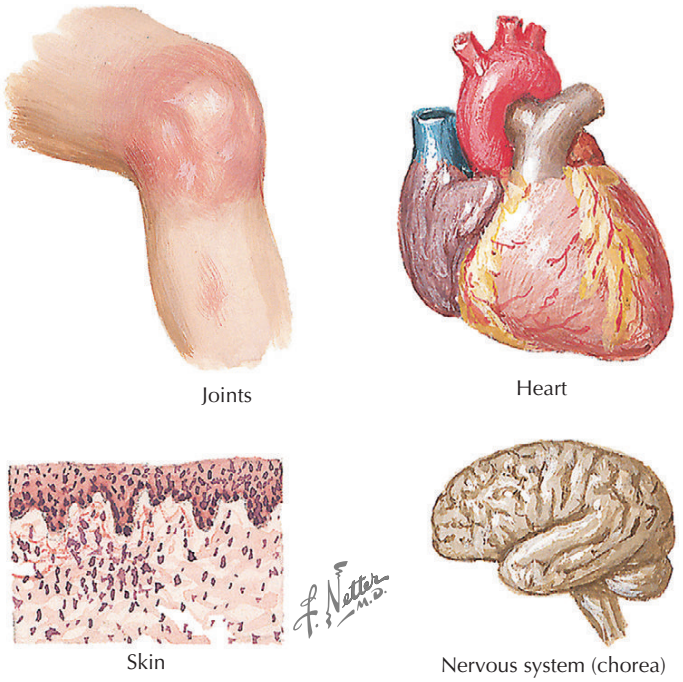


Figure 33-5 Acute rheumatic fever.

Table 33-3 Modified Centor Score

CRITERIA	POINTS
Temperature >38° C	1
Absence of cough	1
Swollen, tender anterior cervical nodes	1
Tonsillar swelling or exudate	1
Age	
3-14 years	1
15-44 years	0
45 years or older	−1

Adapted from McIsaac WJ, Kellner JD, Aufricht P, et al: Empirical validation of guidelines for the management of pharyngitis in children and adults, JAMA *291:1587-1595, 2004.*

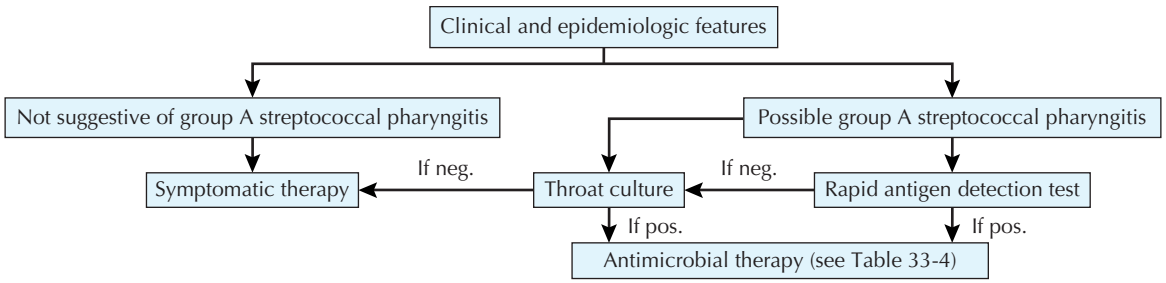


Figure 33-6 Risk assessment for group A streptococci. *(From Bisno AL, Gerber MA, Gwaltney JM Jr, et al: Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis,* Clin Infect Dis *35:113-125, 2002.)*

Table 33-4 Antimicrobial Therapy for Group A Beta-Hemolytic Streptococcal Pharyngitis

DRUG	DOSE	DURATION
Oral		
Penicillin V	250 mg bid or tid for children 250 mg tid or qid for adolescents and adults 500 mg bid for adolescents and adults	10 days
Intramuscular		
Penicillin G: benzathine	600,000 units for patients ≤27 kg (60 lb) 1.2 million units for patients >27 kg	1 dose
Penicillin G: benzathine and procaine mixtures*	Varies with formulation	1 dose
Patients Allergic to Penicillin		
Erythromycin	Varies with formulation	10 days
First-generation cephalosporin†	Varies with formulation	10 days

*Dose should be based on benzathine component.
†Only if no immediate type I hypersensitivity to β-lactam.

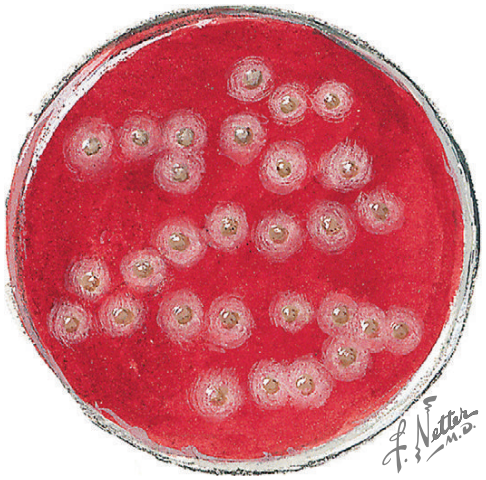


Figure 33-7 Example of group A *Streptococcus* on plate with beta-hemolysis.

Equally important to the accuracy of a test is the adequacy of the sample. Obtaining a proper throat swab, especially in children, is frequently challenging and time-consuming. An adequate specimen for testing requires that the swab sample both tonsils and the posterior pharyngeal wall. Results obtained from swabs obtained by a blind pass have little to no value if they are negative for GAS.

Testing for pathogens other than GAS in uncomplicated acute pharyngitis is rarely required. The finding of non–group A streptococci in a patient with uncomplicated pharyngitis is rarely helpful, as it may represent normal flora. In GAS-negative patients with findings suggestive of *A. haemolyticum*, a routine throat culture may not be sufficient to identify the organism. In patients with persistent sore throats, cultures for *F. necrophorum* require an anaerobic throat culture. All specimens for virus isolation should stipulate the virus requested (e.g., HSV, enterovirus, or adenovirus) and should be transported in the appropriate viral medium at 4° C. All concern regarding *C. diphtheriae* should be addressed to an infectious disease specialist and local health officials.

TREATMENT

Symptomatic patients with laboratory confirmation of GAS should receive antimicrobial therapy (see Table 33-4). Benefits of treatment include prevention of ARF, a decrease in suppurative complications, and a shortened course of illness. Penicillin remains the drug of choice for treatment of GAS pharyngitis because of its narrow spectrum of activity, proven record of efficacy, safety, and cost. Penicillin V is the preferred oral choice; however, for children requiring an oral suspension, amoxicillin is an acceptable alternative because of its palatability. Ampicillin offers no advantages over penicillin V. Although injectable penicillins offer single-dose convenience, their routine use is uncommon and affords no other advantage except in ensuring compliance. Oral penicillin and amoxicillin are effective with either twice-daily or three-times-daily administration, and the duration is 10 days. Shorter courses may be effective but are not recommended. Patients allergic to penicillin without a history of immediate or type I hypersensitivity to penicillin can be treated with a cephalosporin or macrolide. The use of erythromycin,

clarithromycin, and azithromycin should be limited to individuals allergic to penicillin because of increasing reports of macrolide resistance among strains of GAS in the United States and worldwide. Starting appropriate antimicrobial therapy within 9 days of disease onset is sufficient to prevent ARF.

GAS remains uniformly susceptible to penicillin. However, cephalosporins have been promoted as first-line therapy for GAS pharyngitis based on data indicating their superiority over penicillin in eradicating GAS from the oropharynx. According to meta-analysis, eradication rates in children for penicillin and cephalosporins are 81% and 93%, respectively, whereas clinical cure rates are 86% and 94%, respectively. Among adults, however, there are no clinically significant differences between penicillin and cephalosporins (87% versus 92% eradication; 90% versus 95% clinical cure). The validity of these comparisons continues to be debated and both the Infectious Diseases Society of America (IDSA) and American Academy of Pediatrics (AAP) continue to recommend penicillin as first-line therapy, although cephalosporins may be considered as an alternative choice.

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ADDITIONAL RESOURCE

The IDSA guidelines for the diagnosis and management of GAS pharyngitis are available at www.idsociety.org, in the guidelines section.

Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Sanjay Sethi

34

ABSTRACT

Exacerbations are episodes of increased respiratory and systemic symptoms in patients with underlying chronic obstructive pulmonary disease (COPD), usually induced by bacterial and/or viral tracheobronchial infection. These episodes are a major contributor to the morbidity, and in advanced disease to the mortality, associated with COPD. A careful clinical evaluation with selected application of diagnostic tests should be followed by individualized management including supportive care, bronchodilators, antibiotics, and corticosteroids. Exacerbations can be partially prevented with current treatment of COPD. Advances in our understanding of exacerbation mechanisms are still required to optimize outcomes and initiate effective preventative measures.

DISEASE BURDEN

COPD is a universal disease related primarily to tobacco smoking but also to other noxious smoke and fume exposures. The current estimate of prevalence in adults is about 10%, and COPD is the sixth leading cause of death worldwide. Almost all patients with COPD experience repeated episodes of worsening respiratory symptoms and lung function, termed *exacerbations*. Exacerbation incidence increases with worsening airflow obstruction. Exacerbations are major reasons for healthcare usage in patients with COPD, and in advanced disease major causes of hospitalization and mortality. They are associated with worsening health status and airflow obstruction. Consequently, adequate clinical management and prevention of exacerbations have become important parts of managing this disease.

RISK FACTORS

The risk factors for development of COPD are well defined; however, there is a wide variation in the frequency of exacerbation occurrence in patients with COPD, and the mechanisms are currently poorly understood. Frequency of exacerbations does increase with worsening lung function. In milder stages of COPD, the average frequency is one episode every 4 years but increases to about one per year in moderate disease and to two or more episodes per year in severe disease. Infection with bacteria or viruses is the underlying cause of the majority of exacerbations. Furthermore, it is clear that in COPD there is increased susceptibility to bacterial (and possibly viral) infection of the lower respiratory tract. The normal lung has a multifaceted defense system to maintain sterility of the lower airways in spite of repeated exposure to infectious organisms by inhalation or microaspiration. Impairment of specific innate lung defense mechanisms determines the frequency of exacerbations, and those that are currently being investigated include reduced mucociliary clearance, release of antimicrobial polypeptides into the airway, and macrophage phagocytic function.

CLINICAL FEATURES

Exacerbations are defined by increased respiratory symptoms, the cardinal ones being dyspnea, increased sputum production, and sputum purulence (Figure 34-1). Additional respiratory symptoms include cough, chest discomfort, and wheezing. Systemic symptoms are common and include fatigue and sleep disturbance, with fever seen in only 20% of episodes. Symptom intensity has to exceed day-to-day variability, and symptoms should be present for at least 24 hours and up to 2 weeks before presentation. The severity of an exacerbation depends on the underlying lung disease as well as the magnitude of the acute episode. Findings on examination can therefore range from minimal findings to respiratory failure. Chest examination usually reveals diminished breath sounds, with wheezing and localized rales seen in a few patients. Findings consistent with lung consolidation or pleural effusion should prompt a search for alternative diagnoses as discussed later. Exacerbations with severe underlying COPD can manifest as respiratory distress and alteration of mental status because of hypercapnia and consequent acute respiratory acidosis.

DIAGNOSTIC APPROACH

Tracheobronchial infection with bacteria or a virus is responsible for up to 80% of exacerbations. Such infection induces airway inflammation, mucus hypersecretion, and bronchial narrowing, which in turn result in the classic clinical manifestations. However, symptoms that resemble an exacerbation can occur in patients with COPD because of other clinical entities. Most important among these differential diagnoses are pneumonia and congestive heart failure. Other important but less common clinical entities include pulmonary embolism, other systemic infections, and noncompliance with medications.

Because of wide variations in severity and clinical findings, the diagnostic approach needs to be specifically tailored to each exacerbation. In mild to moderate exacerbations, when the expectation is that outpatient treatment will suffice, and when the other possible diagnoses are unlikely based on clinical evaluation, no further diagnostic testing is necessary. Chest x-ray examination is indicated if there is clinical suspicion for pneumonia or congestive heart failure (Figure 34-2). A spiral computed tomography angiogram for pulmonary embolism should be considered if the exacerbation has an atypical presentation

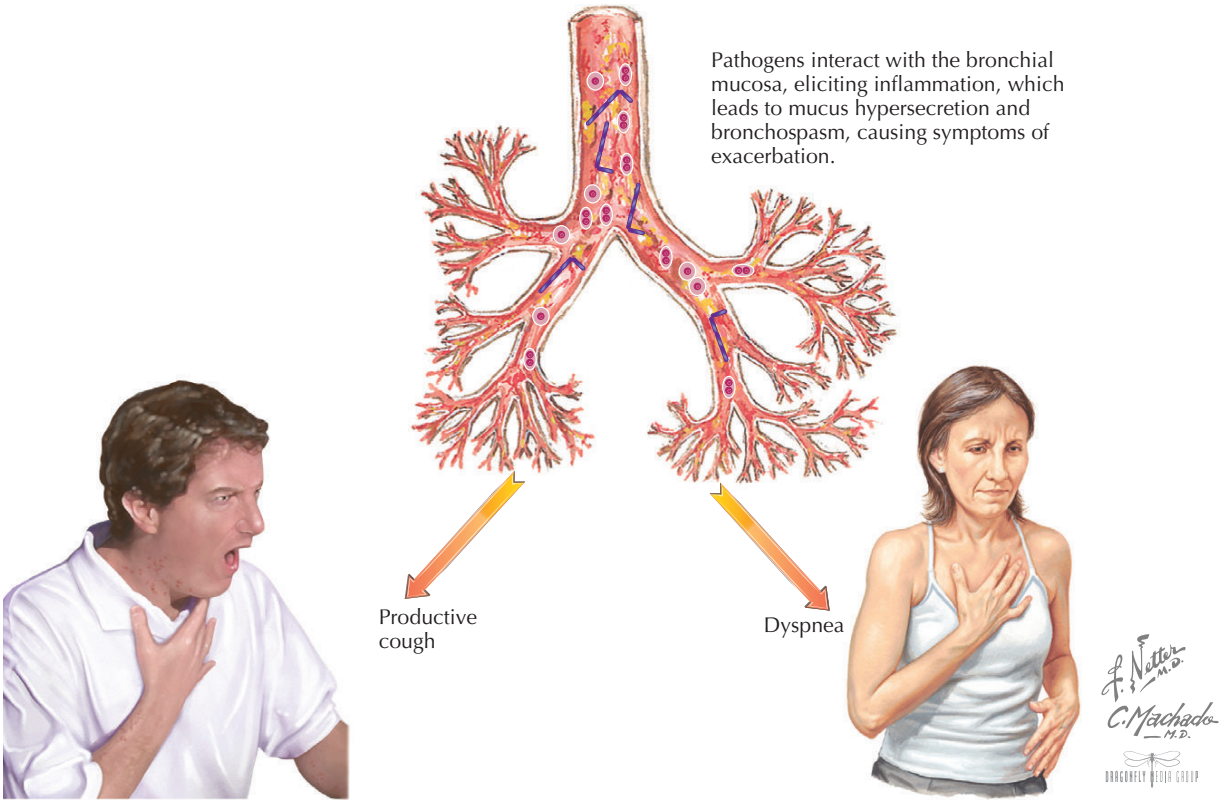

Figure 34-1 Cardinal manifestations of exacerbation of chronic obstructive pulmonary disease.

including sudden onset, absence of sputum changes, pleuritic chest pain, and hemoptysis.

Sputum gram stain and culture have limited utility in exacerbations because of their limited sensitivity and specificity. Clinical situations in which they may be useful are in patients with early relapse or nonresponse to treatment and in patients with very severe airflow obstruction in whom infection with *Pseudomonas aeruginosa* is a possibility.

MANAGEMENT

A multifaceted approach to treatment of exacerbations is usually indicated. Intensification of bronchodilators, attention to nutrition and hydration, and symptomatic treatment of cough and expectoration are often used. In patients with hypoxemia, oxygen supplementation and, in the presence of respiratory failure, ventilatory support—preferably with noninvasive ventilation—are indicated. Specific treatment of exacerbation includes systemic antibiotics and corticosteroids (Figure 34-3).

Several placebo-controlled trials support the use of antibiotics in moderate to severe exacerbations. Concerns about cost, emergence of antibiotic-resistant pathogens, and appropriate use are best addressed by adopting a stratification approach to antibiotic choice in exacerbations.

Systemic corticosteroids have also been found to be useful in moderate to severe exacerbations in placebo-controlled trials, when administered concurrently with antibiotics. Current recommended doses are in the range of 40 to 60 mg of prednisone (or equivalent) daily for 7 to 10 days.

PROGNOSIS

Exacerbations are associated with considerable morbidity and mortality. Among patients admitted to intensive care, in-hospital mortality of 20% to 25% and 1-year mortality of 50% have been reported. Introduction of noninvasive ventilation is likely to result in improved clinical outcomes in these patients; however, large-scale observational data with this modality are not yet available. Patients hospitalized with exacerbation but not in intensive care have a 6% to 12% mortality rate. In outpatient exacerbations, outcomes are currently suboptimal, with a 25% to 33% rate of treatment failure and/or relapse seen in these patients. Early appropriate intervention could improve these outcomes in the future.

PREVENTION

Prevention of exacerbations has now become one of the major goals of COPD management. With current therapeutic approaches, up to a 40% relative reduction in exacerbations has been seen. Yearly influenza vaccination and a single pneumococcal vaccination are indicated. Maintenance treatment of the underlying COPD with inhaled long-acting anticholinergic and β-agonist bronchodilators, as well as with inhaled corticosteroids, has been shown to decrease exacerbation frequency in COPD. Similar benefits have been seen with low-dose theophylline, as well as with mucolytics such as *N*-acetylcysteine and carbocysteine when used without inhaled corticosteroids. Surgical lung volume reduction and pulmonary rehabilitation also reduce exacerbation-related healthcare usage.

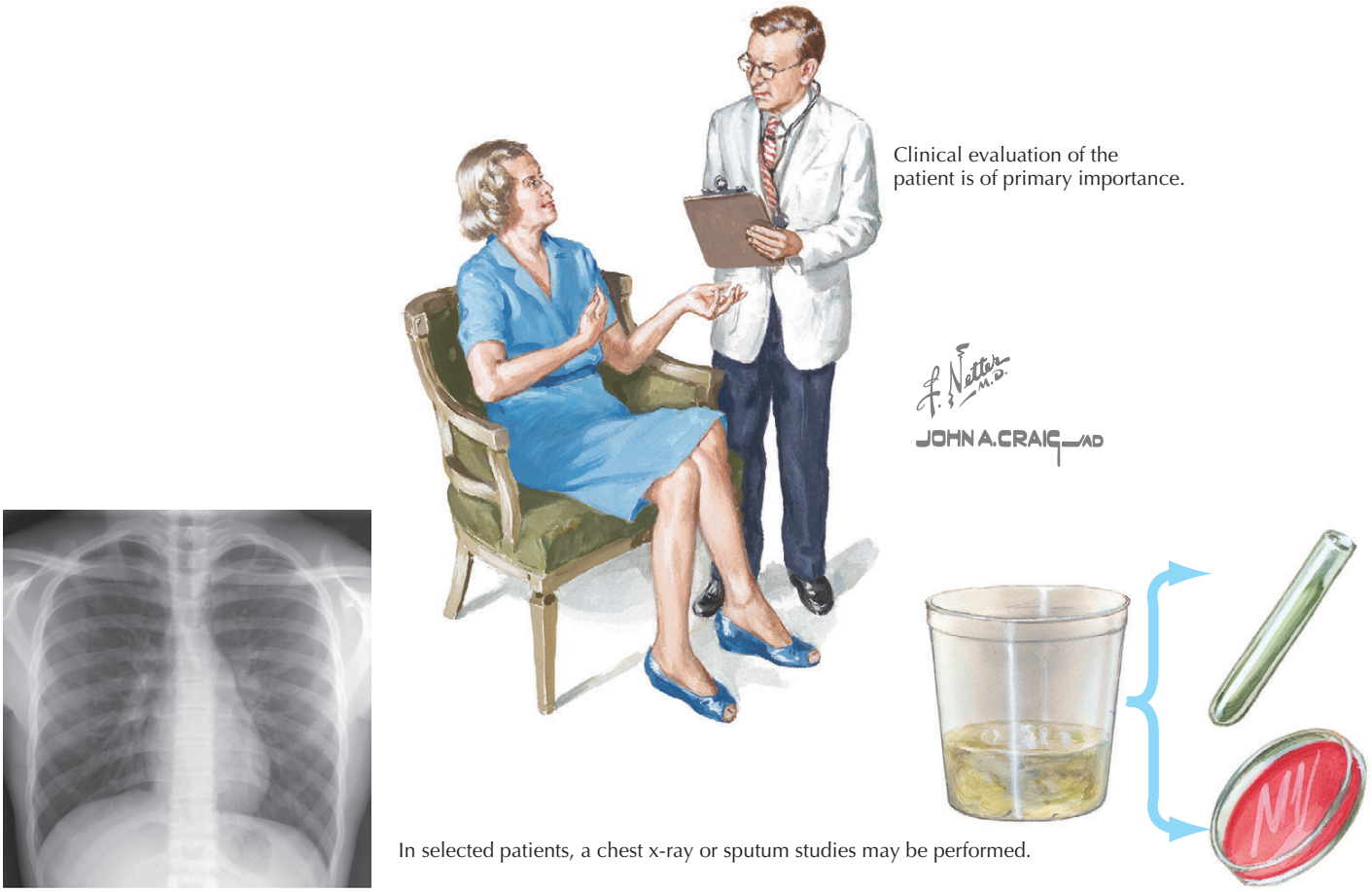

Figure 34-2 Clinical evaluation of exacerbation.

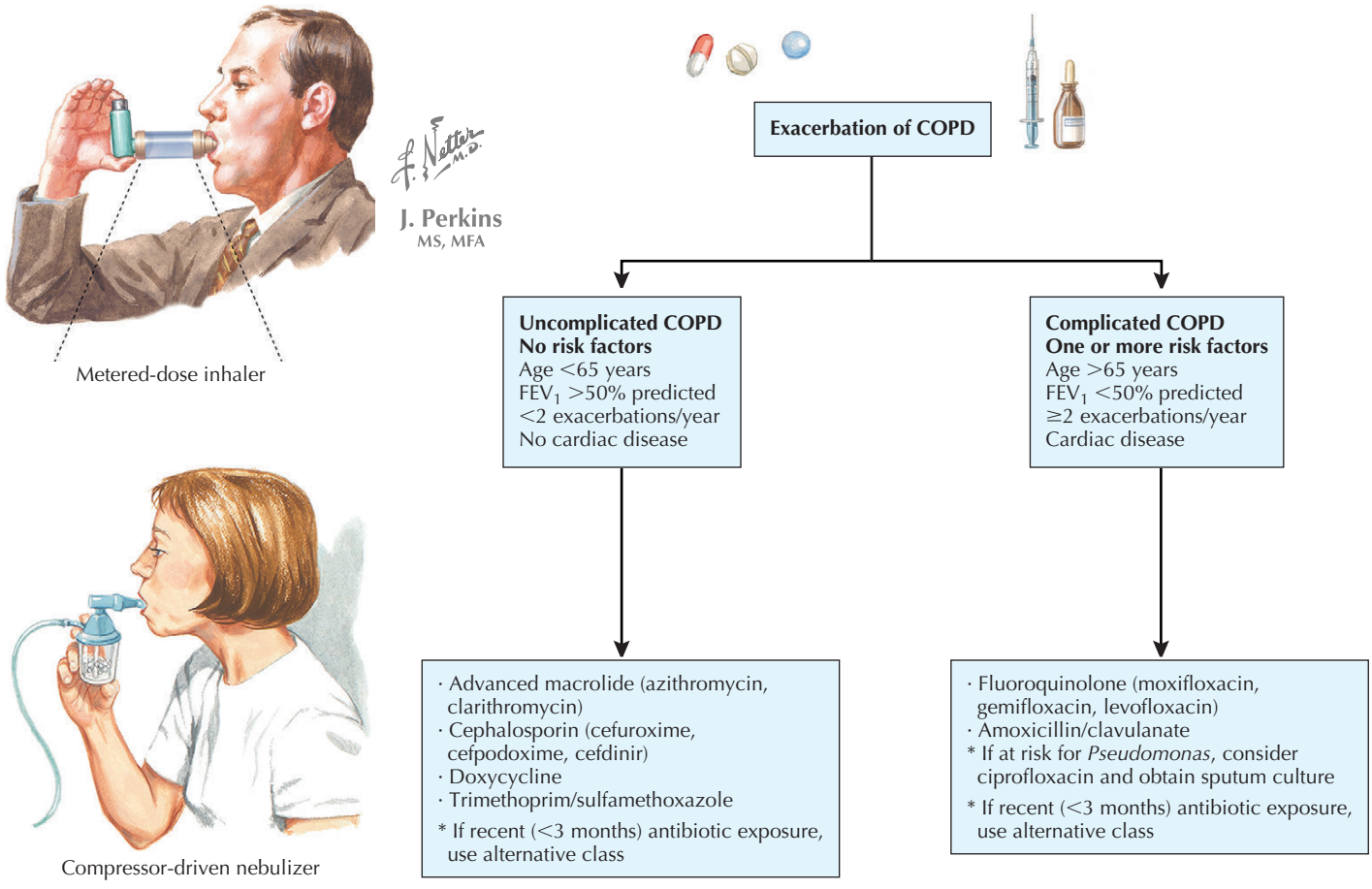

Figure 34-3 Treatment of exacerbation.

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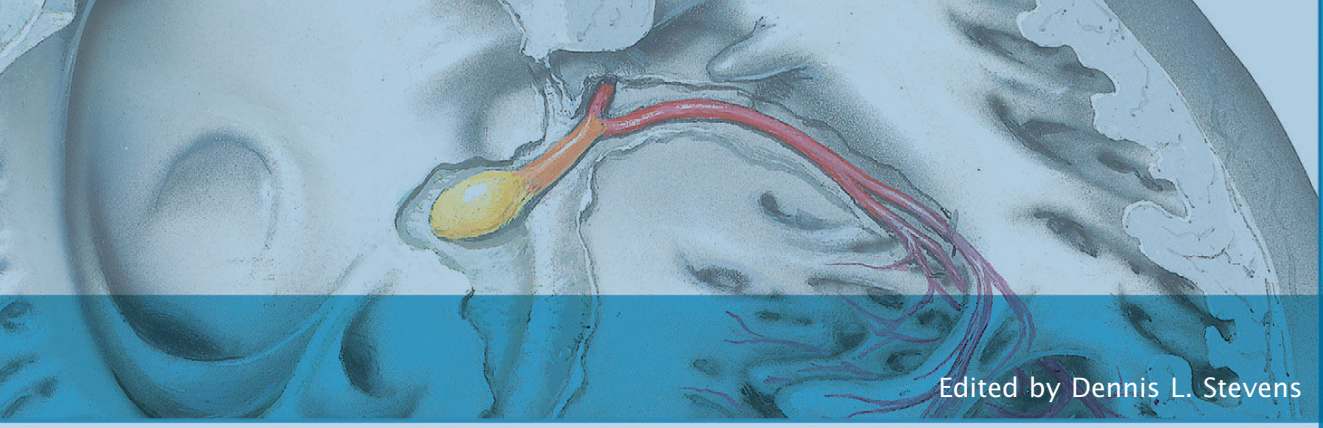
Walters JA, Gibson PG, Wood-Baker R, et al: Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev* (Online) 2009(1):CD001288. *A systematic analysis of placebo-controlled trials of corticosteroids in exacerbations of COPD.*

ADDITIONAL RESOURCES

American Thoracic Society. Available at: www.thoracic.org. American and European Thoracic Societies combined guidelines for COPD.

Global Initiative for Chronic Obstructive Lung Disease. Available at: www.goldcopd.com. Global guidelines for COPD.

National Heart, Lung, and Blood Institute, National Institutes of Health: COPD. Available at: www.nhlbi.nih.gov/health/public/lung/copd. Patient information for COPD.



SECTION IV

Edited by Dennis L. Stevens

Systemic Infections

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39 *Urinary Tract Infections*
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Introduction to Systemic Infections

Dennis L. Stevens

35

Systemic infections encompass a broad range of clinical entities including endocarditis, meningitis, osteomyelitis, nonbacterial infections such as disseminated tuberculosis, and fungal infections such as coccidiomycosis and histoplasmosis. In all these scenarios, infection develops in organs normally protected by innate and adaptive immune processes. In the last decade, the systemic manifestations of microbial infections have been categorized in terms of severity. For example, the terms *systemic inflammatory response syndrome* (SIRS), *sepsis*, and *septic shock* all describe increasingly severe inflammatory responses and/or systemic infections. One caveat to this stratification system is that an infection may result in profound systemic signs of inflammation without causing a systemic infection per se. For example, localized pneumococcal infection of the sinuses, middle ear, or lung may result in systemic signs of inflammation, whereas only when the infection disseminates, resulting in bacteremia and meningitis, does a systemic infection ensue.

Systemic infection invariably results when the innate and adaptive immune systems fail to contain a primary infection. Thus complement deficiency and hypogammaglobulinemia are risk factors for systemic pneumococcal and meningococcal infections. Clearly the additive effects of type-specific immunoglobulin G (IgG) coupled with complement-enhanced opsonophagocytosis prevent systemic complications of infection with *Haemophilus influenzae*, *Streptococcus pneumoniae*, or *Neisseria meningitides*. In fact, in populations immunized against *H. influenzae* and *S. pneumoniae*, systemic infections caused by these microbes have become rare. Splenic sequestration and clearance of blood-borne pathogens are also crucially important in preventing systemic infections, and clearly asplenia is commonly associated with fulminant infections caused by pyogenic microbes.

In recent years, systemic and disseminated infections have been more commonly recognized and reported in immunocompromised patients because of the epidemic of acquired immunodeficiency syndrome (AIDS), the increased frequency of transplantation, and the introduction of potent immunomodulatory therapies directed against tumor necrosis factor (TNF) and interleukin-1 (IL-1). These reports substantiate the important role of the normal host response to infection.

There is evidence that some bacterial systemic infections have specific relationships to age, whereas others are associated with gender or race. For example, group B streptococcal meningitis is related to the neonatal period, and *H. influenzae* infection is most common in children aged 6 months to 6 years. Systemic mycoses such as coccidiomycosis show clear increase in the frequency of dissemination among patients of Filipino or African descent. In terms of gender, there is also a clear predilection for disseminated *Coccidioides immitis* infection in females, though this is entirely related to pregnancy. These relationships are of sufficient strength that pregnant women, particularly those of black or Filipino descent, should not be employed in either clinical or research laboratories that perform studies on *C. immitis*.

Besides host factors, specific microbial traits are clearly associated with the ability to cause systemic infection. For example, endocarditis is most commonly caused by gram-positive cocci such as viridans streptococci, enterococcal species, *Streptococcus bovis*, *Staphylococcus aureus*, and *Staphylococcus epidermidis*. This remarkable molecular epidemiology is supported by simple laboratory studies demonstrating that these gram-positive bacteria adhere to heart valve endothelium with far greater avidity than gram-negative microbes.

Hematogenous osteomyelitis is clearly a systemic infection because bacteremia seeds proximal and distal long bones or paravertebral plexuses, resulting in acute bone infection and destruction. Here there is an age relationship, because proximal and distal osteomyelitis usually occurs in younger individuals before the epiphyseal plate closes and at a time when blood flow to this plate is maximal. With increasing age above adolescence, osteomyelitis of the proximal and distal long bones is a rare event. In sharp contrast, vertebral osteomyelitis is predominately related to increasing age, and the source of *Staphylococcus* may be either arterial or venous channels. The venous channels include Batson's plexus, which drains the lower urinary tract and provides retrograde flow to the paravertebral plexus. Though *S. aureus*, including methicillin-resistant *S. aureus* (MRSA), is most commonly implicated in hematogenous osteomyelitis, the mechanism causing the transient bacteremia and "homing" to proximal long bone or vertebrae is entirely unknown. Interestingly, the likelihood of cure of hematogenous osteomyelitis of the long bones is excellent, particularly in preadolescent children—probably a result of the augmented blood flow to the epiphyseal centers and enhanced delivery of complement, polymorphonuclear leukocytes, and antibiotics to the site in reasonable concentrations.

In contrast, osteomyelitis of the midshaft of long bones occurs in people of any age group and is more common in younger individuals participating in activities conducive to fractures. Closed fractures rarely become infected. However, compound fractures are more prone to infection because (1) the injury site is exposed to skin microflora as well as exogenous microbes from clothing, soil, water, and so on, and (2) injury induced by the penetration of bone fragments through the skin, fascia, and muscle frequently also destroys the blood supply. Thus this type of osteomyelitis is not really a systemic infection. Management of midshaft long bone osteomyelitis is complex because of poor bone repair, attenuated inflammatory reaction, and diminished delivery of antibiotics to the site of infection. Postadolescent osteomyelitis of this type is even more difficult

in patients with intrinsic deficits of vascular integrity, such as individuals with diabetes. An aggressive approach including surgical debridement, pathogen-directed antibiotic treatment for 6 weeks, and long-term suppression with oral agents provides the best results. In complex cases, myocutaneous transplantation combined with the approach just described offers some hope.

In summary, systemic infections are a diverse group of clinical entities caused by bacteria, fungi, and other pathogens. Clinical and epidemiologic studies have clearly implicated host factors including age, gender, and specific deficiencies of adaptive and innate immunity as prerequisites or risk factors for poor outcomes. Microbial virulence factors clearly are important for the development of specific systemic infections, and innate immune responses contribute to the systemic manifestations. Thus the initial encounter between the innate immune system and the invading microbe determines whether infection will develop and what the signs, symptoms, and morbidity will be. It is rather ironic that early attenuation of the innate immune response predisposes to establishment of infection, and yet after infection a robust response may contribute to morbidity. Clearly, continued basic scientific and clinical research is necessary to improve knowledge of bacterial, viral, and fungal pathogenesis and to provide new tools to improve outcomes.

Endocarditis

Sky R. Blue, Casi M. Wyatt, and Thomas J. Coffman

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ABSTRACT

Infective endocarditis (IE) is a serious infection involving the interior of the heart, most commonly the heart valves. It is predominantly bacterial, caused especially by *Staphylococcus aureus.* This chapter will review the pathogenesis, clinical features, diagnosis, treatment, and prevention of this condition for both native valves and prosthetic valves.

IE has always been a diagnosis that many physicians approach with anxiety and trepidation. The diagnosis can be elusive, the complications severe, and the treatment arduous. This has not changed significantly since the times of William Osler: "Few diseases present greater difficulties in the way of diagnosis than malignant endocarditis, difficulties which in many cases are practically insurmountable" (William Osler in the Gulstonian Lectures on Malignant Endocarditis, 1885). Endocarditis and the many protean manifestations have been known for decades—long before the antibiotic era. These complications and manifestations have been eloquently described by many pioneers of medicine since the mid-1700s, including Morgagni, Virchow, Wilks, Janeway, Roth, and Bowman. The modern era of medicine has led to an increase not only in the risk of endocarditis but also in the ability to diagnose endocarditis. Endocarditis is now likely to manifest much differently—more acutely and without the widespread stigmata observed in the past. However, despite great strides in the microbiologic isolation of causative organisms, echographic diagnosis, and antimicrobial treatment, the mortality remains high, contributing to the ongoing anxiety regarding this age-old disease.

PATHOGENESIS

The pathogenesis of IE usually starts with an area of endocardial injury leading to platelet-fibrin deposition. The next step requires a microorganism to enter the bloodstream and adhere to the area of injury. Injury and infection most commonly occur on the valve leaflets but can also occur on or near congenital defects, chordae, chamber walls, prosthetic valve attachments, pacemaker leads, or any other endocardial location where conditions are met. Subacute bacterial endocarditis most commonly occurs on the downstream side of a significant pressure gradient related to the rheumatic heart lesions, bicuspid aortic valve, or a variety of congenital heart lesions such as ventricular septal defect. Predisposing factors select organisms to enter the bloodstream, and once present, adherence factors determine the likelihood of a particular organism causing endocarditis. Adherence facilitates the initial colonization of the valve surface. Certain species of bacteria—for example, *Staphylococcus* and *Streptococcus* species—produce the majority of the human cases of endocarditis because of their ability to adhere to damaged tissues of the heart. Conversely, *Escherichia coli* can be a common cause of bacteremia from urinary or gastrointestinal sources but is a rare cause of endocarditis because it lacks these adherence factors.

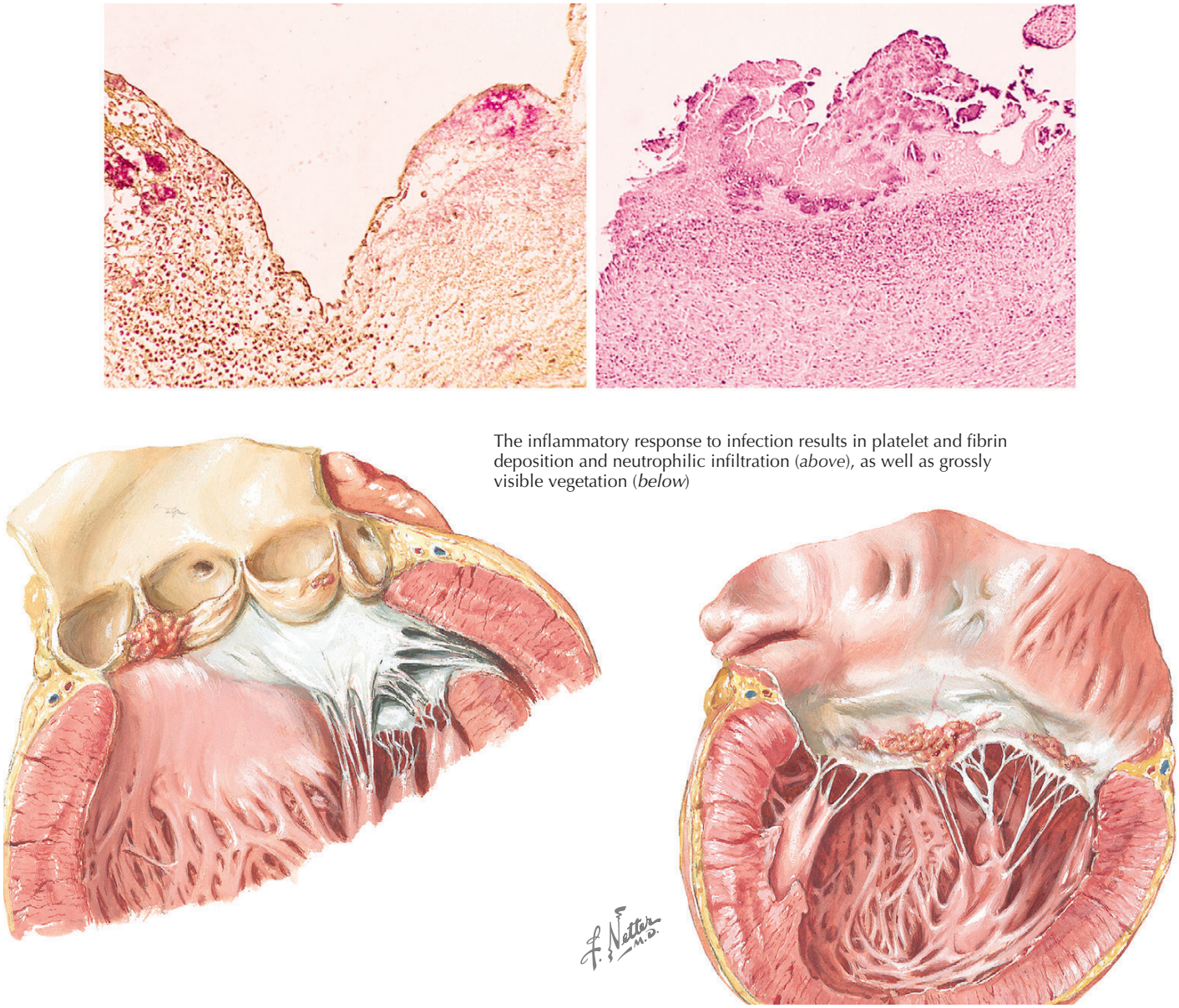
In 1978 Drs. Sheld, Valone, and Sande described the role of dextran, platelets, and fibrin in the adherence of streptococci to damaged endocardial tissue. Staphylococci use a variety of surface-bound adhesion components to bind to fibrinogen for colonization and fibronectin for invasion. Certain coagulase-negative staphylococci such as *Staphylococcus lugdunensis* and *Staphylococcus schleiferi* possess clumping factor binding fibrinogen and fibronectin as a virulence factor. Once attached to the platelet-fibrin nidus, bacteria begin to multiply, increasing coagulation activation, attraction of leukocytes, and growth of inflammation-promoting vegetation (Figure 36-1). This in effect buries bacteria deep within the mature vegetation, contributing to the treatment challenge of IE.

RISK FACTORS

Patient factors that predispose to IE are those that create damage to the valvular surface, increase the incidence of bacteremia, or slow the immune response to infection. Valvular pathology can be seen with congenital processes such as bicuspid aortic valves or septal defects. Valvular damage commonly occurs from atherosclerotic changes and rheumatic fever. Injection drug use can also lead to valvular injury and also frequently introduces bacteria into the bloodstream and therefore is a frequent risk factor seen in younger individuals. Hemodialysis likewise creates opportunity for frequent episodes of transient bacteremia owing to regular vascular access. Diabetes mellitus and other diseases leading to phagocytic cell dysfunction are predisposing factors in some cases. Men tend to be predominant in most series, with ratios ranging from 3:2 to 9:1. The elderly have nearly five times the risk of younger individuals. This is likely because of the increased prevalence of degenerative valve disease, increased use of invasive procedures, and implanted medical devices. Children (other than those younger than 2 years of age) almost always have underlying congenital heart disease.

ETIOLOGY

The microorganisms that infect the endovascular lining of heart valves are those that, as discussed earlier, have a predilection for or affinity to adhere to the platelet-fibrin nidus. Alternatively, organisms that are a common cause of bacteremia but are less likely to adhere cause endocarditis less frequently. The most common cause of native valve IE (NVE) is *S. aureus*, which has both a high frequency of bacteremia and a high affinity for adherence. The causes of NVE and the frequency as found by the International Collaboration on Endocarditis are as follows: *S. aureus*, 31%; viridans-group streptococci,



The inflammatory response to infection results in platelet and fibrin deposition and neutrophilic infiltration (*above*), as well as grossly visible vegetation (*below*)

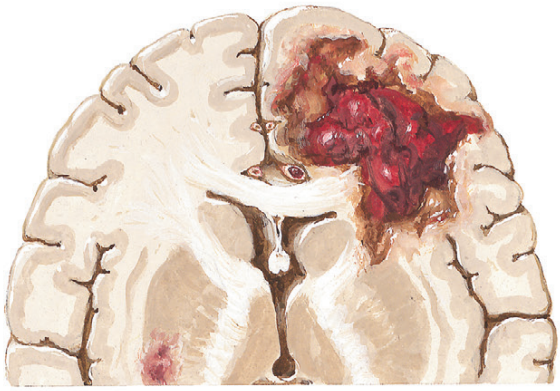
Figure 36-1 Bacterial endocarditis: early lesions.

17%; coagulase-negative staphylococci, 11%; enterococci, 11%; *Streptococcus bovis*, 7%; other streptococci, 5%; HACEK* gram-negative bacteria, 2%; non-HACEK gram-negative bacteria, 2%; fungi, 2%; polymicrobial, 1%; other, 3%; and culture negative, 8%.

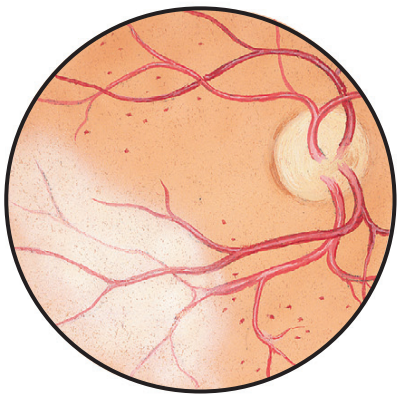
CLINICAL PRESENTATION

The presentation of IE has changed significantly over time, even since the death of Frank Netter. In the time of Osler, endocarditis was considered when persistent protean manifestations were noticed but the syndrome required recognition of diverse clinical findings for diagnosis. Improvements in blood culturing techniques, especially antibiotic binding resins and automated systems, have enhanced earlier diagnosis, and hence the clinical presentation is substantially different in modern times. Thus the first presenting sign of an eventual diagnosis of IE is usually a positive blood culture. This type of presentation precedes the classic manifestations of endocarditis by weeks to months depending on the virulence of the offending organism. Endocarditis may manifest anywhere along this continuum. IE is often classified based on the acuity of the presentation and the type of valve: acute or subacute and native valve or prosthetic. The diagnosis should be suspected in any patient with evidence of chronic inflammation such as fever, chills, or night sweats, and a corresponding laboratory finding of leukocytosis, anemia, thrombocytosis, or elevated

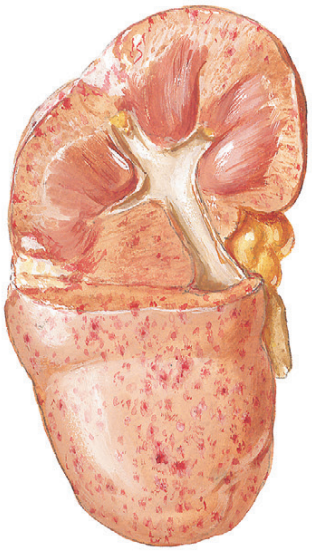
*HACEK indicates the following fastidious gram-negative bacilli: *Haemophilus aphrophilus; Actinobacillus actinomycetemcomitans; Cardiobacterium hominis; Eikenella corrodens;* and *Kingella kingae.*



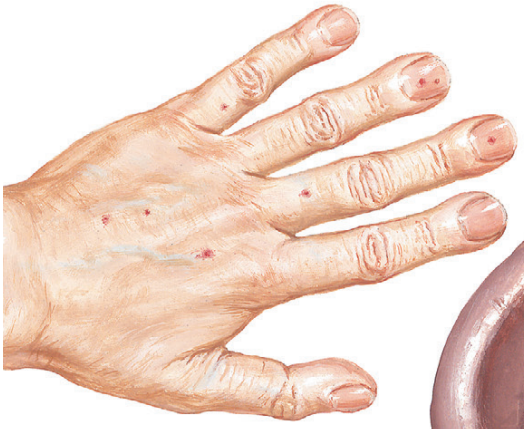
Infarct of brain with secondary hemorrhage from embolism to right anterior cerebral artery; also small infarct in left basal ganglia



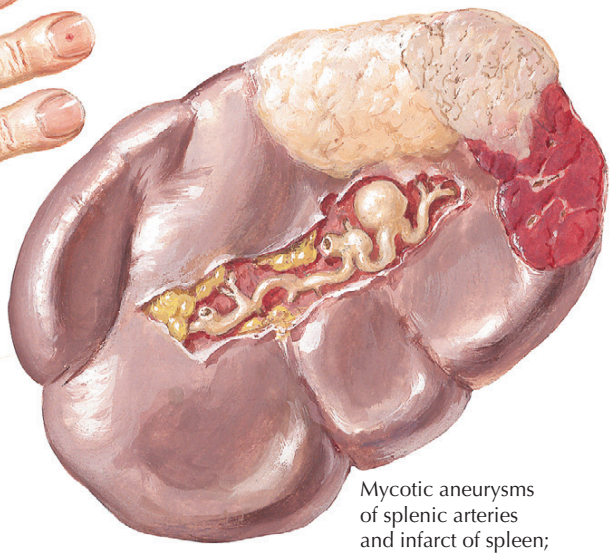
Embolus in vessel of ocular fundus with retinal infarction; petechiae



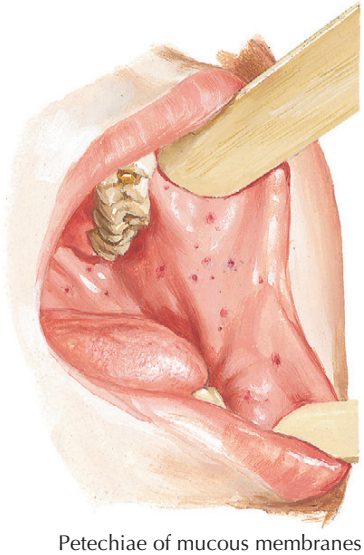
Petechiae and gross infarcts of kidney



Multiple petechiae of skin and clubbing of fingers



Mycotic aneurysms of splenic arteries and infarct of spleen; splenomegaly



Petechiae of mucous membranes

Figure 36-2 Bacterial endocarditis: remote embolic effects.

sedimentation rate. Patients with risk factors should warrant extra suspicion. The classic physical findings now occur more commonly in individuals without access to routine healthcare. Even so, the full spectrum of physical findings such as subungual splinter hemorrhages, Janeway lesions, and Osler's nodes still occur rarely. Instead, more common are worsening valvular dysfunction with resultant early congestive heart failure (CHF) and symptoms resulting from organ-level embolic lesions (Figure 36-2) such as the strokelike findings of slurred speech, facial droop, or focal weakness.

DIAGNOSTIC APPROACH

Part of the fear of IE is that the diagnosis is usually made on the basis of a constellation of clinical and laboratory findings and without direct pathologic evidence of endocardial infection. In general the diagnosis rests on the presence of an intravascular infection and evidence of endocardial involvement. The former is most commonly the growth of a typical organism on several blood cultures. Endocardial involvement is inferred by a new cardiac murmur, echocardiographic evidence of an endocardial vegetation, or a pathologic evaluation of a surgical specimen. Because there is no single definitive test result that is pathognomonic, syndromic diagnostic criteria have been used for many years. The first criteria were proposed in 1977 by Pelletier and Petersdorf. The most recently accepted criteria are often referred to as the "Duke criteria" and have been used in their modified state since 2000 (Boxes 36-1 and 36-2).

Attributed to Hertz and Edler in the 1950s, the advent of two-dimensional and Doppler echocardiography in the 1970s and 1980s changed the diagnostic process for IE. Instead of relying on the pathologic and microbiologic examination of a surgical

Box 36-1 Definition of Terms Used in the Modified Duke Criteria

Major Criteria
- Positive blood cultures
  - Microorganism typical of endocarditis from two separate blood cultures *or*
  - Persistently positive blood cultures drawn more than 12 hours apart or three or more positive cultures drawn over more than 1 hour *or*
  - Single positive blood culture for *Coxiella burnettii* or antiphase I immunoglobulin G (IgG) titer of >1:800
- Evidence of endocardial involvement
  - Positive echocardiogram for endocarditis (see text for discussion)
  - New valvular regurgitation (change in preexisting murmur is not sufficient for major criteria)

Minor Criteria
- Predisposing heart condition or injection drug use
- Fever (38° C or 100.4° F)
- Vascular phenomena
  - Major arterial emboli, septic pulmonary infarcts, mycotic aneurysms, intracranial hemorrhage, conjunctival hemorrhages, Janeway lesions, and so on
- Immunologic phenomena
  - Glomerulonephritis, Osler's nodes, Roth spots, positive rheumatoid factor
- Microbiologic evidence not included above
  - Positive blood culture(s) not meeting major criteria (not including single positive culture for coagulase-negative staphylococci not typically causing endocarditis) or serologic evidence of active infection with organism capable of causing endocarditis
- Echocardiographic minor criteria eliminated

Adapted from Li JS, Sexton DJ, Mick N, et al: Proposed modifications to the Duke Criteria for the diagnosis of infective endocarditis, *Clin Infect Dis* 30:633, 2000.

Box 36-2 Definition of Infective Endocarditis According to the Modified Duke Criteria

Definite Endocarditis
Pathologic Criteria
- Microorganisms identified by culture or histology in a vegetation, embolic lesion, or intracardiac abscess *or*
- Pathology confirmation of active endocarditis by histology of vegetation or intracardiac abscess

Clinical Criteria
- Two major criteria *or*
- One major and three minor criteria *or*
- Five minor criteria

Possible Endocarditis
Clinical Criteria
- One major and one minor criterion *or*
- Three minor criteria

Rejected Endocarditis
Clinical Criteria
- Firm alternate diagnosis for symptoms thought to be manifestations of endocarditis *or*
- Resolution of symptoms thought to be manifestations of endocarditis with antibiotic therapy for 4 days or less *or*
- Does not meet above criteria for definite or possible endocarditis

Pathologic Criteria
- No pathologic evidence of endocarditis on surgical or autopsy specimen after 4 days (or less) of antibiotic therapy

Adapted from Li JS, Sexton DJ, Mick N, et al: Proposed modifications to the Duke Criteria for the diagnosis of infective endocarditis, *Clin Infect Dis* 30:633, 2000.

or autopsy specimen, clinicians could obtain evidence of a pathologic structural abnormality (oscillating intracardiac mass, abscess, or partial dehiscence or a prosthetic valve) to help establish a definitive diagnosis. It should be noted that the absence of echocardiographic findings cannot rule out the diagnosis. For transthoracic echocardiography (TTE), various patient factors can contribute to the lack of sensitivity, such as obesity, hyperinflated lungs, or narrow costal interspaces. Transesophageal echocardiography (TEE) is more sensitive given these constraints, and because of improved image quality it can more easily demonstrate endocardial complications of endocarditis but may fail to identify very early lesions. Studies comparing the two approaches have found sensitivity to differ significantly: 90% or better for TEE compared with 40% to 60% for TTE, whereas specificity was 95% for both approaches. Echocardiographic appearance of lesions also has important implications for diagnosing complications, estimating risk of embolic events, determining the need for surgery, and evaluating treatment response.

TREATMENT

Since the beginning of the era of effective antimicrobial therapy, there has been an expected significant decline in mortality. But despite modern diagnostic techniques, advances in surgical interventions, and timely treatment, individuals still die from this infection. The general principles that guide treatment have evolved over the years but have their roots in Netter's time. Because of the relative paucity of leukocytes and high numbers of bacteria in a vegetation, bactericidal, rather than bacteriostatic, therapy is needed. Because organisms reside deep within the vegetation and may be in a state of reduced metabolism, a prolonged course and combination therapy have evolved as standard of care in many cases (Tables 36-1 to 36-4).

Streptococci

As a group, the viridans group streptococci and *S. bovis* account for many cases of NVE. Penicillin has long been the standard therapy for these organisms. Today the choice, dose, and duration of antimicrobial treatment still depend on the minimum inhibitory concentration (MIC) to penicillin. Early studies looked at 6 and 14 days of therapy and found that although many patients were cured, mortality and relapse rates were still unacceptably high. For susceptible streptococcal species (MIC <0.12) a study of 4 weeks of therapy demonstrated no deaths and no relapses. For organisms with intermediate MIC (0.12 to 0.5), a combination of a β-lactam and an aminoglycoside or 6 weeks of treatment is recommended. Isolates with MIC >0.5 need to have individual therapy optimized based on full susceptibility results and be treated for 6 weeks.

Table 36-1 Treatment for Infectious Endocarditis Caused by *Streptococcu* Species

ORGANISM	ADULT	PEDIATRIC	COMMENTS
PCN susceptible (MIC ≤0.12 mcg/mL) streptococci including viridans group and *Streptococcus bovis*	Penicillin G 12-18 million units/24 hr IV continuously or in four or six equally divided doses for 4 weeks *or* Ceftriaxone 2 g/24 hr IV or IM in single dose for 4 weeks *or* Vancomycin 30 mg/kg q12h IV adjusted for trough values of 10-15 mcg/mL for 4 weeks	Penicillin G 200,000 units/kg/24 hr IV in four or six equally divided doses for 4 weeks *or* Ceftriaxone 100 mg/kg/24 hr IV or IM in single dose for 4 weeks *or* Vancomycin 40 mg/kg/24 hr IV in two or three equally divided doses for 4 weeks	
Streptococci relatively resistant to PCN (MIC 0.12-0.5 mcg/mL) including viridans group and *S. bovis* Streptococci with MIC >0.5 mcg/mL should be treated as recommended for enterococci	Penicillin G 12-18 million units/24 hr IV continuously or in four or six equally divided doses for 4 weeks *or* Ceftriaxone 2 g/24 hr IV or IM in single dose for 4 weeks *plus* Gentamicin 3 mg/kg/24 hr in one dose or divided in two or three equally divided doses for 2 weeks *or* Monotherapy with vancomycin 30 mg/kg q12h IV adjusted for trough values of 10-15 mcg/mL for 4 weeks	Penicillin G 300,000 units/24 hr IV in four or six equally divided doses for 4 weeks *or* Ceftriaxone 100 mg/kg/24 hr IV or IM in single dose for 4 weeks *plus* Gentamicin 3 mg/kg/24 hr in one dose or divided in three equally divided doses for 2 weeks *or* Monotherapy with vancomycin 30 mg/kg q12h IV adjusted for trough values of 10-15 mcg/mL for 4 weeks	Gentamicin dosage adjusted for peak serum concentration 3-4 µg/mL, trough <1 µg/mL when 2-3 divided doses used; nomogram used for single daily dosing

IM, Intramuscularly; *IV,* intravenously; *MIC,* minimum inhibitory concentration; *PCN,* penicillin.

Table 36-2 Treatment for Infective Endocarditis Caused by *Staphylococcus aureus*

ORGANISM	ADULT	PEDIATRIC	COMMENTS
Staphylococcus aureus: Methicillin-susceptible strains	Nafcillin or oxacillin 12 g/24 hr IV continuously or in four or six equally divided doses for 6 weeks *or* Cefazolin 6 g/24 hr IV in three equally divided doses for 6 weeks	Nafcillin or oxacillin 100 mg/kg/24 hr IV in four or six equally divided doses for 6 weeks *or* Cefazolin 100 mg/kg/24 hr IV in three equally divided doses for 6 weeks	Use vancomycin or daptomycin for patients with severe anaphylactic allergies to β-lactams
Methicillin-resistant strains of *S. aureus* and coagulase-negative *Staphylococcus*	Vancomycin 30 mg/kg/24 hr IV in two equally divided doses adjusted for trough values of 10-15 mcg/mL for 6 weeks *or* Daptomycin 6-10 mg/kg/24 hr IV in single dose for ≥8 weeks	Vancomycin 40 mg/kg/24 hr IV in two or three equally divided doses for 6 weeks	

IV, Intravenously.

Staphylococcus aureus

The treatment of *S. aureus* IE is determined on the basis of methicillin susceptibility. Susceptible strains are best treated with semisynthetic penicillins such as nafcillin or oxacillin. The addition of an aminoglycoside for the first 2 weeks of therapy has been found to be associated with a more rapid clearing of the bacteremia, but cure rates were not different and the aminoglycoside group was associated with a higher incidence of renal dysfunction. Subsequently guidelines have left the recommendation for 3 to 5 days of aminoglycoside as optional. A recent review found no clinical benefit with the addition of an

Table 36-3 Treatment for Enterococci Strains

ORGANISM	ADULT	PEDIATRIC	COMMENTS
Enterococci strains susceptible to penicillin, gentamicin, and vancomycin	Penicillin G 18-30 million units/24 hr IV continuously or in six equally divided doses for 4-6 weeks *or* Ampicillin 12 g/24 hr IV continuously or in six equally divided doses for 4-6 weeks *or* Vancomycin 30 mg/kg/24 hr IV in two equally divided doses adjusted for trough values of 10-15 mcg/mL for 6 weeks *plus* Gentamicin 3 mg/kg/24 hr IV or IM in three equally divided doses for 4-6 weeks	Penicillin G sodium 300,000 units/kg/24 hr IV in four to six equally divided doses for 4-6 weeks *or* Ampicillin 300 mg/kg/24 hr IV in four to six equally divided doses for 4-6 weeks *or* Vancomycin 40 mg/kg/24 hr IV in two or three equally divided doses for 6 weeks *plus* Gentamicin 3 mg/kg/24 hr IV or IM in three equally divided doses for 4-6 weeks	Vancomycin therapy only recommended for patients allergic to penicillin and ampicillin Gentamicin dosage adjusted for peak serum concentration 3-4 mcg/mL, trough <1 mcg/mL
Enterococci strains: β-lactamase– producing penicillin-resistant strains but susceptible to aminoglycoside and vancomycin Infectious diseases consultation recommended	Ampicillin-sulbactam 12 g/24 hr IV in four equally divided doses for 6 weeks *or* Vancomycin 30 mg/kg/24 hr IV in two equally divided doses adjusted for trough values of 10-15 mcg/mL for 6 weeks *plus* Gentamicin 3 mg/kg/24 hr IV or IM in three equally divided doses for 6 weeks	Ampicillin-sulbactam 300 mg/kg/24 hr IV in four equally divided doses for 6 weeks *or* Vancomycin 40 mg/kg/24 hr IV in two or three equally divided doses for 6 weeks *plus* Gentamicin 3 mg/kg/24 hr IV or IM in three equally divided doses for 6 weeks	If strain is gentamicin resistant, then >6 weeks of ampicillin-sulbactam therapy will be needed Vancomycin therapy only recommended for patients allergic to penicillin and ampicillin Gentamicin dosage adjusted for peak serum concentration 3-4 mcg/mL, trough <1 mcg/mL
Enterococci strains: intrinsically penicillin resistant but susceptible to aminoglycoside and vancomycin Infectious diseases consultation recommended	Vancomycin 30 mg/kg/24 hr IV in two equally divided doses adjusted for trough values of 10-15 mcg/mL for 6 weeks *plus* Gentamicin 3 mg/kg/24 hr IV or IM in three equally divided doses for 6 weeks	Vancomycin 40 mg/kg/24 hr IV in two or three equally divided doses for 6 weeks *plus* Gentamicin 3 mg/kg/24 hr IV or IM in three equally divided doses for 6 weeks	
Enterococci strains resistant to penicillin, aminoglycoside, and vancomycin Infectious diseases and cardiothoracic surgical consultation necessary	*Enterococcus faecium:* Linezolid* 1200 mg/24 hr IV/PO in two equally divided doses for ≥8 weeks *or* Daptomycin 6-10 mg/kg/24 hr IV in single dose for ≥8 weeks *Enterococcus faecalis:* Imipenem-cilastatin 2 g/24 hr IV in four equally divided doses for ≥8 weeks *plus* Ampicillin 12 g/24 hr IV in six equally divided doses for ≥8 weeks *or* Ceftriaxone 2 g/24 hr IV or IM in one dose for ≥8 weeks *plus* Ampicillin 12 g/24 hr IV in six equally divided doses for ≥8 weeks	*E. faecium:* Linezolid* 30 mg/kg/24 hr IV or PO in three equally divided doses for ≥8 weeks *or* Quinupristin-dalfopristin 22.5 mg/kg/24 hr IV in three equally divided doses for ≥8 weeks *E. faecalis:* Imipenem-cilastatin 60-100 mg/kg/24 hr IV in four equally divided doses for ≥8 weeks *plus* Ampicillin 300 mg/kg/24 hr IV in four to six equally divided doses for ≥8 weeks *or* Ceftriaxone 100 mg/kg/24 hr IV or IM in one dose for ≥8 weeks *plus* Ampicillin 300 mg/kg/24 hr IV in four to six equally divided doses for ≥8 weeks	Cure with antimicrobial therapy alone may be <50% Quinupristin-dalfopristin only effective against *E. faecium* and can cause severe myalgias, which may require discontinuation of therapy

IM, Intramuscularly; *IV,* intravenously; *PO,* orally.
*Linezolid is not Food and Drug Administration (FDA) approved for >4 weeks; hematologic abnormalities may occur with use of linezolid, especially after 2 weeks of therapy.

Table 36-4 Treatment for HACEK Organisms

ORGANISM	ADULT	PEDIATRIC	COMMENTS
HACEK group (see text for list of organisms)	Ceftriaxone 2 g/24 hr IV or IM in single dose for 4 weeks *or* Ampicillin-sulbactam 12 g/24 hr IV in four equally divided doses for 4 weeks *or* Ciprofloxacin 1000 mg/24 h PO or 800 mg/24 h IV in two equally divided doses for 4 weeks	Ceftriaxone 100 mg/kg/24 hr IV or IM in single dose for 4 weeks *or* Ampicillin-sulbactam 300 mg/kg/24 hr IV in four equally divided doses for 4 weeks *or* Ciprofloxacin 20-30 mg/kg/24 hr IV or PO in two equally divided doses for 4 weeks	Therapy should be guided by susceptibility testing Fluoroquinolones generally not recommended for patients <18 years old

IM, Intramuscularly; *IV,* intravenously; *PO,* orally.

aminoglycoside to balance the potential toxicity. Methicillin-resistant strains are generally treated with vancomycin, but daptomycin has been shown to be noninferior to standard therapy.

Enterococci

Because of intrinsic resistance in enterococci to cephalosporins and potential for resistance to penicillins, vancomycin, and aminoglycosides, treatment needs to be individualized based on susceptibility patterns. In general, however, combination treatment with ampicillin or penicillin with an aminoglycoside for 6 weeks has been the standard for susceptible strains. Because of toxicity from aminoglycosides, combination treatment is often shorter and therapy is concluded with a β-lactam alone. Unique combinations such as ampicillin and ceftriaxone or combinations including newer agents have been evaluated in small clinical or experimental series.

Surgical Therapy

The decision to proceed with surgical therapy for the treatment of IE is complex and requires collaboration between cardiac surgeons, cardiologists, and infectious disease specialists. Surgery is needed in approximately 50% of IE cases, and the risk of reinfection after a valve replacement is 2% to 3%. Few randomized controlled trials comparing surgical therapy with medical therapy alone or comparing early with late surgical therapy exist, so current guidelines are based on retrospective and prospective cohort studies using either regression analysis or propensity matching to attempt to decrease bias, but inherent limitations of these types of studies remain. Randomized, controlled studies comparing early surgery with medical management are ongoing.

In 2006 the American College of Cardiology (ACA) and American Heart Association (AHA) created guidelines regarding surgical therapy for IE. Clinical trial evidence in conjunction with expert opinion supports surgical therapy for IE in the following situations: valve dysfunction leading to hemodynamic instability and heart failure, resistant organism or fungal infections, abscess formation, and fistula or conduction disturbances such as heart block (Box 36-3).

The hemodynamic stability of the patient is the most critical component when determining the need for surgical therapy.

Box 36-3 Possible Indications for Surgical Treatment of Infective Endocarditis

- Moderate to severe heart failure
- Valve dehiscence, obstruction, or leaflet perforation
- Periannular or aortic root abscess
- Fistula formation
- New conduction abnormalities such as heart block
- Multidrug resistant organisms
- Fungi
- Recurrent emboli or progressive vegetation despite appropriate antibiotic

Adapted from Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research and Interdisciplinary Working Group, *Circulation* 116:1736-1754, 2007.

CHF from IE causing hemodynamic instability has the biggest impact on prognosis and is the most common cause of death from IE. Moderate to severe CHF is an independent risk factor for 6-month mortality. Aortic valve endocarditis most commonly results in hemodynamic failure, and there is approximately a 50% mortality rate associated with aortic valve endocarditis–associated CHF without surgery. Mitral and tricuspid valves are less likely to cause heart failure and tend to have less hemodynamic compromise. Heart failure can occur suddenly from perforation of a valve leaflet, ruptured mitral chordae, valve obstruction by bulky vegetation, or development of an intracardiac shunt from a fistula. Echocardiogram can confirm the clinical diagnosis of heart failure. If signs of CHF are present, an immediate evaluation by a surgeon should be performed. Patients who develop heart failure may have higher operative mortality rates, especially those with class III or IV CHF, renal insufficiency, or advanced age, but overall mortality decreases from about 50% to 15% in these patients when surgery is performed in conjunction with medical therapy versus medical therapy alone. It is important to keep in mind, though, that heart failure can develop more slowly from progressive valve dysfunction even during the course

of appropriate medical therapy, so clinical vigilance must be maintained.

In addition to heart failure, surgery should also be considered early for IE from fungi or left-sided IE from resistant bacteria such as *Pseudomonas aeruginosa*, resistant strains of enterococci, or methicillin-resistant *S. aureus*. It may also be necessary for fastidious organisms such as *Coxiella burnettii* (Q fever) or brucellosis.

Although the evidence is less conclusive, consideration of surgery should also be given in patients with persistently positive blood cultures after 1 week on appropriate antibiotic therapy, anterior mitral leaflet vegetation, persistent vegetation after systemic embolization, increase in the vegetation size despite appropriate antibiotic therapy, periannular extension and abscess, prosthetic valve endocarditis (PVE), or mycotic aneurysms. Anterior mitral valve vegetations, especially larger than 1 cm, have the highest risk of embolization, and early surgery may prevent embolization, which is greatest in the first 1 to 2 weeks of infection. Perivalvular abscesses that can be successfully treated without surgery are smaller than 1 cm and have no complications such as heart block, echocardiographic progression of abscess, or valve dehiscence or insufficiency. If embolization to the central nervous system has occurred, the appropriate timing for surgery remains controversial. Guidelines for the timing of surgical intervention were created based on expert opinion and suggest the following: for small emboli <2 cm without hemorrhage, delay surgery for 72 hours; for emboli <2 cm with hemorrhage, delay surgery for 15 days; for emboli >2 cm with no hemorrhage, delay surgery for 15 to 28 days; and for emboli >2 cm with hemorrhage, delay surgery at least 28 days.

Surgical repair consists of valve repair versus replacement with either a mechanical or bioprosthetic valve. Repairing the valve rather than performing a full replacement decreases the amount of prosthetic material in place, which may decrease the risk of future infections. Valve repair is possible in only a limited number of cases and usually consists of vegetectomy followed by pericardial patch or placement of pericardial patch for small leaflet perforations. Valve repair may be preferable to replacement in young patients and in patients with a history of intravenous drug use. Valve replacement is necessary if severe valve dysfunction is present. If the aortic valve is involved, then surgery includes placing an aortic homograft, reconstructing the aorta, and replacing the aortic valve with a mechanical valve (Figure 36-3). Sometimes the required surgery includes only chordal repair or annular support. Right-sided endocarditis can often be managed medically, but surgery may be needed owing to difficult-to-treat bacteria and fungi. Infection of these valves often occurs in patients using intravenous drugs. Surgical therapy for tricuspid disease can include tricuspid valvectomy or vegetectomy with valvuloplasty. Tricuspid valve replacement is not usually performed, and even though the patient may later develop right-sided heart failure, this can often be managed medically.

In addition to surgical therapy, patients must also receive an appropriate antibiotic for an extended duration as already outlined. If there is evidence of active infection, such as culture-positive valve tissue or acute inflammation on pathology evaluation, at the time of valve replacement, then antibiotics should continue, with day 1 of therapy being the day of surgery.

PROSTHETIC VALVE ENDOCARDITIS

PVE complicates a minority (1% to 6%) of all prosthetic valves but accounts for up to about 35% of all cases of IE. The overall mortality rate of PVE is approximately 23%, and higher with *S. aureus* infections and fungal infections. Men are affected more frequently than women, and the mean age is 65. Risk factors for PVE include healthcare-associated infections, infected central venous catheters, and hemodialysis. Staphylococci, including both *S. aureus* and coagulase-negative staphylococci, are the most common cause of healthcare-associated PVE, whereas most community-associated PVE is caused by enterococci, viridans streptococci, and fastidious and intracellular organisms.

Although the diagnosis and treatment are similar to those of NVE, the timing of infection in relationship to the surgery affects the pathogenesis of infection, the clinical course, and often the pathogen involved. Infection is categorized as early-onset PVE (EO-PVE) and late-onset PVE (LO-PVE) from the time of surgery until development of infection (Table 36-5). The greatest risk of developing infection is within 2 months after surgery, and LO-PVE occurs more than 6 months after surgery.

In the first few months after surgery, the sutures, the valve cuff, and the valve itself become endothelialized. Until that time, these foreign body surfaces are in direct contact with host tissues, providing a direct conduit for infection. Bacteria may adhere and the prosthetic material can be seeded at the time of surgery, or bacteria can be introduced hematogenously at some time during the postoperative period. The prosthetic surfaces are coated with host proteins, especially fibrin and fibrinogen. These proteins facilitate adhesion by certain organisms such as *S. aureus*, which is the most common cause of EO-PVE. These infections manifest at the site at which prosthetic material meets native tissue, resulting in many of the complications of PVE including loosening sutures, causing periprosthetic leaks, or extension into the annulus, causing an abscess. The abscess can cause a fistula or rupture that can result in intracardiac shunting.

After these foreign materials have been endothelialized, the area functions more like native tissue, and it is more difficult for organisms to adhere and cause infection. Because a less abrupt

Table 36-5 Most Common Causes of Early-Onset and Late-Onset Prosthetic Valve Endocarditis (PVE)

INCIDENCE	EARLY-ONSET PVE	LATE-ONSET PVE
Highest	*Staphylococcus aureus*	*Staphylococcus aureus*
	Coagulase-negative staphylococcus	Coagulase-negative staphylococcus
	Culture negative	*Streptococcus* including viridians group
	Enterococcus	*Enterococcus*
	Gram-negative organisms	Culture negative
Lowest	*Streptococcus*	Fungi

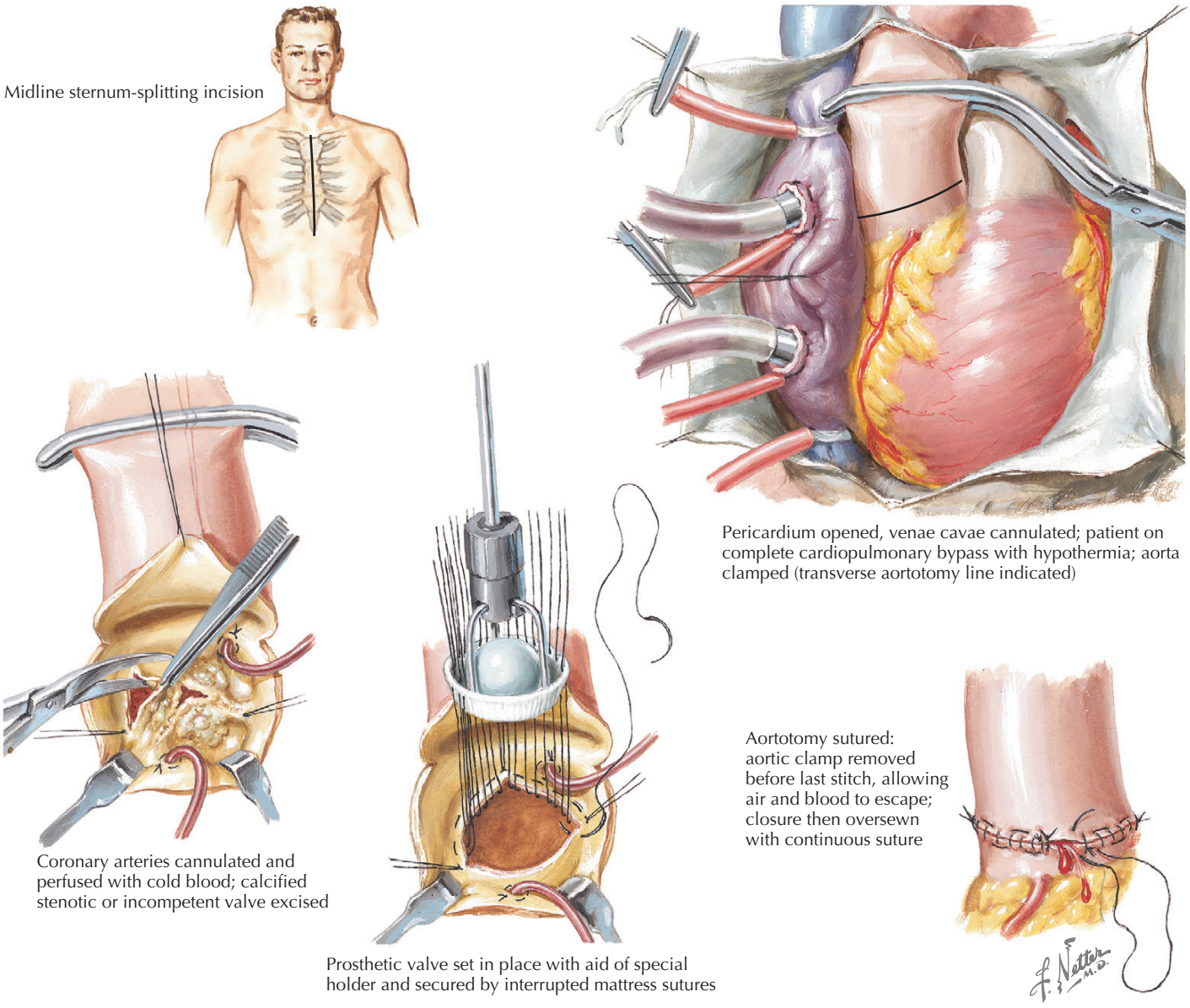


Figure 36-3 Aortic valve replacement.

interface exists between prosthetic and host tissues, the perivalvular tissues are less commonly infected, and the pathogenesis and microbial spectrum of the infection is similar to that of NVE.

Many of the complications of PVE are similar to those of NVE and include CHF, conduction disturbances, embolization, and metastatic spread of infection. Mortality increases with age over 65 years, healthcare-associated infection, *S. aureus* infection, persistent bacteremia, heart failure, intracardiac abscess, and stroke. The type or location of the prosthesis and the time of onset of infection have not been identified as independent risk factors for mortality.

Mechanical valves and bioprosthetic valves have different modes of infection, but there is no clear evidence to state one type of valve is less likely to become infected. Both types of valves develop infection at the cuff, but the bioprosthetic can develop infection of the cusp and can lead to rupture. The mechanical valve material does not readily permit bacterial adhesion to the valve itself, and infection is limited to the cuff. In addition to this, the bioprosthetic valve may promote platelet and thrombin deposition as it ages over time and may have an increased risk for infection (Figure 36-4), but this has not been shown conclusively.

The use of echocardiogram in diagnosing the infection and complications of the infection is similar to that in NVE, and TEE is more sensitive than TTE. The modified Duke criteria were designed to assist in diagnosis of NVE and should be used with caution if blood cultures are negative, but TEE has been shown to improve the sensitivity of the modified Duke criteria in diagnosing PVE.

Treatment of PVE should be a collaborative effort among cardiac surgeons, cardiologists, and infectious disease experts.

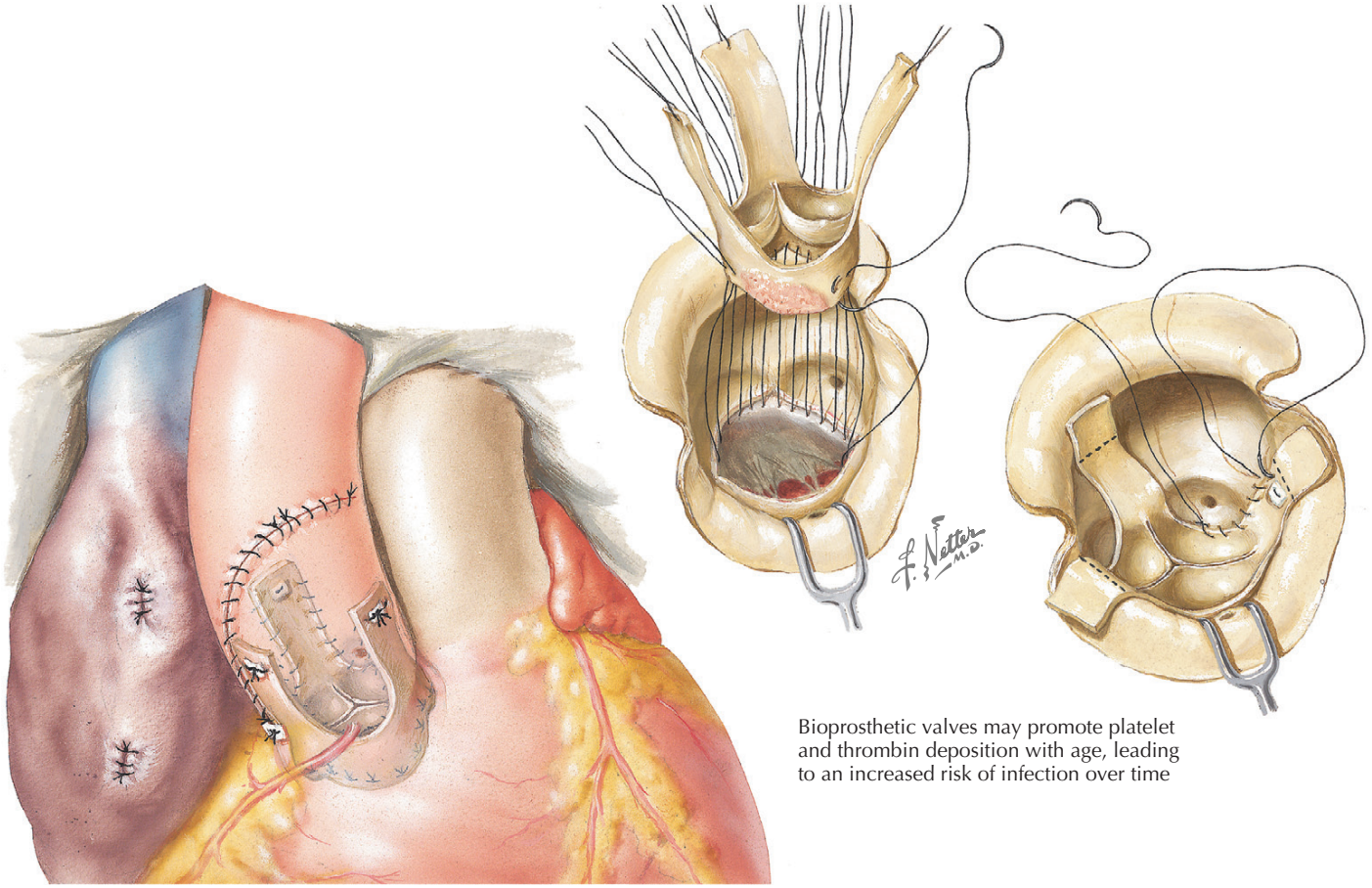


Figure 36-4 Aortic valve homograft.

Guidelines for surgical therapy mirror those for NVE (see Tables 36-1 to 36-4). Surgery is generally not indicated for an uncomplicated infection with a susceptible organism. Contraindications do exist for patients meeting these criteria and include a central nervous system embolic event complicated by hemorrhage, history of inoperability based on prior surgical history, and high operative risk based on comorbid conditions or poor prognosis from an underlying comorbid condition. As with NVE, evidence of active infection based on culture growth or pathology evaluation necessitates that therapy begin on the day of surgery.

PREVENTION

In 2007 the AHA revised guidelines regarding the prophylactic use of antibiotics before dental, genitourinary, and gastrointestinal procedures. Historically, antibiotics were given before these procedures to prevent IE caused by viridans group streptococci, which are normal skin, oral, and gastrointestinal tract flora, because this organism causes up to 50% of community-acquired NVE. Data linking the timing of dental procedures and the temporal development of IE are lacking. There have been no prospective, randomized, controlled trials studying antibiotic prophylaxis and the prevention of IE associated with dental procedures. It is well known that certain dental procedures can cause bacteremia, but it is also known that normal daily activities such as teeth brushing and flossing, chewing, and using a toothpick also result in bacteremia of a similar magnitude to that of dental procedures. In fact, it has been estimated that brushing teeth twice daily for 1 year exposes a person to bacteremia 154,000 fold more than a single tooth extraction. In a person with underlying periodontal disease, bacteremia associated with daily activities may be even more commonplace. Thus prophylaxis for IE with dental procedures seems unwarranted given the same risk of bacteremia with routine daily activities. Promoting overall good oral health may have a greater impact on decreasing rates of IE than routine prophylaxis before dental procedures.

The AHA also determined, though, that certain underlying cardiac conditions carry an increased lifetime risk for development of IE and a higher risk of complications from IE (Box 36-4). Owing to this fact, the AHA continues to state that prophylaxis for dental procedures that involve the "manipulation of gingival tissue or the periapical region of teeth or perforation of oral mucosa" is acceptable. Antibiotic prophylaxis is no longer recommended for patients with mitral valve prolapse (Table 36-6).

In addition to addressing dental procedures, changes were also made in the guidelines regarding antibiotic prophylaxis with respiratory, genitourinary, and gastrointestinal procedures.

Table 36-6 Antibiotic Prophylaxis with Dental Procedures*

	ANTIBIOTIC	ADULT	CHILDREN
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral	Ampicillin	2 g IM or IV	50 mg/kg IM or IV
	or		
	Cefazolin or Ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
	or		
	Clindamycin	600 mg IM or IV	20 mg/kg IM or IV
Allergy to penicillins	Cephalexin	2 g	50 mg/kg
	or		
	Clindamycin	600 mg	20 mg/kg
	or		
	Azithromycin	500 mg	15 mg/kg

Adapted from Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research and Interdisciplinary Working Group, *Circulation* 116:1736-1754, 2007.
IM, Intramuscularly; *IV,* intravenously.
*All are given as a single dose 1 hour before the procedure.

EVIDENCE

Aksoy O, Sexton DJ, Wang A, et al: Early surgery in patients with infective endocarditis: a propensity score analysis, *Clin Infect Dis* 44:364-372, 2007. *After controlling for the many predictors of mortality, these authors found that surgical therapy was associated with significant long-term survival benefit.*

Durack DT, Lukes AS, Bright DK: New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service, *Am J Med* 96:200-209, 1994. *Now somewhat of a historical reference but useful in understanding the use of echocardiography and criteria-based diagnosis for endocarditis.*

Li JS, Sexton DJ, Mick N, et al: Proposed modifications to the Duke Criteria for the diagnosis of infective endocarditis, *Clin Infect Dis* 30:633, 2000. *This paper outlines the "modified Duke criteria" currently accepted as the diagnostic standard.*

Murdoch DR, Corey GR, Hoen B, et al: Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study, *Arch Intern Med* 169:463-473, 2009. *The authors describe the presentation and bacterial etiology of infective endocarditis with a modern prospective cohort study.*

Pelletier LL Jr, Petersdorf RG: Infective endocarditis: a review of 125 cases from the University of Washington hospitals, 1963-1972, *Medicine (Baltimore)* 56:28, 1977. *This is the first criteria-based diagnostic approach.*

Vikram HR, Buenconsejo J, Hasbun R, Quagliarello VJ: Impact of valve surgery on 6-month mortality in adults with complicated, left-sided native valve endocarditis: a propensity analysis, *JAMA* 290:3207-3314, 2003. *This was an important paper demonstrating a reduced mortality in patients treated with valve surgery for complicated left sided endocarditis.*

Wang A, Athan E, Pappas PA, et al: Contemporary clinical profile and outcome of prosthetic valve endocarditis, *JAMA* 297:1354-1361, 2007. *A good description of prosthetic valve endocarditis in a prospective cohort from the International Collaboration on Endocarditis.*

Box 36-4 Antibiotic Prophylaxis before Dental Procedures

Antibiotic prophylaxis before dental procedures is recommended in the following situations:
- Patients with prosthetic heart valve or prosthetic material from previous repair
- Patients with previous infective endocarditis
- Patients with congenital heart disease limited to:
  - Unrepaired cyanotic heart disease
  - Completely repaired cyanotic heart disease in the first 6 months after the procedure
  - Repaired congenital heart disease with residual defect near the site of the prosthetic material
- Cardiac transplantation patients who develop valvulopathy

Adapted from Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research and Interdisciplinary Working Group, *Circulation* 116:1736-1754, 2007.

When a patient with one of the underlying conditions listed in Box 36-1 undergoes an invasive procedure of the respiratory tract that includes an incision or biopsy, including tonsillectomy, then prophylactic antibiotics should be used. It is no longer recommended to use antibiotic prophylaxis solely to prevent IE with invasive genitourinary or gastrointestinal procedures.

ADDITIONAL RESOURCES

Baddour LM, Wilson WR, Bayer AS, et al: Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association: endorsed by the Infectious Diseases Society of America, *Circulation* 111:e394-e434, 2005. *This is considered to be the most authoritative guideline currently available.*

Silverman ME, Upshaw CB Jr: Extracardiac manifestations of infective endocarditis and their historical descriptions, *Am J Cardiol* 100:1802-1807, 2007. *A review of the rich history and descriptions of the extracardiac manifestations of IE.*

Wilson W, Taubert KA, Gewitz M, et al: Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research and Interdisciplinary Working Group, *Circulation* 116:1736-1754, 2007. *Guidelines for the prevention of infective endocarditis from a panel of experts and review of the current evidence on prevention is presented here. This paper represents a major change in recommendations from the previous version in 1997.*

Meningitis

Thomas A. Kurrus and Martin G. Täuber

37

ABSTRACT

Meningitis is defined as an acute inflammation of the membranes surrounding the brain and spinal cord. This inflammation results from locally produced cytokines (primarily interleukin [IL]-1, IL-6, and tumor necrosis factor [TNF]) and is most commonly caused by infectious agents such as bacteria, viruses, spirochetes, rickettsiae, protozoa, and helminths. In addition, meningeal inflammation may result from parameningeal infectious foci or may represent a parainfectious, postinfectious, or vaccination-associated syndrome. Noninfectious causes of meningeal inflammation include reactions to medications, autoimmune diseases, vasculitis, and malignant tumors (Figure 37-1). Whereas nonbacterial causes of meningitis often produce significant patient discomfort but are not life-threatening, bacterial invasion of the meninges constitutes a true medical emergency necessitating rapid identification and early initiation of appropriate therapy (Box 37-1). The overall mortality of untreated bacterial meningitis approaches 100%, but even with the advent of potent antimicrobial agents, morbidity and mortality remain unacceptably high.

ANATOMIC AND PHYSIOLOGIC CONSIDERATIONS

The meninges consist of three layers that surround the brain and spinal cord. The outer layer, the dura, is composed of tough, white, fibrous connective tissue. The middle layer is the arachnoid, which is composed of a thin layer with numerous thread-like strands attaching it to the innermost layer, the pia. This is a thin, delicate membrane that is tightly bound to the surface of the brain and spinal cord. The subarachnoid space lies between the arachnoid and the pia, is filled with cerebrospinal fluid (CSF), and is traversed by the blood vessels of the brain. Meningitis is primarily an infection and inflammation of the CSF in the subarachnoid and ventricular spaces that involves the adjacent meninges, the traversing vessels, and brain structures.

CSF is produced by the choroid plexus in the lateral, third, and fourth ventricles. These structures consist of projections of vessels and pia mater into the ventricular cavities. CSF is produced by both filtration and active transport and circulates from the lateral ventricles into the third and fourth ventricles. The CSF then circulates through apertures in the fourth ventricle into the subarachnoid space over the surfaces of the brain and down the spinal cord. CSF is reabsorbed back into the bloodstream via the arachnoid villi located along the superior sagittal and other intracranial venous sinuses and around the spinal nerve roots. The movement of CSF and cellular components across arachnoid villi occurs via transport within giant vesicles and thus functions as a one-way valve (Figure 37-2).

There exist two interfaces between the blood and the brain. The largest and best known is the blood-brain barrier (BBB). It functions to protect the interstitial fluid of the brain from changes in the blood levels of ions, amino acids, peptides, and other substances. In contrast, fat-soluble molecules, including those of oxygen and carbon dioxide, anesthetics, and alcohol, can pass through the lipids in the capillary walls and gain access to all parts of the brain. The smaller and less direct interface is between the blood and the CSF. This controls the composition of the CSF and is primarily dependent on secretion in the choroid plexus. The blood-CSF barrier also exists in the pia mater where the astrocytes overlying the basement membrane of the pia are separated by junctions that affect the movement of constituents from the CSF to the brain. Both barrier systems are important for the regulation of CSF hydrodynamics and exchange of substances, including antibiotics and drugs, between the blood and the CNS compartments. They also contribute to the immunologic response of the brain by facilitating the presentation of antigens to immunologic cells and by participating in the inflammatory cytokine and chemokine network.

Normal CSF is clear and colorless. CSF sampled from the lumbar spine in adults contains 15 to 45 mg of protein per deciliter and 50 to 80 mg of glucose per deciliter, corresponding to two thirds of the normal blood glucose values. It may also contain up to five mononuclear cells and five red blood cells (RBCs) per microliter, although more than three polymorphonuclear leukocytes (PMNs) per microliter are considered abnormal. The pressure measured at lumbar puncture (LP) is 100 to 180 mm H_2O with the patient in lateral recumbent position and 200 to 300 mm H_2O in the sitting position.

Accidental breach of one of the small vessels in the lumbar region at the time of spinal tap may allow the entry of peripheral blood into the CSF sample, increasing the number of both white blood cells (WBCs) and RBCS. The coloration of the fluid from such a traumatic tap may vary from pink to red and often shows progressive clearing in sequentially gathered collection tubes. Correction for CSF contamination with peripheral blood can be accomplished by subtracting one WBC from the CSF count for every 500 to 1500 RBCs seen, provided the peripheral WBC count is within normal range.

Xanthochromia, a yellow to amber color of the fluid, results from the breakdown of RBCs and the release of hemoglobin components into the CSF. Xanthochromia requires at least 6 hours to develop, and its presence should prompt the clinician to evaluate the patient for previous intracerebral bleeding by computed tomography (CT) imaging and other appropriate tests.

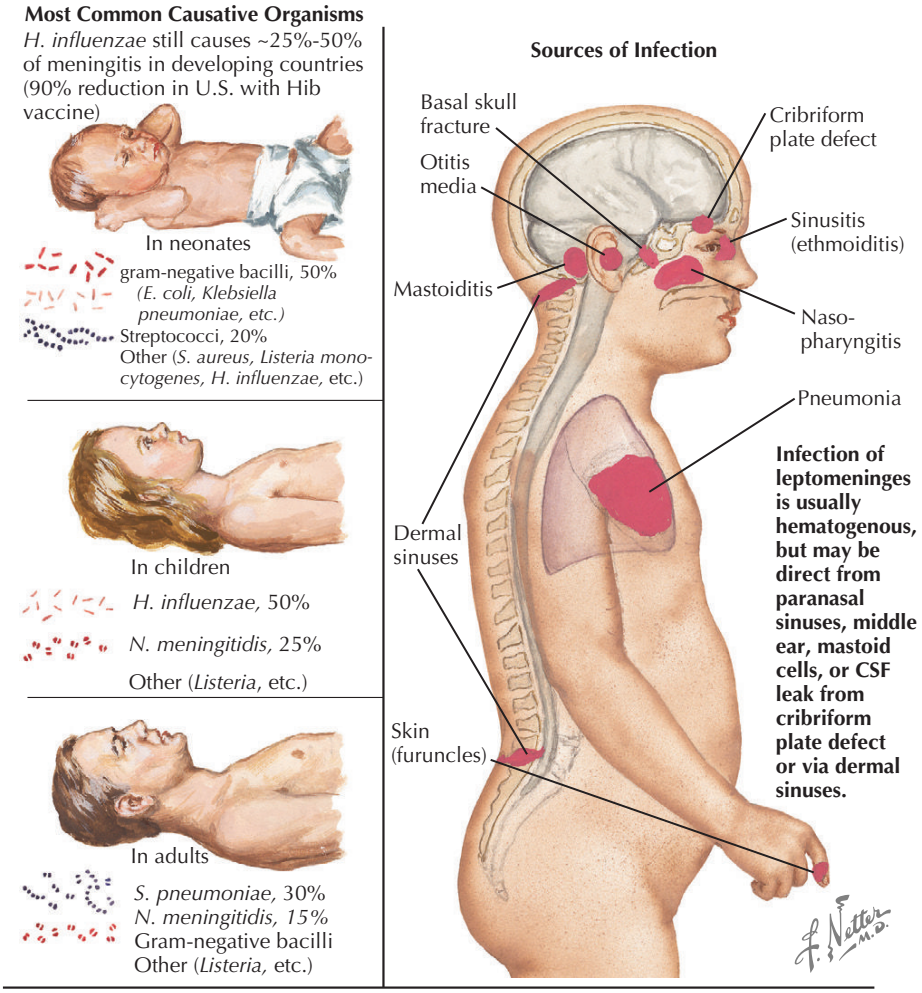


Figure 37-1 Bacterial meningitis.

Box 37-1 Definitions

Meningitis: The inflammation of the subarachnoid space and adjacent structures surrounding the brain and spinal cord. Typical clinical manifestations are fever, headache, nuchal rigidity, and altered mental status. The cerebrospinal fluid (CSF) is abnormal.

Encephalitis: Inflammation of the brain parenchyma with accompanying clinical evidence of abnormal brain function including altered mental status, motor or sensory deficits, altered behavior, or personality change. The CSF findings are variable. Meningoencephalitis represents a clinical syndrome in which inflammatory changes involve both the brain parenchyma and the subarachnoid space.

Community-acquired meningitis: Meningitis acquired in the community setting. There are multiple causes, including viral, bacterial, and fungal. The cause and frequency may be influenced by seasonality, geographic location, age, and immunologic status of the host.

Nosocomial meningitis: Meningitis acquired in a medical care setting, usually associated with neurosurgery or trauma. Other sources include hematogenous spread of bacteria from distant infections, indwelling devices and drains, and vascular access catheters.

Aseptic or viral meningitis: Clinical and laboratory signs of meningeal inflammation with negative routine cultures in a patient who has not received prior antibiotic therapy. Viral infection is the most common cause. Other causes include drug hypersensitivity, reaction to intrathecal medications, and some vasculitides.

Chronic meningitis: Evidence of meningeal inflammation lasting for 4 or more weeks.

Recurrent meningitis: Recurrent episodes of meningeal inflammation. This can occur in both community-acquired (6%) and nosocomial (11%) settings. Recurrent meningitis mandates evaluation for immunologic or anatomic host defects. Indwelling medical devices may be involved.

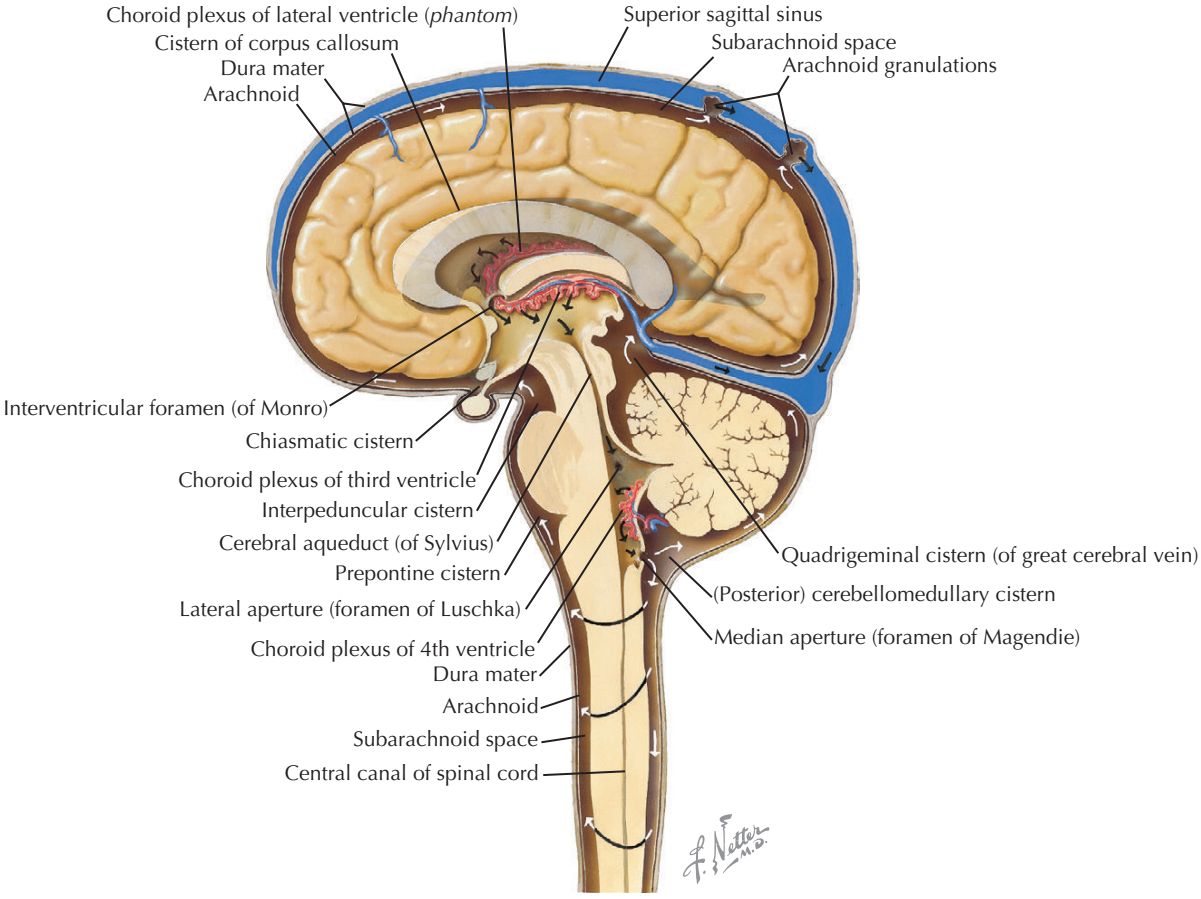


Figure 37-2 Circulation of cerebrospinal fluid.

EPIDEMIOLOGY AND MICROBIOLOGY

Bacterial meningitis can occur as either community-acquired or nosocomial disease. The epidemiology and microbiology of community-acquired bacterial meningitis varies greatly with age, geographic location, and host status. Most cases of community-acquired meningitis in children and adults are caused by *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae*, and *Listeria monocytogenes* (Tables 37-1 and 37-2). In newborns, *Escherichia coli* and group B *Streptococcus (Streptococcus agalactiae)* are important pathogens. With the exception of *N. meningitidis*, meningeal pathogens cause sporadic cases of meningitis and usually show a peak incidence during the cold months of the years. *N. meningitidis* can cause small or large epidemics, the most devastating of which tend to occur in the sub-Saharan "meningitis belt," where during epidemics hundreds of thousands of persons can fall ill and thousands die. Whereas meningitis in sub-Saharan Africa and other regions with hot weather is often caused by type A meningococci, other serotypes (B, C, less commonly Y and W135) play a role in sporadic cases and smaller epidemics in other parts of the world.

The introduction of routine infant conjugate vaccines to *H. influenzae* type b in 1990 and to seven epidemiologically prevalent serotypes of *S. pneumoniae* (4, 6B, 9V, 14, 18C, 19F, 23F) in 2000 dramatically changed the incidence and microbiology of both childhood and adult meningitis in the United States and other developed countries. Twenty to 30 years ago, *H. influenzae* was the leading cause of bacterial meningitis in children (45%), followed by *S. pneumoniae* (18%) and *N. meningitidis* (14%). Routine immunization of infants against *H. influenzae* type b has reduced the number of cases of invasive disease by 55% and the number of cases of *H. influenzae* meningitis by 94%. Similar reductions in the number of pneumococcal meningitis cases have been documented since the introduction of the pediatric pneumococcal conjugate vaccine (PCV-7). Comparing the incidence between 1998-1999 and 2004-2005 among children younger than 2 years of age, there was a decline of 64%, whereas the incidence for the entire population declined by 30%, presumably as a consequence of the induction of herd immunity protecting also nonvaccinated segments of the population, such as the elderly. Consequently the hospitalization rate for pneumococcal meningitis was halved from 1986 to 2004 from 1.1 to 0.55 per 100,000 population.

Over the past three decades, antimicrobial resistance among *S. pneumoniae* isolates has dramatically increased worldwide. In the late 1970s, strains of penicillin-resistant pneumococci were isolated in South Africa and Spain. By the early 1990s, penicillin-resistant clones had spread globally. In addition, resistance to macrolides and other antibiotics escalated in tandem with resistance to penicillin. Whereas penicillin resistance does not

Table 37-1 Organisms That Cause Bacterial Meningitis

ORGANISM	AGE RANGE AND FREQUENCY	PATHOGENESIS	RISK FACTORS	RECENT INFORMATION
Streptococcus pneumoniae	Most common cause and highest mortality of community-acquired meningitis in all ages	Hematogenous spread from nasopharyngeal colonization	Advanced age, HIV infection, direct extension across skull fracture, sickle cell disease, immunosuppression	Marked decrease in frequency in both children and adults after PV-7 vaccine
Neisseria meningitidis	Endemic worldwide, epidemic in sub-Saharan Africa Increased frequency in adolescents and young adults	Hematogenous spread from nasopharyngeal colonization	Infants and young children, household contacts of case patients, asplenia, and terminal complement deficiencies	Fluoroquinolone resistance in serogroup B in North Dakota and Minnesota; recent change in prophylaxis in these areas recommended Still no vaccine for group B
Haemophilus influenzae	Once the leading cause of BM in the under-5 age group Mortality 3% to 6% with frequent neurologic residua	Hematogenous spread from nasopharyngeal colonization	Nonimmunized infants and young children Native Indian and Alaskan population at increased risk	Incidence of Hib disease in infants and young children decreased 99% since introduction of conjugate vaccine
Listeria monocytogenes	All age ranges but highest in newborns and older adults Responsible for up to 20% in age group over 60	Entry from gastrointestinal tract and placenta	Older age groups Fetus Corticosteroid excess HIV	Soft cheese, milk, and processed meats traced in recent outbreaks
Coagulase-negative *Staphylococcus*	All ages	Dermal or surgical placement of foreign body in the CNS	Surgery and foreign body, especially ventricular shunt	Difficult to diagnose
Group B *Streptococcus* (GBS)	Meningitis occurs in 5% to 10% of early-onset cases (12 hours-6 days) and 35% to 40% of late-onset cases (7-90 days)	Acquired in utero or on passage through the birth canal	Maternal colonization Early disease more common with <37 wk gestation, premature membrane rupture, chorioamnionitis, GBS maternal bacteremia	Soft cheese, milk, and processed meats traced in recent outbreaks
Staphylococcus aureus	All ages Rare cause of community-onset meningitis	Bacteremia, dermal defect, or foreign body	Surgery and foreign body, especially ventricular shunt Endocarditis	Resistance to methicillin makes therapy difficult Anecdotal reports only, mortality approaches 70%
Gram-negative rods	Most common in neonates and infants Also seen in the elderly with neurosurgery or advanced medical illness	Bacteremia from various causes, endocarditis	Advanced age, severe medical illness, neurosurgery	Fortunately relatively rare Multidrug resistance with *Acinetobacter* and *Klebsiella*

BM, Bacterial meningitis; *CNS,* central nervous system; *Hib, H. influenzae* type b; *HIV,* human immunodeficiency virus; *PV-7,* Pneumococcal conjugate vaccine.

Table 37-2 Probability of Bacterial Cause of Meningitis by Age

ORGANISM	>1 MO TO 19 YR	ADULT UP TO 60 YR	ADULTS >60 YR
Streptococcus pneumoniae	33%	60%	70%
Neisseria meningitidis	29%	20%	3%
Haemophilus influenzae	4%	10%	3%
Group B *Streptococcus*	18%	4%	3%
Listeria monocytogenes		6%	20%

preclude the use of the drug for most infections outside the central nervous system (CNS), empirical treatment regimens for bacterial meningitis had to be adjusted significantly because of this new development (see section on treatment). Because the strains targeted by the heptavalent vaccine not only are responsible for the majority of invasive pneumococcal disease in children but also represent some of the strains with the highest rates of antimicrobial resistance, the relative rates of invasive disease caused by antimicrobial-resistant *S. pneumonia* declined by 55% after the introduction of the pneumococcal vaccine. This decrease was most pronounced in children younger than 2 years of age, but there was also a decrease in persons older than 65 years of age.

Nosocomial meningitis usually occurs as a complication of neurosurgery or after head trauma. Postoperative CNS infection can manifest as meningitis, brain abscess, or subdural or epidural empyema. Depending on the virulence of the involved organisms, infection becomes clinically apparent within hours to days or even weeks after invasive procedures in the head or spine. The causative organisms differ significantly from community-acquired meningitis, with *Staphylococcus aureus*, coagulase-negative staphylococci, *Propionibacterium* species, and gram-negative rods predominating. The incidence of nosocomial meningitis after neurosurgery is approximately 1.5% following craniotomy procedures. In addition to recent neurosurgery, risk factors for infection include placement of CSF drainage and other foreign material, head trauma within 1 month, and CSF leaks.

Recurrent meningitis can occur in both the community and nosocomial settings. Recurrence has been documented in up to 6% of community-acquired meningitis and is often associated with deficiencies of one of more terminal complement components in the case of recurrent neisserial infections, or an immunoglobulin deficiency, a defect in the reticuloendothelial system such as splenectomy, or a chronic CSF leak in the case of recurrent pneumococcal meningitis. Recurrent nosocomial meningitis is somewhat more common, with a rate approaching 11%. The usual risk factors include a breach in the cranial vault or an indwelling medical device. The mortality from recurrence appears higher than from single-event disease.

The term *aseptic meningitis* has been applied to patients with clinical and laboratory signs of meningeal inflammation who have negative bacterial cultures. Most cases of aseptic meningitis are of viral cause. Other causes include cases of partially treated bacterial meningitis; infections with mycobacteria, fungi, spirochetes, borreliae, and parasites; hypersensitivity reactions to medication; and malignancy. Depending on the cause, the extent of CSF inflammation and the cellular composition can vary widely. Primarily mononuclear CSF pleocytosis and mild chemical abnormalities are seen with viral meningitis, whereas other causes can result in mixed cellular inflammations (e.g., tuberculous meningitis) or predominantly granulocytic inflammation resembling bacterial meningitis (e.g., fungal and parasitic infections). Parameningeal bacterial foci, such as frontal or mastoid sinusitis and otitis media, can also produce CSF inflammation resembling bacterial meningitis, often with negative bacterial cultures of the CSF.

Most cases of viral meningitis in adults and children are caused by enteroviruses and typically occur in the late summer and early fall. All members of the herpes virus family can produce an aseptic meningitis syndrome. Primary herpes simplex virus 2 (HSV-2) genital infection may be associated with clinically significant meningitis in up to 36% of cases, and women appear more likely to develop meningitis than men. HSV-2 is also believed to be a major cause of Mollaret's syndrome, a recurrent benign lymphocytic meningitis. A subset of patients with primary human immunodeficiency virus infections will develop meningitis or meningoencephalitis manifested by headache and confusion as well as occasional focal neurologic deficits. Other common causes of viral meningitis include mumps, varicella zoster virus, arthropod-borne virus, West Nile virus, lymphocytic choriomeningitis, and several adenovirus serotypes. With several of these viruses, meningitis can be accompanied by signs of encephalitis (see Table 37-1).

PATHOGENESIS AND PATHOPHYSIOLOGY

The pathogenesis of community-acquired bacterial meningitis involves initial mucosal colonization followed by secondary hematogenous spread and seeding of the subarachnoid space across the BBB or the blood-CSF barrier. Colonization of the nasopharynx involves successful mucosal attachment and evasion of the mucosal defenses. The seasonal variation of the disease is most likely related to seasonal differences in the likelihood of being colonized with pathogenic bacteria, which is favored in the cold months by low temperature, dry air, and infections caused by viral respiratory pathogens. Smoking is another factor favoring mucosal colonization with meningeal pathogens.

The bacterial capsule, which covers the surface of all pathogens that cause hematogenous meningitis (with the exception of *Listeria*), mediates survival of the pathogen in the bloodstream long enough to allow it to reach the CNS. The capsule and other surface structures are involved in a complex interaction with endothelial cells of the BBB and blood-CSF barrier, to which the organisms can attach and are then transported from the luminal to the CNS side of the barrier.

In some cases meningitis evolves from a contiguous local infection, such as otitis media, mastoiditis, or sinusitis. In these cases bacteria gain access to the subarachnoid space *per continuitatem* or by venous or lymphangitic spread, bypassing the stage of (transient) bacteremia. Nosocomial meningitis usually results from direct entry into the CNS after trauma or neurosurgery. It can also occur via bacteremia from a distant site of infection or by microembolic spread from an intravascular infectious focus, such as an infected catheter.

After successful entry into the CSF, the bacteria, which are protected from phagocytosis by their capsule, multiply rapidly in an environment of low opsonic capacity. CSF inflammation, the basis for clinical symptoms of meningitis, is produced by the interaction of bacterial components with host cells equipped to recognize pathogen-associated molecular patterns (PAMPs)—that is, bacterial cell wall fragments, lipopolysaccharides (endotoxin), and others. Proinflammatory cytokines (e.g., IL-1, IL-6, and TNF-α) and chemokines (e.g., IL-8) are essential mediators of the CSF inflammation and contribute to ensuing pathophysiologic changes such as brain edema and cellular dysfunction of endothelial and glial cells. As a result of increased intracranial

pressure, loss of cerebral blood flow autoregulation, and vasospasms and thrombosis of cerebral vessels caused by inflammation, cerebral blood perfusion can become impaired globally or focally. The clinical CNS effects include headaches, altered mental status, coma, focal sensory and motor deficits, and seizures.

The pathogenesis of most viral meningitis syndromes involves colonization of specific mucosal surfaces followed by hematogenous spread to the CNS. Viruses may also reach the CNS by spread along both cranial and peripheral nerves, as has been documented in HSV-1 and rabies infections. Analogous to bacterial meningitis, various inflammatory cytokine elevations have been detected in the CSF of patients with viral meningitis. After the development of the CNS inflammatory response, alterations in the BBB may permit the entry of immunoglobulins and other serum proteins into the CSF.

CLINICAL FEATURES

The cardinal symptoms of bacterial meningitis consist of a classic tetrad of fever, headache, nuchal rigidity, and altered mental status. Only a minority of patients manifest all four, but at least two of the four are present in more than 90% of adult patients with bacterial meningitis. Other common symptoms of bacterial meningitis include photophobia, nausea and vomiting, seizures, and sensory or motor deficits. Patients with meningococcal infection often develop a petechial rash that may progress to frank ecchymosis.

Patients at the extremes of life (neonates and those over 65 years of age) and the immunosuppressed are less likely to show classical symptoms of meningitis. In neonates, irritability and failure to feed and thrive may be early symptoms. Neonates with enteroviral meningitis may develop a very severe form of meningoencephalitis and a rapidly progressive sepsis syndrome characterized by multisystem organ failure and very high morbidity and mortality rates. Elderly patients can demonstrate confusion or generalized malaise without prominent fever, headaches, or other characteristic meningeal signs. The diagnosis may further be complicated in elderly patients by more marked neurologic impairment and higher rates of comorbid conditions. Tuberculous meningitis causes a subacute febrile illness with headache and lassitude, often with a stuttering dynamic over several weeks. With time, complaints become progressively more intense and are associated with nausea, vomiting, confusion, cranial nerve deficits, and other focal neurologic deficits.

The severity of headaches and fever in patients with viral meningitis is often similar to that seen in patients with bacterial meningitis, although alterations of mental status are typically absent or mild. Furthermore, patients with viral infections frequently complain of other systemic symptoms including lethargy, nonspecific malaise, nausea, or emesis and diarrhea. Depending on the infecting virus, patients may also have rashes, including vesicular rashes of herpetic infections, or lymphadenopathy.

All patients with suspected meningitis should be examined for the presence of nuchal rigidity. The extent of nuchal rigidity can vary widely, and it may be absent with early or mild (viral) meningeal inflammation, as well as in deeply comatose patients with bacterial meningitis. Both Kernig's and Brudzinski's signs have a low sensitivity to detect bacterial meningitis and are rarely performed nowadays, even though they have a high positive predictive value if present (Figure 37-3). Nuchal rigidity in *Listeria* meningitis is reported to be less common and movement

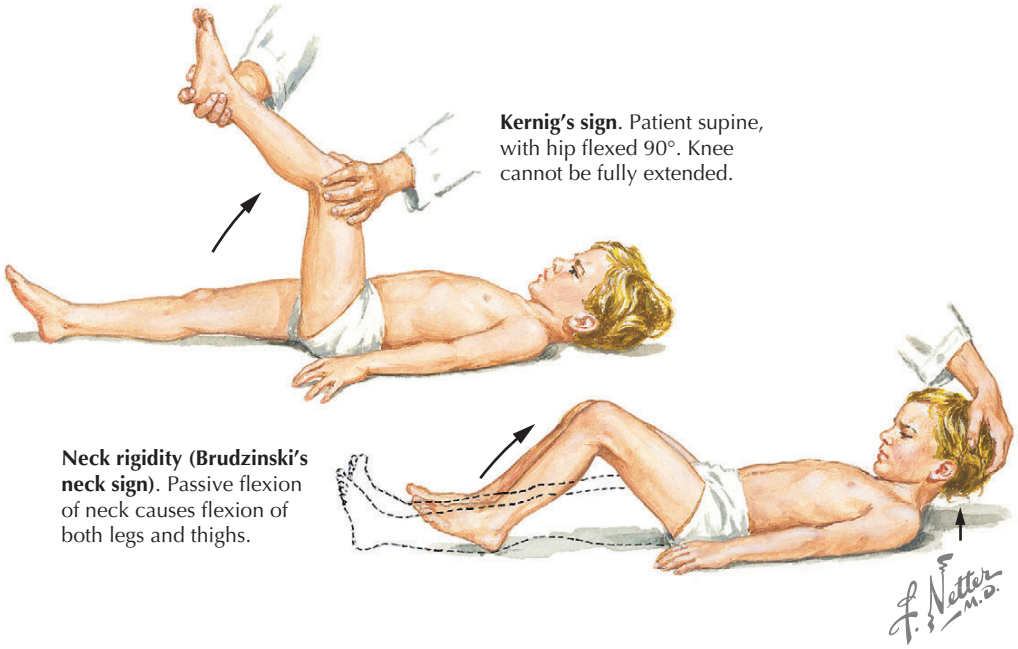


Figure 37-3 Kernig's sign and Brudzinski's sign.

disorders more common than in meningitis cause by other bacteria.

DIAGNOSIS

Meningitis should be considered in the differential diagnosis of all febrile patients with a significant headache, with changes in the level of consciousness, or with neurologic dysfunction. The history should focus on the onset and severity of symptoms, systems review, family and social history, recent travel, immunizations, and present medications as well as past history of high-risk behavior. A complete physical examination with special attention to neurologic deficits, nuchal rigidity, and skin rashes, and routine blood and urine evaluations are part of the workup of any patient with suspected meningitis. It is important that a manual differential WBC count be requested with the complete blood count, as automated counts may miss or underrepresent the immature cells in the peripheral blood. Samples for blood culture times two should be drawn *before* antibiotic therapy from all patients suspected of having meningitis. Many institutions will also add the determination of inflammatory markers such as C-reactive protein and serum procalcitonin levels. Their role in the differential diagnosis of different forms of meningitis is not firmly established and needs further studies.

Examination of the CSF is essential for the diagnosis of infections of the CNS. Sampling is usually done by means of LP, with insertion of a needle at the L3/4 or L4/5 intervertebral space (Figure 37-4). The procedure is usually performed with the patient in the lateral recumbent position to allow the measurement of CSF opening pressures, which must be routinely recorded. A total of 5 to 15 mL should be removed and placed in sequentially numbered plastic tubes for cell counts, cultures, and protein and glucose concentrations. Differential cell counts comparing values of the first and last portion of the specimen should be requested if there is suspicion of a traumatic tap. Volumes up to 20 to 30 mL may be safely removed for additional studies such as immunoglobulin values, molecular amplification studies, or fungal or *Mycobacterium tuberculosis* cultures. Repeat sampling of CSF 24 hours after the initial tap may be considered when there is a persistent discrepancy between clinical findings and the findings from the first CSF sample. The practice of end-of-therapy taps to confirm cure of the infections has largely been abandoned.

The rare occurrence of cerebral herniation after the removal of CSF via LP has prompted many clinicians to request cranial imaging before the procedure. The 2004 Infectious Diseases Society of America (IDSA) Guidelines for Management of Bacterial Meningitis, based on a prospective study, recommend limiting CT screening before LP to patients with one or more of the following findings:

- Impaired cellular immunity
- Previous CNS disease
- Recent-onset seizures (within 1 week)
- Decreased level of consciousness
- Focal motor or cranial abnormalities
- Papilledema

In patients without any of these findings, the likelihood of relevant abnormalities on CT scan precluding the safe performance of LP is very low. However, all patients with documented bacterial meningitis should undergo cranial CT evaluation within the first days of treatment to detect focal infections (sinusitis, mastoiditis) and intracranial complications of meningitis (subdural empyema, cerebritis, ischemia) (Figure 37-5).

When the diagnosis of bacterial meningitis is considered probable but neuroimaging is not available, the benefit of LP in patients with moderate to severe impairment of consciousness or patients considered to be immunocompromised clearly outweighs the risk. Contraindications to performing LP include intracranial mass lesions with evidence of intracranial hypertension and uncorrected, severe hemorrhagic diathesis.

In patients with suspected meningitis, CSF should be promptly examined for absolute and differential cell count. An elevated WBC count documents an inflammatory (or malignant) process in the subarachnoid space. Even though this may be produced by a variety of inflammatory conditions, bacterial meningitis must be the primary consideration in all patients with compatible clinical findings. Acute bacterial meningitis is

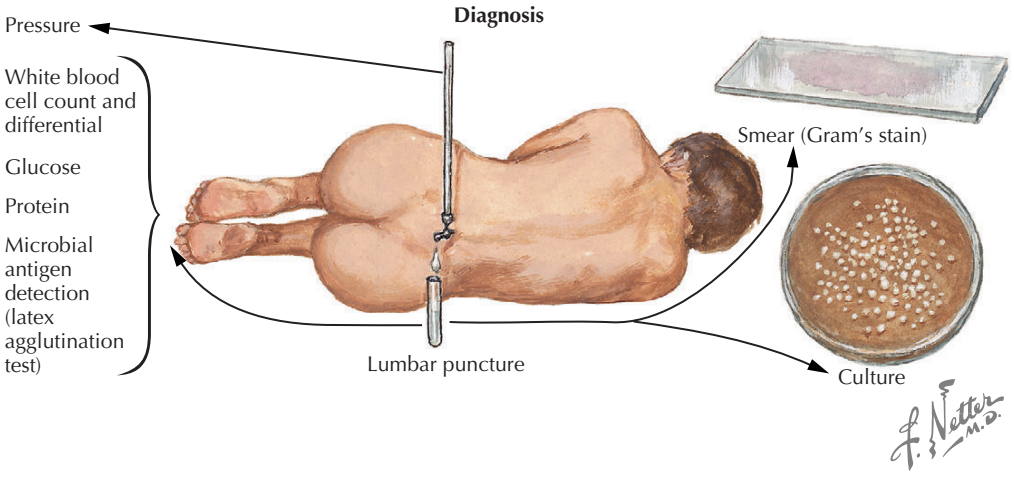


Figure 37-4 Lumbar puncture.

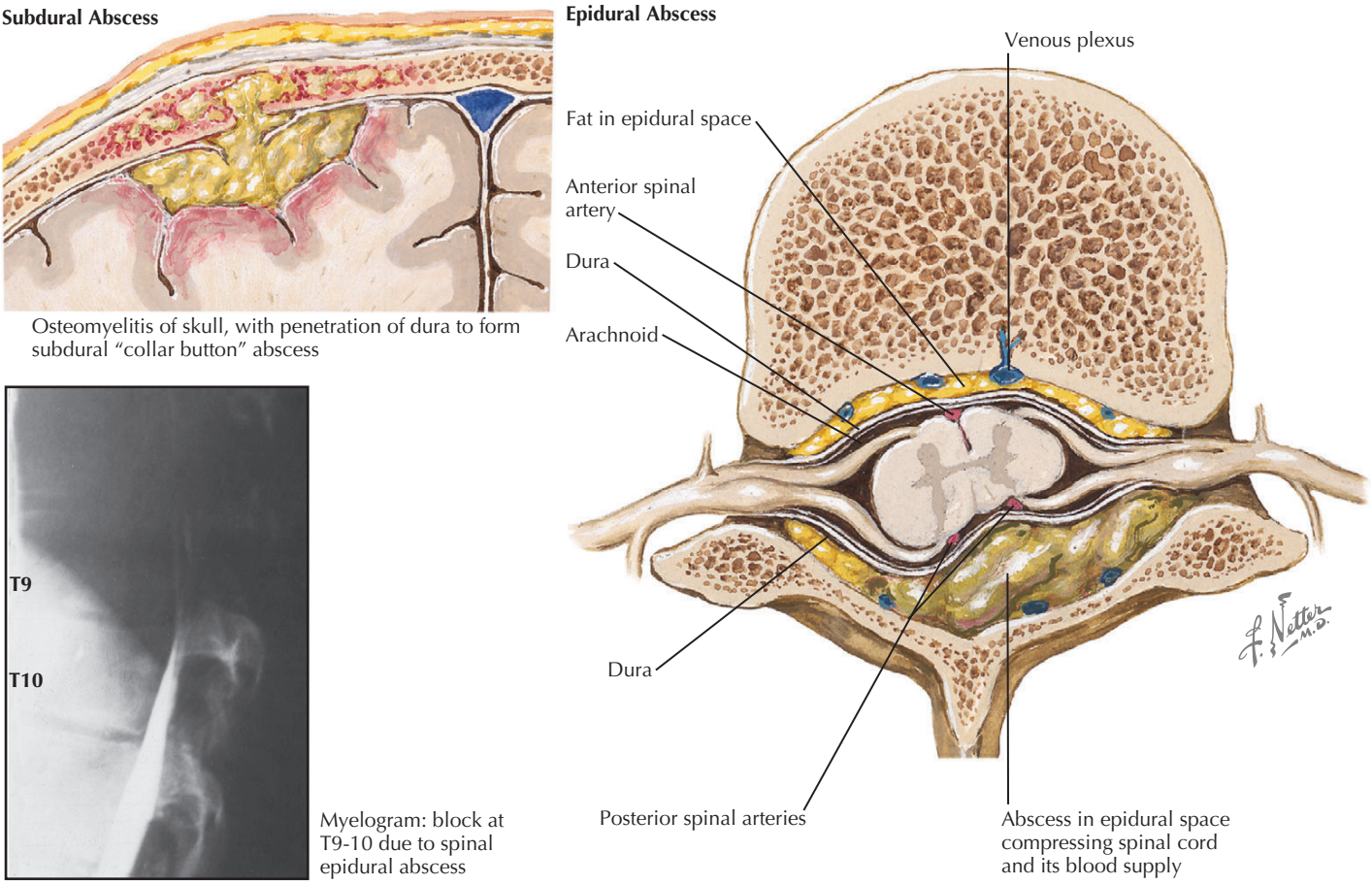


Figure 37-5 Parameningeal infections.

typically associated with a marked predominance of PMNs over mononuclear cells (Table 37-3), as well as elevated opening pressure, increased concentrations of CSF protein and lactate, and reduce glucose concentrations relative to the concomitant serum glucose level. Peripheral WBC count greater than 15,000, CSF leukocyte count greater than 1700, CSF neutrophil percentage greater than 80, protein greater than 230 mg/dL, and a CSF/blood glucose ratio less than 0.33 are all highly suggestive of a bacterial cause in adults. The values for children differ slightly, with CSF leukocyte count greater than 1800 with a neutrophil percentage greater than 80, CSF protein greater than 120 mg/dL, and CSF/blood glucose ratio less than 0.3. A scoring tool has been devised using these values and has been referred to as the "Meningitest." It is reported to have positive and negative predictive values of 97% and 94%, respectively.

Viral causes of meningitis can be associated with mildly elevated CSF WBC counts with a predominance of granulocytes very early in the course, whereas later the vast majority of cells are mononuclear. Mixed mononuclear and granulocytic CSF inflammation is typically seen with meningitis caused by *M. tuberculosis* and *L. monocytogenes.* The finding of eosinophils in the CSF is not diagnostic and may occur with bacterial, viral, and parasitic infections.

Analysis of the CSF must include routine gram staining, as this may help to identify the organisms in up to 70% of cases of bacterial meningitis. Identification of the invading organism must be attempted by appropriate cultures and other methods. With the availability of newer sensitive and specific methods to detect the genetic material of pathogens, older tests to detect microbial antigens (latex and limulus lysate tests) play a lesser role. Some viral and parasitic pathogens can best be diagnosed by the documentation of antibody production in the CSF compartment.

The diagnosis of meningitis in the postneurosurgical patient is often difficult, especially if the patient has had a ventricular or posterior fossa procedure. The triad of fever, neck stiffness, and change in neurologic status is nonspecific after neurosurgery. CSF analysis may be difficult to interpret, as many of the usual markers may be abnormal from brain manipulation, underlying brain pathology, or bleeding. The neurosurgical literature suggests the use of total CSF cellularity and glucose and lactate levels in the prediction of postoperative meningitis, but proof depends on documentation of a pathogen. Empirical therapy remains warranted in clinically suggestive cases.

Despite advances in microbiology culture and organism recovery, no organism can be identified in 10% to 30% of the CSF specimens in suspected bacterial meningitis. Although some organisms are difficult or impossible to culture, prior antibiotic therapy accounts for many of the negative cultures. In order to minimize the influence of antibiotics on recovery of

Table 37-3 Cerebrospinal Fluid Analysis in the Diagnosis of Meningitis*

PARAMETERS	WBC COUNT (cells/mm^3)	DIFFERENTIAL	GLUCOSE (mg/dl)	PROTEIN (mg/dL)	STAINS	ANTIBODY OR MOLECULAR STUDIES
Normal values	0-5/mm^3	Mononuclear	0.6 mg/dL of serum	23-38	Negative	
Routine bacterial, community acquired	>1000	>80 PMNs, lymphocytes occasionally in GNB neonatal disease	<40	100-500	Gram stain all CSF specimens Positive 60%-90%	PCR for partially treated disease or negative cultures in meningococcal disease Culture before treating
Listeria	100-5000	PMNs > lymphocytes 70%-80% Lymphocytes predominate 20%-30%	<40 in 40% of recent series	50-500 Most <200	May appear as diphtheroids on Gram stain Positive smears <40%	PCR may prove helpful
Tuberculous	50-300	Mononuclear, PMNs in early and treated disease (IRIS)	<45 in 80%	50-300 Values 1-3 g with CSF obstruct	Large volume (15 mL) gives higher yield for both AFB stain and culture	PCR available from reference laboratories
Lyme (Borrelia)	Usually <500	Mononuclear >90% lymph	Normal unless longstanding	Slight increase, up to 600 reported	No stains Patient should be seropositive by two-tiered ELISA–Western Blot	PCR sensitivity low Negative CSF antibody or PCR does not exclude CNS disease
Syphilis (findings more common in secondary disease)	>10 cells in most cases	Mononuclear	<55 mg/dL in 50%	Increased in 78% 50-250	No stains available	CSF FTA-ABS combined with serum antibody PCR promising
Cryptococcus-negative HIV	20-200	50%-80% mononuclear	<45	>45	India ink + 50%	CSF + 90% negative serum antigen test result does not rule out CNS infection; LP needed
Cryptococcus-HIV	0-5	50%-80% mononuclear	<45	>45	Organism count often quite high—India ink + 70%	CSF antigen positive in ≥90% Negative serum antigen test result rules out CNS disease
Coccidiomycosis	5-200	Mononuclear >10% eosinophils in up to 30% patients	<45 Occasional values <10	50-200 Values 1-3 g with CSF obstruction	Spherules occasionally seen on smear, indicate high infectious burden	Complement fixation antibodies for IgG or immunodiffusion IgM and IgG in CSF
Viral, general	50-1000 (>1180 predictor of bacterial diagnosis)	Early PMN (12-24 hr) with enterovirus Most other viruses >90% lymphocytes	>45	50-250	Negative	Antibody test for West Nile preferred PCR for others often not available Rabies PCR available from CDC
Mumps, HSV infection, lymphocytic choriomeningitis virus	50-250 Occasionally 500+	>90% lymphocytes	Rarely <45	50-300	LCM may look like gram-positive coccidiomycosis on Gram stain	PCR for HSV preferred test PCR for mumps and measles limited availability

AFB, Acid-fast bacillus; *CDC*, Centers for Disease Control and Prevention; *CNS*, central nervous system; *CSF*, cerebrospinal fluid; *ELISA*, enzyme-linked immunosorbent assay; *FTA-ABS*, fluorescent treponemal antibody absorption test; *GNB*, gram negative bacilli; *HIV*, human immunodeficiency virus; *HSV*, herpes simplex virus; *IgG*, immunoglobulin G; *IgM*, immunoglobulin M; *IRIS*, immunologic reconstitution inflammatory syndrome; *LCM*, lymphocytic choriomeningitis; *LP*, lumbar puncture; *PCR*, polymerase chain reaction; *PMN*, polymorphonuclear leukocyte; *WBC*, white blood cell.

*Values recorded on this chart should be considered for reference and are not absolute.

organisms from CSF, samples should be cultured in a large excess of liquid broth if patients received antibiotics before the LP. With this, most bacterial pathogens should still be recovered from the CSF up to at least 2 hours after effective therapy has been initiated.

MANAGEMENT OF PATIENTS WITH SUSPECTED MENINGITIS AND ANTIMICROBIAL THERAPY

The prognosis of patients with bacterial meningitis is critically dependent on rapid initiation of effective therapy. Consequently, the timely accomplishment of certain objectives is a hallmark of the appropriate management of patients with bacterial meningitis. These objectives include the following:

- Early consideration of bacterial meningitis in the differential diagnosis in patients with suggestive symptoms (see previous section on clinical features)
- Establishment of venous access to immediately obtain blood samples for blood cultures and other laboratory tests
- Cardiopulmonary stabilization, if necessary; airway protection measurements if indicated
- Decision about the sequence of LP and head CT (see previous section on diagnosis)
- Institution of appropriate empirical antibiotic therapy, combined with adjunctive therapy with dexamethasone, if appropriate, either immediately after blood samples have been drawn or after the LP has been performed (if LP is performed without prior CT)
- Decision about admission to the intensive care unit and assessment of need for intracranial pressure monitoring and control of intracranial hypertension

These objectives are to ensure that there is no delay in instituting empirical therapy and life-supporting measures, while maximizing the chance of detecting the causative agent. Corresponding local guidelines and procedures should be established and disseminated.

Empirical Antibiotic Therapy

Several guidelines, including one by the IDSA in 2004, cover in detail the recommendations regarding empirical and guided antimicrobial therapy of bacterial meningitis. Because the spectrum of potential pathogens differs somewhat among different patient groups, empirical therapy has to be selected based on patient characteristics, but also on local resistance patterns, particularly of pneumococci.

In adult patients the primary organisms to be covered are *S. pneumoniae* and *N. meningitides*, plus *L. monocytogenes* in the elderly or immunocompromised patient. Pneumococci are typically treated with a third-generation cephalosporin, which is combined with vancomycin if high level resistance to β-lactam antibiotics is a concern. The cephalosporin is also highly effective against meningococci that continue to be uniformly sensitive to this class of drugs. Neither cephalosporins nor vancomycin are adequate for the treatment of *Listeria*, for which an aminopenicillin has to be added to the empirical regimen. In allergic patients the cephalosporin can be replaced by meropenem (if not contraindicated because of type I penicillin allergy) or a quinolone to cover pneumococci and meningococci, and the aminopenicillin can be replaced by trimethoprim-sulfamethoxazole to cover *Listeria*.

Neonates should be empirically treated with ampicillin plus cefotaxime or ampicillin plus an aminoglycoside to include *L. monocytogenes*, group B streptococci, and gram-negative rods in the coverage. For infants and children, the choice of empirical therapy is not different from that for adults younger than 50 years old without immunocompromising conditions (i.e., a cephalosporin plus vancomycin).

In patients with postneurosurgery meningitis, staphylococci and gram-negative rods have to be covered by the empirical therapy, and a combination of vancomycin with a broad-spectrum β-lactam (usually cefepime or meropenem) is recommended.

The cited guidelines also specify the most appropriate therapy for the guided therapy once the infecting organism has been identified and tested for antibiotic sensitivities. The guidelines also make recommendations regarding the appropriate duration of antibiotic therapy depending on the isolated pathogen.

Among the viral causes of encephalitis, effective therapy is available only for herpes viruses and human immunodeficiency virus. Empirical therapy for viral meningitis with acyclovir can typically be withheld until initial evaluation has confirmed the diagnosis of herpes meningitis. However, sometimes the possibility of herpes simplex encephalitis is entertained in patients with suspected bacterial meningitis and severe mental status alterations. In these patients, empirical coverage with high-dose intravenous acyclovir (15 mg/kg every 8 hours) may be indicated until the cause of the disease has been clarified.

For dosages of antibiotics, see published recommendations (http://prod.hopkins-abxguide.org/diagnosis/nerurologic/bacterial_meningitis).

Adjunctive Therapy with Dexamethasone

Despite more than two decades of clinical research, the role of adjunctive therapy of bacterial meningitis with corticosteroids, in particular dexamethasone, is still not completely clear. Available data suggest that children with *H. influenzae* meningitis showed a beneficial effect of dexamethasone mostly on hearing loss. The benefit is less clear in children with pneumococcal meningitis or with regard to other endpoints, such as overall neurologic outcome. On the other hand, a prospective multicenter study in adults in Europe has documented a clear benefit with regard to adverse outcome (death or severe neurologic sequelae) in patients with pneumococcal meningitis. More recent studies from Africa and Asia have not been able to reproduce the marked benefit found in the European studies, in part probably because of differences in study populations and the medical setting.

Despite some lingering questions, we agree with the 2004 recommendations by the IDSA that dexamethasone should be used in children with suspected or proven *H. influenzae* meningitis, as well as in adults with suspected or proven pneumococcal meningitis. Regarding dexamethasone for childhood meningitis

caused by *S. pneumoniae*, the available data are inconclusive, and there is no agreement among experts, leaving this difficult decision to the treating physician and the family of the affected child. The recommended dose is 0.15 mg/kg every 6 hours for a maximum of 4 days, and the first dose should be given a few minutes before or concomitant with the first antibiotic dose.

Dexamethasone has documented benefits in reducing intracranial hypertension during meningitis and should be considered in critically ill patients in the intensive care unit. Several other approaches to reduce intracranial pressure have been attempted, but no rigorously controlled trials are available. These include elevation of the upper body, repeated removal of CSF, mannitol, pentobarbital coma, and others. A clinical study found a beneficial outcome in children with bacterial meningitis when glycerol was included in the adjunctive treatment. Hyperventilation, if it leads to significant CO_2 reduction, can cause harm by exaggerating vasospasms and cerebral ischemia and should not be used as a primary approach to reduce intracranial hypertension in patients with meningitis.

PROGNOSIS

In patients with bacterial meningitis, mortality rates remain high in cases caused by *S. pneumoniae* and *L. monocytogenes* (20% to 30%) and are somewhat lower with *N. meningitidis* (5% to 10%). If carefully examined, up to 50% of patients who survive pneumococcal meningitis will show signs of neuronal impairment that may be permanent in many of them. Thus bacterial meningitis remains a serious disease with regard to both mortality and morbidity.

Viral meningitis (excluding encephalitis) has usually a much more favorable prognosis, with negligible rates of mortality and long-term sequelae, even though many patients take weeks to months to fully recover after a severe form of viral meningitis.

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Osteomyelitis

Russell W. Steele

38

ABSTRACT

There are three distinct presentations of osteomyelitis, defined by the mechanism by which infectious agents are introduced into bone: (1) hematogenous infection from bacteremia; (2) local spread from contiguous foci such as abscesses, insect bites, or infected exanthematous lesions; and (3) direct inoculation after trauma, invasive procedures, or surgery. There is no particular geographic distribution, and the incidence is not known because it is not a reportable disease, but bone infection is relatively common, with cases diagnosed by most primary care physicians at least yearly. It is more common in males (2.5 times more than in females), and approximately 40% of cases occur in patients younger than 20 years of age.

Hematogenous Osteomyelitis

Hematogenous osteomyelitis originates in the metaphysis of tubular long bones adjacent to the epiphyseal growth plate. Thrombosis of the low-velocity sinusoidal vessels from trauma or embolization is considered the focus for bacterial seeding in this process. This avascular environment allows invading organisms to proliferate while avoiding the influx of phagocytes, the presence of serum antibody and complement, the interaction with tissue macrophages, and other host defense mechanisms. The proliferation of organisms, the release of organism enzymes and byproducts, and the fixed-volume environment contribute to progressive bone necrosis (Figure 38-1).

Clinical Features

The signs, symptoms, and pathologic progression vary by age (Figure 38-2 and Table 38-1). Tubular long bones are primarily involved, especially of the lower extremities (Table 38-2).

Etiology

The bacterial and fungal causes of hematogenous osteomyelitis demonstrate an age-specific pattern (Table 38-3). Other epidemiologic factors, predisposing chronic diseases, and exposure history may suggest unusual pathogens (Table 38-4).

Differential Diagnosis

The differential diagnosis of hematogenous osteomyelitis includes pyomyositis, cellulitis, toxic synovitis, septic arthritis, thrombophlebitis, or, in a patient with sickle cell disease, a bone infarction.

Chronic Osteomyelitis

By definition, continuation of bone infection for more than 30 days is termed *chronic osteomyelitis*. This can occur with both hematogenous and contiguous-focus disease, but it is most commonly seen with contaminated open fractures or placement of orthopedic stabilizing devices such as metal rods and screws. Persistent drainage and development of sinus tracts are common. Bone loss may be extensive (Figure 38-3). Removal of the foreign body and any necrotic bone is usually necessary to clear the infection, and antibiotics must be continued for months until there is clear clinical and radiographic evidence of resolution.

Diagnostic Approach

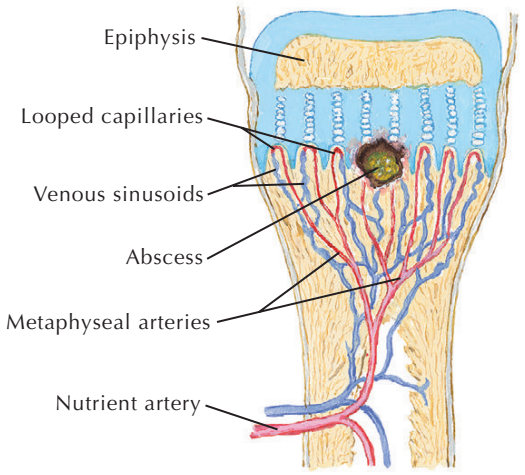
The diagnosis of osteomyelitis is confirmed with isolation of organisms from bone, subperiosteal exudate, or contiguous joint fluid. Needle aspiration through normal skin over involved bone at a subperiosteal site or at the metaphyseal area combined with aspiration from a potentially involved joint should be performed by an orthopedic surgeon. Aspirates of involved focal areas yield positive cultures in only 50% to 60% of cases that have not been pretreated with antibiotics. However, because early institution of antimicrobial therapy is so common, even fewer suspected cases are culture positive.

Blood cultures have been reported to be positive in as many as 50% of cases, so samples should be obtained routinely before initiation of antimicrobial therapy.

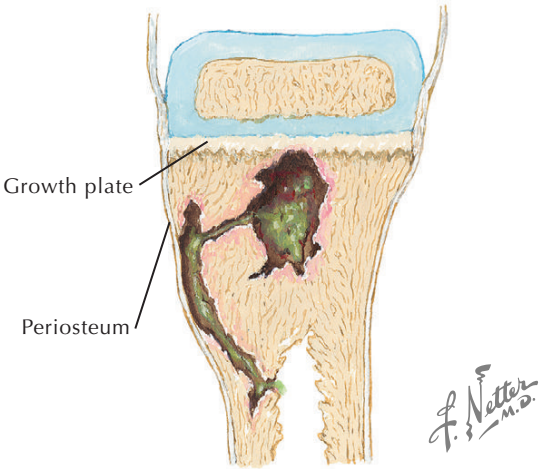
The most sensitive radiographic procedure for establishing a diagnosis of osteomyelitis, localizing disease, and determining the need for surgical intervention is magnetic resonance imaging (MRI). However, many experts still prefer a technetium bone scan because it is less expensive and will identify multifocal disease. Routine plain radiographs should initially be obtained, because they are readily available and may identify other causes of bone pain. The diagnosis of osteomyelitis on routine radiographs can be subtle to obvious (Table 38-5) depending on the duration of disease and are adequate for differentiating patients with trauma, including physical abuse. Radiographs are also fairly sensitive for identifying leukemic infiltrates, which represent one important cause of bone pain.

Diagnosis of bone infection is enhanced with the use of MRI scans, which can be completed in minutes, or technetium scanning, which requires 2 hours to complete. One of these studies should be obtained for any patient who has obvious evidence of focal bone pathology, fever of undetermined cause with bone tenderness on physical examination, and an elevated C-reactive protein (CRP) or sedimentation rate, or suggestive findings on routine radiographs. Both imaging procedures can also aid in directing aspirate procedures for diagnosis and culture.

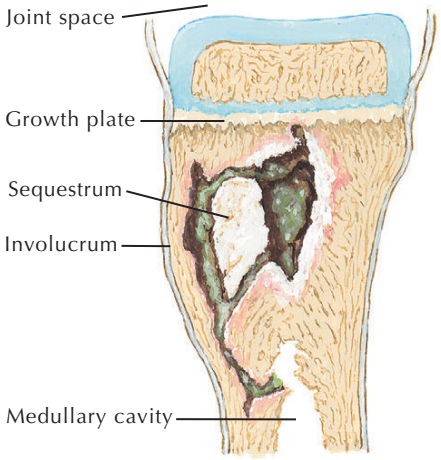
Pathogenesis



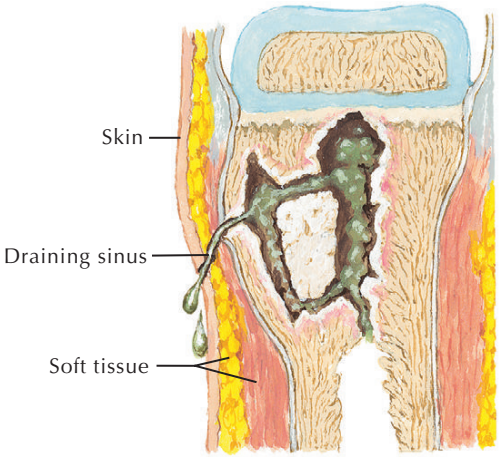
Terminal branches of metaphyseal arteries form loops at growth plate and enter irregular afferent venous sinusoids. Blood flow is slowed and turbulent, predisposing to bacterial seeding. In addition, lining cells have little or no phagocytic activity. Area is catch basin for bacteria, and abscess may form.



Abscess, limited by growth plate, spreads transversely along Volkmann canals and elevates periosteum; extends subperiosteally and may invade shaft. In infants under 1 year of age, some metaphyseal arterial branches pass through growth plate, and infection may invade epiphysis and joint.



As abscess spreads, segment of devitalized bone (sequestrum) remains within it. Elevated periosteum may also lay down bone to form encasing shell (involucrum). Occasionally, abscess is walled off by fibrosis and bone sclerosis to form Brodie abscess.



Infectious process may erode periosteum and form sinus through soft tissues and skin to drain externally. Process is influenced by virulence of organism, resistance of host, administration of antibiotics, and fibrotic and sclerotic responses.

Figure 38-1 Pathogenesis of hematogenous osteomyelitis.

Table 38-1 Hematogenous Osteomyelitis: Signs and Symptoms

	NEWBORN	OLDER INFANT AND YOUNG CHILD (2 wk–4 yr)	OLDER CHILD, ADOLESCENT, AND ADULT (>4 yr)
Systemic symptoms*	Clinical sepsis, irritable, especially to touch; pseudoparalysis	Pain, limp, refusal to use affected limb	Focal signs and symptoms, less restriction of movement; local pain; mild limp; fever, malaise
Signs	Red, swollen, discolored local site; massive swelling	Marked focality; point tenderness; well-localized pain	Focal signs; point tenderness very localized
Pathology	Thin cortex; dissects into surrounding tissue	Cortex thicker; periosteum dense	Metaphysical cortex thick; periosteum fibrous and dense
Progression	Nidus (purulent) rapidly progresses†; subperiosteal purulence spreads; secondary septic arthritis	Subperiosteal abscess and edema; metaphyseal involvement	Cortical rupture rare
Radiograph	Useful early—periosteal and bony changes	Later findings confirmatory; early changes—deep soft-tissue swelling	Bony changes apparent only after 7-10 days of involvement

*May be subclinical; constitutional symptoms (fever, malaise, anorexia, irritability) are no different among the different age groups; also no correlation with severity of constitutional symptoms and ultimate severity of subsequent osteomyelitis.
†Residual effects may be anticipated in up to 25% of newborns.

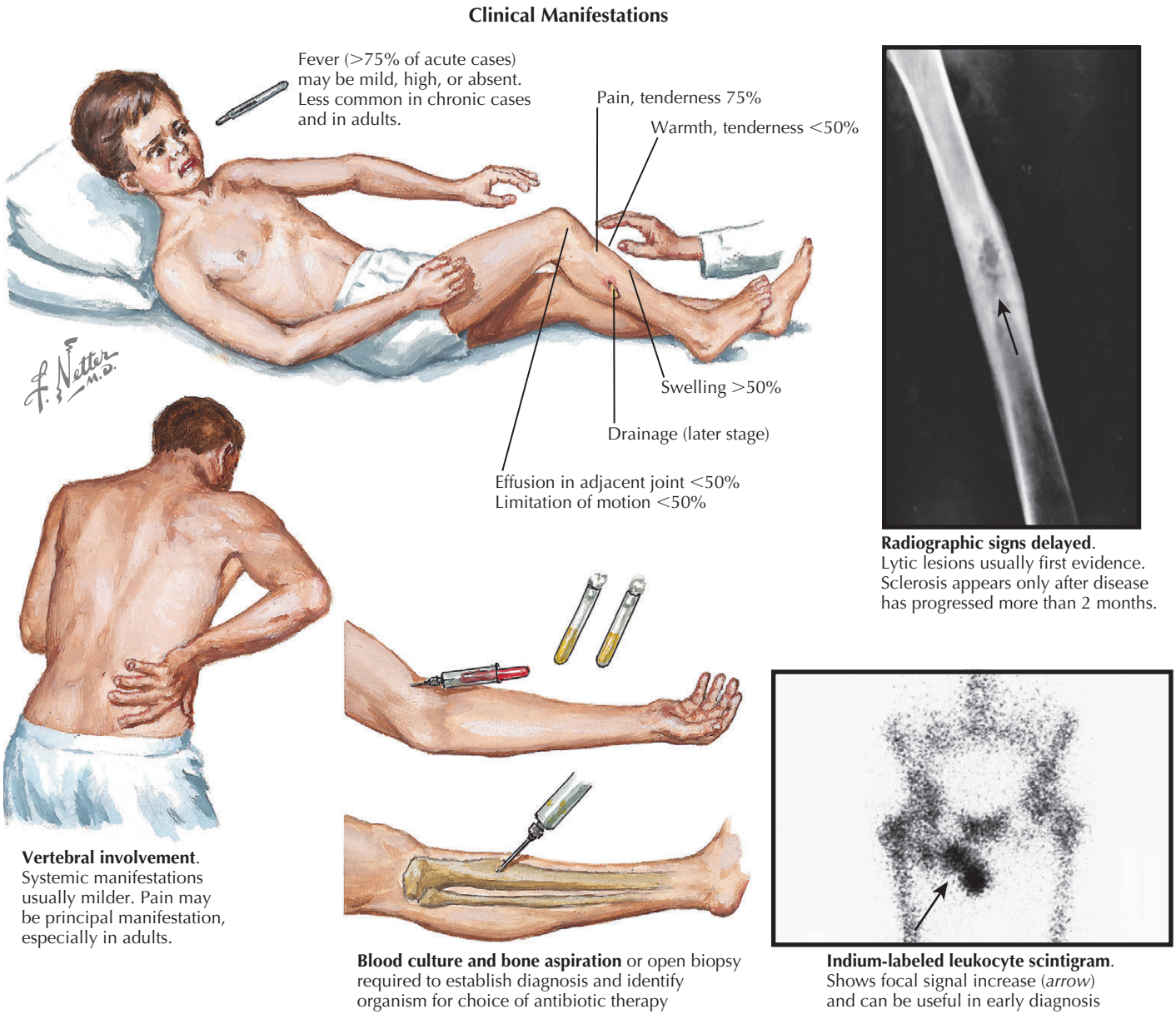


Figure 38-2 Clinical manifestations of hematogenous osteomyelitis.

Table 38-2 Site of Bone Involvement

SITE	FREQUENCY (%)
Femur	36
Tibia	33
Humerus	10
Fibula	7
Radius	3
Calcaneus	3
Ilium	2

Table 38-3 Etiology of Hematogenous Osteomyelitis

NEONATES		INFANTS, CHILDREN, AND ADULTS	
Staphylococcus aureus	40%	*S. aureus*	80%
Group B streptococci	30%	Group A streptococci	7%
Coliforms	10%	*Salmonella* species	6%
Others	20%	Others	7%
Neisseria gonorrhoeae		Coliforms	
Pseudomonas aeruginosa		*Streptococcus pneumoniae*	
Candida species		*Candida* species	
		Anaerobes	

In situations where osteomyelitis is suspected on physical examination but the technetium bone scan is equivocal or nondiagnostic, secondary radionuclide imaging including MRI may be performed. In selected cases, including pelvic, vertebral, or small bone (hands or feet) osteomyelitis, the use of MRI or computed tomography (CT) is useful in establishing a diagnosis or directing surgical intervention. A technetium- or indium-labeled white blood cell (WBC) scan using tagged autologous leukocytes requires 24 hours of imaging for completion and has only limited usefulness. Gallium scanning requires 24 to 48 hours, may be difficult to read (midline scans) owing to uptake in the bowel, and has been replaced by MRI, CT, and WBC scans.

Table 38-4 Specific Causes of Osteomyelitis

CLINICAL CIRCUMSTANCES	PROBABLE CAUSE
Common Causes	
Human bite	Anaerobes
Dog or cat bite	*Pasteurella multocida*
Puncture wound of foot	*Pseudomonas aeruginosa*
Sickle cell disease	*Salmonella* species
Rheumatoid arthritis	*Staphylococcus aureus* (from joint) *P. multocida*
Diabetes mellitus	Fungi
Newborns	Group B streptococci *Escherichia coli* *Salmonella* species
Uncommon Causes	
Facial and cervical area; in the jaw; sinus drainage; lytic bone changes with "eggshell" areas of new bone	*Actinomyces* species
Vertebral body or long bone abscesses; systemic signs and symptoms	*Brucella* *Salmonella*
Regional distribution; systemic findings; vertebral body, skull, long bone involvement	*Coccidioides*
Skin lesion; pulmonary involvement; skull and vertebral bodies most common, but long bone involvement is reported	*Blastomyces*
Very distinct, slowly progressive bony lesions can occur	*Cryptococcus*
Exposure to cats, fever of unknown origin, liver granulomas, chronic adenitis	*Bartonella henselae* (cat scratch disease)

Nonhematogenous Osteomyelitis

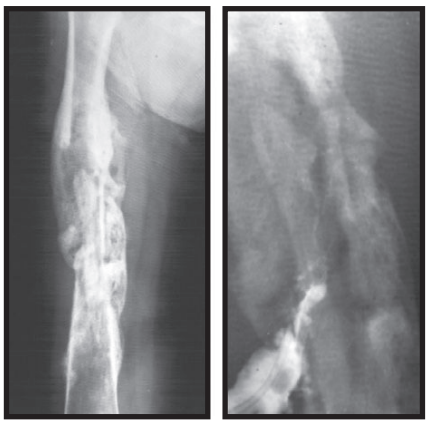
Bone involvement arises through spread from a contiguous focus of infection or direct inoculation. Common predisposing factors are trauma, burns, and nail puncture wounds of the foot. Infections in deep sites such as retropharyngeal and renal abscesses may also spread to bone (Figure 38-4). The following are the more common types of nonhematogenous osteomyelitis.

Pseudomonas Osteochondritis

The predilection of *Pseudomonas* to involve cartilaginous tissue and the relative amount of cartilage in children's tarsal-metatarsal region are the reasons for this infection being classified as an "osteochondritis." The classic history is a nail puncture through a tennis shoe. This entity is seen as early as 2 days postinjury but frequently requires up to 21 days to manifest clinically. The proper initial management of this trauma is vigorous irrigation and cleansing of the puncture wound in conjunction with tetanus prophylaxis. On diagnosis of *Pseudomonas* osteochondritis from

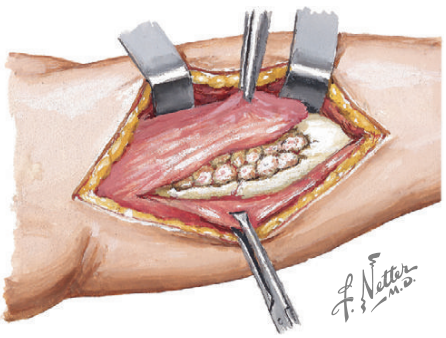
Table 38-5 Radiographic Diagnosis of Hematogenous Osteomyelitis

DAY	CHANGES
0-3	Local, deep soft-tissue swelling; near metaphysical region or with localized findings
3-7	Deep soft-tissue swelling; obscured translucent fat lines (spread of edema fluid)
10-21	Variable—bone specific; bone destruction, periosteal new bone formation



Fracture of femur treated with intramedullary rod. Postoperative infection developed and rod was removed. Persistent drainage and sinus tract developed. Radiograph *at left* shows sequestra and radiolucent lesions consistent with chronic osteomyelitis. Sinogram *at right* reveals sinus tract extending to site of fracture.

Sequestra surgically removed, sinus tract excised, and all dead and infected tissue thoroughly débrided.



Bone defect packed with cancellous bone autograft from ilium overlaid with muscle flap from vastus lateralis muscle. Patient remained free of pain and drainage.

Figure 38-3 Chronic osteomyelitis.

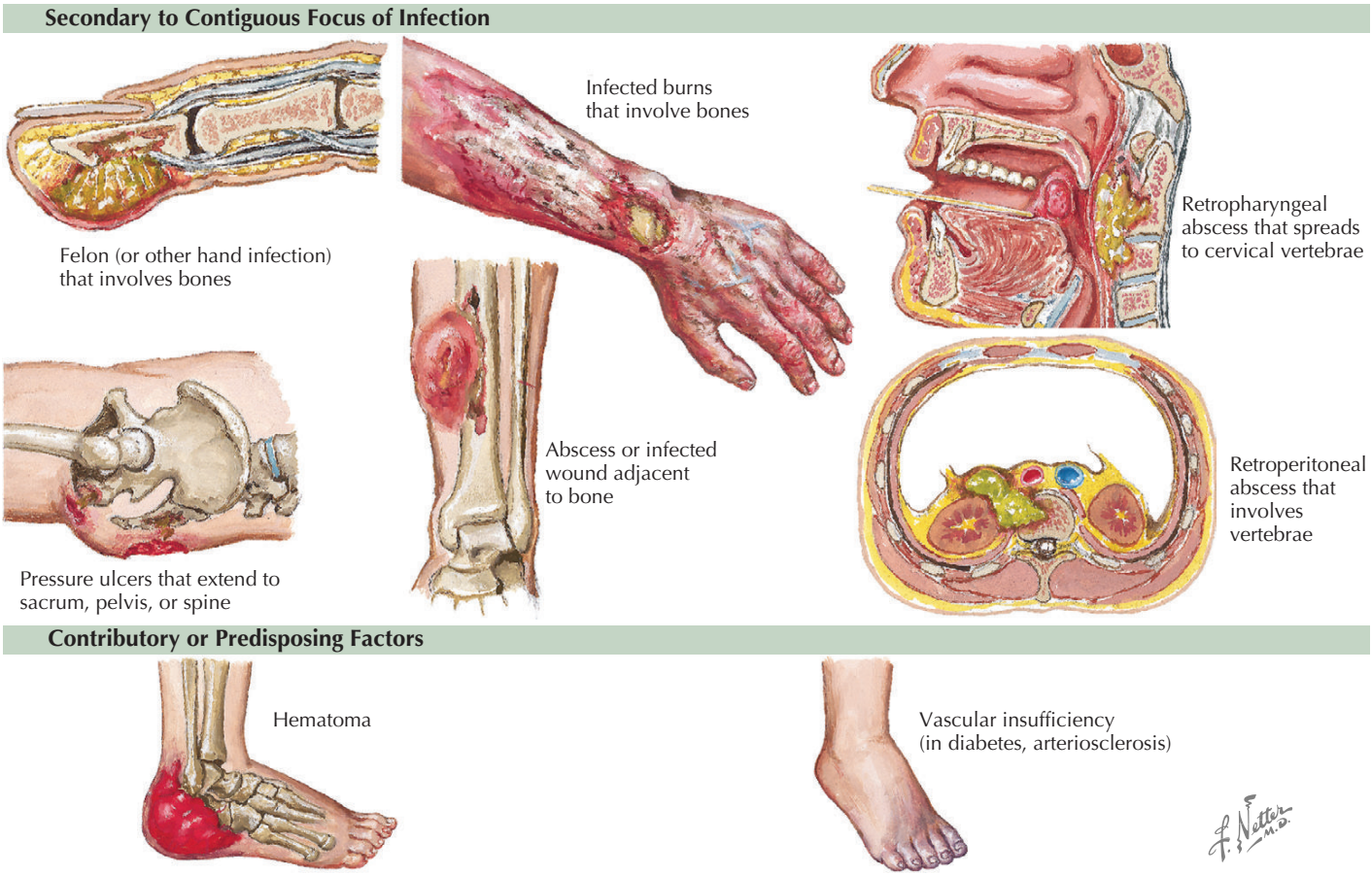


Figure 38-4 Direct causes of osteomyelitis.

wound drainage culture or surgical curettage culture, intravenous antibiotics should be initiated and guided by antibiotic sensitivity testing. The crucial factor in successful therapy is complete evacuation of all necrotic, infected bone and cartilage. If this is accomplished, only 7 to 10 days of parenteral antibiotics are necessary (depending on soft-tissue healing and appearance) for completion of therapy. *Pseudomonas* osteochondritis of the vertebrae or pelvis should lead one to suspect intravenous drug abuse as a cause.

Patellar Osteochondritis

Patellar osteochondritis is seen most commonly in children 5 to 15 years of age when the patella has significant vascular integrity. Direct inoculation via a puncture wound yields symptoms within 1 week to 10 days. Constitutional symptoms are uncommon. *Staphylococcus aureus* is the most common cause. Radiographs may take 2 to 3 weeks to show bone sclerosis or destruction.

Contiguous Osteochondritis

In contrast to other forms of bone and cartilage infection, contiguous osteochondritis is more common in adults. It is associated with nosocomially infected burns or penetrating wounds. The clinical course characteristically includes 2 to 4 weeks of local pain, skin erosion, ulceration, or sinus drainage. Multiple organisms are common, and draining sinus cultures correlate well with bone aspirate or biopsy cultures. *S. aureus*, streptococci, anaerobes, and nosocomial gram-negative enterics are the causative organisms; peripheral leukocyte count or erythrocyte sedimentation rate is usually normal. It is important to be aware of predisposing conditions (Table 38-6).

Pelvic Osteomyelitis

Bones involved, in order of frequency (highest to lowest), are the ilium, ischium, pubis, and sacroiliac areas. The tendency for multifocal involvement is high in the pelvis compared with other sites. The symptoms may be poorly localized with vague onset; hip and buttock pain with a limp are frequently the only findings. Tenderness to palpation in the buttocks or the sciatic notch or positive sacroiliac joint findings suggest this diagnosis. The differential diagnosis includes mesenteric lymphadenitis, urinary tract infection, and acute appendicitis. Patients with inflammatory bowel disease have an increased risk for the development of pelvic osteomyelitis.

Vertebral Osteomyelitis

The vertebral venous system is valveless with a low-velocity bidirectional flow, likely the predisposing factors for vertebral

Table 38-6 Predisposing Conditions for Contiguous Osteochondritis

Closed fractures	Osteomyelitis one to several weeks postfracture; after postfracture pain subsides, the pain recurs with progression; local erythema, warmth, and fluctuation; fever common; osteomyelitis applies to this circumstance
Open fractures	Thorough debridement and wound cleansing paramount; lower infection rates have been reported in patients receiving prophylactic first-generation cephalosporin for open fractures; the consequence of infection can be significant; *Staphylococci, Streptococci,* anaerobes, and *Clostridium* species or gram-negative enterics, depending on the environment related to the trauma, should be considered; tetanus prophylaxis vital
Hemodialysis	Increased risk because of multiple procedures with intravascular cannulas; ribs, thoracic spine, and bones adjacent to indwelling catheters; *Staphylococcus aureus* and *Staphylococcus epidermidis* commonly found

Table 38-7 Simplified Management of Osteomyelitis

PHASE	MANAGEMENT
Initial: day 0-3, inpatient	Obtain CBC and CRP Begin IV antibiotics (e.g., clindamycin) Repeat CBC and CRP when patient is afebrile and clinical response observed CRP <3 mg/dL or returning to normal, proceed to next phase
Continued therapy: day 4-21, outpatient	Oral antibiotics (e.g., linezolid [or cephalexin if susceptible]), at two to three times the usual dose
Completion: day 21 (ESR <30 mm/hr)	Obtain ESR; if <30 mm/hr, stop antibiotics
Delayed response: day 21-42 (ESR >30 mm/hr)	ESR >30 mm/hr Obtain MRI scan Surgical debridement if bone inflammation and destruction identified Continue oral antibiotics Repeat ESR at 42 days <30 mm/hr: stop antibiotics >30 mm/hr: repeat MRI scan, consider continued surgical and/or medical management ×6 wk

CBC, Complete blood count; *CRP,* C-reactive protein; *ESR,* erythrocyte sedimentation rate; *IV,* intravenous; *MRI,* magnetic resonance imaging.

Table 38-8 Antimicrobial Therapy for Osteomyelitis

INFECTION	ANTIMICROBIAL AGENTS
Empirical Therapy for Osteomyelitis and Septic Arthritis	
Neonate (0-28 days)	Vancomycin *plus* cefotaxime or ceftriaxone
Infants and children	Clindamycin, vancomycin, or linezolid
Puncture wound to foot	Gentamicin,* tobramycin, or amikacin *plus* ceftazidime, ticarcillin, or meropenem *plus* clindamycin, vancomycin, or linezolid†
Specific Therapy‡	
Methicillin-sensitive *Staphylococcus aureus* (MSSA)	Cefazolin, clindamycin, oxacillin, nafcillin
Methicillin-resistant *S. aureus* (MRSA)	Clindamycin, vancomycin, or linezolid
Group B streptococci	Penicillin
Group A streptococci	Penicillin
Streptococcus pneumoniae	Penicillin sensitive—penicillin Penicillin resistant—ceftriaxone, cefotaxime Penicillin or cephalosporin resistant—clindamycin, vancomycin, or linezolid
Enterobacteriaceae	Meropenem, cefepime Alternative: aminoglycoside or third-generation cephalosporins, depending on sensitivities
Neisseria gonorrhoeae	Ceftriaxone
Pseudomonas aeruginosa	Aminoglycoside *plus* cefepime, ceftazidime, or ticarcillin
Salmonella species	Third-generation cephalosporins
Candida albicans	Amphotericin B ± 5-flucytosine or liposomal AmpB or fluconazole
Anaerobes	Penicillin, clindamycin, or metronidazole
Continuation: Oral Therapy§	
S. aureus	Clindamycin or linezolid Cephalexin if susceptible
Streptococci (group A)	Penicillin or amoxicillin
S. pneumoniae	Penicillin or amoxicillin; third-generation cephalosporins; clindamycin
Enterobacteriaceae	Ampicillin or trimethoprim-sulfamethoxazole (TMP-SMX)
N. gonorrhoeae	Cefixime
P. aeruginosa	Ciprofloxacin or other quinolones
Salmonella species	Amoxicillin, TMP-SMX or third-generation cephalosporins
C. albicans	Fluconazole
Anaerobes	Penicillin, metronidazole, or clindamycin
Culture negative	Coverage for *S. aureus* (see above)

*Aminoglycoside choice guided by *Pseudomonas* sensitivities in your hospital.
†Concomitant wound infection, Gram stain positive.
‡Inpatient or home intravenous therapy.
§Oral continuation (modified by sensitivity testing).

body osteomyelitis. It is common for two adjacent vertebrae to be involved while sparing the intervertebral disk. Spread to the internal venous system (epidural abscess) or the external venous system (paraspinous abscess) are complications of this infection.

The symptoms of vertebral osteomyelitis include constant back pain (usually dull), low-grade fever, and pain on exertion; the signs may include paraspinous muscle spasm, tenderness on palpation or percussion of the spinal dorsal processes, and limitation of motion. The symptoms can be present for 3 to 4 months without overt toxicity or signs of sepsis. Radiographs show rarefaction in one vertebral edge as early as several days and progress to marked destruction, usually anteriorly, followed by changes in the adjacent vertebrae and new bone formation.

Treatment

Staphylococci are the infecting organisms in 80% to 90% of cases with gram-negative enterics (associated with urinary tract infection), *Pseudomonas* species (intravenous drug abusers), and a small percentage of miscellaneous organisms (see Table 38-3). Because approximately half of *S. aureus* strains are methicillin resistant (MRSA), parenteral antibiotic therapy for presumed staphylococcal involvement including MRSA (e.g., clindamycin, vancomycin, or linezolid) should be initiated, with consideration given to a needle aspirate or bone biopsy for culture and sensitivity testing first. Treatment should also include surgical drainage (especially if cord compression is present) and immobilization (bed rest versus casting).

Most cases of hematogenous osteomyelitis are culture negative after 21 days of therapy (Table 38-7). Exceptions are vertebral osteomyelitis, which should be treated for 6 weeks, and puncture wound osteochondritis caused by *Pseudomonas*, which only requires 7 to 10 days of antimicrobial therapy after adequate surgical debridement (Table 38-8).

ADDITIONAL RESOURCES

Floyed RL, Steele RW: Culture-negative osteomyelitis, *Pediatr Infect Dis J* 22:731-735, 2003. *This paper describes the complexities of diagnosing and treating patients with negative blood and bone cultures.*

Kaplan SL: Challenges in the evaluation and management of bone and joint infections and the role of new antibiotics for gram positive infections, *Adv Exp Med Biol* 634:111-120, 2009. *This review article discusses old and new treatments for bone and joint infections in the era of MRSA infections.*

Peltola H, Unkila-Kallio L, Kallio MJK: Simplified treatment of acute staphylococcal osteomyelitis of childhood, *Pediatrics* 99:846-850, 1997. *Classic paper describes treatment of hematogenous osteomyelitis in children.*

Sawyer JR, Kapoor M: The limping child: a systematic approach to diagnosis, *Am Fam Physician* 79:215-224, 2009. *A clinically useful article that discusses the differential diagnosis of children with painful bone and joint symptoms and recommends a diagnostic and therapeutic approach.*

Weichert S, Sharland M, Clarke NM, Faust SN: Acute haematogenous osteomyelitis in children: is there any evidence for how long we should treat? *Curr Opin Infect Dis* 21:258-262, 2008. *An in-depth review article that discusses the type and duration of treatment of hematogenous osteomyelitis in children.*

Urinary Tract Infections

Dimitri M. Drekonja and James R. Johnson

39

ABSTRACT

Urinary tract infection (UTI), an acute bacterial infection of the urinary bladder, kidney, or collecting system, is among the most commonly diagnosed infectious diseases. The spectrum of disease is broad, ranging from simple cystitis to septic shock. Highly active and bioavailable oral antimicrobials have made therapy for UTI convenient and inexpensive. However, widespread use (including overuse) of these drugs has promoted the emergence of antimicrobial resistance, so clinicians now increasingly find themselves without reliably active oral options for empirical UTI therapy. Strategies for optimizing care and prolonging the utility of currently available drugs include (1) following evidence-based practice guidelines; (2) not treating patients with asymptomatic bacteriuria (ABU); and (3) using fluoroquinolone (FQ)-sparing therapy in appropriate patients.

RISK FACTORS

Known risk factors for UTI include female gender, a history of previous UTI, and, among adolescent or adult women, sexual intercourse and use of spermicide-based contraception. The risk of UTI also increases with age and the presence of certain conditions, including medical illnesses and anatomic or functional abnormalities of the urinary tract, which also lead to a more diverse range of causative microorganisms and decrease the likelihood of treatment success. Presence of such so-called complicating conditions defines a UTI episode as "complicated" versus "uncomplicated." Examples of complicating conditions include but are not limited to urinary obstruction (anatomic or functional), other urinary tract abnormalities, use of an intermittent or indwelling urinary catheter, nephrolithiasis, chronic kidney disease, and diabetes mellitus (Figure 39-1).

CLINICAL FEATURES

The clinical presentation of UTI varies with the anatomic site of infection. This chapter will present UTI as two main syndromes, cystitis and pyelonephritis, but will also touch on entities such as febrile UTI, ABU, and catheter-associated UTI (CAUTI). Cystitis denotes symptomatic infection or inflammation of the bladder, whereas pyelonephritis (Figure 39-2) denotes infection of the renal pelvis and parenchyma. Although the patient's clinical presentation may not accurately reflect the actual anatomic localization of UTI and inflammation, precise localization is not needed for effective management, because this can be guided adequately by the clinical presentation alone. The implications of medical and urologic complicating conditions will be discussed as appropriate.

Cystitis (Lower Urinary Tract Infection)

The typical presentation of cystitis is the abrupt onset of irritative voiding symptoms, including dysuria, frequency, and urgency. Gross hematuria and a change in urine odor may occur. Suprapubic discomfort and tenderness are sometimes present. Historical features that increase the likelihood of cystitis in a woman with some combination of these manifestations include absence of vaginal discharge, personal or family history of UTI, recent sexual activity, and spermicide-based contraception. Risk factors for UTI caused by an antimicrobial-resistant organism include recent antimicrobial use and, in the United States, recent travel to a developing country. Possible alternative diagnoses in patients with symptoms suggesting cystitis includes urethritis (caused by *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or herpes simplex virus) and vaginitis (caused by *Candida* or *Trichomonas* species). Other considerations include nephrolithiasis, irritant or atrophic vaginitis or urethritis, prostatism (in elderly men), and diabetes mellitus (especially if the main symptom is urinary frequency).

The microbiology of uncomplicated cystitis is well described. *Escherichia coli* is the predominant organism, causing 80% to 90% of cases. *Staphylococcus saprophyticus* is responsible for 5% to 10% of cases, with the remainder being caused by non–*E. coli* gram-negative bacilli or, rarely, enterococci. In the presence of a complicating condition, the microbiology of cystitis is more variable, although relevant data are scarce. *E. coli* remains the most commonly isolated pathogen but to a lesser extent than in uncomplicated cystitis, whereas other gram-negative bacilli and gram-positive cocci such as enterococci, *Streptococcus* species, *Staphylococcus aureus*, and coagulase-negative staphylococci are relatively more frequently encountered.

Pyelonephritis (Upper Urinary Tract Infection)

The presentation of pyelonephritis is varied, ranging from mild flank pain to urosepsis requiring aggressive hemodynamic support and other intensive care modalities. Typical features include flank or back pain and fever, often accompanied by nausea and vomiting. Relevant historical information is similar to that for cystitis, although gastrointestinal symptoms may be more important to elicit, to assess for both systemic toxicity and the feasibility of oral therapy. The pathognomonic physical finding of pyelonephritis is tenderness over the costovertebral angle, usually accompanied by fever; abdominal tenderness, tachycardia, and/or hypotension also may occur. The differential diagnosis includes diverticulitis, appendicitis, ectopic pregnancy, pelvic inflammatory disease, endocarditis, and nephrolithiasis. Perinephric and intrarenal abscess should also be

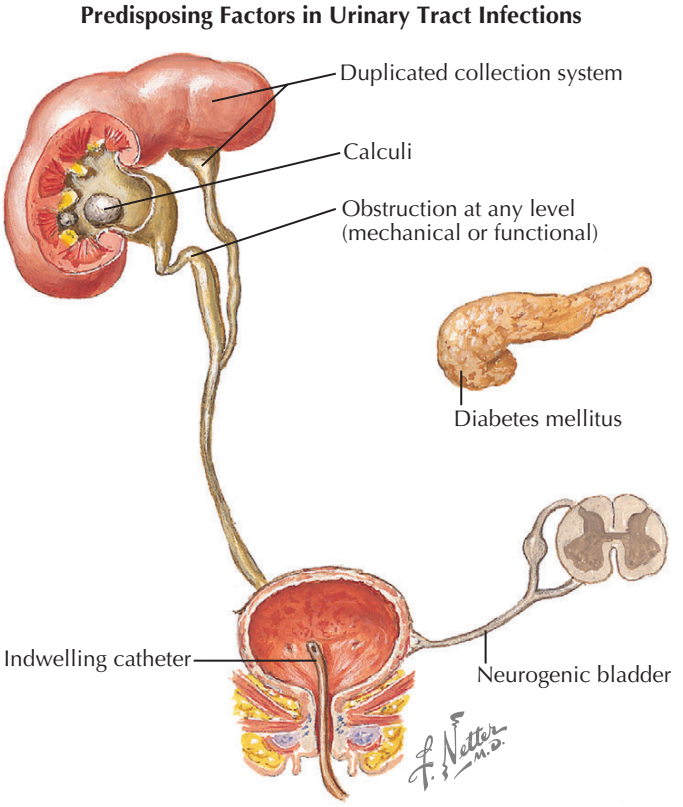


Figure 39-1 Possible complicating conditions predisposing to urinary tract infections that are more frequent, are more difficult to eradicate, and are caused by a more diverse list of microorganisms than uncomplicated urinary tract infection.

considered, the latter particularly if *S. aureus* is subsequently isolated from blood cultures. For both cystitis and pyelonephritis, underlying complicating conditions should be sought, because their presence may influence the diagnostic and therapeutic approach.

The spectrum of causative organisms in uncomplicated pyelonephritis is largely similar to that in uncomplicated cystitis, with *E. coli* being the most common pathogen. Minor differences include that *S. saprophyticus* is less common, whereas non–*E. coli* gram-negative bacilli are more common. In patients with a complicating condition the range of potential microorganisms is wider, confounding accurate prediction, although *E. coli* is usually still the single most prevalent organism.

Other Urinary Tract Infection Syndromes

Febrile UTI and *urosepsis* are terms sometimes applied to a syndrome characterized by fever presumably caused by UTI, with or without irritative voiding symptoms suggesting cystitis, but without clinical evidence of pyelonephritis (i.e., flank pain or tenderness). Blood cultures are positive in a minority of patients. ABU, infrequent in otherwise healthy individuals, increases in frequency with age and the presence of complicating conditions. Screening for ABU is discouraged for most patients, although it is recommended during pregnancy and before urologic surgery. CAUTI, a subset of complicated UTI, denotes UTI occurring in the presence of an indwelling urinary catheter. Although this term is commonly applied whenever a positive urine culture (UC) is encountered in a patient with an indwelling catheter, irrespective of the presence or absence of clinical manifestations attributable to UTI (e.g., suprapubic or urethral discomfort, or otherwise unexplained indicators of systemic inflammation), it is best used only when such manifestations are present. Presence of bacteriuria (or pyuria) in a catheterized patient who lacks such symptoms or findings should be interpreted not as CAUTI but as ABU occurring in the presence of an indwelling catheter (i.e., catheter-associated ABU), which does not require treatment.

Acute prostatitis, a relatively uncommon condition, is characterized by fever, perineal pain, dysuria, and extreme prostate tenderness. In contrast, patients with chronic prostatitis, a much more common condition, rarely have significant prostate tenderness. They often have only mild irritative voiding symptoms and therefore may initially be diagnosed as having cystitis. Chronic prostatitis should be considered as a possible underlying persisting nidus of infection in a man having repeated episodes of cystitis, particularly if the same organism is consistently isolated from UCs. Unapparent prostatic involvement is common in men with febrile UTI, as reflected in an acutely elevated prostate-specific antigen concentration that returns to baseline after resolution of the UTI episode.

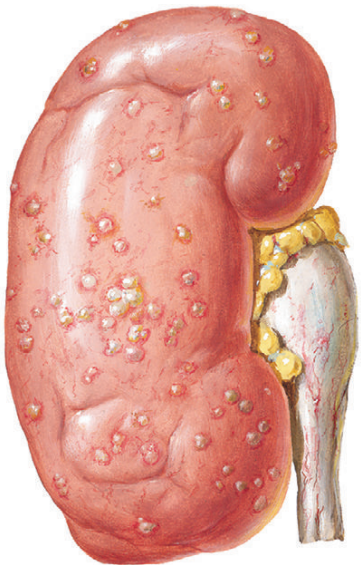
DIAGNOSTIC APPROACH

Cystitis

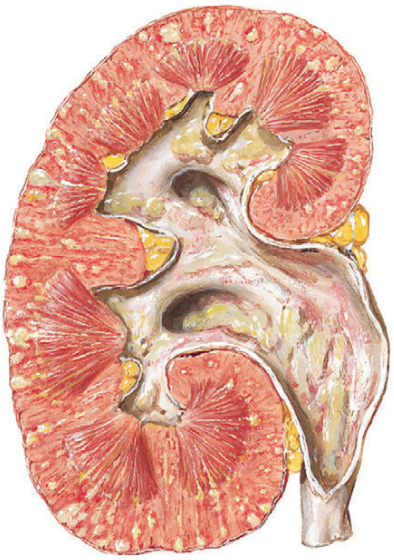
For patients with a first episode of cystitis, a history and physical examination directed toward the symptoms and findings discussed earlier, combined with urinalysis (UA), are usually sufficient to make the diagnosis of cystitis with fairly high certainty. The typical microscopic UA findings of cystitis are pyuria and bacteriuria (Figure 39-3). If a rapid test (e.g., urine dipstick) is used, surrogate markers (leukocyte esterase for pyuria, nitrites for bacteriuria) should be present. Positive urine microscopy or a rapid test in a patient with symptoms consistent with cystitis support initiation of antimicrobial therapy, which should be chosen based on local susceptibility data. UC is not generally recommended for reproductive-age women with a first episode of cystitis, although routine avoidance of UCs in such patients can lead to biased cumulative susceptibility data because of the resulting relative oversampling of patients with more severe or recurrent (previously treated) infections. In contrast, a pretherapy UC should be performed for suspected UTI occurring in older women, men, and patients with complicating conditions, because of the more unpredictable urine microbiology in these patient groups.

For patients with suspected cystitis who lack complicating conditions and have had a prior episode of laboratory-confirmed cystitis, the typical clinical constellation is sufficient to diagnose cystitis without a need for any urine testing. Indeed, management can be done safely over the telephone or by using self-initiated therapy without the patient even coming in for in-person evaluation. However, it may be advisable for a patient who in the past 6 months has been treated for cystitis or has

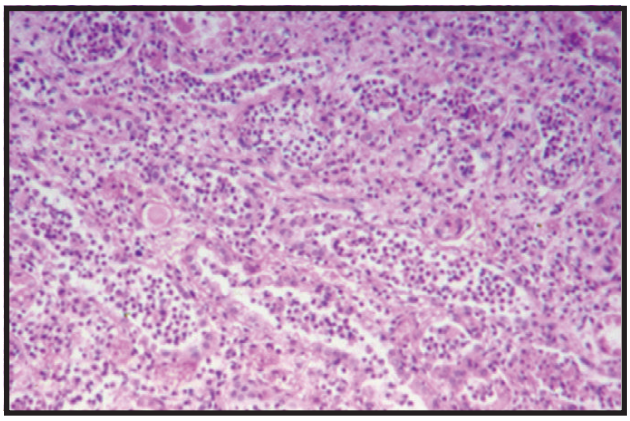
Pyelonephritis
Acute Pyelonephritis: Pathology



Surface aspect of kidney: multiple minute abscesses (surface may appear relatively normal in some cases)

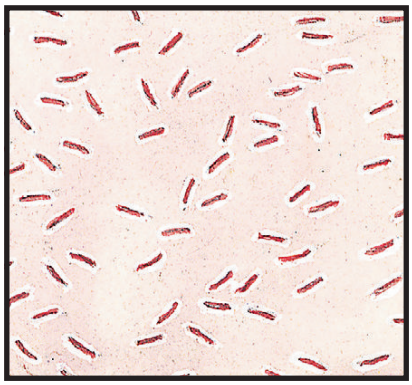


Cut section: radiating yellowish gray streaks in pyramids and abscesses in cortex; moderate hydronephrosis with infection; blunting of calyces (ascending infection)

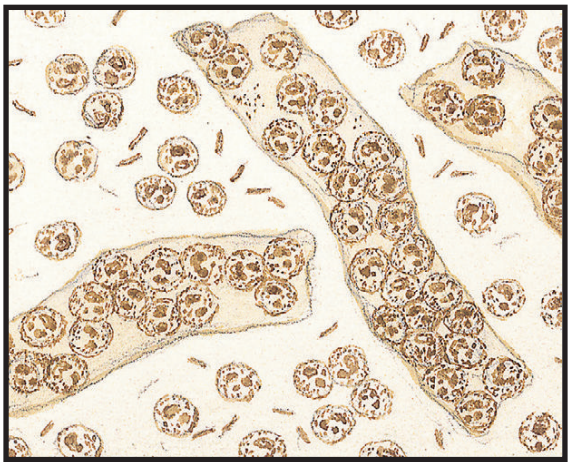


Acute pyelonephritis with exudate chiefly of polymorphonuclear leukocytes in interstitium and collecting tubules

Figure 39-2 Pyelonephritis, with numerous small abscesses visible on the serosal surface and within the renal parenchyma and pelvis. The image at right shows renal cortex with the typical neutrophilic infiltrate seen in acute pyelonephritis.



Urine smear stained to demonstrate Gram-negative bacilli, typical for either cystitis or pyelonephritis



Pyuria with white blood cell casts, typically seen only in pyelonephritis or noninfectious renal inflammatory processes

Figure 39-3 Microscopy findings of urinary tract infection.

received any antimicrobial therapy to have a pretherapy UC done as a part of the evaluation for suspected cystitis, even if the diagnosis is not in question, because of the increased risk of a resistant urine organism.

Pyelonephritis

The recommended diagnostic approach to pyelonephritis is similar to that for cystitis, with the exception that a pretreatment UC is highly advisable, both for early detection of possible resistance to the initial antimicrobial regimen and to guide a step-down to narrower-spectrum and oral therapy when possible. Aside from the UC and a serum creatinine measurement for adjustment of antimicrobial dosage, very little laboratory testing or imaging is needed. If the diagnosis is uncertain, the imaging modality of choice (to demonstrate pyelonephritis and its complications and to screen for other possible causes) is contrast-enhanced computed tomography.

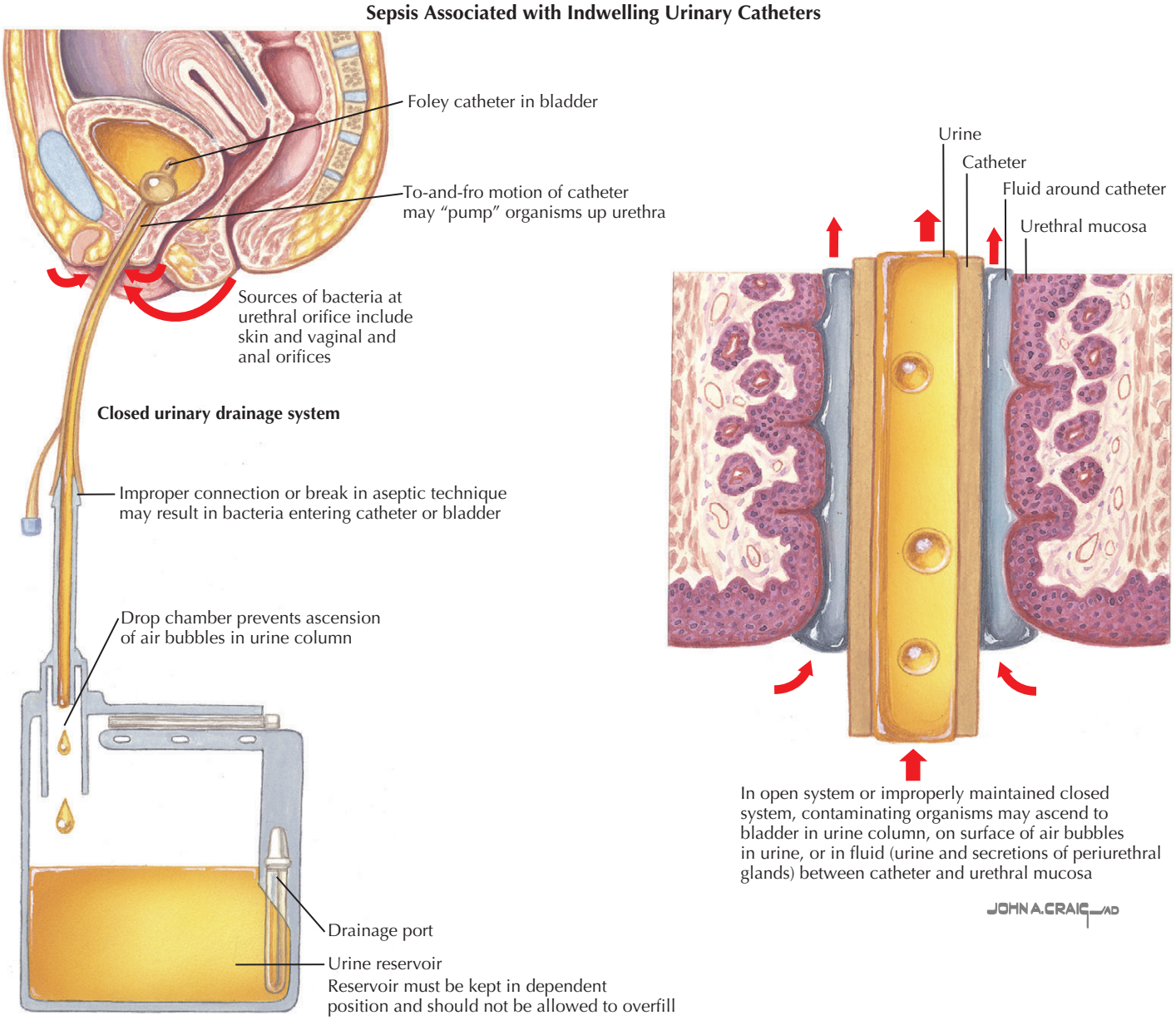


Figure 39-4 Indwelling urinary catheter.

Complicated Cystitis and Pyelonephritis

Patients with cystitis who have an underlying complicating condition should have a pretreatment UC obtained, because of the more varied microbiology than in uncomplicated cystitis. In contrast, with pyelonephritis the presence of a complicating condition per se need not influence the diagnostic approach for most patients (because the UC is already mandatory). However, a suspicion of possible urinary obstruction (e.g., based on a history of past obstruction, underlying conditions predisposing to obstruction, or suggestive symptoms) should lower the threshold for imaging to exclude obstruction. Emphysematous pyelonephritis, a rare but severe form of pyelonephritis in which gas from microbial metabolism accumulates within the renal parenchyma, should be considered if a patient with pyelonephritis and poorly controlled diabetes mellitus has severe abdominal or flank pain, septic shock, or rapid clinical deterioration.

Other Urinary Tract Infection Syndromes

Patients with febrile UTI should be evaluated in the same manner as those with pyelonephritis, including obtaining a pretreatment UC. Patients suspected of having symptomatic CAUTI also should have a UC obtained, preferably from the sampling port on the drainage tubing (not the collecting bag), using aseptic technique (Figure 39-4). For patients who lack symptoms or other manifestations suggesting infection, especially those referable to the urinary tract, UTI should not be considered or tested for except during pregnancy and before

urologic surgery, in which settings ABU should be routinely screened for and treated if found. Significant prostate tenderness suggests acute prostatitis. The causative organism can usually be isolated by standard UC, although in sexually active men testing for *N. gonorrhoeae* should be considered. Chronic prostatitis is suggested in men by repeated isolation of the same organism in serial UCs, despite the absence of prostate-localizing symptoms or tenderness. Prostate-specific antigen testing may be useful to provide additional evidence of prostatic involvement and can be followed as a measure of response to therapy.

MANAGEMENT AND THERAPY

Cystitis

Therapy for cystitis in an otherwise healthy woman should be of short duration, with 3 days of trimethoprim-sulfamethoxazole (TMP-SMX) or FQ being equally effective, assuming relatively similar rates of resistance among relevant uropathogens. Guidelines from the Infectious Diseases Society of America (IDSA) recommend the use of TMP-SMX if the local *E. coli* susceptibility prevalence is at least 80%, whereas if the prevalence of resistance to TMP-SMX exceeds 20%, an alternative agent (e.g., FQ) may be preferred. However, widespread use of FQs has been accompanied by an increasing prevalence of resistance to these agents. The rise in FQ resistance is of concern, given the utility of these agents as oral therapy for more severe forms of UTI, such as pyelonephritis. FQ-sparing regimens for cystitis that should be considered include 5 days of nitrofurantoin and single-dose therapy with fosfomycin, although the latter has lower success rates than TMP-SMX, FQs, or nitrofurantoin. Amoxicillin-clavulanate and oral extended-spectrum cephalosporins are alternative (but little-studied) options if antimicrobial resistance or patient factors preclude the use of the agents just listed.

The optimal duration of therapy for cystitis in men, and in women with complicating conditions, is poorly defined. Cystitis in men with no complicating conditions may respond to short-course (3-day) therapy, although experience is limited. Some authorities consider male sex to be a somewhat complicating condition and would thus extend therapy to 7 days, which is also a frequently recommended (albeit poorly studied) duration of therapy for complicated cystitis in women. Cystitis in men with known complicating conditions probably should be treated even longer (e.g., for 10 to 14 days), although better evidence is needed here, as well.

Recurrent Cystitis

Recurrent episodes of cystitis are a significant burden for both patients and providers, because repeated exposure to antimicrobials selects for resistant microorganisms, increases costs, and imposes the inconvenience of repeatedly accessing the medical care system. Preventive options for women with recurrent UTI include continuous (e.g., daily or thrice weekly) prophylactic antimicrobial therapy, postcoital therapy (if UTI episodes typically occur after sexual intercourse), and behavior change (e.g., postcoital micturition and avoidance of spermicide-based contraception). Self-initiated therapy is an effective way for women to terminate recurrent UTI episodes quickly once they are noticed, without the inconvenience, cost, and delays associated with an urgent visit to a clinic or the extensive antimicrobial exposure associated with continuous prophylaxis. Daily consumption of cranberry juice or extract is a nonpharmacologic method for preventing UTI that may be effective for motivated patients, although the supporting evidence from clinical trials is limited. Probiotic therapy (e.g., with *Lactobacillus* preparations) has even less supporting clinical evidence, despite biologic plausibility and intuitive appeal. For older men with recurrent UTI episodes that presumably involve the same organism (according to species and susceptibility profile), therapy of longer duration to eradicate a possible persisting prostatic (PPP) focus is a potentially useful strategy.

Pyelonephritis

For patients with pyelonephritis, the preferred initial route of therapy and treatment setting are influenced by the severity of illness and presence of comorbidities. Oral outpatient therapy for pyelonephritis is appropriate for otherwise healthy patients who are tolerating oral intake and lack hypotension and tachycardia. In contrast, hospital admission for parenteral therapy and close observation is advisable for patients with pyelonephritis who have severe underlying medical conditions or who exhibit hemodynamic instability or vomiting. However, some patients (for instance, an otherwise-healthy woman with suspected pyelonephritis who is normotensive but tachycardic) may not fit neatly into either group. Such a patient can be managed in the emergency department with intravenous fluids and an initial dose of a parenteral antimicrobial. If the patient is responding well to this therapy, discharge on an oral antimicrobial agent is appropriate, whereas if the response is insufficient, hospital admission is advisable.

The increasing prevalence of TMP-SMX resistance in *E. coli*, combined with the serious consequences of inadequately treated pyelonephritis, has made TMP-SMX monotherapy unsuitable for empirical pyelonephritis therapy in many locales. However, if susceptibility of the urine organism to TMP-SMX is confirmed, TMP-SMX remains an excellent drug for completing therapy. Currently in the United States, FQs are the only oral agents with (1) predictable activity against *E. coli* in patients with uncomplicated UTI and (2) suitable pharmacokinetics for treatment of pyelonephritis. Ciprofloxacin 250 mg twice daily for 7 days and levofloxacin 750 mg once daily for 5 days are both effective and proven regimens, with ciprofloxacin having an inexpensive generic formulation. Nitrofurantoin, although active against most *E. coli* UTI isolates, achieves effective levels only in the urine and so should not be used in the treatment of pyelonephritis, which is a tissue-invasive process. Fosfomycin is available in the United States only as an oral formulation that has been studied only for single-dose therapy for cystitis; consequently, this agent has little relevance for treating pyelonephritis.

Parenteral options for pyelonephritis include ceftriaxone (and other extended-spectrum cephalosporins), ticarcillin-clavulanate and piperacillin-tazobactam, carbapenems (including imipenem, ertapenem, and so on), aztreonam, aminoglycosides, and FQs. Local susceptibility data, toxicity, ease of administration, and cost all influence the choice of agent. Deescalation of

broad-spectrum empirical therapy should occur as soon as susceptibility data are available, preferably to an oral antimicrobial if the patient's condition has improved sufficiently. High-dose levofloxacin is the only regimen with clinical trial data supporting a 5-day course of therapy; for all others, 7 to 14 days of therapy are recommended. Longer treatment courses are unnecessary and increase the risk of adverse events and selection for resistance. Initial use of an agent with antienterococcal or antistaphylococcal activity can be considered if suspicion is high for these organisms, based on recent culture, urine gram stain, or patient-specific risk factors.

The response of uncomplicated pyelonephritis to an active antimicrobial regimen is usually rapid, with fever and other manifestations generally improving if not resolving within the first 48 hours. If the response is insufficient or delayed the patient should be reevaluated, with consideration given to the possibility of a resistant organism, a renal abscess or emphysematous pyelonephritis, obstruction, or an incorrect initial diagnosis. Repeat UC, an empirical change in antimicrobial therapy, and evaluation for a drainable focus of infection or other causes of the patient's symptoms should all be considered.

The optimal duration of therapy for pyelonephritis occurring in men, and in patients of either gender with complicating conditions, is unclear. Although 10 to 14 days have been recommended, additional research is needed.

Other Types of Urinary Tract Infection

As with pyelonephritis occurring in men and patients with complicating conditions, the optimal duration of therapy for febrile UTI and CAUTI is unknown. Febrile UTI is customarily treated similarly to pyelonephritis, with treatment duration adjusted for gender and presence of complicating conditions. For CAUTI, 10 to 14 days of therapy are reasonable. Catheter exchange during antimicrobial therapy may reduce the risk of relapse caused by persisting organisms within a catheter-adherent biofilm. ABU should not be treated outside of specifically defined situations (pregnancy and urologic surgery), as discussed earlier. Preferred therapy for prostatitis consists of FQ or TMP-SMX, assuming a susceptible organism, because of superior prostatic penetration compared with other antimicrobials. FQ therapy for 2 weeks usually suffices for acute prostatitis or febrile UTI in men (which often involves the prostate), whereas extended therapy (i.e., up to 4 weeks of an FQ or 6 to 12 weeks of TMP-SMX) is sometimes used for chronic prostatitis, particularly after failure of shorter-duration therapy.

SUMMARY

UTI is a commonly encountered clinical problem, which makes an efficient, cost-effective approach to diagnosis and treatment essential. Awareness of relevant host factors, local susceptibility data, and common pitfalls in UTI management is necessary for effective and safe management. A major challenge in the field is the rising prevalence of antimicrobial resistance among uropathogens. Widespread adoption of evidence-based treatment approaches may help to slow this worrisome trend, although the difficult scenario of a patient with an infection amenable only to parenteral therapy is likely to become increasingly common. Efforts should be made to select empirical therapy based on local susceptibility data, to deescalate to narrow-spectrum therapy as soon as possible, and to treat as long as necessary, but not longer, based on patient-specific factors.

EVIDENCE

Gupta K, Hooton TM, Roberts PL, Stamm WE: Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women, *Arch Intern Med* 167:2207-2212, 2007. *An open label trial evaluating TMP-SMX for 3 days versus nitrofurantoin for 5 days. Clinical and microbiologic outcomes were not significantly different, suggesting that nitrofurantoin may be a viable FQ-sparing regimen for cystitis treatment.*

Harding GKM, Zhanel GG, Nicolle LE, et al: Antimicrobial treatment in diabetic women with asymptomatic bacteriuria, *N Engl J Med* 347:1576-1583, 2002. *A trial randomizing female subjects with ABU to antimicrobial treatment versus no treatment. No benefit was observed in the treatment group, whereas there was significant evidence of harm from adverse drug events.*

Hooton TM, Winter C, Tiu F, Stamm WE: Randomized comparative trial and cost analysis of 3-day antimicrobial regimens for treatment of acute cystitis in women, *JAMA* 273:41-45, 1995. *A study examining efficacy, safety, and cost of four different three-day regimens for uncomplicated cystitis. TMP-SMX was superior to the three comparators; however, none of the comparators was a quinolone or FQ.*

Iravani A, Tice AD, McCarty J, et al: Short-course ciprofloxacin treatment of acute uncomplicated urinary tract infection in women: the minimum effective dose. The Urinary Tract Infection Study Group, *Arch Intern Med* 155:485-494, 1995. *A multicenter study demonstrating that ciprofloxacin given for 3 days was an effective treatment for uncomplicated cystitis.*

Talan DA, Stamm WE, Hooton TM, et al: Comparison of ciprofloxacin (7 days) and trimethoprim-sulfamethoxazole (14 days) for acute uncomplicated pyelonephritis in women: a randomized trial, *JAMA* 283:1583-1590, 2000. *A multicenter trial evaluating therapy for pyelonephritis in the ambulatory setting. Ciprofloxacin was associated with an increased proportion achieving clinical and microbiologic cure, with the TMP-SMX failures occurring among subjects with an isolate that was resistant to TMP-SMX.*

ADDITIONAL RESOURCES

American College of Physicians (ACP): *American College of Physicians Physician's Information and Education Resource* (ACP PIER). Available at: pier.acponline.org. Accessed April 29, 2009 (personal or institutional subscription required). *An online resource providing evidence based information on a variety of diseases, including separate sections on UTI and pyelonephritis.*

Infectious Disease Society of America (IDSA): IDSA website. Available at: www.idsociety.org. Accessed April 29, 2009. *A site maintained by IDSA. Practice guidelines are available for cystitis and ABU, and Catheter Associated UTI.*

UpToDate: UpToDate website. Available at: uptodateonline.com. Accessed April 29, 2009 (personal or institutional subscription required). *An online resource supplying topic-specific reviews, which are written, and updated frequently, by experts in the field.*

Systemic Fungal Infections

Carol A. Kauffman

40

ABSTRACT

The endemic mycoses are geographically restricted pathogens that exist as molds in specific environmental niches and that infect persons who encounter them. In the United States, the major endemic mycoses are histoplasmosis, blastomycosis, and coccidioidomycosis. The extent of disease manifested by a given patient depends on both the inoculum of the organism and the ability of the host to mount an effective immune response. The route of infection is almost always inhalation of the infectious conidia into the alveoli, and therefore the major clinical manifestations are pulmonary. In addition, all of the endemic mycoses have the potential to disseminate hematogenously, and disease manifestations, especially in immunosuppressed patients, can reflect this widespread dissemination. In general, severe infection is initially treated with an intravenous amphotericin B formulation, which can later be changed to an oral azole agent. Mild to moderate infection is treated with an oral azole agent. With appropriate antifungal therapy, the prognosis is excellent for most infections with the endemic mycoses.

This chapter focuses on infection with the major endemic mycoses: histoplasmosis, blastomycosis, and coccidioidomycosis. Other systemic fungal infections, such as cryptococcosis, aspergillosis, and candidiasis, which primarily cause infection in immunosuppressed hosts, will not be discussed here. The fungi that cause the endemic mycoses are all dimorphic; they exist as molds in the environment and as either yeasts or spherules in tissues. Each organism occupies a different environmental niche and occurs in specific geographic areas (Figure 40-1). Infection occurs when a person is exposed to the conidia (sometimes called *spores*) produced by the organism as it grows in the environment as a mold. These fungi cause infection in normal hosts as well as those who have defects in the host immune response. A spectrum of disease manifestations can occur after inhalation of the conidia, depending on the number of conidia inhaled and the immune status of the host. Hematogenous dissemination is common for all of these organisms, and it is possible for reactivation to occur years later.

EPIDEMIOLOGY

Histoplasmosis is the most common endemic mycosis, infecting hundreds of thousands of persons yearly. Most persons in the highly endemic area were infected before adulthood. *Histoplasma capsulatum* thrives in highly nitrogenous soils in the Mississippi and Ohio River valleys, in multiple locations in Central and South America, and in focal areas of the Eastern United States, Southeast Asia, and the Mediterranean basin. The organism grows to high concentrations in caves rich in bat guano. Activities that disperse the conidia include landscaping, demolition of old buildings, cleaning debris from attics or barns, and spelunking. Although most cases are sporadic, outbreaks of varying sizes frequently occur. The largest outbreak occurred during an urban demolition project in Indianapolis and caused infection in hundreds of thousands of persons.

Blastomycosis occurs most frequently in the south central and north central United States, the midwestern Canadian provinces, and areas bordering the St Lawrence seaway, but *Blastomyces dermatitidis* is found also in the Middle East and in Africa. The environmental niche for *B. dermatitidis* is thought to be soil and decaying wood. In many reports, middle-aged men account for most cases, and a well-described scenario is blastomycosis occurring in both a hunter and his dog.

There are two species of *Coccidioides*. *Coccidioides immitis* includes isolates from California, and *Coccidioides posadasii* includes isolates from other areas. The endemic area for *Coccidioides* species includes the southwestern U.S. desert regions known as the *lower Sonoran life zone* and areas of Central and South America that have this same type of ecosystem. Environmental cycles of rain and drought in the desert are important in the growth and dispersal of *Coccidioides* species. Dust storms and activities that involve disruption of desert soil can lead to widespread dispersal of the conidia and increased risk for persons in the area. The exodus to the sun belt has contributed to an increase in the number of cases of coccidioidomycosis in older adults who are experiencing their first exposure to this organism.

CLINICAL FEATURES

Most patients infected with one of the endemic mycoses are asymptomatic or have such mild symptoms that it is thought that they have a self-limited viral illness. Therefore the discussion of symptoms and signs that follows concentrates on fewer than 5% of persons exposed to these organisms. When symptoms do occur, the predominant manifestations are pulmonary, which is not surprising given that the portal of entry is the lungs for these fungi. For all of these fungi, dissemination during the early stages of infection is common; this occurs before the host establishes cellular immunity to the organism and is able to contain the infection. In most cases, dissemination is silent and not associated with clinical manifestations. However, patients who are immunosuppressed or who are exposed to a high inoculum of the organism can become acutely ill with disseminated infection, and others will be seen at a later time point with focal infection at a site to which the organism had spread hematogenously. Although the pulmonary manifestations are often similar among these three endemic mycoses, clinical manifestations of disseminated infection are somewhat different for each organism.

Histoplasmosis

Patients who have symptoms associated with acute pulmonary histoplasmosis usually manifest fever, nonproductive cough, anterior chest discomfort, myalgias, and fatigue. Patchy nodular infiltrates are noted on chest radiographs. Most patients are initially treated for community-acquired bacterial pneumonia with antibiotics. Only when the infection persists is the possibility of a fungal infection considered, and then appropriate diagnostic studies are undertaken.

Severe pneumonia develops in a minority of patients and manifests as high fever, dyspnea, nonproductive cough, and hypoxemia (Figure 40-2). Diffuse infiltrates are noted on the chest radiograph and may progress to acute respiratory distress syndrome (ARDS). Immunosuppressed patients are more likely to develop severe pulmonary infection.

Chronic cavitary pulmonary histoplasmosis, which mimics tuberculosis, occurs mostly in older adults who have chronic obstructive pulmonary disease (COPD). Patients usually manifest fever, fatigue, anorexia, weight loss, cough productive of purulent sputum, and hemoptysis. Chest radiographs show upper lobe cavitary lesions, and fibrosis is seen in the lower lung fields (see Figure 40-2).

The complications of pulmonary histoplasmosis include mediastinal granuloma and mediastinal fibrosis. Patients with mediastinal granuloma have persistent mediastinal and hilar lymphadenopathy, and symptoms related to the enlarged nodes include dysphagia, chest pain, and nonproductive cough when the involved nodes impinge on mediastinal structures. Most patients have gradual resolution of symptoms as the lymphadenopathy regresses. Mediastinal fibrosis is a rare and often fatal complication in which excessive fibrosis occurs in response to mediastinal histoplasmosis and can entrap the great vessels and bronchi. The symptoms are progressive and include dyspnea, cough, wheezing, and hemoptysis. Heart failure, pulmonary emboli, and superior vena cava syndrome can occur.

Acute disseminated histoplasmosis is seen mostly in patients who are immunosuppressed, including those who have acquired immunodeficiency syndrome (AIDS), have received a transplant, or have been treated with corticosteroids or tumor necrosis factor (TNF) antagonists. Young infants are also at risk for disseminated histoplasmosis. Symptoms include chills, fever, fatigue, anorexia, and weight loss; sepsis syndrome with ARDS and disseminated intravascular coagulation can occur. Hepatosplenomegaly and skin and mucous membrane lesions are frequently present, and pancytopenia and elevated liver enzymes are common.

Chronic progressive disseminated histoplasmosis occurs mostly in middle-aged to elderly patients with no known immunosuppression. Patients often have fever of unknown origin with weeks to months of fever, night sweats, weight loss, and fatigue. Hepatosplenomegaly and mucosal ulcerations (Figure 40-3) and symptoms and signs of adrenal insufficiency are often noted.

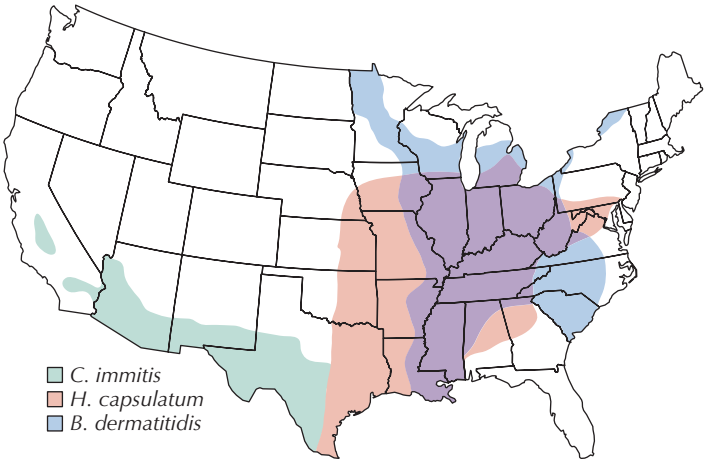
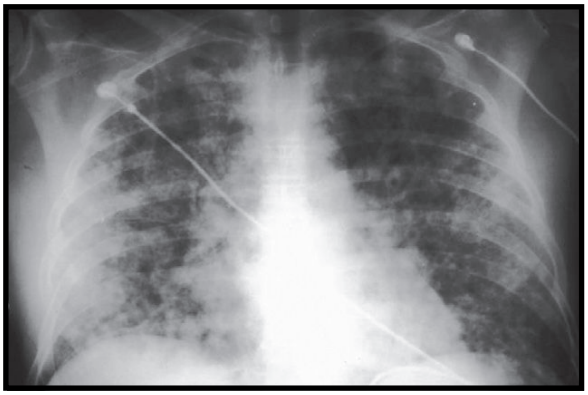


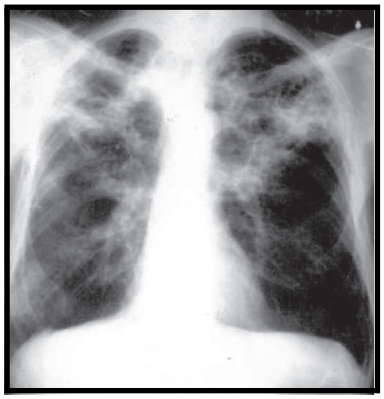
Figure 40-1 Geographic distribution of the endemic mycoses in the United States.

Blastomycosis

The symptoms and signs of acute pulmonary blastomycosis are fever, cough, and myalgias; a localized pulmonary infiltrate is seen on chest radiographs. The diagnosis is usually community-acquired bacterial pneumonia, and most patients are treated with antibiotics. Only when the infection persists is the

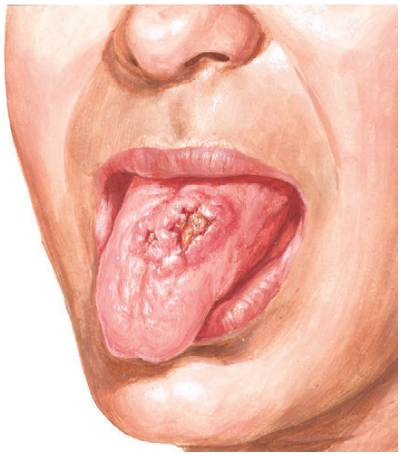


Severe acute pulmonary histoplasmosis



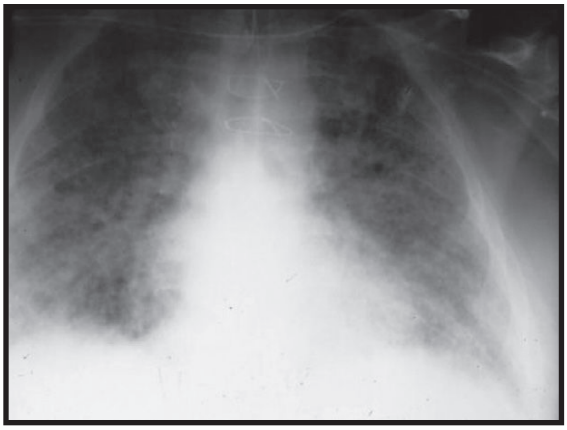
Chronic cavitary pulmonary histoplasmosis in 60-year-old man with emphysema

Figure 40-2 Pulmonary histoplasmosis.

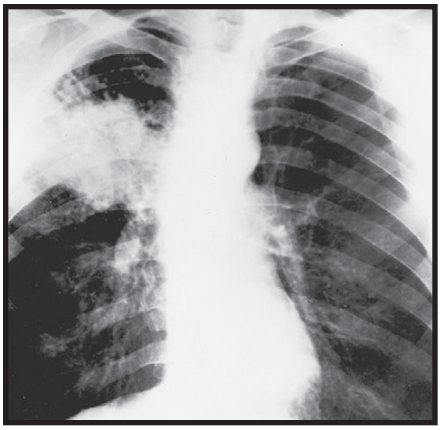


Ulcerating lesion of tongue due to histoplasmosis. Lesion is identical in appearance to carcinoma of tongue

Figure 40-3 Mucosal ulceration.



Severe acute pulmonary blastomycosis with ARDS in a 56-year-old man.



Chronic pulmonary blastomycosis showing lesion in upper lobe of right lung. Radiographic pattern may, however, be very diverse.

Figure 40-4 Pulmonary blastomycosis.

possibility of a fungal infection considered and then appropriate diagnostic studies are undertaken. A minority of patients have severe pneumonia; these patients often progress quickly to severe hypoxemia and ARDS (Figure 40-4).

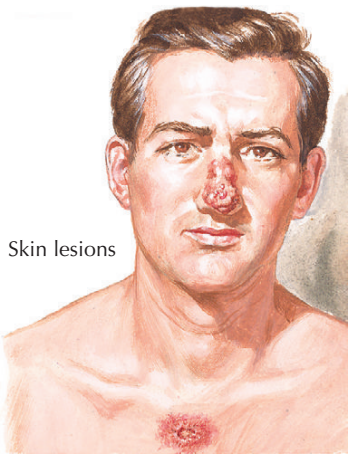
Chronic pulmonary blastomycosis can be mistaken for tuberculosis or lung cancer. The symptoms include fever, night sweats, weight loss, fatigue, dyspnea, cough, sputum production, and hemoptysis. The chest radiograph shows upper lobe cavitary infiltrates, masslike lesions, or multiple nodular lesions (see Figure 40-4). Hilar and mediastinal lymphadenopathy occur less often than with histoplasmosis.

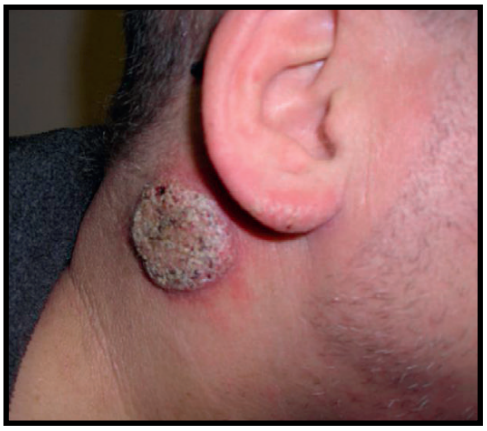
Cutaneous lesions are the most common manifestation of disseminated blastomycosis. Classically, the lesions are nonpainful, well-circumscribed nodules or plaques that are verrucous and have punctate draining areas in the center (Figure 40-5). The lesions can also be painful ulcerations or pustular nodules. The skin lesions of blastomycosis can be mistaken for those caused by nontuberculous mycobacteria, bromide use, and pyoderma gangrenosum. Patients with skin lesions may or may not have pulmonary manifestations; in many, the pneumonia has resolved by the time the skin lesions appear. Osteoarticular blastomycosis may be contiguous to skin lesions or may occur at distant sites. The genitourinary tract is another frequent site of disseminated infection, and the prostate is the usual target organ. Prostatic nodules, with or without symptoms of prostatism, are found.

Blastomycosis is more severe in immunosuppressed patients, although it is seen much less commonly than histoplasmosis and coccidioidomycosis in patients with AIDS, transplant recipients, and patients receiving TNF antagonists. In these patients, the disease is usually disseminated to multiple organs, and severe pulmonary manifestations are also more common.

Coccidioidomycosis

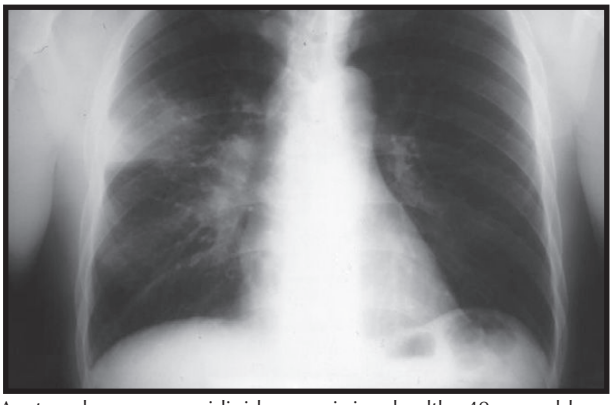
Acute pulmonary coccidioidomycosis usually manifests with fever, fatigue, cough, dyspnea, myalgias, and arthralgias. Erythema nodosum is not uncommon during acute pulmonary coccidioidomycosis. Chest radiographs show a patchy pneumonia; hilar lymphadenopathy can also occur (Figure 40-6). Symptoms may persist for weeks to a few months but gradually resolve in almost all persons. Acute pulmonary coccidioidomycosis is often



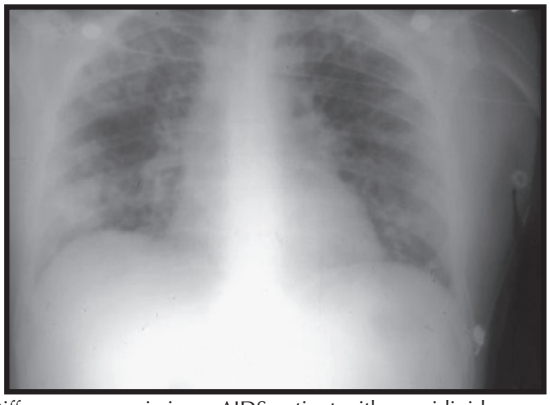


Verrucous skin lesion of blastomycosis in a 30-year-old man

Figure 40-5 Skin lesions in blastomycosis.



Acute pulmonary coccidioidomycosis in a healthy 40-year-old man



Diffuse pneumonia in an AIDS patient with coccidioidomycosis

Figure 40-6 Pulmonary coccidioidomycosis.

diagnosed as community-acquired bacterial pneumonia, and antibiotics are prescribed. The diagnosis is thought of only later when there is no response to antibiotic therapy. In immunosuppressed hosts or when exposure to the organism is extensive, severe pneumonia, sometimes progressing to ARDS, can occur (see Figure 40-6). This is a common manifestation of coccidioidomycosis in AIDS patients with low CD4 counts.

Several pulmonary complications are more common with coccidioidomycosis than with the other endemic fungi. Cavitary lesions, usually solitary and thin walled, may persist for months to years. Hemoptysis is frequent, and the cavity can rupture into the pleural space. Older adults and those who have COPD or diabetes mellitus are more likely to develop chronic progressive cavitary coccidioidomycosis.

Very few patients infected with *Coccidioides* species go on to develop symptomatic disseminated infection. This is more common in African Americans and people of other dark-skinned ethnicities, those who are immunosuppressed, especially AIDS patients, and perhaps pregnant women. The sites involved most often are skin, subcutaneous tissues, osteoarticular structures, and meninges (Figure 40-7). The skin lesions can be papular, pustular, or plaquelike and often ulcerate and drain.

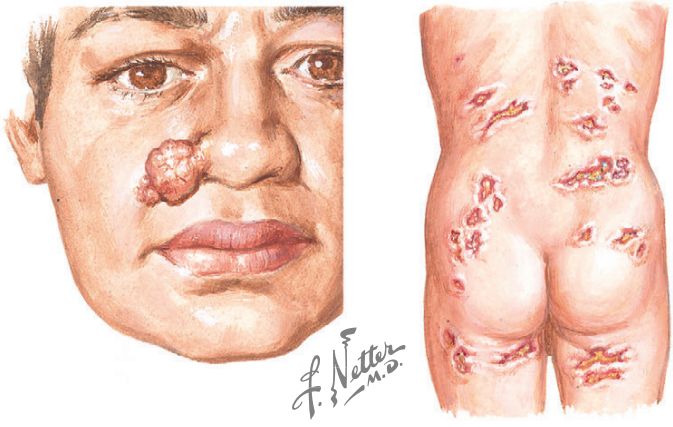


Figure 40-7 Skin lesions in coccidioidomycosis.

Subcutaneous abscesses often form sinus tracts with purulent drainage. Osteoarticular infection is common and may occur contiguous to subcutaneous abscesses and skin lesions or at distant sites. Vertebral involvement is common, but any bone can be involved, and extensive destruction is often seen.

Meningitis is the most feared complication of disseminated coccidioidomycosis. The patient may have only chronic meningitis, or this can be one manifestation of disseminated infection. Symptoms include headache, confusion, behavioral changes, cranial nerve palsies, and signs of increased intracranial pressure. Cord involvement at any level can also occur and causes back pain, weakness, or bowel and bladder dysfunction.

DIAGNOSTIC APPROACH

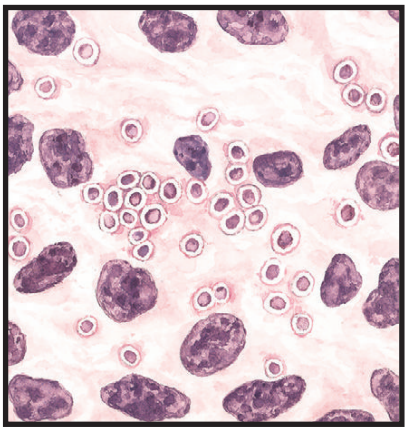
In general, the diagnosis of infection with one of the endemic mycoses can be made most expeditiously by histopathologic demonstration of the organisms in biopsy specimens from involved organs. However, the definitive diagnosis still requires growth of the organism in culture. Serology and antigen detection are variably helpful in certain clinical circumstances for each of the endemic fungi.

Growth of *B. dermatitidis* and *H. capsulatum* in culture takes several weeks; *Coccidioides* species usually grow in several days to a week. *H. capsulatum*, but rarely the other fungi, can be grown from blood using the lysis-centrifugation (isolator tube) system. The endemic fungi grow as molds at room temperature (Figure 40-8). Commercially available deoxyribonucleic acid (DNA) probes that are specific for *B. dermatitidis* and *H. capsulatum* are used to confirm the identification of the mold as soon as growth occurs. Because *Coccidioides* species are classified as potential bioterrorism agents, clinical laboratories are obligated to send the mold to a reference laboratory for identification.

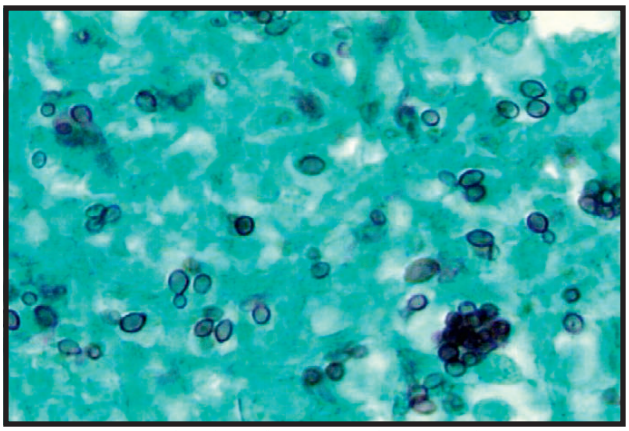
Tissue obtained for biopsy should be stained with methenamine silver or periodic acid–Schiff (PAS) stain to visualize the yeast forms of *H. capsulatum* and *B. dermatitidis*. *Coccidioides* spherules are large and readily seen with hematoxylin and eosin stain, but fungal stains better define these structures. *H. capsulatum* appears as uniform, 2- to 4-μm oval budding yeasts (Figure 40-9). For patients with disseminated disease, biopsy samples of bone marrow, liver, lymph nodes, or lesions on mucous membranes or skin reveal the organisms. *B. dermatitidis* can be seen in respiratory secretions and lung tissue; the calcofluor fluorescent stain or tissue fungal stains show the distinctive 8- to 15-μm broad-based budding yeast (Figure 40-10). Biopsy of skin lesions characteristically shows pseudoepitheliomatous hyperplasia, and fungal stains reveal the thick-walled yeasts with a single broad-based bud. Identification of the large 20- to 80-μm spherules that contain numerous endospores in tissue biopsies, respiratory secretions, or purulent material from abscesses establishes the diagnosis of coccidioidomycosis (Figure 40-11).

Serology plays an important role in the diagnosis of coccidioidomycosis and certain forms of histoplasmosis, but not blastomycosis. Serology is not as useful in immunosuppressed patients, who may not mount an antibody response. Both complement fixation (CF) and immunodiffusion tests are available. Patients with chronic cavitary and acute pulmonary histoplasmosis and those with disseminated histoplasmosis almost always have positive results with both the CF and immunodiffusion

Figure 40-8 Endemic fungi grow as molds at room temperature.

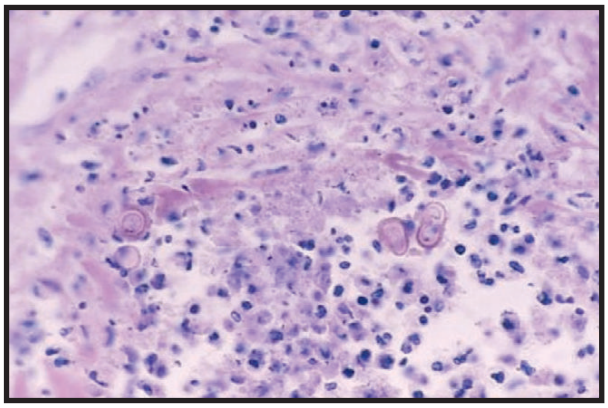


H. capsulatum in tissue

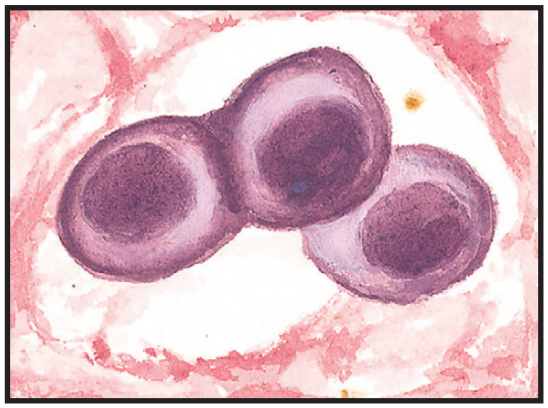


Lung tissue stained with methenamine silver stain showing the oval, narrow-based budding yeasts of *H. capsulatum*

Figure 40-9 *Histoplasma capsulatum.*

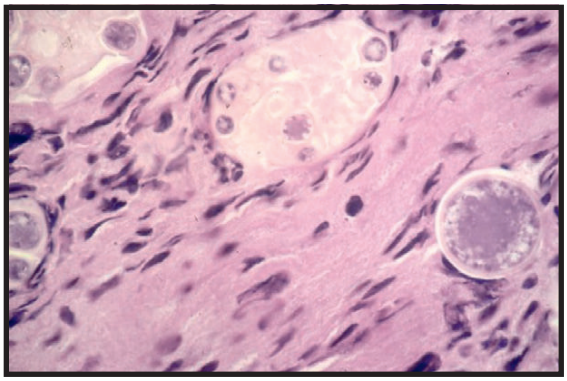


Lung tissue stained with periodic acid Schiff stain showing the large, thick-walled, broad-based budding yeasts of *B. dermatitidis*



Very high-power view of a budding and nonbudding organism

Figure 40-10 *Blastomyces dermatitidis.*



Lung tissue stained with hematoxylin and eosin showing several large spherules, some of which contain endospores, typical of *Coccidioides* species

Figure 40-11 *Coccidioides.*

assays. The diagnosis of acute coccidioidomycosis is aided by the detection of IgM antibodies, which are usually measured by immunodiffusion. IgG antibodies measured by CF assay appear later and persist longer. Rising CF titers may reflect worsening of infection and dissemination. A positive CF antibody test for *Coccidioides* in cerebrospinal fluid is diagnostic of coccidioidal meningitis. Serologic assays for blastomycosis are neither sensitive nor specific and do not help establish a diagnosis of blastomycosis.

An antigen assay to detect cell wall galactomannan has proved extremely useful for the diagnosis of disseminated histoplasmosis, and a similar assay for *B. dermatitidis* may prove useful for the diagnosis of moderately severe to severe blastomycosis. The *H. capsulatum* antigen assay is helpful for diagnosis in patients with acute pulmonary histoplasmosis, but not for chronic pulmonary forms of this disease. Experience with the antigen assay for *B. dermatitidis* is limited; it is not known whether it will be useful for patients who have focal infection. Both of these assays show cross-reactivity among patients with either infection and also are positive in patients who have paracoccidioidomycosis and penicilliosis.

TREATMENT

For all of the endemic mycoses, treatment of mild to moderate infection should be with an azole and of moderately severe to severe infection with an amphotericin B formulation, followed by an azole after the patient has shown a clinical response. A lipid amphotericin B formulation, at a dose of 3 to 5 mg/kg daily, is preferred to decrease the risk of nephrotoxicity and for superior activity in histoplasmosis, but amphotericin B deoxycholate, 0.7 to 1 mg/kg daily, can be used. Itraconazole is the azole of choice for histoplasmosis and blastomycosis, and coccidioidomycosis can be treated with either itraconazole or fluconazole. When itraconazole is used, a loading dose of 200 mg three times daily for 3 days should be given, followed by 200 mg once or twice daily. Itraconazole capsules require both food and acid for absorption; agents that decrease gastric acid must be avoided. Itraconazole suspension is given on an empty stomach and does not require acid for absorption. With either formulation, serum itraconazole levels should be performed to help ensure efficacy. Absorption of fluconazole is not problematic, but for both azoles, drug-drug interactions must be carefully sought and dealt with.

Histoplasmosis

The following recommendations are based on Infectious Diseases Society of America (IDSA) guidelines for the management of histoplasmosis (Table 40-1). Patients who have acute pulmonary histoplasmosis usually do not require treatment. If the patient has symptoms that last more than 4 weeks, therapy with itraconazole 200 mg daily for 6 to 12 weeks is recommended. All patients who have chronic cavitary pulmonary infection require antifungal therapy. Itraconazole is recommended at a dosage of 200 mg twice daily for 1 to 2 years. Patients who develop severe pulmonary infection should be treated initially with a lipid formulation of amphotericin B, 3 to 5 mg/kg daily. After a favorable response is noted, therapy can be changed to oral itraconazole.

Mediastinal granuloma is often treated with a course of itraconazole, 200 mg once or twice daily, for 6 to 12 weeks, but benefit is not always found. Mediastinal fibrosis does not respond

Table 40-1 Recommended Treatment Regimens for Histoplasmosis

TYPE OF INFECTION	RECOMMENDED THERAPY
Acute pulmonary	
Mild, moderate	<4 weeks of symptoms, therapy not recommended >4 weeks of symptoms, itraconazole 200 mg once or twice daily for 6-12 weeks
Severe	Lipid AmB 3-5 mg/kg daily *or* AmB-d 0.7-1 mg/kg daily, until improved clinically, then itraconazole 200 mg twice daily for 12 weeks total
Chronic cavitary pulmonary	Itraconazole 200 mg twice daily for at least 12 months
Mediastinal granuloma	Antifungal therapy not usually recommended, but itraconazole 200 mg twice daily, can be tried for 6-12 weeks
Mediastinal fibrosis	Antifungal therapy not effective; vascular stents may be useful
Disseminated	
Mild, moderate	Itraconazole 200 mg twice daily for 12 months
Severe	Liposomal AmB 3-5 mg/kg daily, until improved clinically, then itraconazole 200 mg twice daily for 12 months total Long-term suppressive therapy with itraconazole may be required in immunosuppressed patients

AmB, Amphotericin B; *AmB-d,* amphotericin B deoxycholate.

to antifungal therapy. The most effective treatment appears to be selective placement of stents in obstructed great vessels.

All patients who have disseminated histoplasmosis should be treated with an antifungal agent. Mild to moderate disease can be treated with itraconazole, 200 mg twice daily; severe infection and infection in immunosuppressed patients should be treated initially with a lipid formulation of amphotericin B. Liposomal amphotericin B (AmBisome), 3 mg/kg daily, is recommended based on the results of a blinded, randomized treatment trial that showed that this agent was superior to amphotericin B deoxycholate for initial therapy of AIDS patients with severe disseminated histoplasmosis. Therapy can be changed to itraconazole, 200 mg twice daily, after clinical improvement is noted. Immunosuppressed patients may require prolonged suppressive therapy with itraconazole, 200 mg daily. Suppressive therapy can be stopped in AIDS patients whose CD4 counts have remained >200/μL for at least 1 year. Fluconazole is not as active as itraconazole; if this agent is used, the dose should be 800 mg daily. There are only anecdotal case reports on the use of voriconazole and posaconazole for histoplasmosis. These azoles are likely effective, but there are not enough data to recommend their use at this time. The echinocandins do not have activity against *H. capsulatum* and should not be used.

Table 40-2 Recommended Treatment Regimens for Blastomycosis

TYPE OF INFECTION	RECOMMENDED THERAPY
Pulmonary	
Mild to moderate	Itraconazole 200 mg once or twice daily for 6-12 months
Severe	Lipid AmB 3-5 mg/kg daily, *or* AmB-d 0.7-1 mg/kg daily until improved clinically, then itraconazole 200 mg twice daily for 6-12 months
Disseminated	
Mild to moderate	Itraconazole 200 mg once or twice daily for 6-12 months
Severe	Lipid AmB 3-5 mg/kg daily, *or* AmB-d 0.7-1 mg/kg daily until improved clinically, then itraconazole 200 mg twice daily for 6-12 months
Immunosuppressed host	Lipid AmB 3-5 mg/kg daily, *or* AmB-d 0.7-1 mg/kg daily, until improved clinically, then itraconazole 200 mg twice daily for 12 months Long-term suppressive therapy with itraconazole may be required if immunosuppression cannot be reversed

AmB, Amphotericin B; *AmB-d,* amphotericin B deoxycholate.

Blastomycosis

The following recommendations are based on the IDSA guidelines for the management of blastomycosis (Table 40-2). With the exception of acute pulmonary blastomycosis in which all symptoms and signs have already resolved before diagnosis, all patients who have blastomycosis, even mild pneumonia or a single cutaneous lesion, should be treated with an antifungal agent. For patients with severe pulmonary disease, those who are immunosuppressed, and the uncommon patient who has widespread visceral involvement, lipid amphotericin B, 3 to 5 mg/kg daily, should be used as initial therapy. After the patient has shown clinical improvement, it is appropriate to change to oral itraconazole, 200 mg twice daily. Patients with mild to moderate pulmonary blastomycosis and those who have skin lesions, osteoarticular involvement, or other focal infection can be treated with itraconazole, 200 mg once or twice daily. Treatment is generally given for a total of 6 to 12 months; patients who have moderately severe to severe infection and those with osteoarticular involvement should receive therapy for at least 12 months. Immunosuppressed patients for whom the immunosuppression cannot be reversed may require long-term suppressive azole therapy.

Fluconazole is not as effective as itraconazole; if it is used, a dose of 800 mg daily is recommended. Voriconazole appears to be effective, but this is based on anecdotal case reports only. There are no reports of using posaconazole for blastomycosis. The echinocandins are not active and should not be used.

Coccidioidomycosis

The following recommendations are based on IDSA guidelines for the management of coccidioidomycosis (Table 40-3). Most patients with acute pulmonary coccidioidomycosis do not require therapy with an antifungal agent. However, if the patient has symptoms for 3 to 4 weeks with no improvement, is immunosuppressed, or is at high risk for dissemination (African American, Filipino), treatment with either fluconazole, 400 mg daily, or itraconazole, 200 mg twice daily for 3 to 6 months should be given. Severe diffuse coccidioidal pneumonia should be treated initially with amphotericin B; after the patient has had a clinical response, therapy can be changed to an oral azole. Patients with chronic pulmonary coccidioidomycosis also require antifungal therapy, generally with an azole. Except for acute pulmonary infection, treatment should continue for at least 12 months.

Patients who have disseminated coccidioidomycosis should always be treated. Those who are seriously ill and immunosuppressed patients should receive amphotericin B until improvement is noted. Patients who have mild to moderate disease and are not immunosuppressed can be treated with either itraconazole or fluconazole. For osteoarticular coccidioidomycosis, itraconazole has proved superior to fluconazole. Treatment is generally given for at least 12 months. Immunosuppressed patients may require lifelong azole therapy to prevent relapse.

Table 40-3 Recommended Treatment Regimens for Coccidioidomycosis

TYPE OF INFECTION	RECOMMENDED THERAPY
Acute pulmonary	
Mild to moderate	Antifungal therapy usually not needed Itraconazole 200 mg twice daily *or* fluconazole 400 mg daily for 3-6 months for those who remain symptomatic >2 months
Severe	Lipid AmB 3-5 mg/kg daily *or* AmB 0.7-1 mg/kg daily, until improved clinically, then itraconazole 200 mg twice daily, *or* fluconazole 400 mg daily for at least 12 months
Chronic pulmonary	Itraconazole 200 mg twice daily, *or* fluconazole 400 mg daily, for at least 12 months
Disseminated	
Mild, moderate	Itraconazole 200 mg twice daily, *or* fluconazole 400 mg daily, for at least 12 months
Severe	Lipid AmB 3-5 mg/kg daily, *or* AmB-d 0.7-1 mg/kg daily, until improved clinically, then itraconazole 200 mg twice daily, *or* fluconazole 400 mg daily for at least 12 months. Long-term suppression with an azole suggested in immunosuppressed patients
Central nervous system	Fluconazole 800 mg daily; intrathecal AmB-d may be needed for refractory cases; azole treatment must be lifelong

AmB, Amphotericin B; *AmB-d,* amphotericin B deoxycholate.

There are anecdotal reports of success with voriconazole and posaconazole for treatment of pulmonary, disseminated, and central nervous system coccidioidomycosis. The echinocandins appear to have no activity against *Coccidioides* species and should not be used.

Coccidioidal meningitis is difficult to treat. Fluconazole is the agent of choice, in part because of its superior penetration into the cerebrospinal fluid. The initial studies used 400 mg daily, but most physicians in the endemic area now use at least 800 mg daily. Voriconazole also achieves high cerebrospinal fluid concentrations and has been used successfully in patients with meningitis. Itraconazole and posaconazole do not achieve high cerebrospinal fluid concentrations, but both have been reported to be effective in small series. For patients in whom remission is not achieved with azoles, amphotericin B deoxycholate is given as intrathecal injections. The injections are often given into the cistern because of the extensive basilar meningeal involvement seen with this disease. Patients who have *Coccidioides* meningitis must be treated with suppressive azole therapy for life to avoid relapse.

PROGNOSIS

Most patients who have pulmonary or disseminated histoplasmosis, even those with AIDS, respond quickly to antifungal agents, and treatment success rates are greater than 90%. One exception is those patients who have chronic cavitary pulmonary histoplasmosis, who frequently have progressive respiratory insufficiency in spite of treatment with antifungal agents. More than 90% of patients with blastomycosis respond to antifungal therapy. However, the mortality rate for those patients who have severe pulmonary blastomycosis and ARDS remains over 50%. Coccidioidomycosis is the least likely endemic mycosis to respond to antifungal therapy. Success rates with azole agents are 70% for soft-tissue infections and 50% to 60% for those with chronic pulmonary infection. Patients who have *Coccidioides* meningitis must be treated with suppressive azole therapy for life to avoid relapse. For all the endemic mycoses, if immunosuppression cannot be reversed, long-term suppressive azole therapy is recommended.

EVIDENCE

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ADDITIONAL RESOURCES

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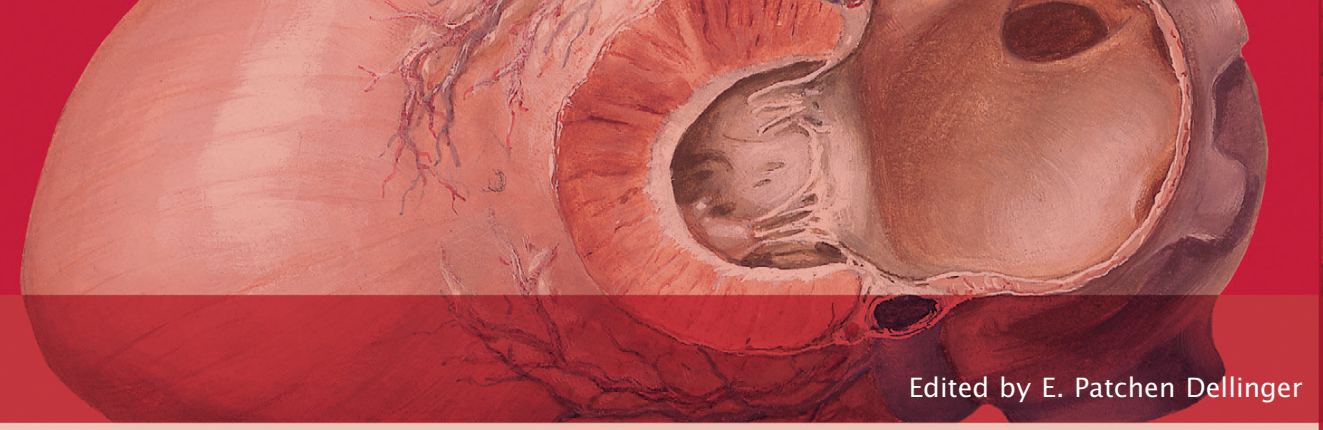

SECTION V

Edited by E. Patchen Dellinger

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Surgical Infections: Introduction and Overview

41

E. Patchen Dellinger

Surgical infections cover a broad range of infections, many of which are not obviously similar to one another, do not occur in the same organ system or anatomic location of the body, or do not even necessarily share common pathogenic flora. Many think of surgical infections as those that follow a surgical procedure, and that can certainly be true for an incisional surgical site infection (SSI) or a postoperative intraabdominal abscess. However, the common thread of a surgical infection is that it stems from, or causes in its evolution, an anatomic or physical condition that must be corrected or ameliorated for the infection to resolve. Common features of many surgical infections include transgression of an epithelial barrier (either skin or gastrointestinal, respiratory, or urologic epithelium) by a surgeon, trauma, tumor, or ischemia, or obstruction of a hollow organ as may occur with an appendicolith, a bowel obstruction, a common bile duct stone, or a ureteral stone. Some surgical infections, such as subcutaneous abscesses or superficial SSIs, may resolve with this correction alone and not require antibiotic treatment at all. Others need a combination of anatomic manipulation and antimicrobial treatment. The physical treatment of a surgical infection has been termed "source control." Source control may involve extensive surgical treatment such as debridement of a necrotizing soft-tissue infection or something as simple as removing sutures from a recent surgical incision to let the skin fall open and an SSI drain. Source control may require a surgeon to remove an appendix, close a perforated ulcer, or remove a segment of colon involved in diverticulitis; it may be managed by a gastroenterologist who removes a common duct stone in a person with cholangitis and places a stent across the ampulla; or it may involve an interventional radiologist who inserts a percutaneous drain into a subphrenic abscess. Prosthetic infections usually require removal of the prosthesis for resolution. In each case a mechanical or anatomic source control maneuver is essential to the resolution of the surgical infection, and in most cases antimicrobial treatment is needed as well.

Although some surgical infections, such as a superficial abscess or superficial SSI, may allow diagnosis in a straightforward manner, others, such as appendicitis, diverticulitis, and cholangitis, require knowledge of anatomy and physiology and the natural history of the infection for accurate and timely diagnosis. Some surgical infections masquerade as "medical" infections such as necrotizing fasciitis, initially resembling a simple cellulitis. Some can be occult with minimally virulent pathogens such as chronic foreign body infections involving a vascular prosthesis or prosthetic joint. In contrast to many medical infections that are caused by a single pathogen possessing a virulence characteristic that allows it to evade host defenses, many surgical infections are caused by a mixture of normal endogenous flora that reside on mucosal surfaces and cause disease only after mechanical violation of the epithelial barrier. Thus many surgical infections are caused by an anatomic injury just as they subsequently require an anatomic correction for resolution. In the chapters that follow in this section on surgical infections, the authors will illustrate these facets for the individual surgical infections discussed.

Acute Appendicitis

Heather M. Vasser and Daniel A. Anaya

42

ABSTRACT

Acute appendicitis is the most common surgical emergency, and appendectomy is the most common emergency operation, with more than 250,000 procedures reported annually in the United States. Acute appendicitis results from appendiceal endoluminal obstruction, typically caused by a fecalith. Although no specific risk factors have been identified, it is slightly more common in males and in the young and the elderly, with more advanced disease on presentation in the elderly. Clinical findings in combination with basic laboratory tests are often enough to establish the diagnosis, and imaging studies, such as abdominal ultrasound or computed tomography (CT), can be helpful to confirm the diagnosis and rule out other potential pathologies in selected individuals. The treatment for acute appendicitis is appendectomy, and the laparoscopic approach is preferred, given its association with better postoperative outcomes. In later stages, appendicitis may be complicated with phlegmon or intraabdominal abscess. For these patients, aggressive medical treatment with broad-spectrum antibiotics and percutaneous drainage when indicated is the initial treatment of choice, and the operative approach is reserved for when this treatment fails and in the setting of peritonitis. Interval appendectomy after an episode of appendicitis treated with antibiotics, although still controversial, must be considered to minimize the risk of recurrent inflammation, which is associated with worse outcomes. Good outcomes are generally seen in patients diagnosed and treated early, and this should be the main goal when approaching patients with suspected acute appendicitis.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Appendicitis is the most common surgical emergency in the United States and worldwide. It is characterized by acute inflammation of the appendix and generally caused by proximal endoluminal obstruction. No specific geographic or endemic distribution has been reported. The cumulative lifetime risk of appendicitis ranges from 7% and 12%. It has remained stable over time, with appendectomy rates constant during the past several decades and reported at 10 per 10,000 patients per year. Appendectomy is the most common emergency operation performed worldwide, with over 250,000 operations per annum in the United States. Based on population-level data derived from a nationwide administrative database, in 1997 alone over 260,000 appendectomies were performed in the United States, with a median cost close to USD $11,000 per patient and an estimated overall cost of over USD $2.5 billion.

RISK FACTORS

Endoluminal obstruction is the most common cause of appendicitis, with fecaliths being found in 40% of cases of simple appendicitis, 65% of gangrenous appendicitis, and 90% of ruptured appendicitis. Less common causes of obstruction include lymphoid hypertrophy—usually caused by a virus infection in children (mesenteric adenitis)—tumors, seeds, parasites, and inspissated barium. Obstruction leads to appendiceal dilatation with subsequent transmural congestion, venous obstruction, and ischemia. Delayed presentation can result in gangrenous appendicitis with associated perforation and subsequent abscess formation or peritonitis (Figure 42-1). Gender is associated with different incidence of appendicitis, with a male/female ratio of 1.3:1. Similarly, certain age groups are associated with an increased incidence of appendicitis at its different stages. Appendicitis (nonperforated) is more common among adolescents and young adults, with a peak incidence in the second and third decades, whereas perforated appendicitis is more common in children and in the elderly.

CLINICAL FEATURES

Taking an accurate history and performing a physical examination are of utmost importance and provide the main clues to an early and accurate diagnosis of appendicitis. The classic presentation is characterized by early periumbilical colicky abdominal pain, which subsequently migrates to the right lower quadrant. This was first described by Murphy and is present in at least 50% of all patients. The periumbilical nature of early pain (within 1 to 12 hours of onset of symptoms) is a referred pain from visceral innervation of the midgut. With progression of the local inflammatory process, the parietal peritoneum becomes inflamed, which results in migration of the pain to the right lower quadrant. Occasionally pain is described as originating at this site during the early phase of appendicitis. Nausea and vomiting occur in 75% of patients, although it is not prominent or prolonged. The sequence of symptoms helps to confirm the diagnosis; in more than 95% of cases of acute appendicitis anorexia is the first symptom, followed by abdominal pain and then vomiting. A different sequence of events is usually associated with other pathologies included in the differential diagnosis. A recent meta-analysis evaluating signs and symptoms associated with acute appendicitis was unable to identify any one specific isolated diagnostic finding to help confirm acute appendicitis but identified migrating pain as a sequence of events strongly associated with this diagnosis.

Physical examination is extremely helpful when evaluating a patient for appendicitis. Although in early nonperforated

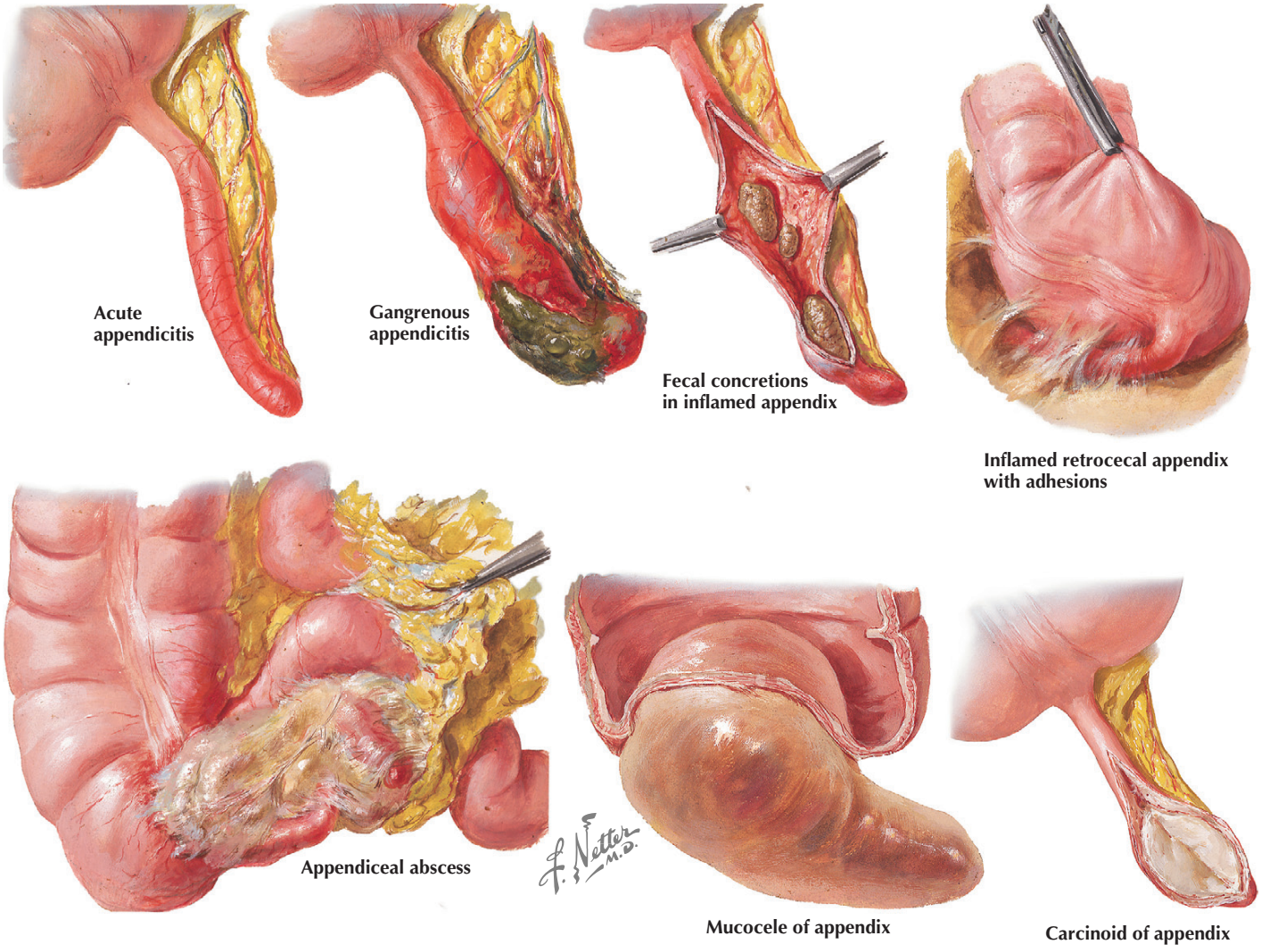
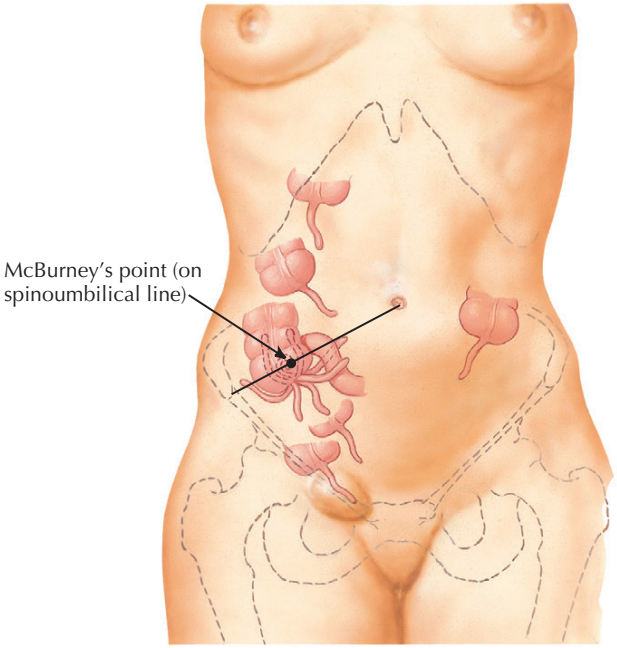


Figure 42-1 Diseases of the appendix: inflammation, mucocele, tumors.

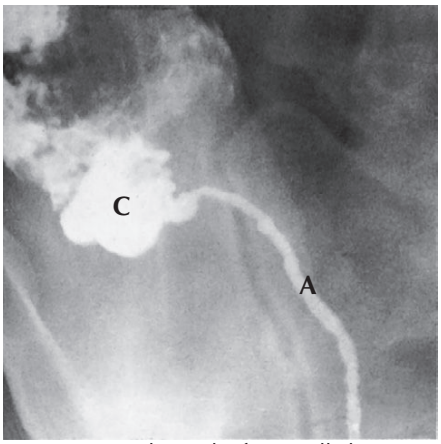
appendicitis vital signs are relative unchanged, temperature elevation of 1° C and a mildly elevated heart rate are common. High fever and tachycardia with hypotension are more common in advanced presentations and should raise suspicion of other diagnoses when present during the early course. Tenderness on palpation over McBurney's point is the classic physical examination finding, particularly when the appendix is located in an anterior or posterior retrocecal but intraperitoneal position (Figure 42-2). Other findings can be present with locations in the retroperitoneal or pelvic areas. Specifically, a retrocecal retroperitoneal appendix typically causes flank or back tenderness, whereas a pelvic appendix may cause rectal and/or suprapubic pain (see Figure 42-2). Other important findings include rebound tenderness as well as referred pain in the right lower quadrant when pressure is exerted in the left lower quadrant, the Rovsing sign. More uncommon but important signs associated with the specific location of the inflamed appendix include the psoas and the obturator signs. A psoas sign, or pain while extending the psoas muscle, is present in cases of a retroperitoneal inflammation, and an obturator sign, or pain on passive internal rotation of the right thigh, suggests a pelvic location.

DIAGNOSTIC APPROACH

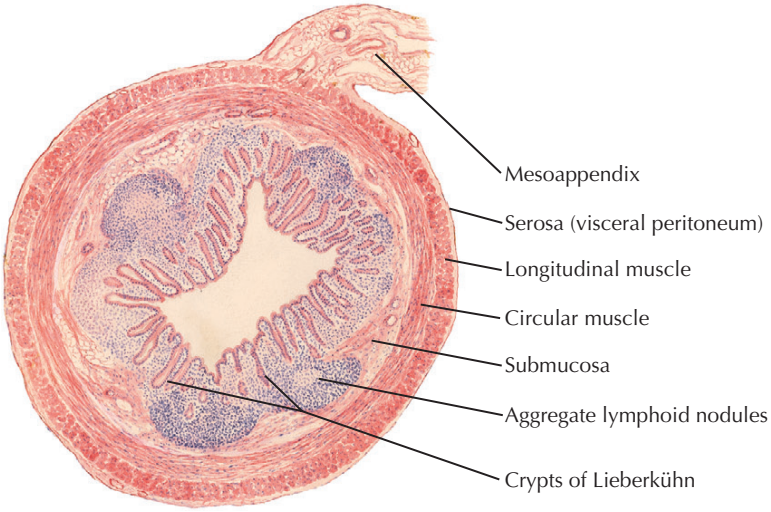
Once a thorough history and physical examination have been completed, laboratory findings and integration of all data can help confirm the diagnosis. Laboratory tests should include a complete blood count, urinalysis, basic metabolic panel, and pregnancy test for all female patients of childbearing age. Leukocytosis ranging from 10,000 to 18,000 cells/mm^3 and an elevated absolute neutrophil count are common in patients with simple early appendicitis. White blood cell counts greater than 18,0000 cells/mL^3 correlate with perforated appendicitis or appendiceal abscess. A urinalysis helps to rule out a urinary tract infection because bacteriuria is not typically seen in patients with appendicitis. A basic metabolic panel may reveal electrolyte abnormalities derived from anorexia, vomiting, and secondary dehydration. A pregnancy test is important to rule out an ectopic pregnancy in all females of childbearing age.



Variations in position of appendix



Barium radiograph of unusually long appendix (*A*, Appendix; *C*, cecum)



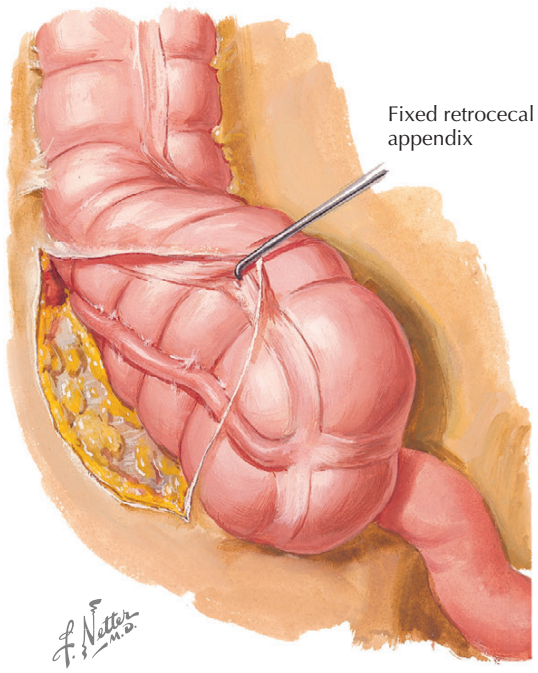


Figure 42-2 Vermiform appendix.

The combination of findings derived from the history and physical examination and results from the initial laboratory tests can usually be enough to confirm the diagnosis or suspicion of acute appendicitis, particularly in the most common and typical cases. The most typical presentation will be a young adolescent male with a 1- to 2-day history of periumbilical pain radiating to the right lower quadrant with rebound positive or negative Rovsing sign and mild leukocytosis. More delayed presentations, 4 to 5 days from the beginning of pain, are characterized by the presence of fever, tachycardia, rebound, and positive Rovsing sign, and occasionally a right lower quadrant mass may be felt, suggesting the presence of an abscess or phlegmon. Less commonly, late presentations progress to diffuse peritonitis characterized by diffuse abdominal pain and a more severe systemic inflammatory response.

Other tools can be used to help confirm the diagnosis. Findings from history, physical examination, and laboratory tests can also be used to calculate the Alvarado score. This score is based on eight data points and was developed to help confirm the diagnosis of acute appendicitis using clinical and initial laboratory findings (Table 42-1). Higher scores are directly associated with higher likelihood of appendicitis; scores lower than 5 are unlikely to represent appendicitis, whereas those higher than 6 or a score of 10 are considered consistent and highly consistent with appendicitis, respectively.

Special considerations should be given to the elderly, young children, and the pregnant. Both the elderly and children usually present later with longer duration of prehospital symptoms. In addition, findings in these populations are somewhat atypical. In older patients, periumbilical migratory pain is almost always

Table 42-1 Alvarado Score

FINDINGS	SCORE POINTS
Symptoms	
Pain migration	1
Anorexia	1
Nausea and vomiting	1
Signs	
Right low quadrant pain	2
Rebound tenderness	1
Temperature ≥37.3° C	1
Laboratory Results	
Leukocytosis	2
Left shift	1
Total score	**10**

absent, and pain located in the right lower quadrant is reported in only 80% of cases. The accuracy of the Alvarado score also declines in this population, with less than 50% of patients having scores higher than 7. This uncommon presentation is associated with more advanced disease, including higher rates of perforations and abscess formation, which in combination with more associated comorbidities result in worse overall outcomes, including longer lengths of stay and higher rates of postoperative complications and death. In children younger than 5 years old, the inability to give an accurate history often limits an earlier diagnosis, which can result in similar patterns of diagnosis, treatment, and outcomes as those observed in the elderly. In the pregnant patient, as the gravid uterus enlarges the appendix moves cephalad (Figure 42-3). This is an important consideration that changes the location of pain as well as the surgical approach when the diagnosis is confirmed.

Finally, other differential diagnoses must be considered when evaluating patients with right lower quadrant abdominal pain, including urinary tract infections, diverticulitis, perforated ulcer, ectopic pregnancy, ruptured ovarian cyst, ovarian torsion, pelvic inflammatory disease, testicular torsion, inguinal hernia, Meckel's diverticulum, Crohn's enteritis, gastroenteritis, and complications derived from a colonic or small bowel tumor.

When using the described approach to work up patients with suspected acute appendicitis, a false-positive diagnosis can still be made. This results in negative appendectomy, which has been reported to occur in 15% of patients, as reported by both clinical and population-level analyses. The negative appendectomy rate is higher for females (22% versus 9% for males) and even higher for women of reproductive age (up to 26%). A negative appendectomy rate of 10% to 15% is generally accepted, considering that a low threshold for operation can avoid the complications derived from delayed diagnosis including perforation, and this strategy is additionally supported by a low cost to the patient and the healthcare system.

A more thorough workup including the use of imaging studies (CT or ultrasound) has been advocated with the primary goal of improving the accuracy of the diagnosis. Two prospective studies have shown a decrease in the number of unnecessary admissions and appendectomies with CT. However, a longitudinal population-level study suggested that despite the introduction of ultrasound and CT scanning, the rates of negative appendectomies have remained unchanged over time, arguing against a routine use of these diagnostic strategies. Imaging studies should be considered selectively, when the diagnosis is unclear and in patients with higher risk of negative appendectomy. CT scan is the preferred diagnostic test, although ultrasound is a good alternative particularly in children and thin patients, as well as in pregnant women or women of childbearing age, to delineate uterine and/or ovarian pathology.

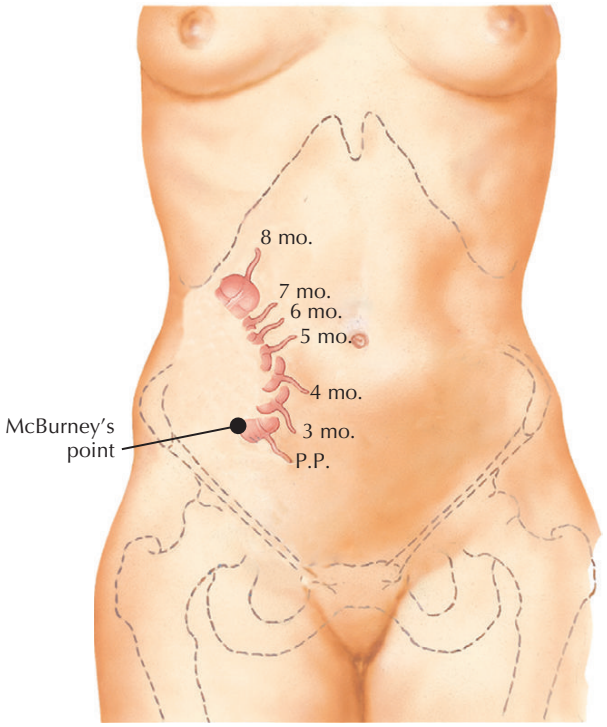


Figure 42-3 Appendix migration at different stages during pregnancy.

CLINICAL MANAGEMENT AND TREATMENT

The treatment for acute appendicitis is appendectomy. Early acute appendicitis is generally managed with surgery and prophylactic antibiotics to minimize the risk of surgical site infection (SSI). If no perforation or focal peritonitis is encountered, there is generally no need for continuation of antibiotics after surgery, because the main infectious source has been removed—source control. For perforated appendicitis, appendectomy should be performed and systemic antibiotics continued for 5 to 7 days or until fever and leukocytosis have resolved. *Escherichia coli* and *Bacteroides fragilis* are the main organisms isolated in acute simple and perforated appendicitis. However, both anaerobic bacteria and other gram-negative organisms may be present, and polymicrobial infections are most common. The Surgical Infection Society (SIS) has recommended different single- and multiple-agent regimens based on the best available evidence, generally derived from randomized controlled trials. Single-agent regimens include cefoxitin, cefotetan, and

ticarcillin-clavulanic acid; and multiple-agent therapies include a third-generation cephalosporin, monobactam, or aminoglycoside combined with antianaerobic coverage with agents such as metronidazole or clindamycin.

Delayed presentation, usually defined as presentation after 5 days or longer since onset of symptoms, is associated with abscess formation plus or minus phlegmon or diffuse peritonitis. Outcomes in these patients are worse than in those with early presentation. For these patients a CT scan is generally recommended. If a phlegmon is identified, the patient is admitted and treated with systemic antibiotics, bowel rest, and physiologic support. If the CT scan reveals an abscess, it should be drained via a percutaneous approach whenever feasible, and medical treatment as described previously should be initiated. Nonsurgical treatment has been reported to fail in approximately 7% to 10% of patients. Failure of medical treatment is defined as worsening abdominal pain, continuous fever, leukocytosis, and/or progression to focal or diffuse peritonitis. In these cases the patient should be taken promptly to the operating room for surgical management to include drainage and resection of the involved tissues, which often requires a cecectomy or hemicolectomy, and drain placement.

Management of nonperforated appendicitis with antibiotics alone (nonsurgical management) has been reported after initial experience in cases where surgical treatment was not available, such as in remote areas or isolated conditions (e.g., submarines). A recently published randomized controlled trial involving 252 male patients concluded that this nonsurgical strategy could be used in the setting of acute appendicitis. However, this approach is associated with adverse outcomes such as a high readmission rate (14% to 35%) and failure of medical treatment requiring surgery in the presence of more advanced disease. Because of these potential complications and the relatively benign course after appendectomy, early operative intervention with or without antibiotics (following previously outlined guidelines) is the treatment of choice whenever this strategy is available, and medical or antibiotic treatment alone should be reserved for well-selected patients in whom an operation may pose a greater risk or for those in whom surgical management is not immediately available.

For patients in whom appendectomy was not performed during the acute presentation, an interval appendectomy can follow 6 weeks to 3 months after the patient has recovered from the initial event. Although the need for this subsequent operation remains somewhat controversial, different studies have reported a high recurrence rate (10% to 30%), supporting strongly considering subsequent appendectomy. If an observant strategy is followed, subsequent studies must be completed to rule out neoplastic disease in selected individuals.

Lastly, there has been some debate regarding the best surgical approach for appendectomy: laparoscopic versus open. Results from multiple randomized controlled trials have been reported, and a recent review of the literature favored the laparoscopic approach because of better postoperative outcomes including lower rate of SSI, shorter length of stay, and faster return to work. Although the direct costs, operative time, and incidence of intraabdominal abscesses may be higher, the laparoscopic approach is currently the standard of care given the reported benefits after surgery.

PROGNOSIS

The outcomes after appropriate treatment for acute appendicitis have improved significantly during the last two decades, with current low morbidity and mortality rates. However, complications and mortality increase significantly in the elderly and the pregnant female. Fetal mortality ranges from 0% to 1.5% in cases of simple appendicitis to 20% to 35% in cases of perforation, hence the need for early and aggressive therapy in pregnant patients. The most common complication after appendectomy is SSI, typically affecting the superficial wound. The risk of SSI ranges from 1% to 20% and increases in perforated appendicitis and in the elderly population. Most common, superficial SSI can be treated with local wound care and antibiotics if surrounding cellulitis is present. Deeper SSI (intraabdominal abscess) is less common but does occur, particularly in those treated for perforated appendicitis. The diagnosis is made with CT or ultrasonography in patients with worsening abdominal pain during the postoperative period or those with signs and/or symptoms of sepsis. In the vast majority of cases, these abscesses can be treated with percutaneous drainage. Surgical management is seldom required, although it must be considered when large multiloculated abscess are present and in patients with multiple diffuse abscesses not amenable to the percutaneous approach.

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Acute Ascending Cholangitis and Suppurative, Toxic Cholangitis

Patrick S. Wolf and James O. Park

43

ABSTRACT

Acute ascending cholangitis is a biliary tract infection resulting from bile duct obstruction. It carries potential for significant morbidity and mortality and requires prompt diagnosis and treatment. Clinical presentation can range from a mild, self-limited course to a serious, life-threatening condition requiring emergent intervention. Patients typically have some combination of fever, jaundice, and abdominal pain. A methodic patient history and imaging workup can usually elucidate the cause of the biliary obstruction. Therapy should be initiated swiftly and relies on aggressive resuscitation, appropriate antibiotics, and prompt biliary decompression. Outcome largely depends on the underlying cause of biliary obstruction and timely recognition and treatment.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Although it is difficult to assess the exact incidence of acute cholangitis, an estimated 10% to 15% of the more than 1 million patients diagnosed with gallstones annually in the United States will have stones in the common bile duct. Of these patients, over half will develop symptoms of acute cholangitis—a conservative yet significant figure of 50,000 to 75,000 cases per year. Although the disease is prevalent worldwide, in Western countries over 85% of bile duct stones originate from the gallbladder, whereas in East Asian countries where liver fluke infections are endemic, primary brown pigment stones are a significant source of recurrent pyogenic cholangitis.

PATHOGENESIS

Ascending cholangitis is an infection of the intrahepatic and extrahepatic biliary system that occurs as a consequence of stagnant bile. It is well established that both biliary obstruction and bacterobilia are necessary for clinical disease manifestation (Figure 43-1). Diminished biliary outflow, most commonly caused by stone disease, predisposes to infection of the normally sterile, free-flowing bile. The consequent bacterial proliferation, together with disrupted hepatocellular tight junctions from increased intraductal pressures, results in release of systemic mediators and even overt bacteremia through translocation into the hepatic veins or perihepatic lymphatics. Patients with indwelling biliary stents for malignant strictures and patients who have undergone surgical biliary-enteric reconstruction have colonized biliary systems and can develop cholangitis even with low-grade obstruction. Other causes of biliary obstruction include primary sclerosing cholangitis, parasitic infestation *(Clonorchis, Opisthorcis)*, and acquired immunodeficiency syndrome (AIDS) cholangiopathy.

RISK FACTORS

Because the majority of cases in the United States result from choledocholithiasis, the risk factors for ascending cholangitis parallel those of gallstone disease: advanced age, female gender, obesity, metabolic syndrome, rapid weight loss, gallbladder stasis, cirrhosis, and Crohn's ileitis. Also, given that bacterobilia is a prerequisite for development of cholangitis, biliary interventions that introduce bacteria into the bile duct place the patient at risk of developing cholangitis. This is evident in patients with malignant strictures. Although it is rare for such patients to develop cholangitis *de novo*, the risk of cholangitis is significantly increased after biliary manipulation, especially with inadequate drainage.

CLINICAL FEATURES

The classic presentation of acute ascending cholangitis as described by Jean-Martin Charcot in 1877 consists of the triad of fever, jaundice, and right upper quadrant pain (Figure 43-2). However, only 56% to 70% of all patients seeking medical attention for cholangitis exhibit all three elements. Fever is the most common presenting symptom, occurring in upwards of 90% of patients. Jaundice is variable and can be absent, especially in patients with a partially occluded biliary stent as the cause of cholangitis. Abdominal pain, although common (70%), is typically mild in nature; severe pain or tenderness on examination should raise the suspicion of an alternative diagnosis, such as acute pancreatitis, cholecystitis, or perforated viscus. A more advanced form of disease, manifested by signs and symptoms of septic shock, including hemodynamic instability and altered mental status (Reynolds' pentad), is identified in a small subset (5% to 7%) of critically ill patients and requires prompt recognition and intervention for optimal outcome given the higher risk of multiorgan failure.

DIAGNOSTIC APPROACH

Cholangitis should be suspected in any patient with the triad of fever, jaundice, and right upper quadrant abdominal pain. Whereas the differential diagnosis remains broad for patients with more ambiguous complaints, a careful patient history may provide clues to narrow the diagnostic focus and elucidate the mechanism causing biliary obstruction. Patient-related factors that should raise the suspicion of mechanical biliary obstruction predisposing to cholangitis include a known history of gallstones,

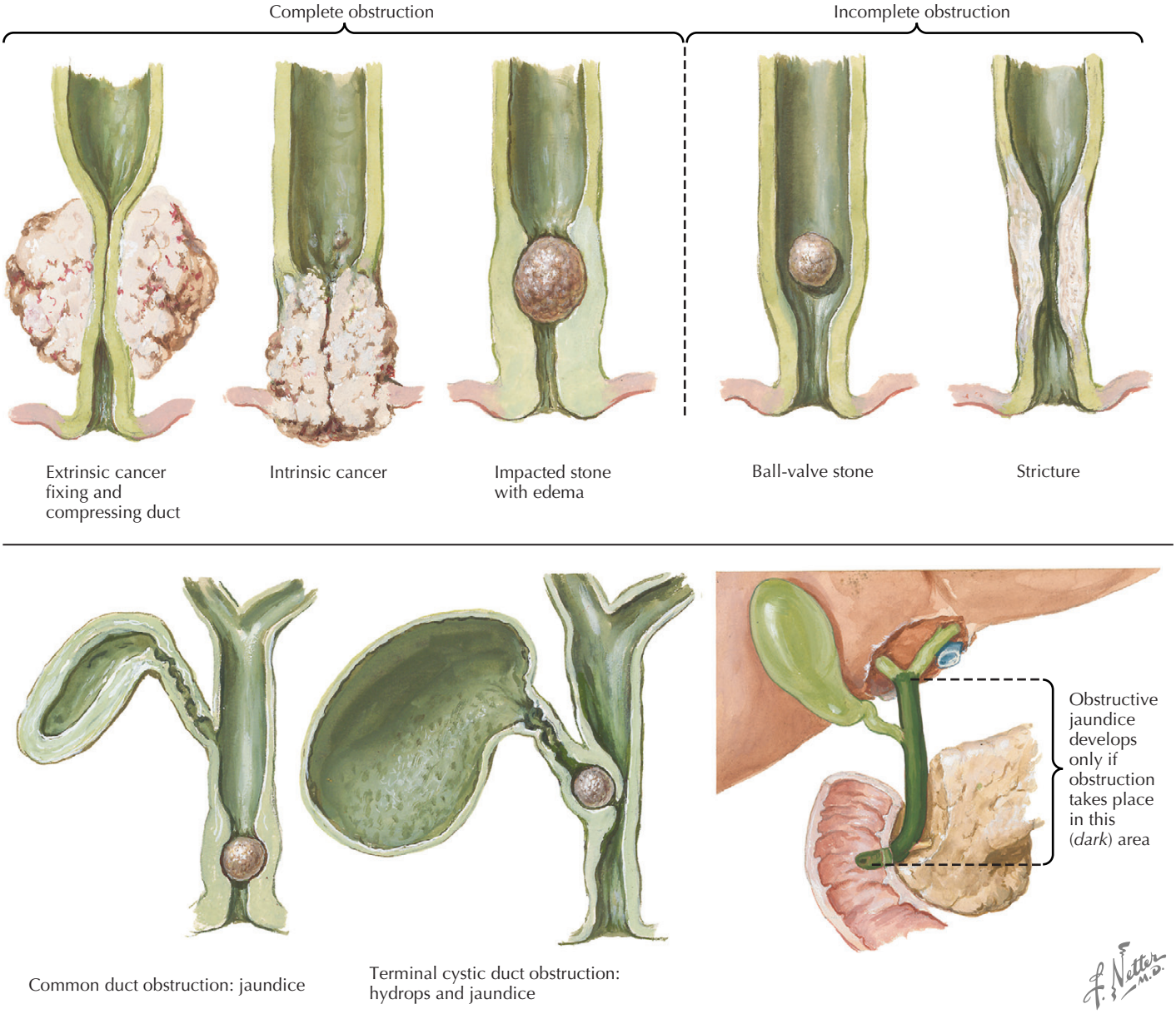

Figure 43-1 Mechanisms of biliary obstruction.

biliary colic, and pancreatitis. A history of back pain, weight loss, and acholic stools may indicate a biliary or pancreatic malignancy. Lastly, any history of surgical biliary reconstruction and endoscopic or percutaneous bile duct manipulation must be sought. Physical findings in patients with cholangitis are often nonspecific. Rigors are frequently described but variably detected. Abdominal tenderness is common and typically localized to the right upper quadrant, but overt peritoneal signs are unusual. Persistent tachycardia and hypotension herald advanced disease and warrant expedient resuscitation and treatment.

Laboratory evaluation typically demonstrates conjugated hyperbilirubinemia and elevation of alkaline phosphatase and γ-glutamyltranspeptidase, confirming biliary obstruction and injury. Leukocytosis with neutrophil predominance is common in immunocompetent patients and may be quite marked, indicating the systemic nature of the disease. Hyperamylasemia is present in roughly one third of patients and indicates more distal common duct obstruction with or without concomitant pancreatitis. Bile and blood cultures, which are positive in more than 80% and 20% to 70%, respectively, may help tailor antibiotic selection. Enteric gram-negative organisms such as *Escherichia coli*, *Klebsiella*, and *Enterobacter* and gram-positive organisms such as *Enterococcus* are the most common isolates. Antibiotic-resistant strains (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*), anaerobic organisms *(Clostridium*, *Bacteroides)*, and fungi are more commonly seen in patients with indwelling stents, prior biliary-enteric surgery, or severe infections.

Imaging is an important adjunct in the workup of patients suspected of having cholangitis and can confirm biliary dilatation, demonstrate the cause of cholangitis (e.g., choledocholithiasis or pancreatic mass), and rule out other causes for the patient's symptoms. Right upper quadrant ultrasound is an

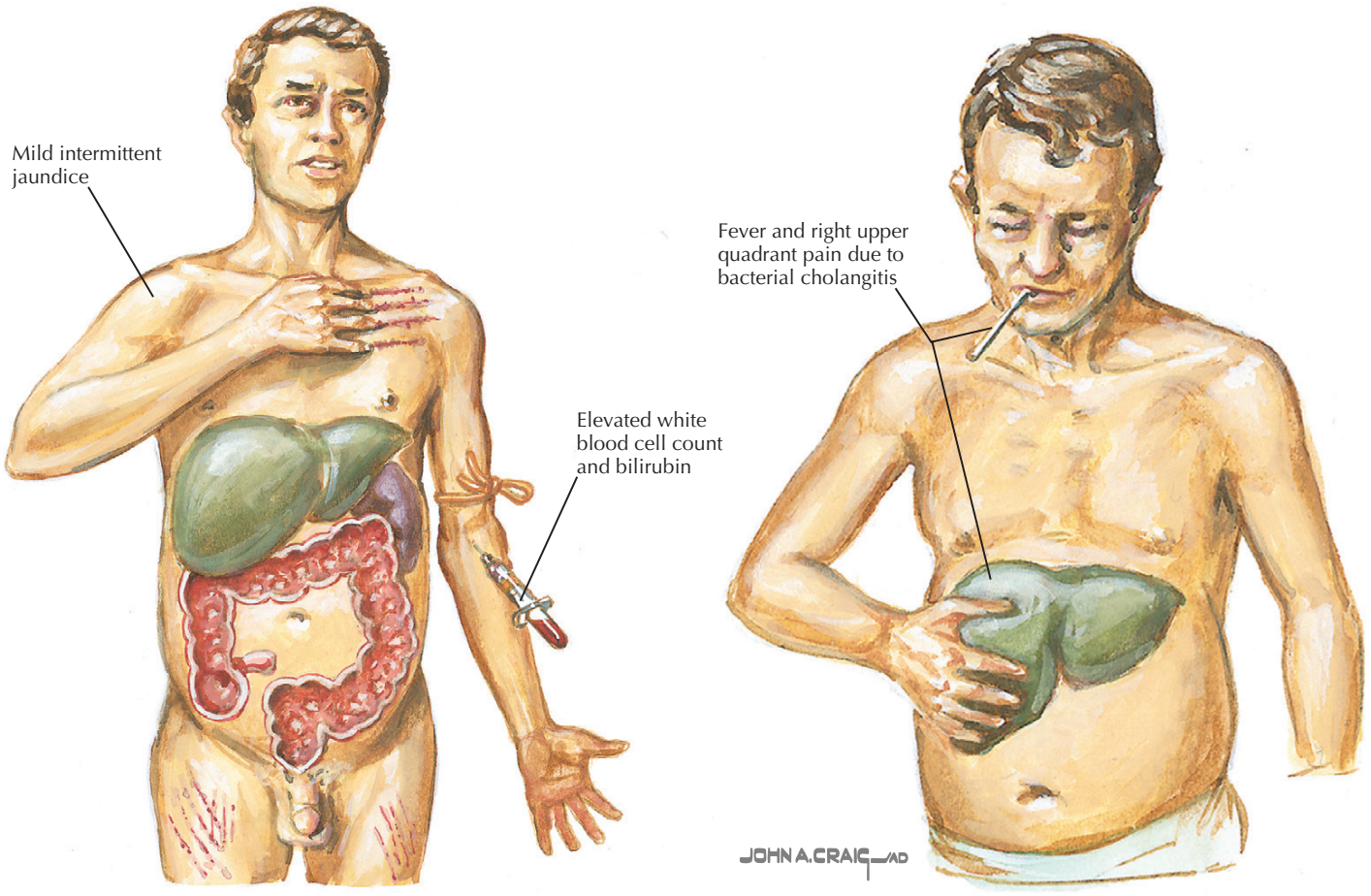

Figure 43-2 Clinical manifestations of acute cholangitis.

excellent modality to evaluate biliary pathology, as it is a quick, noninvasive, and cost-effective study that is sensitive in detecting biliary ductal dilatation and gallstones, although the sensitivity to common bile duct stones is relatively low and is operator dependent. Computed tomography effectively detects biliary dilatation and has the added benefit of a more detailed assessment for coexistent pathology such as liver abscesses, although it is not effective in diagnosing choledocholithiasis. Magnetic resonance cholangiography is costly and time-consuming, and should not be the first test of choice in evaluating a patient with suspected cholangitis. However, it can be reserved for cases in which more accurate delineation of intraductal pathology (e.g., cholangiocarcinoma) is necessary. Direct cholangiography via either an endoscopic or a percutaneous transhepatic approach is generally required for patients diagnosed with cholangitis, as these interventions clearly delineate biliary ductal anatomy and can be used to relieve the biliary obstruction.

CLINICAL MANAGEMENT AND TREATMENT

Once the diagnosis of cholangitis has been established, effective treatment relies on two principles: antibiotic therapy and biliary ductal decompression. Although most patients are clinically stable with normal hemodynamics, it must be stressed that those who have advanced disease require intensive care unit monitoring and aggressive resuscitation consisting of intravenous hydration and correction of coagulopathy. Treatment delay in these critically ill patients frequently portends a poor prognosis.

Early administration of antibiotic therapy is of paramount importance in all patients with cholangitis. In the absence of microbiologic data on a given patient, broad-spectrum, empiric antibiotic therapy covering enteric gram-negative and gram-positive aerobes and anaerobes should be initiated. Antibiotic selection should favor drugs that achieve high biliary concentrations. Fluoroquinolones, extended-spectrum penicillins, carbapenems, and aminoglycosides are all excellent choices for empiric therapy while awaiting blood or bile culture results. Treatment duration depends in part on the presence of bacteremia. Patients found to have positive blood culture results require 10 to 14 days of antibiotics. In the absence of bacteremia, length of antibiotic therapy depends on adequate treatment response as manifest by resolution of leukocytosis and fever, as well as success of biliary decompression.

Biliary decompression is the next step in management of acute cholangitis. Endoscopic and percutaneous transhepatic modalities are well established and effective at achieving successful biliary drainage and are preferred over a surgical approach, because they have lower morbidity and provide better outcomes in prospective, randomized trials (Figure 43-3).

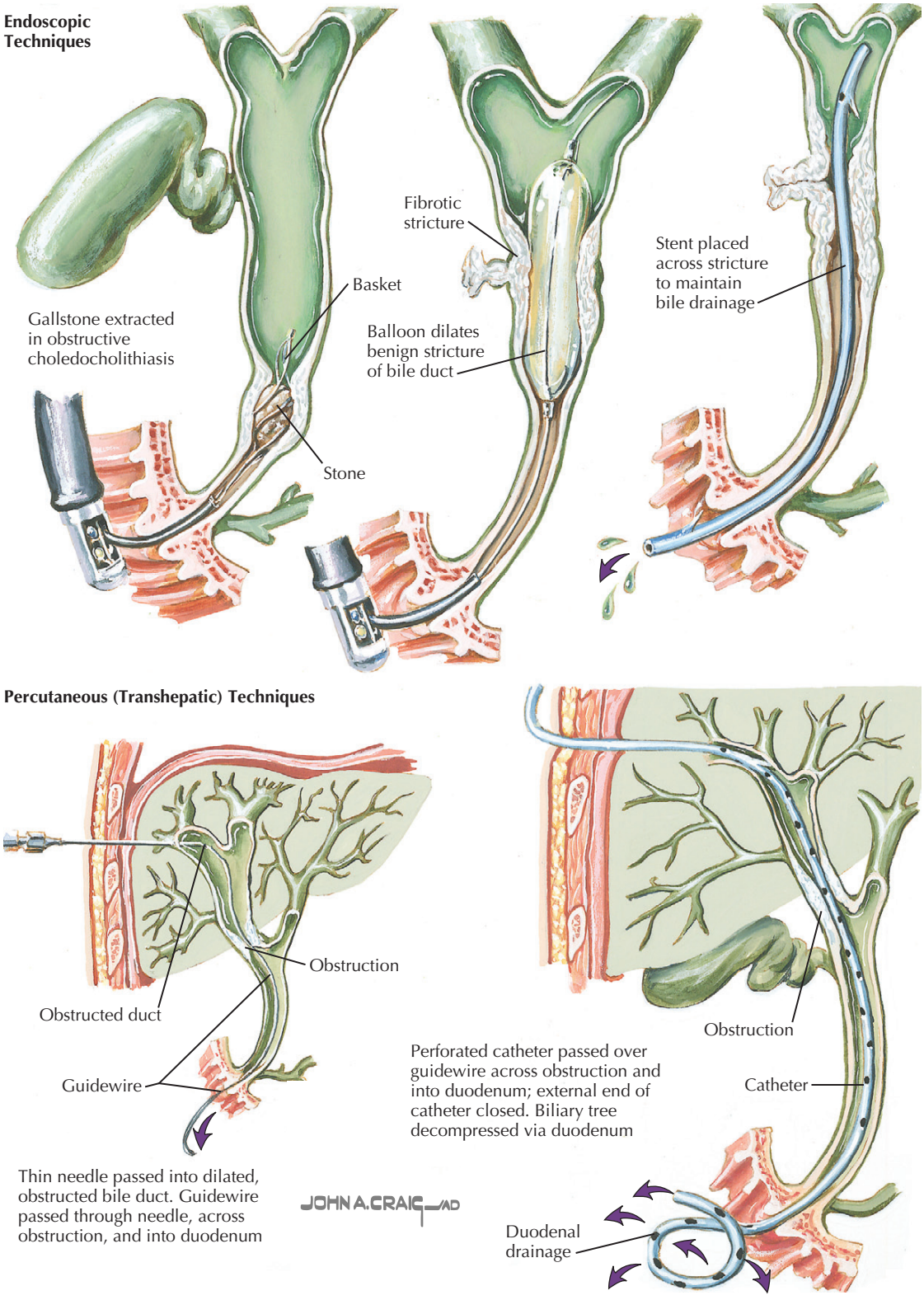

Figure 43-3 Nonoperative biliary decompression.

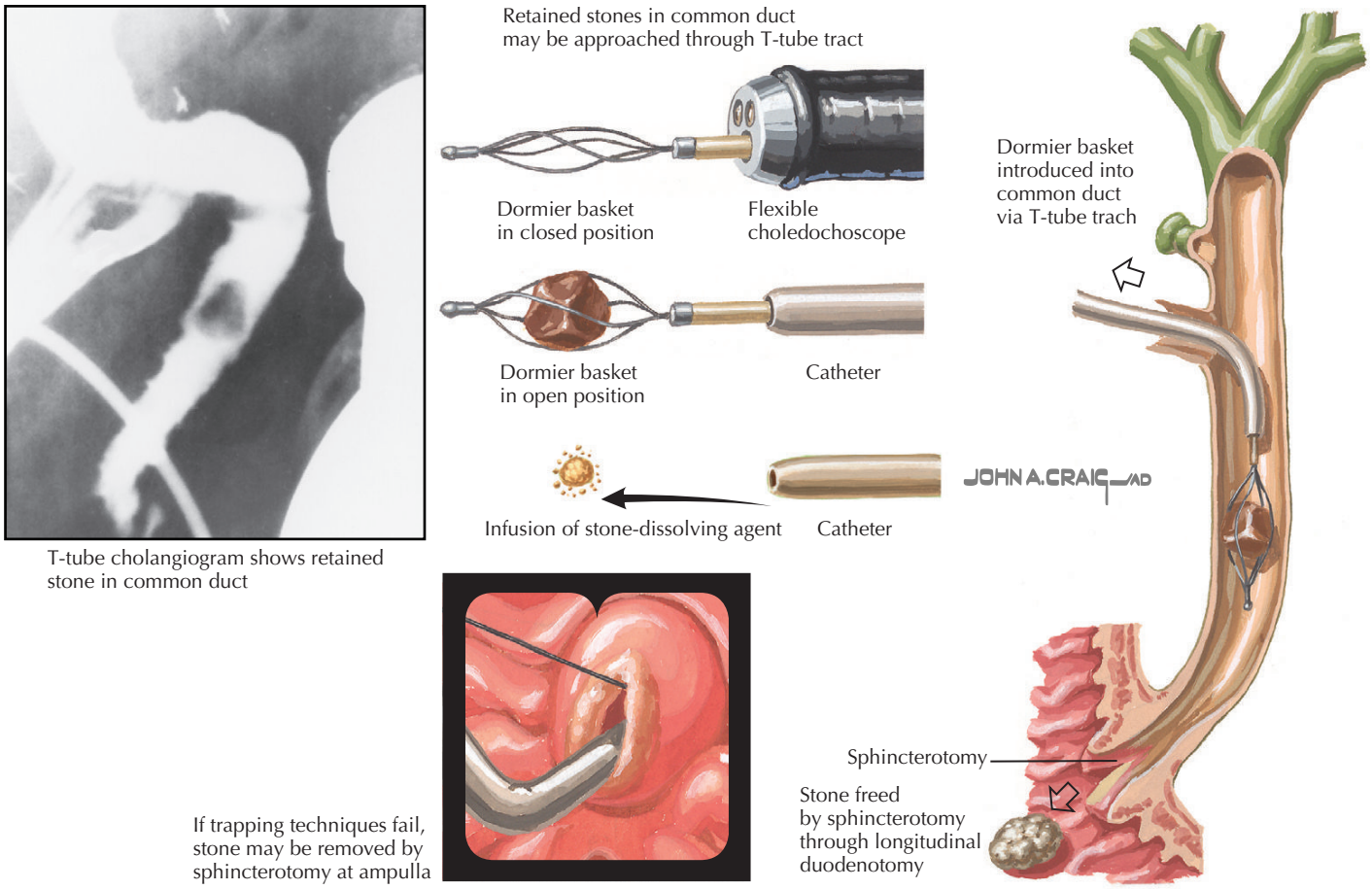

Figure 43-4 Operative biliary decompression.

Endoscopic retrograde cholangiopancreatography (ERCP) is the first-line procedure of choice; therefore consultation with an experienced gastroenterologist early in the course of therapy is essential. ERCP is effective in decompression of the biliary tract in 90% of cases, and culture or pathologic specimens can be obtained concurrently. Patients in whom endoscopic biliary decompression fails or those who cannot undergo the procedure secondary to anatomic restrictions (e.g., Roux-en-Y hepaticojejunostomy or gastric bypass) should be referred for percutaneous transhepatic cholangiography (PTC) with external biliary drain placement. A small subset of patients will not achieve decompression with either ERCP or PTC and should be referred to a surgeon for discussion of surgical options (Figure 43-4). Choledochotomy and T-tube placement are advocated over common bile duct CBD exploration and cholecystectomy to reduce morbidity in these cases. Mortality rates are historically high for this group of patients, so all efforts should be made to achieve decompression via less invasive approaches.

Timing of biliary decompression depends on the clinical response to intravenous hydration and antibiotics. Biliary drainage can be performed on an elective basis before discharge in 80% of cases when the cholangitis responds well to antibiotic therapy. Emergent biliary decompression is necessary in severe cases, allowing for better biliary penetration of antibiotics. This small subset of patients who continue to manifest signs of sepsis after 12 to 24 hours of antibiotics should proceed emergently to decompression. Although beyond the scope of this discussion, once the acute episode has been controlled, definitive therapy should be targeted at the underlying cause of biliary obstruction. Depending on the cause, this frequently involves a multidisciplinary approach involving a surgeon, gastroenterologist, and radiologist.

PROGNOSIS

Prompt recognition and initiation of treatment are of paramount importance in reducing morbidity from acute cholangitis. In general, outcomes are worse for malignant causes of obstruction and in patients with significant comorbidities. Most series cite an overall mortality of 5% for all patients with ascending cholangitis. However, mortality figures remain high (50%) in patients with severe cholangitis resulting in multiorgan dysfunction. Predictors of worse outcome include advanced age, renal failure, coexistent liver abscess, and malignant stricture.

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Acute Diverticulitis

Natasha S. Becker and Daniel A. Anaya

44

ABSTRACT

Diverticulitis of the colon is an extremely common disease accounting for close to 300,000 hospital admissions each year in the United States. The disease involves perforation of diverticula, which are herniations of the bowel mucosa through the bowel wall at points of intrinsic weakness. They most often occur in the sigmoid colon. Diet, specifically a low-fiber diet, has long been considered a causative factor, leading to constipation and increased colonic pressures. Recent studies have examined obesity and smoking as risk factors, but no definite conclusions have been reached. Patients with diverticulitis most often demonstrate left lower quadrant pain, fever, and other signs of sepsis. Presentation and clinical course can range from mild to severe, including an acute abdomen in cases of free perforation. Diagnosis may be confusing, and other causes of acute abdomen must be considered, including perforated colorectal cancer. Currently, computed tomography (CT) is considered the standard of care and can also provide guidance for the therapeutic option of percutaneous drainage. Treatment of acute diverticulitis must be individualized to the patient's clinical presentation and consists of antibiotic treatment, possible drainage, and possible surgical intervention if needed for source control. Treatment of patients who are initially treated without surgery is an area of debate. Currently the American Society of Colon and Rectal Surgeons (ASCRS) recommends an individualized approach for each patient based on age, comorbidities, and frequency and intensity of attacks.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Diverticula of the colon can be one of two main types. True diverticula are congenital, consist of all layers of the bowel wall, and are more common in the Eastern hemisphere. These are not the subject of this review. Acquired diverticula (false) are more common and form when the mucosa and submucosa of the bowel herniate through the bowel wall. This occurs at areas of intrinsic weakness in the colonic wall, between the teniae at points where the vasa recta come through the circular muscular layer (Figure 44-1). In the Western world, acquired (false) diverticula are more common in the left side of the colon, specifically in the sigmoid colon, where higher intraluminal pressure is required to move stool forward, particularly in the absence of fiber, resulting in herniation through one or more of the four predominantly weak areas of the colonic wall (see Figure 44-1).

Diverticula themselves are asymptomatic but can become symptomatic with inflammation (diverticulitis) or bleeding. It is difficult to assess the overall prevalence of diverticulosis, but autopsy studies have suggested that the prevalence increases with age, with less than 10% of individuals younger than 40 years of age having diverticula versus over 60% occurrence in those over age 80. It is estimated that 10% to 25% of persons with diverticula will develop diverticulitis.

Several studies have illustrated a higher incidence of diverticula and diverticular disease in western countries. Diverticular disease is rare in Asia and Africa, although the incidence appears to be rising as these areas become more industrialized. This has led to the hypothesis that environmental factors, specifically diet, may play a key role in development of the disease. It is interesting to note that of the small number of patients in Eastern countries who do have diverticular disease, a large percentage (>75%) have right-sided disease, most of which involve true diverticula.

Diverticulitis is the result of perforation of one or multiple diverticula and is characteristically an extraluminal process (peridiverticulitis). It is very common in the United States and Western and industrialized countries. A recent review used the National Hospital Discharge Survey and estimated that diverticulitis accounts for 300,000 admissions and 1,500,000 days of inpatient care annually in the United States. One study demonstrated that over 50% of all sigmoid resections and over 30% of all colostomies performed in the state of Washington were done for diverticulitis. The cost of treatment in the United States is over $2500 billion per year.

RISK FACTORS

The risk of diverticular disease increases with age, as the prevalence is less than 10% in individuals younger than age 40 and increases to over 60% in individuals older than age 80. Age is also an important risk factor for development of diverticulitis, with mean age of affected patients reported to be around 62 years and with increasing prevalence in older adults. Incidence appears to be fairly even among male and females. Diverticulitis has been linked to several environmental factors including diet, obesity, and smoking. It is theorized that a low-fiber diet leads to small hard stools that require increased intraluminal colonic pressures, muscular hypertrophy, and segmentation of the colon, which leads to radially directed pressure and subsequent perforation. Support for this theory comes from several studies including an autopsy review that found that Japanese immigrants exposed to a Westernized diet had a 52% incidence of colonic diverticula versus 1% of time-matched native Japanese. Links have been sought between obesity and smoking and diverticular disease, but studies have yielded conflicting results and the confounder of diet complicates interpretation.

Patients who have had one episode of diverticulitis are at increased risk for subsequent attacks. A retrospective review of a statewide hospital discharge database showed that 19% of patients who underwent initial nonoperative treatment for diverticulitis had a subsequent admission for a recurrent episode.

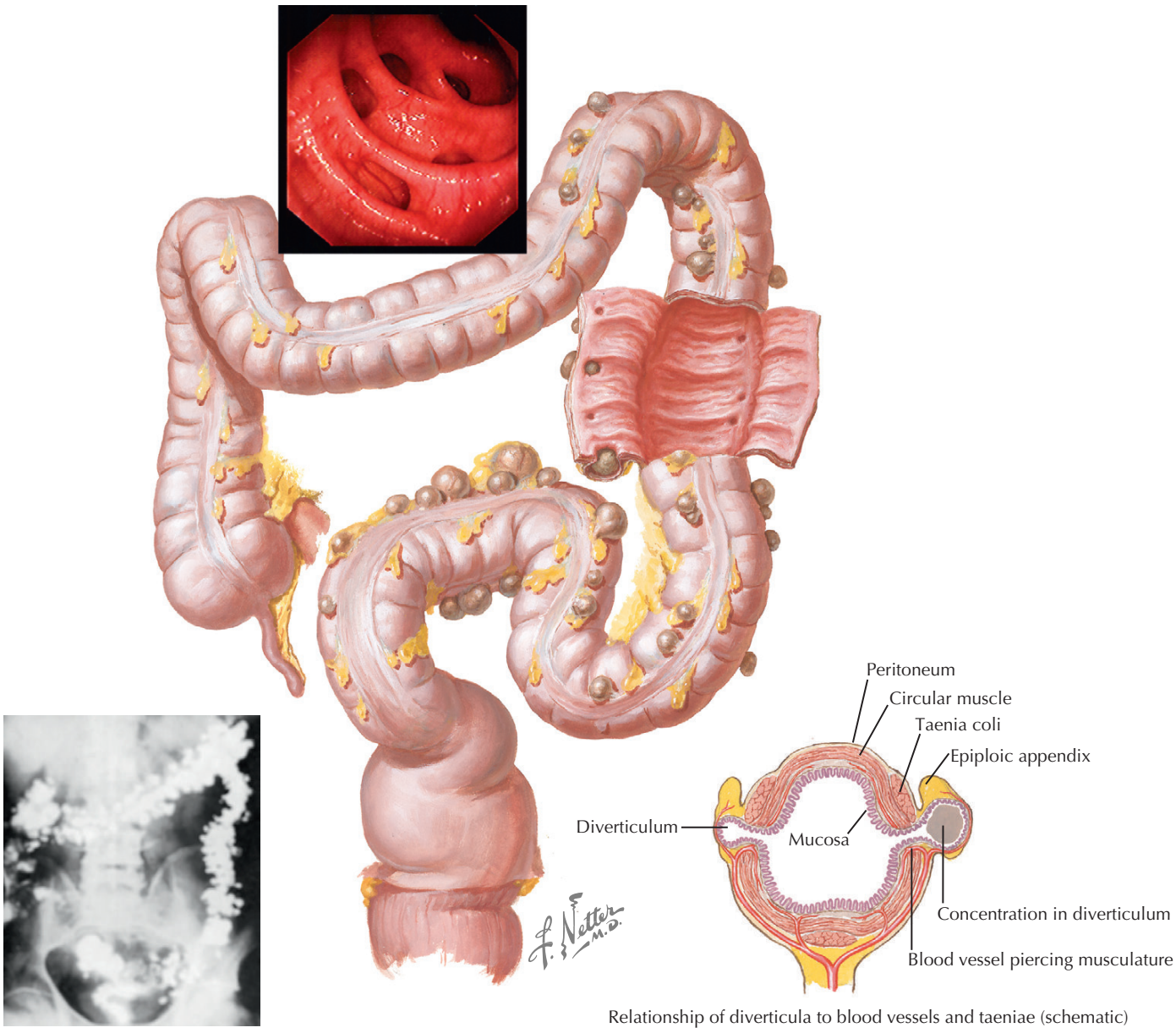


Figure 44-1 Diverticulosis.

CLINICAL FEATURES

Diverticulitis can manifest with a wide range of symptoms from mild intermittent abdominal pain to acute abdomen with sepsis and multiorgan failure. Early or mild diverticulitis (contained microperforation or macroperforation) causes abdominal pain that often starts in the periumbilical area and then localizes to the left lower quadrant as peritoneal irritation develops. Patients may complain of nausea, fever, and malaise. Symptoms may be quite nonspecific at this point, and differential diagnoses may include gastroenteritis, urinary tract infections or obstruction, appendicitis, inflammatory bowel disease, or bowel obstruction. If the inflammatory process extends beyond a contained perforation, the patient will develop more severe abdominal pain, nausea, and vomiting associated with ileus, fevers, and more systemic symptoms of sepsis. This can progress to generalized peritonitis with a presentation of acute abdomen and even multiorgan failure. Patients in later stages of disease are usually in extremis and require emergent resuscitation and immediate abdominal exploration for control of intraabdominal sepsis. Differential diagnoses include any other process that leads to generalized peritonitis (Figure 44-2) and must include the possibility of perforated colon cancer. Elderly patients may demonstrate more subtle clinical features and therefore have more advanced disease by the time diagnosis is made. Elderly patients have a higher likelihood of postoperative complications and prolonged hospitalization. Because the U.S. population of patients older than 75 years of age is growing rapidly (33% increase from 1998 to 2005), this cohort of patients is an important subset of patients who will be encountered with diverticulitis.

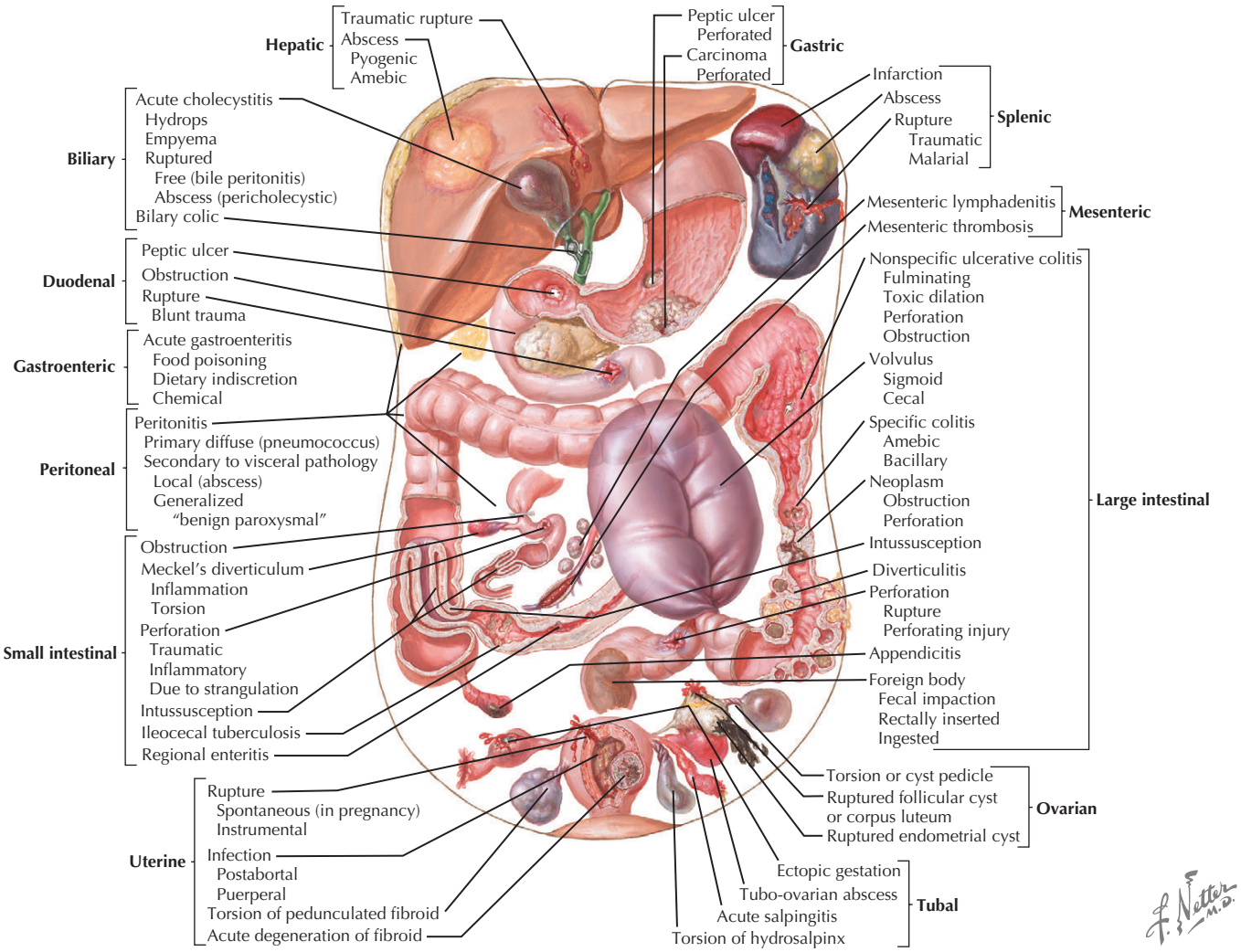


Figure 44-2 The acute abdomen.

DIAGNOSTIC APPROACH

Patients may complain of generalized abdominal pain that then localizes to the left lower quadrant. Previous episodes of diverticulitis or resolved undiagnosed abdominal pain should be ascertained. If patients have undergone screening colonoscopy in the past, these studies should be reviewed and presence and location of any diverticulosis and/or other colonic diseases (e.g., neoplasms) should be noted. Basic laboratory workup for abdominal pain should be performed to include a complete blood count, electrolytes, and renal function. Coagulation studies and electrocardiogram should be performed in patients who may require surgical intervention.

Plain films of the abdomen are often obtained and may be useful to reveal pneumoperitoneum in the case of free colonic perforation. In the past, contrast enema was widely used for diagnosis of diverticulitis. It provides excellent detail of the colonic mucosa, but little information is gained about the extraluminal area, where manifestations of diverticulitis will be most evident. There is also a risk of perforation given the friable nature of the inflamed colon, and hence it is contraindicated during the acute episode. However, a complete colon and rectal evaluation with barium enema or colonoscopy (preferably) should be completed 6 to 8 weeks after the acute episode has resolved to characterize the extent of the disease and rule out other potential diagnoses (e.g., cancer) (Figure 44-3). Currently, CT scan is considered the optimal diagnostic study for diverticulitis. It has several advantages, including the ability to reveal extraluminal extent of disease and also other possible intraabdominal sources of sepsis (Figure 44-4). It is also a guide to alternative therapeutic modalities such as percutaneous drainage of diverticular abscesses, which is the preferred alternative to surgery in the absence of peritonitis.

A complete history and physical in combination with CT scan can help classify diverticulitis in two main categories: uncomplicated and complicated diverticulitis. Uncomplicated diverticulitis is characterized by left lower quadrant pain without signs of systemic involvement. If CT imaging is performed, patients are found to have pericolic soft-tissue stranding. Treatment can usually be done on an outpatient basis with oral

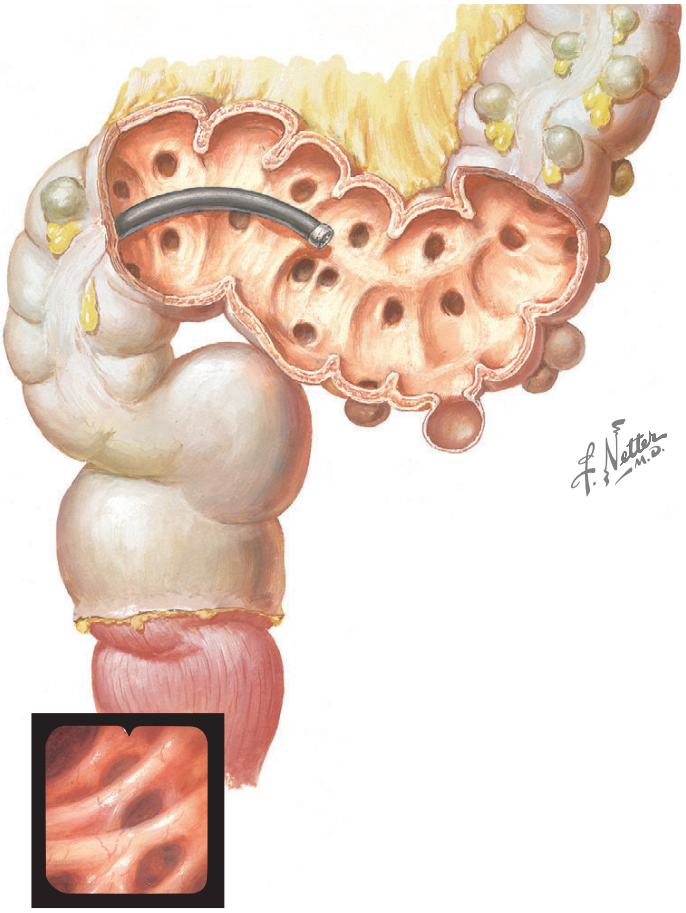


Figure 44-3 Diverticulosis.

Table 44-1 Initial Intravenous Antibiotic Treatment for Intraabdominal Infections per the Surgical Infection Society Guidelines (2010)

ANTIMICROBIAL AGENT	INTRAVENOUS DOSE	DURATION
Ticarcillin-clavulanate	3.1 g q6h	4-7 days after adequate source control obtained
Cefoxitin	2 g q6h	
Ertapenem	1 g q24h	
Moxifloxacin	400 g q24h	
Tigecycline	100 mg once then 50 mg q12h	
Cefazolin (+ metronidazole)	2 g q6h	
Cefuroxime (+ metronidazole)	1.5 g q8h	
Ceftriaxone (+ metronidazole)	1-2 g q12-24h	
Cefotaxime (+ metronidazole)	1-2 g q6-8h	
Levofloxacin (+ metronidazole)	750 mg q24h	
Ciprofloxacin (+ metronidazole)	400 mg q12h	

Data from Solomkin JS, Mazuski JE, Bradley JS, et al: Diagnosis and management of complicated intraabdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America, Clin Infect Dis *50:133-164, 2010.*

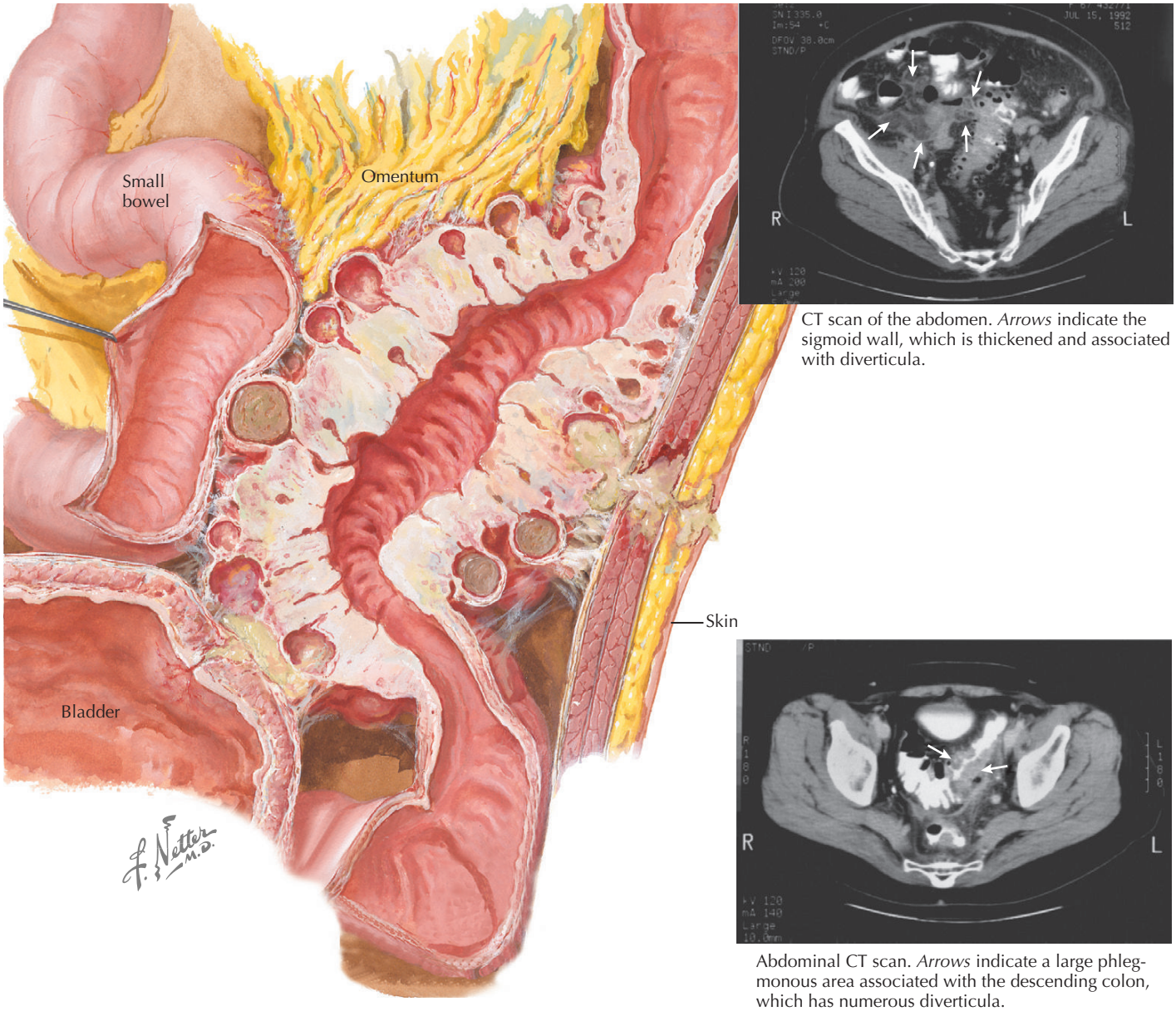
antibiotics. *Complicated diverticulitis* refers to diverticulitis with the formation of abscess, obstruction, free perforation leading to peritonitis, or fistula formation.

In addition, CT scan findings in complicated diverticulitis are classified using the Hinchey system, providing practical information that can be used to guide initial therapy. Hinchey stage I denotes a pericolic abscess, stage II a retroperitoneal or pelvic abscess, stage III purulent peritonitis, and stage IV feculent peritonitis.

CLINICAL MANAGEMENT AND DRUG TREATMENT

In general, principles for management of diverticulitis include appropriate antimicrobial therapy with or without source control (i.e., percutaneous or operative drainage and resection when indicated), bowel rest, and physiologic support. Treatment for Hinchey stages I and II includes antibiotics to cover colonic microorganisms (including anaerobes and gram-negative rods). Appropriate antibiotic regimens are listed in Table 44-1. Percutaneous drainage of pericolic abscess in the stable patient has become common, yet it is unclear the size of abscesses that warrant drainage versus antibiotic treatment alone. A case-control study comparing percutaneous drainage with antibiotic treatment alone found that patients in whom nonoperative treatment fails, those requiring drainage not amenable to a percutaneous approach, and those with signs of sepsis may require operative intervention.

Hinchey stages III and IV represent purulent peritonitis and feculent peritonitis, respectively. Treatment for free perforation includes immediate operation with drainage and resection of the involved colon. In the past, a three-stage approach was used, with initial drainage and a diverting colostomy, followed by resection of the involved colon, and a third operation for colostomy closure. This often led to clinical deterioration a few days after the first operation, presumably because the source of sepsis was left intact. By the 1980s, operative treatment evolved to a two-stage approach. Most commonly, this is done in a two-stage approach with Hartmann's procedure, defined as resection and removal of the sigmoid colon with formation of a temporary end colostomy. Advantages of this operation include adequate source control and relative ease, and safety as no new anastomosis is fashioned in the setting of intraabdominal contamination. However, this approach requires a second operation to take down the colostomy, which has led some to question whether similar outcomes can be obtained with a one-stage operation of resection with primary anastomosis (usually done with diverting ileostomy). Although preliminary results appear promising, studies have shown no decrease in the incidence of colostomy after emergent surgery for stage III or IV diverticulitis. The one-stage approach remains an area of controversy, and most would agree that the one-stage approach should be considered only in carefully selected individuals.



CT scan of the abdomen. *Arrows* indicate the sigmoid wall, which is thickened and associated with diverticula.

Abdominal CT scan. *Arrows* indicate a large phlegmonous area associated with the descending colon, which has numerous diverticula.

Figure 44-4 Diverticulitis, with computed tomographic scan showing a thickened wall and diverticula.

In 2000, the ASCRS recommended that elective colectomy be performed in patients who experienced two episodes of uncomplicated diverticulitis. This recommendation was based in part on the belief that patients having an episode of diverticulitis were at much higher risk for recurrent episodes and emergent surgery in the future. Recent studies have challenged this assumption. A population-based evaluation of patients admitted for diverticulitis but treated nonoperatively found that only a small percentage of patients (6%) required emergent colectomy and/or colostomy. An additional study constructed a Markov model to evaluate the mortality risk, risk of colectomy, and cost of treating diverticular disease nonsurgically, after the acute episode of diverticulitis had resolved with medical management. The authors concluded that nonoperative treatment led to lower mortality rates and was cost saving. The ASCRS recommendations were revised in 2006, and it is now advised that the need for elective colectomy after resolved episodes of acute diverticulitis should be reviewed individually and should be based on age, medical condition, frequency and severity of attacks, and presence of persistent symptoms.

In any patient with signs and symptoms consistent with diverticulitis (abdominal pain, sepsis, colon thickening on CT scan), perforated colorectal cancer is a diagnosis that has to be considered and ruled out. If the patient undergoes emergent surgery, the specimen should be carefully evaluated for malignancy. If the patient recovers and has conservative treatment without surgical intervention the colon must be evaluated with colonoscopy or barium enema after acute inflammation has resolved.

PROGNOSIS

After an attack of diverticulitis that is treated surgically, most (>95%) patients do well without recurrence of symptoms (assuming that complete resection of the sigmoid colon and any other diverticulum-bearing colon has been performed). Patients who were treated nonoperatively may have recurrent episodes. A 1969 review of patients with diverticulitis reported that 25% of patients were readmitted with a second attack, 4% with a third attack, and 2% with a fourth attack. Each admission was associated with a higher chance of emergent surgery. More recent studies have challenged these results, finding that 19% of patients were readmitted with a second attack but that the risk of emergent colectomy was not increased in this group.

Complications can occur after acute attacks of diverticulitis. The most common of these include fistulas, most often colovesicular, and strictures. Colovesicular fistulas may lead to repeated urinary tract infections and urosepsis. Strictures may manifest as intermittent or complete bowel obstructions. Again, malignancy must be ruled out, as colorectal cancer may manifest in a similar fashion. Both of these complications require surgical intervention with resection of the involved colon.

PREVENTION AND CONTROL

There is little evidence for effective methods of prevention for diverticulitis. As low-fiber diet has been linked to a higher incidence of diverticulosis at a population level, it follows that a high-fiber diet may reduce the incidence of diverticulum formation. One small study evaluated high-fiber diets in patients with known diverticulosis and found a lower rate of subsequent operations. Based on these data it is reasonable to recommend a high-fiber diet in patients with known diverticular disease (Figure 44-5). In addition, it is important to educate patients regarding the risk of recurrent episodes of acute diverticulitis, so that subsequent episodes can be identified early and managed successfully with medical therapy (antibiotics).

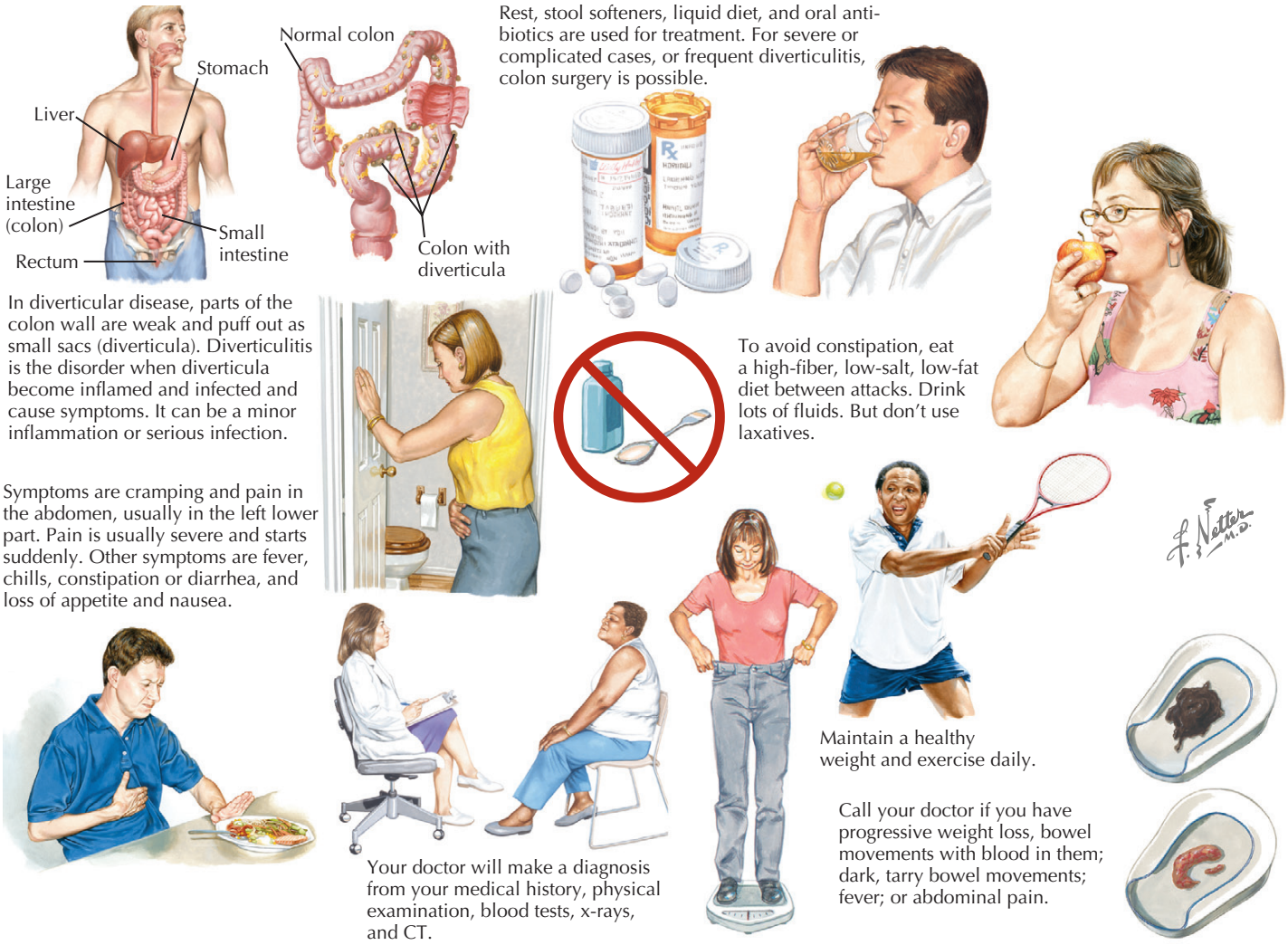


Figure 44-5 Managing your diverticulosis.

EVIDENCE

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Hydatid Cyst Disease (Echinococcosis)

Austin L. Spitzer, Paul S. Pottinger, and James O. Park

45

ABSTRACT

Hydatid cyst disease or echinococcosis is a worldwide parasitic infection caused by the *Echinococcus* tapeworm larvae. Of the seven recognized species, *Echinococcus granulosus* and *Echinococcus multilocularis*, which cause cystic echinococcosis (CE) and alveolar echinococcosis (AE), respectively, pose clinically significant and potentially lethal public health risks. Human infection occurs after incidental ingestion of the parasite eggs from the stool of infected animals. Most of these cysts are solitary and occur in either the liver or the lungs. Although the cysts displace healthy tissue, the primary infection is typically asymptomatic unless rupture or mass effect occurs. Definitive diagnosis for most cases is by imaging with ultrasound or computed tomography (CT), although immunodiagnostic assays can be a useful adjunct in both primary diagnosis and follow-up. Surgery has the potential to remove the cysts and lead to complete cure; however, successful eradication requires the entire elimination of the parasite without intraoperative contamination or compromise of affected organ system(s). Alternatively, percutaneous aspiration, injection, and reaspiration (PAIR) has emerged as a less invasive treatment option in patients with CE who present high surgical risks because of underlying pathophysiology or who are remote from surgical care facilities.

A common feature of all strains of *Echinococcus* is the use of dogs and other canids (e.g., wolves and coyotes for *E. granulosus* and foxes for *E. multilocularis*) as definitive hosts, which are infected during ingestion of raw visceral organs from intermediate hosts (e.g., sheep refuse) that contain hydatid cysts with viable protoscolices. After ingestion, the protoscolices attach to the canid's intestinal mucosa, where they mature into adult tapeworms, each several millimeters long. After 4 to 5 weeks, the released eggs are shed into the feces, and it is when these eggs are accidentally ingested by a human host that infection occurs. The larvae are released from the eggs and penetrate the intestinal epithelium. Subsequently, larvae are passively transported through blood or lymph to target organs where they may develop into a hydatid cyst. The life cycle is shown in Figure 82-1.

The host ultimately forms a pericyst, a capsule of connective tissue, in an effort to isolate the parasite, which forms two inner layers: a nucleated germinal layer and an acellular laminated layer (Figure 45-1). The exact time for the development of protoscolices within cysts is unknown, although it is believed to be more than 10 months after exposure. The liver (60%) and/or lungs (20%) are infected in the majority of cases, and in *E. granulosus* infection a solitary lesion typically develops; however, some patients develop multiple cysts. In endemic areas the kidney is the third most common organ involved, constituting 2% to 3% of reported CE cases, and involvement of the heart and mediastinum in hydatidosis is extremely rare, reported in 0.5% of patients who underwent surgery for thoracic hydatidosis in one series (Figures 45-2 and 45-3). Classically, an intact hydatid cyst has been classified as a simple cyst. A perforated cyst, with or without infection, has been referred to as "complicated" if it has ruptured into neighboring areas.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Hydatid cyst disease is seen worldwide but is endemic in the Mediterranean, Asia, South America, North Africa, and Australia, where the definitive and intermediate hosts live in close contact in herding environments. The focus of this chapter, CE, occurs in all age groups, although in areas of endemic infection the majority of symptomatic cases occur in individuals from 4 to 40 years of age (Figure 45-4).

RISK FACTORS

In endemic areas, transmission of human echinococcosis is significantly related to certain occupations such as farm laborers and workers in animal husbandry. Communities involved in sheep herding demonstrate the highest rates of infection.

CLINICAL FEATURES

The initial phase of infection is asymptomatic. Small, well-encapsulated or calcified cysts typically do not induce major pathology, and thus patients may remain asymptomatic for years or permanently. There are no pathognomonic features, and clinical symptoms occur only after a highly variable incubation period. However, hepatic hydatid cysts can cause significant upper abdominal pain, hepatomegaly, cholestasis, biliary cirrhosis, portal hypertension, and ascites. Furthermore, the cysts may rupture into the biliary tract or peritoneal and pleural cavities, possibly causing anaphylaxis and seeding secondary infections.

DIAGNOSTIC APPROACH

The primary diagnosis of hepatic CE disease is typically based on radiologic identification of cystic structures, the clinical evolution of the disease, and appropriate history revealing risk factors for hydatid cysts. Ultrasound demonstrates well-defined, circumscribed, anechoic lesions without infiltration of the surrounding tissues in uncomplicated cases, and can also demonstrate complications such as intrabiliary rupture and infection.

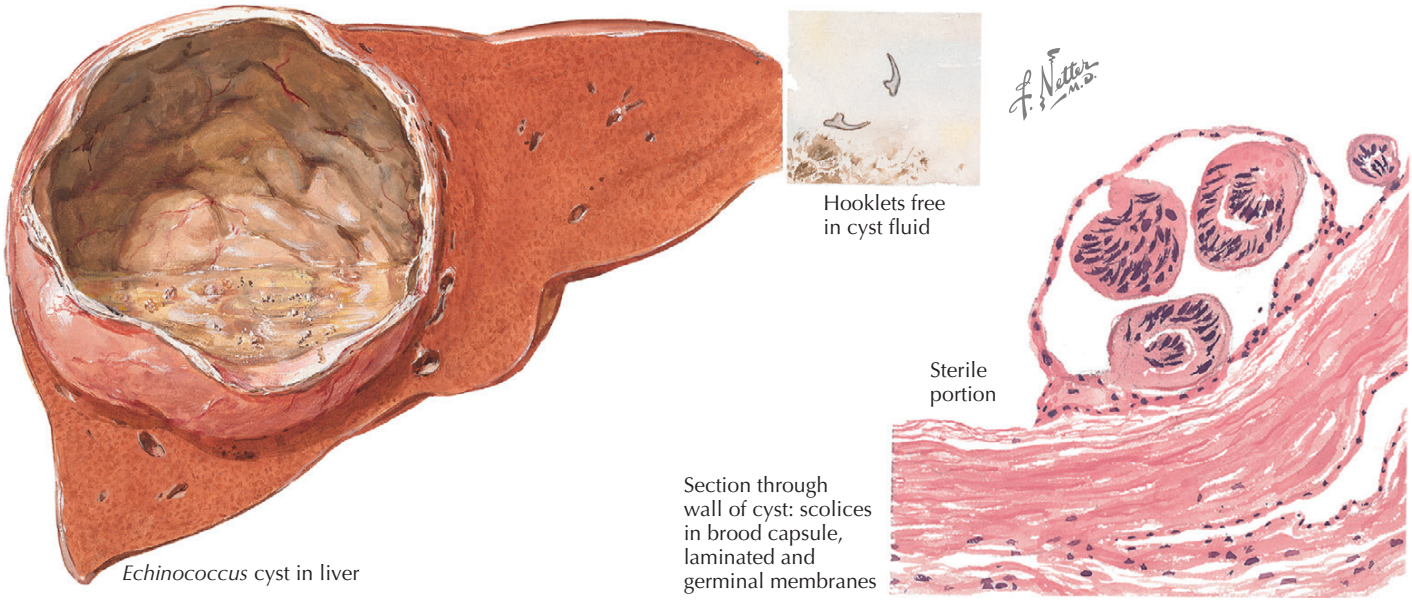


Figure 45-1 Cystic echinococcosis in the liver.

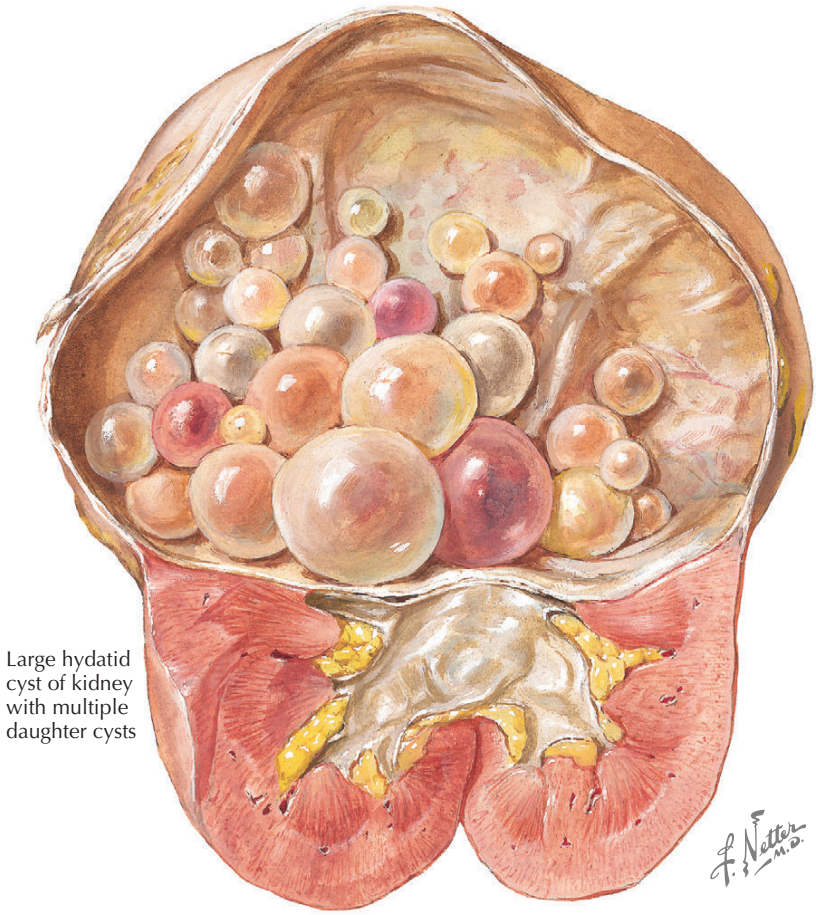


Figure 45-2 Cystic echinococcosis in the kidney.

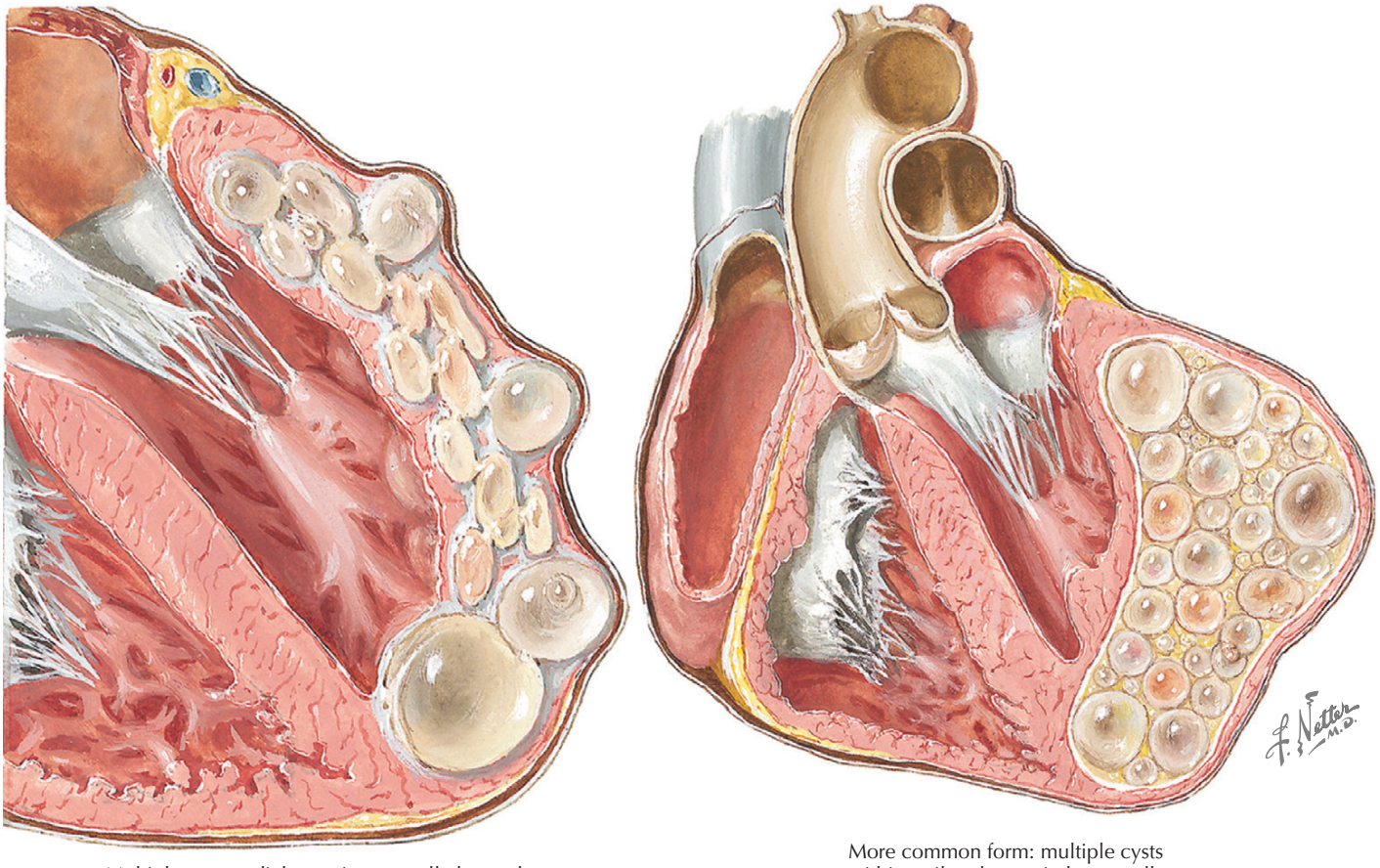
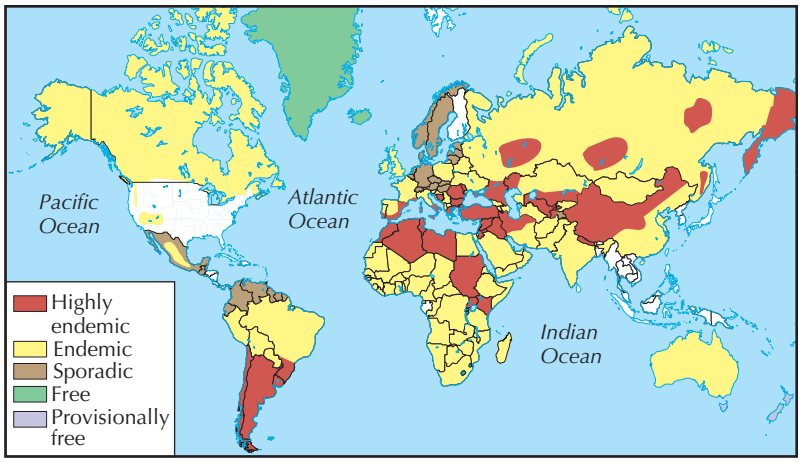


Figure 45-3 Cystic echinococcosis in the heart.



Note: exact indentification of endemic and highly endemic areas in all regions is not possible because of incomplete or lacking data

Figure 45-4 Approximate geographic distribution of *Echinococcus granulosus* (1999). *(Data from Eckert J, Schantz PM, Gasser RB, et al: Geographic distribution and prevalence of* Echinococcus granulosus. *In* WHO/OIE manual on echinococcosis in humans and animals: a public health problem of global concern, *Paris, France, 2001, World Organization for Animal Health and World Health Organization.)*

In addition, in questionable cases of CE, specimens obtained by ultrasound-guided aspiration can be examined for protoscolices, rostellar hooks, and *Echinococcus* antigens (see Figure 45-1). Albendazole prophylaxis is recommended for 4 days before aspiration and should be continued for at least 1 month after puncture of a lesion ultimately diagnosed and resected as *E. granulosus.* CT is considered the diagnostic modality of choice if available, given its superior accuracy, and magnetic resonance imaging (MRI) may help define changes in the hepatic venous system or identify atypical presentations. Immunodiagnosis is a

useful adjunct in the primary diagnosis and in the follow-up after surgical or pharmacologic treatment. However, the quantitative complement fixation assay used for this purpose is unavailable in many nations where disease is endemic.

CLINICAL MANAGEMENT AND DRUG TREATMENT

There are several options for treatment, including surgery, PAIR, and chemotherapy. For asymptomatic individuals, as previously mentioned, an observatory approach can be attempted with appropriate supervision, provided that the cysts are considered to be at relatively low risk for rupture, based on size, location, and patient activities. Entire surgical removal of the cyst cures the patient; however, there are both temporary and permanent contraindications to surgery based on the difficulty of reaching the lesion, advanced age or comorbidities, pregnancy, small or calcified cysts, and potentially lack of adequate medical care in certain endemic areas. In these individuals albendazole is the drug of choice, although it is suspected not to be parasiticidal, given recurrence rates after discontinuation.

Although the technical procedure of choice is still debated, given the lack of controlled trials, the accepted objective is the entire elimination of the parasite without intraoperative spillage or compromise of healthy tissue. In light of the concern for recurrent disease, debate exists regarding the importance of removing the pericyst and hepatic tissue (radical resection) versus conservatively evacuating the cyst alone. The level of evidence is inadequate to inform the correct level of aggressiveness; however, there is support for the safety of a laparoscopic approach and the use of omentoplasty to prevent abscess formation. Because spilled cyst fluid may contain viable protoscolices that could implant in the peritoneal cavity during surgery or cause anaphylaxis, protection of the operating field is imperative before emptying or resecting the cyst with either the radical or the conservative approach. The peritoneal and/or pleural cavities should be isolated with dry gauze or gauze soaked with parasiticidal solution or 20% hypertonic saline. After access is established and control of the cyst wall verified, the cyst is punctured and evacuated using a large-caliber suction device, and resection is then performed in either fashion. If there is any question of possible spillage of cyst contents during the case, patients are offered postsurgical treatment with 10 mg of albendazole per kilogram, usually for 8 weeks.

An alternative to surgical intervention is the PAIR technique, in which the cyst is punctured transcutaneously under ultrasound guidance and the parasite is killed through repeated aspiration and injection of scolicidal agents such as 20% hypertonic saline. For simple hydatid liver cysts that do not abut the liver capsule, this appears to be a safe and attractive option, especially in endemic areas without the option for more aggressive intervention. Many infectious disease specialists recommend treating with antiparasitic drugs such as albendazole for up to 8 weeks postprocedure. Chapter 82 provides further details on cyst staging and treatment options.

PROGNOSIS

The mortality rate for CE is estimated to be 0.2 per 100,000 population, with a case-fatality rate of 2.2%. In contrast, the mortality rate for untreated AE caused by *E. multilocularis* has generally been accepted to be 100% at 15 years from diagnosis. However, survival has improved dramatically among those with alveolar disease who are treated with albendazole.

PREVENTION AND CONTROL

Effective CE prevention programs should focus on stemming transmission to either the intermediate or the definitive host. Preventive measures include improved education and sanitation (e.g., thoroughly cooking food, washing hands vigorously, and discontinuing feeding raw sheep offal to work dogs), contact avoidance of dog and fox waste, and deworming treatment of dogs with praziquantel. The EG95 vaccine, containing antigens cloned from the oncosphere, has shown promise in the prevention of transmission in intermediate hosts such as sheep and cattle. Efforts to interrupt the life cycle of the parasite in the "definitive" canid hosts have not been as successful but would ideally complement the effectiveness of vaccination of the intermediate hosts.

ADDITIONAL RESOURCES

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Frider B, Larrieu E: Treatment of liver hydatidosis: how to treat an asymptomatic carrier? *World J Gastroenterol* 16:4123-4129, 2010. *Considers alternatives in the treatment of an asymptomatic carrier—surgery, albendazole, PAIR, or wait and watch—with a review of the natural history of CE and the evolution of treatment modalities.*

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Intraabdominal Abscess

Christopher M. Watson and Robert G. Sawyer

46

ABSTRACT

All intraabdominal abscesses (IAAs) result from the inoculation of a normally sterile site such as the nonluminal aspects of an organ or of the small quantity of peritoneal fluid that naturally resides in the abdomen. The risk factors include interventional procedures of intraabdominal organs, local inflammatory conditions of these same organs, and penetrating abdominal trauma. Diagnosis depends on a clinical examination by an experienced clinician in conjunction with appropriate imaging. Treatment requires source control and early, appropriate antibiotics. Prognosis is excellent, and recurrences often respond to similar treatments.

GEOGRAPHICAL DISTRIBUTION AND DISEASE BURDEN

All IAAs result from the inoculation of a normally sterile site such as the nonluminal aspects of an organ or of the small quantity of peritoneal fluid that naturally resides in the abdomen (Figure 46-1). In health, this fluid is approximately 50 mL in quantity and flows in a typical pattern determined by the various peritoneal reflections and potential spaces. These potential spaces include the pelvis, the lesser sac, the subdiaphragmatic spaces, both right and left paracolic gutters, and between "loops" or folds of peritoneum, mesenteries, or omentum. Normally the fluid either is continuously reabsorbed or passes through tiny pores in the diaphragm and is reabsorbed in the pleural spaces. Increased amounts of fluid, such as occurs with ascites or after irrigation during an operation, will continue to flow along these typical routes unless altered by the surgical procedure itself. For example, after gastric resection and anastomosis, a common site for fluid to collect is in the retrogastric space made with dissection during the operation. Additional mechanisms for alteration of the flow of peritoneal fluid may arise in association with intraabdominal infections. Localized adhesions will alter the flow and may result in isolation of this fluid and an increased risk of infection. This fluid may then become inoculated by direct spread from the inflammatory process, such as with perforated appendicitis or a leaking bowel anastomosis, or, less likely, from indirect spread from the bloodstream. Solid organs themselves may also become inoculated with pathogens via the bloodstream, which results in a localized infection, for example, hepatic and splenic abscesses. Intraabdominal organs may also develop abscesses from microperforations or macroperforations, as seen with periappendiceal and pericolonic abscesses. Also, after penetrating trauma to the abdomen, fluid collections may become inoculated with skin or bowel flora.

It is unclear how the prevalence of IAAs differs around the world. Studies from Europe, North America, and Japan seem to imply a relatively similar incidence and pathophysiology, including the organisms most commonly cultured. It is obvious, however, that a large number of abscesses are iatrogenic in nature, following abdominal surgery or arising from device-associated bloodstream infection. Because of this, noniatrogenic infections, such as periappendiceal or peridiverticular abscesses, certainly compose a higher percentage of cases in which high-technology medical care is unavailable.

RISK FACTORS

The most common risk factors for IAA are diseases that lead to perforation of a hollow viscus. These conditions can be categorized as either naturally occurring or iatrogenic. The most common noniatrogenic conditions associated with IAA include congenital gastrointestinal, urologic, or gynecologic anomalies; diverticular disease (particularly common in the elderly); abdominal penetrating trauma; and causes of intestinal obstruction that can secondarily lead to perforation and abscess formation, including hernias and adhesions. The most common medical interventions that are associated with subsequent IAA are gastrointestinal endoscopy and surgical procedures on the gastrointestinal, urologic, or gynecologic organs. Postoperative IAA can further be categorized as a new-onset intraabdominal infection if there is an anastomotic leak or as an organ space surgical site infection when an abscess develops in the operative site in the absence of any connection to a hollow viscus.

CLINICAL FEATURES

IAAs manifest in many different ways. If part of a primary inflammatory process, such as diverticulitis, pancreatitis, or appendicitis, abscesses often result in vague abdominal complaints, possibly localized to the site of inflammation, often with accompanying fever and leukocytosis. Similarly, patients with hepatic and splenic abscesses have indistinct symptoms with possible focal abdominal pain and organomegaly. When an abscess forms postoperatively, such as the pelvic abscess after colorectal surgical procedures, patients often have a blunted examination owing to prolonged hospitalization, antiinflammatory medications, and narcotics, or their signs and symptoms may be incorrectly attributed to incisional pain and tenderness. In addition, these postoperative patients may manifest only inflammation with tachycardia or prolonged ileus. Even more difficult to evaluate are patients with inflammatory bowel disease, functioning solid organ transplants, or any other form of iatrogenic immunosuppression, because they may have no specific symptoms at all. In all patients, a high index of suspicion coupled with clinical experience is needed to make the diagnosis expeditiously because of the deep anatomic location of the underlying process.

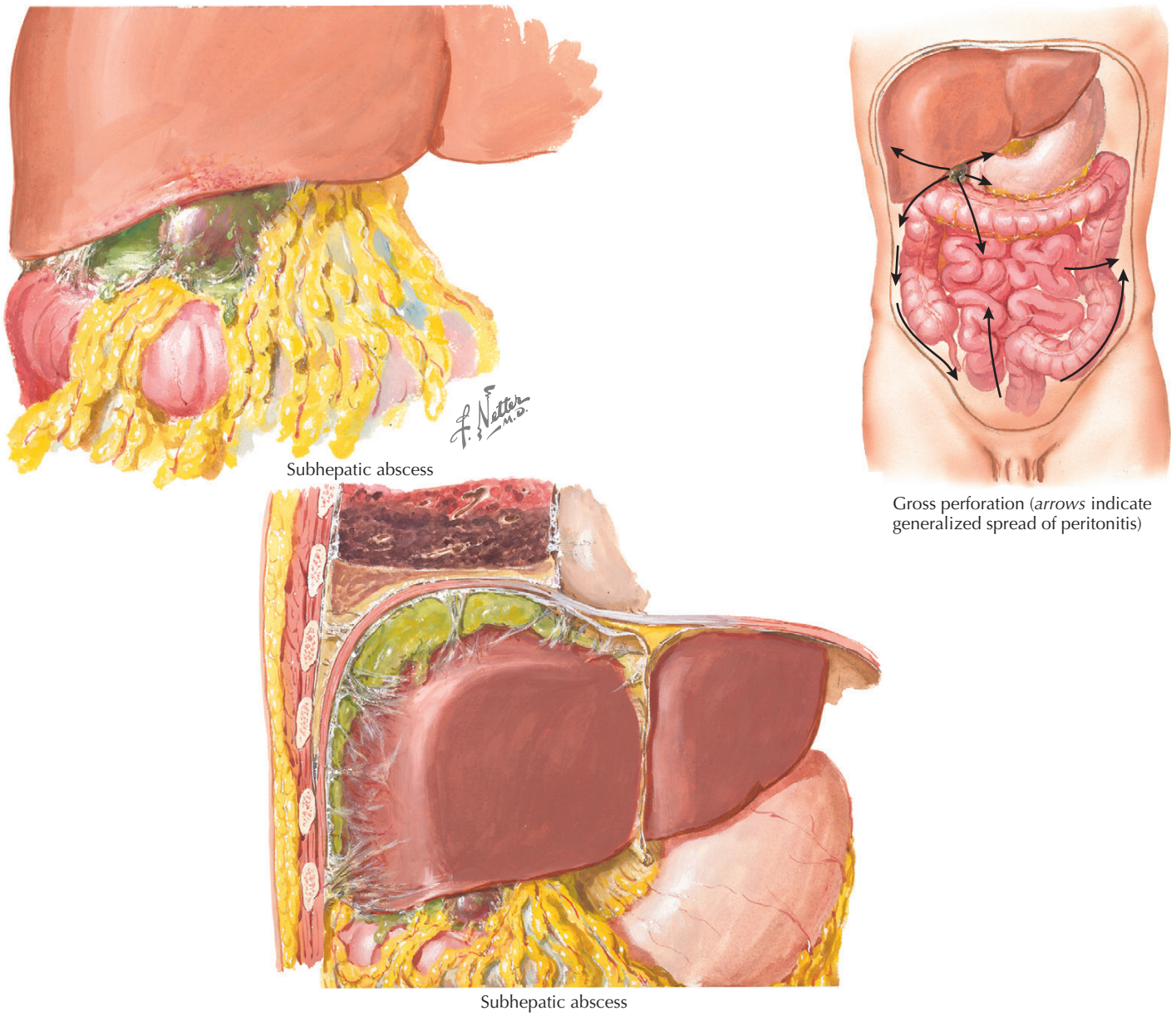


Figure 46-1 Perforation, subphrenic abscess.

DIAGNOSTIC APPROACH

After a thorough history and physical examination, computed tomography (CT), as with most inflammatory conditions of the abdomen and pelvis, is considered the diagnostic modality of choice. Preferably, intravenous (IV) contrast is administered in order to help discriminate noninflammatory fluid collections from abscesses. In some cases, however, IV contrast is contraindicated owing to allergy or renal insufficiency. In such instances, stranding of surrounding tissues and extraluminal air may lead one toward the diagnosis of abscess, but in the early postoperative period (generally considered to be less than 7 days after an operation), these changes are expected and the examination may still be considered indeterminate. If rapid diagnosis is critical, percutaneous aspiration may be required in order to sample the fluid for pathogens and confirm or exclude active infection. If CT is contraindicated, focused abdominal ultrasound or magnetic resonance imaging can be used as an alternative, although the latter does not allow for intervention at this time. Fluid should be described both qualitatively and quantitatively. Once an abscess is confirmed or suspected, aspiration of fluid (with or without placement of a drain), should be performed under CT or ultrasound guidance, and the fluid should be sent for Gram stain; white blood cell count; aerobic, anaerobic, and fungal culture cultures; and occasionally chemistries to help clarify a diagnosis, such as amylase in the case of a presumed pancreatic process or creatinine when a urologic origin is suspected.

Depending on anatomic location of the IAA, there may be subtle differences in the complete diagnostic evaluation required

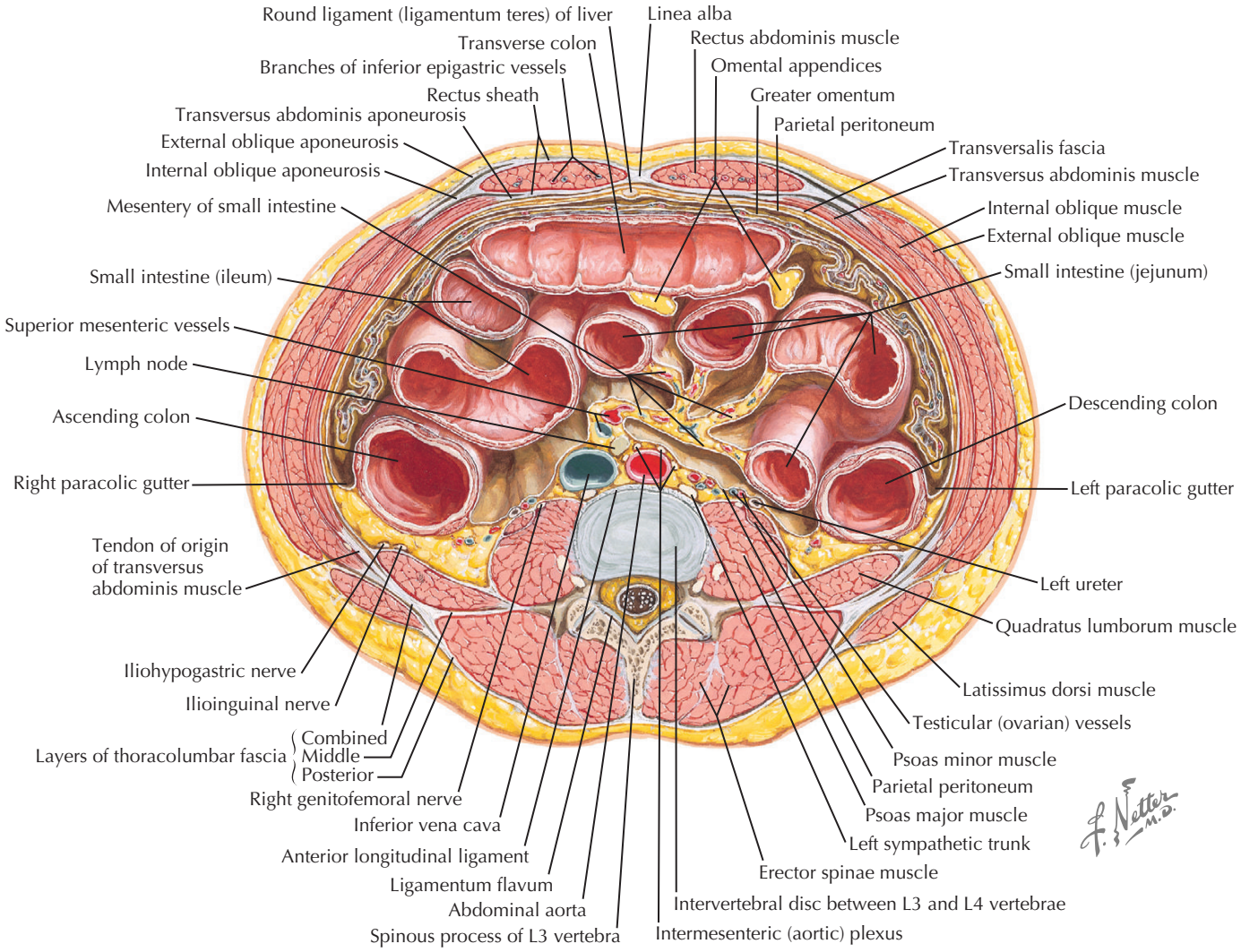


Figure 46-2 Peritoneum.

(Figures 46-2 and 46-3). For abscesses associated with penetrating abdominal trauma, inflammatory bowel disease, or any intraabdominal operation, evaluation of intestinal continuity should be performed as soon as possible. Frequently the diagnosis of a gastrointestinal leak can be made simply by examining drainage material when it is noted to be consistent with succus or bile. A more precise diagnosis may require an additional CT scan using Gastrografin by mouth and rectum to assess for extravasation of contrast. After a drain is in place, a sinogram can also be helpful in delineating a fistula tract and determining the origin of any leak from a hollow viscus.

The diagnosis of perinephric or renal abscesses is aided by the ready evaluation of the urine. Patients with urinary symptoms or who have persistent pyuria, bacteriuria, or funguria should be suspected of having an IAA related to the urinary tract, particularly in the setting of flank discomfort. An ultrasound or CT scan should be obtained, and the underlying pathology usually is easily confirmed.

Pancreatic abscesses present a unique challenge in terms of making an accurate diagnosis because of two associated though noninfectious diseases: pancreatic pseudocyst and pancreatic necrosis. All three are frequently an end result of pancreatitis, and all three can cause abdominal pain and tenderness and evidence of the systemic inflammatory response syndrome (SIRS). Pancreatic abscesses can occur when either a pseudocyst or necrosis becomes secondarily infected through local invasion, translocation from the gastrointestinal tract, or seeding from the bloodstream. If active infection is suspected and its diagnosis would lead to a change in management, aspiration of peripancreatic fluid is indicated with or without placement of a drain. In the setting of a pseudocyst, this quite frequently is done via percutaneous or transgastric open or endoscopic drainage. In the setting of known pancreatic necrosis, where nonoperative management is almost always pursued for disease without active infection, simple needle aspiration is performed, because drain placement does not appear to improve the outcome from uninfected necrosis.

Peridiverticular abscesses are common given the considerable prevalence of diverticular disease in the western world. Their diagnosis has been revolutionized with the widespread availability of CT scanning, but a CT scan alone cannot differentiate a benign peridiverticular abscess from an abscess

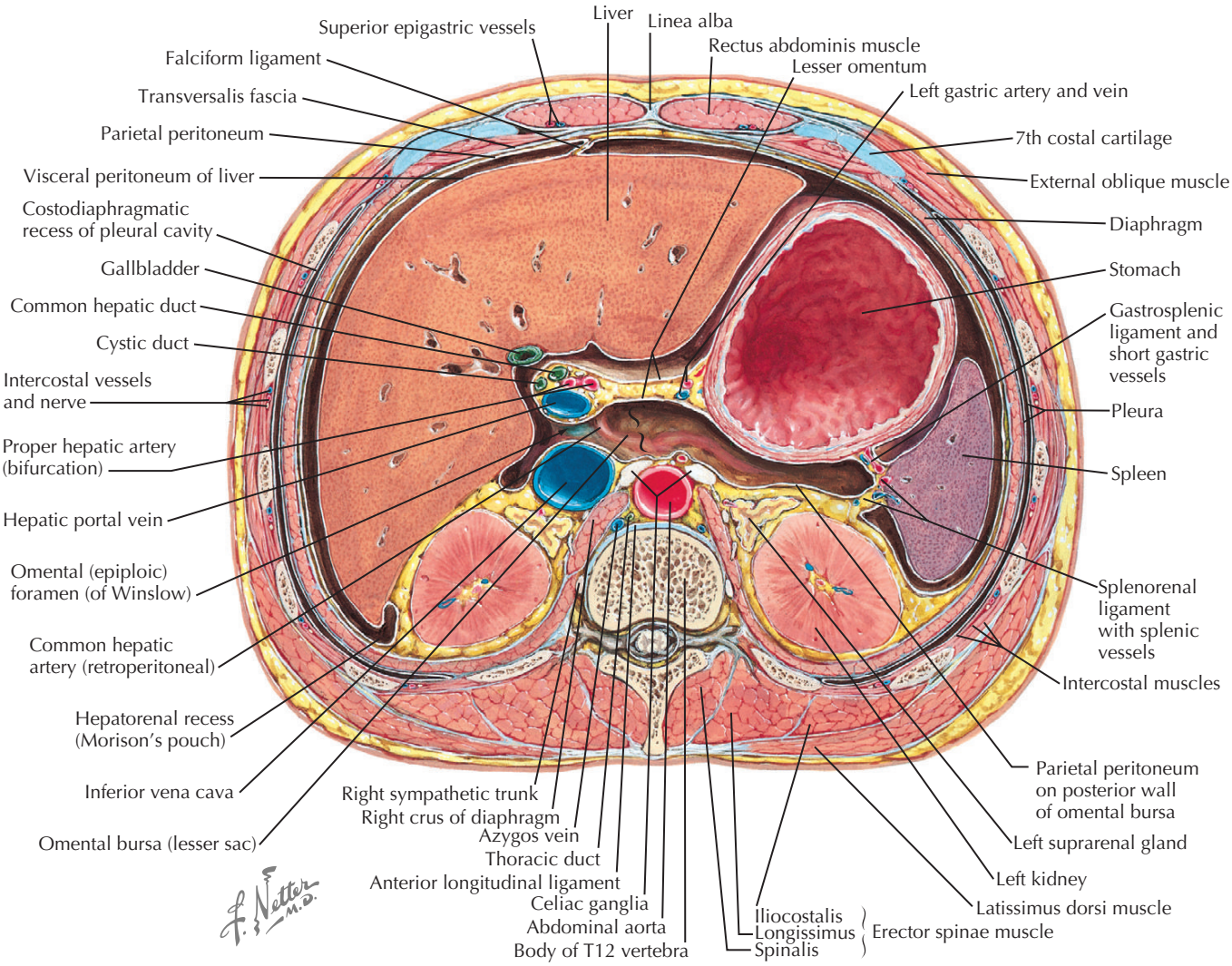


Figure 46-3 Schematic cross-section of abdomen at T12.

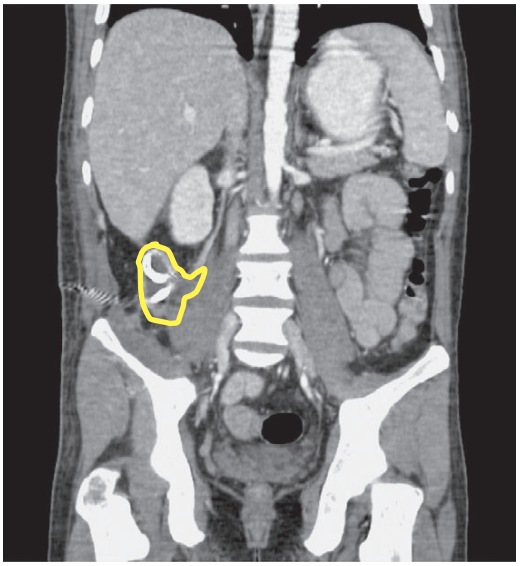
associated with a localized colon cancer. Because of this, cancer must be ruled out either by operative pathology (if emergency operation is required) or by colonoscopy if nonresectional management is initially elected and successful.

CLINICAL MANAGEMENT AND DRUG TREATMENT

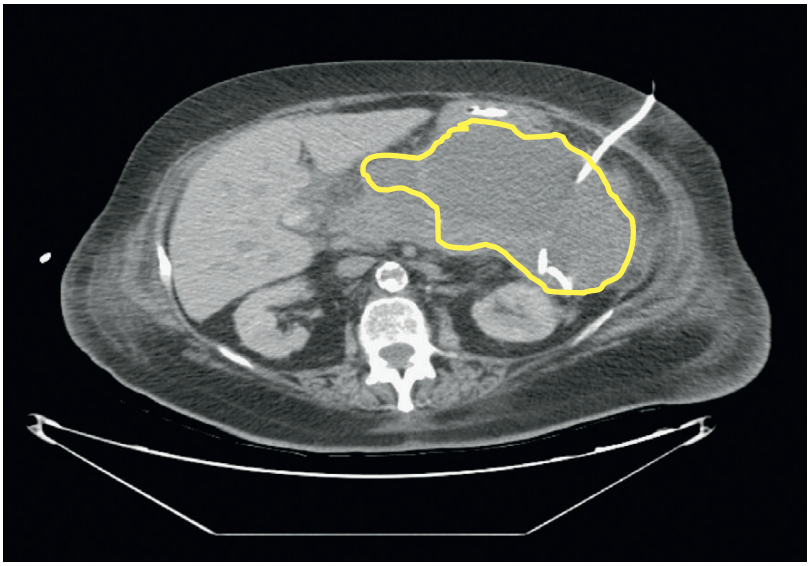
After the diagnosis of an IAA is made, preparations should be made for source control including removal of the majority of infected material. This goal often can be achieved initially with percutaneous drainage and catheter placement (Figure 46-4) but may require open surgical intervention if the IAA is in an area that cannot be accessed safely by image-guided percutaneous approaches.

Similar to the differences in diagnosis based on the site of an IAA, management is dependent on location. Organ space surgical site infections without an associated fistula can almost always be managed with a percutaneous drain and a relatively brief course of antimicrobials, perhaps 3 to 7 days. Postoperative infections that are associated with a connection to a hollow viscus require more complicated management. Occasionally, relatively long-term percutaneous drainage in a clinically stable patient combined with a brief course of antimicrobials will result in the closure of a small fistula, and the patient will need no other intervention. Many patients, however, will require an additional operation to attain adequate source control, ranging from diversion to resection of a leaking anastomosis to resection and diversion. The exact nature of these more complex operations is beyond the scope of this chapter.

Pancreatic abscesses also present a unique and challenging problem. An isolated abscess without necrosis can be treated as other IAAs with aspiration and catheter drainage combined with antibiotics. If surrounding necrosis is present, though, open surgical necrosectomy should be considered because antibiotic penetration of necrotic tissue is very poor and necrotic tissue is incompletely evacuated by drains. Necrosectomy was previously performed more frequently and was associated with a very high mortality and significant complications, including prolonged mechanical ventilation, secondary infections, and the frequent



Right pericecal abscess (*outlined in yellow*) with drain inserted



Pancreatic abscess (*outlined in yellow*) with drain inserted

Figure 46-4 Abscess drainage.

creation of enterocutaneous fistulas. More recently, a notable trend has surfaced incorporating a more conservative approach to pancreatic necrosis, including the infected variety. Although controversial, antimicrobial treatment and physiologic support without debridement as long as the patient is not clinically deteriorating have been used with success. After the patient has stabilized, the remaining focus of pancreatic necrosis can be resected under less adverse conditions using a less invasive approach, including laparoscopy in experienced hands.

Diverticular abscesses are usually adjacent to a perforated colonic diverticulum and are often amenable to catheter-based drainage and 3 to 7 days of antibiotics. Once the acute inflammatory process has resolved in 4 to 6 weeks, most surgeons suggest resection of the involved segment. Similarly, abscesses associated with appendicitis can be successfully treated by catheter-based drainage, if technically feasible, and antibiotics with delayed appendectomy in 4 to 6 weeks. This approach has been shown to be safe and cost-effective, particularly in children with complicated appendicitis. An alternative, particularly in those with significant comorbidities or the elderly, is drainage alone without interval appendectomy. These decisions should always be made in conjunction with a surgeon.

The choice of empirical antibiotics should be based on the most likely organism determined by the site of perforation, the patient's history of resistant pathogens, and local antibiograms. Of note, most IAAs should be considered community-acquired intraabdominal infections if the patent has received less than 48 hours of antimicrobials and did not have a prolonged stay in the hospital or other healthcare facility before the diagnosis of IAA. For community-acquired infections, the location of the gastrointestinal perforation (stomach, duodenum, jejunum, ileum, appendix, or colon) guides the clinician toward the infecting flora. Established infection from a source beyond the proximal small bowel is usually caused by facultative and aerobic gram-negative organisms; infections from a source beyond the proximal ileum will also generally have an anaerobic component. Many antibiotics are available and appropriate as empirical therapy, and none has been found to be clearly superior to others. Guidelines from the Infectious Diseases Society of America (IDSA), the Surgical Infection Society, the American Society for Microbiology, and the Society of Infectious Diseases Pharmacists contain evidence-based recommendations for the selection of antimicrobial therapy for adult patients with complicated intraabdominal infections, including IAA. Many regimens are available, including monotherapy and antimicrobial combinations, and depend largely on whether the IAA is community acquired or healthcare associated. We favor monotherapy for the empirical treatment of IAA because of ease of administration, including moxifloxacin or ertapenem for community-acquired IAA and piperacillin-tazobactam, meropenem, or imipenem-cilastatin for healthcare-associated infections. Of course it cannot be overemphasized that tailoring antimicrobial therapy based on culture results is a pillar of good antibiotic practice. Although data are lacking in this regard, the duration of antimicrobial therapy for IAA with adequate source control should be 3 to 7 days, whereas the duration for infections with poor source control (e.g., pancreatic necrosis) may last for 14 or more days and depends on clinical response.

PROGNOSIS

If IAA is treated appropriately and early, the prognosis is good; most IAAs resolve quickly, drains can be removed after days to weeks, and the patient can be followed clinically. These good results are probably related to the fact that abscess formation itself indicates that a robust immune response has occurred and that the infection has already been naturally contained, unlike the pathophysiology seen with diffuse peritonitis. Recurrence, which can occur in up to 25% of cases, can usually be treated with another catheter placed into the collection and a new

course of antimicrobials. Of course, repeat cultures should be obtained because the likelihood of a resistant pathogen being present is higher with a recurrence.

PREVENTION AND CONTROL

Prevention must be targeted at changing underlying risk factors for IAA. Naturally occurring risk factors can probably be controlled only in a population-based manner, such as through dietary interventions to decrease the risk of diverticular disease or societal efforts to reduce violence and prevent traumatic bowel injuries. In terms of iatrogenic IAA, proper and precise sterile surgical technique decreases the likelihood of postoperative IAAs but cannot prevent them completely. Large-volume irrigation may lower the risk of postoperative IAA and is widely practiced among surgeons, but this is almost entirely based on anecdotal data. A prospective study or 87 patients with peritonitis evaluated the effects of irrigation (with saline and antibiotic irrigation) versus no irrigation with regard to mortality, length of stay, wound infections, and medical complications and found no significant difference in any of these. A later study evaluating very large volumes (>30 L) of irrigation in peritonitis also found no benefit to the practice. Perioperative antibiotics almost certainly reduce the rate of IAA after elective surgery. Data derived from clinical trials of antibiotic prophylaxis for surgical procedures, however, almost always focus on the rate of incisional surgical site infections and are underpowered to discern a difference in postoperative IAA or organ space surgical site infections. In terms of preventing IAA after nonelective procedures, perioperative antibiotics have been shown to prevent IAA, as demonstrated in a recent Cochrane review of antibiotic use for appendectomy in the setting of appendicitis. Whether or not variously proposed adjuvant treatments during an operation decrease the rate of postoperative abscesses is not known. It is theorized that the prevention of adhesion formation may help to reduce the rate of postoperative IAA, but this has not been proven. Some early data in animals suggest that intraperitoneal fibrinolysis may decrease the rates of IAA, but this intervention is far from clinical application.

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Liver Abscess: Pyogenic and Amebic Hepatic Abscess

47

Patrick S. Wolf and James O. Park

ABSTRACT

The two main types of liver abscesses are pyogenic and amebic. Recently, pyogenic liver abscesses have begun to be diagnosed much more commonly, and the majority result from biliary and intraabdominal infection. Amebic liver abscess is a complication of *Entamoeba histolytica* dysentery. The clinical presentation of both types of liver abscess is similar, and often vague and nonspecific, necessitating a high index of suspicion for prompt diagnosis and treatment. Ultrasonography and computed tomography (CT), along with culture and serology, correlated to clinical signs and symptoms, aid in establishing the diagnosis. Treatment of pyogenic liver abscess requires percutaneous drainage combined with antimicrobial therapy. Open surgical drainage is reserved for treatment failures or for patients requiring concomitant surgical treatment of an intraabdominal source. In contrast, amebic liver abscess responds well to amebicidal treatment and rarely requires drainage. Outcomes are largely dependent on the underlying cause and the severity of illness at presentation.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Pyogenic liver abscess is the predominant (>80%) form of liver abscess and accounts for half of all visceral abscesses. Its incidence has risen in the last three decades, currently accounting for two of every 10,000 hospital admissions. A primary invasive liver abscess syndrome caused by *Klebsiella* pneumonia has been described most commonly in East Asia but also in other regions. Approximately 10% of the world's population (50 million annually) is infected with *E. histolytica*, with the majority of cases occurring in developing countries. Amebic liver abscess is the most common form of extraintestinal manifestation of amebiasis.

PATHOGENESIS

An understanding of the underlying source of liver abscesses is important not only in aiding the prompt recognition of this sometimes elusive diagnosis, but also for accurate prognostication for the patient and complete treatment of the disease. For pyogenic abscesses the myriad causes includes biliary disease, portal venous seeding from intraabdominal infections, bacteremia from extraabdominal sites, and direct extension from either right upper quadrant abscesses or trauma (Figure 47-1). The cause of pyogenic liver abscess has undergone a major shift from portal pyemia to biliary complications, where currently the most common source is primary biliary pathology or procedures. Biliary obstruction resulting from calculi and benign or malignant stricture predisposes to ascending cholangitis and subsequent development of liver abscesses. Endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), or surgical biliary reconstruction can introduce microorganisms into the liver and predispose to hepatic abscess formation. Intraabdominal infections such as appendicitis and diverticulitis are well-known sources of liver abscess via portal venous seeding. Hematogenous arterial seeding can occur from extraabdominal sites such as in infective endocarditis. Suppurative cholecystitis and perforated peptic ulcers may lead to hepatic abscess via direct extension. Radiofrequency ablation (RFA) of liver tumors is an increasingly recognized source of pyogenic liver abscess. Blunt or penetrating liver trauma may predispose to abscess formation through direct inoculation of microbes into devitalized liver tissue. A small subset of patients will have cryptogenic hepatic abscess without an identifiable source.

Amebic liver abscess is an extraintestinal complication of *E. histolytica* dysentery, which is transmitted via a fecal-oral route. Amebiasis results from ingestion of cysts of the protozoan *E. histolytica*, which liberate the trophozoite form of the parasite in the intestine (Figure 47-2). In complicated cases, intestinal wall invasion and subsequent seeding of the liver via the portal vein occur. In the liver the trophozoites cause an acute inflammatory response that results in granuloma formation and liver necrosis, leading to the classic "anchovy paste" amebic liver abscess.

RISK FACTORS

Diabetes mellitus, underlying hepatobiliary or pancreatic malignancy, and previous biliary manipulation or reconstruction are risk factors for development of pyogenic liver abscess. Risk of developing amebic liver abscess has been found to correlate with origin from or travel to an endemic area, usually in developing countries with poorer socioeconomic and sanitation conditions. It is also more prevalent in adult men and immunocompromised hosts.

CLINICAL FEATURES

The clinical presentation of pyogenic and amebic liver abscess can be quite variable and nonspecific, making accurate and prompt diagnosis a challenge. Although fever and abdominal pain are frequently observed (around 75% to 90%), patients often have a wide range of other signs and symptoms including anorexia, lethargy, jaundice, and weight loss (Figure 47-3). Peritonitis is an infrequent (approximately 5%) finding but may

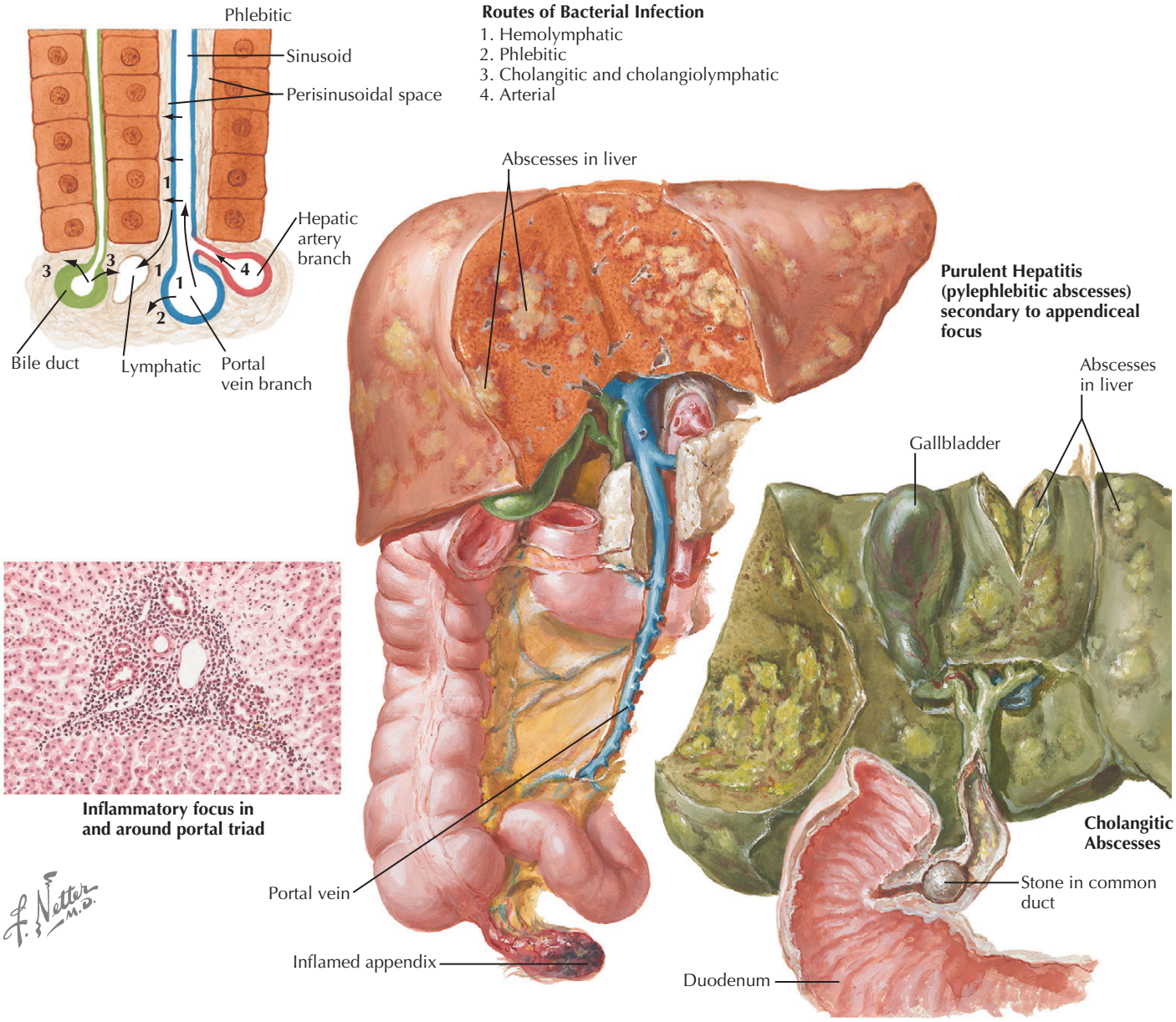

Figure 47-1 Etiology of pyogenic liver abscess.

occur with free rupture of the abscess. A small subset of patients may have overt sepsis manifested by high fevers and cardiovascular collapse. The differential diagnosis of a patient with these nonspecific symptoms is extremely broad, and additional history to narrow the diagnostic focus is necessary. Inquiries regarding a history of biliary disease, intraabdominal infection, trauma, or endocarditis should be sought. Amebic abscess should be considered if a history of travel to an endemic area is discovered. The majority of patients with amebic abscess develop signs and symptoms of illness within 3 to 5 months of travel to the endemic region.

DIAGNOSTIC APPROACH

As history and physical examination findings are generally nondiagnostic of pyogenic or amebic liver abscess, laboratory and radiographic studies are necessary. Leukocytosis is a common finding, although the expected eosinophilia is not commonly seen with amebiasis. Mild elevation of the transaminases is also common. Hyperbilirubinemia and alkaline phosphatase elevation may occur and may indicate an obstructive biliary source of disease. Blood cultures demonstrate gram-negative and anaerobic bacteremia in the setting of a lower gastrointestinal source of disease, whereas gram-positive cultures are more frequent in arterial sources of pyogenic liver abscess such as endocarditis. If amebic abscess is suspected, serologic testing for antibodies to *E. histolytica*, present in 95% of cases, is useful. Although fecal microscopy and culture can be performed, these are usually low yield or difficult to perform.

Imaging is a key component in the diagnostic workup of liver abscesses. Ultrasound is frequently used as an initial study, as it is rapid, is noninvasive, avoids radiation exposure, and is a good

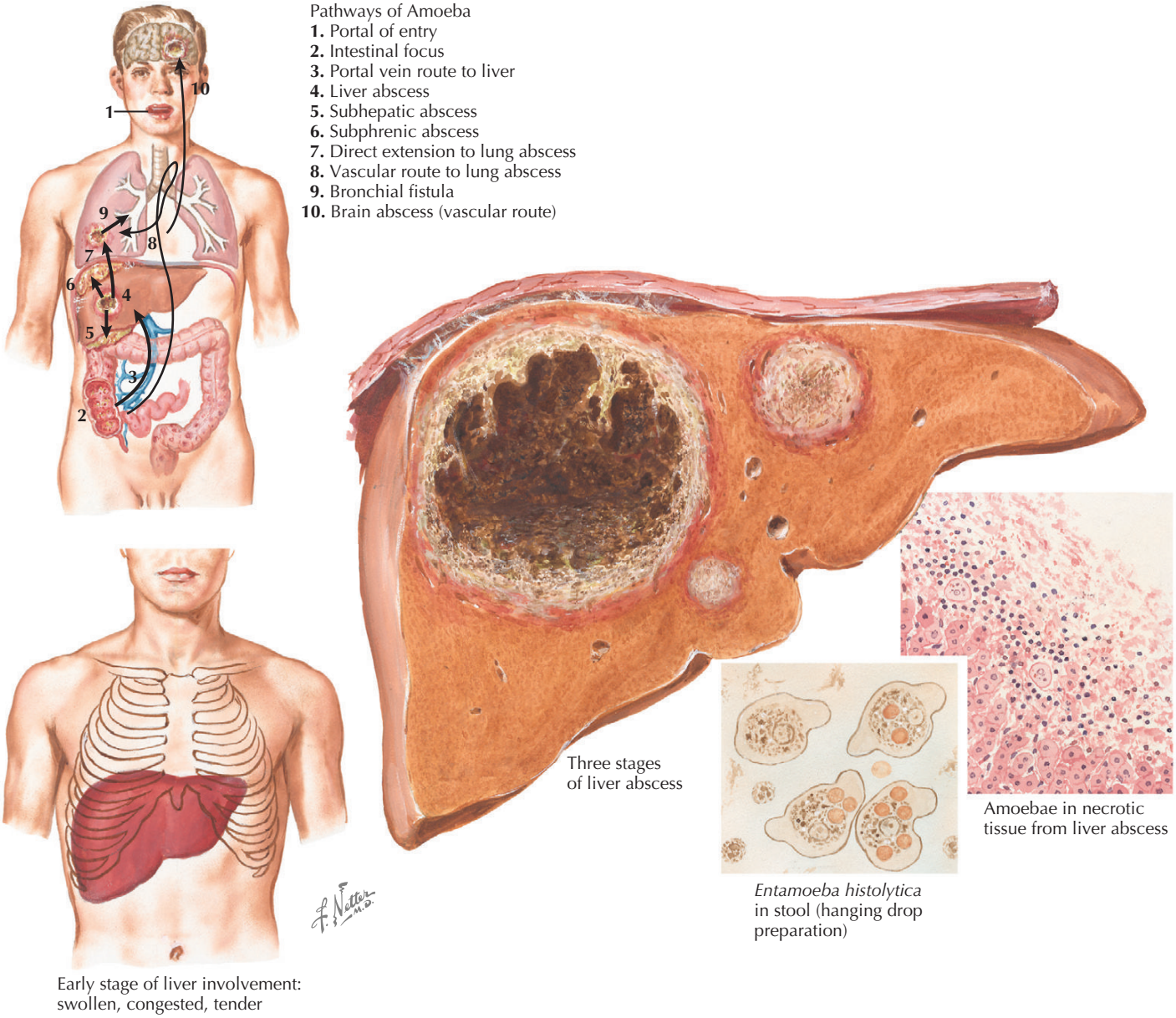

Figure 47-2 Pathogenesis of amebic liver abscess.

modality to evaluate concomitant biliary pathology. It demonstrates good sensitivity and specificity for detection of abscesses; however, small abscesses and those located near the dome of the liver may be more difficult to detect. Furthermore, ultrasound is less likely to diagnose an extrabiliary, intraabdominal source for the liver abscess. CT is an excellent modality to diagnose liver abscess and provides higher specificity than ultrasound. CT imaging can also detect the primary cause of liver abscess in a majority of cases. Magnetic resonance imaging (MRI) is time-consuming, is expensive, and does not generally provide a diagnostic advantage over CT. Neither CT nor MRI is able to differentiate between pyogenic and amebic liver abscess. Occasionally a gallium scan can be used to differentiate the two entities if necessary.

CLINICAL MANAGEMENT AND TREATMENT

As with any abscess, the primary principle of treatment of pyogenic liver abscess is drainage. Adjunctive measures include appropriate antibiotic therapy and a thorough search for and treatment of the precipitating cause. Empiric broad-spectrum antibiotics should be promptly instituted in any patient diagnosed with a hepatic abscess. Therapy should ideally be instituted before drainage and should be based on the probable source of infection and local antibiotic resistance data. Antibiotic therapy can subsequently be tailored once culture and susceptibility results become available. Length of therapy should be individualized based on clinical response and the complexity of the source.

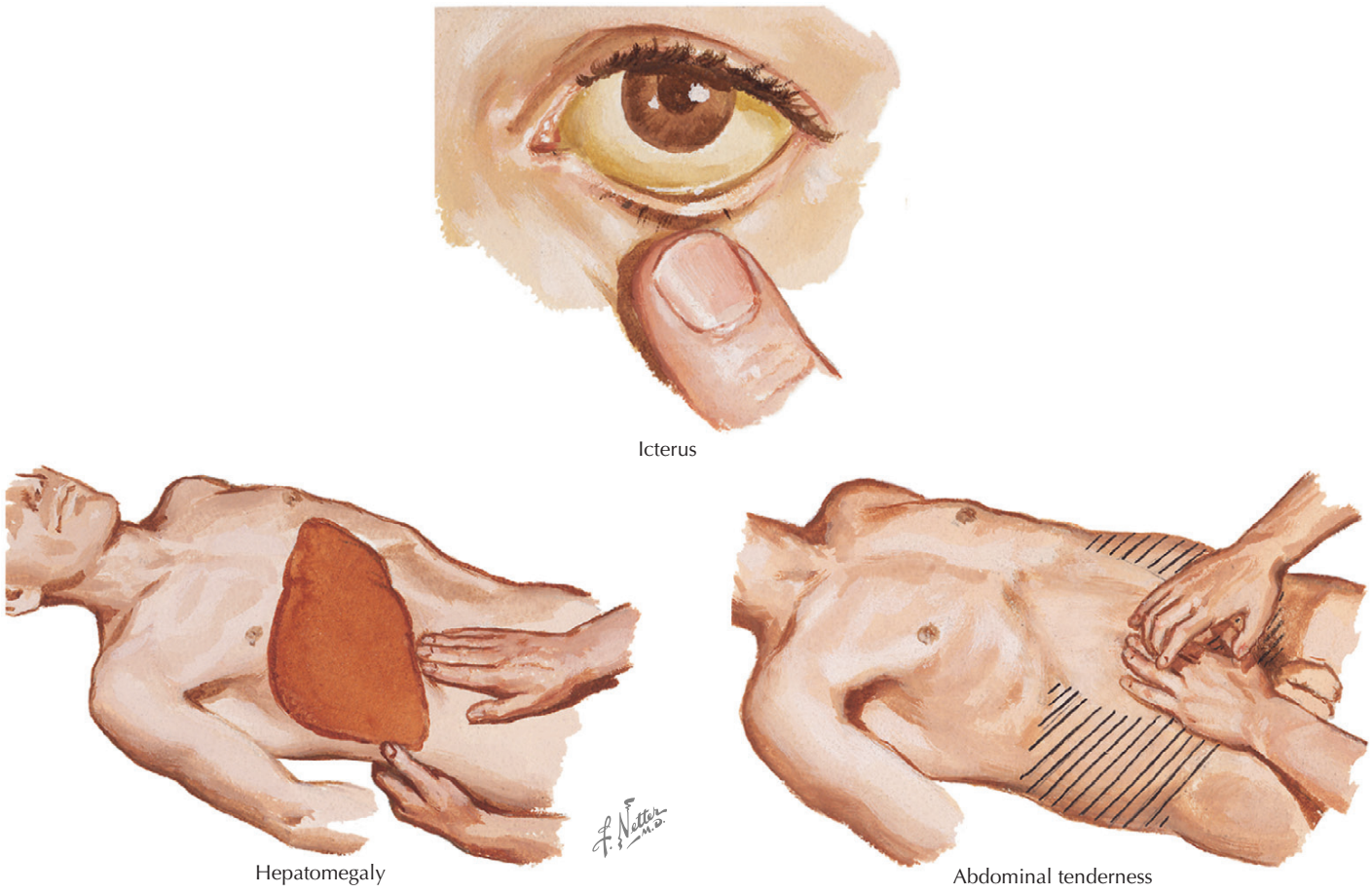

Figure 47-3 Physical examination findings suggestive of hepatic abscess.

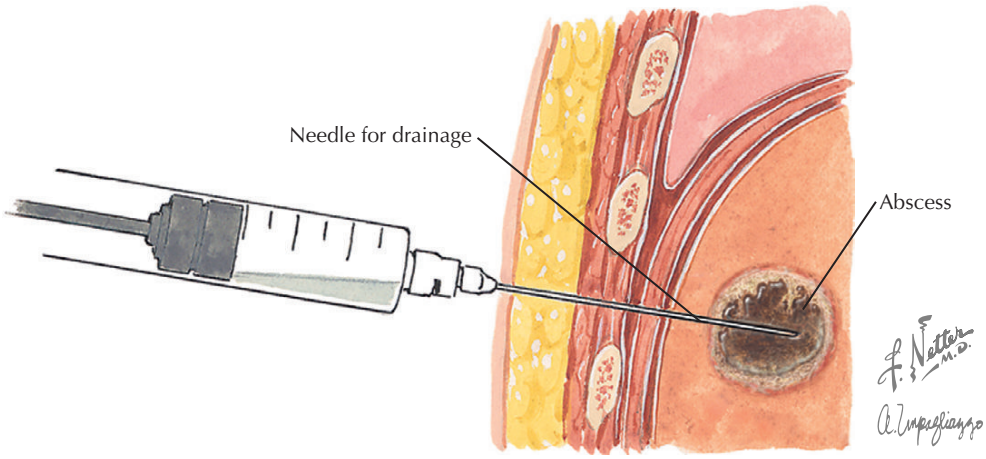

Figure 47-4 Percutaneous drainage of liver abscess.

Abscess drainage can be accomplished via various modalities, including percutaneous, laparoscopic, or open surgical approaches. Although percutaneous drainage of liver abscess was uncommon until the 1980s, improvements in imaging technology have made this approach the initial treatment modality of choice in managing pyogenic liver abscesses, with success rates reported in upwards of 90% of cases (Figure 47-4). Both percutaneous aspiration and drain placement have been used to treat abscesses. Simple, one-time aspiration has published success rates of around 60% to 90%. Factors that predict success with aspiration include solitary, unilocular, small (<5 cm) abscesses with thin walls and nonviscous content. If aspiration fails, drainage catheter placement is indicated. Although drain placement in general has been demonstrated to be more effective than simple aspiration, it typically results in longer hospital stays and is more prone to complications such as bleeding or

iatrogenic injury to the biliary system. Successful nonoperative management of pyogenic liver abscess is predicated on an aggressive approach to catheter management, with repeat imaging and catheter manipulation and/or upsizing should drainage be suboptimal.

Open surgical drainage of pyogenic liver abscess is reserved for cases in which percutaneous drainage attempts have failed, or when an acute concomitant intraabdominal source of abscess is in need of surgical therapy, such as perforated diverticulitis. Frank rupture of an abscess into the intraperitoneal space is also an indication for primary operative therapy. The operative approach to liver abscess involves accurate localization of the abscess cavity within the liver parenchyma, complete evacuation of pus, and thorough debridement of necrotic liver tissue and loculations. Drain placement is commonly used. In rare instances, formal liver resection may be necessary for adequate treatment. Circumstances prone to require resection include multiple small abscesses confined to a specific anatomic location of the liver, hepatic atrophy caused by biliary obstruction and abscess of the affected segment(s), abscess that causes significant parenchymal destruction, and hepatolithiasis.

In contrast to pyogenic liver abscess, amebic liver abscesses are generally treatable with antibiotics alone. Metronidazole is the treatment of choice and is effective in treating both liver abscess and intestinal amebiasis. More than 90% of patients achieve cure with a 10-day course of therapy. Chloroquine is used as a second-line agent if patients do not respond to metronidazole therapy. Drainage of amebic liver abscess is rarely necessary and is generally performed only if medical management fails or if there is suspicion of a superimposed pyogenic abscess.

PROGNOSIS

Overall mortality from hepatic abscess has declined over the past several decades. This is attributed to precise imaging, effective antimicrobial therapy, and improved availability of intensive care and has paralleled the shift from primary operative therapy to more conservative percutaneous treatment approaches. In general, expected mortality is less than 20% for both pyogenic and amebic sources of disease. Outcome is becoming increasingly dependent on the underlying cause of the hepatic abscess and comorbidities, rather than on the liver abscess itself. Risk factors predicting a graver prognosis include more severe underlying illness as predicted by Acute Physiology and Chronic Health Evaluation (APACHE) score, abscess rupture, and multiple abscesses.

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Necrotizing Soft-Tissue Infections

Daniel A. Anaya and E. Patchen Dellinger

48

ABSTRACT

Necrotizing soft-tissue infections (NSTIs) are highly lethal infections that share common features including the presence of necrotic tissue and the need for surgical debridement (among other therapies). The nomenclature of these infections has typically been complicated and often confusing because different terms are used to describe specific types of NSTI based on anatomic location, causative organisms, and other features. The use of the term *necrotizing soft-tissue infection* is advocated because it groups all of these different categories and helps in establishing a common pathway to diagnosis and management. Advanced NSTIs are relatively easy to recognize based on characteristic local findings as well as severe systemic derangement but are also associated with a high mortality rate. Early diagnosis is a key step to improved clinical outcomes, but it is not always a straightforward task. A high index of suspicion, based on risk factors and clinical presentation, coupled with biochemical, imaging, physiologic, and histopathologic studies can help confirm or rule out the diagnosis of NSTI. Surgical exploration is the ultimate diagnostic (and therapeutic) strategy and must be performed whenever in doubt. Management of NSTI includes early and complete debridement, broad-spectrum antimicrobial therapy, and physiologic and nutritional support. A number of prognostic factors have been identified and a prognostic score developed; these tools may help in selecting patients who may benefit from a more aggressive surgical strategy and/or more novel treatments.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

NSTIs include a wide range of skin and soft-tissue infections (Figure 48-1) characterized by the presence of necrotic tissue and need for debridement as part of the therapeutic strategy. The nomenclature of these infections is complicated, because multiple terms have been used to describe them based on anatomic location, causative organism, and other features. There is no known geographic distribution for these infections, except those related to specific risk factors as discussed in the "risk factors" section of this chapter.

Given the rarity of these infections, it is hard to estimate accurate disease burden measures. However, population-level studies using administrative and insurance-based databases have estimated an incidence of 4 per 100,000 person-years and an estimated 500 to 1500 new cases diagnosed every year in the United States. Additionally and as a consequence of the increasing number of *Staphylococcus*-related NSTIs, the incidence of NSTIs among other skin and soft-tissue infections appears to have increased over time.

Despite a lack of evidence-derived data on the impact on health and cost of NSTIs, it is well known that NSTIs are highly lethal infections and when successfully treated are associated with significant effects on quality of life including prolonged hospitalizations, disfiguring procedures, and need for long rehabilitation treatments. Furthermore, the prolonged length of stay, need for repeated operations, and intensive care unit (ICU) care carry important healthcare costs.

RISK FACTORS

Few studies have compared patient and other baseline characteristics of NSTI with those of nonnecrotizing skin and soft-tissue infection populations. Two such studies were able to identify intravenous drug use as well as diabetes mellitus as conditions more commonly associated with NSTI. Furthermore, selected series of patients with NSTI have shown its high prevalence among injection drug users and have identified those with muscle or subcutaneous injections as particularly susceptible to developing NSTI. In addition, NSTI outbreaks have been reported in patients with drug use associated with contaminated heroin lots (e.g., "black tar heroin"). Other series evaluating NSTI populations, although not methodologically able to identify risk factors, have found associations with older age, chronic comorbidities, obesity, alcohol and drug use, malnutrition, immune suppression, and specific medications (steroids and nonsteroidal antiinflammatory drugs [NSAIDs] among others). These conditions do appear to be commonly associated with patients presenting with NSTI; however, to date there is no hard evidence suggesting their predictive, risk-related, or causative association with NSTI. In particular, although adequate epidemiologic studies have identified an association between NSTIs and NSAID use, it is more likely that patients with NSTIs take NSAIDs during the initial phase of their infection than that NSAID use predisposes individuals to development of NSTI.

CLINICAL FEATURES

Clinical manifestations of NSTI vary significantly based on the timing of presentation and its relation to extent and degree of the infectious process. The necrotizing component can involve any layer of the skin and soft tissues, including the skin and subcutaneous tissue, superficial fascia, deep fascia, and/or muscle (see Figure 48-1). Based on the primary cause, different anatomic areas can be involved, including, in order of frequency, the extremities, perineum, trunk, and head and neck. Severe and advanced NSTIs are characterized by tense edema, ecchymosis, bullae or blisters, pain out of proportion, and crepitus. Most commonly, at these advanced stages, systemic manifestations

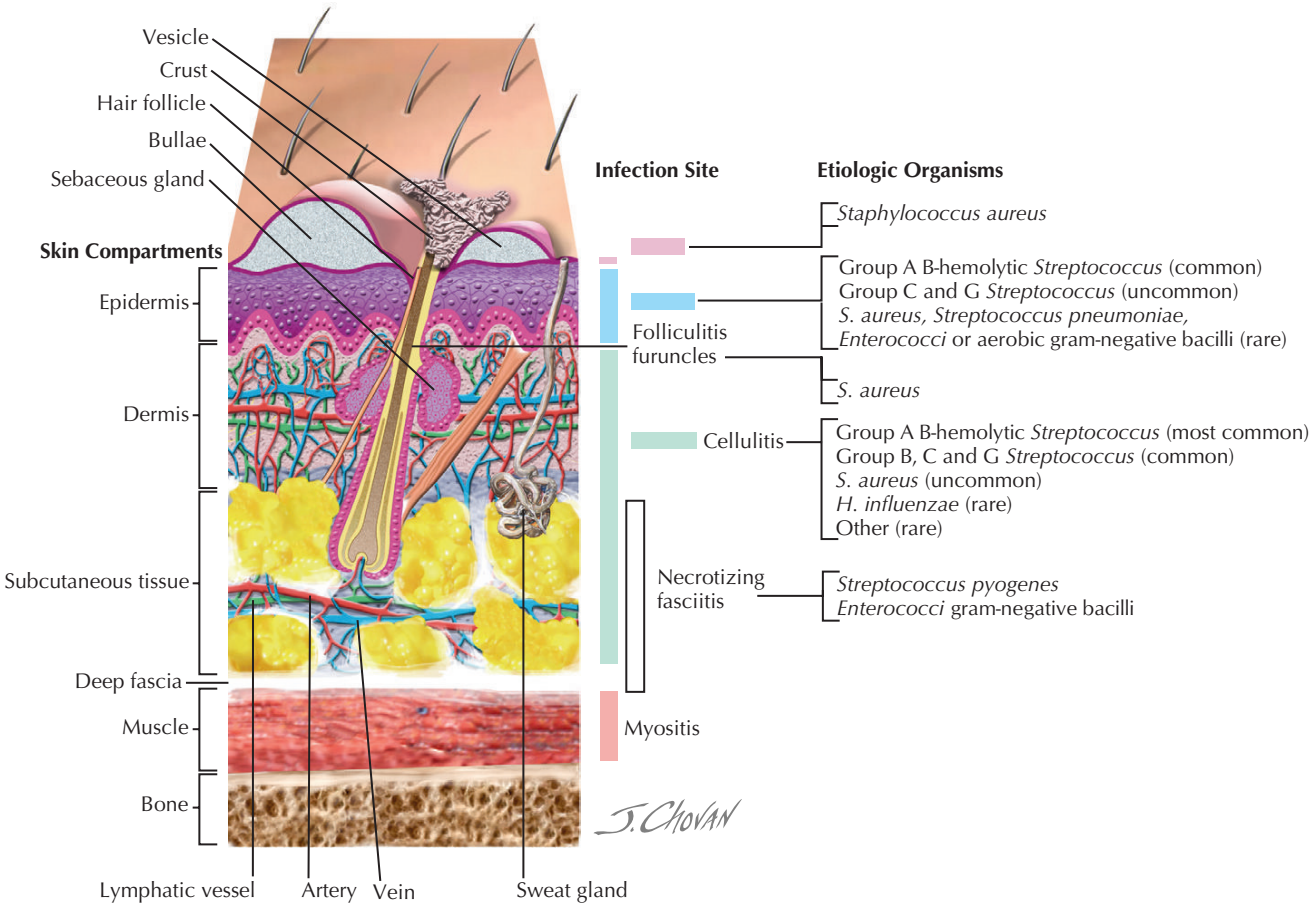

Figure 48-1 Cross-section of the skin showing layers and types of infections.

including fever, tachycardia, hypotension, and shock are the *sine qua non* of NSTI (Figure 48-2).

The vast majority of patients with early NSTI have less ominous signs and symptoms. Typically a preceding event localized to the involved area can be recalled, although in up to 20% of cases no precipitating event is identified. Initial symptoms are difficult to differentiate from those of nonnecrotizing soft-tissue infections (e.g., cellulitis, erysipelas) and include warmth, erythema, and pain with or without fever and tachycardia. Progression of the infection is variable and can occasionally be prolonged but usually occurs over 2 to 5 days. Once the necrotizing component starts to spread, however, the more ominous findings described earlier ensue and progress rapidly, leading to an overwhelming systemic infection as well as rapid progression of the local involvement. It is essential, then, to identify these NSTIs early in their course, preventing uncontrolled local spread and systemic involvement. In some specific cases, progression from the time of the inciting event can be extremely rapid. Specifically, clostridial and Group A streptococcal infections as well as those caused by mucormycosis and *Vibrio* species are characteristically aggressive, with rapid local progression and severe systemic derangement, and are associated with the highest mortality rates.

DIAGNOSTIC APPROACH

One of the most challenging aspects of managing patients with NSTI is the ability to diagnose it early during its course. Early diagnosis with aggressive surgical source control is the most important therapeutic strategy. It is not uncommon, however, to be faced with evaluating these patients once the infection is rapidly progressing with severe systemic compromise and when ominous findings make the diagnosis more straightforward. The diagnosis of NSTI is purely clinical, and when in doubt it should be confirmed or ruled out with surgical exploration. This is a crucial concept that allows early identification with timely debridement, maximizing the opportunity to control the infection and its systemic manifestations and leading to better overall outcomes.

A large number of research studies have focused on different tools that may help identify patients with NSTIs early in their course. The most important step in achieving this goal is to have a high index of suspicion, based on risk factors as well as clinical presentation. Once NSTI is considered as a potential diagnosis, biochemical, imaging, physiologic, and histopathologic studies can be used. In a study by Wall and colleagues (2000), the authors found that a white blood cell count >15,400 and serum sodium level <135 mmol/L were associated with NSTI.

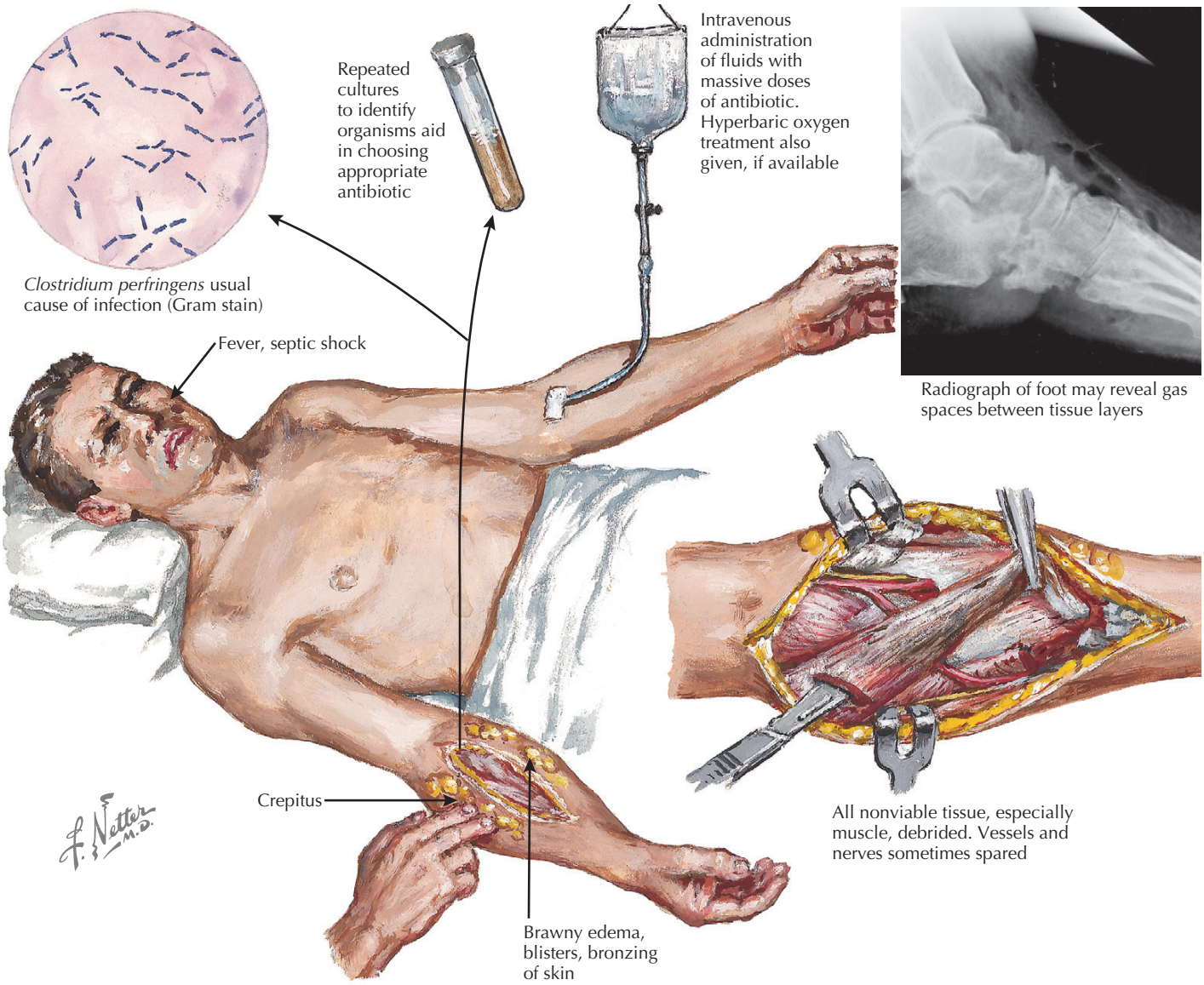

Figure 48-2 Necrotizing soft-tissue infections.

Although the positive predictive value (PPV) was only 26%, the negative predictive value (NPV) was 99%, making these values useful for ruling out NSTI when neither of these criteria is present. Wong and co-workers (2004), in a more comprehensive study, compared patients with and without NSTIs. The authors identified a series of factors associated with NSTI and designed a diagnostic score based on their presence: white blood cell count, hemoglobin, serum sodium, serum glucose, serum creatinine, and C-reactive protein. The PPV and NPV of this score were over 92% and 96%, respectively, highlighting the accuracy and clinical utility of this tool.

Imaging tests can also help establish the diagnosis of NSTI and are useful in patients with equivocal findings and no evidence of sepsis or shock. Radiographs, ultrasound, computed tomography (CT), and magnetic resonance imaging (MRI) have all been studied. In general, evidence of subcutaneous gas is pathognomonic of NSTI and should prompt emergency surgical debridement; however, this is a late finding and is less frequent than previously thought, present in only 24% of patients. Additional and earlier findings include thickening of the underlying soft tissues and decreased enhancement of the deep fascial layers. These findings are not specific for NSTI but can increase the suspicion and direct further diagnostic efforts or surgical exploration for diagnosis.

Other studies have focused on evaluating the transcutaneous oxygen saturation with good PPV and NPV. However, this test is limited to patients with adequate vasculature and hence is less useful for those with multiple comorbidities, including peripheral vascular disease. Finally, frozen section biopsy has been used to confirm the diagnosis of NSTI before formal surgical exploration and debridement. Typical microscopic findings include leukocyte infiltration, thrombosis of small arteries and veins, and necrosis of the involved layer. This test is limited by the subjective interpretation and availability of the pathologist.

However, when there is sufficient clinical suspicion to perform biopsy, the diagnosis is usually evident to the naked eye.

The most important strategy in diagnosing NSTI is a high index of suspicion followed by immediate surgical exploration. This cannot be emphasized enough and constitutes the difference between early control of infection versus more extensive delayed debridement in the setting of septic shock, multisystem organ failure, and a significantly higher risk of death. Intraoperative findings supporting the diagnosis of NSTI include the presence of necrotic tissue, easy finger dissection through normally fixed planes, foul-smelling "dishwater" pus, thrombosed vessels, and lack of bleeding during transection of involved tissues.

CLINICAL MANAGEMENT AND DRUG TREATMENT

The management of NSTI follows the principles for any other surgical infection: source control, antimicrobial therapy, and physiologic and nutritional support; however, more than with any other infection, source control is paramount and needs to be instituted as early as possible. Early and complete debridement of necrotic and involved tissues is associated with lower mortality rates. Often, scheduled reexplorations for complete and thorough examination and reexcision of newly involved areas are necessary and should be performed anytime the initial process is extensive or with findings consistent with worsening local or systemic infection.

NSTIs are typically polymicrobial in the vast majority of cases, and antimicrobial therapy should be instituted at time of diagnosis with broad-spectrum antibiotics to cover gram-positive, gram-negative, and anaerobic bacteria. Monomicrobial infections, although less common, are becoming more frequent. Group A streptococcal infections as well as those caused by *Clostridium* species are commonly monomicrobial in nature. This is often difficult to determine before culture results; however, aggressive, rapidly progressing infections should raise the index of suspicion, and surgical explorations scheduled every 24 to 48 hours until source control is achieved should be strongly considered. A particularly high white blood cell count is often a clue to the presence of clostridial infections, which often are associated with hyponatremia as well. Initial empirical broad-spectrum antimicrobials that cover these organisms (e.g., high-dose penicillin, tigecycline, piperacillin-tazobactam) should be used, and subsequent narrowing of the antibiotics when sensitivities are reported is encouraged. A recent trend has been the increasing incidence of community-acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA)–related soft-tissue infections, including NSTI. Recently multiple series have repeatedly reported on this trend, and it is not uncommon for these infections to be monomicrobial as well. Although in these cases the progression of the infection is not as fast or as extensive as with other monomicrobial infections, specific antibiotics covering CA-MRSA (e.g., vancomycin, tigecycline, linezolid) should be empirically started as well.

Clindamycin at high doses has been used as a protein synthesis inhibitor to reduce toxin production in group A streptococcal and clostridial infections in which the rapid local and systemic events are exotoxin mediated. Some reports have shown improved outcomes with this strategy. Other studies have evaluated intravenous immunoglobulin (IVIg) and hyperbaric oxygen as adjunctive strategies in managing these patients. At the current time the use of these treatments is experimental, and although some studies have reported adequate outcomes, there are no high-level data supporting their routine use.

Finally, nutritional support is paramount for these patients, who experience a long period of a hypercatabolic state. Similarly, ICU care is essential and has contributed significantly in decreasing early mortality rates while the infection source is being adequately controlled. A high proportion of these patients will develop septic shock and multisystem organ failure, requiring aggressive physiologic support, including ventilator, cardiac, and renal support, as well as support of other involved systems.

PROGNOSIS

A recent pooled analysis of published data from NSTI series revealed an overall mortality rate of 34%. Multiple studies have focused on identifying specific prognostic factors in different NSTIs, including age, comorbidities, diabetes mellitus, obesity, injection drug use, clostridial and group A streptococcal infections, mucormycosis, leukocytosis, renal failure, acidosis, Acute Physiology and Chronic Health Evaluation II (APACHE II) score, and delayed surgical treatment, among others. The findings from these series are often not generalizable owing to the inherent selection of patients in these single-institution reports. Furthermore, the majority of these factors develop during the management of these patients, hence limiting their utility in stratifying patients by prognosis early during the infection. To overcome some of these limitations, Anaya and colleagues (2009) evaluated a wide range of patient and physiologic characteristics at the time of emergency room evaluation in two large referral centers and identified six independent prognostic factors: heart rate >110, temperature <36° C, creatinine >1.5 mg/dL, age >50, white blood cell count >40,000, and hematocrit >50. A prognostic score able to stratify patients by risk of mortality at the time of first assessment was developed. The first three variables add 1 point each when present, and the last three add 3 points each when present. A score of 6 was associated with a mortality rate of over 88%, whereas the mortality for those with scores of 3 to 5 was 24% and for those with scores of 0 to 2 was only 6%. Although this scoring system still warrants external validation, it may become very useful in early stratification and identification of high-risk patients who may benefit from more aggressive surgical debridement or other alternative and more novel treatment strategies. It should be noted that these findings are valid when early and aggressive surgical debridement is performed, as was done by these experienced centers—this is probably a reason why the overall mortality rate in their population was below 20%. It is clear, though, that delayed surgical treatment is the most important prognostic factor and has been universally correlated with the highest mortality rates.

PREVENTION AND CONTROL

There are few data on how to prevent the occurrence of NSTI. An important concept is the observation that a proportion of

patients with nonnecrotizing infections, when left untreated, can progress to develop NSTI. With this in mind and without a clear understanding of the pathophysiology of NSTI at present time, it should be emphasized that any type of skin and soft-tissue infection has the potential for developing into NSTI and that early diagnosis and treatment are the most important steps in avoiding such progression and/or improving outcomes when it has already occurred.

EVIDENCE

Anaya DA, Bulger EM, Kwong YS, et al: Predicting mortality in necrotizing soft tissue infections: a clinical score, *Surg Infect (Larchmt)* 10:517-522, 2009. *This is the largest multiinstitutional study evaluating predictors of survival in NSTI. A clinical score was developed to stratify patients based on risk of death at the time of initial evaluation.*

Anaya DA, McMahon K, Nathens AB, et al: Predictors of mortality and limb loss in necrotizing soft tissue infections, *Arch Surg* 140:151-157; discussion 158, 2005. *This is one of the largest studies evaluating prognostic factors and determinants of adverse outcomes (mortality and/or limb amputation) in patients with NSTI. It also highlights the more severe course typically seen in patients with clostridial infections.*

McHenry CR, Piotrowski JJ, Petrinic D, Malangoni MA: Determinants of mortality for necrotizing soft-tissue infections, *Ann Surg* 221:558-563; discussion 563-565, 1995. *This is a large study evaluating specific prognostic factors and determinants of mortality in patients with NSTI.*

Miller LG, Perdreau-Remington F, Rieg G, et al: Necrotizing fasciitis caused by community-associated methicillin-resistant *Staphylococcus aureus* in Los Angeles, *N Engl J Med* 352:1445-1453, 2005. *This study brings attention to the trend of increasing CA-MRSA infections, including those causing NSTI.*

Singh G, Ray P, Sinha SK, et al: Bacteriology of necrotizing infections of soft tissues, *Aust N Z J Surg* 66:747-750, 1996. *This study focuses on describing the nature (polymicrobial or monomicrobial) of and the most common microorganisms leading to NSTI.*

Wong CH, Khin LW, Heng KS, et al: The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections, *Crit Care Med* 32:1535-1541, 2004. *This is a large study that evaluates multiple potential predictors of NSTI and develops a much more elaborate and accurate score to help confirm (or rule out) the diagnosis of NSTI.*

ADDITIONAL RESOURCES

Anaya DA, Dellinger EP: Necrotizing soft-tissue infection: diagnosis and management, *Clin Infect Dis* 44:705-710, 2007. *This review encompasses all aspect of NSTI.*

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Green RJ, Dafoe DC, Raffin TA: Necrotizing fasciitis, *Chest* 110:219-229, 1996. *This is a comprehensive review of NSTI.*

Pallin DJ, Egan DJ, Pelletier AJ, et al: Increased U.S. emergency department visits for skin and soft tissue infections, and changes in antibiotic choices, during the emergence of community-associated methicillin-resistant *Staphylococcus aureus*, *Ann Emerg Med* 51:291-298, 2008. *This article goes over important epidemiologic and healthcare-burden aspects of soft-tissue infections within the United States.*

Wall DB, Klein SR, Black S, de Virgilio C: A simple model to help distinguish necrotizing fasciitis from nonnecrotizing soft tissue infection, *J Am Coll Surg* 191:227-231, 2000. *This article identifies predictors of NSTI versus nonnecrotizing infections and develops a simple score to help establish the diagnosis.*

Weiss KA, Laverdiere M: Group A *Streptococcus* invasive infections: a review, *Can J Surg* 40:18-25, 1997. *This review goes over the available data on epidemiology, pathophysiology, clinical presentation, treatment, and prognosis of group A* Streptococcus *infections, including those in the skin and soft tissues.*

Anorectal Abscess and Fistula in Ano

Arden M. Morris

49

ABSTRACT

Considering the frequent exposure to a large bacterial load and high pressure, infection of the anorectal crypts with a resultant abscess or fistula is relatively uncommon. Limited epidemiologic data indicate an annual incidence of about 9 cases per 100,000 in the population, most commonly affecting people aged 30 to 50 years. Approximately 30% of patients with an initially treated abscess will experience a subsequent abscess recurrence or frank anorectal fistula formation. Male gender, smoking, diabetes, and inflammatory bowel disease (IBD) are risk factors for the initial anorectal abscess formation. However, recurrence is not associated with gender, smoking, human immunodeficiency virus (HIV) status, sedentary lifestyle, or perioperative antibiotic use according to the majority of studies. Instead, the single most important predictor of recurrence or fistula formation is age under 40 years. Other possible predictors of recurrence, supported by studies in widely divergent settings, include infection with *Escherichia coli* and absence of diabetes mellitus.

ETIOLOGY AND CLINICAL FEATURES

The pathogenesis of fistula formation is thought to occur during anal crypt obstruction by inspissated mucus or stool in more than 90% of cases (Figure 49-1). The initial cryptoglandular insult represents an internal opening—that is, an opening into interstitial tissues from within the anal canal. As trapped bacteria proliferate and mucus and pus accumulate, an abscess forms and erodes through adjacent tissue planes, resulting in classic signs of tenderness, redness, swelling, and heat. Thus most patients become aware of their symptoms later in the stages of abscess formation. Patients will generally complain of throbbing or dully aching pain that is aggravated by walking, straining, coughing, and sneezing.

Abscess progression can proceed in any direction. If the abscess is eroding superiorly or in a transsphincteric manner, a swollen mass is not always present. Urinary retention, fever, or even septicemia may accompany the anorectal pain and is an important clue to the presence of an abscess in cases of cephalad or otherwise obscure infectious erosion. In most cases the abscess will erode toward the perianal margin. Without intervention, most abscesses eventually will rupture through the anal margin skin. Formation of this external opening provides tremendous physical relief as well as some anxiety to the patient.

HISTORY AND PHYSICAL EXAMINATION

During the initial consultation, a thorough history is paramount and should include documentation of any previous similar events; previous anorectal surgery or other trauma; previous obstetric injury; previous history of sexual assault; personal or family history of IBD or colorectal cancer; symptoms consistent with potentially undiagnosed IBD such as unintentional weight loss, chronic diarrhea, or abdominal pain; and symptoms consistent with lymphoma, leukemia, or HIV infection such as weight loss, night sweats, lymphadenopathy, or unexplained fevers. Obtaining and documenting a thorough history will provide guidance for an appropriately aggressive treatment plan and potential use of medical as well as surgical therapies.

Careful documentation of bowel habits is also prudent and should include frequency of defecation; fecal urgency or incontinence to gas, liquid, or solids; presence of pain or bleeding with defecation; and sexual dysfunction. If there are any concerns regarding risk of colorectal cancer, such as bleeding per anus, or changes in stool caliber, the patient should be referred for colonoscopic evaluation after the anorectal pain and infection have been addressed.

A comprehensive physical examination must be conducted to rule out underlying or concomitant diseases. The examination of the perineum, often referred to in the medical record as the "digital rectal exam," should be preceded by ensuring patient privacy and respectful treatment, with strong consideration given to having an additional medical staff person in the examination room. The most important part of the physical examination is alerting the patient before physically touching the perineum.

Documentation of the physical examination should include the appearance of the perineum, specifically the condition of the skin; presence of erythema; presence of abnormal pigmentation, papular lesions, or masses; and potential perianal soiling, which can indicate compromised continence. It is important to examine the perineum anterior to the anus including the intertriginous folds between the perineum and thighs. In the presence of induration, an inflamed mass, or an external opening, the location should be documented as "posterior," "anterior," "right," and/or "left." Describing lesions using a clock face can be very confusing in subsequent examinations during which the patient may be in prone, supine, or lateral positions.

After visualization, the anus and perineum should be tested for neuromuscular function. The presence of an intact sacral spinous pathway is documented by the presence of an "anal wink" with light touch (after warning the patient). Previously noted erythema, induration, or external fistula opening should be palpated for the presence of a firm cord of tissue that can help to define a fistulous tract. The gluteal muscles should be distracted to examine for the presence of an anterior or posterior midline fissure. This maneuver also helps to identify whether the patient is too tender to tolerate insertion of a finger into the anal canal or digitation. If the patient is unable to tolerate digitation, 2% viscous lidocaine can be applied or the examination

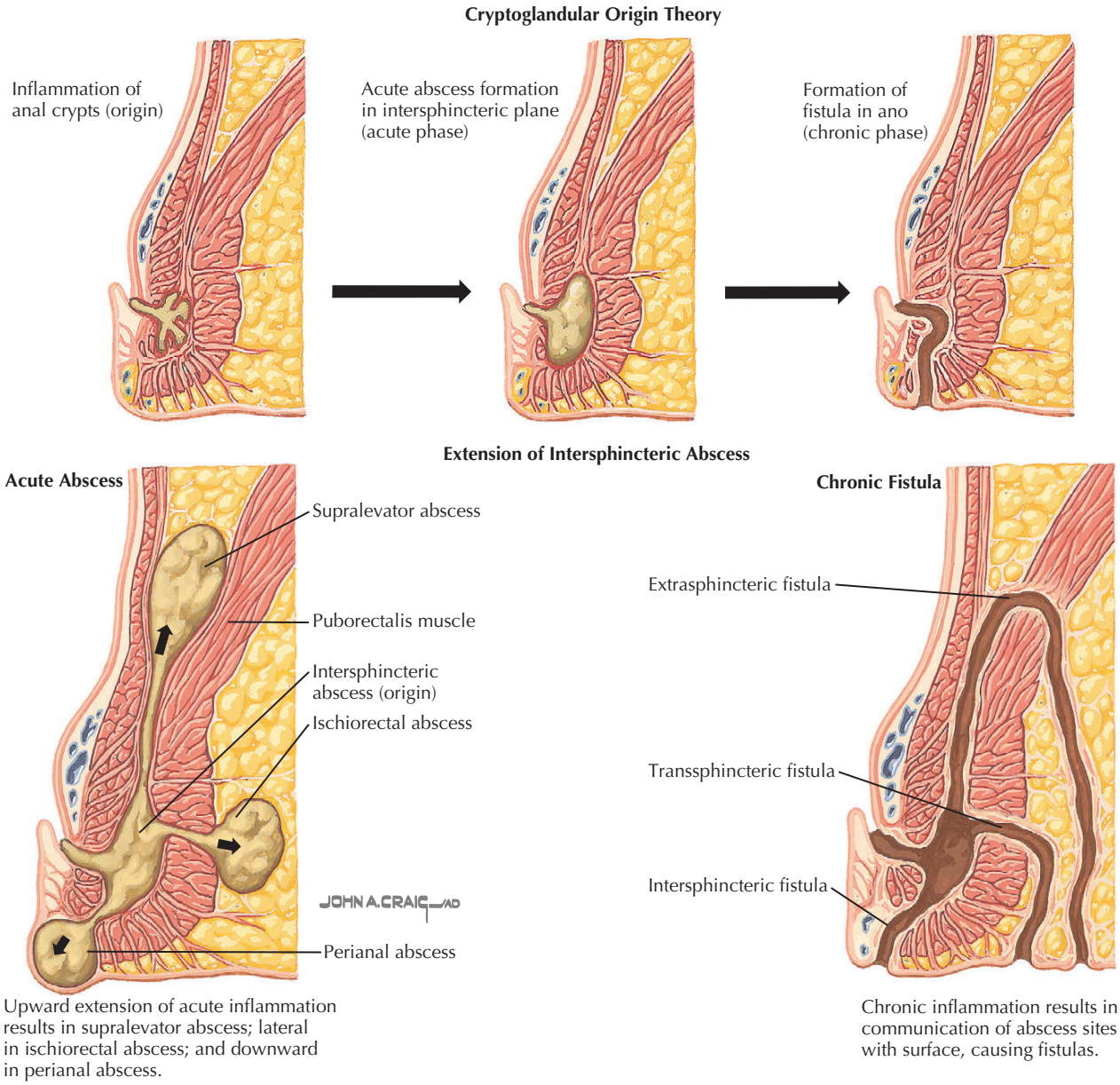

Figure 49-1 Anorectal abscess and fistula in ano.

should be conducted in a setting that permits sedation or general anesthesia. If the patient is able to tolerate digitation, a finger should be gently and slowly inserted into the anal canal. After noting baseline anal sphincter tone, the examiner should request that the patient squeeze then relax the anal sphincter. This permits assessment of anal sphincter function; it is particularly important to note a diminished squeeze in the medical record. The patient should also be asked to bear down and then relax. This request may be confusing and it can be helpful to repeat and explain. The puborectalis muscle will feel like a thick band posterior and just cephalad to the anal sphincter. The puborectalis muscle should relax when the patient bears down. If the puborectalis muscle tightens instead, the patient may have paradoxic puborectalis function, thus substantially increasing anal canal pressures during defecation and mechanically promoting cryptoglandular infection. Finally, the distal rectum should be palpated to search for evidence of a supralevator fluctuance or tenderness that would require intraoperative drainage.

ABSCESS LOCATION AND MANAGEMENT

The anal glands lie between the internal and external sphincter muscles, and therefore infected glands commonly originate in the intersphincteric space. As the infection spreads along fascial planes and potential spaces, abscesses and their management are defined by their location. In order of frequency these abscesses are perianal, ischioanal, intersphincteric, and supralevator (Figure 49-2). Anorectal abscesses that have not spontaneously ruptured should be incised and drained as soon as possible. Antibiotics are rarely indicated except in the presence of

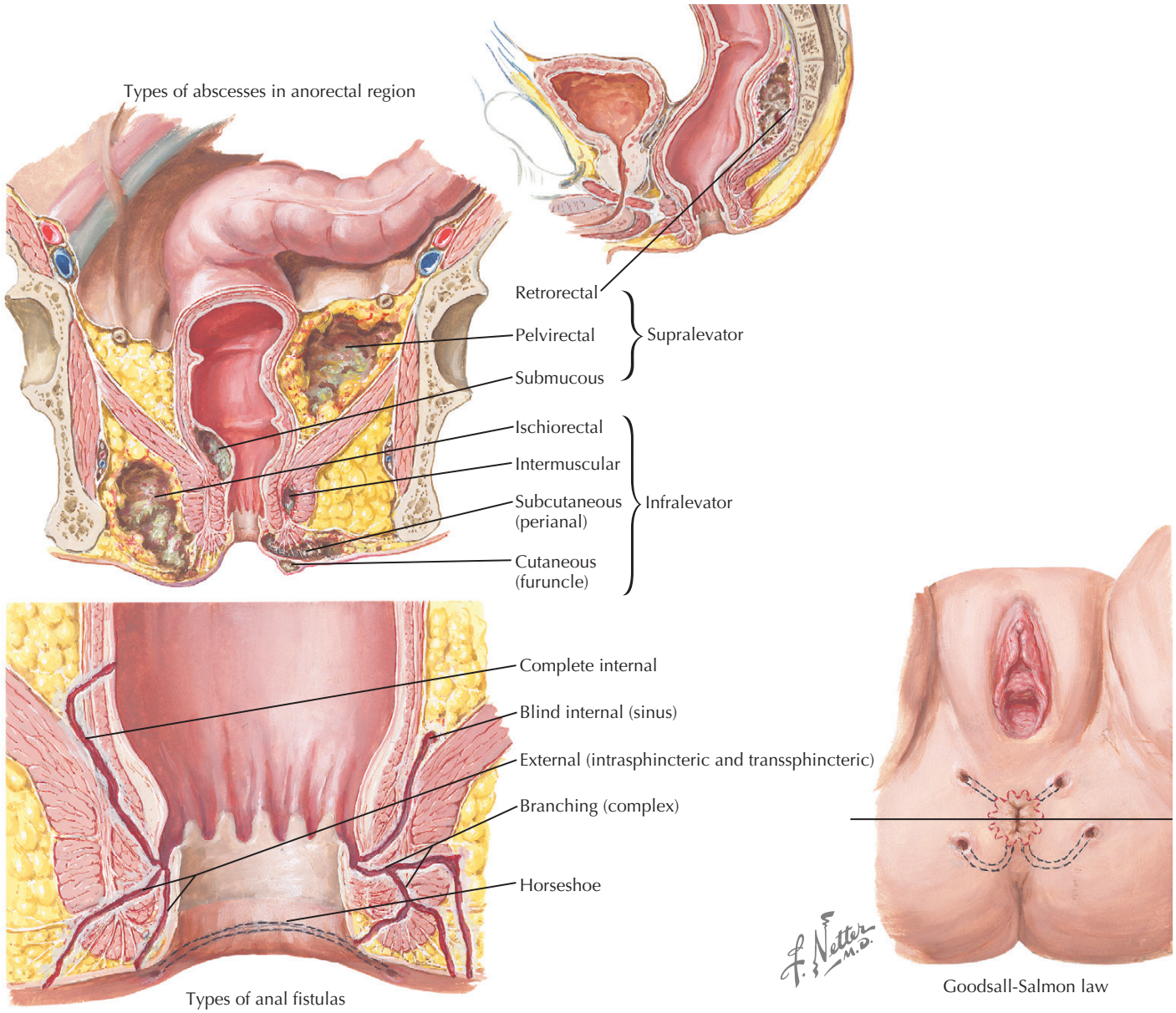

Figure 49-2 Proctologic conditions: anorectal abscess and fistula.

cellulitis or immune compromise. Among patients with Crohn's disease, oral metronidazole or ciprofloxacin and sometimes other Crohn's-specific medication may reduce symptoms and speed healing. If widespread induration or crepitance is present, the patient will require urgent operative debridement. A plain radiograph can help to clarify the presence of gas in the tissue planes. Necrotizing perineal fasciitis or Fournier's gangrene is a surgical emergency that will be addressed more fully in the chapter describing necrotizing fasciitis.

Perianal abscesses are usually small and often can be drained with the patient under local anesthesia in the clinic or emergency room (Figure 49-3). The skin overlying the abscess cavity is elliptically excised. A linear incision is avoided to prevent premature healing of the external opening. The cavity should be curetted and irrigated. Packing of a perianal or perirectal abscess should be avoided, as it is painful, promotes maintenance of the potential space, and prevents collapse and healing of the cavity. If the elliptic incision appears to close with dependent positioning, it can be marsupialized with a running locked baseball stitch circumferentially using absorbable suture. Postoperative care includes pain control, warm sitz baths, a fiber supplement, and avoidance of constipation.

Unilateral ischioanal abscesses, located in the ischioanal fossa, should be incised and drained similarly to perianal abscesses. Bilateral ischioanal or horseshoe abscesses are located in the deep postanal space with extension to the bilateral ischioanal spaces. A horseshoe abscess should be drained through the deep postanal space by incising the skin longitudinally between the tip of the coccyx and the anus to expose the anococcygeal ligament (Figure 49-4). The anococcygeal ligament is incised longitudinally, and the deep postanal space is opened. After the abscess cavity is drained, a counter-incision is made on one or

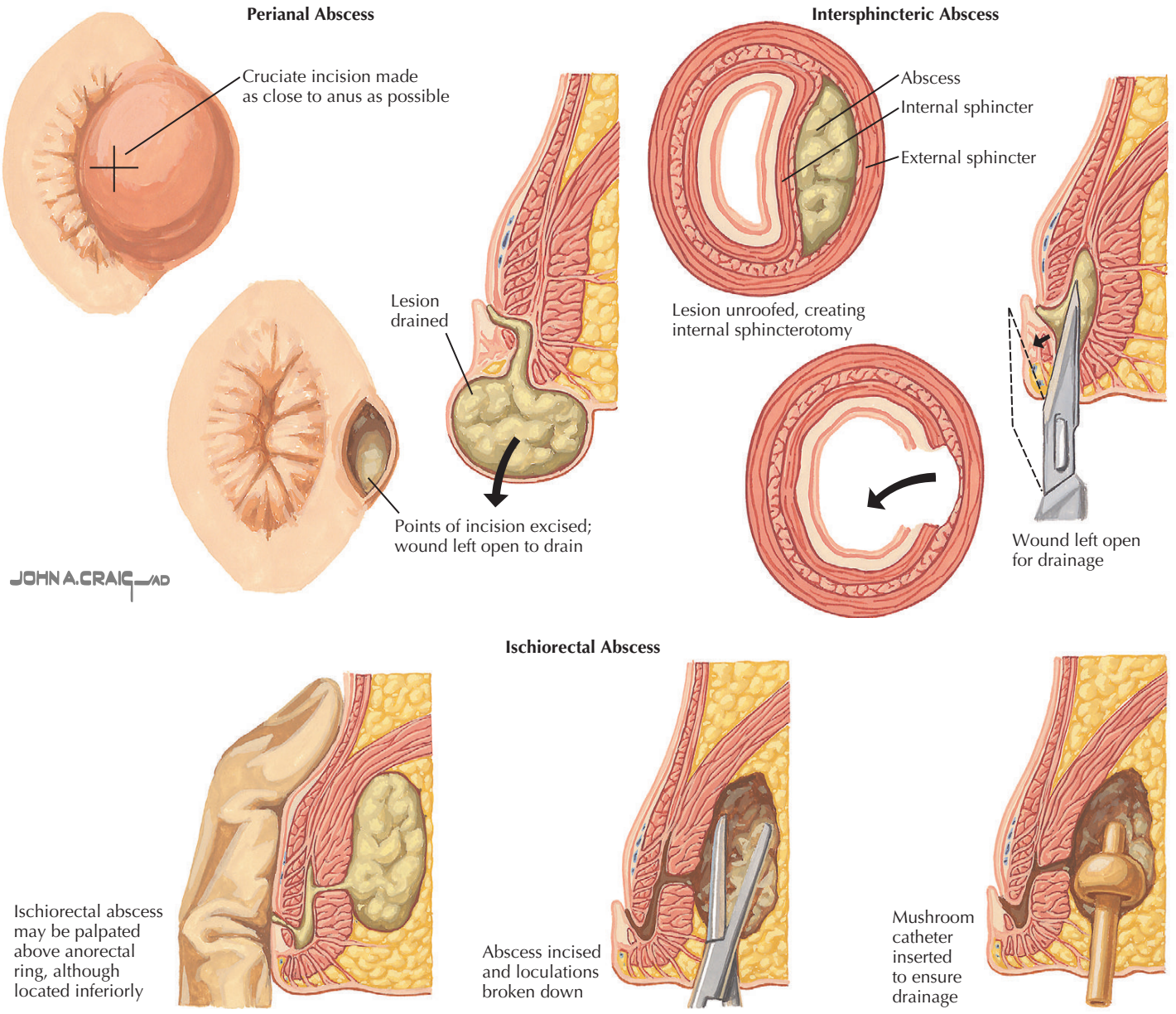

Figure 49-3 Surgical management of anorectal abscess.

both limbs of the ischioanal space, and a loose seton (preferably of soft Silastic tubing) can be placed.

Intersphincteric abscesses differ from perianal and ischioanal abscesses in several important ways. Visualization is less useful because evidence of induration or swelling is absent. Anorectal pain is often so severe that digitation of the anal canal in an awake patient is impossible. The patient will experience deep tenderness most notably in the posterior deep anal space, and an indurated mass can be palpated cephalad to the dentate line. Intersphincteric abscesses must be drained by incising the internal sphincter muscle. Incision of 25% to 50% of the internal anal sphincter muscle rarely results in changes to bowel control. Among male and many younger female patients, even incision of 100% of the internal anal sphincter is unlikely to result in noticeable changes.

Supralevator abscesses are uncommon and originate in several ways—via cephalad extension of an intersphincteric abscess, cephalad extension of an ischioanal abscess, or caudad extension of an intraabdominal process such as Crohn's disease. The origin of the abscess dictates the treatment plan. Incision and drainage of the abscess into the incorrect space may result in formation of an iatrogenic fistula. Therefore an appropriate workup is key, beginning with digitation that reveals a tender mass above the level of the anorectal ring and followed by imaging with computed tomography, magnetic resonance imaging (MRI), or less commonly endorectal ultrasound. A supralevator abscess that is secondary to upward extension of an intersphincteric abscess should be drained into the rectum. An abscess that is an upward extension of an ischiorectal abscess should be drained through the ischioanal fossa. If the abscess is

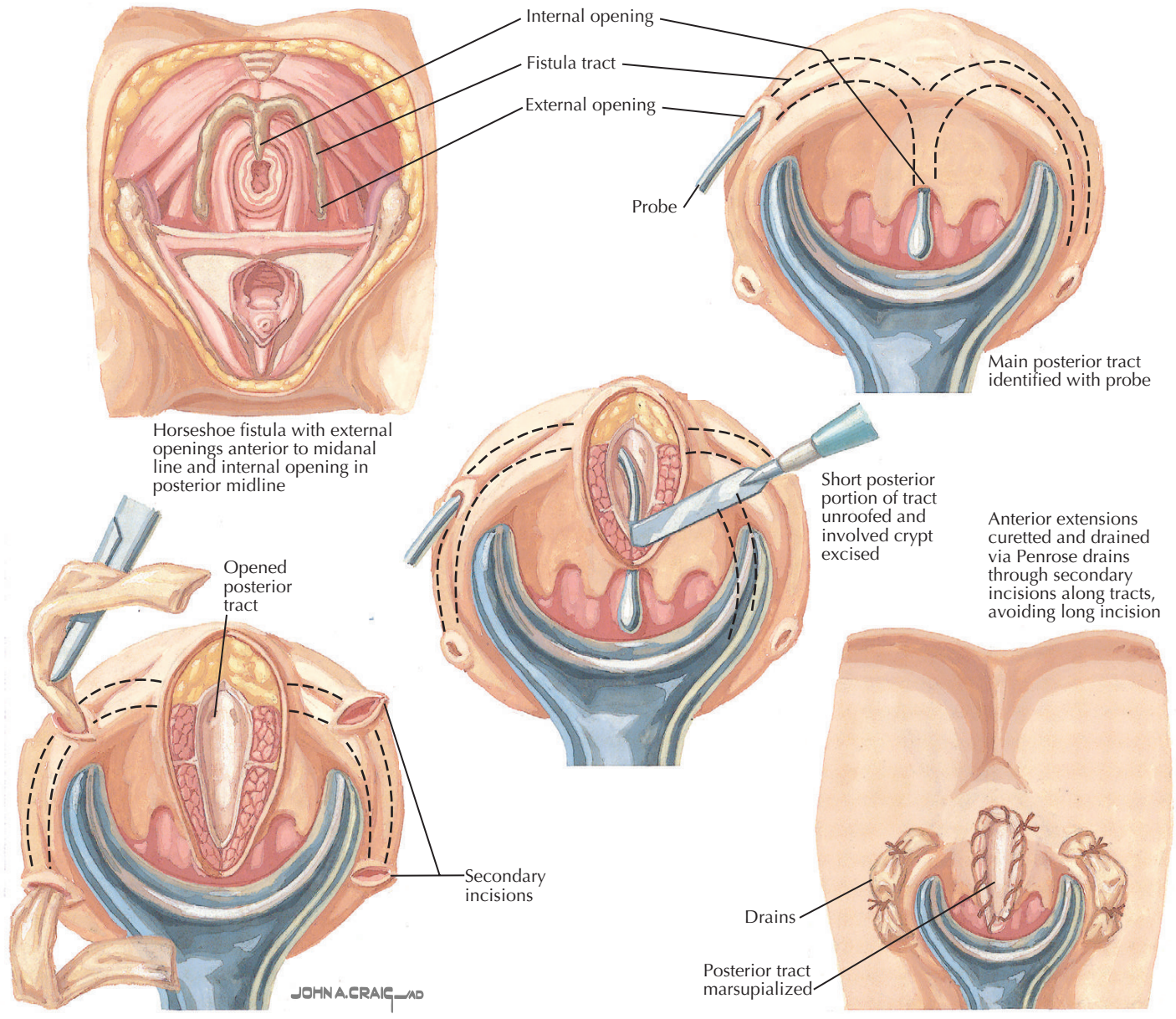

Figure 49-4 Anorectal disorders: surgical management of horseshoe fistula.

secondary to an intraabdominal disease such as neoplastic or Crohn's disease, the supralevator abscess is drained into the rectum, through the ischioanal fossa, or through the abdominal wall with concurrent treatment of the primary disease.

FISTULA IN ANO ETIOLOGY AND EVALUATION

In multiple studies conducted in separate settings, anorectal abscesses recur or "convert" to fistulas in approximately 30% to 40% of cases. By inference, therefore, the internal opening representing the original source of the problem spontaneously heals in more than 60% of cases. When the internal opening does not heal or a "recurrence" develops, it is useful to simply consider the infection a true fistula in ano with an internal opening and one or more external openings.

Appropriate evaluation and treatment of a fistula in ano are predicated on correct identification of the internal opening and the fistula tract. Evaluation begins with a careful history as described earlier. Several disorders may mimic fistula in ano and must be considered in the differential diagnosis. Hidradenitis suppurativa is differentiated by the presence of multiple perianal skin openings with surrounding leatherlike skin or with no obvious association with the anal canal. A careful history may reveal previous intertriginous infections in the groin folds or axilla. A pilonidal sinus with perianal extension can be identified by prior history or by the presence of midline pilonidal pits in the gluteal cleft cephalad to the point of the coccyx. IBD should be considered and ruled out as noted previously. Diverticulitis of the sigmoid colon with fistulization to the perineum is exceedingly rare. Aggressive anal condylomata and low rectal and anal canal carcinomas also may manifest as fistula in ano.

On physical examination, in addition to the maneuvers described for assessing anorectal abscess, the provider may note that the external opening of the fistula is an erythematous area of granulation tissue with purulence expressed during compression. The track may be palpable as an indurated cord. Identification of the internal opening during physical examination can be challenging. A useful but not foolproof rule of thumb is Goodsall's rule that external openings anterior to the anus will track radially to an internal opening at the dentate line, whereas external openings posterior to the anus will track to the posterior midline at the dentate line. In the clinic setting, anoscopy may help to clarify the location. In the operating room, a fistula probe can be inserted into the external opening and passed along the tract. It is not always possible to pass the probe, and *it is paramount to avoid creating a false passage or an artificial internal opening during this process*. The suspected internal opening should be confirmed with injection of hydrogen peroxide through an angiocatheter into the external opening. Concurrent endorectal ultrasound can be extremely effective in demonstrating the tract and internal opening. If the internal opening remains elusive in spite of these maneuvers, the external opening should be extended, vigorously curettaged, and reflushed with peroxide. The external opening heals quickly and well in most patients, so opening it further generally should not present a problem except in the case of underlying Crohn's disease or leukemia or lymphoma. If the internal opening still is not apparent, the preferential imaging study is MRI.

Similar to anorectal abscess, the four main forms of fistula in ano are defined by the relation of the fistula tract to the sphincter muscles (see Figure 49-2). An intersphincteric fistula tract is in the intersphincteric plane. The external opening usually is in the perianal skin close to the anal verge. A transsphincteric fistula tract starts in the intersphincteric plane or in the deep postanal space. The fistula tract crosses the external sphincter and opens externally from the ischioanal fossa, as in horseshoe abscess. Suprasphincteric fistulas start in the intersphincteric plane proceeding cephalad laterally and superiorly to the puborectalis muscle, then caudad between the puborectalis and levator ani muscles into the ischioanal fossa. Extrasphincteric fistula tracts can traverse in either direction from the perineal skin through the ischioanal fossa and levator ani muscle to penetrate the rectal wall.

FISTULA IN ANO MANAGEMENT

Management of fistula in ano is based on eliminating the source of infection (the internal opening) and establishing drainage without compromising anal continence. When the fistula does not cross the external sphincter, the simplest means to accomplish this is fistulotomy, wherein a fistula probe is placed through the tract and electrocautery is used to lay it open. Epithelial granulation tissue can be curetted, and if necessary the unroofed fistula can be marsupialized. Failure to open the entire track may lead to fistula recurrence. Fistulectomy or excision of the entire fistulous track confers no healing benefit over fistulotomy but is associated with more pain and higher rates of anal incontinence.

When the fistula crosses the external anal sphincter, a simple fistulotomy may be less desirable. Although transection of the posterior external sphincter muscles does not always jeopardize anal continence, older patients and especially women with anterior fistulas may be prone to reduced anal continence postoperatively. In lieu of transecting the external anal sphincter, drainage can be accomplished with placement of a cord of nonreactive material or seton in the fistula tract (Figure 49-5). The seton will facilitate drainage of the infected space by stenting the external opening. Over a 6- to 8-week interval, the seton permits resolution of infection and narrowing of the tract. Historically, tight or cutting setons were used to slowly erode through the sphincter and create fibrosis. Cutting setons are associated with substantial pain and loss of anal continence. At this time their use is strongly discouraged.

After adequate drainage and resolution of infection, if fistulotomy is not an option then the internal opening may be closed with absorbable suture and fibrin glue, or a collagen plug may be placed in the fistula tract. Although fibrin glue application fails in more than 50% of cases, it has several distinct advantages over other treatment options. It is associated with few to no side effects, can be applied multiple times, and can be used in patients with complex fistulas and few other options. Use of a collagen plug drawn through the fistula tract and fixed with suture is slightly more promising than fibrin glue but also is associated with a high recurrence rate in more recent studies.

In patients in whom less invasive therapy fails, an anal advancement flap is another interventional option and can be combined with placement of a plug or glue. With the patient in appropriate position, the fistula tract is identified. A U-shaped flap of mucosa is created that includes and extends just beyond the internal fistula opening. The distal strip of the flap is excised, removing the internal opening. The flap is then advanced to cover the tract and sutured in place. Owing to disruption of tissue planes, an anal advancement flap has the best chance of success with its first attempt.

ANAL FISTULA ASSOCIATED WITH CROHN'S DISEASE

The presence of Crohn's disease should be suspected in cases of multiple fistula recurrence, extremely delayed perineal healing, or the presence of multiple tracts originating in the upper anal canal, lower rectum, or even the abdomen. Aggressive medical therapy is encouraged. Metronidazole and ciprofloxacin may be useful. Infliximab, a monoclonal antibody directed against tumor necrosis factor, has shown some efficacy in reducing the fistula burden. Aggressive surgical intervention is discouraged because of extremely poor healing and risk to continence. The most judicious intervention is local curettage, flushing with hydrogen peroxide, laying open only superficial tracts, and opening abscess cavities. In some hands, anorectal advancement flaps have met with good success and should be considered during Crohn's quiescence. Long-term indwelling setons are often the best choice for this patient population.

Rectovaginal Fistula

A rectovaginal fistula is a communication between the anterior wall of the anal canal or rectum and the posterior wall of the vagina. Rectovaginal fistulas are classified as low if a perineal

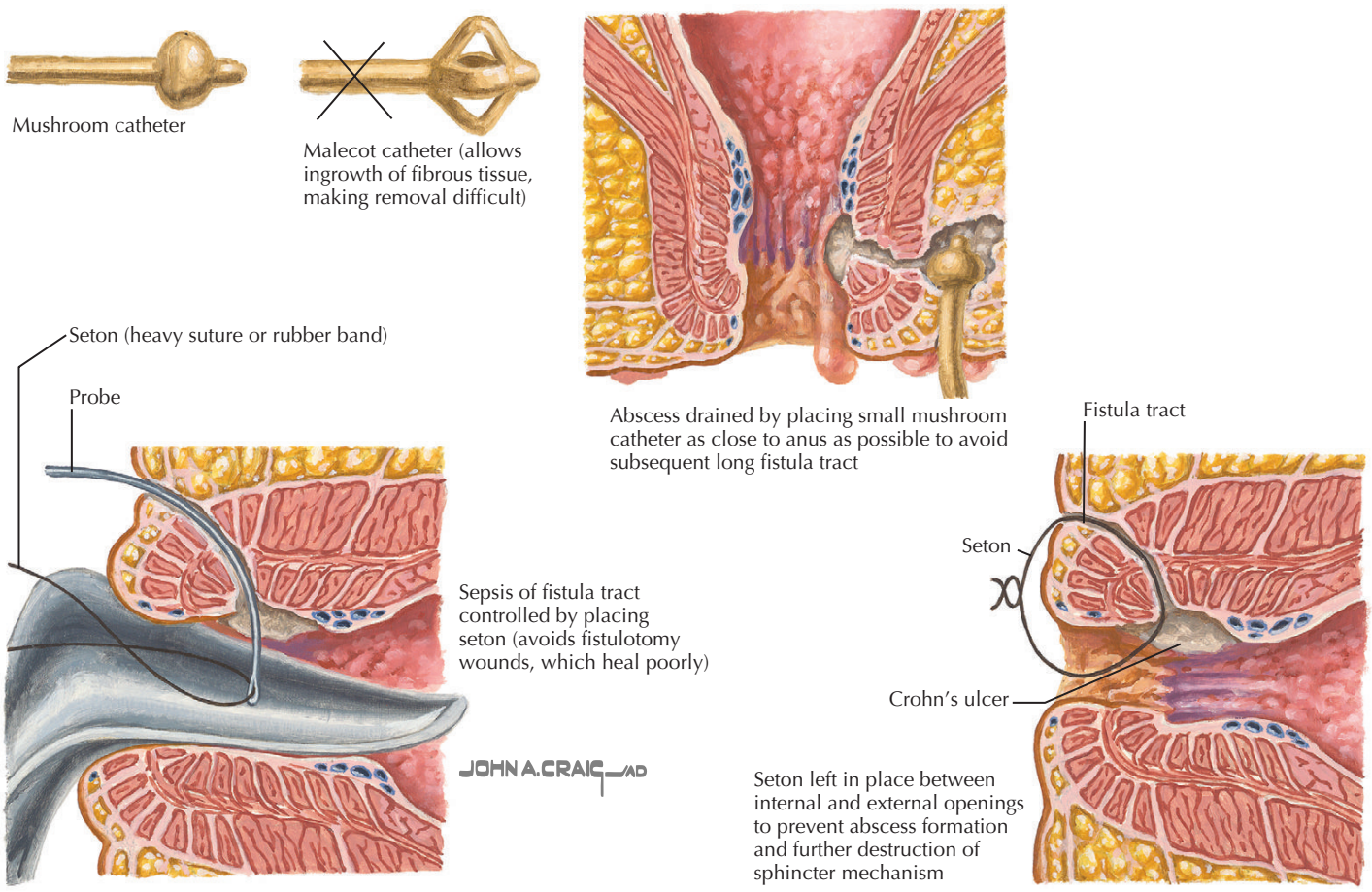

Figure 49-5 Appearance and management of anorectal Crohn's disease.

approach to repair is possible and high if a repair can be accomplished only transabdominally. For low or small fistulas, the most common complaint is passage of gas per vagina. On digital examination of the anal canal, an anterior scar or defect may be present. Bimanual examination of the rectum and the vagina can also detect the internal opening in the anal canal. Obstetric injury accounts for most cases, and approximately 50% of low, small rectovaginal fistulas will heal spontaneously. For a low, simple fistula that does not heal spontaneously, an anorectal advancement flap yields the best result after the inflammation has subsided—generally 3 to 6 months postpartum. If the rectovaginal fistula is associated with anal incontinence, an anal sphincteroplasty is also performed. In experienced hands, endorectal advancement flap treatment for simple rectovaginal fistula has shown 83% primary healing. For recurrent rectovaginal fistulas, a tissue interposition graft may facilitate complete healing.

For large fistulas, the most common complaint is vaginal discharge with fecal odor and painful vaginitis. Patients with middle or high fistulas should be assessed with proctoscopy. If a fistula is suspected but cannot be demonstrated, a tampon can be placed in the vaginal canal and 100 mL of diluted methylene blue instilled into the anorectum. The tampon is then removed and checked for evidence of blue staining. Barium enema is rarely helpful but may be indicated in patients with IBD or previous radiation to the pelvis. For midlevel or high rectovaginal fistulas, simple fistulas with healthy adjacent tissue are repaired by transabdominal mobilization of the rectovaginal septum, division of the fistula, and layer closure of the rectal defect. If the local tissues have been damaged by irradiation, infection, or inflammatory diseases, an extended low anterior resection with coloanal anastomosis should be considered.

Although a diverting colostomy is unnecessary for most simple rectovaginal fistulas, a preliminary colostomy should be considered for complex rectovaginal fistulas. For elderly or unfit patients, radiation-induced fistulas, and rectovaginal fistulas associated with Crohn's disease, a permanent colostomy may be the procedure of choice.

SUMMARY AND FUTURE EFFORTS

In summary, anorectal abscess and fistula disease generally originate with anal cryptoglandular disease. With appropriate drainage, most abscesses are cured. However, a substantial minority will recur or redevelop as fistulas, indicating that the original insult or internal opening never resolved. Treatment is focused on drainage, obliteration of the internal opening when feasible, and avoidance of anal sphincter compromise. Understanding the relationship of the fistula tract to the pelvic anatomy is crucial to appropriate treatment planning. Stepwise increase in

the aggressiveness of operative treatment is prudent, especially in patients with Crohn's disease. After all, as noted by J. Alexander-Williams (1976), "fecal incontinence … is the result of aggressive surgeons and not of progressive disease."

EVIDENCE

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Peritonitis

Christopher M. Watson and Robert G. Sawyer

50

ABSTRACT

Peritonitis is a generic term defined as inflammation of the peritoneal lining. Infectious peritonitis is subdivided into spontaneous or primary bacterial peritonitis, secondary peritonitis, peritoneal dialysis–associated peritonitis, and tertiary peritonitis. Each of these entities has a unique population of patients affected, presenting signs and symptoms, commonly isolated pathogens, diagnosis, and treatment. Therefore it is important to know the difference so that efficient use of resources can be undertaken, allowing for rapid diagnosis and treatment and thereby decreasing morbidity and mortality. This chapter focuses on secondary and tertiary peritonitis only, as primary peritonitis is essentially a nonsurgical disease.

GEOGRAPHIC DISTRIBUTION AND DISEASE BURDEN

Secondary Peritonitis

Secondary peritonitis (an intraabdominal infection caused by a breach in the gastrointestinal tract or other hollow viscus) is one of the most commonly treated conditions by general surgeons. The overall prevalence of secondary bacterial peritonitis and intraabdominal infection in an inpatient surgical service may be as high as 75%. There is little reason to believe that there is a significant geographic difference in the distribution of secondary peritonitis across the world. Reports from Europe, North America, and Asia appear to describe similar origins and pathogens associated with the pathology of this state. In areas without high-technology healthcare, diseases may also be similar, though some notable exceptions do occur, such as bowel perforations related to typhus or parasitic diseases.

Tertiary Peritonitis

Tertiary peritonitis, defined loosely as a recurrent or persistent intraabdominal infection after initial treatment, has become more common as modern technology allows the support of increasingly ill patients. In a study from 1998, the rate of tertiary peritonitis after secondary peritonitis was 74%, but more recently, depending on the definition and study type, 20% to 25% of patients with secondary peritonitis go on to develop tertiary peritonitis. Unlike secondary peritonitis, the geographic distribution of tertiary peritonitis is not even. Because tertiary peritonitis by definition results from the treatment of secondary peritonitis, it generally occurs in areas where the resources required for high-intensity medical care are found. In fact, tertiary peritonitis must be considered one of the surprise sequelae of the rise of critical care and is fairly uniquely a disease found in wealthy countries.

RISK FACTORS

Secondary Peritonitis

Risk factors for secondary bacterial peritonitis include any inflammatory condition in the peritoneal cavity, ranging from the extension of localized inflammatory conditions such as appendicitis, pancreatitis, cholecystitis, and pelvic inflammatory disease (PID) to perforation of hollow visceral organs such as the stomach, small bowel, or colon. It can also arise after blunt or penetrating abdominal trauma. In addition, inflammatory bowel diseases such as ulcerative colitis and Crohn's disease can lead to peritonitis. Finally, peritonitis can develop in any patient after undergoing an abdominal operation. Postoperative infections, including anastomotic dehiscences and Centers for Disease Control and Prevention (CDC)–defined organ space surgical site infections (where there is no gastrointestinal leak), can occur after as many as 10% of gastrointestinal procedures. Previous abdominal operation, perioperative transfusion, open surgery compared with laparoscopic surgery, older age, longer surgery, emergency or trauma surgery, additional procedures, high-risk surgeries, comorbidities, blood loss, tumor location, obesity, and hypoalbuminemia have been associated with an increased risk of these organ space infections. In a study evaluating only abdominal trauma patients, multivariate logistic regression analysis implicated abdominal trauma index score greater than 24, contamination, and admission to an intensive care unit (ICU) as independent predictors for the development of organ space surgical site infections.

Tertiary Peritonitis

The major risk factors for the development of tertiary peritonitis include malnutrition, a high Acute Physiology and Chronic Health Evaluation (APACHE) II score, the presence of organisms resistant to antimicrobial therapy, organ system failure, pancreatic or small bowel source, drainage only at initial intervention, and gram-positive and fungal pathogens. Obviously, previous secondary peritonitis is a prerequisite for tertiary peritonitis and therefore cannot truly be considered a risk factor.

CLINICAL FEATURES

Secondary Peritonitis

A complex interplay between the patient's systemic response to contamination and the peritoneum's ability to contain the contamination ultimately determines the presentation. For example, the immunocompetent, healthy patient may rapidly contain contamination and manifest minimal systemic illness, resulting

in a small, localized abscess, as in periappendiceal abscesses or diverticular abscesses. Another patient who is immunocompromised may display no systemic signs of disease and be found to have diffuse contamination with no apparent containment, resulting in a rapid decline without intervention. Between these two extremes lies the classic patient with initial contamination resulting in minimal systemic manifestations that progress to diffuse peritonitis and systemic toxicity. Source control, if complete and combined with antimicrobial therapy, will resolve the peritonitis, but if incomplete may result in abscess formation or tertiary peritonitis (Figure 50-1).

In general, patients will report symptoms of progressive abdominal pain, often beginning acutely in a focal area and progressing to diffuse involvement. This sequence is different from that seen for appendicitis without perforation, in which abdominal discomfort begins throughout the abdomen then localizes to the right lower quadrant. The disparity can be explained by the fact that appendicitis is not considered secondary peritonitis until rupture, at which time diffuse peritonitis and diffuse abdominal pain do occur. On examination, the immunocompetent patient with peritonitis will have exquisite tenderness with minimal pressure and possibly rebound tenderness and rigidity of the abdominal wall (often referred to as *involuntary guarding*). If the patient is examined early, the tenderness, similar to subjective pain, may be localized to a small area or region, but as the disease worsens and more peritoneum becomes inflamed, the tenderness will become more diffuse. In addition to the typical systemic signs of infection, patients may exhibit respiratory insufficiency, hepatic insufficiency, oliguria, ileus, or obstipation.

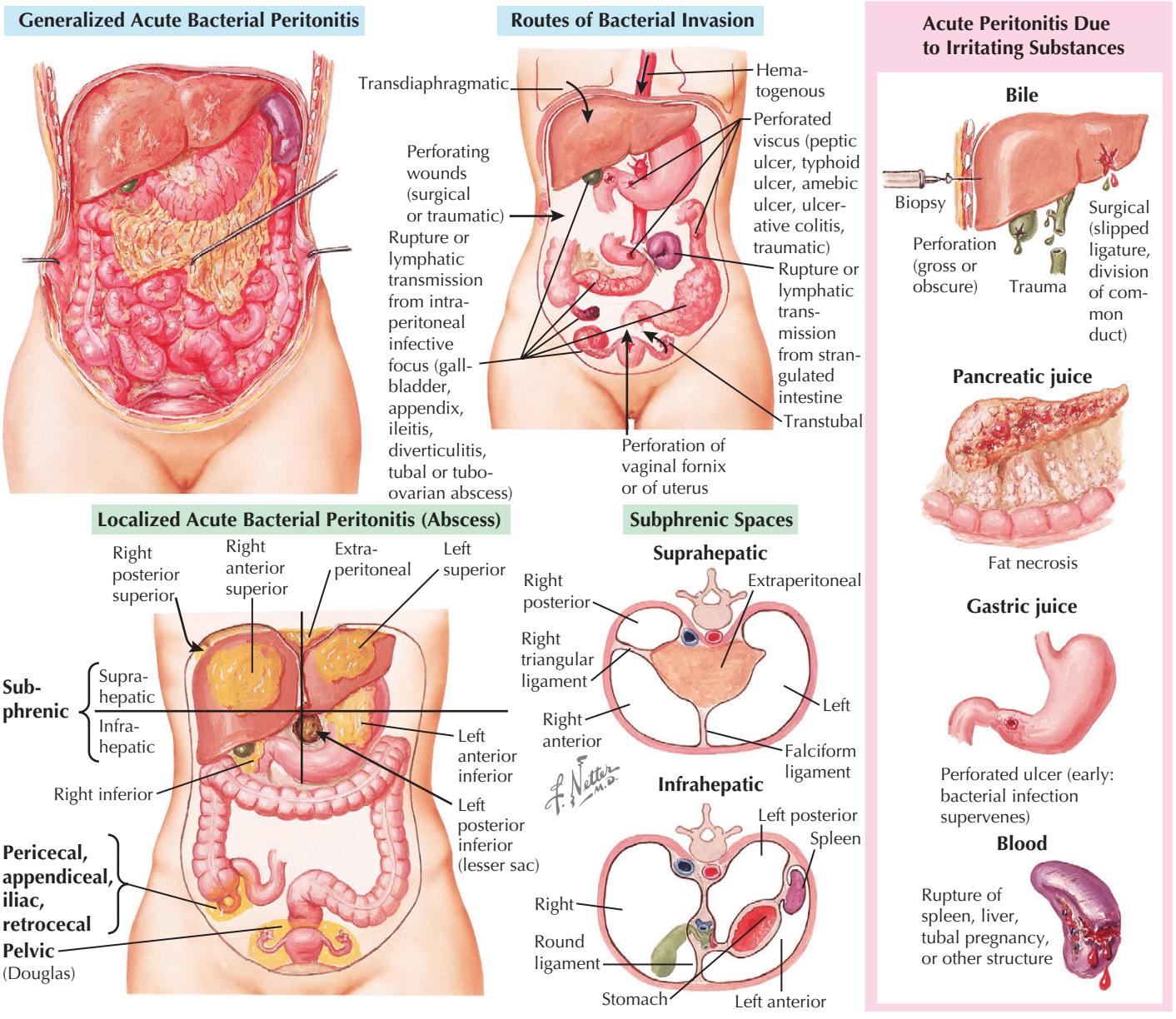


Figure 50-1 Acute peritonitis.

Tertiary Peritonitis

Because of the frequently associated severe, systemic disease present, the history and physical examination may be limited in these patients by the use of narcotics and sedative-hypnotics, as well as difficulties communicating as a result of mechanical ventilation. Also, iatrogenic or noniatrogenic immunosuppression, which is probably present in variable degrees in all forms of critical illness, can contribute to the lack of clinical findings. When signs and symptoms are present, they are the same as those of secondary peritonitis.

DIAGNOSTIC APPROACH

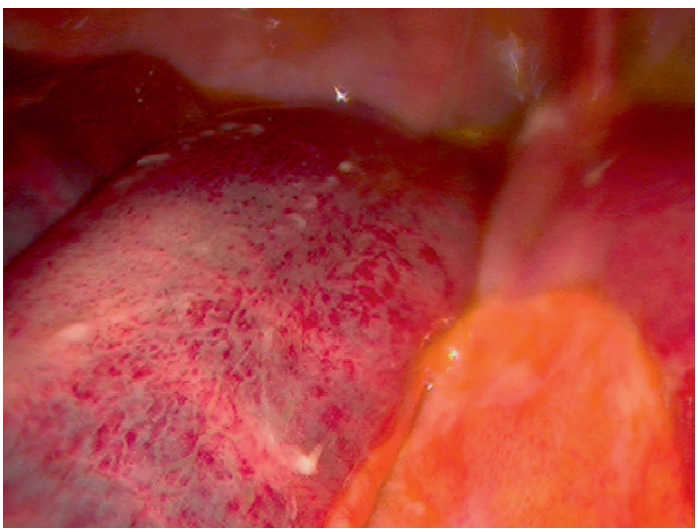
Secondary Peritonitis

Once peritonitis has been diagnosed, the exact cause must be further investigated and treated. A patient with peritonitis who is unstable or in shock and *does not* respond to resuscitation should go directly to the operating room for exploratory laparotomy or laparoscopy as a diagnostic study as well as to achieve definitive source control. A similar patient that *does* respond to resuscitation may undergo specific studies to evaluate the source of peritonitis. This may allow for nonoperative management in certain limited situations.

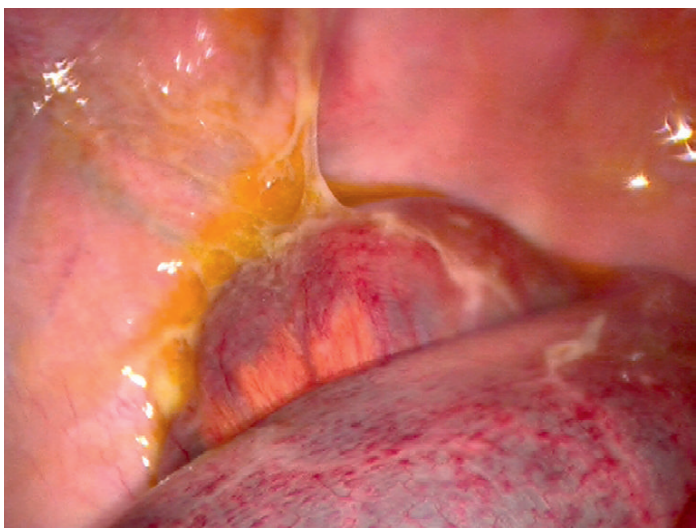
Specific pain distributions both temporally and spatially can direct the experienced clinician toward the correct differential diagnosis. In general, however, the best initial radiographic examination is computed tomography (CT) of the abdomen and pelvis. Whether or not intravenous, oral, and/or rectal contrast agents are used is directed by the initial examination and the differential diagnosis, and this decision can be aided by consultation with the radiologist. Intravenous contrast agents aid in the visualization of specific inflammatory conditions such as an abscess or appendicitis. In addition, other signs of inflammation include stranding or localized inflammation of the mesentery, intramesenteric fat, or retroperitoneal fat. Fluid collections can be seen without contrast, but in the absence of findings such as air-fluid levels or layering, the nature of the collection may be difficult to determine. Oral and rectal contrast allow the clinician to evaluate the continuity of hollow viscera. Obstruction will be seen as an abrupt cutoff or transition of oral or rectal contrast, and perforation may show extravasation of contrast into the peritoneum.

An alternative examination is abdominal ultrasound. This may be the initial imaging study of choice in pregnant patients, young children, or patients with suspected gallbladder pathology. It is important, however, to have sufficiently narrowed the differential diagnosis prior to ultrasound in order to allow the technician to focus on a particular region, because generalized examinations of the abdomen frequently lack sensitivity. Gaseous bowel distention may prevent useful ultrasound visualization.

Recently, exploratory laparoscopy has been evaluated as an initial diagnostic study in peritonitis (Figure 50-2). A Turkish study showed that laparoscopy rendered a definitive diagnosis in 93% of patients with peritonitis and was used to treat the underlying disease in 86% (2008). An unnecessary laparotomy was avoided in 17%, and the conversion rate was 14%. Many more studies have shown benefits for laparoscopy in the evaluation and treatment of mild peritonitis, but in most series, patients with severe hypotension or generalized peritonitis were excluded. In the ICU, bedside laparoscopy for the evaluation of peritonitis has been determined to be safe and feasible with high accuracy. Finally, it has been theorized that open abdominal exploration may be the "second hit," leading to worse organ failure postoperatively in many patients. Animal studies appear to support this theory, but human studies are lacking. In the end, it is the stability of the patient and the experience of the surgeon that will dictate whether this is an option for the diagnosis and treatment of peritonitis.



Fibrous exudate in peritonitis



Serosal changes with inflammation

Figure 50-2 Exploratory laparoscopy in peritonitis.

Peritonitis stemming from most perforations will be caused by a fairly consistent set of pathogens, including aerobic gram-negative and anaerobic organisms. Cultures should generally be obtained at the time of exploration or percutaneous drainage, but definitely in the setting of healthcare-associated infections. Isolation of yeast, particularly *Candida* species, is common, and certain risk factors have been associated with an increased likelihood of this, including upper gastrointestinal perforation, biliary or pancreatic perforation or necrosis, an immunosuppressed state, female gender, previous antimicrobial therapy for longer than 48 hours, and intraoperative cardiovascular failure.

Tertiary Peritonitis

The clinical features of tertiary peritonitis are often subtle because many patients are in the ICU and sedated; therefore a high index of suspicion is necessary. Diagnosis is further clouded by concurrent nosocomial infections, often in different stages of therapy. Although careful clinical examination is important, CT scanning is quite frequently necessary to make the diagnosis of tertiary peritonitis in these patients who, by definition, have already had at least one abdominal intervention for infection.

CLINICAL MANAGEMENT AND DRUG TREATMENT

For all types of peritonitis the management scheme is the same: fluid resuscitation and blood pressure support; appropriate, broad-spectrum antibiotic administration; early source control; and deescalation of antibiotics after culture results and antibiotic sensitivities are known. Appropriate empirical therapy is usually based on the specific disease state or organ of origin (e.g., colonic source infections are initially treated with antimicrobials active against aerobic gram-negative rods and anaerobes). Modifications of this principle should be based on local antibiograms and take into account local resistance rates as well as patient-specific factors, such as previous antibiotic usage, recent hospitalization or institutionalization, and previous resistance carrier status. Length of treatment is debated in each category of peritonitis, but in any case, day 1 does not start until source control is achieved.

Secondary Bacterial Peritonitis

Source control should be sought concurrently with antibacterial administration and consists of repair, resection, bypass or diversion of perforation, and resection of necrotic tissue. Blood cultures should be obtained in severely septic patients and empirical antibiotics started before surgical intervention. Once surgical source control has been achieved, specimens should be obtained to guide specific antibiotic therapy. Empirical antibiotics should be based on the most likely organism, determined by the site of perforation, the patient's history of resistant pathogens, and local antibiograms. Of note, most cases of secondary peritonitis should be considered community-acquired intraabdominal infections if the patent has received antimicrobials for less than 48 hours and did not have a prolonged stay in the hospital or other healthcare facility before the onset of secondary peritonitis. Tertiary peritonitis is always a healthcare-associated intraabdominal infection and will be considered in the next section. For community-acquired infections, the location of the gastrointestinal perforation (stomach, duodenum, jejunum, ileum, appendix, or colon) guides the clinician toward the infecting flora. Established infection beyond the proximal small bowel is usually caused by facultative and aerobic gram-negative organisms; infections beyond the proximal ileum frequently are caused by a variety of aerobic and anaerobic microorganisms. Many antibiotics are available and appropriate for empirical therapy, although none has been found to be superior to others. Guidelines from the Infectious Diseases Society of America (IDSA), the Surgical Infection Society, the American Society for Microbiology, and the Society of Infectious Diseases Pharmacists contain evidence-based recommendations for selection of antimicrobial therapy for adult patients with complicated intraabdominal infections. Recommendations are based on whether infections are community acquired or healthcare associated, and include options for monotherapy and combination therapy. The tendency is to favor monotherapy owing to ease of administration, with ertapenem or moxifloxacin used for community-acquired infections and meropenem or piperacillin-tazobactam for healthcare-associated infections in the absence of known resistant pathogens.

In the case of localized peritonitis that does not extend beyond the wall of the organ of origin, such as nonperforated appendicitis or cholecystitis with only focal spillage and containment, antibiotic treatment is basically prophylaxis for the surgical incision and is not needed after the operation. Likewise, a patient with gastric, duodenal, or proximal jejunal perforations without associated malignancy or acid suppression therapy and rapid attainment of source control (within 24 hours of the onset of symptoms) requires only prophylactic antibiotics. Also, if a traumatic bowel perforation is repaired within 12 hours of injury, then a 24-hour course of antibiotics is appropriate. In the case of delayed gross contamination with bowel, biliary, or gastric contents, source control should be followed by a 5- to 7-day course of appropriate antibiotics. If empirical therapy is found to have not been appropriate for the isolated pathogen, the length of therapy may need to be 5 to 7 days after appropriate therapy has begun. For resistant strains and associated bacteremia, a 10- to 14-day course may be more appropriate, although the data to support this contention are weak. Other researchers, however, propose continuation of antimicrobials until systemic signs of inflammation, including leukocytosis and fever, have resolved. If after 5 to 7 days these signs are still present, repeat investigations to assess the adequacy of source control are necessary.

Tertiary Peritonitis

Tertiary peritonitis is by definition a nosocomial or healthcare-associated infection and thus should be treated more aggressively with broader-spectrum antibiotics when antibiotics are required. Unfortunately, many times the presentation is insidious and often masked by other critical illness and underlying organ failure. Patients should be started on antibiotics that cover resistant pathogens common locally but also cover previously treated pathogens. In addition, reevaluation for missed sources of infection, such as another bowel leak or intraabdominal

abscess, should be performed. Again, the Guidelines from the IDSA, the Surgical Infection Society, the American Society for Microbiology, and the Society of Infectious Diseases Pharmacists should be reviewed for specific empirical choices, which are beyond the scope of this publication.

PROGNOSIS

Secondary Bacterial Peritonitis

Mortality is estimated to be 10% to 20%. Postoperative deep and organ or organ space infection showed an odds ratio (OR) of death of 2.6 to 4.5 in different studies. The key to achieving good outcomes, however, is most dependent on the time it takes to obtain adequate source control. When this is done, the mortality is probably less than 5%.

Tertiary Peritonitis

The mortality of tertiary peritonitis is approximately 30%, twice that of secondary peritonitis. Independent predictors of mortality in this population include increasing age (OR 1.06), increasing APACHE II score (OR 1.18), and four comorbidities: cerebrovascular disease (OR 4.3), malignant disease (OR 2.9), hemodialysis dependency (OR 3.8), and liver disease OR 4.2). Compared with secondary peritonitis, however, tertiary peritonitis has not been found to be an independent predictor of mortality but rather a marker of overall disease severity.

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Pyomyositis (Pyomyositis Tropicans)

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ABSTRACT

Pyomyositis, a disease historically seen in tropical climates, is characterized by primary abscess formation in the skeletal musculature. It is increasing in incidence in temperate climates, especially in immunocompromised hosts. In all cases, *Staphylococcus aureus* is the most commonly implicated organism. Clinical presentation is nonspecific, with muscle pain, tenderness, and swelling, accompanied by leukocytosis and fevers in cases with bacteremia. Computed tomography (CT) and magnetic resonance imaging (MRI) are the diagnostic modalities of choice. Treatment most often involves appropriate antimicrobial therapy coupled with abscess drainage.

INTRODUCTION AND EPIDEMIOLOGY

Pyomyositis, also known as *tropical pyomyositis* because of its proclivity for warm climates, is an uncommon disease characterized by primary abscess formation in the skeletal musculature. First described in 1885, it is presumed to arise not from contiguous infections, but by hematogenous seeding. Tropical pyomyositis can affect patients of all ages, with a predominance in children and young adults. It has been widely reported in Asia, Africa, and the Caribbean and accounts for 1% to 4% of all admissions in some tropical countries. In temperate climates, it occurs most commonly in children, as well as in patients with an immunodeficiency. As many as 75% of reported cases are in the immunocompromised, with the incidence of pyomyositis in those with human immunodeficiency virus (HIV) infection as high as 31%. However, reports of pyomyositis in immunocompetent hosts are emerging.

Predisposing factors include immunodeficiency, trauma, injection drug use, concurrent infection, and malnutrition. Many of these risk factors weaken host defenses, possibly because of underlying muscle damage and impaired local immunity.

MICROBIOLOGY

Causative organisms of pyomyositis are most commonly *S. aureus* or group A streptococci, but other streptococcal groups, *Haemophilus influenzae*, *Aeromonas hydrophila*, *Bartonella* species, *Fusobacterium* species, anaerobes, and other enteric flora have also been implicated. *S. aureus* as the offending organism affecting a single muscle group is the most common presentation, though cases of disseminated infection have been reported. Recently, methicillin-resistant *S. aureus* (MRSA) isolates have been recognized as a cause of tropical pyomyositis. *S. aureus* produces virulence factors including enterotoxins, exfoliative toxins, and extracellular proteins that act against host defense mechanisms. Certain strains of MRSA, particularly strains in the community setting that have acquired the Panton-Valentine leukocidin virulence factor, demonstrate proclivity for aggressive, disseminated infections.

CLINICAL FEATURES

Clinical features on presentation include muscle pain, stiffness, swelling, and tenderness. Fever is also present, often in a cyclic pattern owing to bacteremia (Figure 51-1). Onset can often be insidious, and diagnosis elusive. CT, MRI, and ultrasonography are the most commonly used modalities for diagnosis and also aid in therapeutic procedures. MRI is the most sensitive modality for detecting early pyomyositis and evaluating extent of infection, because of higher signal intensity of involved muscles. Laboratory findings are usually nonspecific, though leukocytosis is common in immunocompetent hosts. In temperate regions, blood cultures are positive only 30% of the time, and organisms are usually identified from abscess aspirates.

Three stages of pyomyositis are described. After transient bacteremia, the first or *invasive* stage develops, with edematous and painful musculature caused by bacterial seeding. Aspiration is nondiagnostic, as no abscess has formed. The second or *suppurative* stage is characterized by abscess formation, and the majority of patients are in this stage at presentation (Figure 51-2). In the final or *late* stage, septicemia ensues, with disseminated abscesses and resultant multiorgan dysfunction.

TREATMENT

Though the early stage, pyomyositis can be treated with antibiotics alone; later stages require treatment with appropriate long-term antibiotic therapy coupled with surgical drainage of large abscesses. If feasible, image-guided percutaneous drainage should be the first approach, though surgical intervention may be required in cases with deep infection or extensive muscle involvement. Aspiration or drainage cultures should guide antimicrobial therapy, but empirical therapy should be initiated based on patient characteristics. In immunocompetent patients, empirical therapy against staphylococci and streptococci should be initiated, though coverage for MRSA should always be considered in patients with appropriate risk factors, such as institutionalization, intravenous drug use, or past infection. Broad gram-positive, gram-negative, and anaerobic coverage should be initiated in immunocompromised hosts. There is no consensus on the duration of antibiotic treatment, with reports describing both long-term parenteral therapy and early oral therapy with adequate drainage. However, it is generally accepted that duration of antimicrobial therapy should be directed by clinical

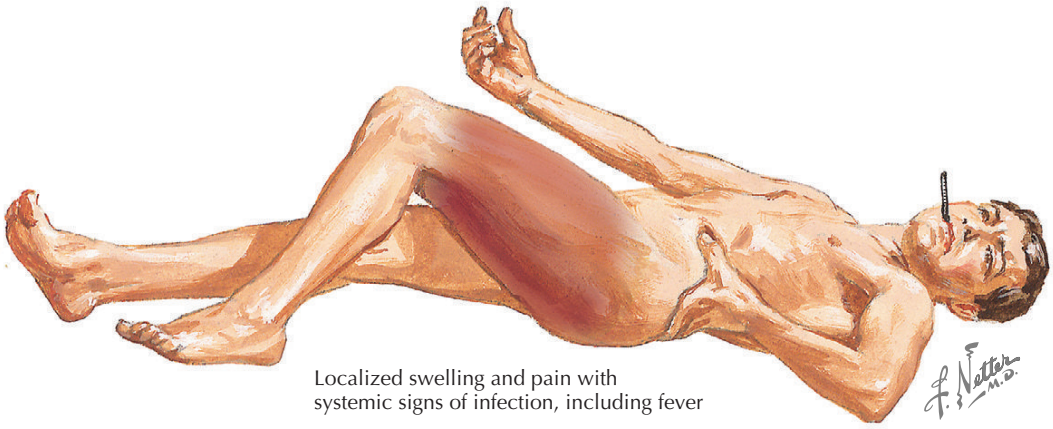

Figure 51-1 Clinical presentation of pyomyositis.

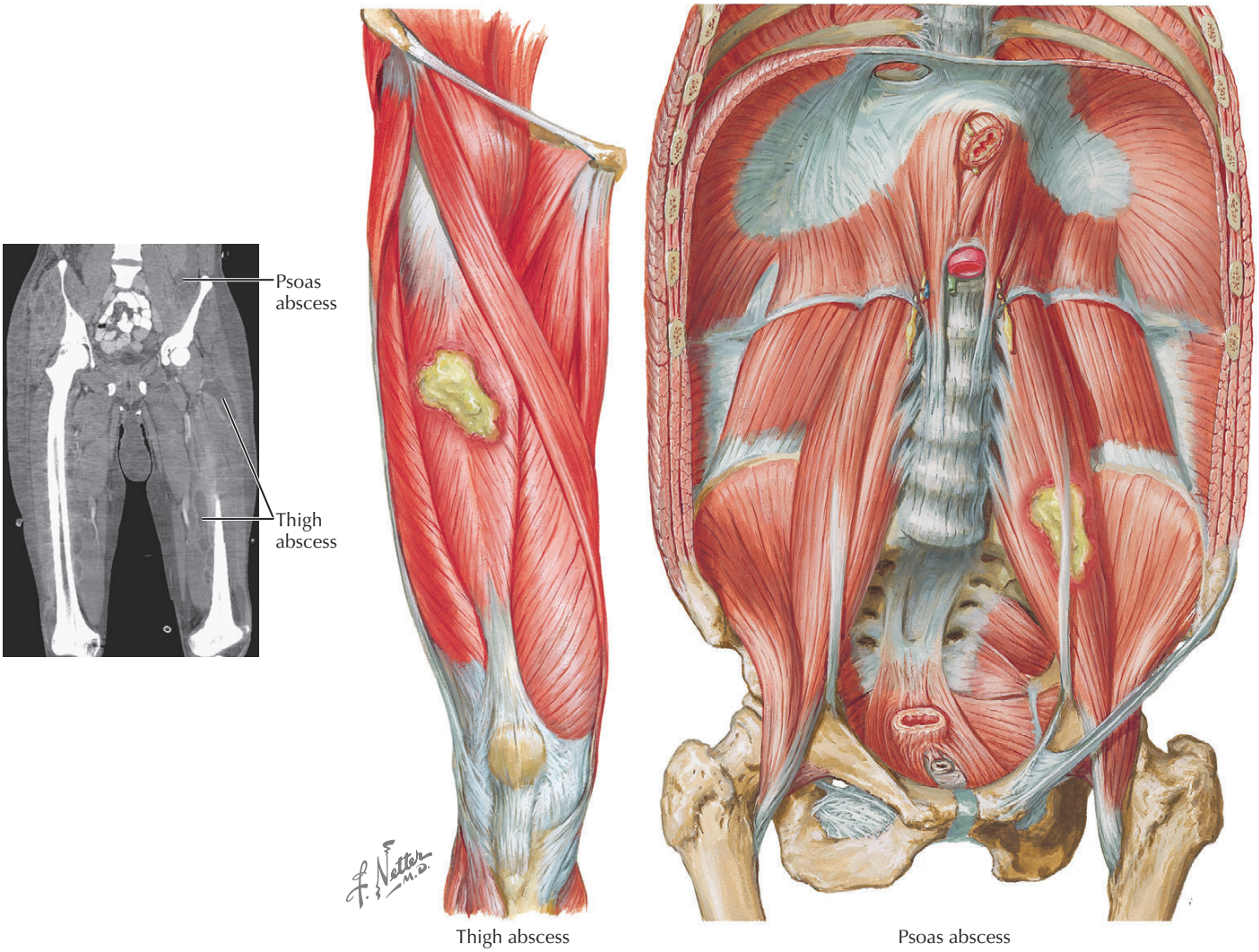

Figure 51-2 Possible anatomic locations of abscesses in pyomyositis.

and radiographic improvement. Assessment of other sources for bacteremia should also be undertaken and antimicrobial therapy modified accordingly. Persistent symptomatology warrants a renewed search and drainage of abscesses, using interventional or surgical approaches.

With appropriate antimicrobial therapy and drainage of abscesses, most patients do very well after treatment for pyomyositis. There can be little residual deformity and minimal loss of function, even in cases with extensive muscle damage. Physical therapy and rehabilitation may be required in severe disseminated cases, though most function is fully recovered. Mortality rates from 1% to 10% have been reported, with rare recurrence of infection, usually in immunocompromised hosts.

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Surgical Site Infections

E. Patchen Dellinger

52

ABSTRACT

Surgical site infections (SSIs), previously known as *wound infections*, remain one of the most common adverse events that occur with hospitalized surgical patients or after outpatient surgical procedures despite many advances in preventive techniques. A February 2010 report from the National Healthcare Safety Network (NHSN) of the Centers for Disease Control and Prevention (CDC) documents SSI as accounting for 17% of all healthcare-associated infections (HAI) among hospitalized patients. Of 100,000 HAIs reported in 1 year, deaths followed SSI in 8000 cases. The incidence of SSI after a surgical procedure is highly variable depending on the type of operation being done and the underlying risk factors of the patient, but the average across the United States is estimated to be 2% to 3% of all procedures. Length of stay and associated costs are dramatically increased when an SSI develops.

DEFINITIONS

SSIs are divided into three categories according to the anatomic extent of the infection at the time of diagnosis: superficial incisional SSI, deep incisional SSI, or organ or organ space SSI (Table 52-1). A superficial incisional SSI occurs within 30 days after the operative procedure *and* involves only skin and subcutaneous tissue of the incision. In addition, the patient has at least one of the following:

- Purulent drainage from the superficial incision
- Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
- At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat, *and* the superficial incision is deliberately opened by the surgeon and is culture positive if cultured *or* is not cultured (a culture-negative finding does not meet the definition for SSI)
- A diagnosis of superficial incisional infection that has been made by the surgeon or attending physician

There are two specific types of superficial SSI. A primary superficial SSI is one that occurs in the primary incision in a patient who has had an operation with one or more incisions. A secondary superficial SSI is one that occurs in the secondary incision in a patient who has had an operation with more than one incision. An example would be the donor site in the leg for a patient who has had a coronary artery bypass with a vein graft taken from the leg.

A deep incisional SSI is one that develops within 30 days of the operative procedure if no implant was left in place during the operation or within 1 year if an implant was left and the infection appears to be related to the operative procedure. By definition, a deep incisional SSI involves deep soft tissues (e.g., fascia or muscle layers of the incision) *and* the patient has purulent drainage *or* the deep incision spontaneously dehisces or is deliberately opened by the surgeon and is cultured or if not cultured the patient has fever (temperature >38° C) or localized pain or tenderness (a culture-negative finding does not meet the definition for SSI). As with superficial incisional SSI, deep incisional SSI can be either primary or secondary.

An organ or organ space SSI involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure. When an organ or organ space SSI is reported, the specific anatomic site involved is also reported. Thus an intraabdominal abscess, an empyema, a mediastinal infection, or a joint space infection after an operation at one of those sites would be reported as an organ or organ space SSI in the abdomen, chest, mediastinum, or joint space. By definition an organ or organ space SSI occurs within 30 days of the operation if no implant was left or within 1 year if an implant was involved. Most organ or organ space SSIs are covered in other chapters of this book and so will not be dealt with further here.

RISK FACTORS

The risk that an SSI will follow a surgical procedure depends on several characteristics of the operative procedure and have been well established for the degree of bacterial contamination expected during the procedure and for the duration of the procedure. Operations are divided into four categories of increasing risk of intraoperative contamination and thus risk of subsequent SSI. Class 1 or clean wounds are incisions made through uninfected tissues without any evidence of inflammation and that do not enter any portion of the respiratory, alimentary, genital, or urinary tract. A clean wound must be closed primarily at the time of the operation.

A class 2 or clean-contaminated wound is one in which the respiratory, alimentary, genital, or urinary tract is entered under controlled conditions and without unusual contamination. This includes any operation involving the biliary tract, appendix, vagina, lungs, or oropharynx.

A class 3 or contaminated wound includes open, fresh, traumatic wounds; any operation that encounters acute, nonpurulent inflammation; operations involving gross spill from the gastrointestinal tract; or major breaks in sterile technique.

A class 4 or dirty wound is one that involves wounds with established infection, perforated viscera, or old traumatic wounds with retained devitalized tissue. This class implies that any postoperative infection is caused by organisms present at the time of the original operation.

Table 52-1 Summary of Surgical Site Infections (SSIs)

CATEGORY	ONSET	CHARACTERISTICS	CRITERIA
Incisional SSI	Within 30 days of operation	Involves skin and subcutaneous tissue of the incision only	1. Purulent drainage from the superficial incision *or* 2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision *or* 3. At least one of the following signs or symptoms of infection • Pain or tenderness • Localized swelling • Redness • Heat *and* The superficial incision is deliberately opened by the surgeon and is culture positive if cultured *or* is not cultured (a culture-negative finding does not meet the definition for SSI) *or* 4. A diagnosis of superficial incisional infection is made by the surgeon or attending physician
Deep incisional SSI	Within 30 days of operation if no implant left in place Within 1 year of operation if implant left in place	Involves deep soft tissues (for example fascia or muscle layers of the incision)	1. Purulent wound drainage *or* 2. Spontaneous wound dehiscence *or* 3. Surgeon deliberately opens the wound and obtains a positive culture sample *or* 4. Localized pain and tenderness
Organ or organ space SSI	Within 30 days of operation if no implant left in place Within 1 year of operation if implant left in place	Involves any part of the body, excluding the skin incision, fascia, or muscle layers, that is opened or manipulated during the operative procedure	See chapters in this Surgical Infections Section for organ or organ space SSIs involving specific anatomic sites.

Data from many sources demonstrate that operations that take longer to perform have a higher risk of infection. Whether this is because having the incision open longer increases risk or because operations that take longer to perform are intrinsically different from those that can be done more rapidly is not known. It is likely that both factors contribute. An operation may take longer because the tumor was larger, the adhesions were more troublesome, or bleeding was more difficult to stop, all of which could increase infection risk. The NHSN has traditionally divided cases by determining the 75th percentile for the duration of a particular type of procedure, and they assign an extra risk point for any operation that exceeds the 75th percentile. Data also demonstrate that risk is increased for patients with underlying illnesses that cause the anesthesiologist to assign a higher risk score. This score was developed by the American Society of Anesthesiologists (ASA) and is divided into five categories. ASA 1 refers to a normal healthy patient, ASA 2 indicates a patient with mild systemic disease, ASA 3 indicates a patient with severe systemic disease, ASA 4 indicates a patient with severe systemic disease that is a constant threat to life, and ASA 5 indicates a moribund patient who is not expected to survive without the operation. NHSN assigns an additional risk point for a patient with ASA score of 3 or above.

Many other factors specific to the individual patient affect risk of SSI. These include advancing age, diabetes mellitus, high perioperative blood glucose levels independent of a diagnosis of diabetes, hypothermia during the operation, increased blood loss, perioperative transfusion, obesity, malnutrition, cigarette smoking, and preexisting distant site infections, among others. Data regarding the concentration of oxygen administered during and immediately after the operative procedure have been conflicting, although animal data and observational data in limited numbers of humans have demonstrated a relation between low levels of oxygen tension in the fresh incision and an increased risk for SSI.

Preparation for and the conduct of the operation also affect the risk for SSI. The use of good skin preparation with an effective antiseptic and sterile instruments is basic. Glove perforations on the surgical team are associated with an increased risk for SSI. Surgical technique is widely regarded as an important risk factor, but there is no agreement on how to measure it. Shaving the operative site the day before the operation has been shown to increase risk. The administration of appropriate prophylactic antibiotics during the hour before incision is well documented to reduce the risk of SSI in the range of 30% to 60%, and efforts to keep the patient warm and to prevent hyperglycemia also have demonstrated efficacy in reducing risk.

DIAGNOSTIC APPROACH

The majority of SSIs become evident within 2 weeks of the operation, although a minority may be evident much later. It is rare for an SSI to be clinically evident during the first 3 to 5 days. An exception is SSI caused by beta-hemolytic streptococci, which can manifest clinically within 24 to 36 hours. However, these infections are extremely rare. Very obese patients may take considerably longer to manifest local signs of infection. It is common for a patient who has had a major abdominal or chest operation to manifest fever during the first few postoperative days. The majority of these fevers are not associated with any diagnosed infection. Early fever should be followed by an examination of the patient to rule out any obvious early infection. However, empirical antibiotic administration is not indicated for an otherwise well postoperative patient with a fever, and the majority of these fevers resolve without a specific diagnosis. Fever that occurs or persists after the fourth or fifth postoperative day has a much higher likelihood of representing a true infection and should trigger a more vigorous effort at diagnosis.

The physical appearance of the incision provides the most helpful information regarding a possible SSI. Local signs of erythema, swelling, and tenderness are usually present. Purulent drainage may occur spontaneously or only after the wound is opened. Flat erythema around an incision without induration or increased tenderness can occur during the first week and does not usually represent infection. If observed, this will usually resolve spontaneously without administration of antibiotics. The erythema may have a local cause such as tape sensitivity or other noninfectious trauma. Considerable evidence demonstrates that antibiotics begun after a surgical procedure and continued for long periods after the procedure do not prevent or treat SSI.

TREATMENT

When the diagnosis of SSI is made, the incision must be opened for evacuation of the infected material. This is the single most important element of treatment. Although it is common to administer an antimicrobial agent when an SSI is drained, there are actually no data supporting the necessity of this practice. Studies of the management of subcutaneous abscesses found no additional benefit over incision and drainage from the addition of antimicrobial agents, and the only study of SSI management that looked at this issue found no benefit to the addition of antibiotics. If evidence for an invasive aspect of the infection is absent with local erythema and induration less than 5 cm from the wound edges, and if the patient does not exhibit signs of a major systemic response (temperature <38.5° C, pulse <100, white blood cells [WBCs] <12,000) then it is quite reasonable to omit any antibiotics. If there is a marked local or systemic reaction, then administration of antibiotics for a few days is reasonable although unstudied. For clean procedures the most common infecting organisms are skin flora, and a first-generation cephalosporin or penicillinase-resistant penicillin would be reasonable as long as there is not a significant methicillin-resistant *Staphylococcus aureus* (MRSA) problem in the local institution and the patient has no risk factors for MRSA (recent hospitalization, previous MRSA, or recent antibiotics). If the operation was clean-contaminated or contaminated or involved incision in the axilla or perineum, then a drug choice that provides activity against coliforms and anaerobes would be indicated.

When the incision is opened it should be inspected for necrotic tissue and foreign bodies, which should be debrided or removed. Small bits of infected tissue will separate over time with dressing changes and do not need aggressive debridement. When an SSI is drained it should be examined shortly afterward by a surgeon familiar with the original operative procedure. If the original operation entered the abdominal or thoracic cavity, the integrity of the abdominal or chest wall closure should be confirmed. If these are involved, it is a deep incisional SSI, and particular care must be exercised to prevent evisceration or damage to underlying viscera. Typically a wound will be managed with a gauze dressing changed two or three times per day initially and then less often as the wound cleans up. Most SSI are left open to heal by secondary intention. The dressings should not be packed tightly into the incision but should be placed so that all surfaces of the wound are in contact with the dressing. Dressings placed forcefully increase pain and retard wound healing.

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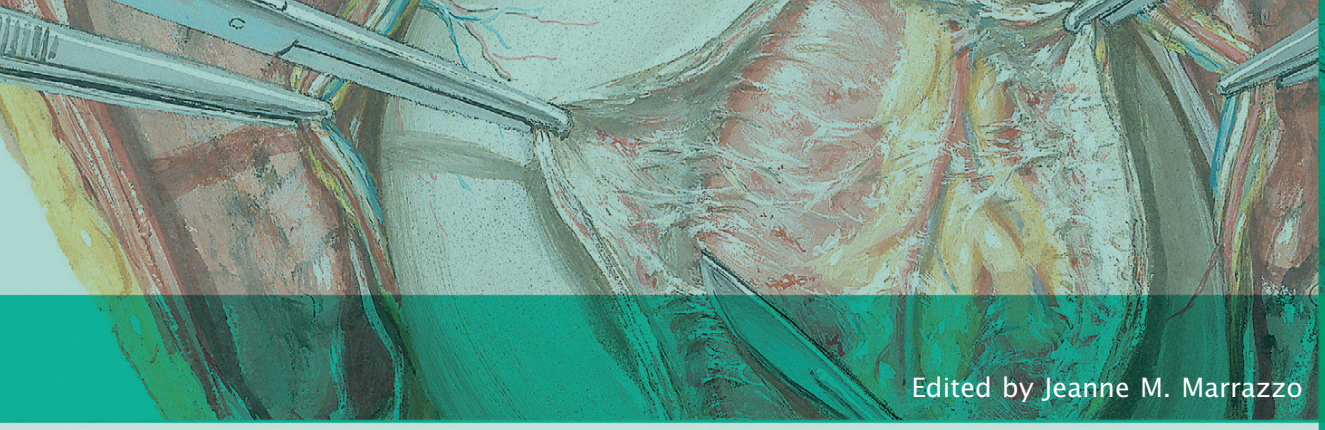

SECTION VI

Edited by Jeanne M. Marrazzo

Sexually Transmitted Infections

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Introduction to Sexually Transmitted Infections

Jeanne M. Marrazzo

53

It has been nearly 15 years since the Institute of Medicine published the landmark report entitled *The Hidden Epidemic: Confronting Sexually Transmitted Diseases*. In that document, an august committee articulated a vision statement to guide its deliberations:

An effective system of services and information that supports individuals, families, and communities in preventing STDs, including HIV infection, and ensures comprehensive, high-quality STD-related health services for all persons.

The committee concluded that four major strategies should form the public and private sector response to what was then recognized as the growing (yet still hidden) epidemic of sexually transmitted infections (STIs): (1) overcome barriers to adoption of healthy sexual behaviors; (2) develop strong leadership, strengthen investment, and improve information systems for STI prevention; (3) design and implement essential STI-related services in innovative ways for adolescents and underserved populations; and (4) ensure access to and quality of essential clinical services for STIs.

Since those ambitious strategies were published, how has the approach to managing and preventing STIs changed? How has the epidemiology of these important infections changed? And most important for readers of this section, has the fourth strategy been addressed? Ensuring the quality of essential clinical services directly touches on the skills of providers of clinical care to people concerned about, at risk for, or manifesting STI-related clinical syndromes.

The need for effective prevention and management of STIs, including human immunodeficiency virus (HIV) infection, remains an exceedingly high priority, both internationally and domestically. The United Nations office on acquired immunodeficiency syndrome (UNAIDS) reported in 2008 that although the rate of new HIV infections has fallen in several countries, these favorable trends are at least partially offset by increases in new infections in others. Equally alarming, the proportion of HIV infections in women is increasing in several countries. In 2008 the U.S. Centers for Disease Control and Prevention (CDC) revised its estimates of the annual incidence of new HIV infections in the United States upward by 40%, an increase from an estimated 40,000 new infections annually to approximately 56,000. As graphically emphasized in a related website (www.nineandahalfminutes.org), in the United States a person is infected with HIV every 9½ minutes. Unfortunately, a large proportion of new HIV infections continue to be diagnosed in late stages of the disease. This fact highlights the need for clinicians to remain familiar with recognition and management of the common opportunistic infections that define clinical AIDS.

In the United States in 2006, most new HIV infections occurred in men who have sex with men (MSM), a population that also continues to sustain the highest incidence of syphilis—an infection many physicians had experience with primarily in the pre-AIDS era, and one completely new to many young physicians. As summarized in the chapter on syphilis, this resurgence has highlighted that clinical recognition of this protean disease—called "the great pretender" by Sir William Osler—continues to present diagnostic and management challenges to those who care for patients at risk, particularly when co-infection with HIV is involved. Persons with HIV are more likely to have atypical manifestations of the genital ulcerations caused by *Treponema pallidum* and atypical results of diagnostic serology tests, and very probably have an increased risk of neuroinvasive disease because of this pathogen.

Apart from HIV, rates of other reportable STIs either have not declined or have actually increased in the last decade. In 2007, more than 1.1 million diagnoses of *Chlamydia trachomatis* were reported to the CDC. Despite this, interventions to detect this common infection in populations most at risk are infrequently performed. For example, rates of routine annual screening for genital chlamydial infections in young women, especially adolescents, remain suboptimal, and many women at low risk (primarily those over age 30 years without other indications) are tested unnecessarily. Moreover, recommendations to routinely retest infected persons 4 to 6 months after treatment (a practice termed *repeat testing*, which is distinct from test of cure) are not frequently adhered to, despite the fact that this approach detects repeat infection in approximately 15% to 40% of those tested.

In 2007, no decline was seen in the number of reported cases of gonorrhea in the United States. Although the failure to note an increase might be viewed in a positive light, the relentless evolution of antimicrobial resistance in *Neisseria gonorrhoeae* continues to present a major challenge. Fluoroquinolones, which offered a new class of effective single-dose oral therapy for this organism in the 1990s, are no longer effective owing to widespread resistance, a trend especially notable in MSM. Providers are now effectively left with only a single class of antibiotics—the cephalosporins—that reliably treat this infection. Concern for nascent development of resistance to this class—a phenomenon that has already been reported—is so great that the most recent CDC sexually transmitted disease (STD) treatment guidelines (2010) for treatment of uncomplicated gonorrhea recommend the use of parenteral (intramuscular) cephalosporin (ceftriaxone) at an increased dose (250 mg) from that recommended in the previous edition 4 years ago. Alternatives to cephalosporin are few, and prospects for future drug development are not presently encouraging.

As noted previously, syphilis is enjoying a resurgence in MSM, especially those co-infected with HIV, but rates of syphilis in the last several years have increased for all races and ethnicities (with the exception of Asians/Pacific Islanders). Finally, sexual transmission of hepatitis C has been increasingly recognized in MSM who report sexual practices involving exposure to blood or even minimal trauma to the rectal mucosa.

These worrisome trends emphasize the need for physicians to be aware of emerging STI-related challenges and of the availability of guidelines and tools to help manage their patients. The CDC STD treatment guidelines have recently been updated. In the 4 years succeeding the previous version, there have been several developments that clinical providers should be aware of. These include very positive developments, such as the licensure and widespread uptake of immunization against several common genital human papillomavirus (HPV) types for women and men. Male circumcision has been validated in three large clinical trials in sub-Saharan Africa as a potent prevention tool against acquisition of HIV and some STIs. Most recently, clinicians working in the field of STI prevention received much-needed encouragement about vaginal microbicides as a vehicle to deliver antiretroviral therapy to reduce the risk of HIV and herpes simplex virus type 2 (HSV-2) acquisition. When used before and after vaginal intercourse, a gel containing tenofovir (1%), a reverse transcriptase inhibitor commonly used to treat HIV infection as part of oral combination antiretroviral therapy, reduced the risk of HIV acquisition in women in South Africa by approximately one third. The reduction in risk of HIV acquisition was even higher—one half—in women who had good adherence to the gel. In an unexpected finding, pericoital use of tenofovir gel also reduced the risk of acquiring HSV-2 infection by one half, as well. These encouraging findings may open the door further to the development of novel topical preventive therapies that could help stem the tide of incidental HIV, and possibly other STIs, until an effective vaccine is available.

The excellent chapters that make up this section cover all of these developments and more. Against the backdrop of providing key epidemiologic trends for each disease, the authors have emphasized that clinical recognition and diagnosis of these infections are not always straightforward. Moreover, therapeutic management of some STIs can be complicated by limited diagnostic capability, co-infections, and immune compromise resulting from HIV infection. In addition to biomedical management of the individual patient who is affected by STIs, clinicians must remember that prevention of these infections requires combinations of biomedical, behavioral, and structural interventions. Among the most promising approaches is expedited partner management, a strategy that allows for treatment of sex partners without in-person evaluation. This approach has been widely adopted and should provide a major tool to control the stubborn epidemics of chlamydia and gonorrhea, in particular.

Although the Institute of Medicine's vision for controlling the hidden epidemic of STIs has not been fully realized, the healthcare field is in an exciting period of renewed hope for advances in diagnosis, therapy, and prevention of these stubborn infections. The state-of-the-art information in the chapters that follow will undoubtedly assist clinicians in contributing to the overall goal of improving the community's sexual health through recognition, management, and prevention of STIs.

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Sexually transmitted disease treatment guidelines, *MMWR Morb Mortal Wkly Rep* 2010 (in press). *These guidelines, derived from comprehensive evidence-based and expert review, are an invaluable resource in assisting clinicians in appropriate diagnosis and management of STIs.*

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Trichomoniasis

Jill S. Huppert

54

ABSTRACT

Trichomoniasis is a sexually transmitted genitourinary infection caused by a motile, pear-shaped parasitic protozoan, *Trichomonas vaginalis*. For many years, efforts to describe the epidemiology and consequences of infection with *T. vaginalis* have been hampered by insensitive diagnostic methods. For example, even though studies published in the 1990s showed that the wet mount is only 36% to 60% as sensitive as culture to detect *T. vaginalis*, wet mount remains the most commonly used test.

Recently, interest in trichomoniasis has escalated owing to evidence that trichomoniasis is more common than gonorrhea, is often asymptomatic, and may increase one's susceptibility to human immunodeficiency virus (HIV). New diagnostic modalities are now available but are rarely used in clinical practice. The use of better diagnostic methods and more widespread testing could greatly reduce the epidemic of this easily treated infection.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Trichomoniasis is estimated to be the most highly prevalent nonviral sexually transmitted infection (STI) in the United States and in the world. Some experts estimate that in 1999, 140 to 180 million new cases occurred worldwide, with 5 to 7.4 million cases in the United States alone. It is difficult to assess the true incidence and prevalence of *T. vaginalis* for several reasons:

- A representative sample of the population is rarely tested. Because there are no screening guidelines, testing depends on local practice and is usually limited to symptomatic women.
- There are no reporting requirements for *T. vaginalis*.
- Laboratory estimates are not produced because the most common test for *T. vaginalis* is a wet mount (microscopic examination of a saline preparation of vaginal discharge), which is generally performed as an in-office test.
- The wet mount has low sensitivity for detection of *T. vaginalis* compared with culture or nucleic acid amplification tests (NAATs). Therefore prevalence estimates for trichomoniasis vary by the population studied and the diagnostic test used.

Recently, two population-based studies provided more precise estimates of the prevalence of *T. vaginalis* in the United States, and two small longitudinal studies allowed for estimation of the incidence in young women. In the 2001-2004 National Health and Nutrition Examination Survey (NHANES), 3754 women (aged 14 to 49 years) provided a self-obtained vaginal swab for NAAT testing. *T. vaginalis* was present in 3.1% of women, a prevalence higher than that of chlamydia (2.5%) or gonorrhea (0.33%). Applying population weights yielded a point prevalence estimate of 2.3 million cases of trichomoniasis in women. Similar results were seen in the National Longitudinal Study of Adolescent Health (Add Health), in which over 11,000 women and men aged 18 to 26 years provided a urine sample for NAAT testing (2005). In this study, *T. vaginalis* infected 2.8% of women and 1.7% of men. In one of the few studies to measure incidence of trichomoniasis, authors described a 6% incidence of *T. vaginalis* in the year after a negative NAAT result and a 30% recurrence of *T. vaginalis* in the year after a positive test result in a cohort of 268 sexually active adolescent women. Another short-term study reported that the incidence of trichomoniasis (7.4%) was higher than the incidence of chlamydia (4.4%) in young black women with asymptomatic bacterial vaginosis (BV). These studies provide evidence that the prevalence and incidence of trichomoniasis are similar to those of *Chlamydia trachomatis* and far higher than those of gonorrhea in U.S. women.

Individual studies have suggested that there is disparity in the geographic distribution of *T. vaginalis* in the United States. This variation was confirmed in the Add Health study, in which the prevalence of *T. vaginalis* was highest in the South (2.8%), followed by the Midwest (2.2%) and the Northeast (2%), and was lowest in the West (1.4%).

RISK FACTORS

Risk factors for trichomoniasis include female gender, African American race, age over 30 years, and various healthcare settings. In addition, some measures of socioeconomic status, behaviors, and vaginal conditions are associated with *T. vaginalis* infection in women (Box 54-1).

In the Add Health study, female gender and African American race were associated with a higher prevalence of trichomoniasis. The proportion of African Americans affected by *T. vaginalis* was 6.9%, compared with 1.2% of white subjects, and the highest prevalence was seen in African American women (10.5%). Similarly, among adult women in the United States, the proportion of African-American women with trichomoniasis was 13.3%, compared with 1.3% of whites.

The association between *T. vaginalis* and race is not found in all studies. Even in population surveys, some of this relationship can be explained by socioeconomic status, access to healthcare, and sexual risk behaviors. For example, in the NHANES study, *T. vaginalis* prevalence was highest in poor women and those with less than high school education.

Age can also be a determining factor in *T. vaginalis* pervasiveness. It is important to note that in contrast to chlamydia, trichomoniasis is more common in older women and men. In

Box 54-1 Factors Associated with *Trichomonas vaginalis* Infection

- Female gender
- African American race
- Age >30 years
- Poverty
- Less than high school education
- Southern United States
- History of sexually transmitted infection or trichomoniasis
- Multiple sexual partners
- Inconsistent condom use
- Douching
- Substance abuse
- Incarceration

population-based studies of Australian Aboriginal women and African American women in the United States, *T. vaginalis* prevalence increases with age and reaches a peak in women over 40 years old. In the Add Health sample, the highest prevalence of *T. vaginalis* (4%) was seen in women and men older than 25 years of age. For men seen in STI clinics, age over 30 years is a consistent risk factor for trichomoniasis. *T. vaginalis* may behave differently than *C. trachomatis* in women because *T. vaginalis* is a vaginal pathogen and does not require the immature cervix favored by chlamydia. In addition, the lack of systematic screening and prolonged duration of infection may result in an increased prevalence of *T. vaginalis* with age.

The prevalence of *T. vaginalis* in certain clinical settings is even higher than population estimates, which suggests that risk factors other than gender and race affect the distribution of infections. In men, the proportion with *T. vaginalis* ranges from 10% to 17% in men seen in STI clinics and up to 58% in young African American men in job-training programs. In women, the prevalence of *T. vaginalis* is reported at 10% to 18% in student health, adolescent, or prenatal clinics, 26% to 32% in STI clinics, 38% to 43% among substance abusers, and nearly 50% among pregnant prisoners.

As with all STIs, sexual behaviors increase the risk of contracting this pathogen. In women these behaviors include multiple partners, older partners, and history of prior STI. In a large STI clinic in the southern United States, those reporting a sexual partner with *T. vaginalis* or a history of substance use had higher prevalence of *T. vaginalis* than those without such histories. An additional risk behavior noted in the NHANES study was douching: *T. vaginalis* prevalence was higher in women who reported this practice.

Some vaginal conditions such as BV may be a risk factor for trichomoniasis, but the mechanism is unclear. Trichomoniasis and BV share clinical signs, risk factors, and outcomes. Clinical signs of BV include a vaginal pH >4.5 and positive amine test, both of which can be found in trichomoniasis. Many studies of BV used only a wet mount to exclude *T. vaginalis*, which may have resulted in underestimation of trichomoniasis. When culture or NAAT is used to define trichomoniasis, 50% to 84% of women with *T. vaginalis* meet Gram stain criteria for BV. Conversely, of those with a Gram stain diagnosis of BV, 20% to 30% had culture-proven *T. vaginalis*. Accordingly, when BV is suspected clinically, it is important to test for *T. vaginalis* using the most sensitive method available.

In men, predisposing factors other than age and race are less well described than in women. Among men in STI clinics, sexual contact with *T. vaginalis*, history of prior STI, and lack of condom use are all associated with a higher prevalence of trichomoniasis.

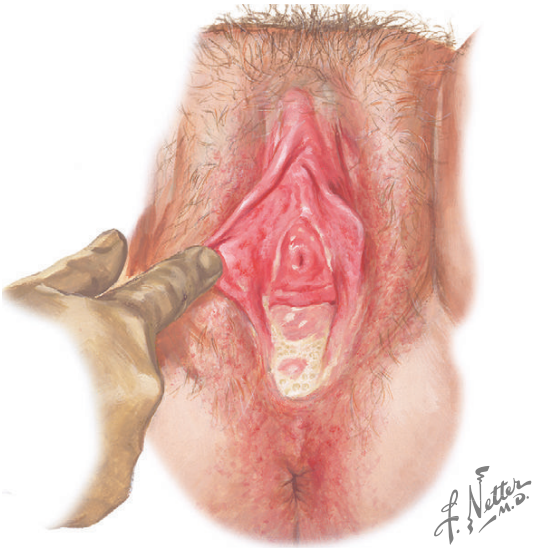
The primary route of transmission is via vaginal sexual intercourse. Inoculation studies have determined that the usual interval between exposure and infection is 5 to 28 days. *T. vaginalis* is easily transmitted between sexual partners. With culture used to detect infection, 80% to 100% of female partners of infected men, and up to 50% of male partners of infected women, have been found to be positive for *T. vaginalis.* When the urine sediment of the male partners was tested for *T. vaginalis* using both culture and polymerase chain reaction (PCR), 70% of male contacts of infected women had trichomoniasis. There is limited information on transmission of *T. vaginalis* via nonheterosexual contact. There are case reports of *T. vaginalis* transmitted via oral sex in HIV-positive men and between lesbian women. Vertical transmission has been reported. Female infants can acquire genital *T. vaginalis* when passing through an infected birth canal, and there are a few reports of neonatal pneumonia that can be attributed to *T. vaginalis*. Nongenital infections may be rare because of the specific environment that *T. vaginalis* requires for growth or because of the difficulty in detecting infections from these sites. Because *T. vaginalis* can survive in saline and on toilet seats or clothing for 20 to 45 minutes, fomite transmission has been speculated to occur. However, such transmission is exceedingly rare. Therefore detection of *T. vaginalis* should be taken as evidence of sexual contact.

CLINICAL FEATURES

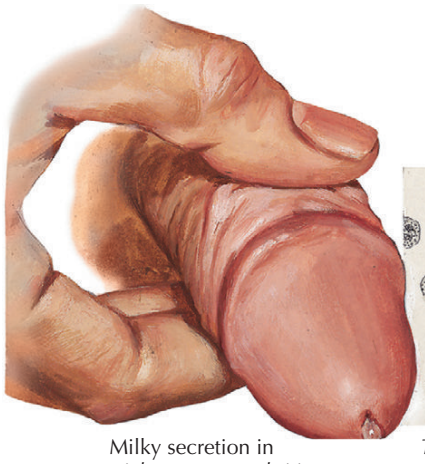
The majority of men and women infected with *T. vaginalis* report no symptoms. In older studies, 50% of women with culture-proven *T. vaginalis* were asymptomatic; in population studies using NAATs, over 90% of women and men were asymptomatic.

When symptoms do develop in women, the typical presentation is vaginal discharge or odor and, less frequently, itching. *T. vaginalis* is found as a cause in 12% to 30% of women with vaginal symptoms. Urinary symptoms can accompany STIs, and it is possible for urinary tract infections (UTIs) and STIs to occur concurrently. Among adolescent women with urinary symptoms, those without a UTI have been found to be more likely to have trichomoniasis (26%) than those with a UTI (9%), and 43% of those with sterile pyuria had trichomoniasis. Therefore an evaluation for *T. vaginalis* is recommended for women with urinary symptoms who are at risk for STIs. Some women with trichomoniasis may have abnormal bleeding, postcoital spotting, or a brown discharge. This bleeding may result from disruption of the vaginal or cervical epithelium that occurs in some *T. vaginalis* infections.

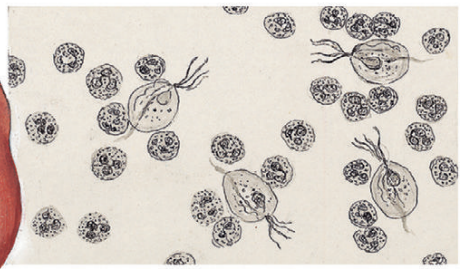
In addition to symptoms of infection, signs that should raise suspicion for trichomoniasis in women are an elevated vaginal pH, the presence of amines, vaginal leukocytosis, and vulvar erythema (Figure 54-1). The characteristic frothy green



Trichomonas vaginal discharge



Milky secretion in *trichomonas urethritis*



Trichomonas vaginalis seen with white cells in wet mount of fresh specimen from vaginal or urethral discharge

Figure 54-1 Trichomoniasis discharge in females and males.

Table 54-1 Diagnostic Features of Various Infections That May Cause Vaginal Symptoms

	Microscopic Examination			*Other Tests*			
	CLUE CELLS	**WHITE BLOOD CELLS**	**PATHOGEN**	**PH**	**AMINE OR "WHIFF"**	**SIALIDASE**	**TV RAPID ANTIGEN**
Normal discharge	<20%	<6 per HPF	Absent	≤4.5	Absent	Negative	Negative
Candida (yeast)	<20%	Variable	Yeast form (buds or hyphae)	≤4.5	Absent	Negative	Negative
Bacterial vaginosis	>20%	<6 per HPF	Absent	>4.5	Present	Positive	Negative
Trichomoniasis	>20%	>10 per HPF	Motile trichomonads	>4.5	Present	Negative	Positive
Possible chlamydia or gonorrhea	>20%	>10 per HPF	Absent	≤4.5	Absent	Negative	Negative

HPF, High-power field; *TV, Trichomonas vaginalis.*

discharge (Figure 54-2) is seen in about 10% of culture-proven infections. The classic colpitis macularis (also known as "strawberry cervix") results from punctate hemorrhages on the cervix (Figure 54-3) and is observed in less than 2% of culture-proven infections. In recent population studies using NAATs, clinical signs were not recorded.

The differential diagnosis of vaginal symptoms includes *T. vaginalis*, candidiasis, BV, and normal (physiologic) variation. Cervicitis, typically caused by *C. trachomatis*, *N. gonorrhoeae*, and less frequently herpes simplex virus (HSV), can produce copious discharge that may manifest as vaginal discharge. Assessment of vaginal pH and wet mount can help to distinguish these infections and inform the choice of empirical therapy while other test results are pending (Table 54-1).

As with women, most men with trichomoniasis are asymptomatic. When symptoms do appear, the typical presentation is nongonococcal urethritis (NGU) characterized by dysuria and urethral discharge (see Figure 54-1) Signs are nonspecific and include a visible discharge and a positive urine leukocyte esterase test result. The differential diagnosis includes other STIs associated with NGU, including *C. trachomatis*, *Mycoplasma genitalium*, and HSV.

DIAGNOSTIC APPROACH

Diagnostic methods differ for men and women (Table 54-2). In women the most commonly used method is the microscopic observation of *motile* trichomonads on the wet mount. Diagnosis can also be made using cytologic characteristics on the Pap smear; however, liquid-based cytology has considerably improved sensitivity and especially specificity over traditional cytology. The wet mount is less sensitive than culture (36% to 60% sensitive). Culture has often been used as the diagnostic gold standard, yet it requires selective media, a microbiology laboratory, and up to 5 days for final reading, and it is not 100% sensitive. A single culture using any of the selective media (such as Diamond's, Trichosel, or the InPouch modifications) is approximately 85% sensitive when compared with three cultures per specimen. Using two specimens from a single patient will increase the yield of culture by about 10%.

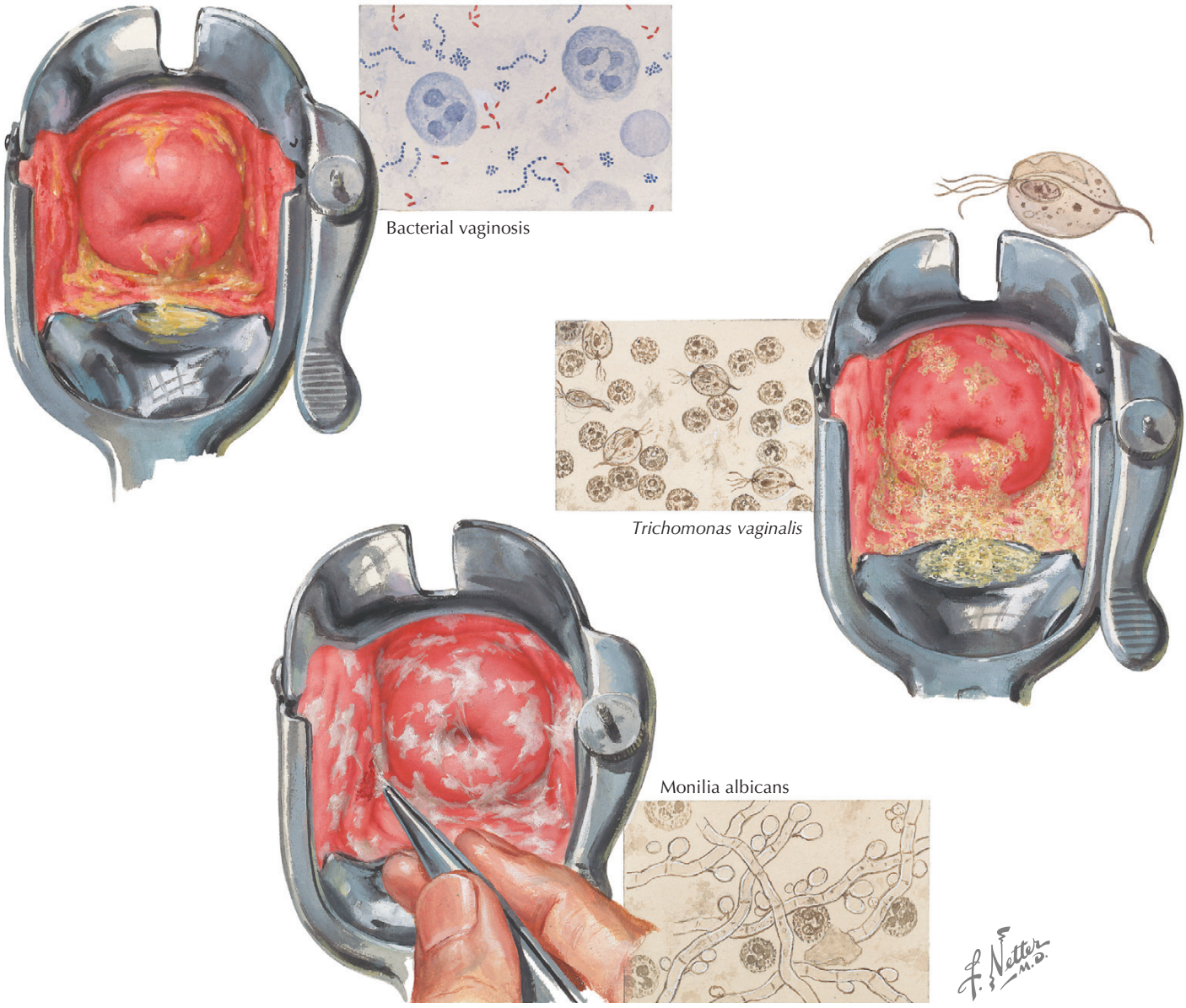


Figure 54-2 Vaginitis.

The currently available rapid antigen test is a point-of-care, lateral-flow test strip device that detects *T. vaginalis* membrane proteins in 10 minutes. It is approved for use on a direct vaginal swab or on the saline preparation used for the wet mount. A comparison of *T. vaginalis* tests using latent class analysis showed that the sensitivity (83% to 90%) of the rapid test was significantly better than that of the wet mount and similar to that of culture and NAAT, with 100% specificity.

An unamplified ribonucleic acid (RNA) test is commercially available and is reported to be 80% to 90% sensitive and 99% specific for *T. vaginalis*, compared with wet mount. However, at present there are no studies comparing it to NAAT or culture; therefore the true sensitivity may be closer to 50% to 60%. Although listed as a rapid test, it requires a full laboratory and 30 to 60 minutes to perform.

Many researchers have developed in-house NAATs to detect *T. vaginalis*. In general, NAATs perform equally well on self- or clinician-obtained vaginal swabs and may be performed on urine samples. Transcription-mediated amplification (TMA) (Aptima, Gen Probe, San Diego, California) is a NAAT method that uses analyte-specific reagents for *T. vaginalis*. It is commercially available but not yet approved by the U.S. Food and Drug Administration (FDA) for diagnosis of *T. vaginalis*. It is presently mainly used in research settings, although it can be validated by individual laboratories for clinical use. TMA has a high sensitivity (96.7%) and specificity (97.5%) compared with in-house PCR detection of *T. vaginalis*.

Because of the limitations of current test methods, a stepwise approach may be beneficial in women. According to the 2010 sexually transmitted disease treatment guidelines published by

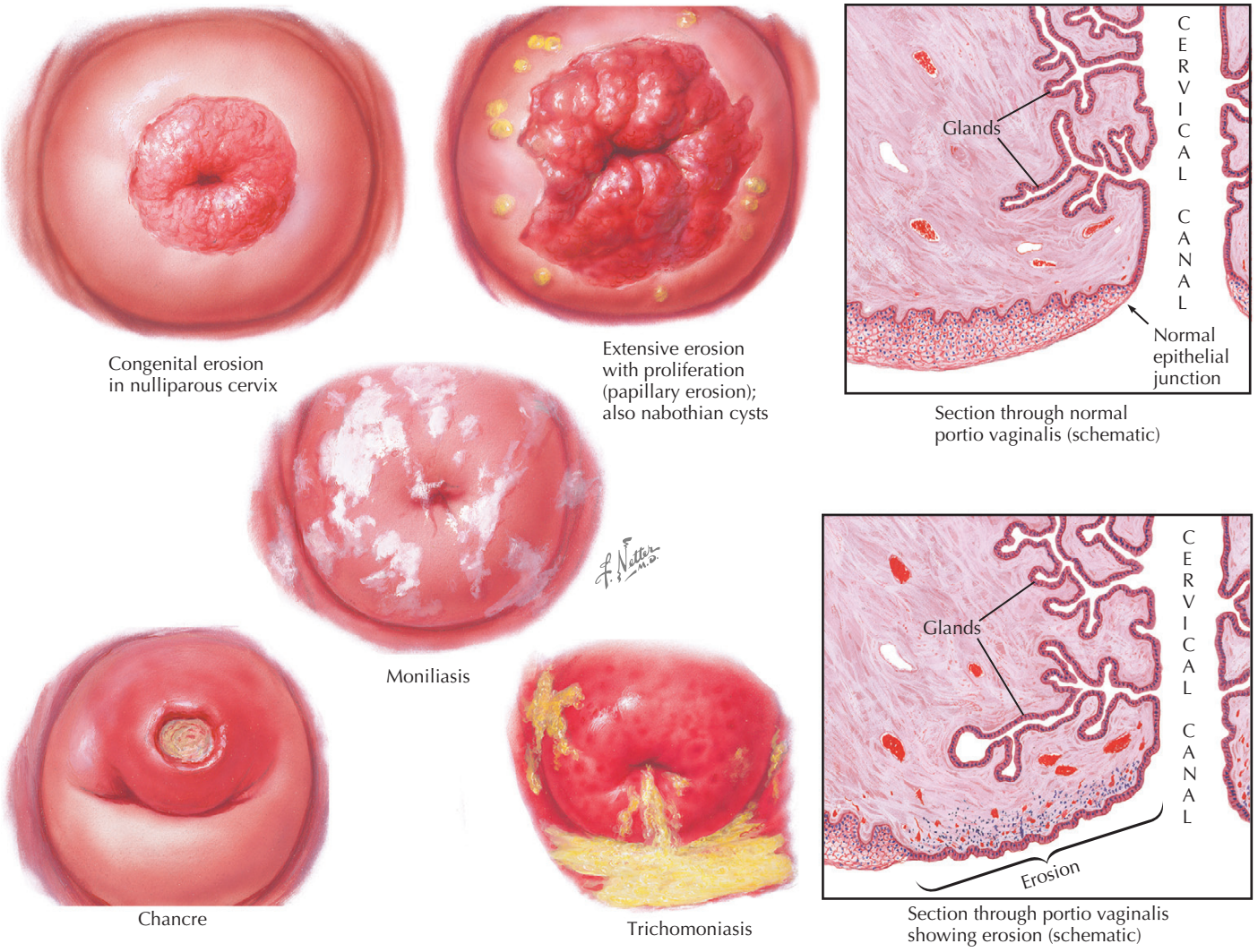


Figure 54-3 Cervicitis.

Table 54-2 Comparison of Diagnostic Methods for *Trichomonas vaginalis*

DIAGNOSTIC METHOD	SENSITIVITY
For Women	
Wet mount	36% to 60%
Conventional pap smear	36% to 55%
Liquid-based pap smear	61% to 90%
Culture	80% to 85%
Rapid antigen	83% to 90%
NAAT	85% to 98%
For Men	
Urinalysis	<20%
Culture (one site)	30% to 66%
Culture (three sites)	60% to 90%
NAAT	97% to 98%

NAAT, Nucleic acid amplification test.

the Centers for Disease Control and Prevention (CDC), culture is recommended when *T. vaginalis* is suspected but not seen on wet mount. Some authors have suggested limiting the additional culture to a subset of women, such as African Americans, those reporting contact with a sexual partner with *T. vaginalis*, or those with a history of substance use. In an STI clinic, adding culture after a negative wet mount to the evaluation of women with any of these three factors resulted in detection of 97.3% of *T. vaginalis* infections. However, in a study of adolescent women, neither race nor prior *T. vaginalis* were predictors of trichomoniasis in women who were wet mount negative. Wet mount followed by a rapid test detected 86% of infections. In both studies, neither clinical laboratory data (such as the presence of white blood cells or clue cells on the wet mount) nor patient-reported symptoms were reliably associated with *T. vaginalis* diagnosis.

We suggest the following diagnostic algorithm for women (Figure 54-4).

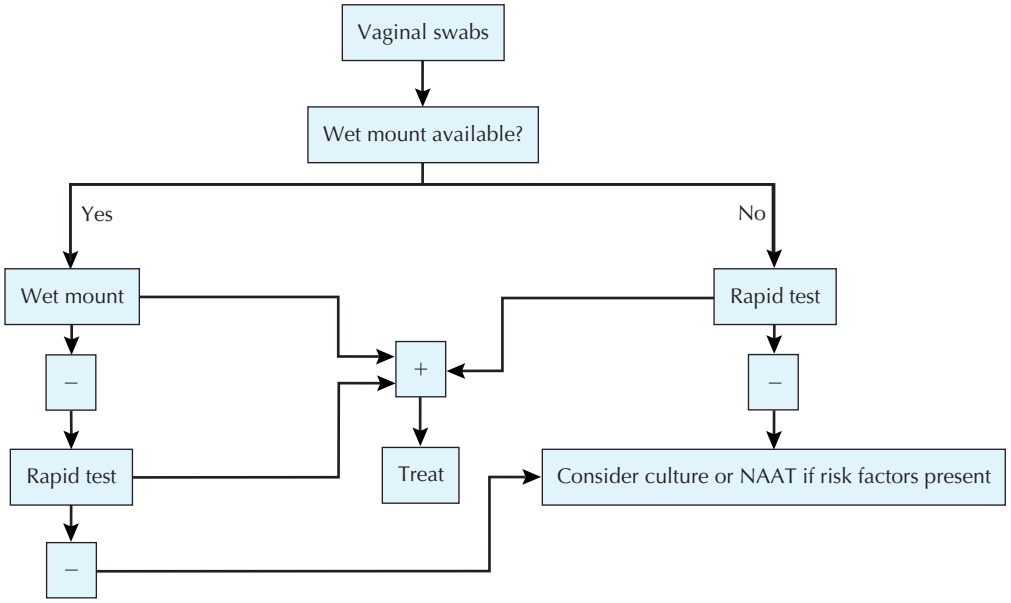


Figure 54-4 Diagnostic algorithm for women.

1. Because the wet mount is a useful and inexpensive test, all women at risk for STIs should have a wet mount performed. When the wet mount swab is obtained, an additional primary vaginal swab could be obtained and held either in saline or as a dry swab.
2. If the wet mount is negative for trichomonads, a rapid antigen test can be performed using the saved primary swab or the used wet mount swab.
3. If both wet mount and rapid antigen test results are negative, consider inoculating a culture using the saved primary swab if one is highly suspicious for *T. vaginalis* or in settings where the prevalence of *T. vaginalis* is high. If NAAT is available, a vaginal swab specimen may yield better detection than a urine specimen.

The diagnosis of *T. vaginalis* infection in men is more difficult and less studied than in women. In many settings the only test available is direct microscopy of a urine sample. Culture can be performed with specimens from urethral swabs, urine sediment, or a semen sample. Culture of both a urethral swab and urine sediment increases the detection of trichomoniasis by 50% over either sample alone; addition of semen culture adds another 25% of cases. Culture in men requires the full 5 days for reading, whereas in women over 95% of cultures are positive within 3 days. NAATs are more sensitive than culture for *T. vaginalis* in men, and a urine sample may be more sensitive that a urethral swab.

In men, we suggest the following diagnostic approach: obtain a urethral swab and a urine sample. Perform direct microscopy of the urine sediment. If negative, the urine sediment or urethral swab can be used to inoculate a culture. To increase yield, consider inoculating the culture with both the urine sediment and the urethral swab. If NAAT is available, it can be performed on the residual urine sample. Check with the laboratory to determine whether whole urine or urine sediment is required for the specific NAAT to be used.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Trichomoniasis can be effectively treated with a single 2-g dose of an oral nitroimidazole (metronidazole or tinidazole). An alternate regimen is metronidazole, 500 mg twice daily for 7 days. Single-dose therapy produces an equivalent cure rate, better compliance, and fewer gastrointestinal side effects than a multidose regimen. However, because older studies reported a 40% failure rate with single-dose metronidazole in men, some experts prefer the multidose treatment in men. Tinidazole has fewer gastrointestinal side effects than metronidazole. Topical medications have high failure rates (>50%). Treatment of sex partners (those with sexual contact with the index patient in the 60 days before diagnosis) is recommended, and the patient should be advised to abstain from intercourse until both partners have completed therapy. In vitro studies suggest that 5% to 9% of *T. vaginalis* isolates demonstrate some resistance to metronidazole. Patients with suspected resistant *T. vaginalis* can be treated with longer courses of metronidazole or a trial of tinidazole or referred to CDC experts for consultation.

PROGNOSIS

Untreated, trichomoniasis has been estimated to persist for up to 4 months in men and 5 years in women. In one longitudinal study of adolescent women, untreated *T. vaginalis* detected by NAAT could persist for up to 12 weeks. Approximately one third of women developed symptoms and sought care. In addition, 27% of NAAT-positive infections resolved without treatment.

The prognosis for an episode of vaginal or urethral infection is excellent. Treatment results in clinical and microbiologic cure in 80% to 95% of cases. In clinical practice, treatment failures are more likely to result from noncompliance or reexposure to an untreated partner than from resistant organisms. In one series, 30% of infected women had at least one more episode

within a year. However, women with trichomoniasis are at increased risk for other health consequences such as other STIs, pelvic inflammatory disease (PID), poor obstetric outcomes, and cervical cancer. Moreover, the high rate of reinfection among women whose infection was adequately treated but who were reinfected by untreated sex partners prompted the CDC to advise repeat testing of all women with trichomoniasis approximately 3 to 6 months after treatment.

T. vaginalis is often considered a biologic marker for high-risk sexual behavior. Not surprisingly, trichomoniasis is often associated with other STIs. In cross-sectional studies, trichomoniasis often coexists with chlamydia and gonorrhea. In the Add Health study, women with *T. vaginalis* infection were four times more likely to be co-infected with *Chlamydia* than women without *T. vaginalis*. Similarly, cross-sectional studies showed *T. vaginalis* infection was associated with HSV and HIV. In the past, it was thought that these co-infections were a result of risk behaviors. However, the associations persist even after controlling for risk behaviors, suggesting that other factors play a role. These associations could be explained by the increased susceptibility of the host resulting from the vaginal inflammation caused by *T. vaginalis*.

In support of this, several longitudinal studies have confirmed a temporal relationship between *T. vaginalis* and serious viral STIs. For example, women infected with *T. vaginalis* are more likely to acquire HIV and HSV. Trichomoniasis also doubles the risk of persistent human papillomavirus (HPV) infection in women. Finally, in both women and men with HIV, co-infection with *T. vaginalis* increases HIV shedding.

There is conflicting evidence regarding the role of trichomoniasis in adverse reproductive health conditions such as PID, poor obstetric outcomes, and cervical cancer. One reason for these conflicting findings is that many prior studies used insensitive diagnostic methods such as the wet mount, which could bias results toward the null. Evidence that *T. vaginalis* contributes to the development of PID includes the following:

1. *T. vaginalis* is associated with elevated vaginal leukocytes and neutrophil defensins, both of which are independently associated with the histologic diagnosis of PID.
2. Among women infected with *C. trachomatis*, those with coexisting *T. vaginalis* infection were more likely to be diagnosed with clinical PID than those without *T. vaginalis* (odds ratio 4.7).
3. Among African women, *T. vaginalis* was associated with a 1.5-fold increase in clinically diagnosed PID (95% confidence interval 1.1 to 2.1), whereas BV, chlamydia, and gonorrhea were not associated with PID.

However, a limitation of these studies is that clinical PID is a less specific outcome measure than PID proven by an endometrial biopsy or laparoscopy.

The literature on trichomoniasis and pregnancy outcomes is also contradictory. For example, several studies showed an increase in preterm birth and low–birth-weight infants in women infected with *T. vaginalis* (using culture or wet mount). However, treatment of culture-positive women with repeated high-dose metronidazole did not reduce the incidence of preterm birth in the Vaginal Infections in Prematurity study. In another study, treatment of trichomoniasis in pregnancy with a standard dose of metronidazole increased the odds of low birth weight (odds ratio 2.5) but not preterm birth or mortality. Recently, reevaluation of the Vaginal Infections in Prematurity study revealed that race may play a role: black women with trichomoniasis were at higher risk for preterm birth (odds ratio 1.2) than black women without trichomoniasis.

Several reports have linked trichomoniasis to HPV and cervical cancer. In a meta-analysis of 24 studies, the combined summary relative risk of cervical dysplasia was 1.9 for women with *T. vaginalis* compared with those without. In a prospective, longitudinal cohort study of 19,114 Finnish women with Pap smear diagnosis of gynecologic infections (HPV, HSV, and *T. vaginalis*) and 10 years of follow-up, both HPV (odds ratio 5.5) and trichomoniasis (odds ratio 6.4) were associated with dysplasia. A more recent study showed that young women with trichomoniasis were less likely to clear HPV than those who were not infected. These findings suggests that *T. vaginalis* is not in itself oncogenic, but that it alters the local flora and host immune responses so that HPV is able to establish persistent infection, which is known to increase a woman's risk for dysplasia.

PREVENTION AND CONTROL

The keys to prevention and control of this widespread and easily treatable STI are improved detection methods and the development of screening guidelines for asymptomatic individuals. Because *T. vaginalis* infection is so widespread, and it increases the risk of both acquiring and shedding HIV, control of *T. vaginalis* may be an important strategy to decrease the HIV epidemic.

Establishing an accurate diagnosis for *T. vaginalis* is paramount to understanding its short- and long-term health effects. For women, although several new diagnostic methods are available, they are not widely used. Given the poor sensitivity of the wet mount, it should be used as a screening tool followed by a more sensitive diagnostic test such as a rapid antigen, culture, or NAAT. In women, it is important to differentiate between BV and trichomoniasis; this would be aided by more sensitive and specific tests for BV.

A significant impediment to the control of *T. vaginalis* is the difficulty in detecting infection in men. Direct microscopy is woefully inadequate, and culture is rarely used and requires multiple specimens per subject. NAAT testing has the highest sensitivity, but in the absence of screening guidelines it is unlikely to come to market in the near future.

Because *T. vaginalis* is highly transmissible, strategies to improve partner notification and treatment are essential. Patient-delivered partner therapy is one approach that has been advocated, but it has not yet been proven to be effective for reducing *T. vaginalis* infection. Standard STI prevention strategies, such as advocating monogamy and consistent condom use, should be employed. Because *T. vaginalis* is associated with poverty, strategies that increase access to healthcare and education may decrease the *T. vaginalis* epidemic. Further study is needed to learn whether improved screening and treatment of asymptomatic *T. vaginalis* infections will prevent serious outcomes.

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Wendel KA, Workowski KA: Trichomoniasis: challenges to appropriate management, *Clin Infect Dis* 44(suppl 3):S123-S129, 2007. *Infectious disease experts from the University of Colorado review advances in diagnosis and treatment and the current controversies regarding management of trichomoniasis.*

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention website. Available at: www.cdc.gov/nchhstp/. *The National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) is the branch of the CDC responsible for public health surveillance, prevention research, and programs to prevent and control HIV and acquired immunodeficiency syndrome (AIDS), other STDs, viral hepatitis, and tuberculosis.*

Cochrane Collaboration: Cochrane Reviews. Available at: www.cochrane.org/reviews/index.htm. *This database offers free access to the abstracts and, where available, the plain language summaries of all Cochrane systematic reviews.*

National Network of STD/HIV Prevention Training Centers (NNPTC): NNPTC website. Available at: http://depts.washington.edu/nnptc/index.html. *The NNPTC is a CDC-funded group of regional centers created in partnership with health departments and universities. The NNPTC provides health professionals with state-of-the-art educational opportunities with an emphasis on prevention, with the goal of increasing the knowledge and skills of health professionals in the areas of sexual and reproductive health.*

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Herpes Simplex Virus Genital Infection

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Nicholas J. Moss and Anna Wald

ABSTRACT

Genital herpes is a globally endemic sexually transmitted disease (STD) and the most common cause of genital ulcer disease. Classically, genital herpes manifests as a cluster of painful vesicular or ulcerative mucocutaneous lesions, but such presentations account for a minority of cases, and the clinical manifestations vary widely. Genital herpes is caused by herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2), two closely related but genetically distinct viruses. HSV-2 causes the greater burden of genital disease worldwide, especially in resource-poor settings, and risk factors for HSV-2 acquisition are similar to those of other STDs. Both HSV-1 and HSV-2 establish latent infection in sensory nerve root ganglia and can reactivate from there to cause epithelial recurrences throughout the life of the patient. These recurrences may cause distress because of both the physical discomfort and the patient's fears of potential stigma, rejection by sex partners, and the possibility of long-term medical complications. The majority of infected patients, however, have mild atypical symptoms or no symptoms at all. Asymptomatic persons can still shed virus in the genital secretions and transmit it to their sex partners. The clinical diagnosis of genital herpes is unreliable, and laboratory testing is necessary for definitive diagnosis. Complications of genital herpes infection include aseptic meningitis and, rarely, disseminated herpes simplex infection in which multiple organ systems can be affected. Life-threatening neonatal herpes infection is the most severe consequence of genital herpes infection in women of childbearing age. Genital herpes reactivations and recurrences are more frequent in human immunodeficiency virus (HIV)–infected patients and other immunocompromised individuals. There is no cure, but effective antiviral therapy is available for treatment of active lesions and suppression of recurrences. Counseling patients about the disease should be a part of any management strategy. Although behavioral measures such as condom use provide partial protection against infection, no broadly effective prophylactic or therapeutic vaccine exists at this time.

EPIDEMIOLOGY

Genital herpes infections occur throughout the world in all settings, including developed and developing nations as well as rural and urban populations. HSV-2 causes the majority of genital herpes infections, with an estimated 500 million people infected worldwide. HSV-1 has been reported as an increasing cause of first episodes of genital ulcer disease in sexually active patients in developed countries, where childhood orolabial infection with HSV-1 may be decreasing. Transmission typically occurs during sexual intercourse or other intimate contact between an infected source partner who is shedding virus from a mucosal site or genital skin and an uninfected partner. Infection requires direct contact of virus-containing secretions with mucosal surfaces or breaks in the skin. The virus does not survive for long outside its human host. *Primary infection* refers to the first infection with either HSV-1 or HSV-2 in an immunologically naïve host. Subsequent infection by the heterologous virus is often called *nonprimary initial infection*. For example, a person with *primary infection* by HSV-1 is still at risk for *nonprimary initial infection* caused by sexual transmission of HSV-2.

Because HSV-infected persons are so frequently asymptomatic, most large surveys of HSV epidemiology rely on assays that detect antibodies to HSV-1 and HSV-2 in sera. In the United States, data from the National Health and Nutrition Examination Surveys (NHANES) for 2005 through 2008 suggest an HSV-2 seroprevalence of 16.2% in persons aged 14 to 49 years. This represents a decrease from an HSV-2 seroprevalence of 21% reported in NHANES between 1988 and 1994, as the age of infection has shifted upward. Among those with HSV-2 antibodies in the 2005 to 2008 NHANES surveys, only 18.9% reported having been diagnosed with genital herpes. By contrast, between 1999 and 2004, seroprevalence of HSV-1 was 57.7%, and 1.8% of those individuals had a history of a genital herpes diagnosis.

HSV-2 seroprevalence figures vary widely among different populations. Women are more susceptible to genital HSV-2 infection and bear a greater burden of disease. In the United States, African Americans have the highest HSV-2 seroprevalence. Because the infection persists in the host, seroprevalence also increases with age. The highest HSV-2 seroprevalences, reaching almost 100%, have been reported in persons with HIV infection and in female commercial sex workers, especially in developing nations.

Risk factors for genital herpes acquisition, as with other sexually transmitted infections, include higher number of lifetime sex partners and a history of unprotected sex. It is interesting to note that risk factors prevalent in the community from which one chooses sex partners are more influential than individual sexual behavior in estimating the risk of HSV-2 infection. For example, African American women with few sexual partners remain at increased risk of acquiring HSV-2 because of the prevalence of the infection among African American men. Condom use reduces the risk of HSV-2 acquisition, and prior exposure to HSV-2 appears to protect against subsequent infection with HSV-1 but not vice versa.

CLINICAL FEATURES

Genital infections with both types of HSV have similar presentations. A single episode of genital herpes cannot be attributed to HSV-2 or HSV-1 by history or physical examination alone. The pattern of disease recurrence provides important

information, though, as HSV-2 tends to recur more frequently than HSV-1. With both viruses, true primary episodes are the most severe, followed by nonprimary initial episodes. Recurrent episodes are the least severe. However, substantial overlap exists in the severity of all types of episodes. Symptoms of the primary episode usually occur within 2 to 12 days of inoculation. Serologic studies have shown that some patients may have a delayed presentation and recognize clinical symptoms only months or years after the infection is established. Such a presentation is termed the *first recognized episode*, as serologic testing can document the presence of a mature antibody profile. Many patients who have clinical disease report atypical or mild manifestations that are not recognized as genital herpes by the patient or the health provider.

Primary Episode

Genital herpes manifests classically as a cluster of painful vesicles on an erythematous base. The primary episode can last 2 to 3 weeks. Over this time the lesions progress to form pustules and then shallow ulcers. New lesions form while older ones coalesce and crust over; therefore lesions in various stages are found at the time of presentation. Lesions do not normally bleed and usually heal without scarring. Mucosal lesions are typically ulcerative without a detectable vesicular stage. Lesions can occur on the external genitalia of either sex as well as on the upper thighs, buttocks, and perianal region (Figure 55-1). Of note, primary lesions are often bilateral, although recurrent lesions may be bilateral as well. Local tender lymphadenopathy and cervicitis may be present. Primary herpes proctitis can also occur in patients engaging in receptive anal intercourse, and ulcers may be seen with anoscopy or sigmoidoscopy.

Atypical lesions can have an appearance ranging from papules to macular lesions, fissures, or excoriations. A spectrum of symptoms including itching, burning, dysuria, and urethral discharge can occur, and lesions may not be obvious on visual inspection. Patients usually report headache, fevers, malaise, and myalgias accompanying the primary genital infection. Nonprimary initial infections with HSV-2 in patients already infected with HSV-1 tend to be milder.

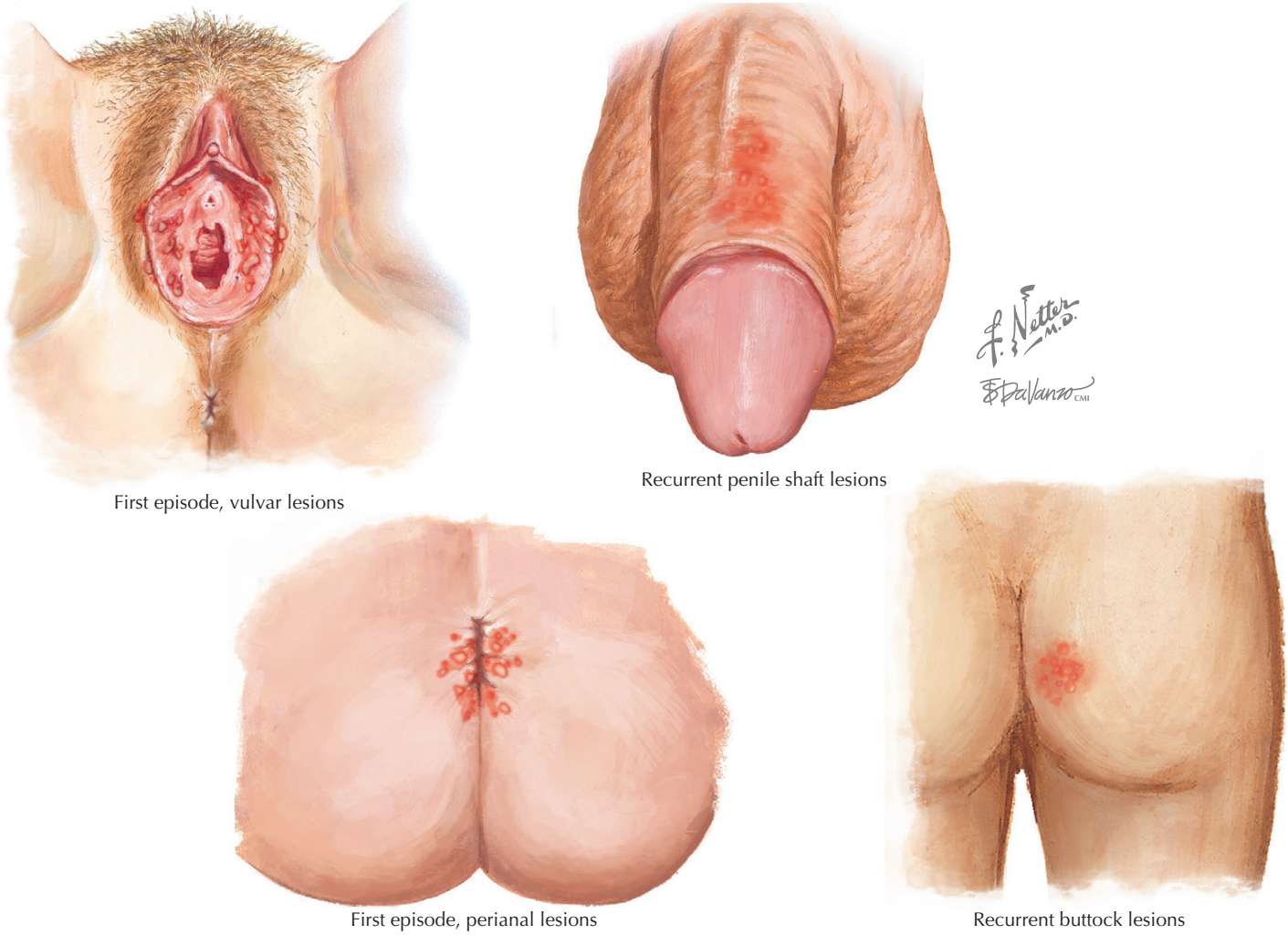

Figure 55-1 Herpes lesions.

Recurrent Episodes

Recurrences are more frequent with genital HSV-2 infection than with HSV-1, thus underscoring the need to differentiate the infecting virus. Most patients with genital HSV-2 infection and around 50% of those with genital HSV-1 infection experience a recurrence within 1 year of the first episode. Among patients who experience recurrences, those with genital HSV-1 typically have a median of one recurrence in the first year of infection, and only a few afterward. In contrast, patients with genital HSV-2 have a median of four recurrences per year, and 20% have more than 10 recurrences in the first year after a primary episode. Over many years, most patients will notice a slight decrease in the frequency of recurrences.

With reactivation of either virus, patients frequently report a local prodrome that consists of itching, tingling, or pain before the development of a frank lesion. Recurrent episodes tend to be milder and shorter than the primary episode, lasting 4 to 7 days, on average. Compared with the primary episode, patients have fewer lesions, usually in a unilateral distribution, and typically lack systemic symptoms (see Figure 55-1). Recurrent lesions can occur on or near the genitalia, and HSV infection should always be considered during evaluation of lower abdominal, lower back, thigh, or buttock sores. In men, recurrences typically occur on the shaft of the penis, not on the glans or in the urethra. In women, recurrences often occur on the vulva. Recurrent lesions can also affect the perianal area in both sexes, even in patients without a history of receptive anal intercourse, because of the shared nerve supply with other genital sites of primary infection. As with primary infection, atypical presentations are common. Patients and clinicians often confuse genital herpes sores with minor superficial trauma (e.g., penis caught in the zipper or trauma from intercourse), tinea cruris, vulvovaginal candidiasis, or other irritating skin abnormalities.

The triggers for recurrent episodes are incompletely understood; patients sometimes report local trauma, sunlight, and fever, although there is usually no identifiable predisposing event. Psychological stress has also been reported as a trigger, and animal data support the concept of stress resulting in HSV reactivation. The frequency and severity of recurrent genital herpes is significantly increased in immunocompromised persons such as HIV-infected and transplant patients, highlighting the role of cellular immunity in containing HSV infection.

Periodic asymptomatic reactivation and shedding of virus are universal features of HSV-1– and HSV-2–seropositive individuals, even those lacking a prior history of symptoms. Asymptomatic shedding of HSV has been detected to occur as frequently as 1 day in 4 in some studies. Recent research has established that most shedding episodes are short, with about half lasting less than 12 hours. Shedding episodes of longer duration are more likely to produce clinical disease.

Differential Diagnosis

HSV-2 is by far the most common cause of genital ulcer disease, and genital herpes should always be considered in persons with a compatible presentation. The differential diagnosis of genital sores includes genital herpes, primary syphilis, chancroid, and lymphogranuloma venereum (LGV). Some genital herpes lesions are occasionally confused with herpes zoster, especially if they occur at a nongenital site. Laboratory testing is required for definitive diagnosis. It is important to note that in both sexes genital herpes can manifest with only mild discomfort and dysuria, as can genital *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections. Given the high prevalence of these infections in patients seeking care for STDs, screening for them is appropriate in all patients in whom genital herpes is a consideration. Urethritis caused by HSV infection will not respond to antibiotics. Rarely, lesions caused by human papillomavirus or scabies may be confused with genital herpes infection. Finally, malignancies such as squamous cell carcinoma and inflammatory conditions including fixed drug eruption, Behçet's disease, and mucocutaneous manifestations of Crohn's disease should be considered in patients with persistent ulcerative lesions. If the initial evaluation of a persistent genital lesion is negative, a biopsy should be considered. The differential diagnosis for proctitis, beyond genital herpes, is mainly limited to *N. gonorrhoeae* and LGV strains of *C. trachomatis*, although streptococcal and staphylococcal soft-tissue infections of the anus, anal fissures, and perianal abscesses should be considered.

Complications

Important complications of genital herpes include aseptic meningitis and disseminated infection. Some degree of central nervous system involvement occurs in many primary HSV infections, although the need for hospitalization is uncommon. Aseptic meningitis as a complication of genital herpes in adults is seen more often with HSV-2 than HSV-1 and is characterized by fever, severe headache, stiff neck, photophobia, and vomiting. Onset usually occurs within 10 to 14 days of the primary genital lesion. The cerebrospinal fluid (CSF) shows a lymphocytic pleocytosis with mild elevation of protein, and the CSF glucose is often normal. Diagnosis should be confirmed with deoxyribonucleic acid (DNA) amplification testing for HSV in the CSF. Central nervous system involvement in genital herpes infections typically has a benign prognosis, although it can recur and is an indication for long-term suppressive antiviral therapy. Mollaret's meningitis, or idiopathic benign recurrent lymphocytic meningitis, is now considered to be caused by recurrent HSV-2 infection. Other possible neurologic sequelae of genital herpes include hyperesthesia and anesthesia in affected sacral dermatomes, urinary retention, and transverse myelitis. Herpes encephalitis is a life-threatening infection requiring hospitalization and intravenous acyclovir, but it arises as a complication of orolabial HSV-1 infection.

Disseminated herpes simplex infections are also life-threatening and can occur as sequelae of genital infections. They happen most frequently in immunocompromised patients, but they have also been described in primary infections of normal hosts, even in the setting of acyclovir therapy. Hepatitis is common with visceral dissemination. The diagnosis of herpes simplex hepatitis is often missed, and subsequent mortality is high. Cutaneous vesicular lesions may be seen with dissemination but are not necessarily the dominant feature. Patients with disseminated herpes infection are very ill and require emergent hospitalization with intravenous antiviral therapy, even in the absence of definitive diagnosis.

Although patients are often concerned about cancer risk, HSV infections are not associated with the development of malignancy.

NEONATAL HERPES

Neonatal herpes is an infrequent but devastating consequence of maternal genital herpes infection. Most cases result from neonatal exposure to HSV-1 or HSV-2 in the birth canal at delivery. The highest risk to the neonate occurs when the mother acquires primary or nonprimary initial genital herpes infection late in pregnancy. In such cases, the risk may arise from the absence of circulating maternal antibodies or from high maternal mucosal viral load in the early stages of infection. Viral transmission to the neonate most commonly occurs with asymptomatic shedding. Reactivation of genital HSV acquired before the third trimester can also lead to neonatal infection, but this occurs infrequently. Other factors that contribute to neonatal risk include prolonged time with ruptured membranes and mucocutaneous injury to the neonate at birth; both provide a portal of entry for the virus. Prevention strategies for neonatal herpes are discussed later.

GENITAL HERPES AND HIV

As noted earlier, HIV-infected patients have very high rates of HSV-2 infection. This is true partially because of risk factors that characterize both infections, but also because genital HSV-2 increases the risk of HIV acquisition, and HIV infection may increase the risk of HSV-2 acquisition. Genital ulcerations facilitate HIV exposure, and the inflammatory infiltrate of herpetic lesions is rich in HIV target cells. Patients co-infected with HIV and HSV-2 have more frequent clinical recurrences of genital herpes and substantially increased rates of asymptomatic shedding of HSV-2. In addition, HSV-2 reactivation leads to increased plasma HIV RNA and increased HIV mucosal shedding. Given the burden of HSV-2 in HIV infected persons, it is reasonable to test these patients for HSV infection and consider long-term suppressive therapy even in the absence of a recurrence history.

Epidemiologic data suggest that HSV-2 infection increases risk for both acquisition and transmission of HIV via several plausible biologic mechanisms, but recent large randomized controlled trials have failed to show a benefit of suppressive therapy with acyclovir in reducing either acquisition or transmission of HIV. However, suppressive acyclovir therapy has shown a modest benefit in slowing HIV disease progression in individuals co-infected with HIV and HSV-2 who are not on antiretroviral therapy.

PATHOPHYSIOLOGY

Both types of HSV have tropisms for epithelial cells and neurons. New infection occurs with viral entry via mucosal surfaces or skin breaks and penetration into the epithelial layers. Viral replication in epidermal and dermal cells leads to cytolysis and release of large quantities of new virus that subsequently spread locally to neighboring epithelial cells as well as to sensory and autonomic nerve endings. Epithelial cell death and detachment caused by this process lead to lesion formation. Vesicular lesions contain cell debris, inflammatory cells, and free virus. The histology is notable for epithelial cell necrosis with basal ulceration or vesicle formation, multinucleated giant cells with intranuclear viral inclusions, and an inflammatory infiltrate of CD4- and CD8-receptor–positive T cells as well as neutrophils.

After infecting peripheral nerve endings, virus migrates up the axons and replicates in nerve cell bodies in the lumbosacral nerve root ganglia but is not thought to cause nerve cell death. In primary infection, virus spreads within the ganglia and down the axons of newly infected nerve cells to cause lesions at other mucocutaneous sites. Thus the lesions in primary infection are distributed across the territory of multiple nerves, and recurrent lesions can occur at sites different from the original site of inoculation.

After genital infection, HSV establishes latency in the lumbosacral nerve root ganglia, where it persists throughout the life of the host. Successful evasion of the immune response results in periodic viral reactivation, and reactivated virus migrates down the axon to mucocutaneous sites at or near the original site of infection. Asymptomatic shedding of virus at these peripheral sites is frequent. Clinical recurrences are associated with an increased quantity of virus and viral spread within the epithelium to a degree sufficient to cause noticeable lesions. Autonomic nerves are also infected by HSV, but for unclear reasons viral reactivation from autonomic nerves seems to be rare.

The mechanisms of latency and the biologic determinants of recurrent episodes of genital herpes versus asymptomatic shedding are incompletely understood. As noted earlier, patients occasionally report triggers for clinical recurrence, but the manner in which these triggers lead to clinical disease is unclear. Only one HSV DNA transcript is expressed in latently infected nerve cells, and it produces no protein but rather seems to regulate or suppress transcription of other viral genes. The factors that lead to viral reactivation and influence the quantity of virus released are unknown. When clinical lesions do form, CD4-receptor–positive T cells and neutrophils are found early in the local inflammatory infiltrate. Research has shown that infiltration of HSV-2–specific CD8-receptor–positive T cells into lesions is associated with local viral clearance. These cells persist for weeks after lesion healing. It is interesting to note that several viral gene products have been shown to have immunomodulatory activity that may contribute to latency and recurrent disease.

LABORATORY TESTING

Clinical diagnosis of genital herpes has low sensitivity and specificity; therefore confirmatory laboratory testing is essential. Patients with active genital lesions or a history of recurrences should be tested to make the diagnosis of HSV disease and, if needed, to exclude other causes of genital ulcers. Testing should be performed with a methodology that will distinguish HSV-1 and HSV-2 ("type-specific" testing), as this will inform the prognosis for recurrences. Several testing options are available (Table 55-1). If the clinical presentation is strongly suggestive of genital herpes, treatment should begin before the test results return or if laboratory testing is not readily available. Because

Table 55-1 Diagnostic Tests for Genital Herpes

METHOD*	CLINICAL UTILITY	LIMITATIONS
Serology†	Positive HSV-2 serology indicates genital herpes infection. Isolated positive HSV-1 serology may indicate genital infection.‡	Takes 2-12 weeks to turn positive; likely negative during acute infection. Does not test lesions directly.
PCR	Most sensitive test to diagnose lesions. Swab vesicle fluid or ulcer base to obtain specimen.	Not widely available.
Culture	Use to diagnose lesions. Specimen collection as with PCR.	Low sensitivity, especially in old or recurrent lesions.

HSV, Herpes simplex virus; *PCR,* polymerase chain reaction.
*All methods shown can differentiate HSV-1 and HSV-2. Such typing should be ordered routinely.
†Serology = type-specific HSV glycoprotein G serology.
‡A positive HSV-1 serology may be challenging to interpret in a person who lacks a history of genital or oral herpes.

HSV-2 is one of the most common STDs, routine HSV serologic testing should be offered to persons undergoing comprehensive STD screening, as well as those with HIV.

Serologic testing for HSV-1 and HSV-2 provides evidence of past infection and is commercially available. Type-specific serologic testing identifies immunoglobulin G (IgG) antibodies to viral glycoprotein G, which differs between HSV-1 and HSV-2, allowing providers to distinguish these infections. No reliable HSV IgM antibody testing is commercially available to diagnose acute or recent infection. Most type-specific serologic assays have high specificity (>96%), although false-positive results are possible in low-prevalence populations. The sensitivity ranges from 80% to 98% in various studies, and occasional false-negative results can also occur. In acute HSV infection, results of routine serologic testing for HSV-1 and HSV-2 will be negative because the IgG antibody response is delayed and seroconversion takes 2 to 12 weeks. Accordingly, a negative antibody test result in early infection does not rule out the diagnosis of HSV, and repeat testing may be indicated if there is a high suspicion for genital herpes. In addition to laboratory-based serologic testing, rapid "bedside" tests have been developed for HSV-2 that have high sensitivity and specificity. The gold standard for HSV antibody testing is the University of Washington Western Blot assay.

HSV-1 seropositivity is frequently a result of primary oral infection, but serologic testing does not distinguish the site of infection. Serologic evidence of HSV-2, however, is virtually always indicative of genital infection. Given the high prevalence of genital herpes, the combination of compatible genital ulcer disease and serologic evidence of HSV-2 infection is sufficient to make the diagnosis. Persons with HSV-2 antibodies but without any current symptoms are still considered to have genital herpes and can transmit the infection to sexual partners and, for women, to neonates.

Because of the inherent limitations of serologic testing, additional laboratory workup may be indicated in some symptomatic individuals. Direct testing of the lesion can be done with DNA amplification testing or viral culture. The most sensitive tests are based on polymerase chain reaction (PCR) amplification of viral DNA obtained with a swab from a lesion. HSV PCR is available in many laboratories and often is used for CSF testing, but it can also be used for the diagnosis of genital ulcer disease. One caveat is that HSV-infected patients can have asymptomatic shedding of the virus even with genital lesions from another cause, although this situation is unusual. If the clinical presentation is highly suggestive of an alternative diagnosis, this should not necessarily be excluded based on a positive HSV PCR test alone. Viral culture from affected lesions is very specific but is substantially less sensitive than PCR. Furthermore, the sensitivity of culture decreases significantly with recurrences and healed lesions, in comparison with HSV PCR. Type-specific fluorescent antibody (FA) tests can be used to test cellular material from HSV lesions but have largely been eclipsed by other testing methods. A Tzanck smear from the base of a herpes lesion may show viral inclusion bodies, but these are nonspecific and the test has limited clinical utility compared with newer methods.

If genital herpes is suspected, providers can collect samples for these tests by unroofing a vesicle with an 18-gauge needle and rubbing its base with a swab where the virus is replicating in epithelial cells. Intact vesicles may not be present, but ulcer bases can still harbor virus. The procedure can be briefly uncomfortable, and the sensitivity of the diagnostic tests may be decreased if specimen collection is inadequate because of patient discomfort. With a compatible lesion, if the PCR assay result or culture is positive, clinicians can be confident in the diagnosis of genital herpes. In this setting a negative serologic test result with positive PCR assay result or culture suggests primary genital herpes infection. Some laboratories require additional requests to perform HSV typing by culture or PCR; typing should be ordered routinely, as it is essential for discussing the prognosis.

MANAGEMENT

As with other chronic diseases and STDs, management of genital herpes involves counseling patients in addition to providing appropriate medical therapy to treat episodes and suppress recurrences. Both counseling and medical therapy have implications for controlling the transmission of genital herpes of which providers should be aware. Prevention of infection in sexually active patients, reproductive-aged women, and the partners of infected individuals is an important aspect of the management of genital herpes.

Counseling

With any diagnosis of genital herpes, providers should counsel their patients about the meaning of test results, the natural history of HSV infection, transmission risks, and treatment options. Counseling may need to take place at a visit subsequent to initial diagnosis, as patients often cannot comprehend additional information beyond the diagnosis of genital herpes at that time. Patients will want to know about the risk and severity of

recurrences as well as possible complications. They are frequently concerned about transmitting the infection to their sex partners and should be informed that transmission can occur even in the absence of active lesions. Sex partners should be aware that they might already be infected even if they have no symptoms. It is appropriate to recommend the following to infected individuals: disclosure of genital herpes diagnosis to sex partners, avoidance of sex if active lesions or prodrome symptoms are present, use of suppressive antiviral therapy when in a relationship with a susceptible partner, and condom use. These measures decrease but do not eliminate the risk of transmission.

The possibility of neonatal herpes should be discussed with all patients, including men. The risk of neonatal herpes is greatest for infants born of women newly infected late in pregnancy. Because genital herpes can have implications for management at delivery, the diagnosis should be conveyed to the obstetrician and the pediatrician of the newborn. Reproductive ability is not compromised by genital herpes infection.

Medical Therapy

There are several treatment options for primary and recurrent genital herpes as well as for viral suppression (Table 55-2). Antiviral therapy can be administered for an individual episode of HSV, or daily to abrogate most subsequent recurrences during the therapy. In patients with a clinical syndrome compatible with a primary or nonprimary first episode of genital herpes, antiviral therapy should be administered even before diagnostic testing is completed, as it reduces the severity of primary infection and prevents neurologic complications.

The antiviral medications acyclovir, valacyclovir, and famciclovir have all been shown to reduce the severity and duration of genital herpes symptoms. These agents form nucleoside analogues in infected cells that impair the function of the viral DNA polymerase, thereby halting viral replication. Human polymerases are unaffected. Valacyclovir is the prodrug of acyclovir, and famciclovir is the prodrug of penciclovir. The prodrugs are available only in oral form but are more efficiently absorbed in the digestive tract than acyclovir or penciclovir, thus allowing less frequent administration. Acyclovir is available in intravenous, oral, and topical formulations. Initial intravenous acyclovir therapy may be necessary for very severe primary genital herpes cases, immunocompromised patients, and patients with complications of genital infection.

Acyclovir, valacyclovir, and famciclovir are typically well tolerated. Rarely, renal dysfunction caused by crystallization of drug in the renal tubules can be seen in patients receiving intravenous acyclovir, usually for other indications and in patients with comorbid conditions. Type 1 allergic responses to acyclovir have also been reported, and desensitization has been used successfully. Long-term acyclovir use is safe, and no laboratory monitoring is needed. Fewer long-term data are available for valacyclovir and famciclovir.

Acyclovir-resistant HSV-2 is infrequent and almost always occurs in severely immunocompromised patients who have received prolonged antiviral therapy. Resistance is not a concern in immunocompetent hosts, even when they are on long-term suppressive therapy. Resistance testing is indicated in cases of clinical failure of antiviral therapy, however. In immunocompromised patients with documented or suspected acyclovir resistance, intravenous foscarnet should be administered. Such patients should be managed in conjunction with an expert. If intravenous foscarnet is contraindicated because of renal failure, anecdotal reports suggest that topical foscarnet, cidofovir, or imiquimod may be of benefit. Topical therapies for genital herpes, such as topical acyclovir, have not otherwise been shown to have substantial clinical utility. Antiviral therapy does not eradicate HSV from the body and will not prevent the virus from establishing latency, nor will it abrogate future recurrences once therapy is stopped.

Primary genital herpes outbreaks should be treated for 7 to 10 days, but a longer course may be used if lesions persist or in immunocompromised patients. Recurrent episodes can be

Table 55-2 Oral Treatment Options for Genital Herpes

	ACYCLOVIR	VALACYCLOVIR	FAMCICLOVIR
First episode, all hosts	400 mg three times a day for 7-10 days* 200 mg five times a day for 7-10 days	1000 mg twice a day for 7-10 days	250 mg three times a day for 7-10 days
Recurrent Episodes			
Normal host	400 mg three times a day for 5 days 800 mg twice a day for 5 days 800 mg three times a day for 2 days	500 mg twice a day for 3 days† 1000 mg daily for 5 days	125 mg twice a day for 5 days 1000 mg twice a day for 1 day
Immunocompromised	400 mg three times a day up to 800 mg five times a day for 5-10 days	1000 mg twice a day up to 1000 mg three times a day for 5-10 days	500 mg twice a day up to 750 mg three times a day for 5-10 days
Suppression			
Normal host	400 mg twice a day	500-1000 mg once a day	250 mg twice a day
Immunocompromised	400-800 mg two to three times a day	500 mg twice a day	500 mg twice a day

Adapted from Centers for Disease Control and Prevention (CDC), Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2006, MMWR Recomm Rep *55:1-94, 2006.*

*All durations may be extended for persistent disease.

†May be less effective than other regimens in patients with >10 recurrences a year.

treated with a shorter course. The standard approach is 5 days, although recent studies have found success with higher-dose therapy and shorter durations. Patients opting for episodic therapy should be encouraged to have medication on hand and to begin therapy as soon as they notice prodromal symptoms. Prompt initiation of antiviral medication results in reduction in the duration of recurrences by 1 to 2 days, although if therapy is initiated early, the episode may be aborted and never progress to the lesion stage.

Suppressive therapy should be offered as an option for all patients with genital HSV-2 infection. Characteristics that strongly support the use of suppressive therapy include frequent recurrences, psychologically or physically bothersome recurrences, or a susceptible partner. Suppressive therapy has been shown to reduce the frequency of asymptomatic shedding, and when given to patients with a history of genital herpes, it reduces by half the risk of transmission of HSV-2 to sexual partners in heterosexual couples. Asymptomatic source patients and homosexual couples were not included in the transmission study, but if there is a susceptible partner, suppressive therapy should be considered for HSV-2–infected persons in these situations as well. Patients with recurrent aseptic meningitis symptoms also benefit from long-term suppressive therapy. The need for continued suppressive therapy should be assessed in a discussion with the patient, but it is not necessary to interrupt therapy in a patient who continues to desire daily antiviral treatment.

PREVENTION AND CONTROL

In the United States, a prevention strategy for genital herpes has not been designed and may not be possible without an effective prophylactic vaccine. Therefore prevention can be considered only in the setting of patient management rather than as a public health intervention. In sexually active individuals, practicing safer sex can decrease the risk of infection. As noted earlier, condom use has been shown to decrease transmission. In serodiscordant couples, the risk of transmission is decreased but not eliminated when the partner with genital herpes is treated with daily antiviral therapy. Long-term suppressive therapy should be offered to such couples hoping to mitigate the risk of transmission. Suppressive antiviral therapy may also have a benefit in reducing transmission from infected patients who have multiple sex partners, although this has not been evaluated.

The risk of neonatal herpes can be decreased with various strategies. Susceptible pregnant women should avoid sexual contact with infected partners during the third trimester. Suppressive therapy for the partner may reduce the risk of infection, but pregnant women may have heightened susceptibility, and data on the efficacy of this approach are lacking. The risk of neonatal transmission can be decreased with cesarean section before membrane rupture in women who are actively shedding virus, but current management strategies do not identify such women. Suppressive therapy starting at week 36 of gestation has been shown to reduce the risk of cesarean sections done because of HSV lesions at delivery, but it is unknown if it has any effect on neonatal herpes; failures to prevent neonatal herpes have been reported. Acyclovir and probably valacyclovir can be used safely during pregnancy.

Vaccination is likely the key to genital herpes prevention. An HSV vaccine must reduce the incidence of infection and viral shedding in breakthrough infections to have a public health impact. Currently, there is no commercially available vaccine for either HSV-1 or HSV-2. An experimental HSV-2 vaccine that showed promise in earlier trials in preventing infection of women seronegative for both HSV-1 and HSV-2 was recently found to be ineffective in a large clinical trial.

SUMMARY

Genital herpes infections are widespread and cause patients significant distress. The spectrum of disease is broad, ranging from latent infection with only asymptomatic viral shedding to significant recurrent painful ulcerations. Many patients have atypical symptoms, and genital herpes should be considered in any comprehensive evaluation of skin lesions occurring on or near the external genitalia and in any workup for STDs. Several laboratory methods are available to make an accurate diagnosis of genital herpes, and these methods should be used to confirm clinically consistent lesions. Effective antiviral therapies are available to treat primary and recurrent disease, and both medical and behavioral strategies can reduce the risk of sexual transmission of the infection.

ACKNOWLEDGMENTS

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Human Immunodeficiency Virus and Acquired Immunodeficiency Syndrome

Shireesha Dhanireddy

56

ABSTRACT

Human immunodeficiency virus (HIV) infection is a sexually transmitted disease (STD). HIV was first recognized in the early 1980s in the United States when gay men manifested an unusual pneumonia caused by *Pneumocystis carinii* (now *Pneumocystis jiroveci*), but its origins trace back to Africa. Since its discovery in the 1980s, the disease has reached far and wide in its scope, affecting millions of people worldwide. Most infected persons remain asymptomatic for years after acquiring HIV, but as immune function diminishes, clinical manifestations from opportunistic infections appear. Treatment for HIV has improved dramatically over the past two decades, with markedly enhanced antiviral efficacy, decreased pill burden, and improved side effect profiles of medications. With these improved treatments, mortality from HIV has greatly declined in the United States, where for most affected persons HIV is now managed as a chronic disease. Despite these advances, HIV remains a globally devastating disease, and aggressive treatment and prevention programs are still needed to control the epidemic.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Over 33 million people worldwide are currently living with HIV, with 2.7 million new infections and 2 million deaths occurring annually. The latest World Health Organization (WHO) data indicate that the overall incidence globally has slightly decreased from its peak incidence in 1996. Despite this slight decline, huge geographic variations in disease incidence exist. Patients living in low- and middle-income countries account for 97% of the new infections that occur annually. The disease is most concentrated in sub-Saharan Africa, where over 22 million people are living with HIV and 1.9 million people are infected yearly, which contributes to 71% of new infections globally. Areas with increasing incidence include Eastern Europe, Central Asia, and sub-Saharan Africa. Nearly half of new infections occur in adolescents and young adults 15 to 24 years of age. The number of deaths has decreased in Western countries but remains 2 million a year worldwide, with the majority of deaths in resource-limited settings.

In the United States, HIV incidence has remained unchanged for the past several years, with 55,000 new infections occurring annually. The prevalence continues to increase as people are living longer with HIV. Minority populations, particularly African Americans, Hispanics, and Native Americans, are disproportionately affected. Nearly half of all patients diagnosed with HIV in the United States are African American, even though African Americans account for only approximately 13% of the population. Unfortunately, African Americans with HIV have a decreased life expectancy compared with people of other races, likely attributable at least in part to barriers such as poverty and stigma, which can delay access to care. Forty-six percent of new diagnoses of HIV occurred in the southern United States, and half of the deaths attributed to HIV in 2007 occurred in that same region. The majority of HIV-infected persons in the South are African American. Hispanics account for approximately 19% of new diagnoses of HIV in the United States, with rates three times higher in Hispanic men compared with white men and five times higher in Hispanic women compared with white women.

RISK FACTORS

Despite ongoing prevention efforts, new cases of HIV occur at alarming rates yearly worldwide. Unprotected sexual contact remains the main risk factor. In the United States, men who have sex with men (MSM) remain a high-risk group, but a growing number of heterosexual transmissions are occurring and the proportion of women with HIV is increasing. Injection drug use remains a risk factor as well, particularly in certain regions of the country, such as Baltimore, where the prevalence of HIV in injection drug users remains high.

Worldwide transmission of HIV is primarily through sexual intercourse, but vertical transmission still occurs, mostly in resource-limited settings. Rates of vertical transmission have dropped dramatically in the United States since the advent of antiretroviral therapy (ART) administered to infected pregnant women. Without ART, perinatal transmission occurs in approximately 25% of HIV-positive women. Risk during pregnancy is 5% to 10%, with a higher risk of transmission occurring at the time of labor and delivery, up to 15%. The remainder of the perinatal risk occurs during breastfeeding, with longer duration of breastfeeding resulting in greater risk of transmission to the child.

Before 1985, when testing of the blood supply became routine, transfusion of blood products was a risk factor for HIV transmission. Transfusion is no longer a risk factor in the United States, but a significant proportion of the world's blood supply is still not routinely screened for blood-borne pathogens, and transfusion of blood products remains a risk factor for infection.

With all routes of transmission, higher viral loads result in a higher risk of transmission. Data from studies in Uganda on HIV serodiscordant couples have shown higher rates of HIV transmission per coital act in early and late stage infection, as

well as with concomitant genital ulcer disease (mostly related to herpes simplex infection). Bacterial vaginosis has also been associated with increased risk of HIV seroconversion. Lack of male circumcision is associated with increased risk of transmission of HIV infection among both heterosexual men as well as MSM.

Some individuals remain HIV negative despite repeated exposure to HIV-infected persons either through high-risk sexual contact or occupational exposure. These individuals have relative resistance to HIV infection either through inherited genetic defects, such as CCR5Δ32 mutation (*CCR5* is a chemokine that functions as a co-receptor for HIV) or acquired immune mechanisms. The acquired immune mechanisms that result in decreased acquisition of HIV are not currently well understood but remain an area of active research.

CLINICAL FEATURES

The clinical features of HIV are generally related to degree of immunosuppression, and patients may be asymptomatic for many years before presentation. After acute infection, most HIV-infected individuals enter a clinically latent period of variable duration, but typically several years. HIV viral load generally reaches a set point within 1 year of acquisition, but CD4+ T-cell counts gradually decrease at a rate of approximately 50/mm^3 per year. Patients tend to become more symptomatic with opportunistic infections as CD4+ T-cell counts decline (Figure 56-1). Prophylaxis against opportunistic infections and ART have led to decreased incidence of many of the opportunistic infections described later, but HIV-infected individuals remain at continued higher risk for developing malignancies.

Acute Infection

Once exposed to HIV, 40% to 90% of patients develop an acute retroviral syndrome, which most commonly manifests as fever, fatigue, and rash developing typically 7 to 14 days after exposure (see Figure 56-1). Patients may also develop headache, lymphadenopathy, and pharyngitis. Symptoms are often nonspecific and can be mistaken for benign viral syndromes or infectious mononucleosis. Patients whose symptoms of acute infection last longer than 14 days generally have a faster rate of progression to acquired immunodeficiency syndrome (AIDS) than those who have a shorter duration of acute infection symptoms.

Pulmonary Manifestations

Regardless of stage of infection, bacterial pneumonia and tuberculosis (TB) are more common in HIV-infected individuals. Approximately one third of persons living with HIV worldwide are co-infected with *Mycobacterium tuberculosis*, which contributes to nearly one third of HIV-related deaths globally. Data from the U.S. Centers for Disease Control and Prevention

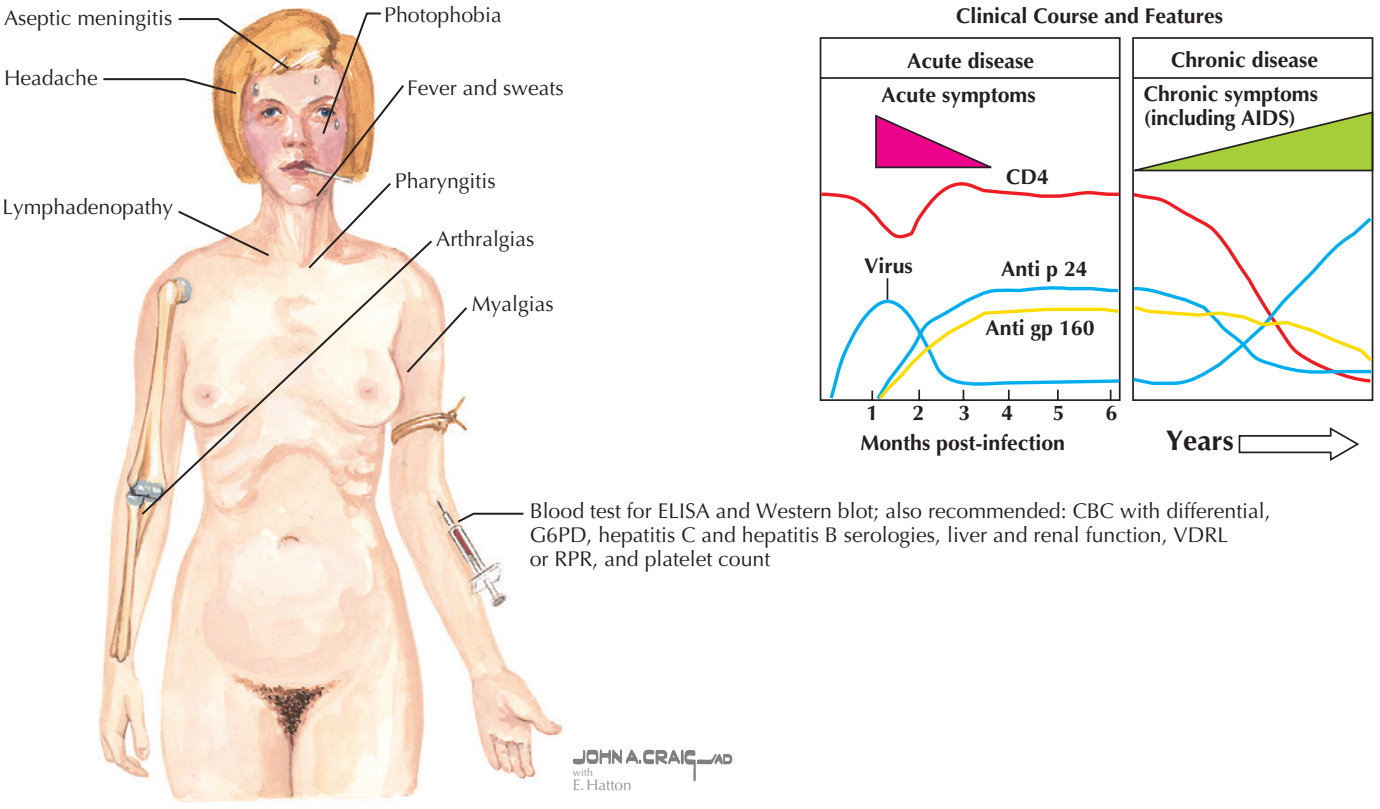
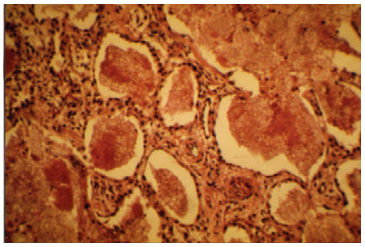
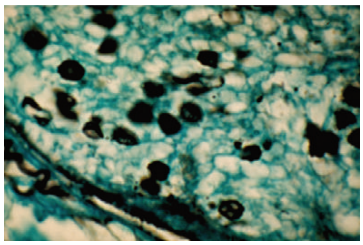


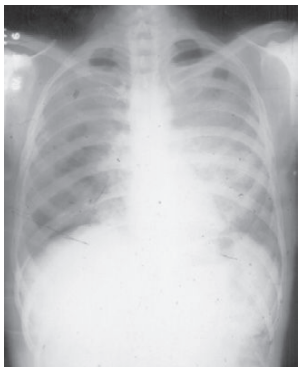
Figure 56-1 Clinical course and features of HIV.



Interstitial lymphocyte and plasma cell infiltration with foamy exudate in avleoli



Methenamine $AgNO_3$ stain showing *Pneumocystis* organisms in lung *(black spots)*



Diffuse bilateral pulmonary infiltrates

Figure 56-2 *Pneumocystis* pneumonia.

(CDC) from 2005 estimated that 9% of all TB cases in the United States occurred in HIV-infected individuals. Before the era of effective HIV treatment, pneumococcal pneumonia occurred at much higher rates in HIV-infected patients. As CD4+ T-cell counts continue to decrease, patients are at increased risk for developing *Pneumocystis* pneumonia (PCP), a fungal pneumonia caused by *P. jiroveci* (Figure 56-2). Patients with PCP typically demonstrate subacute symptoms of shortness of breath and nonproductive or minimally productive cough. Chest radiograph may reveal bilateral interstitial infiltrates classically or can even be read as normal.

Oral Manifestations

Oral candidiasis is also a common initial manifestation of HIV, typically occurring in patients with CD4+ T-cell counts less than 350/mm^3 (Figure 56-3). Other oral manifestations include oral hairy leukoplakia (OHL), an Epstein-Barr virus–associated disease.

Neurologic Manifestations

Patients with more advanced HIV can develop neurologic diseases such as toxoplasmosis, caused by the parasite *Toxoplasma gondii*, which typically affects the brain and most commonly manifests with seizure (Figure 56-4). Other neurologic manifestations include meningitis from *Cryptococcus neoformans*, which can appear subacutely in patients typically with CD4+ T-cell counts less than 100/mm^3. Patients with even more advanced

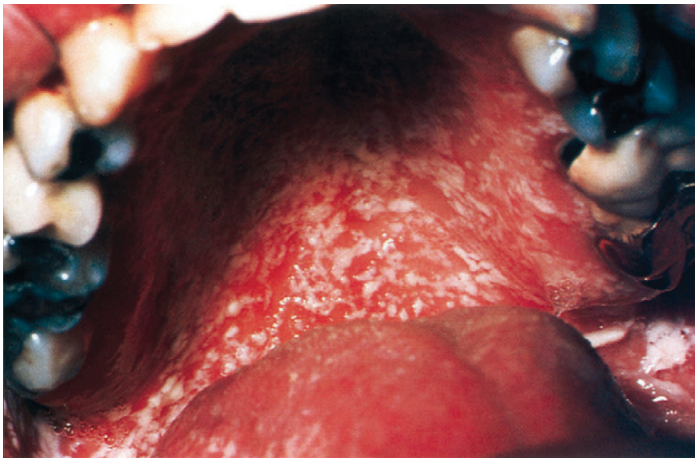


Figure 56-3 Oral candidiasis.

HIV with CD4+ T-cell counts less than 50/mm^3 are at risk for progressive multifocal leukoencephalopathy (PML), caused by JC virus. Patients with PML may have seizures. Before the use of ART, PML was almost always fatal, with a median survival of less than 6 months from the time of diagnosis. Despite ART, PML remains a serious disease that can result in long-term neurologic deficits.

Dermatologic Manifestations

A wide range of dermatologic diseases occur in HIV-infected individuals, some representing limited cutaneous diseases and others indicating systemic infection. Superficial fungal infections such as seborrheic dermatitis are more common in patients with HIV. Cutaneous infections caused by herpes simplex virus (HSV) and varicella-zoster virus (VZV) are common in patients with HIV. Viral warts from human papillomavirus (HPV) are also common. Molluscum contagiosum, caused by a pox virus, can by confused with warts caused by HPV (Figure 56-5). Noninfectious cutaneous conditions such as eosinophilic folliculitis, characterized by pruritic papules typically on the face and trunk, are more prevalent in HIV-infected individuals. Patients with nonblanching violaceous papules or nodules likely have Kaposi's sarcoma, a human herpesvirus 8–associated malignancy that most commonly affects the skin but can also involve the lymph nodes, lungs, and gastrointestinal tract. Less commonly, violaceous lesions may indicate cutaneous bacillary angiomatosis caused by *Bartonella* species, the organism associated with cat scratch disease.

Gastrointestinal Manifestations

Gastrointestinal disease may be directly related to HIV, such as HIV-associated enteropathy, which typically occurs in individuals with low CD4+ T-cell counts and high viral loads, or it may result from an infectious cause. Upper tract disease, esophagitis, is most caused by commonly by *Candida* species, with patients typically having thrush accompanied by odynophagia. Esophagitis may also be caused by cytomegalovirus (CMV) or HSV. Lower gastrointestinal tract disease and diarrhea may result from CMV or parasitic diseases such as

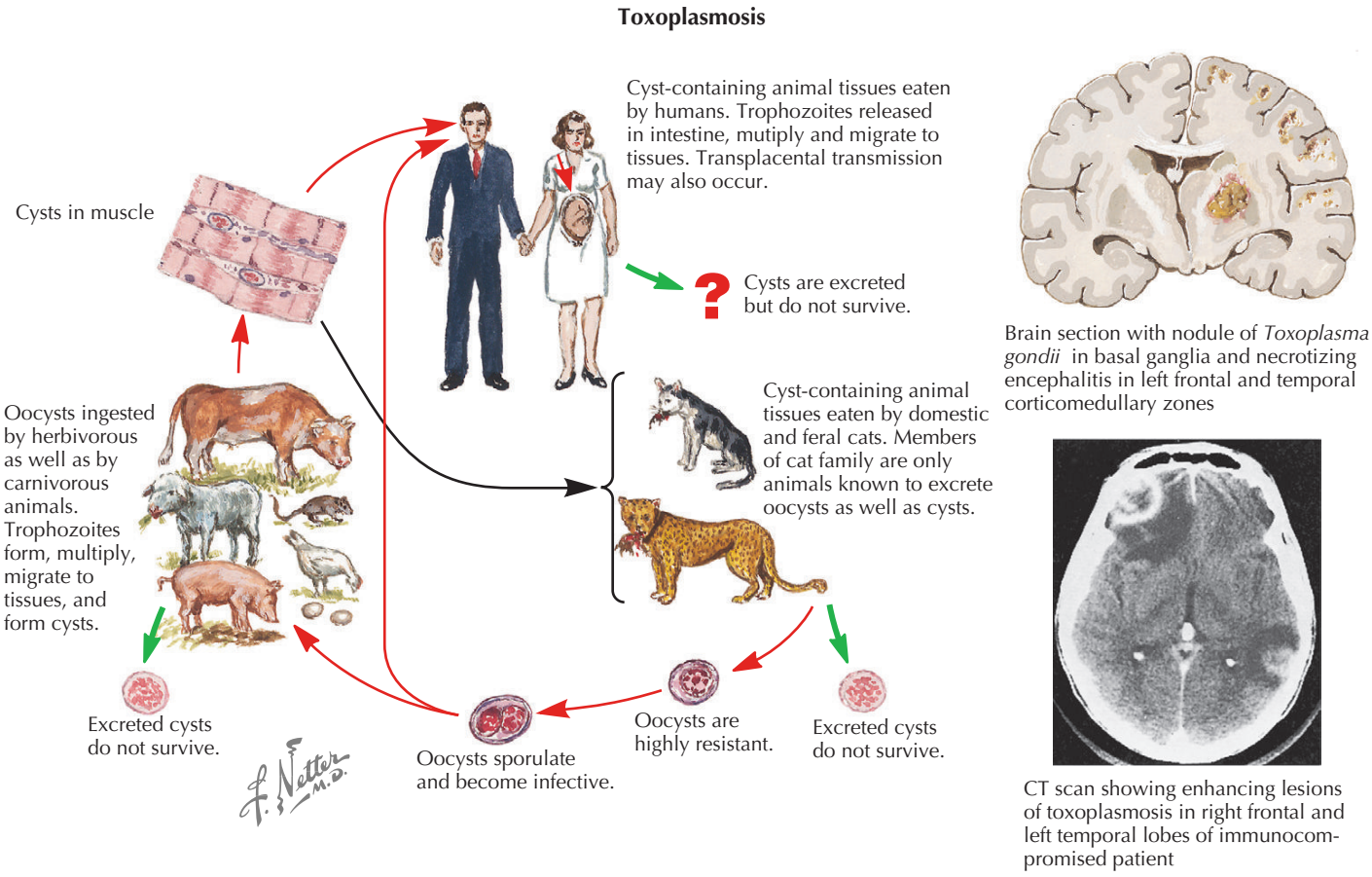
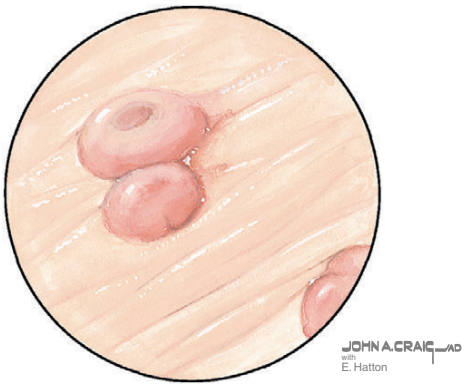


Figure 56-4 Toxoplasmosis.



Magnified view showing typical umbilicated lesion

Figure 56-5 Molluscum contagiosum.

Cryptosporidium parvum, *Isospora*, or Microsporidia. Diarrhea is also a common manifestation of disseminated *Mycobacterium avium* complex (MAC) infection, which also may cause fever and lymphadenopathy.

Malignancy and HIV

HIV-infected individuals are at higher risk for cancers such as non-Hodgkin's lymphoma, Kaposi's sarcoma, and cervical cancer, which are defined as AIDS-defining malignancies. A study comparing the incidence of cancer among HIV-infected individuals with the incidence in the general population found that HIV-infected individuals were at higher risk for not only AIDS-defining malignancies, such as Kaposi's sarcoma, but also non–HIV-associated malignancies such as anal cancer, liver cancer, and lung cancer, among others. In the era of effective ART, rates of AIDS-defining cancers have decreased but rates of non–HIV-associated cancers continue to increase.

DIAGNOSTIC APPROACH

The CDC currently recommends HIV testing for all persons aged 13 to 64 years at least once. Repeat testing should be performed annually for those at risk, including MSM, high-risk heterosexuals, and injection drug users. Unlike other routinely ordered laboratory studies, persons should be informed before testing is done; however, this need not involve the extensive counseling that was mandated before the newer emphasis on routine screening. In addition to screening, testing should be performed on all patients with signs or symptoms consistent with HIV infection or opportunistic infection. Enzyme immunoassays (EIAs) for HIV detect the presence of HIV antibodies. False-negative results are rare except in the setting of acute infection during which antibodies to HIV have yet to develop. Positive EIA results must be confirmed with Western blot, which is more specific for HIV.

Rapid HIV tests were first approved in 1996 but have only recently become more routinely incorporated into clinical care. Rapid tests are also EIAs but can produce results within 20 minutes. As with standard EIA, rapid EIA testing must be confirmed with Western blot.

Ribonucleic acid (RNA) testing is not recommended for routine screening of HIV infection, but it is warranted when acute HIV infection is suspected—for example, in someone with clinical symptoms suggestive of acute HIV infection and recent high-risk behavior. In these cases HIV antibody testing by EIA should also be performed. Typically during acute infection, plasma RNA viral loads are very high, often greater than 1 million copies per milliliter. RNA testing may be used for diagnosis of chronic disease, but false-positive test results have been reported. For cases in which testing antibody results are indeterminate and patient has risk factors for HIV, RNA testing can be useful.

CLINICAL MANAGEMENT AND DRUG TREATMENT

The goal of HIV treatment is to prevent symptomatic disease and improve mortality. ART has been available since 1987 with the introduction of zidovudine, but not until 1996 with the advent of highly active antiretroviral therapy (HAART) did outcomes improve and was treatment recommended for all infected with HIV. Unfortunately, treatment options at that time had numerous adverse effects, including lipodystrophy, peripheral neuropathy, and nephrolithiasis. In the early 2000s, treatment was recommended for only those with symptomatic disease and with lower CD4+ T-cell counts because the risk of adverse events was felt to outweigh benefits of therapy. Over the past decade, ART has been offered to patients with progressively higher CD4+ T-cells counts. Current U.S. guidelines recommend treatment for all patients with CD4+ T-cell counts below 500 and consideration of treatment for all those with HIV regardless of symptoms or CD4+ T-cell counts (Box 56-1). Studies have shown improved mortality rates with earlier initiation of HIV therapy. WHO guidelines updated in 2010 also recognize the compelling data regarding earlier treatment of HIV infection (Table 56-1).

Currently, over 20 different medications from five different classes exist for the treatment of HIV (Figure 56-6). Before initiation of treatment, resistance testing should be performed on all HIV-infected patients to determine if acquired drug resistance is present. Currently, up to 14% of treatment-naïve patients in the United States have drug-resistant virus.

Treatment options have become simpler and better tolerated over the past several years (Boxes 56-2 and 56-3)

Recommendations for initial treatment of HIV have recently changed in the United States to include a relatively new class of medications, the integrase inhibitors. Raltegravir, the only integrase currently available, has been shown to be noninferior to an efavirenz-based regimen and perhaps better tolerated in treatment-naïve HIV-positive individuals.

Once patients begin ART, HIV RNA testing and CD4+ T-cell monitoring should be performed routinely to determine response to therapy. The goal of treatment is both virologic suppression and immune reconstitution.

Box 56-1 Department of Health and Human Services, January 2011: Guidelines for Treatment of Antiretroviral Therapy–Naïve HIV-Positive Adults

Initiate treatment in the presence of the following:
- CD4 count <500*
- Symptomatic disease
- Pregnancy
- Hepatitis B, if treatment for hepatitis B indicated
- HIV-associated kidney disease

Data from Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents—A Working Group of the Office of AIDS Research Advisory Council (OARAC): *Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents,* January 10, 2011, DHHS, pp 1-161. Available at: www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.
*A level of <350 cells/mm^3 is a strong indication to initiate therapy; 350 to 500 is a moderate to strong indication to initiate therapy. For patients with CD4 counts >500 cells/mm^3, 50% of the panel favors starting antiretroviral therapy (ART) and 50% views ART initiation as optional.

Box 56-2 Department of Health and Human Services, January 2011: Preferred Initial Combination Regimens for Antiretroviral Therapy–Naïve Patients

Efavirenz + tenofovir + emtricitabine
Ritonavir boosted atazanavir + tenofovir + emtricitabine
Ritonavir boosted darunavir + tenofovir + emtricitabine
Raltegravir + tenofovir + emtricitabine

Data from Department of Health and Human Services (DHHS) Panel on Antiretroviral Guidelines for Adults and Adolescents—A Working Group of the Office of AIDS Research Advisory Council (OARAC): *Guidelines for the use of antiretroviral agents in HIV-1–infected adults and adolescents,* January 10, 2011, DHHS, pp 1-161. Available at: www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

Table 56-1 2010 World Health Organization (WHO) Guidelines for Treatment

CD4 counts ≤350	Treat with ART
WHO clinical stage 1 or 2 disease	CD4 count testing
WHO clinical stage 3 or 4 disease regardless of CD4 count	Treat with ART
HIV-HBV co-infection if HBV treatment required regardless of CD4 count or WHO clinical stage	Treat with ART
Active TB regardless of CD4 count	Treat with ART as soon as possible after start of TB treatment

Data from World Health Organization (WHO): Antiretroviral therapy for HIV infection in adults and adolescents, Geneva, Switzerland, 2010, World Health Organization.
ART, Antiretroviral therapy; *HBV,* hepatitis B virus; *HIV,* human immunodeficiency virus; *TB,* tuberculosis.

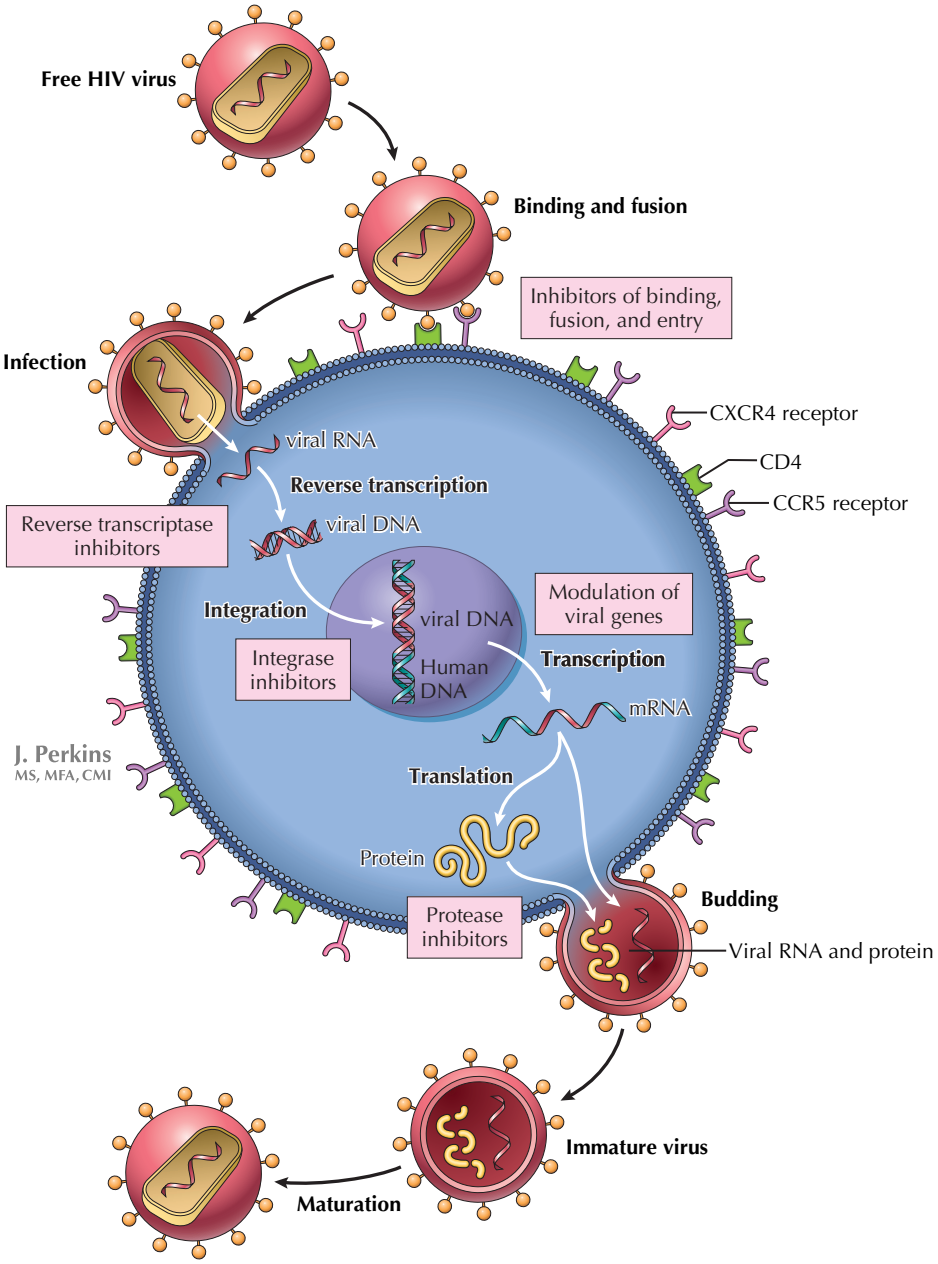


Figure 56-6 Antiretrovirals.

Box 56-3 2010 World Health Organization Treatment Guidelines: What to Start in Antiretroviral Therapy–Naïve Patients

Zidovudine + lamivudine + efavirenz
Zidovudine + lamivudine + nevirapine
Tenofovir + lamivudine (or emtricitabine) + efavirenz
Tenofovir + lamivudine (or emtricitabine) + nevirapine

Data from World Health Organization (WHO): *Antiretroviral therapy for HIV infection in adults and adolescents,* Geneva, Switzerland, 2010, WHO.

In addition to ART, patients with lower CD4+ T-cell counts should receive prophylaxis against opportunistic infections (Table 56-2). For a complete list of pathogens and recommended prophylaxis, please refer to the guidelines for the prevention and treatment of opportunistic infections published by the CDC.

PROGNOSIS

Prognosis for people living with HIV has improved over the past two decades with ART. Mortality from HIV markedly decreased after the introduction of combination ART in 1996. Data from the Antiretroviral Therapy Cohort Collaboration (ART-CC) have shown that the 5-year risk of AIDS or death from the start of antiretroviral treatment ranged from 5.6% to 77%. The main factors influencing outcomes were age, CD4 count at baseline, HIV RNA level, clinical stage, and history of injection drug use. Clinicians may use the risk calculator to estimate risk of progression to AIDS or death (www.art-cohort-collaboration.org).

Despite advances in treatment, no cure exists for HIV. Currently, once patients begin ART, lifelong therapy is recommended. Studies evaluating outcomes of structured HIV treatment interruptions based on CD4+ T-cell counts have

Table 56-2 Opportunistic Infection Prophylaxis

PATHOGEN	INDICATION
Pneumocystis jiroveci	CD4+ count <200 or thrush
Toxoplasma gondii	CD4+ count <100 and *Toxoplasma* IgG positive
Mycobacterium avium complex	CD4+ count <50

IgG, Immunoglobulin G.

revealed that patients whose therapy was interrupted had significantly increased risk of developing opportunistic infections compared with patients who remained on continuous therapy.

A minority of patients with HIV do not progress to AIDS even without treatment. These patients, referred to as *long-term nonprogressors*, maintain relatively high CD4+ T-cell counts and relatively low HIV RNA levels for years. Some patients, however, may have rapidly progressive disease. Both virologic and host immunologic factors play important roles in determining natural history.

As survival continues to improve for individuals with HIV, death from non–AIDS-related diseases is increasing. Further studies are underway to investigate the effects of HIV on aging.

PREVENTION AND CONTROL

Some countries, such as the Dominican Republic and United Republic of Tanzania, have had a decline in the number of new infections as a result of prevention efforts. A steady number of new infections occurs annually in the United States, however, despite prevention measures. Reducing high-risk behaviors that lead to transmission is integral to HIV control and prevention. Safe sex counseling, condom use, and routine HIV testing should be offered to individuals at risk for HIV. Knowing HIV status may reduce high-risk behavior and lead to fewer transmissions. Individuals may also seek care and ART for HIV once diagnosed, thus reducing HIV RNA levels and therefore risk of transmission.

Antiretroviral therapy for at-risk HIV-negative MSM led to a 44% reduction in HIV acquisition in a large multi-national study. Studies are ongoing to evaluate the efficacy of preexposure prophylaxis in HIV serodiscordant couples. If effective, preexposure prophylaxis may markedly reduce the number of new HIV infections. For up-to-date information on recommendations for preexposure prophylaxis, please refer to www.avac.org. Male circumcision has been shown to decrease acquisition of HIV. Other prevention strategies such as topical microbicides with nonspecific antimicrobial activity and suppressive treatment of genital herpes with acyclovir have, disappointingly, not been shown to reduce HIV transmission rates.

HIV vaccine trials have thus far not been successful in preventing acquisition of HIV, with one vaccine trial showing a trend toward an increased number of infections in the vaccinated group. One recent vaccine trial in Thailand, which used a prime boost vaccine strategy in a mostly low-risk heterosexual population, found a modest decrease in seroconversions in the vaccinated group.

EVIDENCE

Antiretroviral Therapy Cohort Collaboration: Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies, *Lancet* 372:293-299, 2008. *This study revealed that people are living longer in the era of highly-active ART, but still not quite as long as individuals without HIV.*

Donnell D, Baeten JM, Kiarie J, et al: Heterosexual HIV-1 transmission after initiation of antiretroviral therapy: a prospective cohort analysis, *Lancet* 375:2092-2098, 2010. *This international study demonstrated that ART led to a 92% reduction in transmission of HIV in serodiscordant heterosexual couples.*

Gray RH, Wawer MJ, Brookmeyer R, et al: Probability of HIV-1 transmission per coital act in monogamous, heterosexual, HIV-1–discordant couples in Rakai, Uganda, *Lancet* 357:1149-1153, 2001. *This study demonstrated that higher viral loads and genital ulceration are associated with increased risk of sexual transmission of HIV.*

Kahn JO, Walker BD: Acute human immunodeficiency virus type 1 infection, *N Engl J Med* 339:33-39, 1998. *Authors review the symptoms associated with acute HIV as well as the early pathophysiology of HIV.*

Patel P, Hanson DL, Sullivan PS, et al: Incidence of types of cancer among HIV-infected persons compared with the general population in the United States, 1992-2003, *Ann Intern Med* 148:728-736, 2008. *Authors found that the incidence of non-AIDS-defining cancers have decreased with the use of ART, but that non-AIDS-defining cancers are still more common among HIV-infected individuals.*

Siegfried N, Muller M, Deeks JJ, Volmink J: Male circumcision for prevention of heterosexual acquisition of HIV in men, *Cochrane Database Syst Rev* 2:CD003362, 2009. *This systematic review of randomized controlled trials of male circumcision for HIV prevention found that male circumcision decreased the acquisition of HIV by heterosexual men by 38% to 66% over a 24 month period.*

Walker AS, Ford D, Gilks CF, et al: Daily co-trimoxazole prophylaxis in severely immunosuppressed HIV-infected adults in Africa started on combination antiretroviral therapy: an observational analysis of the DART cohort, *Lancet* 375:1278-1286, 2010. *This observational anaylsis of a large cohort in Africa found that co-trimoxazole prophylaxis improved mortality and reduced frequency of malaria.*

When to Start Consortium, Sterne JA, May M, et al: Timing of initiation of antiretroviral therapy in AIDS-free HIV-1–infected patients: a collaborative analysis of 18 HIV cohort studies, *Lancet* 373:1352-1363, 2009. *This important international study found that earlier ART initiation at CD4 cell counts above 350 cells/mm^3 was associated with decreased progression to AIDS and fewer deaths.*

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) website. Available at: www.cdc.gov/nchhstp/. *The NCHHSTP is the branch of the CDC responsible for public health surveillance, prevention research, and programs to prevent and control HIV and AIDS, other STDs, viral hepatitis, and TB.*

National Network of STD/HIV Prevention Training Centers (NNPTC): NNPTC website. Available at: http://depts.washington.edu/nnptc/index.html. *The NNPTC is a CDC-funded group of regional centers created in partnership with health departments and universities. The NNPTC provides health professionals with state-of-the-art educational opportunities with an emphasis on prevention, with the goal of increasing the knowledge and skills of health professionals in the areas of sexual and reproductive health.*

University of Washington: HIV web study. Available at: www.hivwebstudy.org. *This website offers interactive case-based tutorials about various clinically relevant HIV topics.*

U.S. Department of Health and Human Services: AIDSinfo. Available at: www.aidsinfo.nih.gov. *This link provides information about current treatment and prevention guidelines as well as information about medications and clinical trials.*

World Health Organization (WHO): WHO website. Available at: www.who.org. *This site offers information about the latest worldwide epidemiology of HIV and international guidelines.*

Human Papillomavirus

Eileen F. Dunne

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ABSTRACT

Genital human papillomavirus (HPV) infection is estimated to be the most common sexually transmitted infection in the United States. Nononcogenic, or "low-risk" HPV types, such as HPV types 6 and 11, can cause benign or low-grade cervical cell changes, genital warts, and recurrent respiratory papillomatosis. Oncogenic, or "high-risk" HPV types, such as HPV types 16 and 18, can cause cervical and other anogenital low-grade and high-grade cell changes, anogenital cancers, and oropharyngeal cancers. Most infections are asymptomatic and do not result in clinical disease. However, persistent oncogenic HPV infection over time can lead to precancers and cancers. Cervical cancer is a leading cause of morbidity and death among women worldwide, and 70% of these cancers can potentially be prevented by prophylactic HPV vaccines.

BACKGROUND

Papillomaviruses are a family of deoxyribonucleic acid (DNA) viruses that infect the epithelium and have a double-stranded, closed, circular genome of approximately 8 kb and a nonenveloped icosahedral capsid. There are over 100 HPV types, which are further characterized as mucosal or cutaneous depending on the epithelium they primarily infect. Cutaneous types cause common skin warts; mucosal types have primary affinity for the genital and oral mucosa and can cause a variety of diseases and cancers including genital warts, recurrent respiratory papillomatosis, cervical and other anogenital cancers, and oropharyngeal cancers. Most infections are asymptomatic, cause no disease, and become undetectable within 2 years of acquisition. However, persistent HPV infection with oncogenic types is the most important risk factor for development of serious diseases including cervical cancer precursor lesions and cervical cancer. This chapter will focus on HPV infection and the genital diseases that can result from infection, including genital warts and cervical cancer precursor lesions and cancers.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF INFECTION AND DISEASE BURDEN

Infection with genital HPV is ubiquitous and occurs commonly throughout the world. HPV prevalence was 26.8% according to a population-based evaluation of 14- to 59-year-old females in the United States. The prevalence of HPV and the most common types infecting the genital mucosa vary in different regions; however, HPV-16 is frequently one of the most common infections. The International Agency for Research on Cancer (IARC) found that age-standardized HPV prevalence varied nearly 20 times among studies across the world, from 1.4% to 25.6%. In some settings there is a peak in persons younger than 25 years old that decreases with age, and in other settings there is a U-shaped curve with the highest prevalence in young persons and a second smaller peak in prevalence in older adults. Some of the differences in HPV prevalence throughout the world may reflect differences in sexual debut and sexual behavior among females and their partners.

Genital warts result from infection with low-risk HPV types (HPV type 6 or 11 most commonly) and are also common. When asked if they had ever been diagnosed with genital warts, almost 6% of men and women in a nationally representative survey of 14- to 59-year-olds in the United States said that they had. A study of four Nordic countries found that 10.6% of women aged 18 to 45 years had been clinically diagnosed with genital warts. There are limited data on the burden of genital warts in low-resource settings, but genital warts are likely to be equally prevalent, if not more prevalent, than in high-resource settings owing to the higher burden of HIV.

In settings in which cervical cancer screening programs exist, HPV-related cervical cell changes that are detected through screening are very common. One study from a U.S. managed care organization found that cytologic abnormalities were detected at a rate of 14.9 per 1000 women. Few settings have registries or data available on cervical abnormalities.

Virtually all cervical cancers are attributed to HPV; HPV-16 and HPV-18 account for approximately 70% of cervical cancers worldwide. The incidence of cervical cancer varies substantially throughout the world. In countries with effective cervical cancer screening programs, the incidence of cervical cancer is low compared with low-resource settings in which limited or no screening exists. For example, in the United States, where cervical cancer screening has been in existence for many decades, there has been an over 70% reduction in cervical cancer cases; cervical cancer is the twelfth most common cancer in the United States, with approximately 11,000 cases and 4000 deaths occurring every year. In low-resource settings, many with no or inadequate cervical cancer screening, cervical cancer is the third most common type of cancer in women and a leading cause of death. According to the latest global estimates, over 500,000 new cases of cervical cancer occur each year, and over 250,000 women die of the disease annually.

RISK FACTORS

Risk factors for genital HPV include young age and increasing numbers of sexual partners; however, a substantial percentage of persons acquire infection even with one sex partner. Genital HPV infection is primarily transmitted by genital contact, usually through sexual intercourse. Transmission can also occur by sexual contact other than sexual intercourse; one study of young women who reported no previous sexual intercourse and had other sexual activity such as genital-genital or genital-oral contact found that the 24-month cumulative incidence of

infection was 7.9% (95% confidence intervals [CIs] 3.5 and 17.1). HPV infection is acquired soon after sexual debut; in one study, the 1-year cumulative incidence of first HPV infection was 28.5%, and the incidence increased to almost 50% by 3 years in young women with one sexual partner. In virtually all studies of HPV prevalence and incidence, the most consistent predictors of infection have been various measures of sexual activity (i.e., the number of sex partners).

Risk factors for genital warts are similar to those for HPV infection and include increasing numbers of sexual partners and young age. The peak prevalence of genital warts is in persons in their early to late 20s. Persons with compromised immune function (including human immunodeficiency virus [HIV] infection and posttransplant status) are more likely to develop genital warts than those with normal immunity. In one study, unadjusted cumulative incidence of anogenital warts over an 8-year period for HIV-uninfected women was 9.3% (95% CI 6.3 to 12.2); for HIV-infected women who initiated highly active antiretroviral therapy (HAART) was 28.4% (95% CI 21.7 to 34.5); and for HIV-infected women who did not initiate HAART was 25.1% (95% CI 18.4 to 31.2).

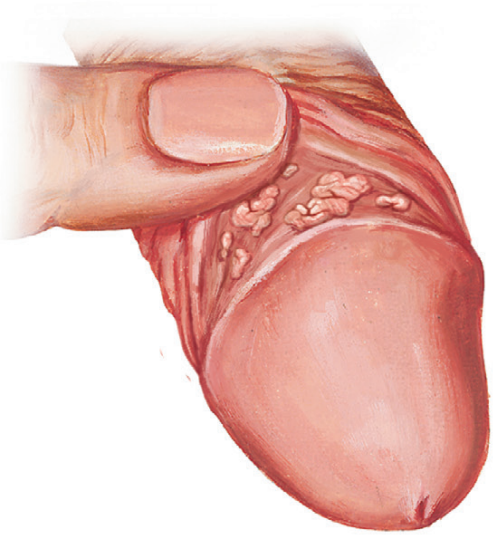
An important risk factor for cervical cancer is not having been screened and/or not having received appropriate follow-up after screening. In the United States, rates of cervical cancer are higher in black and Hispanic women; rates also vary geographically, with higher rates reported in the South, Appalachia, and areas bordering Mexico. The peak age for cervical cancers is among midadult women in their 30s and 40s. Although cervical cancer screening detects lesions earlier and increases the chances of successful treatment, some specific types of cervical cancers are more difficult to detect (adenocarcinomas).

CLINICAL FEATURES

Infection with genital HPV usually causes no signs or symptoms, and infections clear within 2 years. Asymptomatic infection is typically not diagnosed or treated. A common question posed to clinical providers is if partners of patients with genital warts or cervical disease caused by HPV should be tested for HPV infection. There is no reason to test partners routinely for HPV infection because HPV infection is common and often clears on its own. Most sexual partners share HPV types and readily transmit infection to one another. The most important risk factor for development of precancers and cancers is persistent oncogenic HPV infections. Although it is unclear why certain women do not clear infection, it may be explained in part by host immunity and characteristics of the virus.

One of the most common clinical manifestations of HPV is genital warts; more than 90% of genital warts are caused by nononcogenic HPV-6 and/or HPV-11. Warts typically occur 2 to 3 months after incident HPV infection. In one study, 66% of young women with incident HPV-6 or HPV-11 infection developed genital warts by 36 months of follow-up. Genital warts appear as small papules or flat, smooth, or pedunculated lesions. Sometimes they can be soft, pink, or white "cauliflower-like" sessile growths on moist mucosal surfaces (condyloma acuminata), or keratotic lesions on squamous epithelium of the skin with a thick, horny layer (Figure 57-1).

If anogenital warts are detected, some experts recommend that clinicians conduct a complete anogenital examination and screen for chlamydia, gonorrhea, syphilis, hepatitis B, and HIV infection. Detection of genital warts is not a reason to recommend more frequent cervical cancer screening, as the HPV



Condylomata acuminata of the penis

Condylomata acuminata in females

Figure 57-1 Condyloma acuminata.

types that cause genital warts are different from those that cause cancer.

Cervical dysplasia caused by HPV is typically detected through cervical screening using papanicolaou (Pap) tests (either conventional or liquid based) or Pap tests combined with HPV tests (Figure 57-2). Cervical lesions can be caused by either nononcogenic or oncogenic types. Nononcogenic types that infect the cervix can cause low-grade cervical abnormalities (termed *low-grade squamous intraepithelial lesions* [LSILs]). Oncogenic types, when they persist, can lead over time to cervical precancers and cervical cancers. Because cervical precancers and cervical cancers take years to develop, cervical cancer screening is often able to detect lesions early when lesions are small and easier to treat.

DIAGNOSTIC APPROACH

Cervical dysplasia and cancers are diagnosed during routine cervical cancer screening. Cervical Pap testing should begin at age 21 years; new recommendations on cervical cancer screening have been proposed by at least two professional organizations (Table 57-1). All women who are sexually active, including women who have sex with women, are at risk for cervical dysplasia and cancer. The Pap test (liquid or conventional) is a screening test for cervical cell changes, including cervical cancer. Histology (biopsy) remains the current gold standard for the detection of HPV-associated cervical lesions and invasive cancers. Biopsies for histologic diagnosis of the cervix are directed to cervical changes noted by colposcopy.

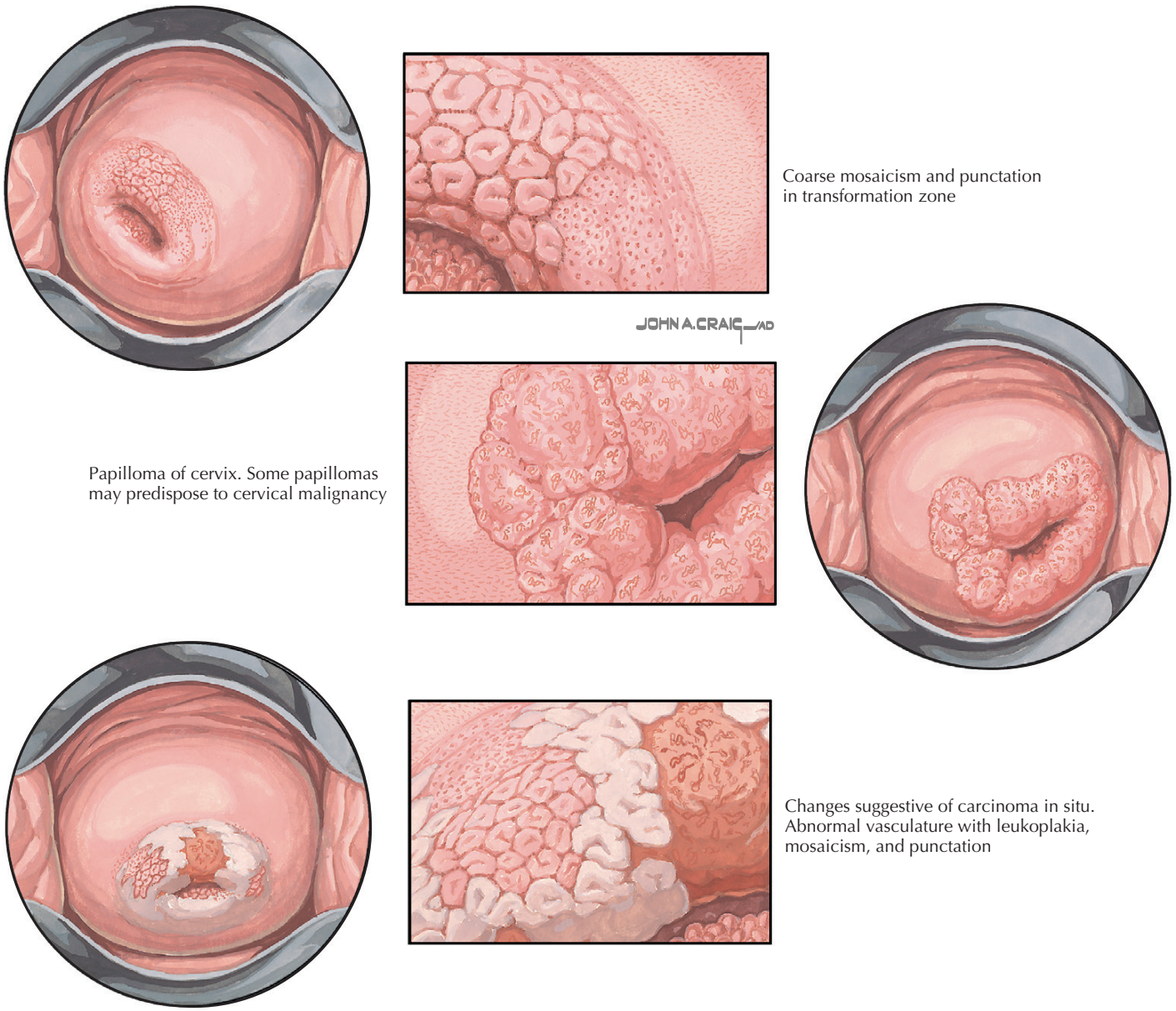


Figure 57-2 Colposcopic views after application of acetic acid.

Table 57-1 Cervical Cancer Screening Guidelines

	AMERICAN CANCER SOCIETY (ACS)[a,b] 2002	U.S. PREVENTIVE SERVICES TASK FORCE (USPSTF)[c] 2003	AMERICAN COLLEGE OF OBSTETRICIANS AND GYNECOLOGISTS (ACOG)[d] 2009
When to Start Screening			
	Approximately 3 years after onset of vaginal intercourse but no later than age 21.[e]	Within 3 years of onset of sexual activity or age 21, whichever comes first. (*A recommendation*)	Age 21 regardless of the age of onset of sexual activity. Should be avoided before age 21. (*Level A evidence*)
Screening Method and Intervals			
Conventional cytology	Annually; every 2-3 years for women age ≥30 years with a history of three negative cytology test results.[f] Sexual history should not be used as a rationale for more frequent screening.	At least every 3 years. (*A recommendation*)	Every 2 years from age 21-29 years (*Level A evidence*); every 3 years for women age ≥30 years with a history of 3 negative cytology tests.[f] (*Level A evidence*)
Liquid-based cytology	Every 2 years; every 2-3 years for women age ≥30 years with a history of three negative cytology test results.[f] Sexual history should not be used as a rationale for more frequent screening.	Insufficient evidence. (*I recommendation*)	Every 2 years from age 21-29 years (*Level A evidence*); every 3 years for women age ≥30 years with a history of three negative cytology test results.[f] (*Level A evidence*)
HPV co-test (cytology + HPV test)	Not recommended under age 30. Age ≥30 years, no more than every 3 years if HPV negative, cytology normal. Sexual history should not be used as a rationale for more frequent screening.	Insufficient evidence. (*I recommendation*)	Age ≥30 years, no more than every 3 years if HPV negative, cytology normal (*Level A evidence*), even with new sexual partners. Not recommended for women younger than 30 years of age.
Primary HPV testing[g]	Not FDA approved.	Not FDA approved.	Not FDA approved.
When to Stop Screening			
	Women age ≥70 years with three or more recent, consecutive negative test results and no abnormal tests in prior 10 years.[f] At-risk women[f] should continue screening as long as they are in reasonable health.	Women age >65 years with adequate recent screening with normal Pap test findings who are not otherwise at high risk for cervical cancer. (*D recommendation*)	Age 65 to 70 years with three consecutive normal cytology tests and no abnormal tests in the past 10 years (*Level B evidence*); an older woman who is sexually active and has multiple partners should continue to have routine screening.

Adapted from Centers for Disease Control and Prevention: Cervical cancer screening guidelines. *Available at: www.cdc.gov/cancer/cervical/pdf/guidelines.pdf.*

FDA, U.S. Food and Drug Administration; *HPV,* human papillomavirus.

[a]Saslow D, Runowicz CD, Solomon D, et al: American Cancer Society guideline for the early detection of cervical neoplasia and cancer, *CA Cancer J Clin* 52:342-362, 2002.

[b]Saslow D, Castle PE, Cox JT, et al: American Cancer Society guideline for HPV vaccine use to prevent cervical cancer and its precursors, *CA Cancer J Clin* 57:7-28, 2007.

[c]U.S. Preventive Services Task Force (USPSTF): *Screening for cervical cancer,* January 2003. Available at: http://www.uspreventiveservicestaskforce.org/uspstf/uspscerv.htm.

[d]ACOG Committee on Practice Bulletins—Gynecology: ACOG practice bulletin no. 109: cervical cytology screening, *Obstet Gynecol* 114:1409-1420, 2009.

[e]Provider discretion and patient choice should be used to guide initiation of screening in women aged 21 years or older who have never had vaginal intercourse and for whom the absence of a history of sexual abuse is certain.

[f]Some exceptions apply (e.g., women who are immunocompromised, have a history of prenatal exposure to diethylstilbestrol [DES], are human immunodeficiency virus [HIV] positive, have previously been treated for cervical intraepithelial neoplasia [CIN] 2 or 3).

[g]Primary HPV testing is defined as conducting the HPV test as the first screening test. It may be followed by other tests (like a Pap) for triage.

There are four U.S. Food and Drug Administration (FDA)–approved tests, including the Digene High-Risk HPV HC2 DNA test (Qiagen), the Digene HPV HC2 DNA test (Qiagen), the Cervista HPV 16/18 test (Hologics), and the Cervista HPV High-Risk test (Hologics). Testing for HPV infection should not be done to screen for HPV infection outside the specific indications during the setting of cervical cancer screening, because, as emphasized earlier, most HPV infections clear and do not result in clinical disease. There is a new HPV 16/18 test also available with limited data on its use, but this test can be used to help manage women with a positive high-risk HPV test result. HPV tests are frequently used inappropriately, so clinical providers should be aware of their utility and indications. The tests are not recommended for screening sex partners, screening men, screening adolescents, diagnosing genital warts, or as a "sexually transmitted disease (STD) test." Although an FDA-approved test, there are no clinical indications for the Digene HPV HC2 DNA test (Qiagen), which tests for both high-risk and low-risk HPV types.

Anogenital warts are diagnosed by physical examination. Topical acetic acid is often used as a diagnostic aid but is not specific for genital warts and may result in unnecessary interventions. Biopsy of suspicious lesions may be necessary in some settings (e.g., if the diagnosis is uncertain; the lesions do not respond to standard therapy; the disease worsens during therapy; the patient is immunocompromised; or warts are pigmented, indurated, fixed, bleeding, or ulcerated).

CLINICAL MANAGEMENT AND DRUG TREATMENT

Treatment is directed at the clinical manifestations of HPV infection, but not the infection itself. The treatment options differ depending on the condition. Treatments for genital warts include patient-applied and provider-administered therapies. Some patients elect to wait to see if genital warts regress on their own. Treatments for cervical precancers and cancers are administered by a provider. Patients with warts that are located on the rectum or cervix, patients with extensive genital warts, and patients whose condition does not respond to a standard course of therapy for anogenital warts should be managed by a specialist. In addition, women with high-grade cervical disease should be managed by a specialist.

Genital warts may remain the same, grow in size and/or number, or regress on their own. Treatment is directed at removing warts primarily for esthetic reasons. Different treatments are available, and no single treatment is ideal for all patients or all lesions. Patients and providers may decide on a treatment option based on convenience, cost, availability, the methods of administering therapy, or other factors (Table 57-2). Treatment can induce wart-free periods, but the underlying viral infection can persist and may result in recurrence (in about 30% of cases). No data suggest that treatment modalities for external genital warts should be different in the setting of HIV infection, although there are fewer data on different therapies in the setting of HIV infection.

Patient-applied therapies should be used only when the warts can be identified and accessed for treatment and there is the likelihood of high compliance. A follow-up appointment several weeks into therapy to determine appropriateness of medication use and response to treatment may be useful. Patient-applied therapies include podofilox 0.5% solution or gel, imiquimod 5% cream, and a new therapeutic, sinecatechins 15% ointment. Patients should apply podofilox solution with a cotton swab or podofilox gel with a finger to visible genital warts twice a day for 3 days, followed by 4 days of no therapy. This cycle may be repeated as necessary for up to four cycles. Patients should apply imiquimod cream once daily at bedtime, three times a week for up to 16 weeks. The treatment area should be washed with soap and water 6 to 10 hours after the application. Sinecatechins 15% ointment should be applied three times a day for up to 16 weeks.

Provider-applied therapies include cryotherapy with liquid nitrogen or cryoprobe, trichloroacetic acid (TCA) or bichloroacetic acid (BCA) 80% to 90%, podophyllin resin 10% to 25% in a compound tincture of benzoin, and surgical removal. There are also other provider-applied therapies with fewer data available and/or more reported side effects. Cryotherapy should be performed every 1 to 2 weeks. Podophyllin resin should be applied to each wart in small amounts and allowed to air dry. To reduce local irritation, the preparation may be thoroughly washed off 1 to 4 hours after application. Both TCA and BCA should be applied sparingly and allowed to dry before the patient sits or stands. If pain is intense, the acid can be neutralized with soap or sodium bicarbonate. A white "frosting" will develop on the wart after the TCA or BCA dries. Both podophyllin and TCA or BCA treatments can be repeated weekly. Anogenital warts may be surgically removed by tangential scissor excision, tangential shave excision, curettage, electrosurgery, or other methods.

Low-grade lesions such as cervical intraepithelial neoplasia (CIN) 1 are managed by follow-up rather than treatment, as these lesions often regress. Treatments for high-grade cervical disease (CIN 2, CIN 3, AIS) are tailored and may include loop electrosurgery excision procedure (LEEP), conization, other surgical options, or cryotherapy. Treatments for cervical cancer depend on the stage of the cancer, the size of the tumor, the patient's desire to have children, and the patient's age and may include chemotherapy, radiation therapy, surgery, or other therapies.

PROGNOSIS

Genital warts are generally a benign condition that resolves with time; most genital warts resolve within 6 months (with or without treatment). However, a large proportion (approximately 30%) of genital warts recur, which can result in frequent office visits, sometimes costly and debilitating treatment, and psychosocial burden. There are rare cases of giant condyloma of Buschke and Lowenstein, a slow-growing, highly destructive condyloma caused by HPV-6 or HPV-11 infection, that may have a focus of squamous cell carcinoma. This tumor does not metastasize but causes severe and local destruction. This condition most commonly occurs in immunocompromised individuals, including patients with HIV infection or posttransplant status.

The prognosis for women with low-grade cervical disease is also good; CIN 1 (a low-grade histologic change) usually clears spontaneously (60% of cases) and rarely progresses to cancer (1%). Lower percentages of high-grade lesions including CIN 2 and 3 spontaneously clear (40% for CIN 2 and 33% for CIN 3), and a substantial number progress to cancer if not treated (5% for CIN 2 and >12% for CIN 3). Treatment of these lesions prevents the progression to invasive cancer. The prognosis for cervical cancers depends on the stage at diagnosis, size of the tumor, and age of the woman.

PREVENTION AND CONTROL

Two prophylactic HPV vaccines have been licensed and recommended for use: a quadrivalent HPV vaccine (Gardasil, Merck & Co.) that prevents HPV types 6, 11, 16, and 18, and a bivalent HPV vaccine (Cervarix, GlaxoSmithKline) that prevents HPV types 16, 18. The quadrivalent HPV vaccine was licensed for use in the United States in June 2006, and the bivalent HPV vaccine was licensed for use in October 2009. Either vaccine is recommended for routine use in 11- or 12-year-old girls, with catch-up vaccination at ages 13 through 26 years. Both vaccines are licensed in multiple countries worldwide and are being used or considered for use. The quadrivalent HPV vaccine is licensed for use in males and may be given to boys and young men aged 9 to 26 years to prevent acquisition of genital warts.

Table 57-2 Recommended Treatment Regimens for Anogenital Warts Based on Anatomic Location

	Patient-Applied Therapy			*Provider-Administered Therapy*				
ANATOMIC LOCATION	**PODOFILOX***	**IMIQUIMOD***	**SINECATECHINS***	**CRYOTHERAPY**	**PODOPHYLLIN***	**TCA OR BCA**	**SURGICAL REMOVAL**	**OTHER**
External genital	X	X	X	X	X	X	X	†
Meatus				X	X			
Vagina				X		X		‡
Cervical or rectal								Biopsy, consult a specialist
Anal or perianal				X		X	X	Digital rectal examination, anoscopy

Adapted from Centers for Disease Control and Prevention (CDC): Sexually transmitted diseases treatment guidelines, 2010, MMWR
BCA, Bichloroacetic acid; *TCA,* trichloroacetic acid.
*Podofilox, podophyllin, imiquimod, sinecatechins not recommended during pregnancy.
†Alternative regimens include intralesional interferon, laser therapy, topical cidofovir, and other.
‡Some experts recommend use of podofilox and imiquimod, but data are limited.

The vaccines do not have any therapeutic effect; neither vaccine prevents progression of infection to disease nor regression of existing lesions. The vaccine would have maximum benefit as a prophylactic vaccine, when given before exposure to HPV infection (i.e., before sexual debut). This is one of the reasons why vaccine is routinely recommended for 11- or 12-year-old girls.

Other strategies such as treatment of existing lesions (genital warts or cervical dysplasia) may reduce but do not eliminate HPV infection. Condoms have been shown to reduce the risk for genital warts, cervical cell changes, and HPV infection; however, infection or disease can occur on sites not covered or protected by a condom. Abstinence is the only sure way to prevent HPV infection, as most sexually active men and women acquire infection at some point in their lifetime.

EVIDENCE

Centers for Disease Control and Prevention (CDC): FDA licensure of a bivalent human papillomavirus (HPV) vaccine (Cervarix) for use in females and updated Advisory Committee on Immunization Practices (ACIP) recommendations for HPV vaccination of females, *MMWR Morb Mortal Wkly Rep* 59:626-629, 2010. *Either the bivalent or the quadrivalent HPV vaccine is recommended for routine use in 11- or 12-year-old girls and can be given to 13- through 26-year-old females if they have not received or completed the vaccine series; vaccine can also be given girls as young as 9 years of age.*

Centers for Disease Control and Prevention (CDC): FDA licensure of quadrivalent human papillomavirus vaccine (HPV4, Gardasil) for use in males and guidance from the Advisory Committee on Immunization Practices (ACIP), *MMWR Morb Mortal Wkly Rep* 59:630-632, 2010. *Quadrivalent HPV vaccine may be given to males 9 through 26 years old to prevent acquisition of genital warts.*

Clifford GM, Gallus S, Herrero R, et al: Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis, *Lancet* 366:991-998, 2005. *This evaluation of cytologically normal women worldwide demonstrates high HPV prevalence that varies by country and region.*

Datta SD, Koutsky LA, Ratelle S, et al: Human papillomavirus infection and cervical cytology in women screened for cervical cancer in the United States, 2003-2005, *Ann Intern Med* 148:493-500, 2008. *This evaluation of HPV prevalence in women screened for cervical cancer at several different venues in the United States demonstrated high HPV prevalence.*

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Infections Caused by *Chlamydia trachomatis*, Including Lymphogranuloma Venereum

William M. Geisler

58

ABSTRACT

Chlamydia trachomatis infections are highly prevalent worldwide, especially in adolescents and young adults, and can cause substantial morbidity. The majority of persons with chlamydia are asymptomatic with normal genital examination findings, and diagnosis of chlamydia usually relies on testing for the bacteria. Despite highly sensitive tests and highly effective therapy, the number of reported chlamydial infections continues to rise. As a chlamydia vaccine is not available, better prevention and control efforts are needed.

C. trachomatis is an obligate intracellular bacterium that infects mucosal surfaces of humans, including oropharyngeal, anogenital, and conjunctival surfaces. *C. trachomatis* can be classified through molecular typing into strains causing ocular infections (trachoma), strains causing nonulcerative oropharyngeal and/or anogenital infections (chlamydia), and strains causing a distinct ulcerative chlamydia syndrome called *lymphogranuloma venereum* (LGV). This chapter reviews the epidemiology, clinical features, diagnosis, treatment, and prevention of chlamydia and LGV.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Chlamydia

Chlamydia is highly prevalent worldwide in both industrialized and developing countries. The World Health Organization (WHO) estimates that approximately 92 million new cases of chlamydia occur worldwide each year. Chlamydia is a reportable infection in the United States and remains the most commonly reported bacterial sexually transmitted infection. Despite declining chlamydia prevalence in some geographic areas with successful screening and treatment programs, the total number of chlamydia cases reported in the United States continues to increase each year and now exceeds 1.2 million cases annually. The majority of chlamydia cases in the United States go undiagnosed, and it is estimated that there are approximately 3 million new chlamydial infections each year. Nationally representative surveys of chlamydia prevalence in adolescents and young adults have revealed a prevalence of up to 5% in females and up to 4% in males. Chlamydia prevalence may be much higher, often higher than 10%, in some venues such as sexually transmitted disease (STD) clinics and correctional facilities. The Southeast U.S. region has the highest chlamydia burden.

Females experience significant health consequences from chlamydial complications. One important chlamydial complication in women is pelvic inflammatory disease (PID), a condition in which the infection spreads to the upper genital tract and can involve the uterus (endometritis), fallopian tubes (salpingitis), ovaries, and/or peritoneum. It is estimated that there are over 1 million new cases of PID each year in the United States, and at least 10% of women with PID will become infertile (with higher infertility rates in women with repeated PID episodes). In the United States, the estimated annual costs attributable to chlamydia and its complications are several billion dollars.

Lymphogranuloma Venereum

There are no reliable estimates of the burden of LGV, because the diagnosis is often missed or is made on clinical findings rather than diagnostic testing results. In general, LGV is thought to be rare and sporadic in industrialized countries. However, there have been LGV outbreaks since 2003 in the Netherlands and other European countries, primarily among men who have sex with men (MSM). In developing countries, LGV may be highly endemic and a common cause of genital ulcer disease. Hundreds to thousands of LGV cases occur annually in parts of East and West Africa, Southeast Asia, India, South America, and the Caribbean.

RISK FACTORS

Among many factors associated with chlamydia, young age is the strongest risk factor. Centers for Disease Control and Prevention (CDC) surveillance studies have demonstrated the highest rates in persons younger than 26 years of age. The chlamydia rate significantly declines in persons older than 29 years of age but still may be substantial in those with other relevant risk factors, including unprotected sexual intercourse with a new partner or multiple sexual partners and trading sex for money or drugs. A prior chlamydial infection is a major risk factor, primarily because of high rates of reinfection from untreated partners. Although chlamydia is common in all race and ethnic groups in the United States, African Americans have the highest chlamydia rate; Hispanics and American Indian/Alaska Natives are also disproportionately affected compared with Caucasians.

In addition to risk factors related primarily to higher-risk sexual behaviors or socioeconomic status (affecting access to healthcare and educational or prevention measures), biological factors may increase chlamydia risk. Cervical ectopy likely increases risk of chlamydia acquisition by providing a greater surface area of susceptible cells for infection. Cervical ectopy is more common in younger females, especially those on oral contraceptive therapy. Bacterial vaginosis has also been associated with chlamydia; bacterial species present in bacterial vaginosis may produce biochemical substrates that favor survival of *C. trachomatis*. Finally, host immune responses and host genetic determinants (e.g., human leukocyte antigen [HLA] types and immune gene polymorphisms) likely play a role in susceptibility to or protection against chlamydia, but these immunogenetic factors in human chlamydial infections are poorly understood at the current time. Risk factors for PID include douching and prior PID, whereas PID rates are lower in pregnant women and in women on hormonal therapy.

Lymphogranuloma Venereum

Studies of LGV outbreaks in industrialized countries revealed that most LGV cases were anorectal infections in MSM who practiced unprotected receptive and/or insertive anal intercourse. Other LGV risk factors indentified were having a large number of sexual partners, being human immunodeficiency virus (HIV) positive, having group sex, and attending "sex parties." Although risk factors for endemic genital LGV in developing countries are less well understood, they likely resemble traditional chlamydia risk factors, except unlike with chlamydia, transmission of LGV can also occur via skin-to-skin contact.

CLINICAL FEATURES

Chlamydia

As discussed in more detail in the following paragraphs, chlamydia causes a diverse spectrum of clinical syndromes (Table 58-1). The incubation period for chlamydia ranges from 7 to 21 days.

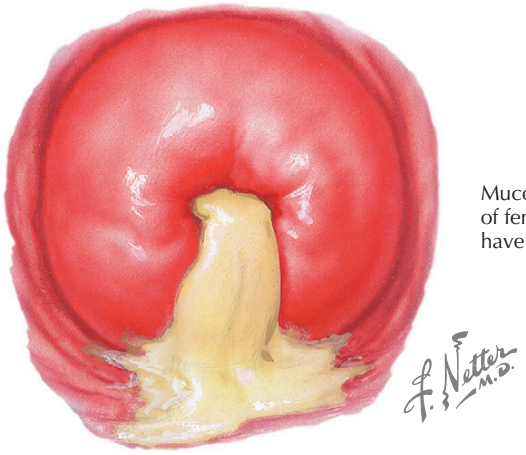
GENITAL INFECTION IN FEMALES

In the female genital tract, *C. trachomatis* primarily infects the endocervix but may also infect the urethra and Bartholin's glands. Over 75% of women with endocervical chlamydia are asymptomatic, and even when symptoms are present, they are nonspecific and often overlap with symptoms found in other vaginal infections (e.g., trichomoniasis or bacterial vaginosis) or endocervical infections (e.g., gonorrhea). Symptoms may include new or increased vaginal discharge, intermenstrual bleeding, or pain during intercourse. Even in the absence of symptoms, 10% or more of women with chlamydia will have signs of infection on pelvic examination. Endocervical discharge (purulent, cloudy, or bloody), easily induced endocervical bleeding ("friability") on insertion of an endocervical swab, and edematous ectopy are the examination findings most suggestive of endocervical chlamydia, yet are nonspecific and may be seen in other sexually transmitted endocervical infections (e.g., gonorrhea); presence of one or more of these findings supports the clinical diagnosis of cervicitis (Figure 58-1). Abnormal vaginal discharge (originating from the endocervix) may also be present. Although cervical ectopy may predispose to chlamydia, ectopy without edema or

Table 58-1 Clinical Syndromes Caused by Chlamydia

WOMEN	MEN	NEONATES*
Urethritis	Urethritis	Conjunctivitis
Cervicitis	Epididymitis	Pharyngitis
Pelvic inflammatory disease	Proctitis or proctocolitis	Respiratory infection
Proctitis or proctocolitis	Conjunctivitis*	
Conjunctivitis*	Pharyngitis	
Bartholinitis	Prostatitis	
Pharyngitis	Reactive arthritis	
Reactive arthritis	Trachoma*	
Trachoma*		

*Not discussed in this chapter.



Mucopurulent endocervical discharge may be present on examination in a small proportion of females with chlamydial endocervical infection, but most chlamydia-infected females have a normal-appearing cervix on examination

Figure 58-1 Mucopurulent cervicitis.

congestion is very common in sexually active female adolescents and young adults, and its presence alone is not indicative of chlamydia.

The majority of women with endocervical chlamydia will have concomitant urethral infection, and a small proportion of these urethral infections may cause painful urination and/or urinary frequency. Urethral chlamydia in young women is often misdiagnosed as a urinary tract infection (UTI) and treated with antibiotics that are not effective against chlamydia (e.g., trimethoprim-sulfamethoxazole), and therefore consideration should be given to screening sexually active young women with urinary symptoms for chlamydia. Concomitant chlamydia of Bartholin's glands may rarely occur, manifesting as ductal erythema and swelling, often with purulent ductal exudate.

Symptoms of PID include pelvic or lower abdominal pain (especially with intercourse), nausea, and fever. Examination findings of PID may include cervical motion tenderness and/or tenderness of the uterus, fallopian tubes, ovaries, and/or abdomen. A distally blocked fallopian tube can fill with serous fluid and become substantially dilated, termed *hydrosalpinx* (Figure 58-2). The majority of subjects with PID will be without symptoms or will have mild pelvic complaints. Short-term complications of PID include tubal and/or ovarian abscesses, and long-term complications include chronic pelvic pain, ectopic pregnancy, and infertility; chlamydia is a leading preventable cause of ectopic pregnancy and infertility worldwide. Overall, the most common clinical presentation of genital chlamydia in females involves no symptoms and normal pelvic examination findings (i.e., no cervical signs).

GENITAL INFECTION IN MALES

In the male genital tract, *C. trachomatis* primarily infects the urethra. Studies employing a universal screening approach have demonstrated that over 50% of males with urethral chlamydia are asymptomatic. However, in some clinical settings such as public health clinics and emergency rooms, the majority of males with chlamydia may have urethral symptoms. This is because males are unlikely to be seen in these clinical settings purely for screening; rather, they are seen for evaluation of bothersome urethral symptoms. Symptoms of urethra chlamydia in males may include painful urination, urinary frequency, meatal itching or discomfort, and urethral discharge. If a male with chlamydia has not voided recently, a urethral discharge may be apparent on examination and typically is clear or cloudy, often with mucus strands (Figure 58-3). Meatal erythema and/or swelling may accompany the discharge. If no spontaneous urethral discharge is noted, the urethra should be stripped and examined again. Abundant purulent discharge, as seen in gonorrhea, is uncommon in chlamydia.

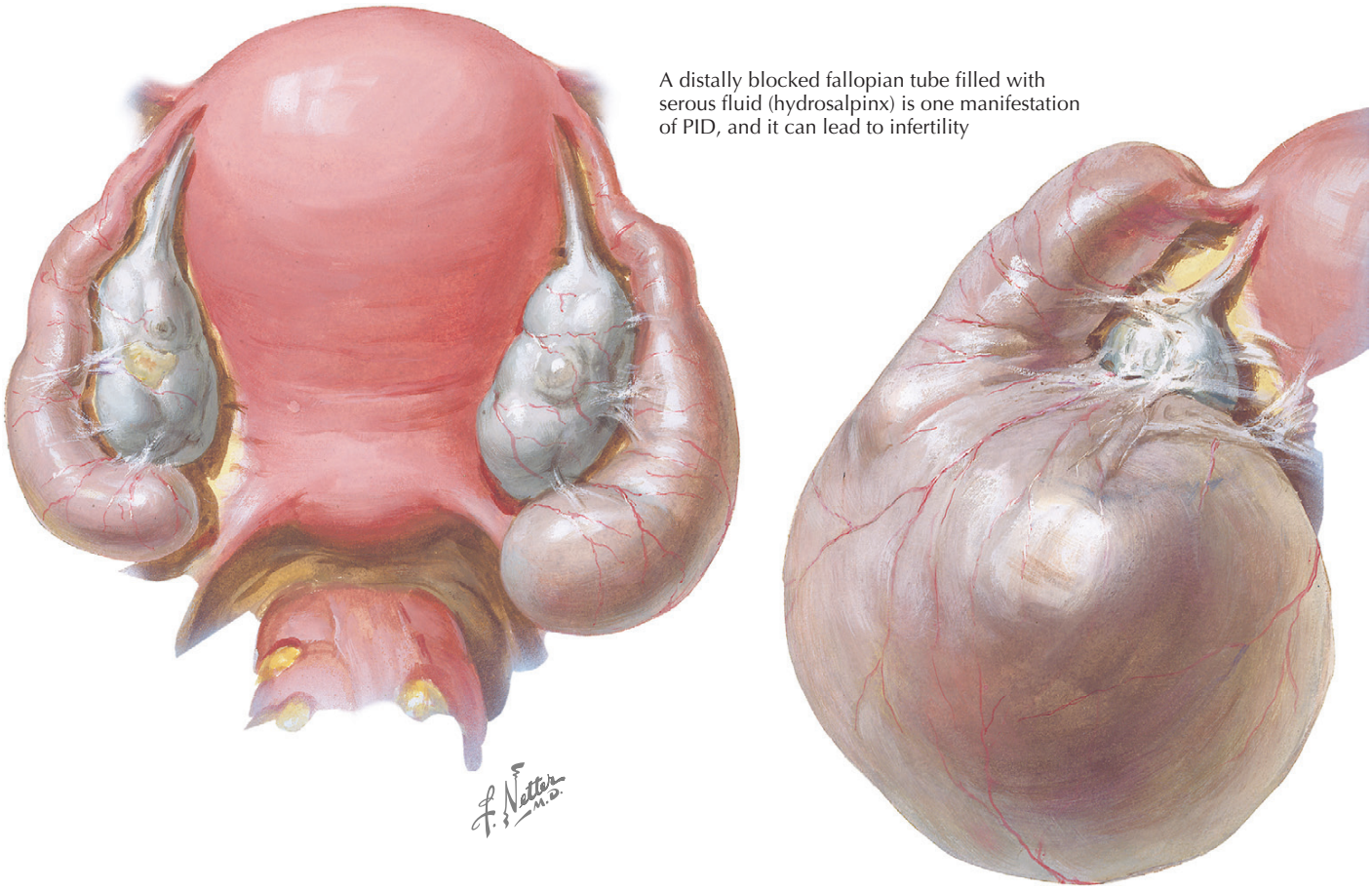


Figure 58-2 Pelvic inflammatory disease.

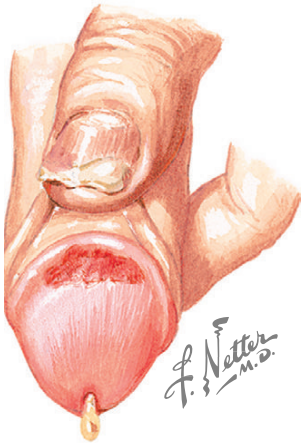


Figure 58-3 Urethritis.

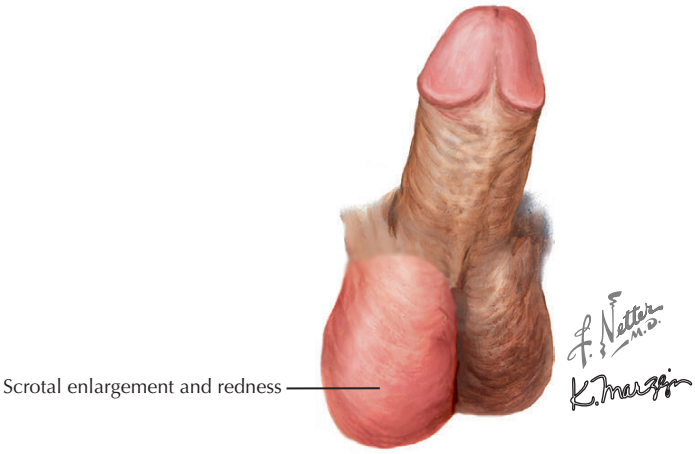


Figure 58-4 Epididymitis.

Males with urethral symptoms but normal urethral examination findings are sometimes misdiagnosed as having a UTI and not tested for chlamydia or treated with antibiotics effective against chlamydia. However, UTIs caused by enteric bacteria are very rare in young sexually active males with anatomically and functionally normal urinary and renal collecting systems; therefore young sexually active males with urethral symptoms should be presumed to have a sexually transmitted urethral infection and undergo appropriate diagnostic testing and treatment. Inguinal lymph node swelling is uncommon in urethral chlamydia (non-LGV) but can occur and is usually mild.

Chlamydia may spread to the upper genital tract in males and cause infection of the epididymis termed *epididymitis* (Figure 58-4). The findings in chlamydia epididymitis are usually unilateral. Symptoms include swelling or pain of the scrotum, testicle and/or epididymis, and, infrequently, fever. On examination, males with epididymitis, may have redness, warmth, and/or swelling of the overlying scrotum. Swelling and tenderness of the involved epididymis is usually present and may be accompanied by testicular tenderness. Short-term complications of epididymitis include testicular abscesses, and long-term complications include chronic testicular pain, chronic epididymitis, and infertility. The most important differential diagnosis of epididymitis is testicular torsion (compromise of testicular arterial blood flow); males with severe acute scrotal pain, especially if associated with recent testicular trauma or prior recurring episodes of testicular pain, should be sent immediately to an urgent care setting for ultrasound to rule out torsion.

Chlamydia has also been reported as a cause of prostatitis, but the epidemiology, clinical features, and clinical course of this clinical presentation are poorly understood and will not be discussed further in this chapter. Overall, the majority of urethral chlamydial infections in males occur without urethral symptoms and with normal genital examination findings.

ANORECTAL INFECTION (NON-LGV CHLAMYDIA)

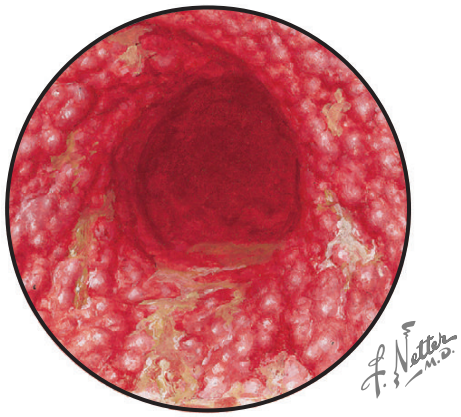
Similar to anorectal LGV (discussed later), non-LGV *C. trachomatis* strains can cause anorectal infection in men or women who practice receptive anorectal intercourse. Anorectal chlamydia has also been diagnosed in women who deny having anorectal intercourse, and it has been postulated that rectal infection may occur in this setting because of cross-contamination of the anal area with chlamydial organisms present in vaginal secretions. The majority of men and women with anorectal chlamydia are asymptomatic. Symptoms that may occur include anorectal pain, itching, mucus, discharge, bleeding, or diarrhea; patients may complain of inability to defecate or spasms and cramping during bowel movements. Patients with anorectal symptoms should ideally be evaluated by anoscopy, and examination findings include anorectal erythema, discharge (mucous, cloudy, purulent, or bloody), or occasionally ulceration (Figure 58-5). Anorectal chlamydia may be misdiagnosed as proctitis caused by non-STD pathogens; however, any patient with proctitis who reports anorectal sexual activity should receive STD testing including chlamydia testing. Anorectal chlamydia can be complicated by strictures, which may affect bowel movement frequency and character of the stools.

PHARYNGEAL INFECTION

C. trachomatis has been detected in pharyngeal specimens, yet it remains unclear whether chlamydial infection of the pharynx causes any clinically significant disease and whether the organism is transmissible from the pharynx. A primary reason for the limited knowledge regarding chlamydia pharyngeal infection is that traditional chlamydia tests, such as culture, perform poorly on pharyngeal specimens. However, with the availability of nucleic acid amplification assays for *C. trachomatis*, the clinical presentation and course of chlamydia pharyngeal infection should become better understood. Limited clinical experience to date suggests that chlamydia infection of the pharynx is mostly asymptomatic with normal examination findings or minimal pharyngeal erythema. Until the clinical significance of pharyngeal chlamydial infections are better understood, a conservative approach to treating these infections is appropriate.

REACTIVE ARTHRITIS

Reactive arthritis (previously called *Reiter's syndrome*) may occur during or shortly after a genital chlamydial infection and is characterized primarily by conjunctivitis and an aseptic rheumatoid factor–negative asymmetric polyarthritis. Other clinical findings may include oral ulcers, uveitis, rashes, inflammation of the sacroiliac joints, and cardiac and neurologic complications. Reactive arthritis occurs more commonly in men and is often linked to HLA-B27 expression; persons with HLA-B27 may have a more aggressive clinical course.



Endoscopy appearance in severe proctitis

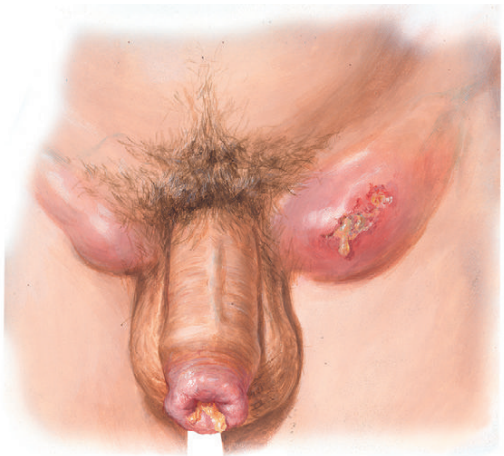
Figure 58-5 Proctocolitis.

Lymphogranuloma Venereum

The clinical features of LGV can be divided into three stages. The primary stage occurs at the inoculation site in approximately 3 to 30 days after exposure. The primary lesion is usually a small asymptomatic genital or rectal papular lesion(s) and/or ulcer(s), which may go unnoticed by the patient and heal without therapy. Other symptoms of urethral, endocervical, or rectal LGV may resemble those described for chlamydia. With genital LGV, examination findings may include a genital papule(s) and/or ulcer(s), urethral discharge (males), and endocervical discharge and/or easily induced endocervical bleeding (females). In colorectal LGV, examination findings may include colorectal ulcers, bleeding, tenderness, and discharge.

Approximately 2 to 6 weeks after the primary stage, the secondary stage occurs at the lymph nodes that drain the inoculation site. The involved lymph nodes increase rapidly in size, sometimes coalescing with adjacent involved nodes, and are often associated with pain and erythema. The lymph nodes become fluctuant and are termed *buboes* (Figure 58-6). Up to one third of buboes may spontaneously rupture and drain purulent material, which can provide pain relief. The draining buboes may form fistulas or sinus tracts. An examination finding of involvement of both inguinal and femoral nodes has been termed the *groove sign* and is highly characteristic of LGV. The secondary stage may be accompanied by constitutional symptoms including fever, chills, headache, myalgias, and fatigue.

The tertiary stage involves chronic or late complications of LGV. Genital LGV may be complicated by chronic extensive ulceration of the external genitalia (which can be destructive) and lymphatic obstruction with genital elephantiasis. Colorectal



Lymph nodes in LGV infection can become enlarged, erythematous, and fluctuant, termed *buboes*. Buboes may spontaneously rupture and drain purulent material, which can provide pain relief.

Figure 58-6 Buboes.

LGV may be complicated by strictures, fistulas, and/or perirectal abscesses.

DIAGNOSTIC APPROACH

Because most chlamydial infections in men and women are asymptomatic, and even when present, symptoms or examination findings are usually nonspecific, population-based detection of *C. trachomatis* involves selective screening of those at highest risk. Chlamydia testing is important for purposes of patient treatment and prevention of complications, patient education, sexual partner treatment, and communicable disease reporting. CDC recommends annual chlamydia screening for all sexually active women 25 years of age or younger, as well as women older than age 25 with chlamydia risk factors (e.g., multiple sexual partners, a new sexual partner). Women with genital complaints or signs of cervicitis or PID should undergo diagnostic testing as well. The benefits of chlamydia screening have been demonstrated in parts of the United States where screening and treatment programs for women have reduced both chlamydia prevalence and PID rates. Pregnant women should be screened for chlamydia at their first prenatal visit; pregnant women younger than age 25 years or with risk factors should be tested again for chlamydia during the third trimester.

Although annual chlamydia screening of sexually active males is not recommended, males with genital symptoms and/or chlamydia risk factors should be tested. Also, males in venues with a high chlamydia prevalence (e.g., STD clinics, correctional facilities) should be tested for chlamydia if resources permit and if testing does not hinder screening efforts in women.

Over the last 30 years there have been considerable advances in the development of diagnostic assays for detecting *C. trachomatis*. Chlamydia culture, traditionally considered the gold standard, was the first chlamydia test available and is still used in some centers for research. However, because culture was more technically demanding, there was a shift toward nonculture chlamydia tests. The earlier nonculture tests were based on detection of chlamydia antigen (enzyme immunoassays and direct fluorescent antibody [DFA] tests) or nucleic acids (nucleic acid hybridization tests [i.e., deoxyribonucleic acid (DNA) probes]). These nonculture tests were less expensive and technically demanding than culture; however, they had lower test sensitivities than culture (except DFA) and failed to detect many chlamydial infections. *C. trachomatis* serologic assays are available but are not useful in the diagnosis of anogenital chlamydia because they do not distinguish past from current chlamydia and may be negative in early or acute chlamydia.

Around the mid-1990s, nucleic acid amplification tests (NAATs) became available for genital chlamydia testing and offered two distinct advantages over earlier tests: (1) higher test sensitivity resulting from amplification of *C. trachomatis* nucleic acids, and (2) greater patient convenience and/or satisfaction in that as an alternative to the usual genital swab specimens collected by examination, NAATs can also be performed with similar accuracy on noninvasively or minimally invasively collected specimens, including urine or self-collected vaginal swabs. NAATs are now the test of choice for diagnosing genital chlamydia; urine is the recommended specimen for NAATs in men, whereas vaginal swab is the recommended specimen for NAATs in women. Most individuals undergoing testing for chlamydia should also receive testing for gonorrhea, because co-infection with chlamydia and gonorrhea is common and their recommended treatments differ; most NAATs include testing for both infections.

Patients who report practicing receptive anorectal intercourse should undergo anorectal chlamydia testing. Chlamydia culture has been used for anorectal testing; however, recent prospective studies demonstrated that NAATs are superior to culture for detecting *C. trachomatis* in anorectal specimens. NAATs are not currently approved by the U.S. Food and Drug Administration (FDA) for testing on anorectal specimens. Therefore to adhere to Clinical Laboratory Improvement Amendments (CLIA) regulations, laboratories must perform in-house validations to use NAATs with anorectal specimens.

Whether to perform oropharyngeal chlamydia testing on persons reporting receptive oropharyngeal sex is debatable, because it is unclear if *C. trachomatis* causes clinical disease of the oropharynx or is transmissible from this site, and because culture has a very low sensitivity for oropharyngeal specimens. However, recent prospective studies also demonstrated NAATs to be superior to culture for detecting *C. trachomatis* in oropharyngeal specimens. As with using NAATs on anorectal specimens, validations are necessary for laboratories performing NAATs on oropharyngeal specimens.

Lymphogranuloma Venereum

In developing countries, a presumed diagnosis of LGV is usually made based on clinical findings. In industrialized countries, LGV diagnosis is still difficult owing to limitations in commercially available tests and is typically either presumed based on clinical findings or is made through specialized LGV testing at CDC or other specialized laboratories. Serologic tests for *C. trachomatis*, including complement fixation (CF) and microimmunofluorescence (MIF) tests, are not standardized and do not reliably differentiate between LGV and non-LGV *C. trachomatis* strains; higher antibody titers (CF titers >1:64 and MIF titers >1:256) are strongly suggestive of LGV when accompanied by compatible clinical findings but are not confirmatory. Detection of *C. trachomatis* by culture or NAATs from anogenital specimens also does not differentiate LGV from non-LGV strains, and therefore the only means to confirm LGV is to have CDC or a specialized laboratory perform OmpA typing on the *C. trachomatis* strain to demonstrate one of the LGV OmpA types. If buboes are present, *C. trachomatis* may be detected in a bubo aspirate, which would be highly suggestive of LGV in this clinical context; however, confirmation by OmpA typing should still be performed if possible. Treatment of LGV should not be delayed while awaiting the results of LGV testing.

CLINICAL MANAGEMENT AND DRUG TREATMENT

To ensure eradication of infection and prevention of reinfection, management of chlamydia and LGV requires a multifaceted approach (Box 58-1).

Box 58-1 Multifaceted Approach to Management of Chlamydia or Lymphogranuloma Venereum

1. Centers for Disease Control and Prevention (CDC)–recommended antibiotic therapy for infected patients and their partners
2. Abstinence from sexual activity for patients and their partners until treatment is completed
3. Test of cure for pregnant patients at 3 weeks after completing treatment
4. Repeat testing approximately 3 months after completing treatment

Table 58-2 Centers for Disease Control and Prevention (CDC)–Recommended Antibiotic Regimens for Uncomplicated Chlamydia

NONPREGNANT	PREGNANT
Azithromycin 1 g PO in a single dose *or* Doxycycline 100 mg PO twice a day for 7 days	Azithromycin 1 g PO in a single dose *or* Amoxicillin 500 mg PO three times a day for 7 days

PO, Orally.
Note: See the text for alternative treatment regimens for chlamydia.

Antibiotic Therapy

UNCOMPLICATED CHLAMYDIA

CDC recommends either azithromycin 1 g orally (PO) single dose or doxycycline 100 mg PO twice a day for 7 days for uncomplicated genital or anorectal chlamydia in nonpregnant individuals (Table 58-2). These regimens are equally efficacious and tolerated well. Azithromycin and doxycycline should be taken with food to minimize gastrointestinal side effects; doxycycline can cause photosensitivity of the skin, and patients should be educated to take appropriate precautions to prevent sunburns. Treatment compliance is higher with azithromycin, although the doxycycline regimen is usually cheaper. Erythromycin base 500 mg PO four times a day for 7 days is an alternative regimen that has a high rate of noncompliance. Two fluoroquinolone regimens, levofloxacin 500 mg PO daily for 7 days or ofloxacin 300 mg PO twice a day for 7 days, are other alternative regimens for chlamydia that do not offer an efficacy advantage over the recommended regimens and are more costly. Ciprofloxacin has poor in vitro activity against *C. trachomatis* and should not be used. Although there has been only limited clinical experience with azithromycin or doxycycline regimens for treating oropharyngeal chlamydia, these regimens are likely efficacious. Antimicrobial resistance has not been a major concern to date. There are no data to suggest that the efficacy of CDC-recommended regimens is altered in HIV-infected individuals, and CDC recommends the same regimens in these patients.

Doxycycline, ofloxacin, and levofloxacin are contraindicated in pregnancy. CDC recommends either azithromycin 1 g PO single dose or amoxicillin 500 mg PO three times a day for 7 days for uncomplicated chlamydia in pregnant women (see Table 58-2). A potential concern regarding the use of amoxicillin for chlamydia in pregnant women is whether this treatment induces persistence of *C. trachomatis*, which has been demonstrated in vitro after exposure to penicillin. Limited clinical studies of amoxicillin for chlamydia in pregnancy have had study design limitations and have not been able to sufficiently address this concern. Azithromycin is advantageous in terms of compliance, and anecdotal experience suggests that azithromycin is far more widely used than amoxicillin. Erythromycin base 500 mg PO four times a day for 7 days is an alternative regimen for chlamydia in pregnancy but has high noncompliance rates. All three antibiotics are pregnancy category B drugs. Considering its efficacy, tolerability, and compliance advantage over other regimens, azithromycin is the overall best option for treatment of chlamydia in pregnancy.

CHLAMYDIA COMPLICATIONS

An initial consideration in managing PID or epididymitis is whether hospitalization is necessary. Patients with PID should be hospitalized if they are pregnant, are unable to tolerate outpatient antibiotics, are not clinically improved within 72 hours of outpatient treatment, or if there is concern about an alternative diagnosis or a complication. Hospitalization for epididymitis is rare and usually occurs because of concerns about a complication, an alternative diagnosis, or failure of outpatient treatment.

Antimicrobial treatment for PID or epididymitis caused by chlamydia is usually started empirically before chlamydia test results are available and is broad enough to cover at least chlamydia and gonorrhea. CDC recommends one of the following empirical regimens for inpatient treatment of PID: (1) cefotetan 2 g intravenously (IV) every 12 hours *or* cefoxitin 2 g IV every 6 hours *plus* doxycycline 100 mg PO or IV every 12 hours, or (2) clindamycin 900 mg IV every 8 hours *plus* gentamicin intramuscularly (IM) or IV with a 2-mg/kg loading dose followed by 1.5 mg/kg every 8 hours (once-daily dosage regimens are an alternative). After 24 hours of clinical improvement, patients may be switched to an oral regimen depending on the initial regimen: either doxycycline 100 mg twice a day or clindamycin 450 mg four times a day for a total PID treatment course of 14 days.

The CDC-recommended outpatient treatment for PID is doxycycline 100 mg PO twice a day for 14 days and a single dose of ceftriaxone 250 mg IM with or without metronidazole 500 mg PO twice a day for 14 days. There are limited studies on the use of azithromycin for PID, but azithromycin is not currently recommended for PID. Recommended outpatient treatment for epididymitis is doxycycline 100 mg PO twice a day for 10 days and a single dose of ceftriaxone 250 mg IM. There are limited studies on the use of azithromycin regimens for PID, but azithromycin in not currently CDC recommended for PID. Adjunctive measures for pain relief in epididymitis include analgesics and scrotal support (e.g., wearing briefs rather than boxers and placing a rolled up towel or blanket under the scrotum for support while sitting or lying). It is recommended that subjects with PID or epididymitis undergo repeat genital examination in about 72 hours to evaluate clinical response to treatment; lack of treatment response or worsening pain may

suggest treatment failure, a complication (e.g., an abscess), or another cause for the clinical presentation.

Reactive arthritis associated with chlamydia is initially treated with antichlamydial antibiotics (necessary duration of treatment is not known) and nonsteroidal antiinflammatory agents. More aggressive reactive arthritis may require disease-modifying antirheumatic drugs (e.g., sulfasalazine and methotrexate). Management of reactive arthritis often requires consultation with a rheumatologist.

LYMPHOGRANULOMA VENEREUM

The CDC-recommended treatment for LGV is doxycycline 100 mg PO twice a day for 21 days. An alternative regimen is erythromycin base 500 mg four times a day for 21 days, and some STD specialists believe that azithromycin 1 g PO once weekly for 3 weeks is probably an effective alternative; however, data supporting the use of these nontetracycline alternative regimens for LGV are limited. As with chlamydia, LGV treatment recommendations are not different for HIV-infected patients. In individuals with tender, swollen inguinal lymph node(s), symptomatic relief can be achieved by aspiration or incision and drainage of the affected lymph node. For pregnant women with LGV, the erythromycin or azithromycin regimens should be used because doxycycline is contraindicated in pregnancy.

Sexual Activity

To prevent transmission to uninfected individuals or reinfection of the patient, it is important to instruct patients with chlamydia or LGV to abstain from sexual activity until both the patient and his or her partner(s) have completed a CDC-recommended treatment regimen and symptoms (if present) have resolved. Completion of the single-dose azithromycin regimen is considered to be 7 days after the single dose is administered. For those persons unlikely or unwilling to abstain from sexual activity during this period, strict compliance with condom use should be reinforced.

Treatment of Sexual Partners

Most chlamydia (and presumably many LGV) treatment failures are a result of reinfection from an untreated sexual partner or a new infection. Treatment of sexual partners of patients with chlamydia or LGV is important, both for preventing reinfection of the patient and for preventing further transmission to other susceptible individuals. Sex partners should be treated if they had sexual contact with the patient during the 60 days preceding symptom onset or the diagnosis. The most recent sex partner should be treated even if the time of the last sexual contact was more than 60 days before symptom onset or diagnosis. Partners of patients with chlamydia should receive either the azithromycin or doxycycline regimen recommended by CDC for chlamydia treatment. CDC recommends that sexual partners of patients with LGV receive CDC-recommended chlamydia treatment regimens rather than CDC-recommended LGV regimens if the partner does not have clinical evidence of LGV disease (the rationale for this may be that subjects exposed to LGV without clinical evidence of infection likely have less invasive disease and may not need the 3 weeks of treatment normally recommended for LGV). There are two main strategies for getting sexual partners treated: partner referral and expedited partner therapy (EPT).

PARTNER REFERRAL

Because many clinical providers do not have the necessary resources, experience, or willingness to perform "partner notification" for chlamydia or LGV, the standard method to get partners of patients with chlamydia or LGV treated is "partner referral," whereby patients notify their partners that they have been exposed to the infection and should themselves be seen by a clinical provider for testing and treatment. However, repeat chlamydia rates are high in patients instructed to refer their partners, suggesting that partner referral is sometimes ineffective in ensuring partner treatment (especially for male partners of female patients).

EXPEDITED PARTNER THERAPY

A promising approach to ensuring more partners of patients with chlamydia are treated is EPT, whereby a partner receives the treatment in an expedited manner without seeing a clinical provider. The primary way that EPT is used is for a patient to deliver the medication directly to the partner, which is termed "patient-delivered partner therapy" (PDPT). An alternative strategy is for the patient to deliver a prescription to the partner. Azithromycin is the chlamydia treatment primarily used in PDPT (rather than doxycycline). EPT is highly acceptable to patients and their partners. Several studies, both observational and clinical trials, have demonstrated a trend toward lower repeat chlamydia rates in patients with chlamydia who use PDPT versus partner referral. The major advantage of EPT is that more sexual partners will get treated, which should decrease rates of repeat chlamydia and lead to an overall decrease in chlamydia prevalence in a given community. Additional information can be found at www.cdc.gov/std/ept.

Follow-up and Repeat Testing

Nonpregnant patients with uncomplicated chlamydia or LGV do not need a test of cure after completion of therapy unless symptoms or signs of infection persist or recur. However, a test of cure (a chlamydia NAAT) at 3 weeks after completion of treatment for uncomplicated chlamydia or LGV infections should be performed for pregnant women, a population in which treatment failures could lead to both maternal and neonatal complications. Repeat chlamydia NAAT earlier than 3 weeks after completion of treatment could yield a false-positive test result (because of residual DNA or RNA from nonviable *Chlamydia*).

Chlamydia recurrence is common in males and females, occurring in up to 10% to 20% within 6 months of treatment. All females with chlamydia should be retested for chlamydia at approximately 3 months after treatment; if resources permit, males with chlamydia should also undergo repeat testing at approximately 3 months after treatment. Some experts recommend repeat testing for women with chlamydia PID as early as

6 weeks after therapy. Some researchers in the United States (and several in Europe) are evaluating the feasibility of repeat chlamydia testing by home self-collection and mailing in specimens, but this practice is still under investigation in the United States. The rate of LGV recurrence in unknown, but it is likely high enough to also warrant repeat testing at approximately 3 months after treatment.

PROGNOSIS

CDC-recommended chlamydia and LGV antibiotic regimens have a high cure rate when the full course of treatment is completed. If not treated, chlamydia tends to persist for weeks to months, and perhaps over a year in a very small proportion of persons. Delays in chlamydia treatment can lead to acute (e.g., upper genital tract disease) and long-term (e.g., infertility) chlamydia complications. Studies have shown that about 2% to 4% of females who have a positive chlamydia screening test but are not treated at the time of screening (owing to having no clinical indication for treatment) will develop PID in the interval between screening and returning for treatment. Delays in treatment may increase the likelihood that exposed partners will acquire infection. Even though patients may complete treatment, there is a high likelihood they will be reinfected within a few months after treatment if their partners are not treated; irrespective of their symptoms, sexual partners should be treated. Because the majority of chlamydial infections are asymptomatic, many patients with chlamydia never see providers for testing and treatment and as a result are at significant risk for "silent" chlamydia complications such as infertility. Genital chlamydia can also increase the risk of acquisition and transmission of HIV.

PREVENTION AND CONTROL

Until an effective chlamydia vaccine is developed, the prevention and control of chlamydia will rely on a comprehensive approach including STD education, chlamydia screening, timely appropriate treatment of patients and their exposed partners, abstinence until treatment completion, and repeat chlamydia testing at 3 months after treatment. Provider compliance rates with CDC-recommended chlamydia screening in women are very low. The availability of chlamydia NAATs should help to facilitate chlamydial screening, because they can be performed on noninvasively collected specimens. However, many barriers to screening exist and need to be addressed, including patients seeking chlamydia screening, patient access to healthcare providers, and some providers not performing chlamydia testing.

Providers need STD education regarding taking a sexual history, performing STD testing, providing CDC-recommended therapy, and educating patients about STDs. Patients need education about risk factors, barrier prevention methods (condoms are highly effective in preventing chlamydia when used properly), symptoms of STDs, and available STD screening tests and treatments. In order to prevent recurrent chlamydia, patient and partner compliance with treatment and abstinence until treatment is complete should be stressed. In order to help prevent chlamydia complications, efforts should be put into place for prompt notification of chlamydia test results and for expediting treatment. As efforts for providing treatment to sexual partners is not always effective, repeat chlamydia testing at approximately 3 months after treatment completion to rule out re-infection should be stressed.

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): *Expedited partner therapy in the management of sexually transmitted diseases*, Atlanta, 2006, U.S. Department of Health and Human Services. Available at: www.cdc.gov/std/treatment/EPTFinalReport2006.pdf. *This CDC report summarizes the available literature on expedited partner therapy (EPT) for the management of the partners of persons with chlamydia and discusses implementation of EPT.*

Centers for Disease Control and Prevention (CDC): Laboratory diagnostic testing for Chlamydia trachomatis and Neisseria gonorrhoeae, Expert Consultation Meeting summary report, January 2009. Available at: www.aphl.org/aphlprograms/infectious/std/Documents/CTGCLabGuidelinesMeetingReport.pdf. *This CDC report provides current recommendations for diagnostic tests and patient sample types to be used for diagnosing chlamydial infections.*

Centers for Disease Control and Prevention (CDC): Male chlamydia screening consultation. Available at: www.cdc.gov/std/chlamydia/ChlamydiaScreening-males.pdf. *This CDC report provides guidance for performing chlamydia screening in men based on available scientific data.*

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Miller WC, Ford CA, Morris M, et al: Prevalence of chlamydial and gonococcal infections among young adults in the United States, *JAMA* 291:2229-2236, 2004. *This article reports the prevalence of chlamydial infection and associated racial/ethnic disparities in a nationally representative sample of young adults in the United States.*

Schachter J, Moncada J, Liska S, et al: Nucleic acid amplification tests in the diagnosis of chlamydial and gonococcal infections of the oropharynx and rectum in men who have sex with men, *Sex Transm Dis* 35:637-642, 2008. *This article provides evidence that nucleic acid amplification tests perform better than culture for the detection of oropharyngeal and anorectal chlamydial infections.*

Infection with *Neisseria gonorrhoeae*

Lori Marie Newman and Kimberly Workowski

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ABSTRACT

Diagnosis of infection with *Neisseria gonorrhoeae*, commonly known as *gonorrhea*, is important because sequelae of untreated gonorrhea can include pelvic inflammatory disease (PID), ectopic pregnancy, infertility, and chronic pelvic pain in women and epididymitis or infertility in men. Infection with gonorrhea also increases risk of both acquiring and transmitting human immunodeficiency virus (HIV). Gonorrhea is the second most common notifiable condition in the United States and disproportionately affects underprivileged populations. Although gonorrhea can be treated with a single dose of antibiotics, increasing spread of antimicrobial resistance has effectively limited optimal treatment to a single class of drugs, the cephalosporins. Diagnosis of gonorrhea in asymptomatic individuals, appropriate treatment, partner management, and prevention of gonorrhea are all important strategies for control of gonorrhea and gonococcal resistance.

EPIDEMIOLOGY

Global estimates suggest that there are approximately 62 million new gonorrhea infections per year. In the United States, gonorrhea is the second most common notifiable condition, second only to chlamydial infection. The total direct medical cost of gonorrhea among persons aged 15 to 24 years was estimated as $77 million in year 2000 dollars. Approximately 350,000 cases of gonorrhea are reported each year, which is considered to represent less than half of all gonorrhea infections because many cases go undiagnosed and unreported. In 2008 the reported gonorrhea rate was 111.6 cases per 100,000 population, a rate which has changed only minimally over the past decade.

Population-based surveys suggest that the prevalence of disease in the general population is low (<1%) but can be markedly higher in specific subpopulations. For example, the National Health and Nutrition Examination Survey (NHANES) found a general prevalence of 0.24% among persons 14 to 39 years old, but a five times greater prevalence (1.2%) among similarly aged non-Hispanic blacks. In 2007 the median positivity of gonorrhea among 12- to 18-year-old girls entering a sample of detention facilities was 5.4%.

Unlike syphilis and chlamydia, gonorrhea rates are similar for women and men. However, gonorrhea disproportionately affects adolescents and young adults, blacks, and individuals living in the South, urban areas, or low-income communities. Racial disparities are greater for gonorrhea than for any other notifiable condition, with reported rates for infection among blacks 19 times higher than among whites.

CLINICAL FEATURES

Urogenital Infection

Clinical presentation of urogenital infection with *N. gonorrhoeae* varies for women and men (Figure 59-1). Gonorrhea is frequently asymptomatic in women, with only approximately 50% of women reporting symptoms such as vaginal discharge, pain or spotting with intercourse, burning with urination, or lower abdominal pain. Although men are more likely to have symptoms, approximately 10% of men infected with gonorrhea are thought to be asymptomatic. Common symptoms for males include urethral discharge, burning on urination, or testicular tenderness. Because some strains of gonorrhea are less likely to cause symptoms than others, the proportion of patients whose presentation is symptomatic will vary by population.

Clinical examination findings of urogenital infection with gonorrhea are generally quite similar to those of other sexually transmitted infections. For women, examination findings may include a purulent, yellow or green-tinged cervical discharge, inflammation of the cervix, cervical motion tenderness, or Bartholin's gland abscess. Clinical examination findings in men include mucopurulent urethral discharge and unilateral testicular tenderness. Other infectious causes that may have a similar presentation include *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Trichomonas vaginalis*, herpes simplex virus infection, and polymicrobial syndromes such as bacterial vaginitis and cervicitis in women, and other causes of nongonococcal urethritis in men.

Rectal and Pharyngeal Infection

Infection with *N. gonorrhoeae* can also cause infections outside of the urogenital tract (Figure 59-2). In both men and women *N. gonorrhoeae* can cause proctitis with or without symptoms (e.g., rectal discharge, tenesmus, pain). Although in men it is usually the result of unprotected anal intercourse, proctitis in women can be acquired through perineal spread from the cervicovaginal region or receptive anal intercourse. Pharyngeal infection with *N. gonorrhoeae* is generally asymptomatic, though some persons may have sore throat or pain with swallowing. Although the prevalence of gonococcal proctitis and pharyngitis varies by population, in men who have sex with men attending sexually transmitted disease (STD) clinics in 2007, median urethral positivity was 8%, rectal positivity was 7%, and pharyngeal positivity was 6%. Studies of heterosexual women with cervical gonococcal infection have found concomitant rectal infection in 35% to 50% and pharyngeal infection in 10% to 20%. Studies of strictly heterosexual men with urethral gonococcal infection

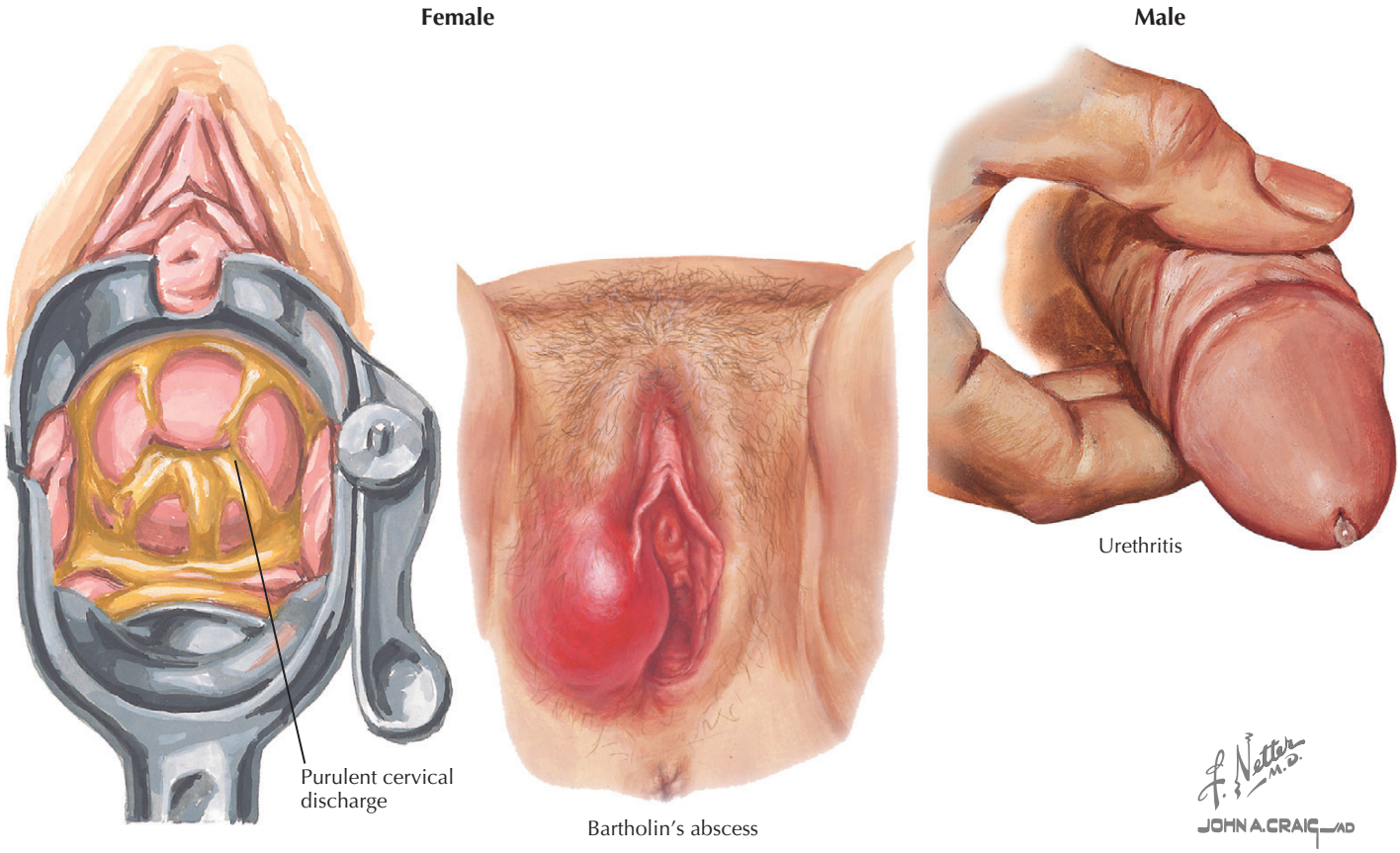

Figure 59-1 Urogenital manifestations of gonorrhea in men and women.

have found concomitant pharyngeal infection in 3% to 7% and rectal infection rarely, if ever.

Ophthalmic Infection

Ophthalmic infection with *N. gonorrhoeae* can occur in both adults and infants, causing a severe conjunctivitis that can result in corneal damage and blindness. In the infant, symptoms appear approximately 2 to 5 days after delivery, generally with a profuse ophthalmic discharge and lid edema. Symptoms may occur later, however, especially if the infant received ophthalmic prophylaxis at birth. Neonatal ophthalmia can also be caused by infection with *C. trachomatis*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Klebsiella pneumoniae*. Although gonococcal ophthalmic infection in the newborn is generally through perinatal transmission, gonococcal ophthalmia in an adult is usually through autoinoculation from an individual infected at a urogenital site or via direct contact with infected genitalia or urine. Adult infection may also cause more subtle symptoms of conjunctivitis (injected sclera, mild discharge) than are commonly seen in the newborn.

Pelvic Inflammatory Disease

Complicated infection in women most commonly manifests as PID. PID, which occurs in approximately 10% to 20% of women with acute gonococcal infection, is the result of infection of the endometrium, the fallopian tubes, or the peritoneum. Women with PID may be asymptomatic or may have lower abdominal pain, fever, and pain or spotting with intercourse. Even if treated appropriately, PID may result in intraabdominal scarring and adhesions that increase the risk of infertility, ectopic pregnancy, and chronic pelvic pain. PID may be caused by single or polymicrobial infections, including *C. trachomatis*, *M. genitalium*, *Ureaplasma urealyticum*, and various anaerobes.

Testicular Infection

Complicated infection in men can cause penile edema or epididymitis, with characteristic symptoms of unilateral testicular pain, swelling, burning on urination, and fever. Because symptomatic men generally seek treatment, very few men progress to develop urethral strictures. Gonococcal infections in men may play a role in male infertility.

Disseminated Gonococcal Infection

Disseminated gonococcal infection (DGI), the result of gonococcal bacteremia, is more common with certain strains of *N. gonorrhoeae* than with others. DGI classically manifests as a dermatitis-arthritis syndrome. The classic presentation of gonococcal skin lesions is a necrotic pustule on an erythematous

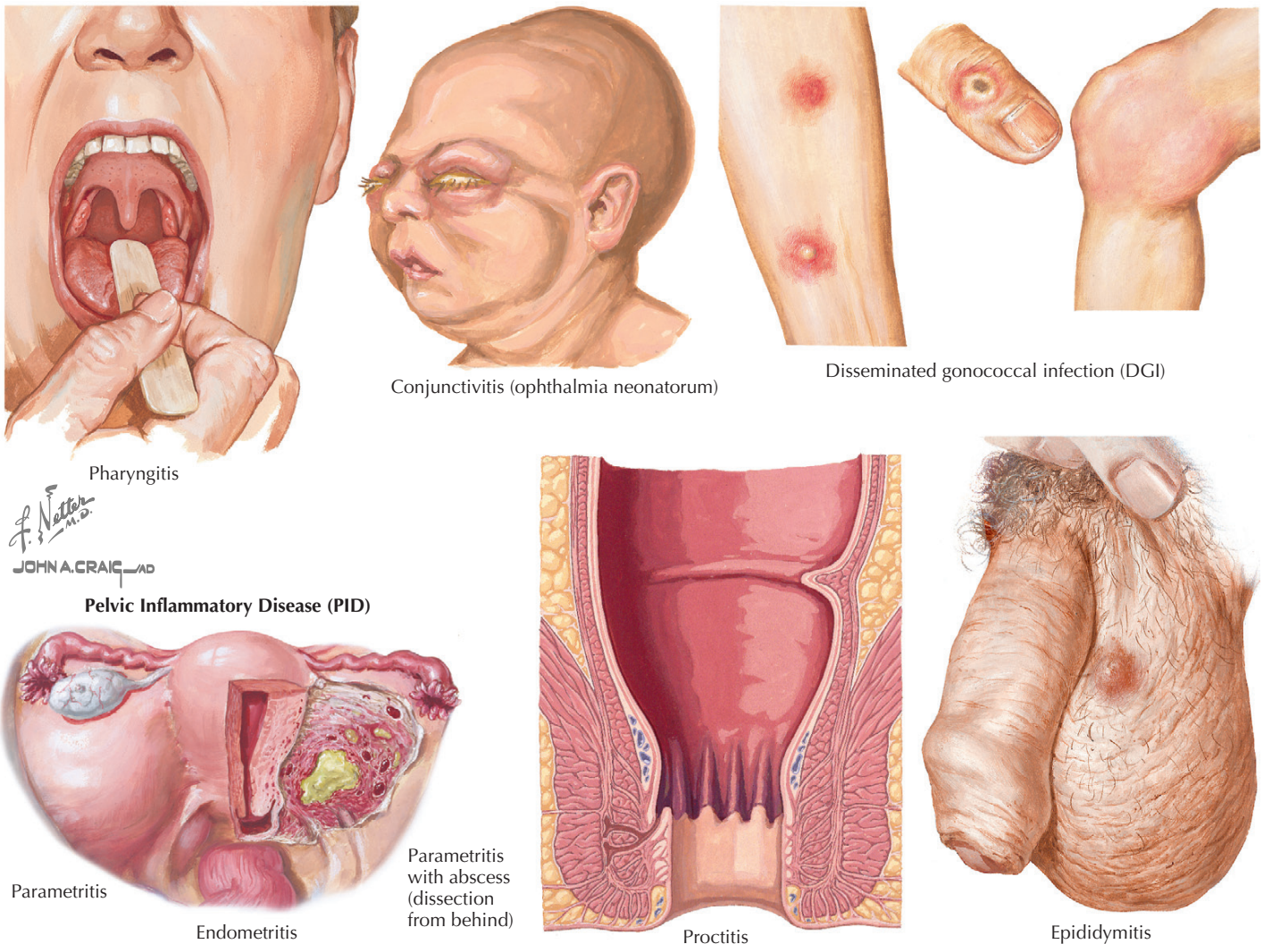

Figure 59-2 Extragenital manifestations of gonorrhea.

base, but they may also appear as macules, hemorrhagic lesions, or papules. The arthritis associated with gonococcal infection generally affects wrists, knees, and ankles, though any joint may be affected. DGI may also cause nonspecific signs and symptoms of sepsis such as fever and low blood pressure. Though rare, DGI can also cause endocarditis or meningitis. The differential diagnosis for DGI includes a broad range of organisms responsible for bacteremia, endocarditis, and meningitis, and in particular, special care must be taken to distinguish infection with *N. gonorrhoeae* from infection with *Neisseria meningitidis*.

DIAGNOSTIC APPROACH

History and Physical Examination

Given the importance of early treatment of gonorrhea to avoid continued sexual transmission of disease, diagnosis of gonorrhea in a symptomatic individual relies on a careful history and physical examination. However, a large proportion of both women and men infected with gonorrhea are asymptomatic. A history should include detailed questions about age of patient, number and sex of sex partners, unprotected penetration of the pharynx, vagina, penis, and rectum, symptoms (e.g., sore throat, genital or rectal discharge, pain on urination, pain on intercourse), STD history (especially previous episodes of gonorrhea), associated high-risk behaviors (e.g., exchange of sex, illicit drug use), pregnancy status, HIV status, concomitant medical conditions, travel history, and recent antibiotic exposure. Physical examination should focus on the skin, pharynx, lower abdomen, external genitalia, vagina, cervix, and rectum.

Laboratory Testing

Laboratory testing should be conducted for all patients with suspected gonococcal infection, even if history or physical examination findings are strongly suggestive of gonorrhea, because management of the patient and the patient's partners is facilitated by having a definitive diagnosis. Given the poor sensitivity and specificity of serologic tests for *N. gonorrhoeae*,

serologic tests should not be used for the clinical diagnosis of gonorrhea.

DIAGNOSIS OF UROGENITAL INFECTION

The presence of gram-negative intracellular diplococci on a Gram stain of a urethral exudate is both highly sensitive (90% to 95%) and highly specific (95% to 100%) for symptomatic males and can be considered sufficiently diagnostic without further testing for infection with *N. gonorrhoeae* (Figure 59-3). In asymptomatic males and both symptomatic and asymptomatic females, Gram stain of urethral or cervical exudate is less sensitive (50% to 70%) but still highly specific (95% to 100%) and should be considered only an adjunct to more sensitive molecular testing.

In general, nucleic acid amplification tests (NAATs) of first-catch urine from men and vaginal swabs from women are the optimal test type for the diagnosis of urogenital gonococcal infection. A NAAT for gonococcal infections is usually performed jointly with NAAT testing for chlamydial infections. NAATs have been found to be more sensitive than culture in most settings and can be performed on a wider variety of specimen types (urine and vaginal, endocervical, or urethral swabs) than can culture or nonamplified deoxyribonucleic acid (DNA) probe tests. However, gonococcal culture is still critical for management in some situations, because only culture specimens can be used to provide antimicrobial susceptibility test results.

DIAGNOSIS OF NONUROGENITAL INFECTION

Although evidence suggests that NAATs have a higher sensitivity than and comparable specificity to culture for diagnosis of rectal and pharyngeal *N. gonorrhoeae* infections, NAATs have not been cleared by the U.S. Food and Drug Administration (FDA) for use on nonurogenital sites. Therefore laboratories must establish performance specifications to satisfy Clinical Laboratory Improvement Amendments (CLIA) compliance standards before reporting results for patient management. Culture of the rectum and pharynx can also be used for diagnosis at these sites and has the additional benefit of allowing for antimicrobial susceptibility testing.

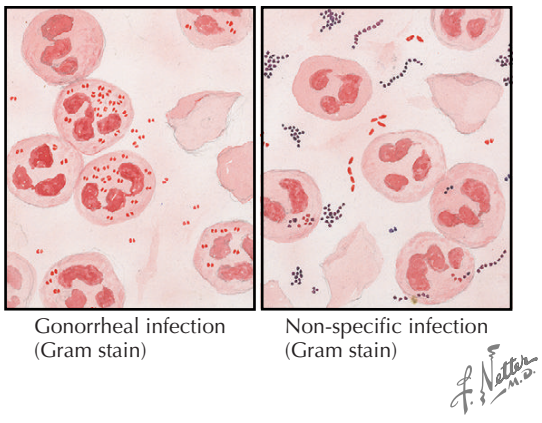

Figure 59-3 Gram stain.

SCREENING FOR INFECTION WITH *NEISSERIA GONORRHOEAE*

The prevalence of gonorrhea varies widely by population; therefore universal screening of all patients is not recommended. The U.S. Preventive Services Task Force (USPSTF) recommends screening all sexually active women, including those who are pregnant, for gonorrhea if they are at increased risk. Women younger than 25 years of age are at highest risk of infection, as are African Americans and men who have sex with men. Additional risk factors include a history of previous gonorrhea, other sexually transmitted infections, new or multiple sex partners, inconsistent condom use, sex work, and drug use. The USPSTF does not recommend routine screening for heterosexual men at increased risk of infection.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Antibiotic therapy for gonorrhea should be safe, highly effective, single dose, and affordable whenever possible. However, selection of antimicrobial therapy for gonorrhea is severely limited owing to the rapidity with which *N. gonorrhoeae* develops resistance to antibiotics. Over the years, *N. gonorrhoeae* has developed widespread resistance to nearly every class of antibiotics routinely used for treatment, including sulfonamides, penicillins, tetracyclines, and fluoroquinolones. Unfortunately, notable resistance to macrolides has also been documented in some areas, and increased use of macrolides may easily promote the spread of resistance. Although only sporadic resistance to aminoglycosides has been documented, the best studied aminoglycoside for the treatment of gonorrhea (spectinomycin) has been generally unavailable in many countries, including the United States. Thus cephalosporins remain the only widely available, effective class of antibiotics for the treatment of gonorrhea. There have been recent reports of treatment failures for oral cephalosporins, as well as gonococcal isolates that have demonstrated decreased susceptibility to oral cephalosporins. Treatment failures have also been documented in persons with pharyngeal infection treated with injectable cephalosporins.

Therefore both efficacy at the site of infection and antimicrobial resistance considerations are important when selecting treatment for *N. gonorrhoeae* infections. The Centers for Disease Control and Prevention (CDC) currently recommends an antibiotic for the treatment of gonorrhea if the efficacy in summed clinical trials is ≥95% with a lower 95% confidence interval of ≥95%, and considers antibiotics as alternative therapies if the efficacy is ≥95% with a lower 95% confidence interval of ≥90%. In addition to efficacy considerations, however, both recommended and alternative antibiotics are recommended by both the CDC and the World Health Organization (WHO) only if fewer than 5% of strains tested demonstrate antibiotic resistance.

Given these considerations, the routine treatment of gonorrhea as recommended by the CDC is limited to cephalosporins (Table 59-1). However, a wide variety of special situations exist that must be taken into account when selecting treatment for gonorrhea. In particular, clinicians must ask patients about possible sexual exposure of the pharynx, because only ceftriaxone 250 mg intramuscularly (IM) or intravenously (IV) in a single

Table 59-1 Centers for Disease Control and Prevention (CDC)–Recommended Antibiotic Regimens for the Treatment of *Neisseria gonorrhoeae* Infections

TYPE OF GONOCOCCAL INFECTION*		ADULT TREATMENT REGIMEN*	COMMENTARY
Uncomplicated infection			
Cervix, urethra, rectum		Ceftriaxone 250 mg IM single dose	Preferred regimen. More effective than 125 mg in eradicating unrecognized pharyngeal infection
	or	Cefixime 400 mg PO single dose	Should not be used if pharyngeal infection suspected
	or	Ceftizoxime 500 mg IM single dose	Less certain efficacy at the pharynx
	or	Cefoxitin 1 g IM + probenecid 1 g PO single dose	Less certain efficacy at the pharynx
	or	Cefotaxime 500 mg IM single dose	Less certain efficacy at the pharynx
	Alternative	Cefpodoxime 400 mg PO single dose	Should not be used if pharyngeal infection suspected
	Alternative	Cefuroxime 1 g PO single dose	Should not be used if pharyngeal infection suspected
	Alternative	Spectinomycin 2 g	Not available in United States; should not be used if pharyngeal infection suspected
	Alternative	Azithromycin 2 g PO single dose	Concerns about ease of development of antibiotic resistance with widespread use
Pharynx		Ceftriaxone 250 mg IM single dose	
Conjunctiva		Ceftriaxone 250 mg IM single dose	
Severe cephalosporin allergy		Azithromycin 2 g PO single dose	
Disseminated gonococcal infection		Ceftriaxone 1 g IM or IV every 24 hr	Continue for 24-48 hours after improvement begins, then switch to cefixime 400 mg PO twice daily to complete at least 1 week of therapy
	Alternative	Cefotaxime 1 g IV every 8 hr	
	or	Ceftizoxime 1 g IV every 8 hr	
Meningitis		Ceftriaxone 1-2 g IV every 12 hr	Continue for 10-14 days and consult specialist
Endocarditis		Ceftriaxone 1-2 g IV every 12 hr	Continue for at least 4 weeks and consult specialist

*Dual therapy for gonococcal and chlamydial infections is recommended by CDC guidelines, because patients infected with *N. gonorrhoeae* are frequently coinfected with *C. trachomatis*. An antibiotic effective against uncomplicated genital *C. trachomatis* infection, azithromycin 1 g PO single dose OR doxycycline 100 mg PO twice daily for 7 days should be added routinely to a cephalosporin gonococcal treatment regimen selected.
IM, Intramuscularly; *IV,* intravenously; *PO,* orally.

dose provides sufficiently high tissue levels in the pharynx to reliably treat gonococcal infection at this site. Patients with a history of severe reaction to penicillin or cephalosporins (e.g., anaphylaxis, Stevens-Johnson syndrome, or toxic epidermal necrolysis) should either be treated with azithromycin 2 g orally in a single dose or have an infectious disease consultation to determine optimal therapy. Pregnant women and persons with HIV infection should receive the same treatment as other persons. Neonatal ophthalmia caused by infection with *N. gonorrhoeae* should be treated with ceftriaxone 25-50 mg/kg IV or IM in a single dose, and the dose should not exceed 125 mg.

An added benefit of using dual therapy to cover both *N. gonorrhoeae* and *C. trachomatis* infections in patients diagnosed with gonococcal infection (see Table 59-1), is that the combination antibiotic regimen may hinder the development of resistant *N. gonorrhoeae* strains. Because patterns of resistance of *N. gonorrhoeae* are constantly changing, it is important for clinicians and health departments to remain alert for changing recommendations for gonorrhea therapy. Updates on the treatment of gonococcal infections can be found on the CDC website at www.cdc.gov/std/treatment.

Partner Management

Treatment of recent sexual contacts is necessary to avoid reinfection and prevent ongoing disease transmission. Patients should be instructed to contact any partner with whom they have had sexual intercourse within the last 60 days to inform them of the possibility of infection and encourage them to seek treatment for gonorrhea and chlamydia. Patients should be instructed to avoid sexual intercourse until they and their partners have received treatment and they no longer have symptoms.

If a patient feels it is unlikely that the partner will seek care, in some states patient-delivered partner therapy is an option (more information is available at www.cdc.gov/std/ept). In patient-delivered partner therapy, a prescription or medication for the treatment of both gonorrhea and chlamydia and

educational materials are provided to the patient to give to his or her partner(s). Educational materials should encourage the partners to seek professional evaluation, especially if symptomatic or allergic to antibiotics. This strategy should not be used for men who have sex with men owing to the risk of co-infection with other STDs or HIV.

Because gonorrhea is a notifiable condition in all states, providers should be aware of both the importance and the utility of notifying the state or local health department of all laboratory-confirmed gonococcal infections. Some state or local health departments will provide assistance in notifying and counseling partners.

Suspected Treatment Failures

Patients who remain symptomatic after treatment should be reevaluated to differentiate among reinfection, infection with a different organism (e.g., *C. trachomatis* or *T. vaginalis*), or treatment failure. Any patient with suspected treatment failure who did not receive at least one dose of ceftriaxone 250 IM should have a gonococcal culture and susceptibility testing before receiving ceftriaxone. Although rare, treatment failures with both oral and injectable cephalosporins have been reported, and gonococcal isolates with decreased susceptibility to cephalosporins have been identified. Clinicians with a patient in whom treatment with a cephalosporin regimen is suspected to have failed or who has a gonococcal isolate with decreased susceptibility should seek expert infectious disease advice, conduct gonococcal culture and susceptibility testing of relevant clinical specimens, consider retreating the patient with at least 250 mg of ceftriaxone IM or IV, ensure partner treatment, and contact state or local health authorities.

Follow-up and Repeat Testing

Similar to recommendations for chlamydial infections, the CDC recommends that all patients diagnosed with gonorrhea undergo a repeat test in 3 months, as reinfection with gonorrhea is quite common. Repeat testing for gonorrhea is distinct from a test of cure (testing shortly after treatment to determine if treatment was effective). Test of cure for gonorrhea is not recommended; after effective therapy, NAAT results may remain positive for at least 2 weeks.

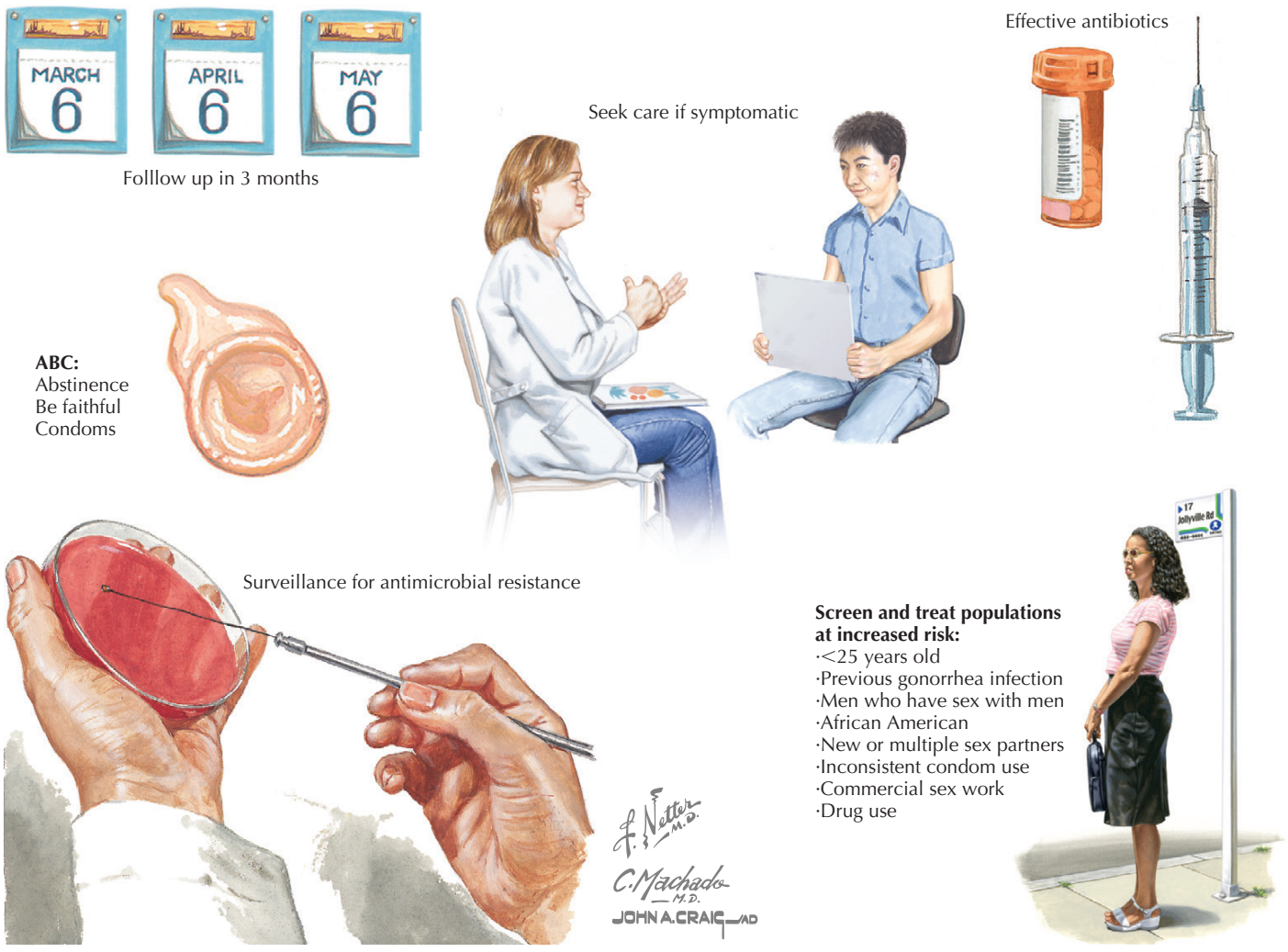

Figure 59-4 Prevention and control strategies for gonorrhea.

PROGNOSIS

Persons who undergo a CDC-recommended or alternative regimen have a high probability of resolution of infection with *N. gonorrhoeae*. Approximately 10% to 20% of patients are reinfected within several months of initial infection, highlighting the importance of partner management in the treatment of gonorrhea. PID, either asymptomatic or symptomatic, may occur in approximately 10% to 20% of women with gonorrhea. Even with appropriate treatment, however, the inflammation and scarring from PID can result in infertility, ectopic pregnancy, and chronic pelvic pain. However, prompt evaluation and treatment may decrease the duration of inflammation and reduce the risk of the sequelae of PID. In men, postinflammatory strictures are rare after antibiotic treatment, and it is unclear how treatment of gonorrhea affects future fertility.

PREVENTION AND CONTROL

General Prevention and Control Strategies

Prevention and control of gonorrhea require multiple strategies (Figure 59-4). On an individual basis, as with other sexually transmitted diseases, the surest ways to avoid transmission are abstinence, long-term mutual monogamy, or correct and consistent use of latex condoms. Patients must be aware of the importance of recognizing symptoms early and seeking care promptly. Clinicians must educate patients regarding the importance of informing partners of their infection and encouraging partners to seek care. Clinicians must ensure that they provide effective antibiotics, provide appropriate counseling and education, and encourage patients to undergo repeat testing in 3 months to reduce risk of reinfection and ongoing transmission. Health departments should educate communities about STD symptom recognition, provide information on access to STD care, provide support for partner management strategies, ensure that clinicians are updated about the latest treatment recommendations, screen and treat populations at increased risk of infection, and conduct routine surveillance for antimicrobial resistance to recommended treatment regimens.

Ophthalmia Neonatorum Prophylaxis

Diagnosis and treatment of gonococcal and chlamydial infections in pregnancy are the best method for preventing neonatal gonococcal and chlamydial disease. However, not all women receive prenatal care, and not all women are tested for gonorrhea and chlamydia in pregnancy. Ophthalmia neonatorum prophylaxis for all newborn infants is important because it is a preventable cause of blindness and is safe, easy to administer, and inexpensive. Therefore all newborns should have erythromycin 0.5% ophthalmic ointment applied once into both eyes as soon as possible after delivery. Infants born to mothers with known untreated gonococcal infection are at high risk of infection; such infants should receive ceftriaxone 25 to 50 mg/kg IV or IM once, not to exceed 125 mg.

EVIDENCE

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Workowski KA, Berman SM, Douglas JM: Emerging antimicrobial resistance in *Neisseria gonorrhoeae:* urgent need to strengthen prevention strategies, *Ann Intern Med* 148:606-614, 2008. *Summarizes the need for, and the components of, a comprehensive prevention strategy to address emerging gonococcal antimicrobial resistance.*

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Syphilis *(Treponema pallidum)*

Stephanie E. Cohen, Joseph Engelman, and Jeffrey D. Klausner

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ABSTRACT

Syphilis is a complex systemic disease caused by the spirochete *Treponema pallidum*. Syphilis is transmitted sexually or congenitally and can involve nearly every organ system. Its clinical progression involves several well-characterized stages: (1) an incubation period of 1 week to 3 months; (2) a primary stage characterized by a chancre (an indurated, nontender ulcer at the site of exposure); (3) a secondary stage, usually several weeks after the resolution of the chancre, associated with a diffuse rash, mucocutaneous lesions, and lymphadenopathy; (4) a latent stage of subclinical infection detected by reactive serologic tests; and (5) a late or tertiary stage involving end-organ damage that includes neurologic, cardiovascular, and gummatous (or late benign) syphilis (Figure 60-1). Penicillin is highly effective against syphilis and remains the treatment of choice. In this chapter we review the etiology, epidemiology, clinical features, diagnostic approach, treatment, and prevention of syphilis.

ETIOLOGY AND PATHOGENESIS

Syphilis is caused by infection with the spirochetal bacterium *T. pallidum* subspecies *pallidum*. *T. pallidum* is a highly motile organism with tapering ends presenting 6 to 14 spirals. Of uniform cylindric shape, the bacteria measure approximately 6 to 15 microns in length and 0.25 micron in width. *T. pallidum* is a slowly metabolizing organism with an average multiplying time of approximately 30 hours. Humans are the only host for the organism. Most cases of syphilis are transmitted by sexual contact (vaginal, anogenital, and orogenital), but it can also be spread congenitally (in utero or, less commonly, during passage through the birth canal). Rare cases of acquisition through blood products have also been reported. On skin-to-skin contact the motile spirochetes from an infected person enter a new host through areas of microtrauma in the skin or mucosa, multiplying locally with resultant systemic dissemination in less than 24 hours. The phospholipid-rich outer membrane of the spirochete contains few surface-exposed proteins; this may help it evade the host immune system. The primary pathologic lesion, found at all stages of the disease, is an obliterative endarteritis, which leads to many of the clinical manifestations of syphilis. Histologic examination of a chancre is characterized by an intense infiltrate of plasma cells, with scattered macrophages and lymphocytes. A granulomatous reaction can also occur.

EPIDEMIOLOGY

The epidemiology of syphilis follows two patterns that are distinct between developed and developing countries. Syphilis incidence in developed nations declined dramatically after the introduction of mass population screening programs and the advent of penicillin therapy. In 2000, infectious syphilis was at a historic low in the United States with only 9756 primary and secondary cases compared with about 100,000 cases in 1946. Similar declines have been observed across Europe and Australia. Currently there is a resurgence of syphilis in high-risk subpopulations in developed countries, particularly among men who have sex with men. In San Francisco and many other large urban areas that have experienced increases in the prevalence of syphilis, approximately two thirds of cases occur in human immunodeficiency virus (HIV)–infected men. Reversal in the control of syphilis in disenfranchised, low-socioeconomic, black, heterosexual subpopulations has also been observed in major metropolitan areas in the southeastern United States.

The unmitigated persistence of syphilis in less developed countries stands in contrast to the changing epidemiology of syphilis in developed nations. Regional data from the World Health Organization demonstrate that approximately 5% of pregnant women seeking antenatal care services in the Western Pacific, sub-Saharan Africa, South Asia, and South America have evidence of recent syphilis infection. This results in a substantial burden of miscarriages, stillbirths, and newborns with congenital infection. An estimated 2 million pregnancies are affected annually worldwide. Congenital syphilis is two to three times more common globally than perinatal HIV infection.

The well-documented increase of syphilis in China (population 1.3 billion) has further raised global concern about syphilis. An aggressive venereal disease control policy of the Chinese government during the 1950s to 1970s effectively eliminated syphilis in China. Because of sociopolitical and economic changes in China, recent data showed a 250- to 1000-fold increase in adult and congenital cases, respectively, in the last decade.

CLINICAL FEATURES

Primary Syphilis

Primary syphilis manifests 1 week to 3 months (median 21 days) after exposure with a painless lesion, a chancre, at the site of inoculation and nontender regional lymphadenopathy. The lesion starts as a papule and rapidly forms an ulcer that is typically nonexudative with a clean base. Primary lesions are most commonly found on the external genitalia but can develop on any site of exposure including the perineum, cervix, anus, rectum, lips, and oropharynx (Figure 60-2). Multiple chancres can occur and are more common in patients with HIV infection. Without treatment, the chancre usually heals on its own within 1 to 3 weeks. Primary syphilis must be differentiated from other causes of genital ulcer disease including other infectious causes

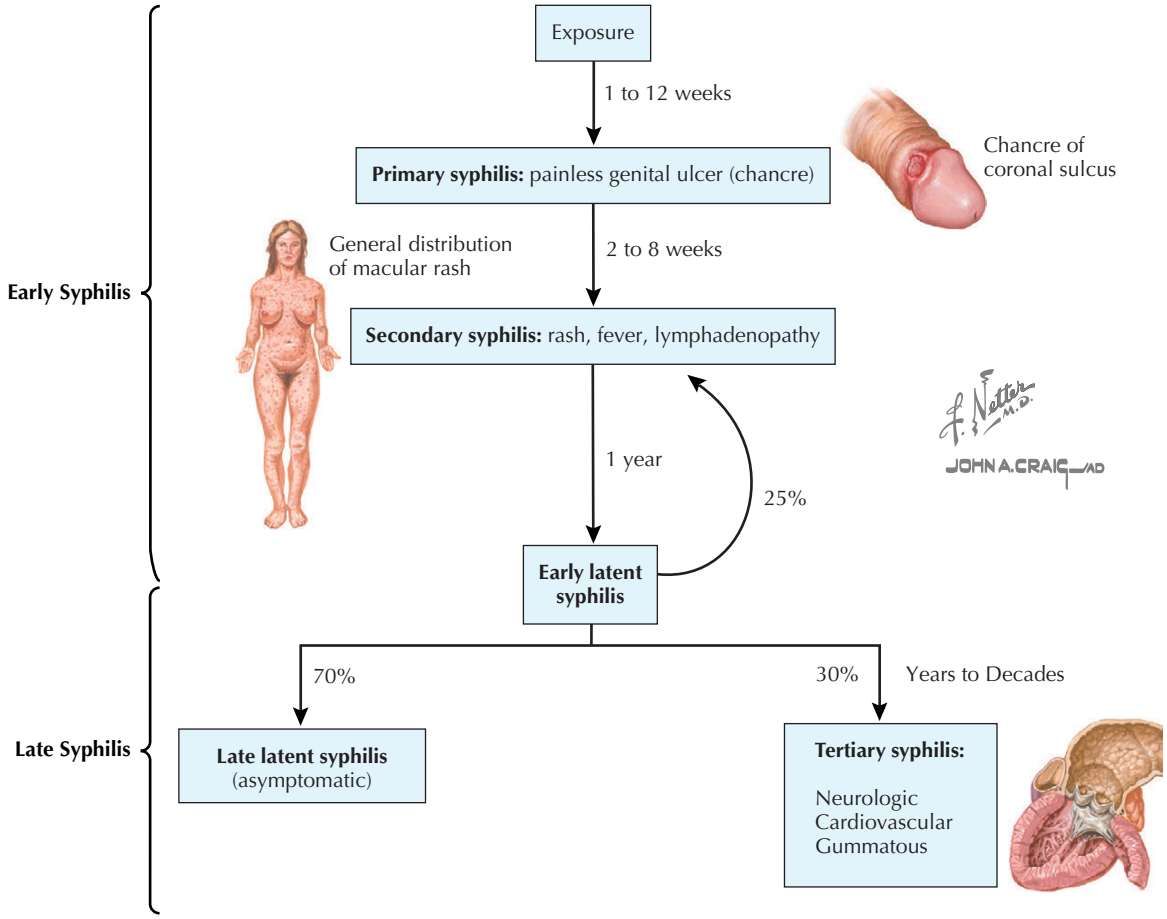


Figure 60-1 Stages of syphilis.

(herpes simplex virus, chancroid, lymphogranuloma venereum, and pyogenic ulcers), as well as noninfectious causes (including trauma, neoplasia, and fixed drug eruptions). Herpetic ulcers, unlike chancres, are usually superficial, vesicular, nonindurated, and painful. Chancroid, caused by *Haemophilus ducreyi*, is uncommon in the United States and is typically nonindurated, painful, and exudative with a necrotic base (Figure 60-3).

Secondary Syphilis

The timing of onset of the secondary stage of syphilis is highly variable. It typically occurs 2 to 8 weeks after the disappearance of a chancre, but in some cases the primary chancre may still be present, and secondary syphilis has been described up to 4 years after initial exposure. The overlap in clinical manifestations of primary and secondary syphilis is more common in patients co-infected with HIV. Many patients do not recall a history of a primary lesion. Secondary syphilis typically manifests with rash, fever, headache, pharyngitis, and lymphadenopathy but has a wide range of possible systemic manifestations including hepatitis, uveitis, meningitis, glomerulonephritis, periostitis, and cerebrovascular accidents.

The cutaneous manifestations of secondary syphilis are quite diverse. The classic exanthem of secondary syphilis is a diffuse maculopapular rash that often involves the palms and soles (Figure 60-4). However, the rash can also be papular, annular, or pustular and can have a fine overlying scale. Other mucocutaneous manifestations include (1) *condylomata lata*, moist heaped-up broad plaques found in intertriginous areas such as the perianal area, vulva, and inner thighs; (2) *mucous patches*, gray, superficial erosions or plaques on the buccal mucosa and tongue, under the prepuce, and on the inner labia; (3) *split papules*, fissured, nodular lesions at the angle of the lips and in the nasolabial folds; and (4) *patchy alopecia*, thinning of hair, eyebrows, and beard from syphilitic involvement of the hair follicle (Figure 60-5). The cutaneous lesions of syphilis, particularly the nonkeratinized mucocutaneous lesions (condylomata lata and mucous patches) contain large concentrations of spirochetes and are highly infectious.

Invasion of the central nervous system (CNS) is common during secondary syphilis and may manifest as an aseptic meningitis, with headache, neck stiffness, and a lymphocytic pleocytosis of cerebrospinal fluid (CSF). The meningeal inflammation is often basilar, leading to unilateral or bilateral cranial nerve abnormalities, particularly of cranial nerves II, III, VI, VII, and VIII.

The diverse manifestations of secondary syphilis earn it the name "the great imitator." Other diseases that should be considered in the differential diagnosis of fever, rash, pharyngitis, and lymphadenopathy include mononucleosis (acute

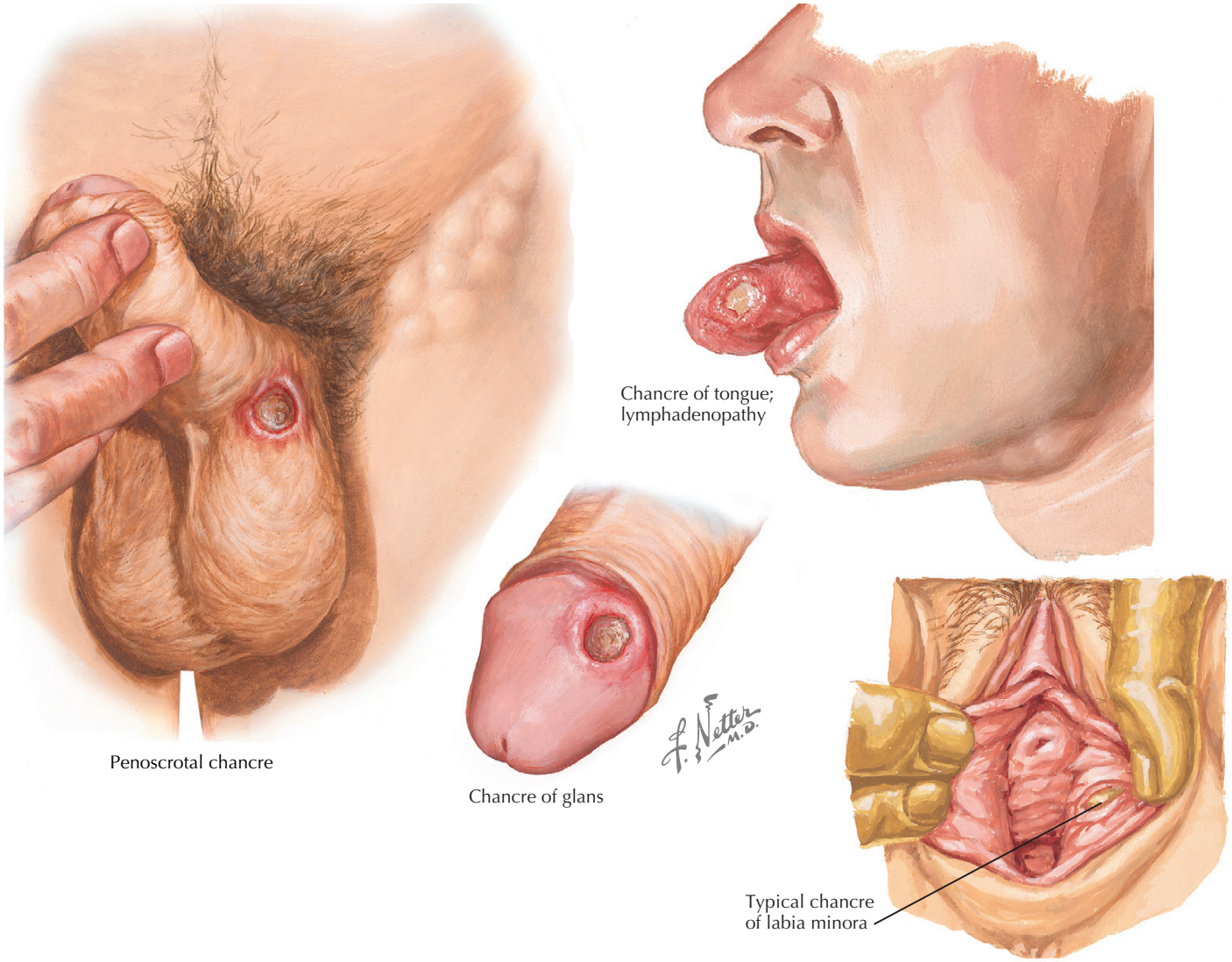


Figure 60-2 Primary syphilitic chancres.

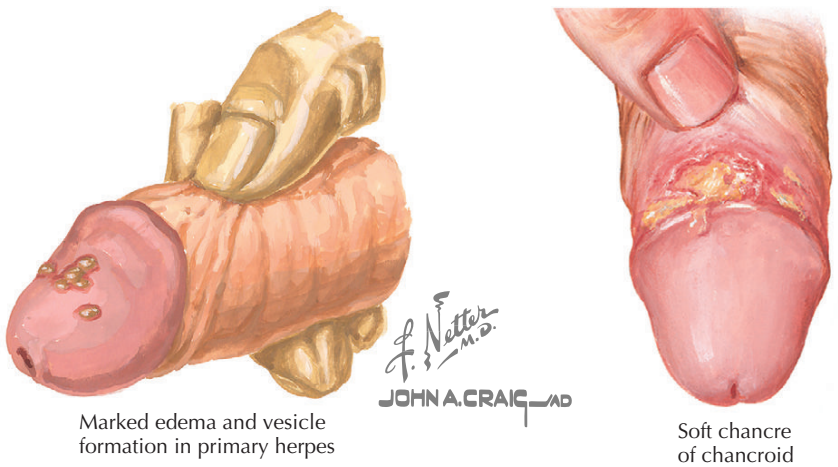


Figure 60-3 Genital ulcers: herpes and chancroid.

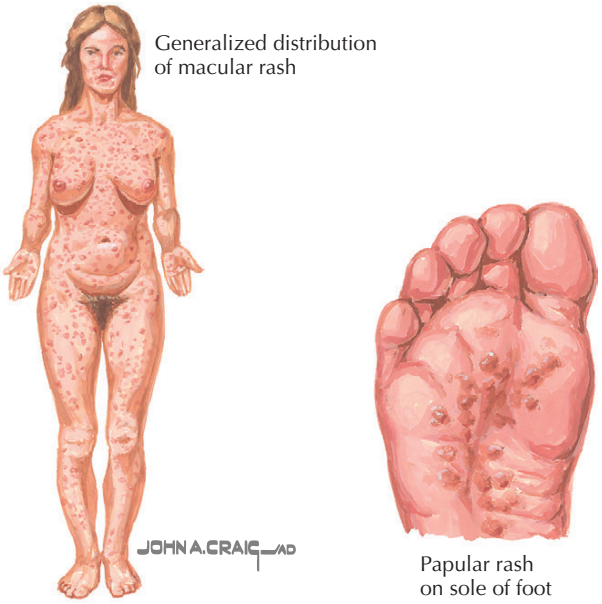


Figure 60-4 Secondary syphilis: diffuse maculopapular rash.

Epstein-Barr virus infection), acute HIV infection, and other viral syndromes. The *condylomata lata* of secondary syphilis should be distinguished from *condylomata acuminata*—multiple, small, raised genital warts caused by HPV (Figure 60-6). Mucous patches can be mistaken for oral candidiasis. Other infections that cause a rash involving the palms and soles include Rocky Mountain spotted fever, meningococcemia, measles, and certain coxsackievirus infections (hand, foot, and mouth disease).

Latent Syphilis

Without treatment, the manifestations of secondary syphilis generally resolve within a few weeks. The disease then enters a latent phase, characterized by a lack of clinical signs of syphilis but positive serologic test results. Observational studies have shown that recrudescent secondary syphilis symptoms can occur in untreated patients up to 5 years after their initial presentation, but generally these relapses occur within the first year. Early latency therefore has been defined as the first year after initial syphilis infection. An asymptomatic patient with a newly reactive serologic test result who had a nonreactive serologic test result during the previous year is also designated as having early latent syphilis. Late latency is the asymptomatic phase longer than 1 year after syphilis infection. Late latent syphilis, unlike early latent syphilis, is not thought to be infectious (except in

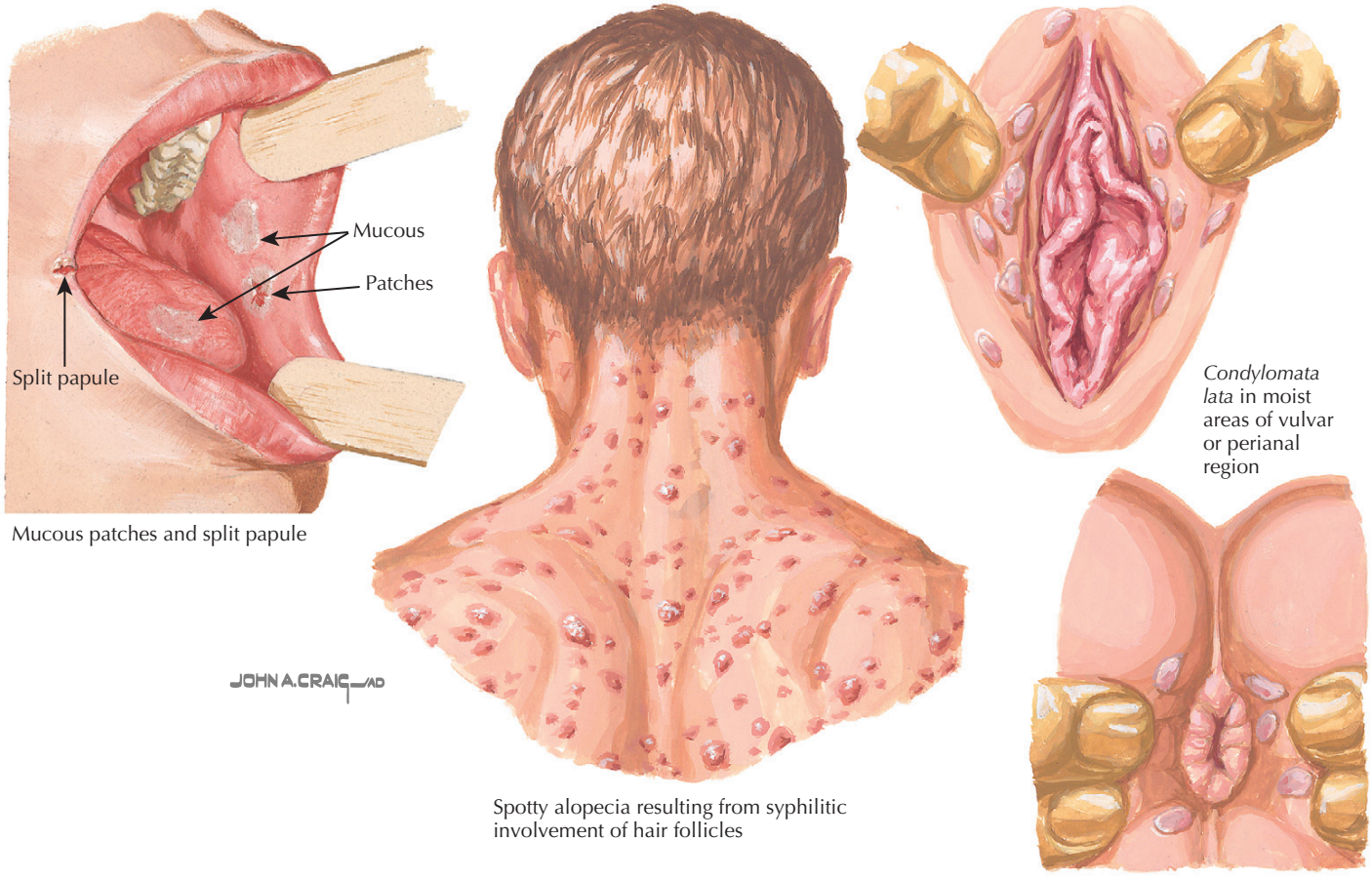


Figure 60-5 Secondary syphilis: mucocutaneous manifestations.

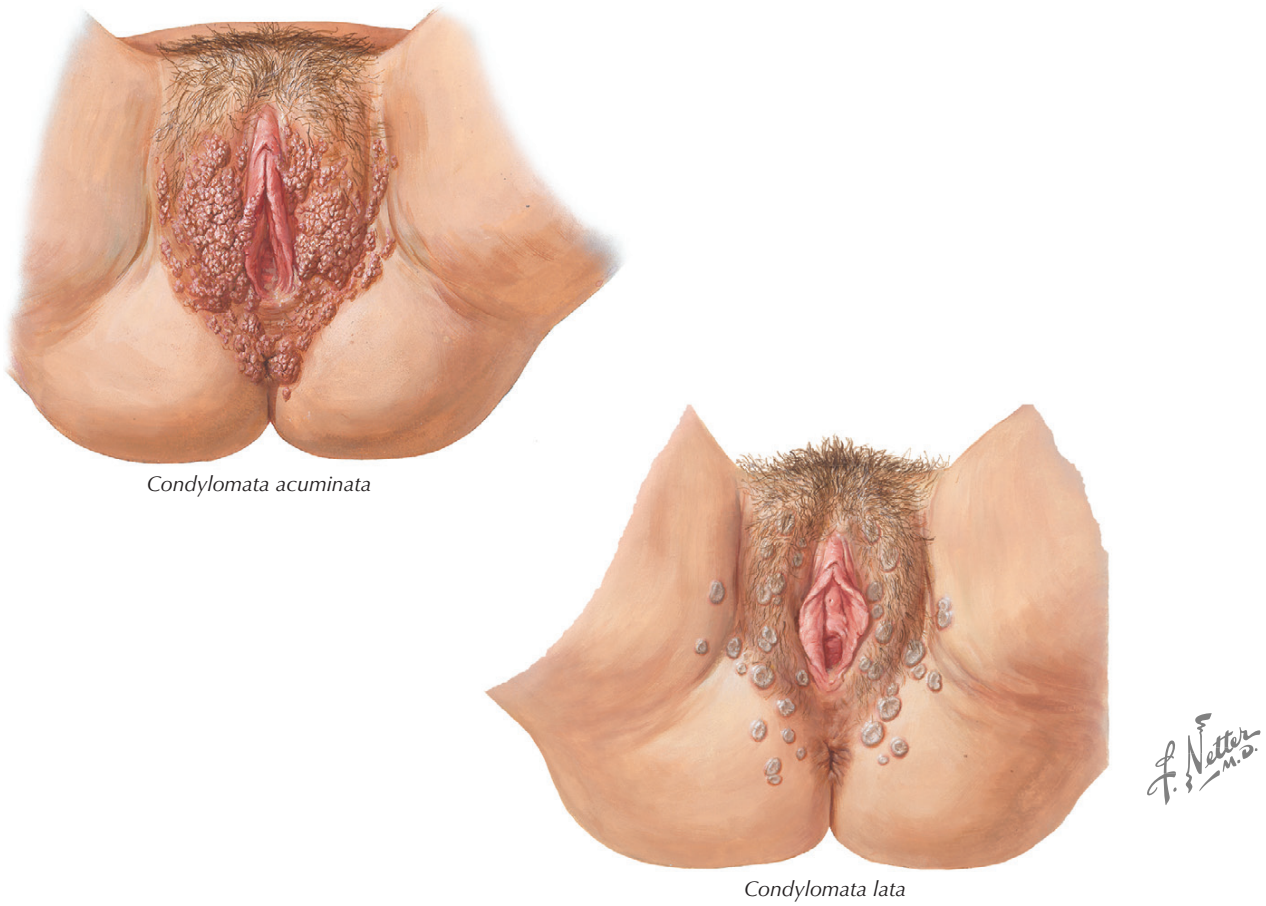


Figure 60-6 Condylomata lata versus condylomata acuminata.

pregnant women) and requires a longer duration of treatment compared with early latent syphilis (see section on treatment, later).

Tertiary Syphilis

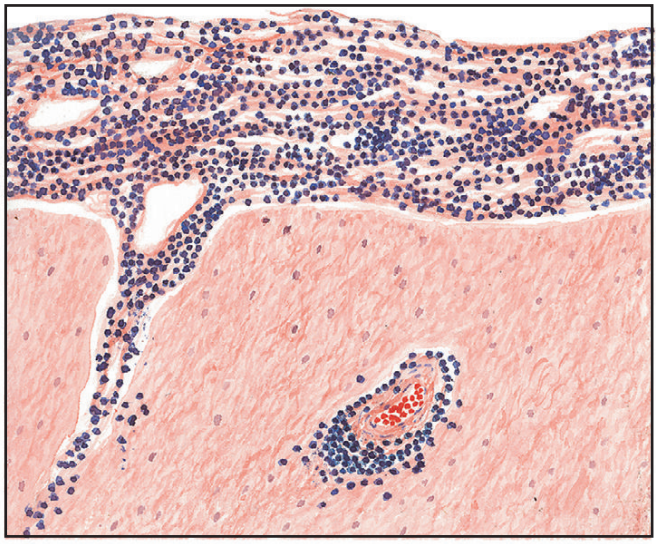
Tertiary syphilis, or late syphilis, occurs in up to one third of untreated patients with latent syphilis and is characterized by end-organ damage. It has become very uncommon in the antibiotic era. In tertiary syphilis, endarteritis leads to cellular necrosis, fibrosis, sclerosis, scarring, and loss of normal tissue parenchyma. The three main types of tertiary disease are neurologic, cardiovascular, and gummatous (or late benign) syphilis.

LATE NEUROSYPHILIS

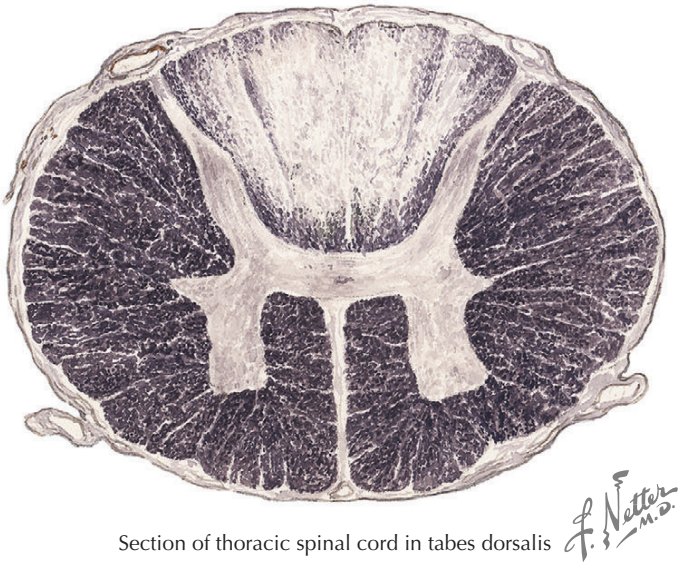
As described previously, acute syphilitic meningitis can occur early in syphilis infection and is a well-described feature of secondary syphilis. Late neurologic complications of syphilis, which manifest after long periods of latency, are caused by meningovascular or parenchymal damage or both and have a range of manifestations. Vascular involvement leading to focal ischemia can cause a myriad of neurologic deficits including hemiparesis, aphasia, and focal or generalized seizures. Classic late neurosyphilis syndromes attributed to parenchymal damage include general paresis and *tabes dorsalis*.

General paresis, also known as *general paralysis of the insane*, is a meningoencephalitis with direct invasion of the cerebrum by *T. pallidum* (Figure 60-7). The encephalitis is chronic and usually manifests in middle to late adulthood after a 15- to 25-year incubation period. A wide range of manifestations includes progressive dementia with changes in personality, affect, sensorium, intellect, and speech. Defects in judgment, emotional lability, grandiose delusions, megalomania, depression, catatonia, amnesia, and hyperreflexia have been described. The Argyll-Robertson pupil, a small, often irregularly shaped pupil that constricts on accommodation but not to light, is a classic though uncommon feature of general paresis.

Tabes dorsalis, syphilitic involvement of the posterior columns of the spinal cord, affected about one third of patients with neurosyphilis in the preantibiotic era (Figure 60-7). Currently *tabes dorsalis* is a very rare condition. As with general paresis, the incubation period ranges from 15 to 25 years. Clinical symptoms include lightning pains, paresthesias, decreased reflexes, abnormalities in peripheral sensation, difficulty walking, and bladder and bowel dysfunction. Patients often have a positive Romberg's sign. A classic description of *tabes dorsalis* includes patients who walk with their heels landing hard on the floor, knees positioned outward, with their feet slapping.



Syphilitic meningoencephalitis with perivascular infiltration



Section of thoracic spinal cord in tabes dorsalis

Figure 60-7 Tertiary syphilis: late neurosyphilis.

While syphilis should be considered in the differential diagnosis of nearly any psychiatric or neurologic presentation, including dementia, late-onset psychosis, and neuropathy, late neurologic manifestations of syphilis are rare in the antibiotic era.

CARDIOVASCULAR SYPHILIS

Endarteritis of the vasorum of the aorta leads to aortitis and aneurysm formation. This usually involves the ascending aorta, which in turn can cause dilation of the aortic ring and aortic regurgitation (Figure 60-8). After the ascending aorta, the transverse aorta and then the descending arch are the next most common sites involved. Chronic inflammation of the coronary arteries can lead to narrowing and stenosis of the coronary ostia, which can ultimately lead to myocardial ischemia, infarction, and congestive heart failure.

GUMMATOUS (LATE BENIGN) SYPHILIS

Gummatous disease is extremely uncommon and is characterized by indolent destructive lesions of the skin, soft tissue, and bony structures. Although the lesions are destructive, they respond rapidly to treatment. Visceral organs, bones, and the CNS can also be involved. The differential diagnosis of lesions of the skin and mucous membranes is broad and will depend on the local epidemiology of other infectious diseases and neoplasms. Conditions to consider in the differential diagnosis of gummatous-appearing skin lesions include Hodgkin's disease, mycosis fungoides, tuberculosis, systemic lupus erythematous, fungal infections, sarcoid, and granuloma annulare.

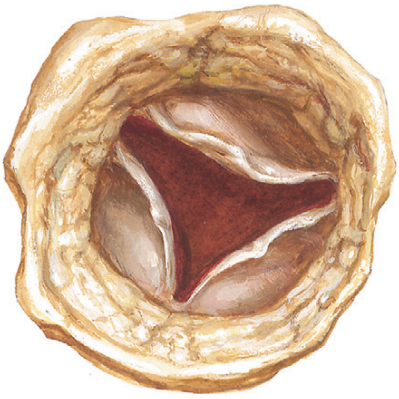
Congenital Syphilis

The manifestations of congenital syphilis are variable and include asymptomatic disease, spontaneous abortion, intrauterine growth restriction, neonatal disease, and neonatal death. The fetus is usually infected transplacentally, and congenital infection rarely occurs before the fourth month of gestation. Congenital infection is most likely to be acquired in the setting of maternal early syphilis; however, it has been documented at any stage of syphilis. Some of the classic features of neonatal disease include rhinitis (snuffles), which typically occurs early in the course of the disease, as well as rash, hepatitis, splenomegaly, and perichondritis or periostitis. Untreated neonates who survive neonatal syphilis enter a latent period. The perichondritis and periostitis can lead to deformities of the nose (saddle nose) and of the metaphyses of the lower extremities (saber shin). Other late manifestations of congenital syphilis include peg-shaped central incisors (Hutchinson's teeth), frontal bossing, and recurrent arthropathy (Figure 60-9).

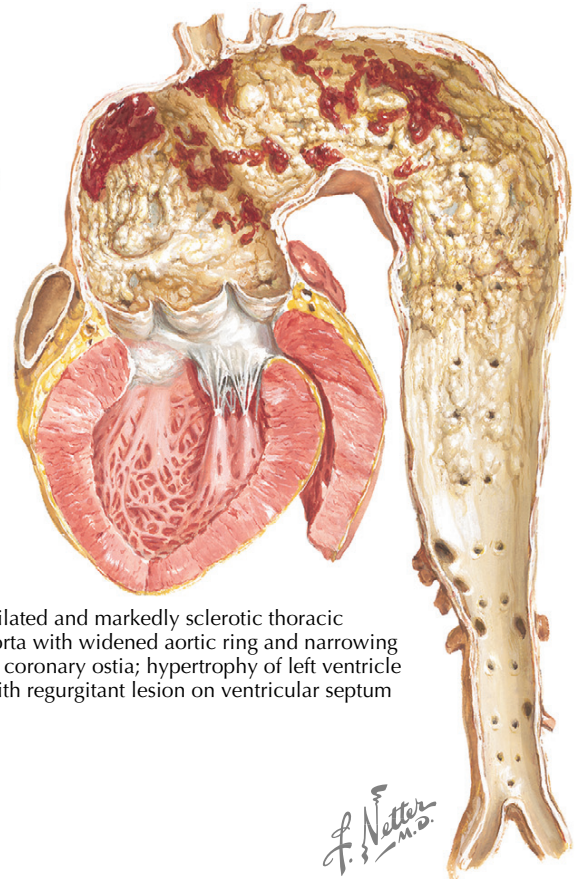
Prevention and early detection of congenital syphilis depend on routine screening of pregnant women for syphilis. All pregnant women should be screened at the first prenatal visit. Women who are at high risk for syphilis infection should be screened again in the third trimester and at delivery (see diagnostic approach).

DIAGNOSTIC APPROACH

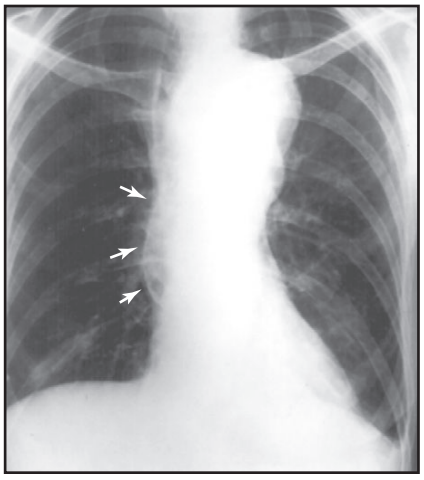
T. pallidum cannot be cultivated in artificial media, is too slender to be observed by light microscopy, and fails to take up traditional Gram stains. It can be visualized using darkfield microscopy, which uses refracted light on a darkened background to identify the spirochete in clinical specimens (Figure 60-10). Whereas polymerase chain reaction (PCR) technology has been used to amplify genetic elements of *T. pallidum* in clinical specimens, there are currently no U.S. Food and Drug Administration (FDA)–cleared molecular amplification assays in use in routine clinical practice. The clinical diagnosis of syphilis is based on the characteristic findings of the skin and mucous membranes and is confirmed with serologic assays measuring antibodies to nontreponemal (rapid plasma reagin [RPR] or



Incompetent aortic valve with taut, separated cusps viewed from above

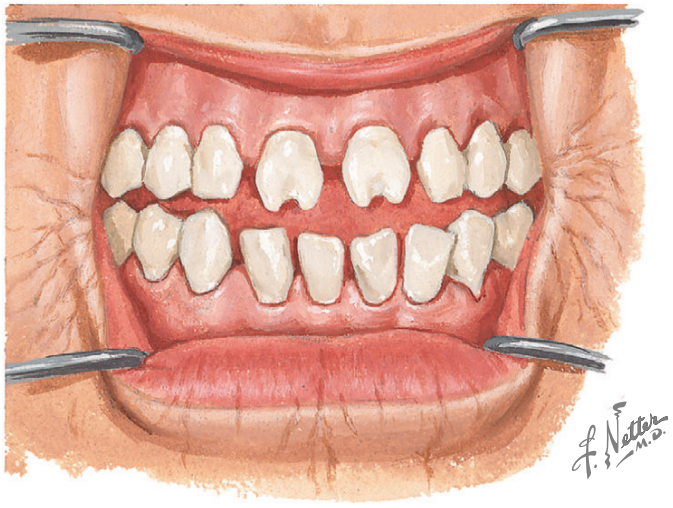


Dilated and markedly sclerotic thoracic aorta with widened aortic ring and narrowing of coronary ostia; hypertrophy of left ventricle with regurgitant lesion on ventricular septum



Calcification of ascending aorta and dilatation of thoracic aorta

Figure 60-8 Tertiary syphilis: cardiovascular complications.



Hutchinson's teeth, scars of healed rhagades (congenital syphilis)

Figure 60-9 Congenital syphilis: Hutchinson's teeth.

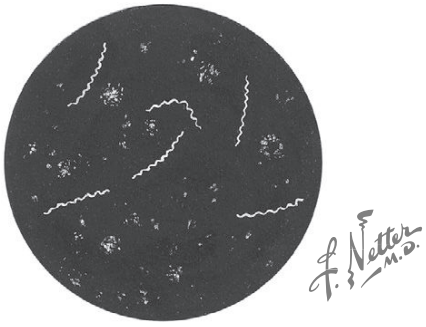


Figure 60-10 Spirochetes in darkfield examination.

Venereal Disease Research Laboratory [VDRL] tests) and treponemal antigens (*T. pallidum* particle agglutination [TPPA], fluorescent treponemal absorption, and enzyme immunoassays [EIA]).

Nontreponemal tests use a laboratory-prepared lecithin-cholesterol antigen to detect treponemal-directed antibody in the patient serum specimen. Nontreponemal tests have a sensitivity of approximately 86% in primary syphilis and 100% in secondary syphilis. Nontreponemal tests are 98% specific, with false-positive results associated with older age, autoimmune disease (e.g., lupus), other infections (e.g., bacterial endocarditis, rickettsial infection, herpes simplex virus [HSV]), chronic liver disease, intravenous drug use, and recent vaccination. Nontreponemal tests can be performed quantitatively, and response to treatment can be demonstrated by declining nontreponemal titers over time.

Treponemal-specific tests are used to confirm the diagnosis of syphilis and to rule out false-positive nontreponemal test results. The treponemal-specific tests currently available in the United States, the fluorescent treponemal antibody absorbed (FTA-ABS), TPPA, and *T. pallidum* hemagglutination assay (TPHA), use true treponemal antigens as a key reagent. Unlike nontreponemal antibody tests, which decline in titer with treatment, treponemal-specific tests remain reactive for the remainder of the life of the individual, irrespective of the success of treatment. Like nontreponemal tests, their sensitivity is lower in primary disease, though they may become reactive before nontreponemal tests in the earliest stages of primary infection. They are 100% sensitive and 99% specific in secondary disease. Reactive laboratory tests for syphilis (treponemal and nontreponemal) are reportable to public health authorities.

Some clinical laboratories and blood banks have begun to use a treponemal EIA in place of a nontreponemal assay as a more cost-effective initial screening test for syphilis. A positive treponemal EIA result will identify persons with a history of treated syphilis and those with untreated or incompletely treated syphilis. If the treponemal EIA result is positive, a nontreponemal test should be performed to determine the titer for monitoring response to treatment. If the nontreponemal test is nonreactive, a second treponemal-specific antibody test (TPPA or FTA-ABS) should be performed, as the initial EIA result could be falsely positive. If both treponemal-specific antibody test results are positive and the nontreponemal test is nonreactive, this could represent latent infection or a previously treated case. In this situation, providers should attempt to document prior treatment; sexually transmitted disease control programs within local health departments can often assist in this effort. If that is not possible, treatment for latent syphilis should be considered.

Primary Syphilis

Evaluation of a patient with a genital ulcer should include (1) sexual, medical, travel, and medication history; (2) examination of oral cavity, skin (trunk, upper and lower extremities, palms and soles, scrotum), and genital and anal areas; (3) examination by darkfield microscopy, if available, of serous exudate from a chancre for the presence of spirochetes; (4) serum RPR or VDRL and TPPA or FTA-ABS (because treponemal-specific tests may be more sensitive in early infection); (5) herpes simplex virus (HSV) PCR or viral culture from swab of ulcer; and (6) test for HIV infection (particularly essential if syphilis is diagnosed).

Secondary Syphilis

A rash of any type in a sexually active individual should be considered as potential syphilis until proven otherwise, particularly if it is bilaterally symmetrical. The typical rash of secondary syphilis does not yield moist specimens for darkfield examination; however, if condylomata lata are present and darkfield microscopy is available, these can be swabbed and examined directly for spirochetes. Nontreponemal tests are highly sensitive in secondary syphilis. A prozone phenomenon can occur when the antitreponemal antibody titer is so high that the characteristic agglutination reaction that produces a reactive specimen cannot occur. When the clinical suspicion for secondary syphilis is high and the nontreponemal test result is negative, the test should be repeated with additional dilutions, usually 1 : 10.

Tertiary Syphilis

Syphilis should be considered in patients with ascending aortic aneurysms or aortic regurgitation. Serologic tests are usually reactive in tertiary syphilis; titers of nontreponemal tests can range from low to very high but are usually lower than in early syphilis. In patients with neurologic findings suggestive of late neurosyphilis and positive serum nontreponemal and treponemal antibody test results, the CSF should be examined. A positive CSF VDRL result establishes the diagnosis of neurosyphilis.

Cerebrospinal Fluid Analysis: Indications and Interpretation

As discussed earlier, syphilis can involve the CNS at any stage of disease. The CSF should therefore be examined in any patient with syphilis and any neurologic or ophthalmic symptoms or signs (cognitive dysfunction, motor or sensory defects, auditory symptoms, cranial nerve palsies, meningismus). The CSF should also be examined in a patient diagnosed with any other form of tertiary syphilis (cardiovascular or gummatous) and in patients who fail to respond to therapy with an appropriate decline in nontreponemal antibody titers.

Whether HIV-infected patients diagnosed with early syphilis without neurologic symptoms or signs require a lumbar puncture (LP) is controversial. The clinical significance of asymptomatic neurosyphilis in the antibiotic era is unclear, and the majority of HIV-infected patients respond appropriately to standard therapy. Thus, as with HIV-uninfected patients, an LP in HIV-infected patients with early syphilis is recommended only if neurologic or ophthalmic abnormalities are present or if the nontreponemal antibody titer fails to fall appropriately after treatment (see treatment section, later) (Figure 60-11).

Lymphocytic pleocytosis (10 to 500 white blood cells [WBCs] per cubic millimeter) and elevated CSF total protein are characteristic of the acute, syphilitic meningitis seen in early syphilis. Fewer cells are seen in the CSF in late neurosyphilis, including syphilitic cerebrovascular disease, general paresis, and tabes dorsalis. An absence of WBCs in the CSF excludes the diagnosis of neurosyphilis. In the setting of a reactive serum nontreponemal and treponemal antibody test, a reactive CSF VDRL confirms the diagnosis of neurosyphilis. However, the CSF VDRL, particularly in early syphilitic meningitis, is not highly sensitive. The role of other serologic tests in the CSF is uncertain. The CSF FTA-ABS has a high false-positive rate but is more sensitive than the CSF VDRL. The CSF FTA-ABS can be used to exclude neurosyphilis in at-risk patients with abnormal CSF and a negative CSF VDRL result.

Congenital Syphilis

The diagnosis of congenital syphilis rests on the identification of syphilis in the mother and a combination of clinical, radiologic, and laboratory findings in the infant. All infants born to

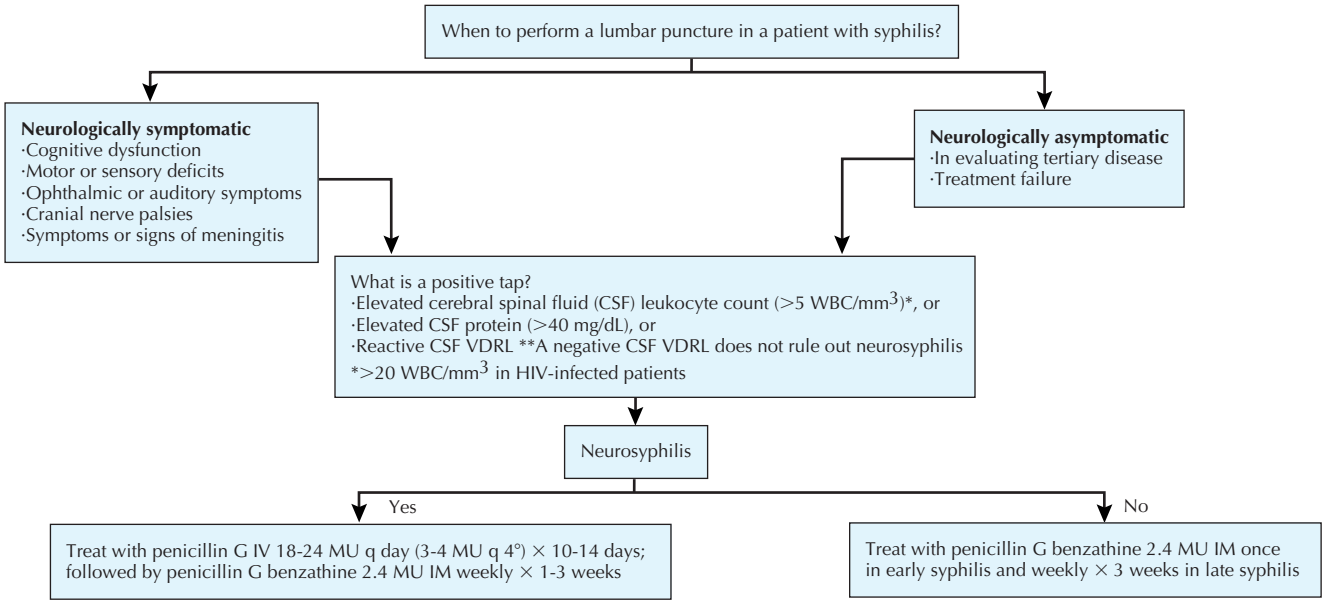


Figure 60-11 Syphilis management: indications for lumbar puncture and cerebrospinal fluid interpretation.

mothers with reactive nontreponemal and treponemal test results should be screened for congenital syphilis by performing of a quantitative nontreponemal antibody test on infant serum (not umbilical cord blood, which can become contaminated with maternal blood). The infant should be examined carefully for signs and symptoms of syphilis. If clinically indicated, the workup may include long-bone radiographs, chest radiograph, liver function tests, cranial ultrasound, ophthalmologic examination, auditory examination, and CSF analysis for VDRL, cell count, and protein. The evaluation and management of congenital syphilis should be performed in consultation with a pediatric infectious diseases specialist.

TREATMENT

Penicillin G remains the treatment of choice for all stages of syphilis. The treatment regimen (route of administration and duration) depends on the stage of disease and site of infection. Early syphilis (primary, secondary, and early latent) can be treated with a single injection of 2.4 million units of intramuscular penicillin G benzathine. A nontreponemal antibody test should be performed on the day of treatment to establish a baseline titer for monitoring the response to therapy. Late syphilis (late latent syphilis and syphilis of unknown duration) is treated with penicillin G benzathine 2.4 million units intramuscular weekly for a total of three injections given a week apart. A lapse of more than 14 days between doses requires restarting treatment. Neurosyphilis is treated with intravenous aqueous penicillin G, 3 million to 4 million units every 4 hours for 10 to 14 days, followed by penicillin G benzathine, 2.4 million units intramuscularly weekly for 1 to 3 weeks. Patients with syphilitic uveitis or other ocular manifestations should be treated according to the recommendations for neurosyphilis.

Although penicillin G remains the treatment of choice, other antibiotics have efficacy and can be used, if necessary, in the setting of penicillin allergy. Doxycycline is effective for early-stage syphilis (100 mg orally twice daily for 14 days) and for late syphilis (100 mg orally twice daily for 28 days). Ceftriaxone can also be used as an alternative to penicillin. Given documented cases of azithromycin treatment failures and evidence of *T. pallidum* resistance to azithromycin in the United States, there is a limited role for azithromycin in the treatment of syphilis (Figure 60-12 and Table 60-1).

Follow-Up

Patients with early-stage syphilis, particularly those with high-titer secondary syphilis, should be counseled about the possibility that they may experience a *Jarisch-Herxheimer reaction* after treatment. This immune-mediated process occurs within 6 to 24 hours of receiving penicillin G and is characterized by the acute onset of fever, headache, and myalgias. Peripheral leukocytosis and transaminitis can also occur. This reaction is usually self-limited and can be managed with antipyretics and nonsteroidal antiinflammatory medications.

The response to treatment should be assessed by the resolution of clinical manifestations and by the decline in nontreponemal antibody titers over time. Successful therapy is determined by a fourfold decline in the nontreponemal antibody test result (e.g., 1:32 to 1:8). When response to treatment is monitored, the same nontreponemal test (either RPR or VDRL), ideally performed at the same laboratory, should be followed serially owing to between-test and between laboratory variability in nontreponemal antibody titer. In early-stage syphilis a fourfold decline should occur within 6 to 12 months of treatment. In late syphilis this decline can take 12 to 24 months. HIV-infected patients with syphilis tend to have a slower decline in nontreponemal antibody titer than HIV-uninfected patients, as will those with a prior history of syphilis. In HIV-infected patients, the expected fourfold decline in titer may not occur until 12 months after treatment of early syphilis and 24 months after treatment of late syphilis. Ideally, all syphilis patients should have follow-up

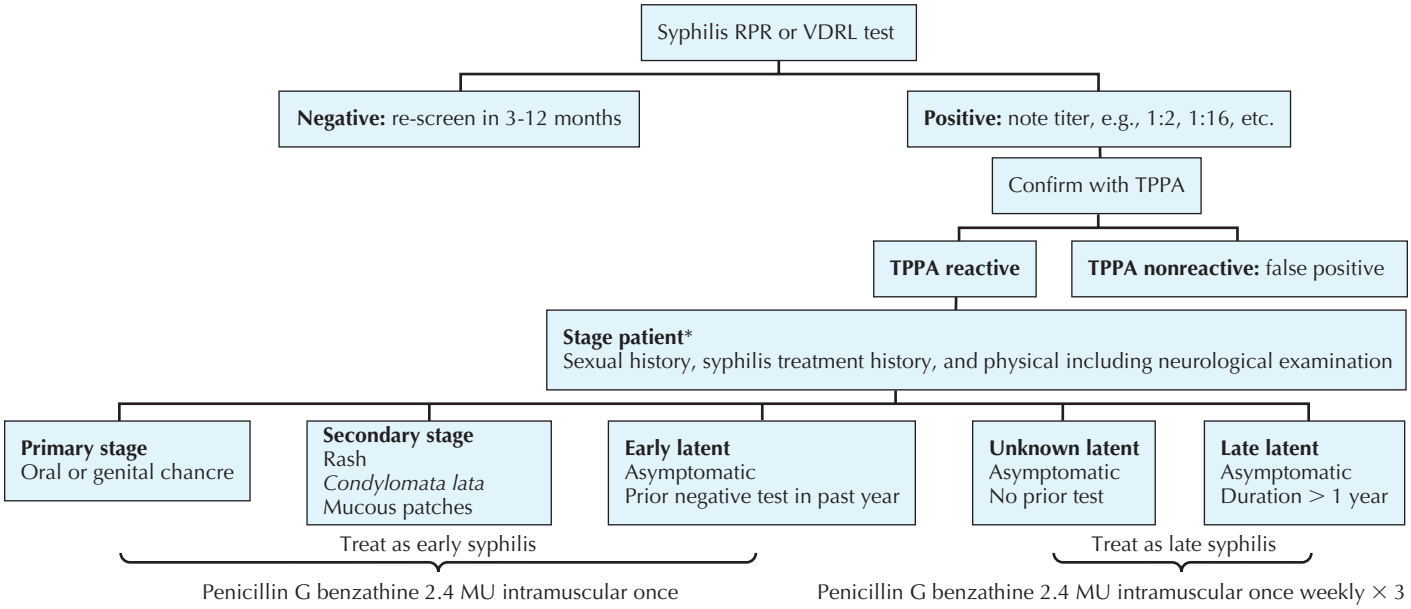


Figure 60-12 Summary of syphilis diagnosis and management. *RPR or VDRL titer ≥1:32 suggests infection prior year.

Table 60-1 Recommended Treatment

	PRIMARY THERAPY	ALTERNATIVE THERAPY	COMMENT
Primary, secondary, and early latent syphilis	Penicillin G benzathine, 2.4 million units IM as a single dose	Doxycycline 100 mg PO 2× daily for 14 days *or* Ceftriaxone, 1 g IM daily for 10-14 days *or* Tetracycline 100 mg PO 4× daily for 14 days	
Latent syphilis of unknown duration and late latent syphilis	Penicillin G benzathine, 2.4 million units IM once weekly for 3 weeks	Doxycycline 100 mg PO 2× daily for 28 days *or* Tetracycline 100 mg PO 4× daily for 28 days	
Neurosyphilis	Penicillin G aqueous, 18-24 million units IV daily (3-4 million units every 4 hr or by continuous infusion) for 10-14 days	Procaine penicillin, 2.4 million units IM daily *plus* probenecid 500 mg PO 4× daily, both for 10-14 days *or* Ceftriaxone, 2 g IM daily for 10-14 days	Follow-up treatment with one to three additional weekly injections of penicillin G benzathine, 2.4 million units IM
Tertiary syphilis (not neurosyphilis)	Penicillin G benzathine, 2.4 million units IM once weekly for 3 weeks		CSF evaluation should be performed before therapy

CSF, Cerebrospinal fluid; *IM,* intramuscularly; *IV,* intravenously; *PO,* by mouth.

titers measured at 3, 6, 9, 12, and 24 months posttreatment. A nontreponemal antibody titer that fails to fall by fourfold over the expected time interval may represent either reinfection or, less likely, treatment failure. By following serial nontreponemal antibody titers, it is easier to distinguish reinfection from treatment failure. If there is concern regarding treatment failure, a CSF analysis should be performed to rule out neurosyphilis. If the CSF is abnormal, the patient should be treated for neurosyphilis. If the CSF is normal, treatment should be reinitiated with penicillin G benzathine 2.4 million units weekly for 3 weeks.

Pregnancy and Congenital Syphilis

Pregnant women with syphilis who are allergic to penicillin should be desensitized and treated with penicillin according

to the guidelines listed earlier. In pregnant women the Jarisch-Herxheimer reaction can precipitate a miscarriage; therefore pregnant women should be treated in a monitored setting. Treatment of neonates with proven or probable congenital syphilis should be done in consultation with a pediatric infectious diseases specialist.

PREVENTION AND CONTROL

Providers can work together with local health departments to prevent the spread of syphilis. Presumptive and confirmed cases of syphilis should be reported within 1 working day of diagnosis. Staff in public health departments are then able to contact and notify sex partners and provide testing and treatment as appropriate. For patients exposed to early syphilis within the previous 3 months, the proper management includes examination, nontreponemal testing (stat, if available) and treatment with intramuscular penicillin G benzathine regardless of serologic test results. For patients exposed to early syphilis who are beyond the 3-month incubation period, treatment depends on clinical examination findings and serologic test results. Presumptive treatment of contacts based on exposure history is essential to prevent reinfection and control the spread of disease.

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Related Syndromes and Less Common Sexually Transmitted Infections

John F. Toney

61

ABSTRACT

Bacterial vaginosis (BV), the most common cause of vaginitis in the United States, is not traditionally described as a sexually transmitted infection (STI) but is well documented to be sexually associated. In the United States, two STIs—chancroid and granuloma inguinale—are uncommon diseases associated with genital ulcerations. These two infections may be encountered outside the United States and are significant risk factors for human immunodeficiency virus (HIV) infection.

BACTERIAL VAGINOSIS

Geographic Distribution and Magnitude of Disease Burden

BV is the most common cause of vaginal discharge in the United States and has a worldwide presence. The prevalence of BV varies by U.S. population studied; reports of the occurrence of BV in college students of 5% to 25% compared with 12% to 35% among STI clinic patients have been published. Estimates from the Centers for Disease Control and Prevention (CDC) 2001-2004 National Health and Nutrition Survey indicate that as many as one in three women of reproductive age are affected at any given time. Racial disparities have been noted with BV occurrence; black and Mexican-American women have significantly higher odds of BV, with prevalence rates of 51.6% and 32.1%, respectively, than white, non-Hispanic women (23.2%). In pregnancy, BV has been associated with preterm delivery and premature rupture of membranes; BV can increase susceptibility to STIs and to the development of pelvic inflammatory disease (PID), postoperative infections after gynecologic procedures, and HIV infection.

Risk Factors

BV is more common in women with a new sexual partner or many sexual partners, in those who have frequent intercourse, or when there is a lack of condom use and in those who practice douching. Studies in monogamous lesbian sexual partners have found concordance between BV diagnosis and the prevalence of BV-associated bacteria. BV has not been considered an STI, but recent investigation suggests this possibility. However, past studies investigating the treatment of male sex partners of women with BV have not proven beneficial in preventing the recurrence of BV.

Clinical Features

In BV, anaerobic and facultative bacteria, including *Gardnerella*, *Prevotella*, *Mycoplasma*, *Mobiluncus*, *Peptostreptococcus*, and other nonculturable bacteria detected investigationally by amplified nucleic acid tests replace hydrogen peroxide–producing lactobacilli, which are the prominent bacteria in the normal vaginal ecosystem. The loss of these protective lactobacilli alters the vaginal pH and is associated with the occurrence of BV.

Women with BV may or may not be symptomatic. Symptoms include a vaginal discharge that may be malodorous (often described as "fishy") and appreciated more commonly after unprotected sexual intercourse or during their menses; pruritus may occasionally be present. Approximately half of woman with BV have no overt symptoms. On vaginal speculum examination, a homogeneous, milky discharge that is adherent to the walls of the vagina is commonly present (Figure 61-1). BV may occur concomitantly with other causes of vaginitis, including trichomoniasis (discussed more completely in Chapter 54) and vulvovaginal candidiasis.

Diagnostic Approach

Evaluating patients with suspected BV is dependant on physical examination of the vagina and microscopic examination of the discharge and pH determination. The amount, consistency, and location of the discharge within the vagina should be noted.

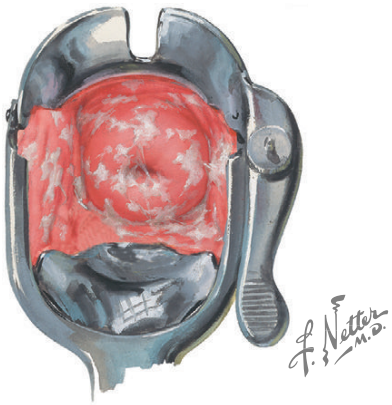
The diagnosis of BV is accomplished by using clinical criteria (Amsel criteria) or a Gram stain of the vaginal discharge. Clinical criteria diagnosis requires three of the following symptoms or signs: (1) a homogeneous, thin, white discharge that smoothly coats the vaginal walls; (2) a fishy odor from the vaginal discharge before or after addition of 10% potassium hydroxide (KOH; i.e., the amine or "whiff" test); (3) a pH of vaginal discharge fluid greater than 4.5; or (4) the presence of clue cells on microscopic examination. A comparison of these criteria with characteristics of other common causes of vaginitis is shown in Table 61-1.

A Gram stain of a vaginal discharge sample is considered the gold standard for laboratory diagnosis of BV, because it shows the relative concentrations of bacteria in the vaginal ecosystem—including the reduction of lactobacilli (long gram-positive staining bacilli) and the increase of bacteria associated with BV, including gram-negative and gram-variable rods and cocci morphotypes (including *Gardnerella vaginalis*, *Prevotella* species, *Porphyromonas* species, and peptostreptococci)

Table 61-1 Differentiating Bacterial Vaginosis, Candidiasis, and Trichomoniasis

	NORMAL	BACTERIAL VAGINOSIS	CANDIDIASIS	TRICHOMONIASIS
Symptoms or presentation		Odor, discharge, itch	Itch, discomfort, dysuria, thick discharge	Itch, discharge, 50% asymptomatic
Vaginal discharge	Clear to white	Homogenous, adherent, thin, milky-white; malodorous "foul fishy"	Thick, clumpy, white "cottage cheese"	Frothy, gray or yellow-green; malodorous
Clinical findings			Inflammation and erythema	Cervical petechiae, "strawberry cervix"
Vaginal pH	3.8-4.2	>4.5	Usually ≤4.5	>4.5
KOH "whiff test"	Negative	Positive	Negative	Often positive
NaCl wet mount	Lactobacilli	Clue cells (≥20%), no or few WBCs	Few WBCs	Motile flagellated protozoa, many WBCs
KOH wet mount			Pseudohyphae or spores if non-*albicans* species	

KOH, Potassium hydroxide; *NaCl,* sodium chloride, *WBCs,* white blood cells.



The discharge appears grayish-white, homogenous, and adheres to the vaginal wall

Figure 61-1 Discharge of bacterial vaginosis.

and curved gram-negative rods (*Mobiluncus* species). Although available in some commercial laboratories, the vaginal fluid Gram stain mainly has been used as a tool in research studies. White blood cells are not usually present in vaginal fluid from a patient with BV; the presence of neutrophils in vaginal fluid suggests the potential of a co-infection at either the cervical or vaginal sites. Cervical papanicolau (Pap) testing is not recommended for the diagnosis of BV because of low sensitivity.

Other commercially available tests that may be useful for the diagnosis of BV include a card test for the detection of elevated pH and amines (QuickVue Advance pH and Amines, Quidel, San Diego, California) and proline iminopeptidase (PIP Activity TestCard, Quidel, San Diego, California). A rapid colorimetric test for the detection of sialidase production in vaginal fluid (Osom BV Blue, Genzyme Corporation, Cambridge, Massachusetts) is also available. However, the deoxyribonucleic acid (DNA) probe-based test for high concentrations of *G. vaginalis* (Affirm VPIII, Becton Dickinson, Sparks, Maryland) has utility in assessment for potential mixed infections, because it also tests for the presence of DNA of *Trichomonas* and *Candida*.

Clinical Management and Treatment

In nonpregnant women, the treatment of BV is intended to relieve vaginal signs and symptoms of infection and reduce the potential for infectious complications associated with abortion or hysterectomy. Because of the increased risk of postoperative infectious complications associated with BV, some specialists suggest providers screen for and treat women with BV before performing elective surgical abortion or hysterectomy. BV has been associated with an increased incidence of other infections (e.g., other STIs including HIV infection), so BV treatment may potentially prevent their occurrence. All women with symptomatic disease should be offered treatment and screened for STIs at appropriate intervals depending on their sexual risk behaviors.

Adverse outcomes associated with BV during pregnancy include premature rupture of the membranes, preterm labor, preterm birth, intraamniotic infection, and postpartum endometritis. Past studies indicate that treatment of pregnant women with BV at high risk for preterm delivery (women who previously delivered a premature infant) might reduce their risk for additional prematurity. Clinicians should consider the evaluation and treatment of high-risk pregnant women with asymptomatic BV. The treatment of asymptomatic BV in women with low- or average-risk pregnancies is controversial and not currently recommended.

The CDC-recommended treatment for BV (Box 61-1) includes using oral metronidazole, 500 mg twice a day for 7 days; or 0.75% metronidazole gel, one full applicator (5 g) intravaginally once a day for 5 days; or 2% clindamycin cream, one full applicator (5 g) intravaginally at bedtime for 7 days. Patients should avoid alcohol ingestion during metronidazole treatment and for 24 hours after treatment. Clindamycin cream is oil-based and might weaken latex condoms and diaphragms for 5 days after use. Topical clindamycin preparations should not be used in the second half of pregnancy, as BV-associated bacteria colonizing the upper genital tract would not receive adequate therapy. A meta-analysis of metronidazole use during pregnancy failed to identify any associated adverse events.

The trichomoniasis dose of metronidazole (2-g single dose) has the lowest efficacy for BV and is no longer a recommended

BOX 61-1 Centers for Disease Control and Prevention Recommended Treatment Regimens for Bacterial Vaginosis

Metronidazole 500 mg orally twice a day for 7 days
or
Metronidazole gel, 0.75%, one full applicator (5 g) intravaginally once a day for 5 days
or
Clindamycin cream, 2%, one full applicator (5 g) intravaginally at bedtime for 7 days

Alternative Regimens
Clindamycin 300 mg orally twice a day for 7 days
or
Clindamycin ovules 100 mg intravaginally once at bedtime for 3 days
or
Tinidazole 2 g orally once daily for 2 days
or
Tinidazole 1 g orally once daily for 7 days

Recommended Regimens for Pregnant Women
Metronidazole 500 mg orally twice a day for 7 days
or
Metronidazole 250 mg orally three times a day for 7 days
or
Clindamycin 300 mg orally twice a day for 7 days

Data from Centers for Disease Control and Prevention (CDC), Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010, *MMWR Recomm Rep* 59:1-110, 2010.

regimen. Additional regimens include metronidazole, 750-mg extended release tablets once daily for 7 days, and a single dose of clindamycin intravaginal cream. Cure rates do not differ between intravaginal clindamycin cream and ovules.

Several studies have evaluated the clinical and microbiologic efficacy of using a human-derived strain of *Lactobacillus* (*Lactobacillus crispatus* strain CTV-05) given as intravaginal suppositories as adjunctive therapy in managing BV; however, clinical trial data are inconclusive at present. There are no data supporting the use of douching for treatment or relief of BV symptoms.

Follow-up visits are unnecessary if symptoms resolve. Because BV recurrence is not unusual, women should be advised to return for additional therapy if symptoms recur. A different treatment regimen from the original management may be considered to control recurrent disease. The optimal management for recurrent BV is unclear; in one trial, after completion of a recommended BV regimen, metronidazole gel 0.75% used topically twice per week for 6 months as suppressive management was effective in maintaining a clinical cure for 6 months.

Prognosis and Recurrence

When recommended therapies are used, cure rates for BV are 70% to 80%. Recurrences with BV are common; approximately one third of women will have a recurrence within 3 months. Data regarding the cause of frequent recurrences of BV are few. The utility of yogurt therapy, acidifying agents, or exogenous oral *Lactobacillus* treatment is disappointing.

Prevention and Control

The consistent use of condoms seems to prevent recurrences of BV. In women with multiple BV occurrences, some specialists consider empirical treatment of male sex partners to see if recurrence rate diminishes, but this approach has not been validated in several studies. Women should be counseled to avoid douching, which can eliminate protective lactobacilli.

CHANCROID

Geographic Distribution and Magnitude of Disease Burden

Chancroid, an infection caused by bacteria of the gram-negative species *Haemophilus ducreyi*, is prevalent in many areas of the world, including Africa, Asia, Latin America, parts of the United States, and the Caribbean. Within the developing countries, chancroid remains a major cause of the genital ulceration syndrome. Reports from Southeast Asia and Africa suggest that, as a result of a rapidly rising incidence of genital herpes, the incidence of chancroid may be declining. In the United States, chancroid usually occurs in discrete outbreaks, although the disease is endemic in some areas, principally among migrant farm workers and poor inner-city residents. Previous U.S. endemic and epidemic chancroid outbreaks have occurred in New York City, New Orleans, Florida, and Texas.

Chancroid is a cofactor for HIV transmission; high rates of HIV infection in patients who have chancroid occur in the United States and other countries. Approximately 10% of U.S. individuals who have chancroid are co-infected with *Treponema pallidum* or herpes simplex virus (HSV); this percentage is higher in persons who acquired chancroid outside the United States.

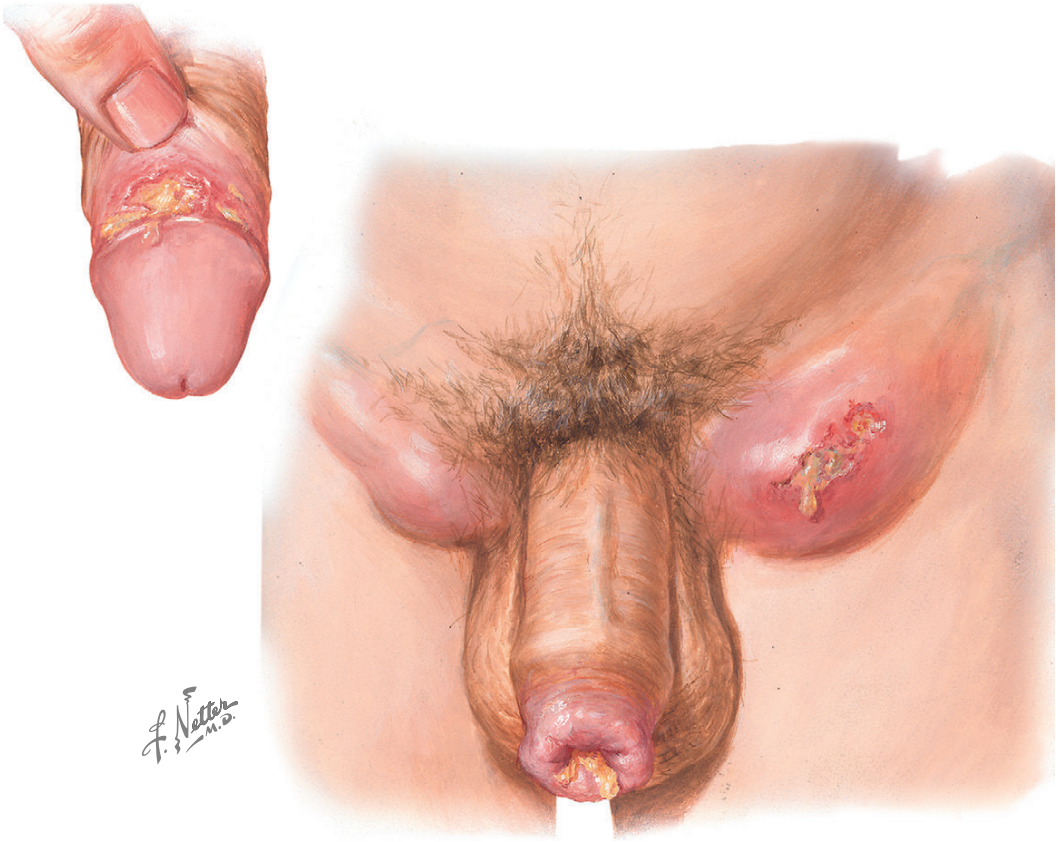
Risk Factors

Chancroid occurs more frequently in men than in women. Infected men are less likely to have used condoms and more likely to report a history of contact with female commercial sex workers or multiple sexual partners in the preceding 3 months. Oral sex has occasionally been implicated in the transmission of chancroid.

Clinical Features

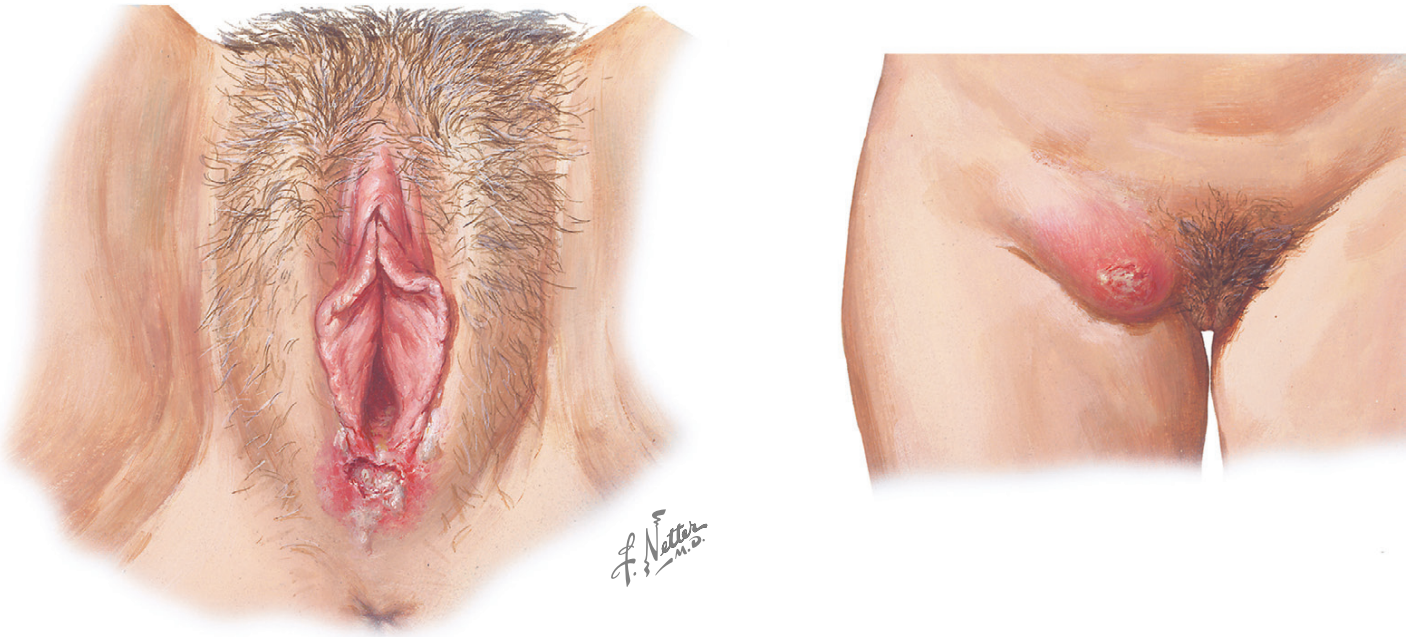
Chancroid is often referred to as a "soft chancre" because the lesions are usually not indurated. After an incubation period of 3 to 7 days, the patient develops painful erythematous papules at the site of contact. The chancroid papules become pustular and then rupture to form shallow painful ulcers with purulent exudates and granulomatous bases. The ulcer edge is typically ragged and undermined.

Men usually have chancroid symptoms directly related to the painful genital lesions or inguinal tenderness (Figure 61-2). In men, lesions typically occur on the prepuce and frenulum. Most affected women are asymptomatic but may have lesions, commonly occurring on the labia majora and less frequently on the vulva, cervix, and perianal area (Figure 61-3). Women have less obvious signs and symptoms, such as dysuria, dyspareunia,



Note the ulcer on the glans and shaft of the penis with a "dirty" base consisting of inflammatory debris and the significant suppurative inguinal lymphadenitis or "bubo"

Figure 61-2 Male chancroid.



Note the ulcer at the inferior introitis and the significant right inguinal bubo

Figure 61-3 Female chancroid.

vaginal discharge, pain on defecation, or rectal bleeding. Constitutional symptoms of chancroid, such as malaise and low-grade fevers, may be present. Painful, tender inguinal lymphadenitis typically occurs in up to 50% of cases, and the lymph nodes may develop into fluctuant, suppurative nodes termed *buboes*. The lymphadenopathy is usually unilateral and tends to be more prevalent in men. If not aspirated or drained through incision, fluctuant buboes can rupture spontaneously. Complications of chancroid in men include phimosis, balanoposthitis, and rupture of buboes with fistula formation and scarring.

Diagnostic Approach

The diagnosis of chancroid based exclusively on the ulcer's appearance is accurate in only 30% to 50% of cases, even in areas where this disease is common and where physicians are experienced in the management of genital ulcer disease (GUD). Significant overlap exists among the major causes of GUD—herpes simplex, syphilis, and chancroid; often, co-infection occurs with two diseases at the same time. Understanding that no cause can be found in 25% to 50% of all cases of GUD is important.

A probable chancroid diagnosis can be made if all the following criteria are met:

- The patient has one or more painful genital ulcers.
- The patient has no evidence of *T. pallidum* infection on darkfield examination of ulcer exudate or on serologic testing for syphilis performed at least 7 days after the onset of ulcers.
- The clinical presentation, the appearance of genital ulcers, and, if present, regional lymphadenopathy are typical for chancroid.
- Results of tests for HSV performed on the ulcer exudate are negative.

Gram staining of an ulcer specimen may show gram-negative coccobacilli singly, in clusters, or in various morphologic forms described as "schools of fish," "railroad tracks," or "fingerprints" (Figure 61-4). Gram-stained ulcer material should not be routinely examined as a tool to diagnose chancroid owing to poor sensitivity and specificity of this test.

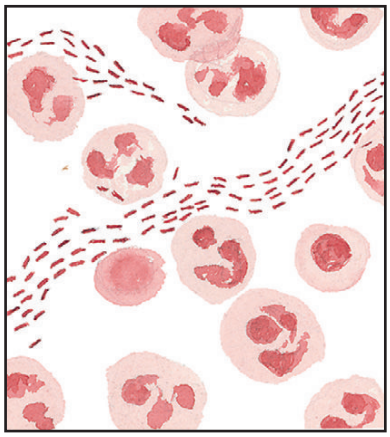


Figure 61-4 Gram stain of *Haemophilus ducreyi* illustrating the "school of fish" bacterial forms.

H. ducreyi is a fastidious bacterium requiring a selective nutritive medium for growth and is an extremely difficult organism to culture from clinical specimens. Culture is the current accepted standard for chancroid diagnosis in most areas, but even in an experienced laboratory, it is only 60% to 80% sensitive. Patients' specimens must either be plated out directly on an appropriate culture medium or sent to the microbiology laboratory for culture as soon as possible for optimal results.

Polymerase chain reaction (PCR) amplification is replacing culture as the diagnostic test of choice in some major medical centers. PCR amplification using a variety of primers may provide a useful alternative to culture for the detection of *H. ducreyi*. Although PCR assays perform well on samples prepared from *H. ducreyi* cultures, they are less sensitive when used to test genital ulcer specimens. A multiplex PCR (M-PCR) assay has been developed for the simultaneous amplification of DNA targets from *H. ducreyi*, *T. pallidum*, and HSV types 1 and 2; it appears more sensitive than standard diagnostic tests for the detection of these causative agents in genital ulcer specimens. The sensitivity of *H. ducreyi* culture relative to the M-PCR assay has been shown to be approximately 75% in studies that have used genital ulcer–derived swabs; unfortunately, the M-PCR assay is not commercially available. No U.S. Food and Drug Administration (FDA)–cleared PCR test for *H. ducreyi* is available in the United States, but the CDC suggests that clinical laboratories that have developed their own PCR test and conducted a Clinical Laboratory Improvement Amendments (CLIA) verification study can perform testing.

Clinical Management and Treatment

CDC-recommended chancroid regimens include azithromycin, 1 g orally in a single dose; ceftriaxone, 250 mg given intramuscularly (IM) in a single dose; ciprofloxacin, 500 mg orally twice a day for 3 days; or erythromycin, base 500 mg orally three times a day for 7 days (Box 61-2). Single-dose oral azithromycin or intramuscular ceftriaxone regimens offer advantages in terms of improved patient compliance; also, there have been worldwide reports of several isolates with intermediate resistance to either ciprofloxacin or erythromycin.

Fluctuant buboes should be aspirated to provide symptomatic pain relief for the patient and to avoid the further complication of spontaneous rupture. Chancroid ulcers treated with the

BOX 61-2 Centers for Disease Control and Prevention Recommended Chancroid Regimens

Azithromycin 1 g orally in a single dose
or
Ceftriaxone 250 mg intramuscularly (IM) in a single dose
or
Ciprofloxacin 500 mg orally twice a day for 3 days
or
Erythromycin base 500 mg orally three times a day for 7 days

Data from Centers for Disease Control and Prevention (CDC), Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010, *MMWR Recomm Rep* 59:1-110, 2010.

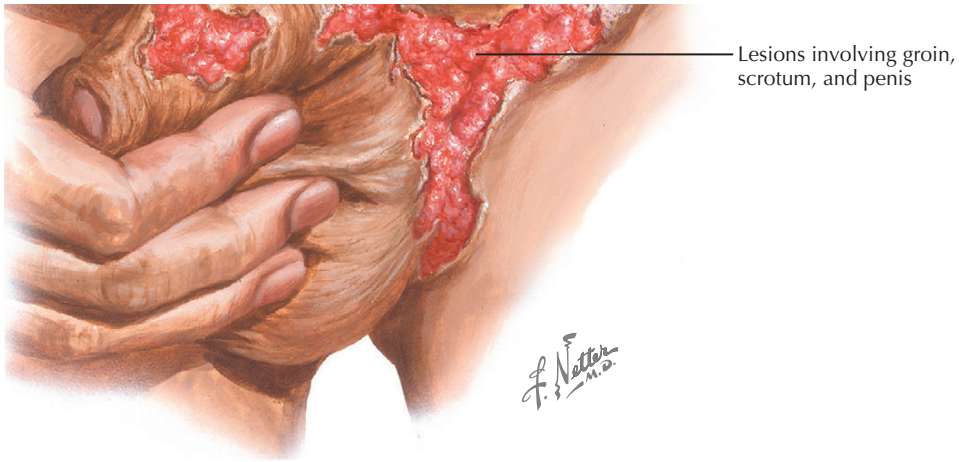


Figure 61-5 Male donovanosis.

appropriate antibiotic agent generally resolve within 7 to 14 days; the time to complete healing depends on the size of the ulcer (larger ulcers may require more than 2 weeks). Chancroid relapses may occur in as many as 5% of patients after antibiotic therapy, and relapses are more common in patients who are uncircumcised or are infected with HIV. If the patient is not HIV infected, repeating the original therapy is usually effective.

Prognosis and Recurrence

The prognosis is excellent if chancroid is treated properly and HIV co-infection is not present. No adverse effects of chancroid on pregnancy outcome have been reported. Chancroid-infected patients who have HIV should be monitored closely because they are more likely to experience treatment failure and to have ulcers that heal slowly.

Prevention and Control

Sex partners of patients who have chancroid should be examined and treated, regardless of whether symptoms of the disease are present, if they had sexual contact with the patient during the 10 days preceding the patient's onset of symptoms. The patient should be strongly advised to avoid sexual contacts while the ulcers are open because they are highly infectious. Patients should be advised to avoid commercial sex workers, to properly and consistently use condoms, and to avoid having multiple partners. Chancroid cases should be reported to the local STI program in states where reporting is mandated.

GRANULOMA INGUINALE (DONOVANOSIS)

Geographic Distribution and Magnitude of Disease Burden

Granuloma inguinale, or donovanosis, is a chronic, slowly destructive, ulcerative disease of skin and subcutaneous tissues caused by *Klebsiella* (formerly *Calymmatobacterium*) *granulomatis*. Rarely identified in developed countries, donovanosis has been endemic in adolescents and adults in some tropical and developing regions, including Papua New Guinea, central Australia, South Africa, and areas of India and Brazil, with sporadic cases reported in the West Indies, South America, and other areas of southern Africa. Accurate current data for most endemic areas are limited; however, in recent years several endemic regions have reported substantial declines in prevalence. The published literature on donovanosis represents few geographic locations, reflects limited microbiologic testing, and relies on syndromic GUD surveillance in areas where donovanosis is thought to be most common.

Risk Factors

The sexual transmission of donovanosis has been controversial, but there is substantial evidence that *K. granulomatis* is transmitted sexually. The proportion of steady sexual partners of people diagnosed with donovanosis who develop disease is 12% to 52%. Although rare, vertical transmission of donovanosis has been reported. There also is evidence that transmission may occur through fecal contamination and autoinoculation. Children rarely are diagnosed with donovanosis; cases in children have been attributed to sitting on the laps of infected adults rather than sexual abuse.

Clinical Features

The incubation period of donovanosis is uncertain; however, experimental lesions have appeared in humans 50 days after inoculation. Donovanosis lesions involve the genitalia (typically the prepuce or glans in men and the vagina or labia minora in women) in 80% to 90% of cases but also can involve the inguinal and anal regions (Figures 61-5 and 61-6). Beginning as a small, single papule or multiple papules at the site of inoculation, donovanosis typically causes painless, easily bleeding ulcers or vegetative lesions. Ulcerative lesions slowly expand and become clean, shallow, well-demarcated ulcer(s) with a beefy red granular base. The clinical presentation also may include hypertrophic, necrotic, or sclerotic variants. In most cases clinical findings are suggestive of donovanosis but are not highly specific.

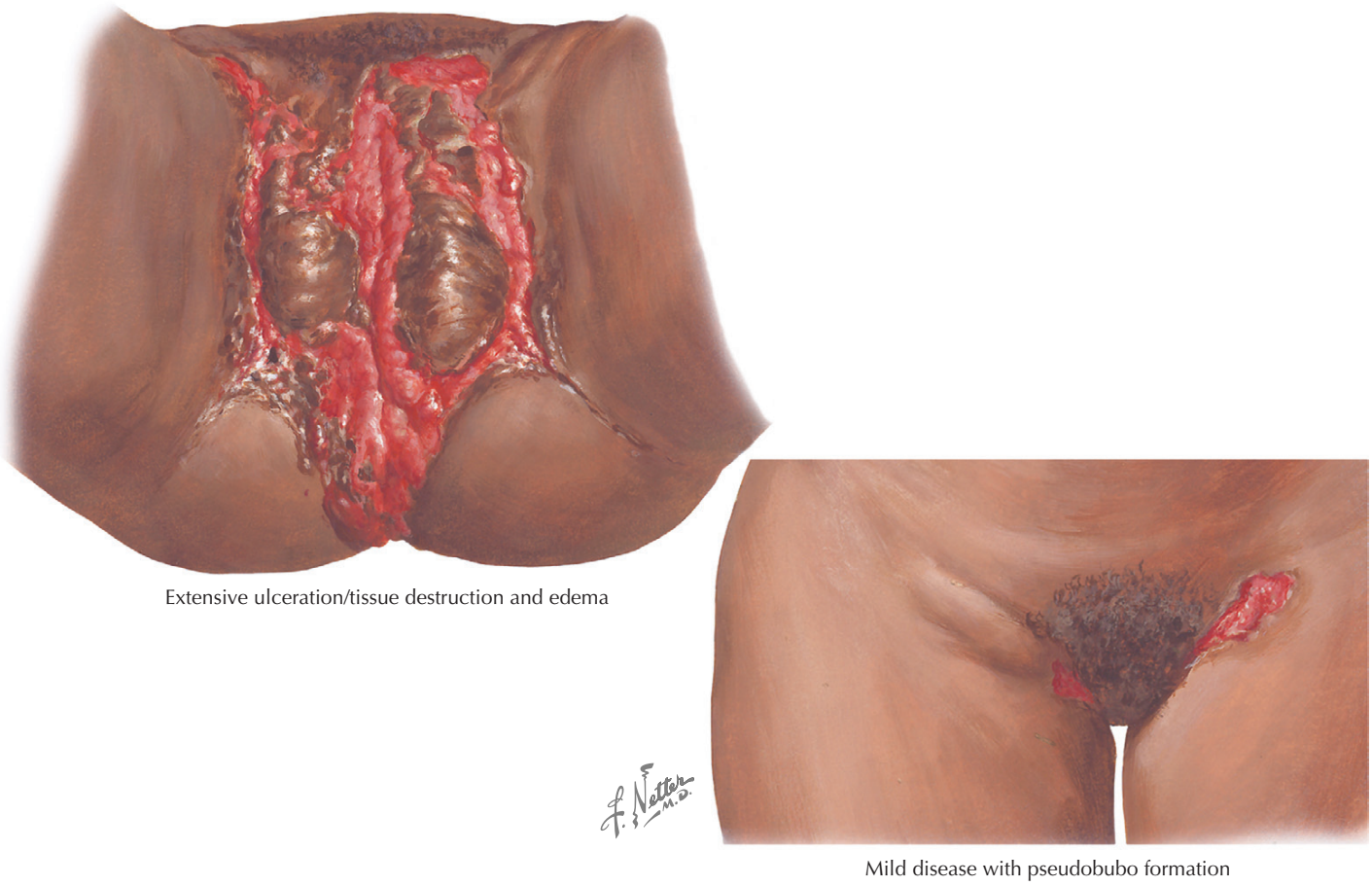


Figure 61-6 Female donovanosis.

Untreated lesions can cause extensive local tissue damage, including pelvic and perianal fistulas, urethral obstruction, and lymphedema. Although uncommon, lesions can develop secondary bacterial infection and cellulitis. Systemic infections can cause fever, weight loss, and anemia. Involvement of the bone, joint, and liver may occur infrequently and is thought to be more common in pregnant women. Involvement of the head and neck also has been described. The prominent inguinal swellings seen in patients with donovanosis have been called "pseudobuboes" because they are subcutaneous granulomas that occur superficially in the area of inguinal lymph nodes.

The differential diagnosis of donovanosis is broad and includes syphilis, lymphogranuloma venereum, chancroid, lymphoma, carcinoma, amebiasis, tuberculosis, blastomycosis, and other granulomatous diseases. People suspected of having donovanosis also should be tested for syphilis and other STIs, including HIV, which may coexist with donovanosis. Donovanosis is thought to increase risk of HIV transmission similar to other GUDs, such as syphilis and HSV infection.

Diagnostic Approach

K. granulomatis is a pleomorphic, intracellular, gram-negative bacterium. Because it is difficult to grow on artificial media, tissue "crush" or biopsy specimens can also be used to identify

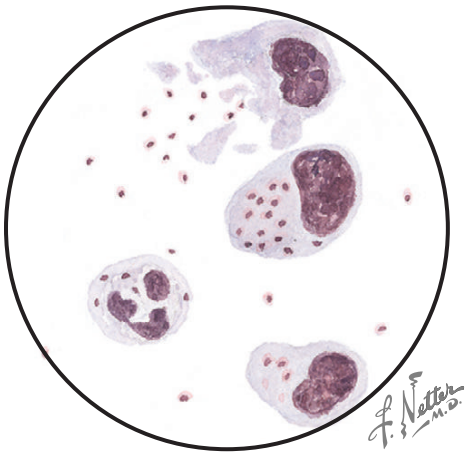


Figure 61-7 Crush preparation of *Klebsiella granulomatis* seen as Donovan bodies intracellularly in mononuclear cells.

K. granulomatis. For tissue crush specimens, granulation tissue is collected from a lesion and crushed between two microscopic slides. "Donovan bodies," safety pin–appearing and clustered in macrophages when stained with Wright or Giemsa stain, are diagnostic for *K. granulomatis* (Figure 61-7). Although not FDA

approved for clinical use, a PCR test for *K. granulomatis* is available for use in some research settings.

Clinical Management and Treatment

A limited number of studies on Donovanosis treatment have been published. Treatment halts progression of lesions, although prolonged therapy is usually required to permit granulation and reepithelialization of the ulcers. Healing typically proceeds inward from the ulcer margins. Several antimicrobial regimens have been effective, but results from a limited number of controlled trials have been published. The recommended first-line therapy for adults with donovanosis according to the CDC's STI treatment guidelines is doxycycline (100 mg orally twice daily). Alternative regimens include trimethoprim-sulfamethoxazole, one double-strength (800 mg/160 mg) tablet orally twice daily for 3 weeks; ciprofloxacin, 750 mg orally twice daily; erythromycin, base 500 mg orally four times a day; and azithromycin, 1 g orally once per week (Box 61-3). Azithromycin appears to be effective, but studies of azithromycin treatment of donovanosis have involved few cases to date. Several antimicrobial regimens have been effective, but a limited number of controlled trials have been published. Pregnancy is a relative contraindication to the use of sulfonamides. Pregnant and lactating women should be treated with the erythromycin regimen; azithromycin might prove useful for treating granuloma inguinale during pregnancy, but published data are lacking. Doxycycline and ciprofloxacin are contraindicated in pregnant women. Persons with both granuloma inguinale and HIV infection should receive the same regimens as those who are HIV negative. With both of these groups, consideration should be given to the addition of a parenteral aminoglycoside (e.g., gentamicin) to these regimens if improvement is not evident within the first few days of therapy.

BOX 61-3 Centers for Disease Control and Prevention Recommended Regimens for Treatment of Granuloma Inguinale

Doxycycline 100 mg orally twice a day for at least 3 weeks and until all lesions have completely healed

Alternative Regimens

Azithromycin 1 g orally once per week for at least 3 weeks and until all lesions have completely healed

or

Ciprofloxacin 750 mg orally twice a day for at least 3 weeks and until all lesions have completely healed

or

Erythromycin base 500 mg orally four times a day for at least 3 weeks and until all lesions have completely healed

or

Trimethoprim-sulfamethoxazole, one double-strength (160 mg/800 mg) tablet orally twice a day for at least 3 weeks and until all lesions have completely healed

Data from Centers for Disease Control and Prevention (CDC), Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010, *MMWR Recomm Rep* 59:1-110, 2010.

Prognosis and Recurrence

Patients should be followed clinically until signs and symptoms have resolved. The risk of complications, such as complete genital erosion and urethral obstruction, can be minimized with early therapy. Relapse can occur 6 to 18 months after apparently effective therapy. Carcinoma is the most serious complication but is relatively rare. Practitioners should consider giving a monitored trial of antibiotic treatment for granuloma inguinale, as the histologic distinction between squamous cell carcinoma and granuloma inguinale may sometimes be difficult to differentiate. Surgical intervention may be required for advanced disease resulting in tissue destruction.

Prevention and Control

Persons who have had sexual contact with a patient who has granuloma inguinale within the 60 days before onset of the patient's symptoms should be examined and offered therapy. However, the value of empirical therapy in the absence of clinical signs and symptoms has not been established.

EVIDENCE

Fethers KA, Fairley CK, Hocking JS, et al: Sexual risk factors and bacterial vaginosis: a systematic review and meta-analysis, *Clin Infect Dis* 47:1426-1435, 2008. *This article is the first to summarize available observational data for BV. It shows that BV is significantly associated with sexual contact with new and multiple male and female partners and that decreasing the number of unprotected sexual encounters may reduce incident and recurrent infection.*

Nygren P, Fu R, Freeman M, et al: Evidence on the benefits and harms of screening and treating pregnant women who are asymptomatic for bacterial vaginosis: an update review for the U.S. Preventive Services Task Force, *Ann Intern Med* 148:220-233, 2008. *There has been continued debate about the value of screening and treating asymptomatic pregnant women for BV; this review found no benefit in treating women with low- or average-risk pregnancies for asymptomatic BV.*

Oakley BB, Tina L, Fiedler TL, et al: Diversity of human vaginal bacterial communities and associations with clinically defined bacterial vaginosis, *Appl Environ Microbiol* 74:4898-4909, 2008. *The compositions of vaginal bacterial communities differ dramatically between subjects with and without BV. These data describe a previously unrecognized diversity in the vaginal ecosystem and in particular in BV-associated bacteria.*

ADDITIONAL RESOURCES

Amsel R, Totten PA, Spiegel CA, et al: Nonspecific vaginitis. Diagnostic criteria and microbial and epidemiologic associations, *Am J Med* 74:14-22, 1983. *This landmark paper provided clearer diagnostic criteria for the diagnosis of BV and remains the standard clinical assessment tool.*

Centers for Disease Control and Prevention (CDC), Workowski KA, Berman SM: Sexually transmitted diseases treatment guidelines, 2010, *MMWR Recomm Rep* 59:1-110, 2010. Available at: www.cdc.gov/std/treatment/2010/default.htm. *This document contains the CDC's recommendations for the management of the wide variety of STIs. Updates to this document can be found at www.cdc.gov/std.*

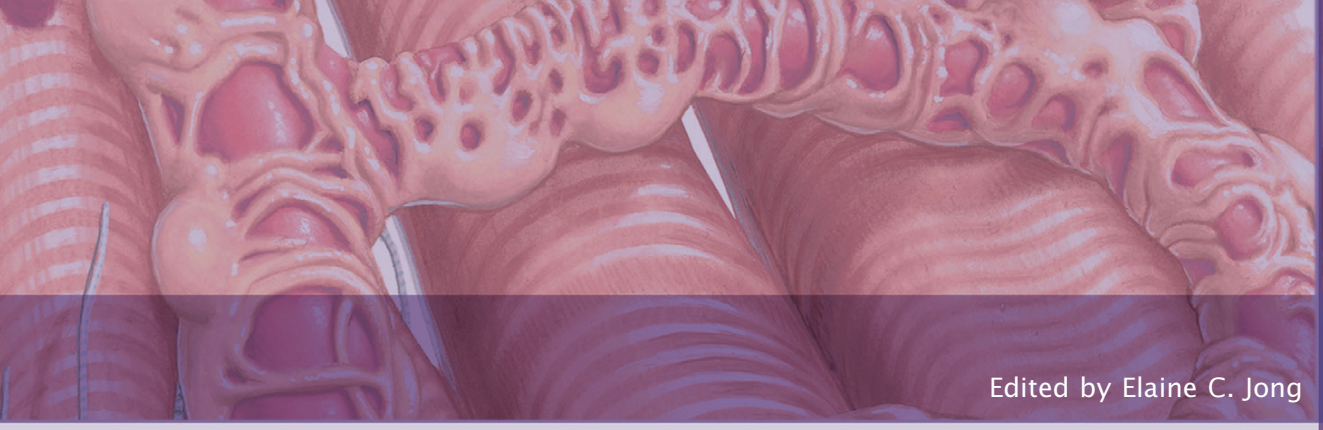
Evans AL, Scally AJ, Wellard SJ, Wilson JD: Prevalence of bacterial vaginosis in lesbians and heterosexual women in a community setting, *Sex Transm Infect* 83:470-475, 2007. (Also see related editorial for this paper: Marrazzo JM: Elusive etiology of bacterial vaginosis—do lesbians have a clue? *Sex Transm Infect* 83:424-425, 2007.) *This article provides insights into the interesting finding of higher BV prevalence in women who report sexual activity with other women. The accompanying editorial is insightful and discusses the limitations and complexities of studies into sexual orientation and disease investigation.*

Hart G: Donovanosis, *Clin Infect Dis* 25:24-30, 1997. *Although an older review, this paper provides significant insight regarding the transmission, clinical features, related laboratory testing, and clinical management of granuloma inguinale.*

Lewis DA: Chancroid: clinical manifestations, diagnosis, and management, *Sex Transm Infect* 79:68-71, 2003. *A concise review of the diagnosis and management of chancroid, including color plates of clinical manifestations.*

Mohammed TT, Olumide YM: Chancroid and human immunodeficiency virus infection—a review, *Int J Dermatol* 47:1-8, 2008. *An informative review of the difficulties of chancroid management in individuals with concomitant HIV infection.*

World Health Organization (WHO): Management of sexually transmitted diseases, 2003, 2003 Geneva, Switzerland, WHO. Available at: whqlibdoc.who.int/publications/2003/9241546263.pdf. *Recommendations for the diagnosis and management of STIs outside of the United States.*



SECTION VII

Edited by Elaine C. Jong

Infections Associated with International Travel and Outdoor Activities

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Introduction to Infections Associated with International Travel and Outdoor Activities

Elaine C. Jong

62

This section covers a variety of diseases that are associated with international travel and outdoor activities. *Travel* in the broadest sense means movement from one place to another, especially journeys to distant or unfamiliar places, and the theme of travel with exposure to exotic infectious diseases has been a recurring one throughout the history of mankind. No matter what the primary purpose of the trip is, travelers more likely than not are going to spend some time outdoors enjoying the scenery, mingling with the local population while shopping or sightseeing, and eating local food prepared by others, thus exposing themselves to multiple modes of disease transmission at the destination.

In a published report based on the GeoSentinel database by Freedman and colleagues (2006), the spectrum of disease among 17,353 travelers who sought healthcare after return home was analyzed in relation to place of exposure. There were regional differences in the frequencies of a given diagnosis: in Asia, dengue fever, typhoid fever, and bacterial pneumonia (in descending order) were the leading causes of illness, followed by hepatitis A and malaria; in the Pacific, hepatitis A was the leading diagnosis, followed by malaria and then bacterial pneumonia; in Africa, malaria was the most frequent diagnosis, followed by bacterial pneumonia and typhoid fever; in the Middle East and Latin America, typhoid fever and malaria were reported, respectively. When the GeoSentinel data were analyzed by mode of transmission, more than 35% of the diseases were vector-borne, almost 25% were respiratory, and approximately 23% were food-borne and/or waterborne.

Travelers' diarrhea is a well-known scourge of international travelers, and commonly episodes are experienced during the trip rather than after return home. Up to 60% of travelers to regions characterized by suboptimal sanitation and sewage treatment systems may experience acute onset of loose watery stools sometimes accompanied by abdominal cramps, anorexia, nausea, and general malaise. Usually, travelers' diarrhea is a self-limited disease that runs its course over 5 to 7 days, but this ailment can seriously affect the enjoyment of a short vacation trip, threaten the success of business trips, and impair the performance of competitive sports participants. Although most cases of travelers' diarrhea are caused by toxigenic *Escherichia coli*, enteroaggregative *E.coli* and other bacteria, remarkable epidemics have occurred recently as a result of noroviruses. Rarely, episodes of travel-associated diarrhea may cause lingering symptoms that prompt travelers to seek a full medical workup after return home.

Diseases acquired by inadvertent contact with animals, insects, and the outdoor environment must be considered in rural travelers and sometimes in urban travelers as well. In this category of infections are rabies, arboviruses, leptospirosis, Lyme disease, tick-borne encephalitis, and primary amebic meningoencephalitis.

In the twenty-first century, advances in telecommunications have resulted in unprecedented access to news of disease outbreaks all over the world. New disease-mapping technologies allow for sophisticated epidemiologic analysis, and advances in molecular biology yield new avenues for rapid diagnosis and novel treatments. Despite all this technologic progress, however, the prevention of diseases in outbound travelers and the detection of imported infectious diseases in returned travelers depends on the acumen of individual healthcare providers, who should always ask, "Where are you going?" and "Where have you been?" as part of the standard medical history. The geography of possible exposures to infectious diseases must be added to the traditional considerations of mode of transmission, incubation time, clinical presentation, and clinical pathology when evaluating a returned traveler who is ill.

This section presents a selection of infectious diseases that may pose significant health risks to the international traveler and to others whose recreational activities or work places them at risk for certain infections transmitted outdoors in natural environments.

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): *Health information for international travel 2010*, Atlanta, 2010, U.S. Department of Health and Human Services, Public Health Service. Available at: http://wwwnc.cdc.gov/travel/content/yellowbook/home-2010.aspx. *This publication is known as the "Yellow Book" and is the authoritative source of U.S. government recommendations for immunizations and prophylaxis for foreign travel. This is an invaluable resource for guiding medical advice to travelers.*

Freedman DO, Weld LH, Kozarsky P, et al: Spectrum of disease and relation to place of exposure among ill returned travelers, *N Engl J Med* 354:119-130, 2006. *This report presents and analyzes unique data on diagnoses made in a population of ill travelers who on return home consulted healthcare providers participating in the GeoSentinel surveillance system.*

World Health Organization (WHO): *International travel and health 2010*, Geneva, Switzerland, 2010, WHO. Available at: http://www.who.int/ith/en/index.html. *This publication is the authoritative source of WHO regulations and recommendations for immunizations and prophylaxis for foreign travel and is a source of information on drugs and regimens available outside of the United States.*

Malaria

Elaine C. Jong

63

ABSTRACT

Malaria is a blood-borne protozoan parasite transmitted from person to person by bites of infected female *Anopheles* mosquitoes in tropical and subtropical regions. There are up to 500 million cases annually worldwide and approximately 1 million deaths. The majority of deaths from malaria are among children in sub-Saharan Africa, where over 85% of the world's malaria deaths occur. Travelers to endemic regions may become infected and return home with asymptomatic infections, becoming ill with high fever, headache, shaking chills, and other symptoms weeks to months after exposure, when parasites that had been incubating in liver cells are released into the circulation, invade red blood cells (RBCs), and replicate to produce succeeding generations of parasites. In the United States approximately 1500 cases are reported annually, with almost all cases in returned travelers.

There are four main species of malaria that cause disease in humans: *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*. Recently a simian species, *Plasmodium knowlesi*, has been recognized as a sporadic cause of some human infections acquired in areas of Southeast Asia. *P. falciparum* and *P. vivax* infections occur most commonly, but *P. falciparum* causes the most severe disease and is the target of major prevention programs, especially in Africa. *P. falciparum* infections may result in death within a few days after the onset of fever, because of high levels of parasitemia (particularly in young children and nonimmune adults such as travelers to hyperendemic areas), if not promptly diagnosed and treated with efficacious drugs.

Emergence of drug resistance to chloroquine, sulfadoxine-pyrimethamine, mefloquine, and other drugs among *P. falciparum* strains has prompted the search for and development of new antimalarial drugs and regimens for both preventing disease (e.g., atovaquone-proguanil) and treating diagnosed infections (e.g., artemisinin combination therapy [ACT] for uncomplicated *P. falciparum* malaria; intravenous artesunate for severe complicated malaria). Research on the development of vaccines against malaria has produced several candidate vaccines, some currently undergoing clinical trials but none yet in commercial production.

EPIDEMIOLOGY

Malaria transmission occurs in Africa, Asia (including Southeast Asia, South Asia, and the Middle East), Eastern Europe, the South Pacific, and Central and South America. The heaviest burden of infection is in sub-Saharan Africa, where malaria is the leading cause of childhood mortality (Figure 63-1).

Humans become infected with malaria from the bites of infected female *Anopheles* mosquitoes, which are nighttime feeders biting from dusk to dawn and generally inhabit altitudes of less than 1500 meters. Mosquitoes acquire the infection when biting and taking blood meals from individuals with untreated malaria, a process during which RBCs containing male and female malaria gametocytes are ingested. After the parasite goes through several developmental stages in the mosquito gut, sporozoites (the stage of the malaria parasite infective for humans) reach the mosquito's salivary glands and are subsequently injected into a capillary during the blood meal (bite) by the infected mosquito, thus leading to new human infections (Figure 63-2). The intensity of transmission in a given area is dependent on the presence of untreated malaria infections in the human population, the prevalent species of *Anopheles* mosquitoes and their host feeding preferences, and environmental conditions such as rainfall, temperature, and humidity that favor mosquito breeding habitat.

The majority of human malaria infections are transmitted by mosquito vectors as described previously, although transplacental infections and blood transfusion–acquired infections may occur. These modes of transmission are special concerns when they occur outside of endemic areas, because healthcare providers may be unfamiliar with and unsuspecting of the diagnosis.

LIFE CYCLE AND CLINICAL FEATURES

The minimum incubation period for malaria is 7 days from the first exposure (bite by an infected mosquito) to the development of fever, although an incubation period of 14 to 30 days is more typical (Table 63-1). The incubation period may be longer if malaria chemoprophylaxis has been taken and there is suboptimal parasite suppression. Initially the clinical onset of a malaria attack is nonspecific, with irregular low-grade fever, fatigue, headache, muscle aches, and a chilly feeling, resembling a flulike illness. As the illness progresses, cycles of high fever and chills begin, which correspond to parasite replication cycles in the RBCs.

After entering the human body through an infected mosquito bite, the malaria sporozoites reach the liver, where they infect primary liver cells (hepatocytes), incubate, and then multiply (see Figure 63-2). After the parasites multiply, each infected hepatocyte ruptures, releasing hundreds to thousands of malaria merozoites into the bloodstream. In the case of *P. vivax* and *P. ovale* infections, some of the parasites reaching the liver may persist as dormant hypnozoites within hepatocytes for periods of several months, and even as long as 4 years, before reactivation and multiplication to initiate a new episode of clinical disease.

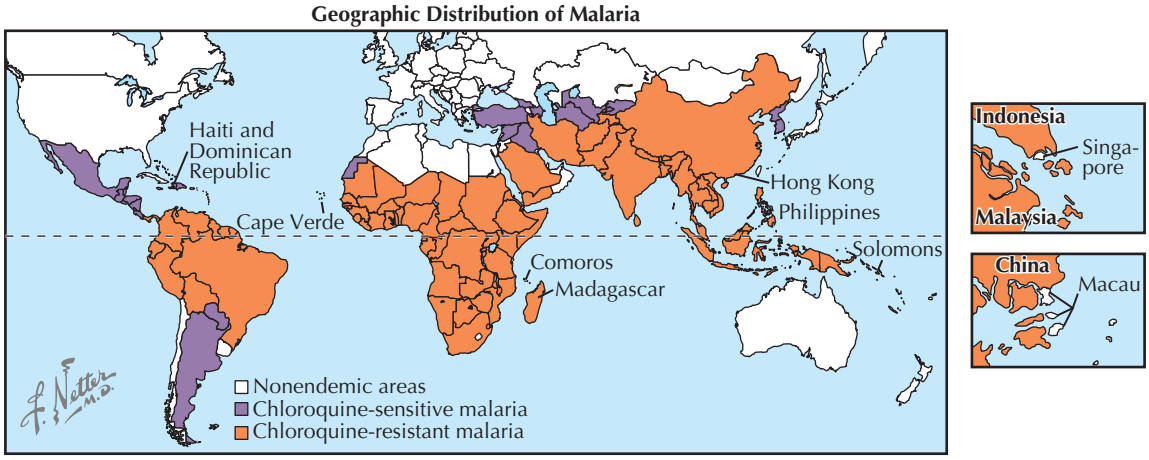

Figure 63-1 Geographic distribution of malaria. *(Data from Centers for Disease Control and Prevention [CDC]:* CDC health information for international travel 2010, *Atlanta, 2009, U.S. Department of Health and Human Services, Public Health Service.)*

Table 63-1 Characteristics of Malaria Species Infecting Humans

FEATURE	*PLASMODIUM FALCIPARUM*	*PLASMODIUM VIVAX*	*PLASMODIUM OVALE*	*PLASMODIUM MALARIAE*	*PLASMODIUM KNOWLESI*
Reservoir of infection	Humans	Humans	Humans	Humans	Macaque monkeys
Predominant geographic area	Sub-Saharan Africa, Asia, South America	Asia, Southeast Asia, Oceania, South America, Africa	Sub-Saharan Africa	South America, Asia, Africa	Southeast Asia
Incubation period*	7-14 days	8-14 days	8-14 days	7-30 days	9-12 days
Dormant liver stage parasites (hypnozoite stage)—relapses may occur	Absent	Present (relapses may occur several months up to 4 years after initial exposure)	Present (relapses may occur several months up to 4 years after initial exposure)	Absent (occult low-grade parasitemia may persist for years)	Absent
Red blood cell (RBC) preference	Circulating RBCs	Reticulocytes†	Reticulocytes	Older RBCs	Circulating RBCs
Typical percent parasitemia	May be >1.0%; severe malaria >5.0%; consider exchange transfusion for >10%	<0.5%†	<0.5%	<0.5%	<0.5%; in some cases may be >1.0%
Rapid diagnostic test (RDT) (United States)	BinaxNOW	BinaxNOW	NA	NA	NA

*The incubation period tends to be shorter, as short as 4 days after infection by direct inoculation (blood transfusion, needlestick, transplacental). The incubation period tends to be longer when there is suboptimal suppression of malaria parasites because of prophylactic drugs that have been taken.
†In pregnancy, the reticulocyte count may be increased and there may be a correspondingly higher level of parasitemia.

The merozoites released by the hepatocytes infect circulating RBCs, subsequently developing into early trophozoites, which appear as ring-shaped forms within RBCs on stained peripheral blood smears. The intraerythrocytic trophozoites subsequently progress through the schizont phase to ultimately produce merozoites that are released on rupture of the infected RBCs. After release, these second-generation merozoites rapidly infect other circulating RBCs and the infection is amplified with the subsequent completion of new erythrocytic cycles that end with rupture of the infected RBCs and release of new generations of infective merozoites.

Each cycle ending in rupture of infected RBCs is accompanied by onset of chills and fever. The symptomatic response is thought to be mediated through cytokines and other factors produced by macrophages and inflammatory cells triggered by hemozoin pigment and other toxic wastes produced during intraerythrocytic parasite development that are released with each new crop of merozoites when the infected RBCs rupture.

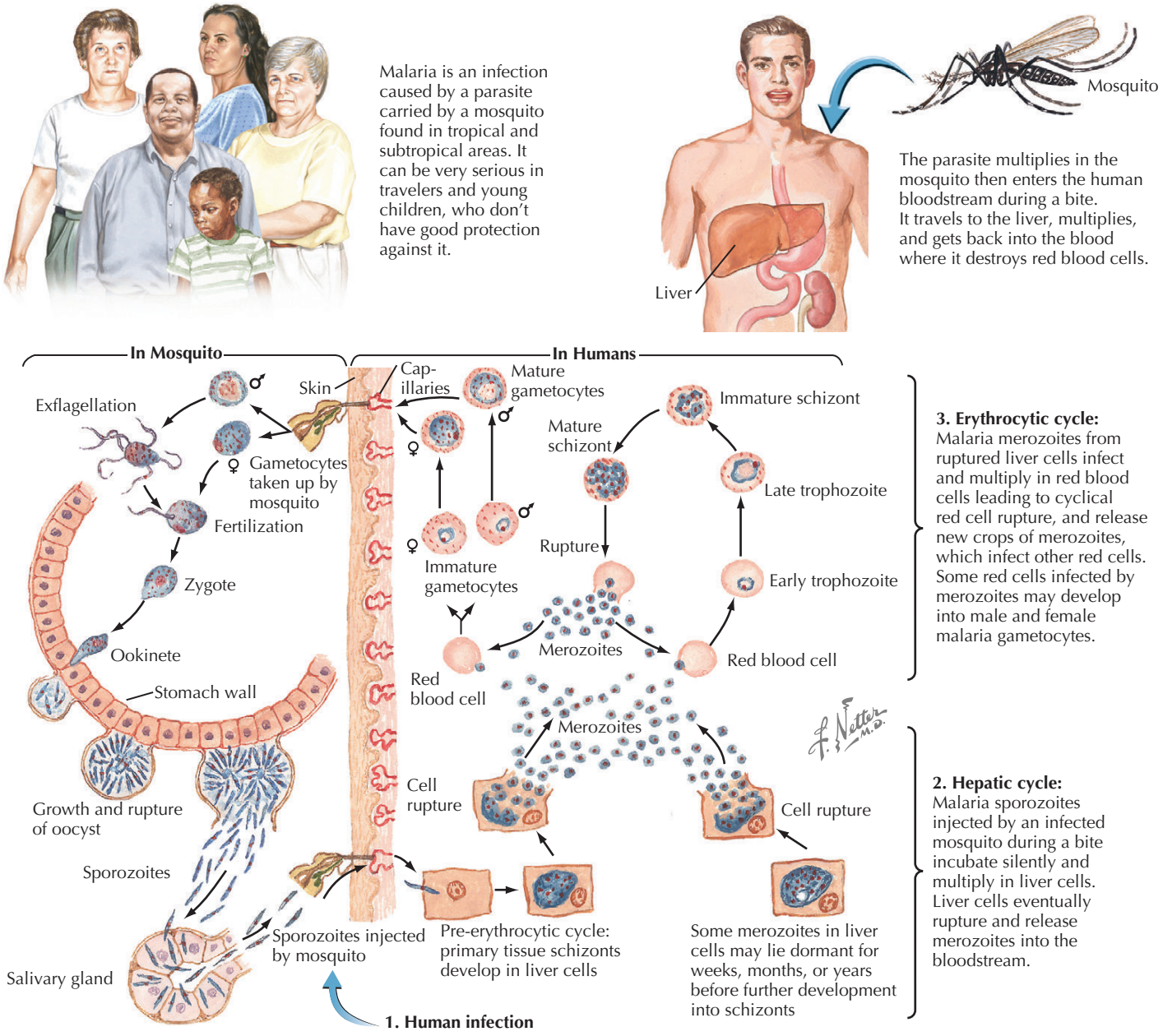

Figure 63-2 Malaria life cycle and transmission to humans.

In addition to chills and fever, the onset of clinical malaria may be accompanied by headache, myalgias, nausea, and vomiting. In nonimmune hosts the fever pattern during the initial days of clinical illness may be irregular, particularly in *P. falciparum* infections. In established infections and in semi-immune patients, each species has a characteristic periodic fever spike separated by an afebrile interval corresponding to the incubation time of the new generation of parasites in the erythrocytic cycle (Figure 63-3). *P. falciparum*, *P. vivax*, and *P. ovale* have a 48-hour periodicity (tertian malaria, fever every third day), and *P. malariae* has a 72-hour periodicity (quartan malaria, fever spike every fourth day), although *P. malariae* tends to cause chronic, asymptomatic infections with low parasitemia. *P. knowlesi* infections have a 24-hour periodicity, and patients with this infection may exhibit a daily fever spike.

Severe systemic complications may develop during *P. falciparum* replication within the RBCs. The merozoites may potentially infect any circulating RBC, leading to a high level of parasitemia (>5%). Parasitized RBCs tend to stick to nonparasitized red cells (called *rosetting*) and also to the capillary endothelium in many end organs. The impairment of the microcirculation by the RBC rosettes and the sludging and sequestration of parasitized RBCs in the end-organ capillaries are thought to impair the microcirculation of vital organs such as the brain and lead to multiple end-organ failure as the *P. falciparum* infection progresses.

During the erythrocytic cycles, some of the RBCs infected by merozoites may develop into male and female malaria gametocytes. Gametocytes cannot directly cause malaria infections in other humans but if ingested by female *Anopheles*

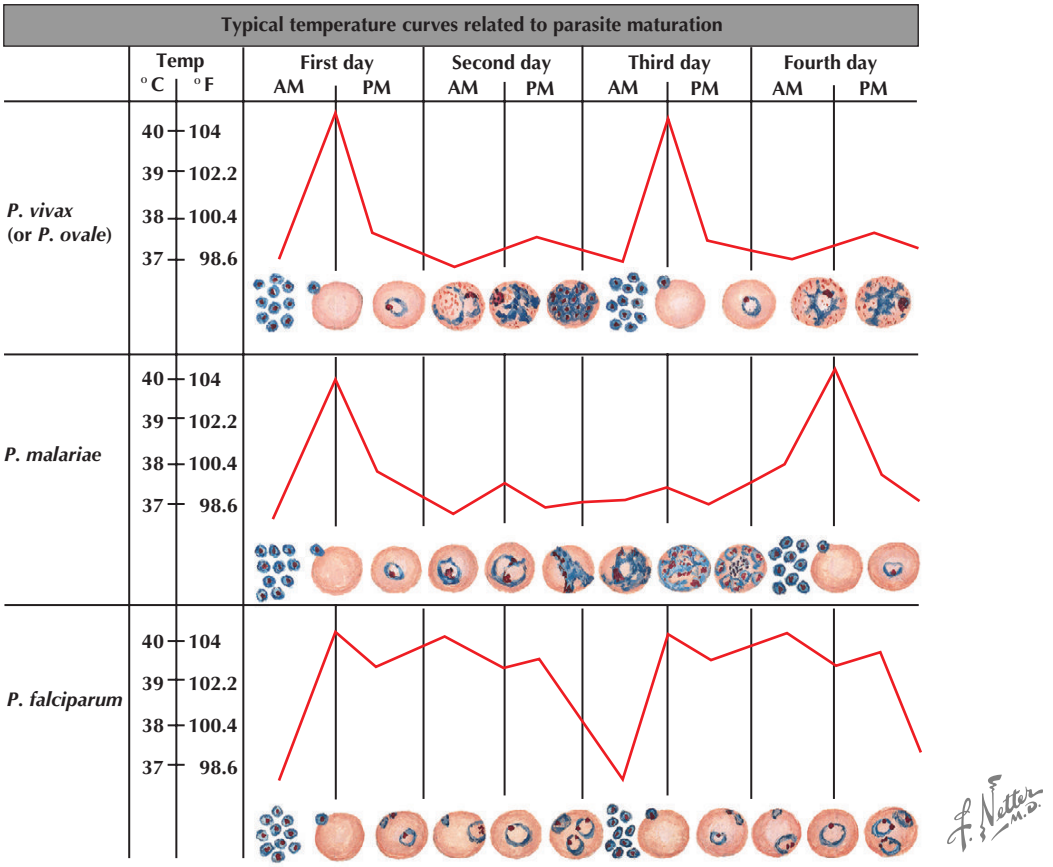

Figure 63-3 Typical temperature curves related to parasite development in red blood cells.

mosquitoes can undergo excystation, fertilization, and reproductive stages in the gut of the mosquito host, promoting continuation of mosquito-vectored transmission (see Figure 63-2).

Malaria gametocytes may be found on peripheral blood smears, even after appropriate treatment has been given, with apparently successful clearance of RBC asexual parasite forms. The gametocytes do not have pathologic implications for the individual patient. However, malaria patients should be protected from mosquito bites after treatment whenever possible, both to prevent patient reinfection from new bites by infected mosquitoes and to prevent new mosquito infections from gametocytes ingested during the bite of an infected patient. One review of the duration of *P. falciparum* gametocyte carriage among patients in clinical trials from East Africa showed that the duration of gametocyte carriage after efficacious treatment was an average of 13 days after ACT treatment, compared with an average of 55 days after non-ACT treatment. Addition of primaquine to ACT resulted in a further reduction in the duration of gametocyte carriage.

DIAGNOSTIC APPROACH

Thick and Thin Blood Smear

The gold standard of malaria diagnosis is a parasitic diagnosis based on finding diagnostic morphologic forms by microscopic examination of thick and thin blood smears prepared with a patient's blood. Presence of parasitized RBCs in the circulation is referred to as *parasitemia;* the percentage of RBCs involved is used to gauge the severity of the malaria infection and is expressed as percent parasitemia.

The morphology of the ring trophozoites, mature trophozoites, schizonts, and gametocytes is used to differentiate the various malaria species when blood smears stained with Giemsa are examined microscopically, and up to three blood samples taken 6 to 8 hours apart should be examined by an experienced microscopist (Figure 63-4). The gametocytes of *P. falciparum* have a distinctive banana-shaped appearance on blood smears and may be contained within RBCs or lie outside of the cells.

On blood smears from infected humans, early ring trophozoite forms of the recently recognized *P. knowlesi* may resemble those of *P. falciparum*, whereas mature forms of *P. knowlesi* trophozoites, schizonts, and gametocytes can be mistaken for those of *P. malariae*. An atypical appearance of the *Plasmodium* species seen in the blood smears and a higher than expected level of parasitemia than is usual for *P. malariae* should raise suspicions of *P. knowlesi* if the patient has traveled in Asia. A definitive diagnosis may not be possible from light microscopy, and samples of the patient's blood may have to be sent to a reference laboratory for species confirmation by molecular testing, such as polymerase chain reaction (PCR) amplification and microsatellite analysis.

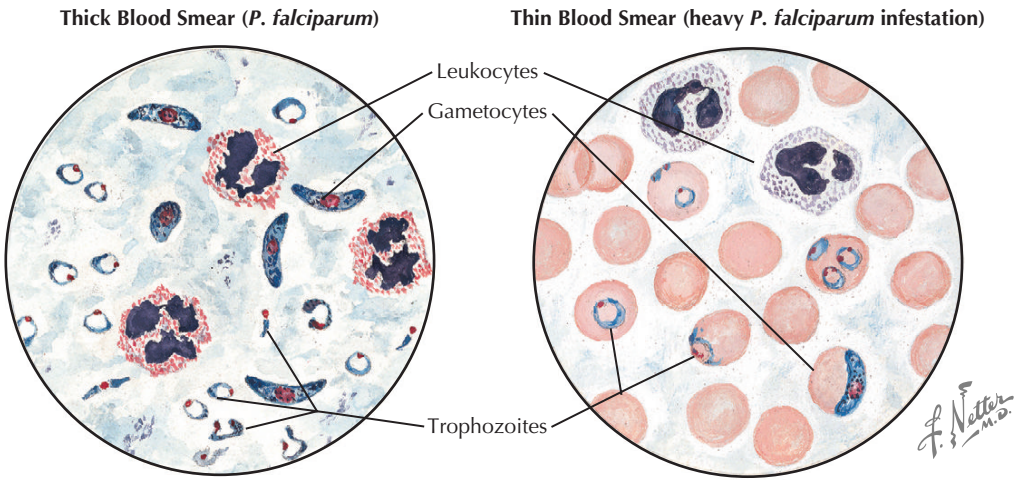

Figure 63-4 Diagnosis of *Plasmodium falciparum* malaria by thick and thin blood smears stained with Giemsa.

Rapid Diagnostic Tests

Microscopy is both time-consuming and expensive and requires trained microscopists. The human and laboratory resources necessary for high-quality parasitic diagnosis by microscopy may not be available in some malaria-endemic areas and in clinics in nonendemic areas that are outside of regional medical centers. Therefore there has been a growing interest in the development of rapid diagnostic tests (RDTs) for malaria that could be used to test individuals with signs and symptoms of malaria who either live in endemic areas or have returned from travel or residence in endemic areas. The RDTs are meant to aid in the diagnosis of malaria, especially in primary healthcare settings, and are not recommended for use by lay travelers for self-diagnosis. There are now several RDTs that demonstrate consistent detection of malaria at low parasite densities (200 parasites per microliter) as well as high parasite densities (2000 or 5000 parasites per microliter), have low false-positive rates, are relatively easy to use, and can detect *P. falciparum* or *P. vivax* infection or both. If positive, the test result may facilitate a more rapid initiation of empirical therapy for the patient with signs and symptoms of malaria with a history of possible exposure: this may be lifesaving in the case of *P. falciparum*.

Standardized evaluations of RDTs are being conducted by the World Health Organization (WHO) in collaboration with the Centers for Disease Control and Prevention (CDC). At the time of writing, one RDT was cleared for distribution in the United States by the U.S. Food and Drug Administration (FDA), the BinaxNOW malaria test (Binax, a subsidiary of Inverness Medical Innovations, Scarborough, Maine). This RDT can detect *P. falciparum* and *P. vivax* antigens using a whole blood sample drawn from a vein or obtained by a finger stick. Performance data showed that for *P. falciparum* the sensitivity and specificity of this test were 99.7% and 94.2%, respectively; for *P. vivax* the sensitivity and specificity were 93.5% and 99.8%, respectively.

The test consists of antimalaria antibodies immobilized at one end of a test strip that target the histidine-rich protein II (HRPII) antigen specific to *P. falciparum*, as well as a panmalarial antigen common to the four malaria species, *P. falciparum*, *P. vivax*, *P. ovale*, and *P. malariae*. According to the package labeling, when a patient's blood sample is applied to the designated spot on the test strip, any malaria antigens present bind to the antibodies, forming antigen-antibody complexes. After a liquid reagent is applied, the complexes migrate along the test strip and are captured by a second set of immobilized antibodies, forming two test lines. A third line at the distal end of the test strip serves as a positive control to show that all the reagents are working and migrating properly. Test lines are positive if both or one of the test lines and the control line turn a pink to purple color, and a positive test result can be used to differentiate the more serious *P. falciparum* infections from infections with the other *Plasmodium* species that can infect humans. Negative results must be confirmed by microscopy of thick and thin blood smears, because clinical performance of the test has not been adequately established for *P. ovale*, *P. malariae*, and *P. knowlesi*.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Patients with malaria may be divided into two categories: uncomplicated malaria and severe malaria. Patients with uncomplicated malaria infections have a low parasitemia, may be uncomfortable but are fully conscious, and do not have preexisting comorbidities that might complicate the course of illness or its treatment. Patients with uncomplicated malaria usually can be treated with oral drug regimens and do not require hospitalization (if the patient is judged to be reliable, home conditions are supportive, and outpatient follow-up is feasible) (Tables 63-2 and 63-3). After initial treatment of infections caused by *P. vivax* or *P. ovale* to eradicate the blood-borne parasites, a course of primaquine phosphate is administered to eradicate the latent hypnozoite forms that may be present in the liver and to prevent relapses.

Severe malaria is most often caused by *P. falciparum* infection, when a parasitemia of >5% develops, or when a person with a blood smear–confirmed malaria infection (or a history of recent possible exposure and no other recognized disease cause) develops one or more of the following clinical problems: impaired consciousness or coma, severe normocytic anemia, renal failure,

Table 63-2 Drugs for Treatment of Uncomplicated Malaria Caused by Chloroquine-Sensitive *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale, Plasmodium malariae,* or *Plasmodium knowlesi* Malaria in Travelers Returning to Nonendemic Countries

DRUG-DRUG COMBINATION	ADULT TREATMENT REGIMEN	PEDIATRIC TREATMENT REGIMEN*	MAIN CONTRAINDICATIONS AND PRECAUTIONS†
Chloroquine phosphate (Aralen and generics)	First dose: 600 mg base (1000 mg salt) by mouth, followed by 300 mg base (500 mg salt) by mouth at 6, 24, and 48 hr Total dose: 1500 base (2500 mg salt OR)	First dose: 10 mg base/kg by mouth, followed by 5 mg base/kg by mouth at 6, 24, and 48 hr Total dose: 25 mg base/kg	Hypersensitivity to chloroquine; history of epilepsy; psoriasis.
Hydroxychloroquine (Plaquenil and generics)	First dose: 620 mg base (800 mg salt) by mouth, followed by 310 mg base (400 mg salt) by mouth at 6, 24, and 48 hr Total dose: 1550 mg base (2000 mg salt)	First dose: 10 mg base/kg by mouth, followed by 5 mg base/kg by mouth at 6, 24, and 48 hr Total dose: 25 mg base/kg	Hypersensitivity to chloroquine; history of epilepsy; psoriasis.
Primaquine phosphate (used to decrease the risk of relapses of *P. vivax* and *P. ovale* infections)	30 mg base by mouth once daily for 14 days Give the first dose of primaquine phosphate with the last dose of chloroquine phosphate or hydroxychloroquine used for treatment of *P. vivax* or *P. ovale*	0.5 mg base/kg by mouth once daily for 14 days: Give the first dose of primaquine phosphate with the last dose of chloroquine phosphate or hydroxychloroquine used for treatment of *P. vivax* or *P. ovale*	G6PD screening must be done before starting primaquine, because primaquine can cause hemolytic anemia in G6PD-deficient persons.

Data from World Health Organization (WHO): International travel and health 2010. *Available at: http://www.who.int/ith/en/index.html. and from Centers for Disease Control and Prevention (CDC):* Health information for international travel 2010. *Available at: http://www.cdc.gov/travel/content/yellowbook/home-2010.aspx.*

G6PD, Glucose-6-phosphate dehydrogenase.

*Pediatric doses should never exceed the adult dose.

†See package inserts for full information on contraindications and precautions.

pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, and/or repeated generalized convulsions.

The treatment of severe complicated *P. falciparum* malaria is beyond the scope of this chapter. Healthcare providers may consult CDC malaria experts through the CDC Malaria Hotline (1-770-488-7788, 8 AM to 4:30 PM, EST; after hours, call 1-770-488-7100 and ask to speak to a CDC Malaria Branch clinician). A current first-line treatment of severe malaria in the United States is intravenous quinidine gluconate plus one of the following: doxycycline, tetracycline, or clindamycin. However, quinidine gluconate has been supplanted by newer drugs in many hospital formularies and is increasingly difficult to obtain. Intravenous artesunate, another highly effective treatment for severe complicated malaria, is available in the United States through an FDA Investigational New Drug (IND) protocol administered by the CDC and can be delivered on an urgent basis for patient treatment as appropriate. Expert consultation also should be obtained for cases of malaria in patients with underlying health conditions, including pregnancy, splenectomy, infection with human immunodeficiency virus (HIV), and immunocompromising conditions or treatments.

PREVENTION AND CONTROL

Measures to prevent and control malaria fall into two categories: environmental interventions and human interventions. Environmental interventions include draining swampy areas and collections of standing fresh water where mosquitoes breed; introducing fish into fresh-water ponds to eat mosquito larvae; applying larvicidal chemicals into ponds, lakes, and slow-moving streams where mosquitoes breed; and spraying the indoors of human dwellings with residual insecticides such as dichlorodiphenyltrichloroethane (DDT) (indoor residual spraying [IRS]). When possible, screens should be installed on window and door openings of dwellings.

Human interventions include preventing exposure to mosquito bites, taking antimalarial drugs to prevent disease (chemoprophylaxis), and using effective antimalarial drugs to treat human infections, thus interrupting the life-cycle stage whereby the mosquitoes become infected while feeding on humans with circulating gametocytes. Exposure to mosquitoes can be lessened by not going outdoors between dusk and dawn and sleeping under a bed net. When it is necessary to go outdoors, applying an insect repellent, such as N,N-diethyl-meta-toluamide (DEET), to all exposed skin areas and wearing external clothing that has been treated with a knock-down insecticide, such as permethrin, can greatly decrease exposure to mosquito bites (see Chapter 69 for further discussion on insect repellents). In several published reports, field studies have shown that sleeping every night under insecticide-treated nets (ITNs) or long-lasting insecticide-impregnated nets (LLINs) is a very effective measure to decrease transmission of malaria in highly endemic areas in Africa.

Recommendations for drugs to be taken for malaria chemoprophylaxis are based on the type of malaria that is likely to be

Table 63-3 Drugs for Treatment of Uncomplicated Chloroquine-Resistant *Plasmodium falciparum* Malaria in Travelers Returning to Nonendemic Countries

DRUG-DRUG COMBINATION	ADULT TREATMENT REGIMEN	PEDIATRIC TREATMENT REGIMEN*	MAIN CONTRAINDICATIONS AND PRECAUTIONS†
Atovaquone-proguanil combination tablet (Malarone)	Adult tablet: 250 mg atovaquone and 100 mg proguanil Adult dose: 4 adult tablets as a single oral dose daily for 3 consecutive days *Note:* Must be taken with fatty foods to enhance absorption.	Pediatric tablet: 62.5 mg atovaquone and 25 mg proguanil (¼ the adult tablet) One dose daily (based on weight) for 3 consecutive days: 5-8 kg: 2 pediatric tablets daily 9-10 kg: 3 pediatric tablets daily 11-20 kg: 1 adult tablet daily 21-30 kg: 2 adult tablets daily 31-40 kg: 3 adult tablets daily >40 kg: 4 adult tablets daily	Hypersensitivity to atovaquone and/or proguanil; severe renal insufficiency (creatinine clearance <30 mL/min). Plasma concentrations of atovaquone are reduced when the drug is coadministered with rifampicin, rifabutin, metoclopramide, or tetracycline.
Artemether-lumefantrine combination tablet (Coartem)	1 tablet: 20 mg artemether plus 120 mg lumefantrine 3-day course of six doses total, taken at 0, 8, 24, 36, 48, and 60 hr Adult dose ≥35 kg: 4 tablets per dose	1 tablet: 20 mg artemether plus 120 mg lumefantrine 3-day course of six doses total, taken at 0, 8, 24, 36, 48, and 60 hr Pediatric weight-based dose: 5 to <15 kg: 1 tablet per dose 15 to <25 kg: 2 tablets per dose 25 to <35 kg: 3 tablets per dose *Note:* Coartem Dispersible is a new formulation that dissolves into a sweetened suspension for easy administration to children.	Hypersensitivity to artemether and/or lumefantrine.
Quinine sulfate *plus* Doxycycline *or* Tetracycline *or* Clindamycin	Quinine sulfate: 542 mg base (650 mg salt) 8 mg base/kg three times daily for 3 days (or 7 days for infections acquired in Southeast Asia) Doxycycline: 100 mg tablet Adult >50 kg: 1 tablet by mouth twice daily for 7 days Tetracycline: 250-mg tablet Adult: 250-mg tablet by mouth four times daily for 7 days Clindamycin: 300 mg base tablet Adult >60 kg: 20 mg base/kg/day divided into three doses per day for 7 days	Quinine sulfate: 8.3 mg base/kg (10 mg salt/kg) by mouth three times daily for 3 days (or 7 days for infections acquired in Southeast Asia) Children 8 years of age and older: doxycycline: 2.2 mg/kg by mouth twice daily for 7 days Children 8 years of age and older: tetracycline: 25 mg/kg/day divided into four doses/day for 7 days Children <60 kg: clindamycin: 20 mg base/kg/day by mouth divided into three doses per day for 7 days	Hypersensitivity to quinine or quinidine; caution in persons with G6PD deficiency, cardiac dysrhythmias, and conduction abnormalities. Hypersensitivity to tetracyclines; liver dysfunction. Hypersensitivity to tetracyclines; liver dysfunction. Hypersensitivity to clindamycin or lincomycin; history of colitis; severe kidney or liver impairment
Mefloquine (Lariam and generics)	1 tablet: 228 mg base (250 mg salt) Adult: 684 mg base (750 mg salt) by mouth as the initial dose, followed by 456 mg base (500 mg salt) by mouth given 6-12 hr after the initial dose Total dose: 1 250 salt (5 tablets)	1 tablet: 228 mg base (250 mg salt) Pediatric weight-based dose: 13.7 mg base/kg (15 mg salt/kg) by mouth as the initial dose, followed by 9.1 mg base/kg (10 mg salt/kg) by mouth given 6-12 hr after the initial dose Total dose = 25 mg salt/kg	Hypersensitivity to mefloquine; history of neuropsychiatric disease; treatment with mefloquine in previous 4 weeks; concomitant halofantrine treatment. Do not give mefloquine within 12 hr of last dose of quinine treatment. Caution: Many drug-drug interactions.

Continued

Table 63-3 Drugs for Treatment of Uncomplicated Chloroquine-Resistant *Plasmodium falciparum* Malaria in Travelers Returning to Nonendemic Countries—cont'd

DRUG-DRUG COMBINATION	ADULT TREATMENT REGIMEN	PEDIATRIC TREATMENT REGIMEN*	MAIN CONTRAINDICATIONS AND PRECAUTIONS†
Dihydroartemisinin-piperaquine (Eurartesim)	One dose daily for 3 consecutive days Adults >50 kg: 3 tablets daily for 3 days Target dose: 4 mg of dihydroartemisinin per kilogram per day and 18 mg of piperaquine per kilogram per day *Note:* Undergoing regulatory review by the European Medicines Agency (EMA). *Note:* A similar drug combination, Artekin, is being studied in clinical investigational trials in Asia.	*Note:* Clinical trials to establish safety and efficacy in children are ongoing.	Hypersensitivity to dihydroartemisinin and/or piperaquine.

Data from World Health Organization (WHO): International travel and health 2010. *Available at: http://www.who.int/ith/en/index.html. and from Centers for Disease Control and Prevention (CDC):* Health information for international travel 2010. *Available at: http://www.cdc.gov/travel/content/yellowbook/home-2010.aspx.*

G6PD, Glucose-6-phosphate dehydrogenase.

*Pediatric doses should never exceed the adult dose.

†See package inserts for full information on contraindications and precautions.

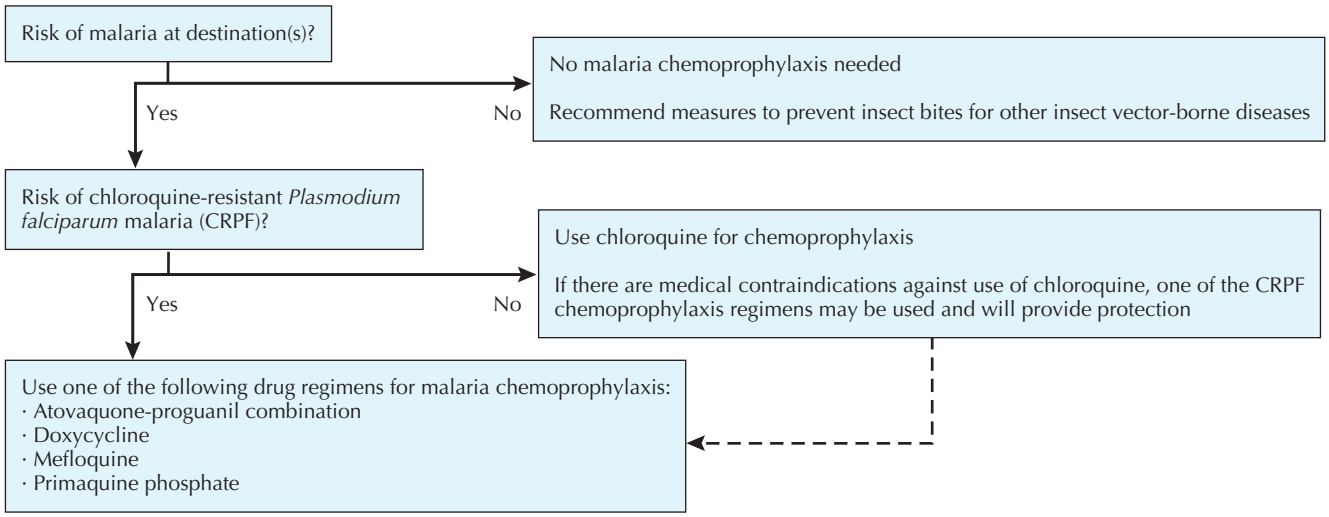

Figure 63-5 Selection of malaria chemoprophylaxis regimen for travelers.

transmitted at a given destination. The recommendations are usually based on whether exposure to chloroquine-resistant *P. falciparum* (CRPF) malaria is anticipated. In scenarios where both CRPF and chloroquine-sensitive malaria *(P. vivax*, *P. malariae*, *P. ovale*, *P. knowlesi)* are present, chemoprophylaxis regimens used against CRPF will cover the chloroquine-sensitive species as well. Figure 63-5 presents an algorithm that may be used to select appropriate malaria chemoprophylaxis. Table 63-4 lists the drugs and regimens that are recommended by the CDC for malaria chemoprophylaxis in adults.

Chemoprophylaxis is highly effective against malaria when taken as prescribed, beginning before travel, taken during travel, and used for an interval after travel in a malaria-endemic area. Table 63-5 illustrates that the dosage schedule and total duration of taking malaria chemoprophylaxis varies depending on the length of the trip and the regimen selected. The most common mistake among travelers is skipping or forgetting doses, so after determining what antimalarial drugs are appropriate for the malaria risk at a given destination, considering daily versus weekly administration schedules may contribute to the final selection.

Although some chemoprophylaxis regimens have been taken with apparent safely for periods of up to 6 years (e.g., weekly chloroquine phosphate), safety of drug regimens currently used

Table 63-4 Drugs Used for Malaria Chemoprophylaxis (Adult)*

SPECIES	MALARIA CHEMOPROPHYLAXIS DRUGS (ADULT DOSES)
Plasmodium falciparum, chloroquine resistant	Atovaquone-proguanil (Malarone), atovaquone 250 mg plus proguanil 100 mg per tablet: one dose daily Doxycycline, 100-mg tablet: one dose daily Mefloquine (Lariam), 250-mg tablet: one dose weekly Primaquine phosphate,† 30-mg base tablet: one dose daily
Plasmodium vivax	Chloroquine phosphate (Aralen and generics), 500-mg tablet (300-mg chloroquine base): one dose weekly Hydroxychloroquine (Plaquenil and generics), 400 mg salt (310-mg hydroxychloroquine base): one dose daily
Plasmodium malariae	Same as *P. vivax*
Plasmodium ovale	Same as *P. vivax*
Plasmodium knowlesi	Same as *P. vivax*
Plasmodium vivax, Chesson strain (chloroquine-resistant *P. vivax*)	Primaquine phosphate†

*Consult www.cdc.gov/travel for recommended pediatric doses and regimens and for contraindications and precautions for use in pregnant and breastfeeding women.
†Glucose-6-phosphate dehydrogenase (G6PD) screening must be done before starting primaquine, because primaquine can cause hemolytic anemia in G6PD-deficient persons.

Table 63-5 Duration of Therapy for Malaria Chemoprophylaxis Regimens

DRUG	CHLOROQUINE-SENSITIVE MALARIA	CHLOROQUINE-RESISTANT MALARIA	PRETRAVEL ADMINISTRATION: TIME BEFORE FIRST POTENTIAL EXPOSURE TO BEGIN MEDICATION	POSTTRAVEL ADMINISTRATION: TIME AFTER LAST KNOWN EXPOSURE TO CONTINUE MEDICATION
Atovaquone-proguanil (daily dose)	Yes	Yes	1-2 days	7 days
Primaquine (daily dose)	Yes	Yes	1-2 days	7 days
Doxycycline (daily dose)	Yes	Yes	1-2 days	4 weeks
Chloroquine (weekly dose)	Yes	No	1 week	4 weeks
Mefloquine (weekly dose)	Yes	Yes	1-3 weeks	4 weeks

to protect against CRPF has been studied only for periods of up to 1 to 2 years of continuous use. For long-stay visitors and others making trips to CRPF areas where there is no access to medical care within 24 hours after onset of a febrile illness, standby emergency therapy (SBET) for malaria may be considered for certain knowledgeable and capable travelers. For SBET, travelers are instructed on how to decrease the risk of exposure to mosquito bites, how to recognize the clinical signs and symptoms of malaria, and are prescribed a treatment course of one of the oral malaria treatment regimens to be used as an emergency measure while seeking professional medical assistance for a presumed clinical attack of malaria. Prolonged chemoprophylaxis is neither feasible nor recommended for the most vulnerable victims of malaria, children living in sub-Saharan Africa. They must rely on environmental interventions and personal protection measures to prevent mosquito bites, treatment of individual infections, and periodic mass treatment programs, until a safe and efficacious malaria vaccine is developed and distributed.

According to the American Association of Blood Banks guidelines, persons who have taken malaria chemoprophylaxis or who have had treatment for diagnosed malaria are deferred from donating blood for 3 years after taking antimalarial drugs. Under these guidelines, solid organ donation is similarly deferred. However, if there is a compelling need for donation of blood or organs from someone who has recently lived or traveled in a malaria-endemic area and has taken malaria chemoprophylaxis, the risk of malaria transmission can be addressed by consulting an infectious diseases or tropical medicine specialist to consider chemotherapy for eradication of possible relapsing or latent malaria. As mentioned previously in the treatment section, the CDC Malaria Branch has telephone consultation with CDC malaria experts available to healthcare providers to discuss difficult or complex cases.

EVIDENCE

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World Health Organization (WHO): *WHO Special Program for Research and Training in Tropical Diseases. Malaria rapid diagnostic test performance: results of WHO product testing of malaria RDTs—round 2 (2009)*, Geneva, 2009, WHO. Available at: http://www.who.int/malaria/publications/atoz/9789241599467/en/ *Results of the second round of product testing of malaria antigen-detecting RDTs completed in 2009. Results of rounds 1 and 2 of testing comprise a single data set, and details on product performance and on the interpretation of results are given.*

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): *Health information for international travel 2010*, Atlanta, 2009, U.S. Department of Health and Human Services, Public Health Service. Available at: http://www.cdc.gov/travel/content/yellowbook/home-2010.aspx. *The chapter on malaria in this reference is essential reading for healthcare providers with patients going to destinations where malaria is a risk. This publication, known as the "Yellow Book," is the authoritative source of U.S. government recommendations for malaria prophylaxis.*

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World Health Organization (WHO): *Guidelines for the treatment of malaria*, ed 2, Geneva, 2010, WHO. Available at: http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html. *Guidelines for malaria case management and treatment recommendations based on updated evidence. Includes discussion of some treatment options that are not yet prequalified by WHO or registered by any stringent medical regulatory authority.*

World Health Organization (WHO): *International travel and health 2010*, Geneva, Switzerland, 2009, WHO. Available at: http://www.who.int/ith/en/index.html. *The chapter on malaria in this reference presents recommendations for malaria prophylaxis that differ in some cases from those in the CDC's* Health Information for International Travel 2010. *Drugs not licensed in the United States are discussed, as well as expanded indications for SBET for presumed malaria in travelers.*

Yellow Fever

Mark D. Gershman and J. Erin Staples

64

ABSTRACT

Yellow fever is a vector-borne disease resulting from the transmission of the yellow fever virus (YFV) to a human from the bite of an infected mosquito. It is endemic to sub-Saharan Africa and tropical South America. Infection in humans is capable of producing hemorrhagic fever, which is often fatal. All travelers to yellow fever–endemic countries should be advised of the risks of the disease and available methods to prevent it, including personal protective measures and vaccine.

ETIOLOGY AND TRANSMISSION

Yellow fever virus (YFV) is a ribonucleic acid (RNA) virus that belongs to the genus *Flavivirus* and is related antigenically to West Nile, St. Louis encephalitis, and Japanese encephalitis viruses. YFV is transmitted to humans primarily through the bite of an infected mosquito, primarily *Aedes* or *Haemagogus* species. Mosquitoes acquire the virus by feeding on infected humans or nonhuman primates and can then transmit the virus to naïve humans or nonhuman primates.

There are three transmission cycles for YFV: sylvatic (jungle), intermediate (savannah), and urban (Figure 64-1). The sylvatic (jungle) transmission cycle involves transmission of the virus between nonhuman primates and tree-hole–breeding mosquito species found in the forest canopy. The virus is transmitted via mosquitoes from monkey to human when the humans encroach into the jungle during occupational or recreational activities. In Africa, there is also an intermediate (savannah) cycle that involves transmission of YFV from tree-hole–breeding *Aedes* species to humans living or working in jungle border areas. In this cycle the virus may be transmitted from monkey to human or from human to human via these mosquitoes. The urban transmission cycle involves anthroponotic transmission of the virus between humans and urban mosquitoes, primarily *Aedes aegypti*.

Humans infected with YFV experience the highest levels of viremia and are infectious to mosquitoes shortly before the onset of fever and for 3 to 5 days thereafter. Given the high level of viremia attained in humans, blood-borne transmission theoretically could occur through transfusions or needlestick injuries.

GEOGRAPHIC DISTRIBUTION

Yellow fever occurs in sub-Saharan Africa and tropical South America, where it is endemic and intermittently epidemic (Figure 64-2). The World Health Organization (WHO) estimates that 200,000 cases of yellow fever occur per year, with 30,000 deaths. However, only a small percentage of these cases are identified because of underreporting. Approximately 90% of all cases occur in Africa. Unvaccinated travelers to yellow fever–endemic countries are at risk of acquiring yellow fever, which might not become clinically apparent until return to their home country. Furthermore, these persons may have a delayed diagnosis because of lack of familiarity with yellow fever among healthcare professionals.

RISK FACTORS

A traveler's risk of acquiring yellow fever is determined by various factors, including immunization status, use of personal protection measures against mosquito bites, location of travel, duration of exposure, occupational and recreational activities while traveling, and local rate of virus transmission at the time of travel. In West Africa, YFV transmission is seasonal, with an elevated risk during the middle of the rainy season through the beginning of the dry season (July to October). However, YFV may be transmitted by *Ae. aegypti* even during the dry season in both rural and densely settled urban areas. In South America, the risk of infection is highest during the rainy season (January to May). Although reported cases of human disease are the principal indicator of disease risk, case reports may be absent because of a low level of transmission, a high level of immunity in the local population (e.g., because of vaccination), or cases not being detected by local surveillance systems. This "epidemiologic silence" does not equate to absence of risk.

CLINICAL FEATURES

Asymptomatic or clinically inapparent infection is believed to occur in most persons infected with YFV (Figure 64-3). Symptomatic infection varies from a mild, undifferentiated febrile illness to severe hemorrhagic disease with jaundice, resulting in death. The incubation period is usually 3 to 6 days. In its mildest form, yellow fever is a self-limited infection characterized by sudden onset of fever and headache without other symptoms. In other patients, there is abrupt onset of a high fever (up to 40° C), chills, severe headache, generalized myalgias, lumbosacral pain, anorexia, nausea, vomiting, and dizziness. The patient appears acutely ill, and examination may demonstrate bradycardia in relation to the elevated body temperature (Faget's sign). The patient is usually viremic during this period, which lasts for approximately 3 days before symptoms abate (the "period of remission"). Many patients have an uneventful recovery at this stage. In approximately 15% of infected persons, the illness reappears in more severe form within 48 hours of remission with fever, nausea, vomiting, epigastric pain, jaundice, renal insufficiency, and cardiovascular instability. Viremia is generally absent during this phase. A bleeding diathesis may occur, with hematemesis, melena, metrorrhagia, hematuria, petechiae, ecchymoses, epistaxis, and oozing blood from the gingiva and

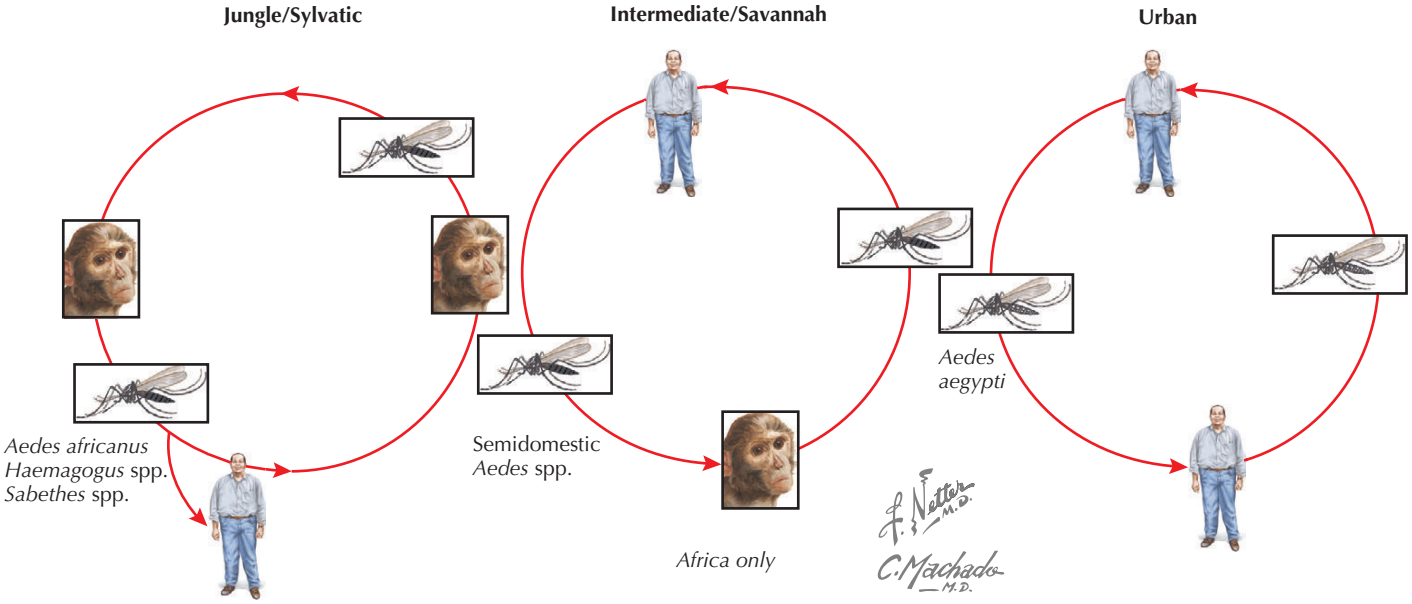

Figure 64-1 Yellow fever virus transmission cycles.

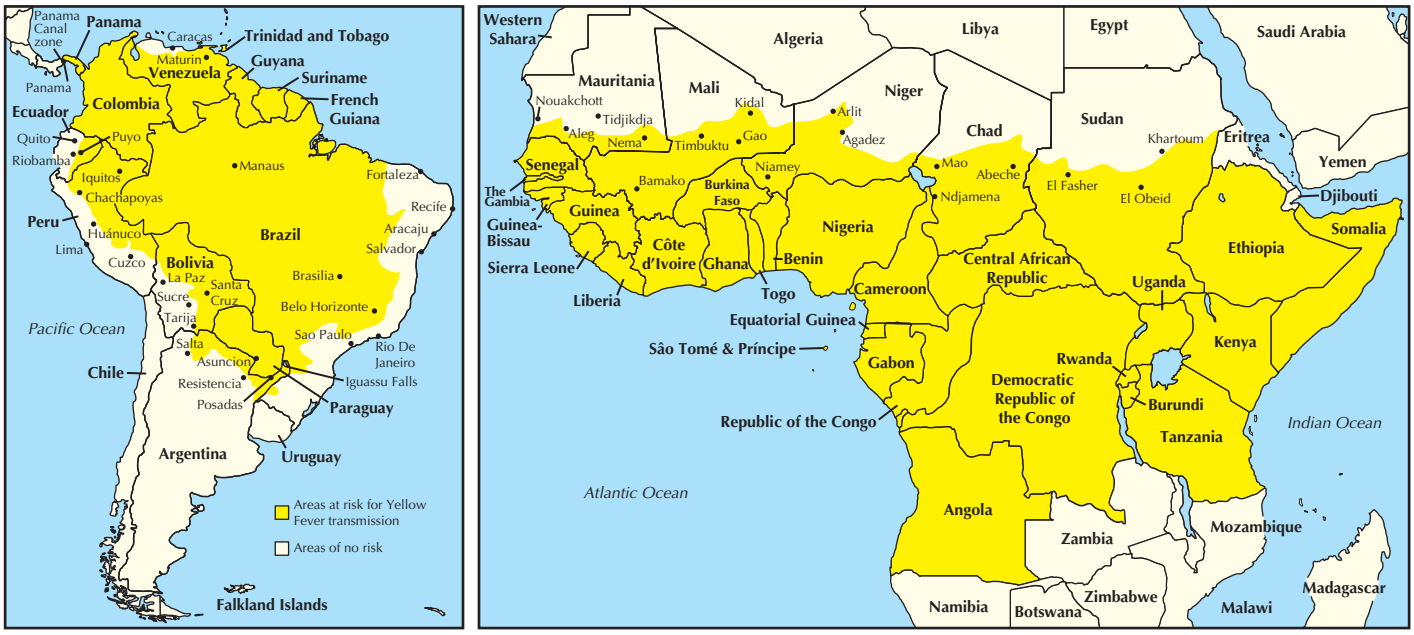

Figure 64-2 Worldwide distribution of yellow fever. *(From Centers for Disease Control and Prevention (CDC):* CDC health information for international travel 2010, *Atlanta, 2009, U.S. Department of Health and Human Services, Public Health Service. At the time of publication, this map is being revised by the World Health Organization [WHO] Informal Working Group on the Geographic Risk of Yellow Fever. For the most current map, please consult www.cdc.gov/travel.)*

needle-puncture sites (Figure 64-4). Physical findings include scleral and dermal icterus, hemorrhages, and epigastric tenderness without hepatic enlargement.

Multiple laboratory abnormalities can be seen in patients with yellow fever, and they can vary based on the severity and stage of illness. Early in the illness there may be leukopenia; however, leukocytosis can occur later in the terminal stage of the disease. Bleeding dyscrasias with elevated prothrombin and partial thromboplastin times, decreased platelet count, and presence of fibrin split products may be found. Hyperbilirubinemia may be present as early as the third day but usually peaks toward the end of the first week of illness. Elevations of serum transaminase levels occur in severe disease, and levels may remain elevated for up to 2 months after onset.

DIAGNOSTIC APPROACH

Preliminary diagnosis is based on the patient's clinical features, yellow fever vaccination status, and travel history, including destination, time of year, and activities. Mild yellow fever cannot be clinically distinguished from a wide array of other infections. Cases of yellow fever with jaundice must be differentiated from viral hepatitis, malaria, leptospirosis, Congo-Crimean hemorrhagic fever, Rift Valley fever, typhoid, Q fever, and typhus, as well as surgical, drug-induced, and toxic causes of jaundice. The other viral hemorrhagic fevers, which usually manifest without jaundice, include dengue hemorrhagic fever; Lassa fever; Marburg and Ebola virus diseases; and Bolivian, Argentinean, and Venezuelan hemorrhagic fevers.

Laboratory diagnosis is generally accomplished by testing serum to detect virus-specific immunoglobulin M (IgM) and G (IgG) antibodies by serologic assays. Serologic cross-reactions occur with other flaviviruses, such as West Nile and dengue viruses, so positive results should be confirmed with a more specific test, such as plaque reduction neutralization test. Early in the illness (first 3 or 4 days), YFV or yellow fever viral RNA can often be detected in the serum by virus isolation or nucleic acid amplification testing, such as reverse transcription–polymerase chain reaction (RT-PCR). However, by the time more overt symptoms are recognized, the virus or viral RNA is usually undetectable. Therefore virus isolation and RT-PCR should not be used for ruling out a diagnosis of yellow fever. Immunohistochemical staining of formalin-fixed material may detect yellow fever viral antigen in histopathologic specimens.

Healthcare providers should contact their state or local health department and the Centers for Disease Control and Prevention (CDC) (970-221-6400) for assistance with diagnostic testing for yellow fever infections, including antibody responses to wild-type virus or the vaccine.

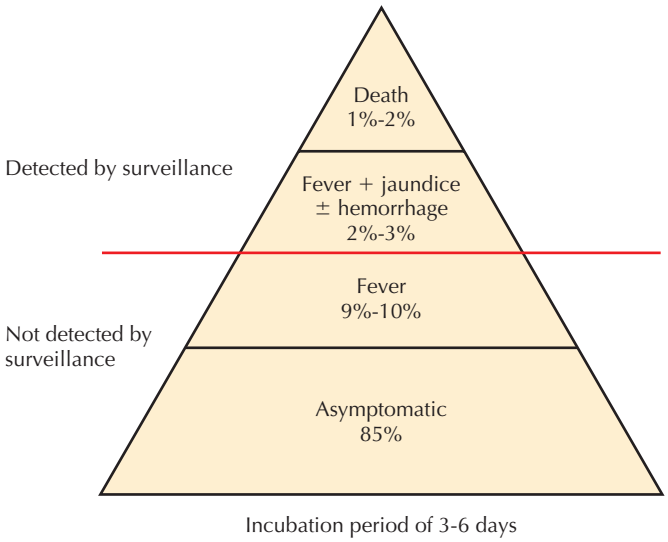

Figure 64-3 Clinical presentation of yellow fever.

CLINICAL MANAGEMENT

Although various drugs have been evaluated or empirically used for yellow fever disease, none has shown specific benefit to date. Management is supportive and based on symptoms. Rest, fluids, and acetaminophen (paracetamol) may relieve symptoms of fever and myalgias. Aspirin and nonsteroidal antiinflammatory drugs (ibuprofen or naproxen) should be avoided because of hemorrhagic complications. Infected persons should be protected from further mosquito exposure (staying indoors and/or

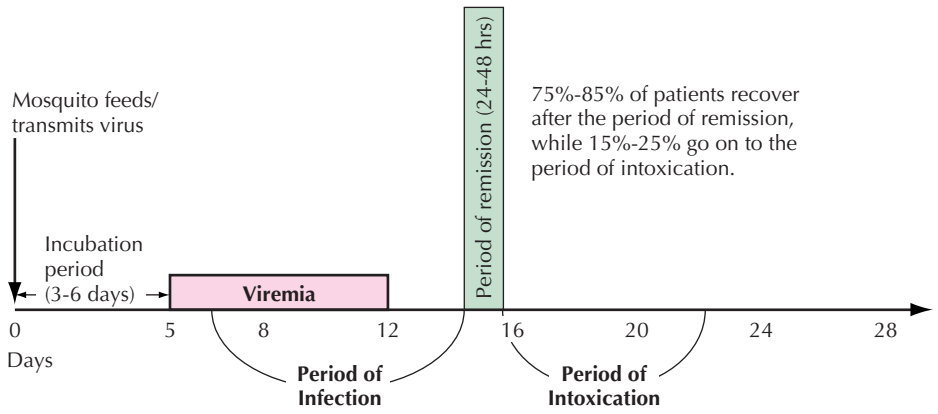

Figure 64-4 Timeline of yellow fever disease.

Period of Infection
Symptoms: Fevers, chills, headache, myalgias, lower back pain, nausea, malaise, prostration, dizziness
Signs: Congestion of face and conjunctivae, relative bradycardia (Faget's sign)

Period of Intoxication
Symptoms: Fevers, vomiting, headache, epigastric pain, prostration, malaise
Signs: Jaundice, tender liver, convulsions, hypotension, anuria, stupor/coma, shock

under a mosquito net) during the first few days of illness so they do not contribute to the transmission cycle.

PROGNOSIS

Most persons with mild illness recover without long-term sequelae. For those with severe disease, the length of illness is variable and the case fatality ratio is 20% to 50%. For those who survive, convalescence is often prolonged, lasting several weeks. Rarely, death can occur at the end of convalescence or even weeks after complete recovery from the acute illness; it is thought to be caused by yellow fever myocardial damage and cardiac arrhythmia. Secondary bacterial infections, such as pneumonia, may complicate recovery. Jaundice has been observed for up to 3 months after recovery from serologically documented yellow fever.

PREVENTION AND CONTROL

All travelers to yellow fever–endemic countries should be advised of the risks of the disease and available methods to prevent it, including personal protective measures and vaccine.

Personal Protective Measures

Personal protective measures against mosquito bites are the best way to prevent mosquito-borne diseases and in the case of yellow fever are the only way to prevent the disease for persons who cannot be vaccinated because of medical contraindications. Travelers should be advised to use insect repellent containing DEET (chemical name: N,N-diethyl-*m*-toluamide or N,N-diethly-3-methyl-benzamide), picaridin, oil of lemon eucalyptus, or IR3535 (chemical name: 3-[N-butyl-N-acetyl]-aminopropionic acid, ethyl ester) on exposed skin and to follow the directions on the label. Additional personal protective measures include wearing long sleeves, long pants, hats, and socks; treating clothes with permethrin; and staying in well-screened or air-conditioned accommodations (Box 64-1). More detailed information can be obtained at wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/protection-against-mosquitoes-ticks-insects-arthropods.aspx.

Vaccine

Yellow fever can be prevented by a live-attenuated viral vaccine. YF-VAX (Sanofi-Pasteur, Swiftwater, Pennsylvania) is the only vaccine approved for use in the United States. A single injection of 0.5 mL of reconstituted vaccine is administered subcutaneously. Because studies suggest that there is no difference in the efficacy of licensed vaccines produced outside the United States, persons who receive yellow fever vaccines in other countries should be considered protected against yellow fever.

Box 64-1 Prevention Measures for Yellow Fever

- Undergo vaccination.
- Use insect repellent on exposed skin.
  - DEET (chemical name: N,N-diethyl-*m*-toluamide or N,N-diethly-3-methyl-benzamide)
  - Picaridin
  - Oil of lemon eucalyptus
  - IR3535 (chemical name: 3-[N-butyl-N-acetyl]-aminopropionic acid, ethyl ester)
- Wear long-sleeved shirts, long pants, hats, socks.
- Treat clothes with permethrin.
- Stay in well-screened or air-conditioned accommodations.

INDICATION

The Advisory Committee on Immunization Practices (ACIP) recommends that the vaccine be given to persons aged 9 months or older who are traveling to or living in areas with risk of yellow fever transmission in South America and Africa. Furthermore, certain countries require proof of vaccination for entry (see International Health Regulations [IHR] section for more detail). The yellow fever vaccine needs to be given 10 days before entering a country that requires proof of vaccination, and revaccination needs to be given at 10-year intervals.

SIMULTANEOUS ADMINISTRATION OF OTHER VACCINES

Yellow fever vaccine can be administered concurrently (at separate sites) with commercially available immuneglobulin, as well as with the following inactivated vaccines: hepatitis A, hepatitis B, diphtheria-tetanus-pertussis, typhoid fever vaccine (Typhim Vi), and meningococcal polysaccharide vaccine (Menomune). No study data are available for simultaneous administration of yellow fever vaccine with other inactivated vaccines. To minimize the potential risk for interference, injectable or nasally administered live vaccines not given on the same day should be separated from yellow fever vaccine by an interval of at least 4 weeks. However, oral Ty21a typhoid vaccine can be administered simultaneously or at any interval before or after yellow fever vaccine.

VACCINE ADVERSE EVENTS

Reactions to yellow fever vaccine are usually not serious, with mild systemic symptoms reported in 10% to 30% of vaccinees. Reported events typically include low-grade fever, headache, and myalgias that begin within days after vaccination and last 5 to 10 days. Serious adverse events, though rare, do occur after yellow fever vaccination. Immediate hypersensitivity reactions characterized by rash, urticaria, or bronchospasm can occur (Figure 64-5). Anaphylaxis after yellow fever vaccine is reported to occur at a rate of 1.8 cases per 100,000 doses.

YELLOW FEVER VACCINE–ASSOCIATED NEUROLOGIC DISEASE

Yellow fever vaccine–associated neurologic disease (YEL-AND) is a serious, but rarely fatal, adverse event. Historically, YEL-AND was seen primarily in infants as encephalitis, but more recent reports have described YEL-AND in persons of all ages. The onset of illness for documented cases is 3 to 28 days after vaccination, and almost all cases have been reported in first-time vaccine recipients. YEL-AND is recognized to manifest in several distinct clinical syndromes, including meningoencephalitis, Guillain-Barré syndrome (GBS), acute disseminated

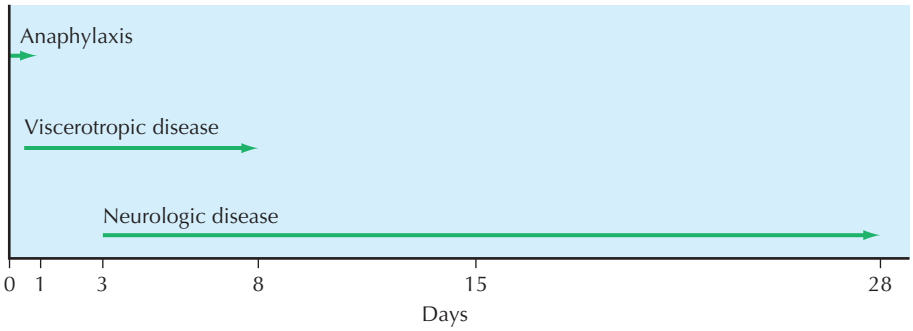

Figure 64-5 Time after yellow fever vaccination until onset of symptoms of serious adverse events.

encephalomyelitis (ADEM), bulbar palsy, and Bell's palsy. Meningoencephalitis occurs as a result of viremia from the vaccine-strain YFV, causing direct viral infection of the meninges and/or the brain (neurotropic disease). The other neurologic syndromes are thought to represent autoimmune manifestations in which antibodies produced in response to the vaccine cause either central or peripheral demyelination. The overall incidence of YEL-AND in the United States is 0.8 per 100,000 doses. The rate is higher in persons 60 years of age or older, with a rate of 1.6 per 100,000 doses in persons 60 to 69 years of age and 2.3 per 100,000 doses in persons 70 years of age or older. Before the age restriction for vaccination, the rate of neurologic disease in infants younger than 6 months of age was 0.5 to 4 per 1000 doses.

The diagnosis of YEL-AND should be suspected in a patient who develops neurologic symptoms, with or without fever, within a month after yellow fever vaccination. Depending on the particular neurologic syndrome, various diagnostic tests may be helpful, including studies of cerebrospinal fluid (culture and RT-PCR for vaccine-strain YFV, or yellow fever–specific IgM antibodies), neuroimaging, electroencephalography, electromyelography, and nerve conduction studies. Healthcare providers should contact their state or local health department and the CDC (970-221-6400) for assistance with diagnostic testing of clinical specimens for yellow fever vaccine virus or antibodies.

Treatment for neurologic disease related to direct viral invasion of the central nervous system (e.g., meningitis or encephalitis) is supportive, although manifestations such as seizures or autonomic dysfunction should be managed accordingly. For autoimmune neurologic manifestations associated with yellow fever vaccine, definitive treatments are available and include intravenous immuneglobulin (IVIG) or plasmapheresis for GBS; and corticosteroids, IVIG, or plasmapheresis for ADEM. Neurotropic or autoimmune neurologic disease associated with yellow fever vaccine should be managed in consultation with a neurologist whenever possible.

YELLOW FEVER VACCINE–ASSOCIATED VISCEROTROPIC DISEASE

Yellow fever vaccine–associated viscerotropic disease (YEL-AVD) was first reported in 2001, although retrospective studies indicate that it occurred at least as far back as 1975. YEL-AVD is a severe illness similar to wild-type disease, with vaccine virus proliferating in multiple organs, causing multiorgan dysfunction to multisystem organ failure and death. To date, more than 55 cases have been reported throughout the world. The onset of illness for YEL-AVD cases is a median of 3 days (range 1 to 8 days) after vaccination, and the case fatality ratio is approximately 65%. Thus far, YEL-AVD has been reported to occur exclusively after the first dose of yellow fever vaccine rather than with booster doses. The overall incidence of YEL-AVD in the United States is 0.4 cases per 100,000 doses. The rate is higher for persons 60 years of age or older, with a rate of 1.0 per 100,000 doses in persons 60 to 69 years of age and 2.3 per 100,000 doses in persons aged 70 years of age or older.

YEL-AVD should be suspected in a patient who develops fever and other systemic symptoms such as nausea, vomiting, or myalgias within 10 days of vaccination. Evaluation and management of patients with suspected YEL-AVD are best done in conjunction with an infectious disease specialist. Because of the potential seriousness of this syndrome, patients suspected to have YEL-AVD need to be observed closely and most will require hospitalization, often in the intensive care unit. In addition to routine hematology, chemistry, and coagulation studies, other laboratory tests that might be helpful in the diagnostic evaluation include creatine phosphokinase (for rhabdomyolysis) and tests for disseminated intravascular coagulation. Blood should be drawn for yellow fever testing, including culture and RT-PCR for yellow fever vaccine–strain virus and YFV-specific antibodies. In fatal cases, if autopsy is performed, both fixed and frozen tissue samples should be collected for yellow fever vaccine virus testing, including immunohistochemical staining and RT-PCR testing. Healthcare providers should contact their state or local health department and call the CDC for assistance with diagnostic testing. There is no specific therapy for YEL-AVD; treatment is supportive, once other diseases have been excluded.

CONTRAINDICATIONS TO YELLOW FEVER VACCINE

Yellow fever vaccine is contraindicated in infants younger than 6 months of age because of the increased risk of vaccine-associated encephalitis. It is also contraindicated in anyone with a history of acute hypersensitivity reaction to any vaccine components, including eggs, chicken proteins, and gelatin. Because yellow fever vaccine contains live virus, it is contraindicated in person with immunocompromising conditions (e.g.,

symptomatic human immunodeficiency [HIV] infection or CD4+ T-lymphocytes <200/mm^3 or <15% of total in children age <6 years, leukemia, lymphoma, generalized malignancy, or diseases of the thymus) or those receiving immunosuppressive or immunomodulatory therapy (e.g., corticosteroids, alkylating agents, antimetabolites, TNF-α inhibitors, IL-1 blocking agents or other monoclonal antibodies targeting immune cells, or current or recent radiation therapy) (Box 64-2).

PRECAUTIONS FOR USE OF YELLOW FEVER VACCINE

Yellow fever vaccine should not be routinely given to infants 6 to 8 months of age. However, the ACIP and WHO recognize situations in which vaccination of an infant aged 6 to 8 months might be considered, such as residence in or travel to a yellow fever–endemic or yellow fever–epidemic zone. Studies indicate that persons aged 60 years or older may be at increased risk of serious adverse events after yellow fever vaccination, with an even higher risk for those persons 70 years of age or older. In deciding whether to administer yellow fever vaccine, the provider and patient should discuss and weigh risks and benefits of vaccination against the destination-specific risk for exposure to YFV.

The safety of yellow fever vaccination during pregnancy or breastfeeding has not been studied thoroughly. Ideally, neither pregnant nor nursing women should be vaccinated with yellow fever vaccine unless travel to a yellow fever–endemic area is unavoidable and the risk of disease outweighs the risk of vaccination. Infants born to women vaccinated during pregnancy should be monitored for evidence of congenital infection or other possible vaccine-associated adverse effects. Persons with asymptomatic HIV infection and CD4+ T-lymphocytes 200 to 499/mm^3 (or 15% to 24% of total in children age <6 years) who cannot avoid potential exposure to YFV should be considered for vaccination (see Box 64-2). Because both pregnant patients and patients with asymptomatic HIV may have altered immune function that might cause reduced seroconversion rates to yellow fever vaccine, consideration should be given to serologic testing to document a protective antibody response before travel.

Box 64-2 Yellow Fever Vaccine Contraindications and Precautions

Contraindications
- Age <6 months of age
- History of hypersensitivity to any vaccine component
  - Eggs
  - Chicken proteins
  - Gelatin
- Primary immunodeficiencies
- Malignant neoplasms
- Symptomatic human immunodeficiency virus (HIV) infection or CD4+ T-lymphocytes <200/mm^3 (or <15% of total in children age <6 years)
- Transplantation
- Immunosuppressive or immunomodulatory therapies*
- Thymus disorder associated with abnormal immune function

Precautions
- Adults ≥60 years of age
- Infants 6 to 8 months of age†
- Asymptomatic human immunodeficiency virus (HIV) and CD4+ T-lymphocytes 200 to 499/mm^3 (or 15%-24% of total in children age <6 years)
- Pregnancy
- Breastfeeding

*Corticosteroids, alkylating drugs, antimetabolites, TNF-α inhibitors, IL-blocking agents, and other monoclonal antibodies targeting immune cells; current or recent radiation therapy (see wwwnc.cdc.gov/travel/yellowbook/2010/chapter-8/immunocompromised-traveler.aspx).
†In special circumstances, infants aged 6 to 8 months can be considered for vaccination.

INTERNATIONAL HEALTH REGULATIONS

The IHR (2005) allow countries to require proof of yellow fever vaccination for entry from travelers arriving from certain countries, even if only in transit, to prevent importation and indigenous transmission of YFV. Vaccinated persons must provide proof of vaccination on an International Certificate of Vaccination or Prophylaxis (ICVP), issued by a medical provider authorized to give yellow fever vaccine and validated with the provider's signature and official yellow fever vaccination center stamp. Travelers who arrive in a country with a yellow fever vaccination entry requirement without a valid certificate of vaccination against yellow fever (ICVP) may be quarantined up to 6 days or denied entry.

Yellow fever vaccination stamps are issued to medical providers by state health departments in the United States. The certificate of vaccination against yellow fever is valid for a period of 10 years, beginning 10 days after vaccination. With booster doses of the vaccine, the certificate is considered valid from the day of revaccination. A physician may issue a waiver to a person for whom the yellow fever vaccine is medically contraindicated. In such a case the physician should fill out and sign the "Medical Contraindications to Vaccination" section of the ICVP. The physician should also give the traveler a signed and dated exemption letter on the physician's letterhead stationery, clearly stating the contraindications to vaccination and bearing the stamp used by the yellow fever vaccination center, to validate the ICVP. The traveler should be advised that issuance of a waiver does not guarantee its acceptance by the destination country. Finally, the physician should inform the traveler of any increased risk of yellow fever infection associated with lack of vaccination and how to minimize this risk by using mosquito protection measures.

For more information about location of yellow fever vaccination centers, ordering and filling out the ICVP, and medical waivers of yellow fever vaccination, refer to the Yellow Fever section in the CDC's *Health Information for International Travel 2010* (available at wwwnc.cdc.gov/travel/yellowbook/2010/chapter-2/yellow-fever.aspx).

Country entry requirements for proof of yellow fever vaccination under the IHRs are different from the CDC's recommendations. Yellow fever vaccine recommendations are public health advice given by the CDC to prevent yellow fever infections among travelers and are subject to change at any time based on disease activity. Therefore travelers should check for relevant travel notices on the CDC Travelers' Health website (www.cdc.gov/travel) before departing.

EVIDENCE

Hayes EB: Acute viscerotropic disease following vaccination against yellow fever, *Trans R Soc Trop Med Hyg* 101:967-971, 2007. *The author reviews the clinical features of 12 detailed published reports of YEL-AVD and discusses possible etiologic mechanisms.*

McMahon AW, Eidex EB, Marfin AA, et al: Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases, *Vaccine* 25:1727-1734, 2007. *The authors summarize 15 cases of YEL-AND reported to the Vaccine Adverse Events Reporting System from 1990 to 2005 and describe the clinical features of the three types of neurologic disease associated with yellow fever vaccine (encephalitis, GBS, and ADEM).*

ADDITIONAL RESOURCES

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Kroger AT, Sumaya CV, Pickering LK, Atkinson WL: General recommendations on immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm Rep* 60:1-61, 2011. *Provides general recommendations for the use of vaccines and offers guidance on the use of live viral vaccines in special populations.*

Monath TP, Cetron MS: Prevention of yellow fever in persons traveling to the tropics, *Clin Infect Dis* 34:1369-1378, 2003. *The authors discuss risk of yellow fever for travelers to endemic countries, summarize cases of imported yellow fever in travelers, and present general considerations regarding yellow fever vaccine for travel.*

Monath TP, Teuwen D, Cetron MS: Yellow fever vaccine. In Plotkin S, Orenstein WA, Offit PA, eds: *Vaccines*, ed 5, Philadelphia, 2008, WB Saunders, pp 959-1055. *Comprehensive review of YFV and yellow fever vaccine, including historical, epidemiologic, clinical, immunologic, and virologic aspects.*

Staples JE, Gershman M, Fischer M, Centers for Disease Control and Prevention (CDC): Yellow fever vaccine: recommendations of the Advisory Committee on Immunization Practices (ACIP), *MMWR Recomm Rep* 59:1-27, 2010. *The current guidelines for yellow fever vaccine use in the United States.*

Travelers' Diarrhea

Martin S. Wolfe

65

ABSTRACT

Acute diarrhea associated with travel is referred to as travelers' diarrhea (TD). TD is defined as a twofold or greater increase in the frequency of unformed bowel movements. Other commonly associated symptoms include nausea, distention, urgency, abdominal cramps, fever, and malaise. Stools may be loose, liquid, or watery. Bloody stools, vomiting, or high fever occurs in fewer affected individuals.

Although TD occurs more frequently in travelers to developing countries, this illness is actually prevalent worldwide. The developing nations in Latin America, Africa, the Middle East, and Asia are among countries considered high-risk destinations; some Caribbean islands and most eastern and southern European countries are intermediate-risk destinations; and North America, northern and western Europe, Australia, New Zealand, Japan, and a number of other Caribbean islands are low-risk destinations. Attack rates are estimated to be 30% to 70% of travelers to high-risk areas.

There is a greater incidence of TD in younger, more adventurous travelers. Onset is usually during the first week of travel because most episodes are caused by bacteria or viruses that have relatively short incubation periods. Exposure can occur later on a trip, particularly from parasites, and symptoms may not appear until travelers return home.

TD is acquired by eating contaminated food, drinking contaminated water, or coming in contact with the contaminated hands of an infected person or food handler. Eating raw vegetables, meat, seafood, dairy products, and unpeeled fruit can place persons at high risk, as can drinking unpasteurized milk, untreated tap or other water, and ice made from untreated water.

AGENTS OF INFECTION

Several bacterial, viral, and parasitic agents cause TD; they have varied incidence and differential features (Figure 65-1).

Bacterial

Enterotoxigenic *Escherichia coli* and enteroaggregative *E. coli* are the most common bacterial causes of TD, accounting for 30% to 50% or more of cases. These organisms produce a relatively mild syndrome that is self-limited, lasting from 2 to 5 days. Less frequent but potentially more serious (invasive) bacteria include *Campylobacter*, *Shigella*, and invasive *Salmonella* species. Their ability to invade the colonic mucosa, leading to dysentery, can cause more severe, debilitating illness. Less common bacteria of concern are *Aeromonas* species, *Plesiomonas shigelloides*, and particularly in the Far East, *Vibrio parahaemolyticus*. *Vibrio cholerae*, the agent of cholera, is a very rare cause of diarrhea among travelers. Food-borne bacterial infections, usually with an incubation period of only a few hours, include *Clostridium* species, *Staphylococcus aureus*, and *Bacillus cereus*, agents that are frequently sources of diarrheal outbreaks. *Clostridium difficile* must be considered when there has been recent use of antimicrobial medication, often administered as initial empirical treatment for TD. Bacteria make up about 80% of TD cases.

Viral

The most common viral causes, composing up to 10% of TD cases, are rotaviruses and noroviruses. Rotaviruses are frequently found in the feces of asymptomatic travelers, indicating widespread exposure to the virus. Norovirus infections often occur as outbreaks, particularly on cruise ships and in other closed living group situations. Vomiting may be a prominent feature of norovirus infection. Most viral cases are relatively mild and short-lived.

Parasitic

Intestinal protozoan parasites make up about 10% of TD cases. Because of relatively longer incubation periods, symptoms may not develop until the traveler returns home. Protozoa with shorter incubation periods include *Cryptosporidium*, with an incubation period of 3 to 8 days. *Cryptosporidium* infections are usually self-limited with a duration of about 2 weeks of symptoms in travelers with normal immune systems but may cause a more prolonged illness in persons with compromised immunity. *Cyclospora* has a 2- to 11-day incubation period and can cause troublesome symptoms unless recognized and treated; it is self-limited after 6 to 8 weeks.

Giardia lamblia is the most common pathogenic protozoan infection in travelers. It has an incubation period of 12 to 14 days, and travelers with TD during a 1- to 2-week trip are not likely to have *Giardia* as the cause unless it was preexisting. Infections with *Entamoeba histolytica* may have a shorter incubation period, perhaps less than 7 days, but usually the onset of symptoms is later. *Dientamoeba fragilis* and *Isospora belli* are potential intestinal protozoan causes of TD, but their incubations periods are not known. The intestinal helminth most associated with acute and chronic diarrhea is *Strongyloides stercoralis*, with an incubation period of at least 2 weeks before intestinal symptoms commence.

DIAGNOSIS

Examination of the stool is most important for proper diagnosis. With enterotoxigenic and enteroaggregative *E. coli*, small bowel pathogens, no white cells are generally present in the watery stool. These bacteria can be suspected on the basis of characteristic watery stool and the relatively short self-limited duration

Etiologic organisms	*E. coli* (enterotoxigenic)	*Shigella*	*Salmonella*	*C. jejuni*	*V. parahemolyticus*	*Rotavirus* Norovirus	*E. histolytica*	*G. lamblia*
Approximate relative incidence of common infectious agents in travelers' diarrhea	50%	15%	5%	10%	2%	14%	2%	2%
Typical clinical features	Diarrhea, nausea, vomiting, malaise, fever	Diarrhea, tenesmus, cramps, fever	Diarrhea, cramps, nausea, vomiting, fever	Diarrhea, cramps, anorexia, fever, malaise	Diarrhea, cramps, vomiting, headache	Diarrhea, cramps, vomiting, fever, myalgia	Diarrhea, alternating with constipation, nausea, gas, cramps, fatigue	Foul diarrhea, cramps, foul gas, distention, rumbling, fatigue, weight loss
Incubation period	4-24 hours	1-3 days	6-48 hours	1-7 days	12-24 hours	18-48 hours	1-3 weeks	12-14 days
Duration of illness	3-4 days	2-7+ days	3-4 days	1-7+ days	1-3 days	1-7 days	3-14+ days	7+ days
Blood in stool	–	+	±	+	±	–	±	–
Proctoscopy: ulcers, friable and hemorrhagic mucosa	–	+	±	+	±	–	±	–
Diagnostic method	Clinical features and exclusion of other agents	Stool culture: EMB agar		Stool culture: selective blood agar	Stool culture: TCBS agar	Rotavirus antigen detection assays of stool by ELISA Norovirus clinical features and exclusion of other agents	Stool examination for parasites Stained slide Concentration	
Fecal leukocytes (seen with invasive bowel pathogens)	–	+	+	+	±	–	Stool ELISA antigen test +	+

Figure 65-1 Travelers' diarrhea: incidence and differential features.

of symptoms. There is no routine available method for the diagnosis of these *E. coli* organisms.

If the stool is mucoid or bloody, or if sheets of white blood cells can be seen microscopically, bacteria such as *Campylobacter* species, *Shigella*, and invasive *Salmonella* are the most likely causative agents. Other, less common potentially invasive bacteria include enteroinvasive *E. coli*, *Yersinia enterocolitica*, and *C. difficile*. *Shigella* and *Salmonella* are diagnosed by standard culture methods. *Campylobacter* species are diagnosed by cultural isolations using selective media and microanaerobic conditions. *Y. enterocolitica* is recovered with routine isolation media. Special media, such as sulfate citrate bile salts agar, are needed to isolate *V. parahaemolyticus*. *C. difficile* should be particularly suspected in a traveler who has recently taken antibiotics; this organism is diagnosed with either a stool enzyme-linked immunosorbent assay (ELISA) test kit or a tissue culture assay.

With rotaviruses or noroviruses, white blood cells are absent. Most cases of viral enteritis are mild and of short duration. *Rotavirus* can be detected by an ELISA test in a commercially available kit. For *Norovirus*, diagnostic assays are presently available only as research tools.

G. lamblia is the most commonly recognized intestinal protozoa in TD, although it is more often found to be the cause of more chronic diarrhea. Other pathogenic protozoa include *E. histolytica*, *D. fragilis*, *I. belli*, and *Cryptosporidium* and *Cyclospora* species. Initial testing for these can be performed on routine examination of preserved stool specimens, using concentration, and with stained slide procedures. ELISA tests for the detection of stool antigens of *G. lamblia*, *E. histolytica*, and *Cryptosporidium* species, available from a number of manufacturers, appear to be more sensitive than routine stool ova and parasite examinations and also can assess posttreatment parasite eradication. The

ELISA test for *Giardia* and *Cryptosporidium* can be performed on preserved stool specimens, but the *E. histolytica* ELISA requires a recently passed fresh stool specimen. A two-stage *E. histolytica* kit can differentiate morphologically similar pathogenic *E. histolytica* from nonpathogenic *Entamoeba dispar. Cryptosporidium* and *Cyclospora* species and *I. belli* are best identified by modified acid-fast stains.

TREATMENT

Oral Fluids and Diet Modification

An otherwise healthy individual with TD is unlikely to develop dehydration and can replace lost fluids and electrolytes with tea, clear broth, or flavored carbonated drinks, along with salted crackers. Dehydration is more of a threat for young children, elderly travelers, and those on medications such as diuretics. Packets of oral rehydration salts, such as CeraLyte (one packet to be diluted in 1 quart of potable water) are available commercially. For most patients, this is the only treatment required, because the diarrheal illness will be of short duration and self-limited. As the acute symptoms decrease, bland, easily digested foods such as rice, bananas, fruit-flavored gelatins, salted crackers, and dry toast can be added to the diet. Alcoholic beverages, fatty and spicy foods, caffeine, and dairy products should be avoided during the acute stage, as they can aggravate symptoms. As stools become formed, the diet can gradually return to normal.

Antimotility and Nonspecific Agents

Loperamide (Imodium) is widely used to treat mild to moderate diarrhea. It can be accompanied by an antimicrobial agent. Loperamide liquid and caplets are available as over-the-counter products; these products should not be administered to children younger than 2 years of age. If symptoms persist over 48 hours or blood or mucus appears in the stool, loperamide should be discontinued. Another antimotility agent, diphenoxylate (Lomotil) can also be used. Diphenoxylate contains atropine and should not be used in older men, as it may cause urinary retention. It has been replaced by loperamide as the drug of choice for treatment of TD.

The antisecretory agent bismuth subsalicylate (Pepto-Bismol) taken as a liquid (1 ounce every 30 minutes until eight doses have been taken) works more slowly than antimotility agents. In the treatment of mild to moderate TD, bismuth subsalicylate decreases the number of stools passed and duration of diarrhea by 50% when compared with no treatment. This product may produce darkening of the stool and tongue from the bismuth component, but this is harmless. Other agents such as kaolin-pectin and probiotics have been found ineffective in clinical trials.

Antimicrobial Treatment

Antibiotics are the most important agents in treating severe and moderate diarrhea, as the most common causes are various bacteria. However, the role of antibiotics in mild diarrhea can be questioned. Perhaps the most common antibiotic used against TD is a fluoroquinolone (particularly ciprofloxacin), often taken empirically for mild diarrhea. This use of a fluoroquinolone may not uncommonly lead to another episode of diarrhea caused by *C. difficile*. Tendinitis and tendon rupture are rarely reported adverse side effects of fluoroquinolone therapy. One genus of bacteria, *Campylobacter*, has developed resistance to fluoroquinolones in such locations as Thailand and Nepal. Travelers with TD acquired during travel to these countries should be treated empirically with an alternative antibiotic, azithromycin (Zithromax), unless specific culture and antimicrobial sensitivity results are available. The recommended course of treatment with a fluoroquinolone cannot be used in pregnant women, but azithromycin can be used instead. Azithromycin is also preferable for children, as fluoroquinolones are not approved for use in children owing to potential drug toxicity (Table 65-1).

A new antibiotic, rifaximin (Xifaxan), has been found to be useful treatment for the most common bacterial causative agent, toxigenic *E. coli* (particularly in studies in Mexico), but it has not proven effective against more serious invasive organisms such as *Shigella* and *Campylobacter*.

The hydroxyquinoline class of drugs (e.g., Entero-Vioform, Mexaform) should never be used for treating diarrhea, because these drugs have never been proven to be effective for this purpose and their use has been associated with blindness and a paralytic syndrome. Although these products have been removed from the U.S. market, they may still be available over the counter in some foreign countries.

Antiparasitic Drugs

Diarrhea and other gastrointestinal symptoms that develop after return from travel may indicate a parasitic infection with a longer incubation period or a bacterial infection contracted late on the trip. Persistent symptoms that recur intermittently suggest a parasitic infection. *G. lamblia* is the most common pathogen causing diarrhea. Other parasites include *E. histolytica*, *Cryptosporidium*, *D. fragilis*, and *Cyclospora*. These parasites should always be considered in a returned traveler with continued symptoms such as abdominal pain, loose stools, foul gas or belching, intestinal rumbles, distention, fatigue, or weight loss. Descriptions of stool examinations for these parasites and recommendations for treatment are thoroughly described in Chapters 75, 76, and 77.

Table 65-1 Drugs for Treatment of Travelers' Diarrhea

DRUG	ADULT DOSAGE	CHILDREN'S DOSAGE
Azithromycin (Zithromax)	1000 mg once or 500 mg once/day × 3 days	10 mg/kg/day on day 1, 5 mg/kg/day on days 2 and 3
Ciprofloxacin (Cipro)	500 mg bid × 3 days	Not recommended
Rifaximin (Xifaxan)*	200 mg tid × 3 days	Not recommended below age 12 years

*Should not be used in infections associated with fever or blood in the stool or in *Campylobacter* or *Shigella* infections.
For more information on intestinal protozoa see Chapters 75, 76, and 77.

PREVENTION

Fecally contaminated food, water, and beverages are the most common vehicles of transmission in infectious diarrhea. During travel in areas of low sanitation, TD may still occur even with diligent attempts to avoid ingesting untreated tap water and products made with it, and raw vegetables and fruits, which are often cultivated, rinsed, and freshened with contaminated water. Frequent oversights include brushing teeth with contaminated water, having ice cubes in drinks, drinking diluted fruit juices and mixed drinks, and eating leafy green salads. Other potentially hazardous foods include dairy products, raw or undercooked seafood and meat, buffet meals set out in warm climates, and food served by street vendors; these food and beverage items should be avoided when possible. A traveler should consume only hot, well-cooked food, fruits that can be peeled, carbonated beverages (weak carbonic acid inhibits bacterial growth), coffee, tea, and reliably purified water. Beer and wine are also safe beverages, when consumed in moderation.

Bottled water sold at some high-risk travel destinations may not be as labeled and may actually be tap water. If possible, select sparkling bottled water ("with gas") instead of still water ("without gas"). Tap water or water from local water supplies in areas of low sanitation should be boiled for 3 minutes, which will kill all dangerous organisms, including hepatitis viruses, and will compensate for thermal barriers (filth) and the lower boiling point of water at high altitude. Alternatively, water can be purified with iodine water-purification tablets such as Potable Aqua. If water is particularly cold, contact time for the tablets should be increased; if the water is turbid, the concentration of tablets should be increased according to package directions. Many portable filters on the market claim to provide safe drinking water. The most effective are those with iodide-impregnated resins, a micropore-type filter, and a carbon filter to improve taste.

Meticulous attention to food and beverage selection and preparation can decrease the likelihood of developing TD, but this is admittedly difficult to achieve. In addition to appropriate food, beverage, and water hygiene, other preventive measures against TD include hand washing, the use of certain nonantimicrobial medications, and the use of prophylactic antibiotics (reserved for special very-high–risk situations). Currently there are no licensed vaccines in the United States against the main causative agents that cause TD, including enterotoxigenic *E. coli*, *Shigella*, or *Campylobacter*. Vaccines against these pathogens are, however, being developed and may be available in the future. Two oral cholera vaccines are licensed in many countries other than the United States, including Dukoral (a two-dose nonliving vaccine) and Orachol (single-dose live vaccine; manufacture of Orachol was recently suspended). Dukoral confers partial protection against some forms of enterotoxigenic *E. coli* that elaborate an enterotoxin that cross-reacts with cholera toxin. A nonantimicrobial agent found helpful in preventing TD is bismuth subsalicylate. A dose of two tablets four times daily taken by adults appears to be a safe and effective means of reducing the occurrence of TD by about 65% in persons at risk for periods of use up to 3 weeks. Salicylate absorption from bismuth subsalicylate may be enough to cause toxicity in those already taking aspirin-containing compounds and may alter anticoagulant control in patients taking Coumadin. High-dose bismuth subsalicylate may cause blackening of the tongue or stool. Bismuth subsalicylate should not be used concurrently with doxycycline used for antimalarial prophylaxis and may not be readily available outside the United States.

A number of antibiotics have been shown to prevent TD when taken prophylactically. However, because the risk of adverse side effects may outweigh the benefits in many situations, most experts advise against the routine use of prophylactic antibiotics by travelers. Some high-risk travelers with underlying medical conditions that could be significantly worsened by diarrhea may consult with their physicians and elect to use prophylactic antibiotic agents for only short periods of time, once the risks and benefits are clearly understood. *Lactobacillus* and other probiotic preparations are safe but have not been proven to prevent TD. If a traveler wishes to use them, he or she should not be complacent regarding proper food and water hygiene.

EVIDENCE

DuPont HL, Ericsson CD, Farthing MJG, et al: Expert review of the evidence base for self-therapy of travelers' diarrhea, *J Travel Med* 16:161-171, 2009. *Strength and quality of evidence for use of medications for self-therapy of TD.*

DuPont HL, Ericsson CDE, Farthing MJG, et al: Expert review of the evidence base for prevention of travelers' diarrhea, *J Travel Med* 16:149-160, 2009. *Strength and quality of evidence for preventive measures against TD, particularly chemoprophylaxis.*

Glass RI, Parashar UD, Estes, MK: Norovirus gastroenteritis, *N Engl J Med* 361:1776-1785, 2009. *Noroviruses are the leading cause of epidemics of gastroenteritis and an important cause of sporadic gastroenteritis in both children and adults.*

Johnson PC, Ericsson CD, DuPont HL, et al: Comparison of loperamide with bismuth subsalicylate for the treatment of acute travelers' diarrhea, *JAMA* 255:757-760, 1986. *Loperamide is more useful than bismuth subsalicylate in self-treatment of acute traveler's diarrhea.*

Norman F, Pérez-Molina J, Pérez de Ayala A, et al: *Clostridium difficile*–associated diarrhea after antibiotic treatment for travelers' diarrhea, *Clin Infect Dis* 46:1060-1063, 2008. C. difficile *is not an uncommon finding in travelers empirically treated with antibiotics (particularly fluoroquinolones) for TD.*

Van Loon FPL, Bennish ML, Speelman P, et al: Double blind trial of loperamide for treating acute watery diarrhoea in expatriates in Bangladesh, *Gut* 30:492-495, 1989. *Based on the results of this and other studies, recommendations for the use of loperamide or bismuth subsalicylate alone for treating mild to moderate TD.*

ADDITIONAL RESOURCES

Drugs for travelers' diarrhea, *Med Lett* 50:58-59, 2008. *Succinct summary, well-referenced, of treatment modalities for TD.*

Ericsson CD, DuPont HL, Steffen R: *Travelers' diarrhea*, London, 2003, BC Decker. *Comprehensive textbook on all aspects of TD; thoroughly referenced.*

Enteric Fever: Typhoid and Paratyphoid Fever

Elaine C. Jong

66

ABSTRACT

Enteric fever is the term used to describe a febrile illness caused by infection with the gram-negative bacterium *Salmonella enterica* serotype Typhi (hereafter *S.* Typhi) or *S. enterica* serotype Paratyphi A, B, or C. *S. enterica* serotype Paratyphi A (hereafter *S.* Paratyphi A) is the predominant agent isolated from cases of paratyphoid fever acquired among international travelers. Typhoid and paratyphoid fever may cause a mild illness manifested by fever, headache, and malaise, or a more severe illness manifested by prolonged high fever as high as 39° to 40° C (102° to 104° F), prostration, abdominal discomfort, bowel dysfunction, and altered mental status. Children and older adults tend to experience more serious illness with infection, although persons in all age groups are susceptible. Infections caused by *S.* Typhi and *S.* Paratyphi A usually cannot be distinguished based on clinical presentation alone, and positive cultures are used to confirm the diagnosis. *S.* Typhi and *S.* Paratyphi A strains with decreased resistance to fluoroquinolone antibiotics have emerged over the past decade on the Indian subcontinent and in Southeast Asia and Central Asia, making treatment of serious infections more challenging. Efficacious vaccines against typhoid fever are available for protection of travelers and for mass immunization programs of residents in highly endemic areas, but a safe and effective vaccine against paratyphoid fever currently is not available.

GEOGRAPHIC DISTRIBUTION

Enteric fever is a global public health problem and tends to be highly endemic in countries where inadequate sanitation allows for ready contamination of food and water with human waste. Epidemics of typhoid fever and high endemic disease rates have been reported in India and countries in South Asia, the Middle East, Central Africa, and South America. Typhoid fever accounts for an estimated 21 million cases and 200,000 deaths worldwide each year. In industrialized nations, most reported cases are among returned international travelers, with local outbreaks resulting from contact with asymptomatic carriers. In 2005, approximately 400 cases per year were reported in the United States, with over 80% associated with international travel.

In 2000 an estimated 5.4 million cases of paratyphoid fever occurred globally. *S.* Paratyphi A accounts for a substantial number of enteric fever cases among returned travelers from India and countries in South Asia, the Middle East, and East Africa. In India, Pakistan, and Indonesia, recent analyses of enteric fever cases show that *S.* Paratyphi A has emerged as the causative agent in a growing proportion of enteric fever cases, and in China it exceeds *S.* Typhi as the cause of enteric fever (Figure 66-1). As with *S.* Typhi, decreased susceptibility to fluoroquinolone antibiotics is widespread among the *S.* Paratyphi A isolates tested. In a Centers for Disease Control and Prevention (CDC) survey of 162 paratyphoid cases reported from April 1, 2005 through March 31, 2006, 92% were *S.* Paratyphi A infections associated with recent travel to Asia, with 87% of the isolates showing decreased susceptibility to ciprofloxacin.

TRANSMISSION AND PATHOGENESIS

Humans are the reservoir for *S.* Typhi and *S.* Paratyphi A infections, with human-to-human transmission taking place through fecal-oral routes. Drinking water and ingesting raw vegetables and fruits, undercooked shellfish, ice cream, and other food products contaminated by impure water sources or the hands of infected food handlers are the usual sources of infection, although flies landing on infected feces and then on food also contribute to food contamination (Figure 66-2). Airborne transmission through aerosols also has been considered a possibility during large outbreaks.

Inoculum size influences the severity of an infection, with a large inoculum tending to cause more severe illness after a relatively short incubation period. Host factors associated with higher morbidity include lowered gastric acidity resulting from medications (e.g., histamine-2 [H_2] blockers, proton pump inhibitors, antacids) or anatomy (partial gastrectomy); immune suppression caused by human immunodeficiency virus infection, cancer chemotherapy, and other conditions or treatments; co-infection with *Helicobacter pylori;* and human leukocyte antigen (HLA) tissue type.

After *S.* Typhi or *S.* Paratyphi A bacteria are ingested in contaminated food and beverages, the bacteria that survive passage through gastric acidity in the stomach pass in the fecal stream to the small intestine. During invasive disease the bacteria invade the microfold cells (M cells) that overlay the lymphoid tissue (Peyer's patches) in the ileum and pass through into the underlying tissue (lamina propria), where they are phagocytized by macrophages and carried to the mesenteric lymph nodes, where they continue to multiply intracellularly. The bacteria within infected macrophages disseminate in the bloodstream to multiple end organs including skin, spleen, liver, biliary tract, kidneys, and bone, causing multiple foci of infection and inflammation. Fever and prostration are caused by release of bacterial lipopolysaccharide (LPS) and other cytotoxic inflammatory mediators (see Figure 66-2).

CLINICAL FEATURES

The incubation period is commonly 10 to 14 days (with a range of 3 to 60 days). Onset of symptoms corresponds with bacteremia. The acute illness is characterized by fever, headache,

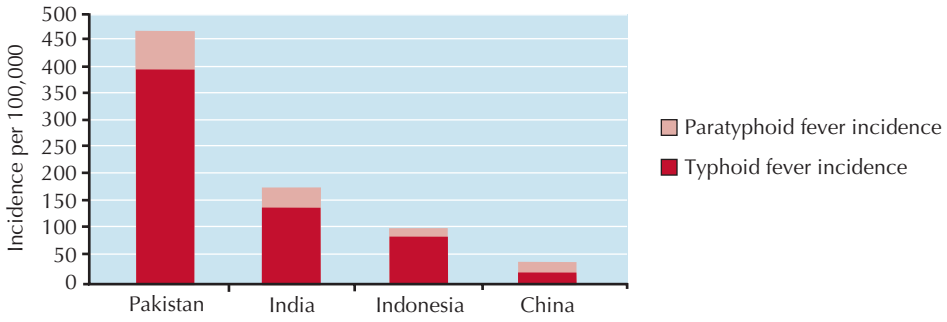

Figure 66-1 Incidence of *Salmonella enterica* serotype Typhi and serotype Paratyphi A in four Asian countries. *(From Ochiai RL, Wang XY, von Seidlein L, et al:* Salmonella *Paratyphi A rates, Asia,* Emerg Infect Dis *11:1764-1766, 2005. Available at: www.cdc.gov/ncidod/EID/vol11no11/05-0168.htm.)*

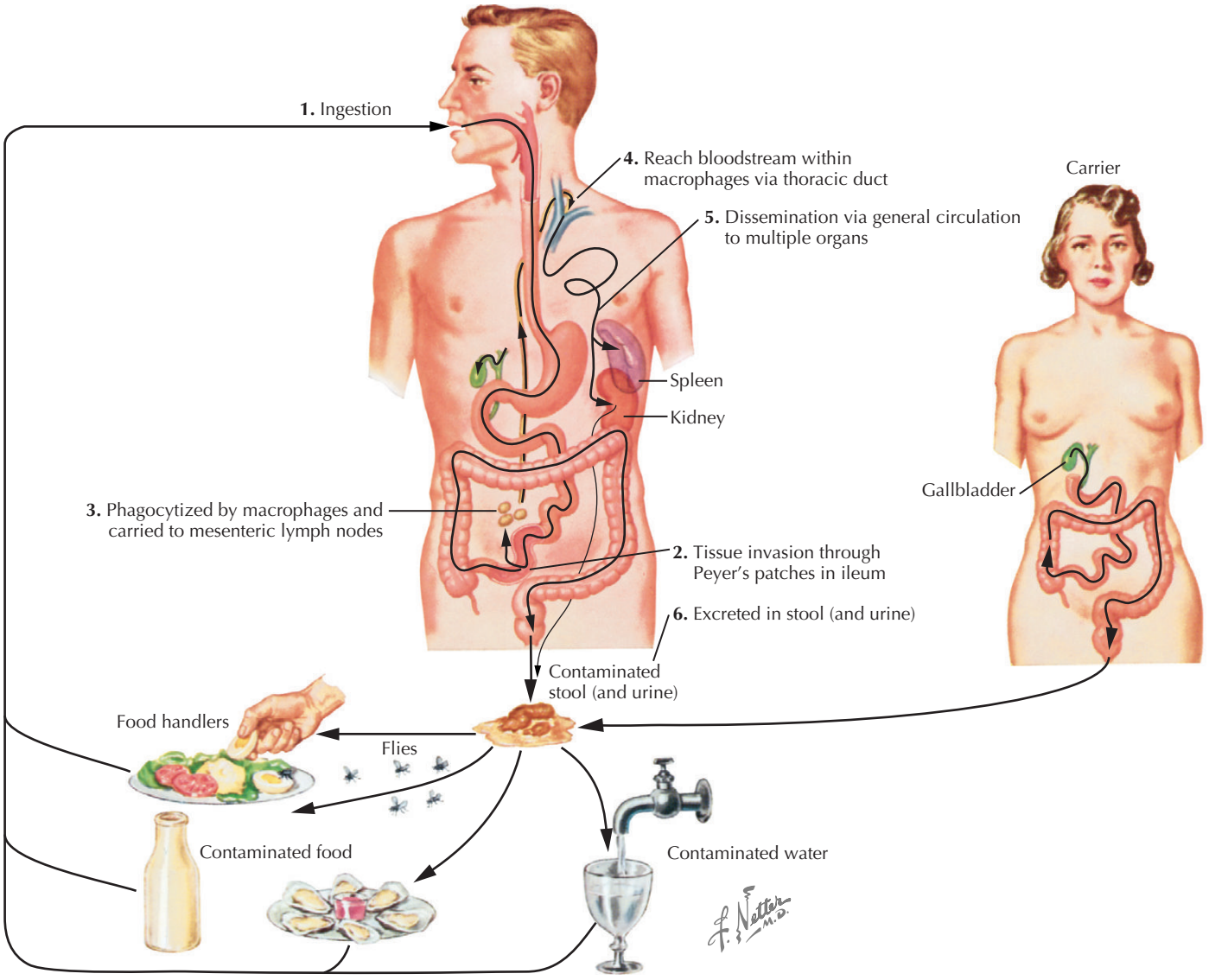

Figure 66-2 Transmission and pathogenesis of enteric fever: typhoid and paratyphoid fever.

malaise, and disturbed bowel function, with constipation more likely to be reported in adults and diarrhea more likely to be reported in children. Some patients develop a macular erythematous rash on the trunk (rose spots) (Figure 66-3). Without appropriate antibiotic treatment, the uncomplicated illness may last for 3 to 4 weeks with gradual recovery, although there is still risk of late-stage relapse or complications. The clinical illness may be accompanied by a sustained but low level of secondary bacteremia. Although paratyphoid fever may have similar signs and symptoms, it is generally a milder disease than typhoid. In some cases, however, it also may cause severe life-threatening disease.

In severe illness there is prolonged fever as high as 39° to 40° C (102° to 104° F), with stepwise temperature elevation and a relative bradycardia (dissociation of the fever-pulse curve). Progressive abdominal discomfort, abdominal distention, and altered mental status (delirium, obtundation, and stupor) may develop over the second week of illness. Complications may include anemia, bacterial hepatitis, melena, intestinal perforation, peritonitis, myocarditis, pneumonia, disseminated intravascular coagulation, thrombocytopenia, hemolytic uremic syndrome, and ultimately death (see Figure 66-3). Despite treatment with appropriate antibiotics and life support measures, typhoid death rates can range from 12% to 30%.

DIAGNOSTIC APPROACH

A history of recent travel to an area of known endemicity justifies inclusion of typhoid and paratyphoid fever in the differential diagnosis. In a returned traveler from the tropics with fever, the

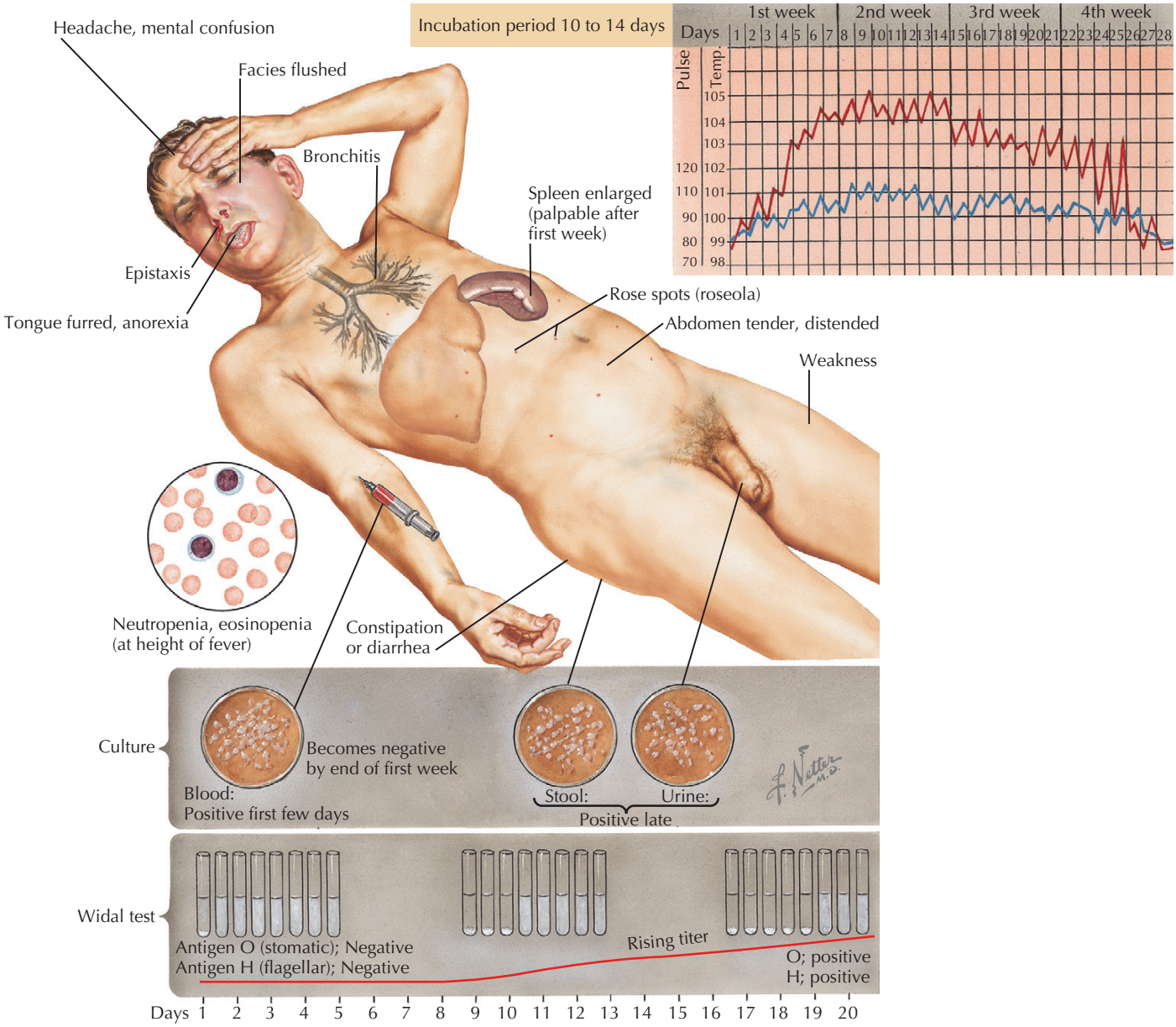

Figure 66-3 Typhoid fever: clinical illness and diagnosis.

differential diagnosis would also include malaria, dengue fever, and leptospirosis, as well as more ubiquitous infections such as influenza, pneumonia, meningitis, and pyelonephritis.

A *confirmed case* of typhoid fever is when the patient has had a fever of 38° C (100.4° F) and higher for longer than 3 days and has a laboratory-confirmed positive culture of *S.* Typhi. Isolation of *S.* Typhi bacteria in cultures of blood, bone marrow, bowel fluid, or specific anatomic lesions is the gold standard for diagnosis. Blood cultures are likely to be positive during the first 7 to 10 days of illness. Bone marrow aspiration cultures are useful if the diagnosis is considered after prolonged illness in the patient, especially if antibiotics have been previously administered. If the diagnosis has been confirmed by a positive culture, then serologic testing is unnecessary.

A *probable case* of typhoid fever is defined as when the febrile patient has a positive serodiagnosis or antigen detection test for *S.* Typhi without isolation of the bacteria in culture. The Felix-Widal test (Widal test) measures serum agglutinating antibody levels against the somatic O (LPS) and flagellar H antigens of *S.* Typhi bacteria. Two serum specimens, acute and convalescent, must be drawn from the patient at least 5 days apart. A fourfold rise between the acute and convalescent antibody levels is diagnostic (see Figure 66-3). However, this test has a false-negative rate of up to 30% in culture-proven cases, and cross-reacting antigens in patients with malaria, typhus, and bacteremia from other enteric bacteria may also confuse the interpretation of test results.

Newer diagnostic tests including polymerase chain reaction (PCR) assays are not universally available. The sensitivity, specificity, positive predictive value, and negative predictive value of rapid serologic tests for typhoid fever such as IDL Tubex-TF (specific immunoglobulin M [IgM] antibodies to *S.* Typhi–specific O9 antigen factor); Typhidot (specific IgM and IgG antibodies to an *S.* Typhi 50-kD antigen); Typhidot-M (specific IgM-only antibodies to an *S.* Typhi 50-kD antigen); and the IgM dipstick test (specific IgM antibodies to *S.* Typhi LPS antigen) may offer superior sensitivity and specificity as well as convenience under field conditions compared with the Widal test, but they are not yet widely used outside of endemic areas.

Diagnosis of paratyphoid fever is based on isolation of *S.* Paratyphi in bacterial culture from specimens, usually blood or stool, followed by serologic tests for somatic (O) and flagellar (H) antigens to confirm serotype. A new rapid test for paratyphoid fever (Tubex-PA) has been developed based on technology similar to that of the Tubex-TF test. The paratyphoid test relies on detection of *S.* Paratyphi A–specific O2 antibodies in patient sera and is still under evaluation.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Patients with mild illness can be managed as outpatients on oral antibiotics, antipyretics, oral hydration, and oral nutrition. Patients with more severe illness manifested by persistent vomiting, severe diarrhea, abdominal discomfort, and/or altered mental status require in-hospital monitoring with parenteral administration of antibiotics, fluids, and ancillary drugs.

The optimal treatment for typhoid fever is not established. Prompt treatment with an appropriate antibiotic is generally recommended, although corticosteroid treatment has not been shown to have a beneficial effect. Antibiotic treatment should be guided by antimicrobial susceptibility testing of culture isolates; however, it is often necessary to initiate presumptive antibiotic therapy while awaiting the results of antibiotic susceptibility tests. In this case, regional epidemiologic data on susceptibility patterns among *S.* Typhi strains should guide the choice of a presumptive drug. The approach to management and treatment of paratyphoid fever follows similar lines.

The choice of antibiotics is complicated by the emergence in Asia of isolates of *S.* Typhi that are multidrug resistant (MDR) to chloramphenicol, ampicillin, and trimethoprim-sulfamethoxazole and have reduced susceptibility to fluoroquinolones. The antibiotic treatment guidelines shown in Tables 66-1 and 66-2 represent a working group consensus in the *Background document: the diagnosis, treatment and prevention of typhoid fever*, published by the World Health Organization Department of Vaccines and Biologicals in May 2003.

Table 66-1 Treatment of Uncomplicated Typhoid Fever

	Optimal Therapy			*Alternative Effective Drugs*		
SUSCEPTIBILITY	**ANTIBIOTIC**	**DAILY DOSE (MG/KG)**	**DAYS**	**ANTIBIOTIC**	**DAILY DOSE (MG/KG)**	**DAYS**
Fully sensitive	Fluoroquinolone (e.g., ofloxacin or ciprofloxacin)	15	5-7*	Chloramphenicol	50-75	14-21
				Amoxicillin	75-100	14
				TMP-SMX	8-40	14
Multidrug resistant	Fluoroquinolone or	15	5-7	Azithromycin	8-10	7
	Cefixime	15-20	7-14	Cefixime	15-20	7-14
Quinolone resistant†	Azithromycin or	8-10	7	Cefixime	20	7-14
	Ceftriaxone	75	10-14			

Data from World Health Organization (WHO): The diagnosis, treatment and prevention of typhoid fever, *p 20. Available at: http://www.who.int/vaccines-documents/DocsPDF03/www740.pdf Accessed February 7, 2011.*

TMP-SMX, Trimethoprim-sulfamethoxazole.

*Three-day courses are also effective and are particularly so in epidemic containment.

†The optimum treatment for quinolone-resistant typhoid fever has not been determined. Azithromycin, the third-generation cephalosporins, or a 10- to 14-day course of high-dose fluoroquinolones, is effective. Combinations of these are now being evaluated.

Table 66-2 Treatment of Severe Typhoid Fever

	Optimal Parenteral Drug			*Alternative Effective Parenteral Drug*		
SUSCEPTIBILITY	**ANTIBIOTIC**	**DAILY DOSE (MG/KG)**	**DAYS**	**ANTIBIOTIC**	**DAILY DOSE (MG/KG)**	**DAYS**
Fully sensitive	Fluoroquinolone (e.g., ofloxacin)	15	10-14	Chloramphenicol	100	14-21
				Amoxicillin	100	14
				TMP-SMX	8-40	14
Multidrug resistant	Fluoroquinolone	15	10-14	Ceftriaxone *or*	60	10-14
				Cefotaxime	80	10-14
Quinolone resistant	Ceftriaxone or	60	10-14	Fluoroquinolone	20	7-14
	Cefotaxime	80	10-14			

Data from World Health Organization (WHO): The diagnosis, treatment and prevention of typhoid fever, *p 23. Available at: www.who.int/vaccines-documents. Accessed January 27, 2008.*
TMP-SMX, Trimethoprim-sulfamethoxazole.

TYPHOID CARRIER

Approximately 1% to 5% of typhoid fever patients become chronic carriers, with carriage of *S.* Typhi in the gallbladder. A chronic carrier is defined as an asymptomatic person who remains culture positive in stool or rectal swab cultures a year after recovery from acute illness. Factors associated with chronic carriage of *S.* Typhi include being over 50 years of age, being female, having gallstones, or having chronic schistosomiasis. Carriage can be eradicated by prolonged administration of antibiotics (e.g., ciprofloxacin 750 mg by mouth twice daily for 28 days), along with definitive treatment of any comorbid condition. A small number of individuals also have been reported to carry the *S.* Paratyphi bacteria after recovery from illness.

PREVENTION

Prevention of enteric fever, as with other common gastrointestinal infections that are spread from human to human, involves both human and environmental interventions. Human factors include personal measures, such as thorough hand washing after defecation and immediately before food preparation, hygienic disposal of human wastes, adequate cooking of food, covering of prepared food to protect it from flies, isolation of infected patients, identification and treatment of chronic carriers, and immunization of susceptible persons with efficacious vaccines. Environmental controls include community systems for pure water supplies, sanitary disposal of human waste products, insect control measures against flies, and mass immunization programs in highly endemic areas.

There are two currently available vaccines against typhoid fever: a purified Vi polysaccharide typhoid vaccine given by injection, and a live-attenuated Ty21a typhoid vaccine administered orally. There is no currently available vaccine against paratyphoid fever, and the two licensed typhoid vaccines do not offer cross-protection. Thus personal hygiene and safe food and water selection are extremely important in preventing this disease.

The Vi polysaccharide typhoid vaccine may be used in persons older than 2 years of age and consists of a single dose administered by subcutaneous injection. Protection is elicited after 7 days, and protective efficacy is estimated to be around 70%. Revaccination is recommended every 2 years for continued risk of exposure.

The live oral attenuated Ty21a typhoid vaccine may be used in persons older than 6 years of age and consists of an enteric-coated capsule given for four doses (United States), each dose taken 2 days apart on an empty stomach. Protection is elicited 10 to 14 days after the last dose, and protective efficacy is estimated to be around 70%. Revaccination is recommended every 5 years for continued risk of exposure, although significant protective immunity has been shown among populations living in endemic areas up to 7 years after immunization. The live oral typhoid vaccine is licensed in Africa, Asia, Europe, and South America. Outside the United States, it is available in both enteric-coated capsule and liquid formulations, is licensed for persons older than 5 years of age, and is approved as a three-dose vaccine series. To ensure vaccine efficacy, antibiotics should not be used for 7 days before and after the immunization series, and most experts recommend waiting 3 days after completion of the immunization series before administration of the first dose of mefloquine or proguanil (used for malaria chemoprophylaxis).

EVIDENCE

Effa EE, Bukirwa H: Azithromycin for treating uncomplicated typhoid and paratyphoid fever (enteric fever), *Cochrane Database Syst Rev* 4:CD006083, 2008. *Evidence-based review on the use of azithromycin in the treatment of enteric fever.*

Fraser A, Paul M, Goldberg E, et al: Typhoid fever vaccines: systematic review and meta-analysis of randomised controlled trials, *Vaccine* 25:7848-7857, 2007. *Evidence-based review comparing the protective efficacy of the Vi polysaccharide typhoid vaccine and the Ty21a live oral typhoid vaccine.*

Thaver D, Zaidi AK, Critchley, JA, et al: Fluoroquinolones for treating typhoid and paratyphoid fever (enteric fever), *Cochrane Database Syst Rev* 4:CD004530, 2008. *Evidence-based review of the use of fluoroquinolones for treating enteric fever in the face of emerging antimicrobial resistance patterns showing decreased sensitivity to fluoroquinolones.*

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): *National typhoid fever and paratyphoid fever surveillance*. Available at: www.cdc.gov/nationalsurveillance/typhoid_surveillance.html. Accessed October 7, 2010. *Description of CDC and the National Antimicrobial Resistance Monitoring System (NARMS) surveillance for typhoid and paratyphoid fever, and link to the current typhoid surveillance form, which seeks to capture enhanced information on cases of paratyphoid fever in addition to typhoid fever.*

Centers for Disease Control and Prevention (CDC): *Typhoid fever: frequently asked questions*, January 10, 2005. Available at: http://www.cdc.gov/ncidod/dbmd/diseaseinfo/files/typhoid_fever_FAQ.pdf. (Accessed February 7, 2011.). *Clearly written summary of key aspects of typhoid fever, written for informing and counseling the general public; valuable for patient counseling.*

World Health Organization (WHO) Department of Vaccines and Biologicals: *Background document: the diagnosis, treatment and prevention of typhoid fever*, Geneva, May 2003, WHO. Available at: http://www.who.int/vaccines-documents/DocsPDF03/www740.pdf. (Accessed February 7, 2011.) *Comprehensive and well-written manual with expert perspective on all aspects of diagnosis, treatment, and prevention of typhoid fever.*

Viral Hepatitis

Michael James Babineaux and Miriam J. Alter

67

ABSTRACT

Viral hepatitis is caused by infection with five distinctly different human viruses that cannot be distinguished from one another without serologic testing (Table 67-1). Hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis delta virus (HDV), and hepatitis E virus (HEV) have distinct differences in their epidemiology, physical structure, pathobiology, and prognosis, yet all involve the liver as the primary target organ. The severity of liver disease that accompanies acute infection with these viruses generally distinguishes them from cytomegalovirus and Epstein-Barr virus, whose primary target is not the liver and which typically cause much milder liver dysfunction during primary infections. The major burden of disease caused by hepatitis virus infections stems from chronic liver damage with progression to cirrhosis and hepatocellular carcinoma (HCC), which occurs in individuals who develop persistent infection. Development of persistent infection is highly dependent on the infecting virus and host factors such as age, co-infections, comorbidities, and underlying immune status. In areas of the world with the highest incidence of HCC (Southeast Asia, sub-Saharan Africa), most cases are attributed to HBV infection. In areas of the world where increase in the incidence of HCC (and cirrhosis) has been more recent (United States, Western Europe, Japan, Australia), the leading cause is HCV infection.

EPIDEMIOLOGY

Hepatitis A

The primary route for HAV transmission is fecal-oral; therefore the incidence of HAV infection is highly related to the prevailing level of hygiene and sanitation. Worldwide, the endemicity of HAV infection differs markedly among and within countries depending on the age groups in which the majority of transmission occurs. In areas with a high endemic pattern of infection, represented by the least developed countries (i.e., parts of Africa, Asia, Central and South America), most persons are infected as young children, and essentially the entire population becomes infected and immune before reaching adolescence. At the other end of the spectrum are the most developed countries (e.g., most areas of North America and Western Europe), in which the endemicity of HAV infection is low. Relatively fewer children are infected, and disease often occurs in the context of communitywide outbreaks, as well as in defined risk groups such as men who have sex with men, illicit drug users, and travelers returning from areas with a high or intermediate endemicity of infection (Figure 67-1).

HAV replicates in the liver, is excreted in bile, and is shed in stool. Peak infectivity occurs during the 2-week period before onset of jaundice or elevation of liver enzymes, when concentration of virus in stool is highest. Concentration of virus in stool declines after jaundice appears. Children can shed HAV for longer periods than do adults, with shedding lasting up to 10 weeks after onset of clinical illness; infants infected as neonates in one nosocomial outbreak shed HAV for up to 6 months, but lifelong shedding of the virus does not occur. In the United States, person-to-person transmission through the fecal-oral route is the primary means of HAV transmission. Transmission occurs most frequently among close contacts, especially in households and extended family settings. Common-source outbreaks and sporadic cases can occur from exposure to food or water contaminated at the source or by infected food handlers. Outbreaks in the context of floods or other natural disasters (e.g., hurricanes) have not been reported in the United States. On rare occasions, HAV infection has been transmitted by transfusion of blood or blood products collected from donors during the viremic phase of their infection.

Hepatitis B

HBV is a blood-borne and sexually transmitted virus. Transmission from infected mothers to their newborns at the time of birth is the most common source for HBV infection among infants. For adults, the primary sources are sexual (male to female and male to male) and percutaneous (e.g., injection drug use) exposures to blood. For all age groups, unsafe therapeutic injections, unscreened blood transfusions, and long-term nonsexual household contact with chronically infected persons are risks for acquiring HBV infection. Chronic infection is more likely to develop in persons infected as infants or young children, but rates of acute disease are highest among adults. Prevalence of chronic infection with HBV (serum positivity for hepatitis B surface antigen [HBsAg]) is high in countries or regions where HBV infections were historically acquired primarily by infants and young children, including countries in South America, Africa, the Middle East, Asia, Southeast Asia, Greenland, and the First Nation populations of northern Canada and Alaskan Native Americans (Figure 67-2). In those countries or regions where universal childhood hepatitis B immunization programs have been implemented, early-aged infections have been virtually eliminated and adults account for the remaining chronic infections.

In the general U.S. population, the overall age-adjusted prevalence of HBV infection (including persons with chronic infection and those with previous infection) is 4.9%. The estimated prevalence of chronic HBV infection is 0.5%, which includes a correction factor to account for the disproportionate

Table 67-1 Overview of Viral Hepatitis Agents

	HEPATITIS A VIRUS (HAV)	HEPATITIS B VIRUS (HBV)	HEPATITIS C VIRUS (HCV)	HEPATITIS D VIRUS (HDV)	HEPATITIS E VIRUS (HEV)
Incubation period	15-50 days (average 28 days)	60-150 days (average 90 days)	14-150 days (average 50 days)	Similar to HBV	15-60 days (average 40 days)
Source of virus	Feces	Blood or blood-derived body fluids	Blood or blood-derived body fluids	Blood or blood-derived body fluids	Feces
Route of transmission	Fecal-oral through close person-to-person contact, contaminated food, water; blood-borne through transfusion rarely	Percutaneous or permucosal through unsafe therapeutic injections and other contaminated healthcare-related equipment, unscreened transfusions or transplants, injection drug use, sex with infected partner, birth to infected mother	Similar to HBV	Similar to HBV	Fecal-oral through contaminated water; zoonotic source
Persistent infection	No	Yes	Yes	Yes	No
Vaccine available	Yes	Yes	No	Yes—co-infection with HBV vaccine No—superinfection	No

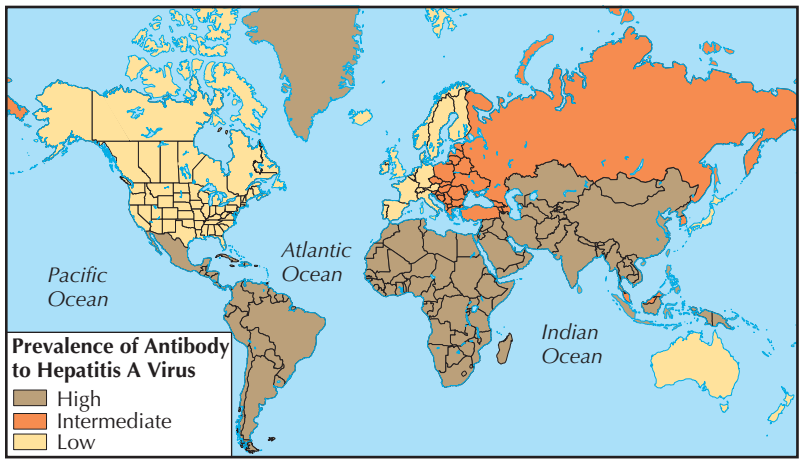

Figure 67-1 Prevalence of antibody to hepatitis A virus, 2006. *(From the Centers for Disease Control and Prevention (CDC):* CDC Health information for international travel 2010, *Atlanta, 2009, U.S. Department of Health and Human Services, Public Health Service.)*

contribution of foreign-born persons (particularly Asian/Pacific Islanders) who have emigrated from countries in which HBV is highly endemic to the number of persons living with chronic HBV infection in the United States. This prevalence translates into approximately 1.5 million persons with chronic HBV infection nationwide.

Hepatitis C

HCV is primarily transmitted by direct percutaneous exposures to infectious blood, most commonly through injection drug use, transfusions from infected donors, and unsafe therapeutic injections. Although less efficient, transmission of HCV by perinatal and sexual exposures also occurs. In developing countries, the strongest risk factor for HCV infection is iatrogenic exposure, whereas in developed countries most HCV infections have been acquired by illegal injection drug use. Worldwide, the prevalence of HCV antibody averages about 2%, corresponding to an estimated 130 million HCV-positive persons (Figure 67-3). In the United States, antibody prevalence is 1.6%, corresponding to an estimated 4 million individuals ever infected with HCV, of which 3 million are chronically infected.

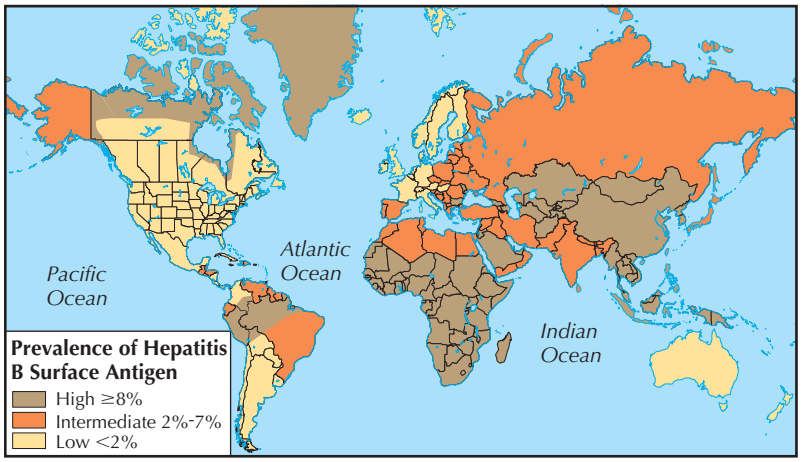

Figure 67-2 Prevalence of chronic infection with hepatitis B virus, 2006. *(From the Centers for Disease Control and Prevention (CDC):* CDC Health information for international travel 2010, *Atlanta, 2009, U.S. Department of Health and Human Services, Public Health Service.)*

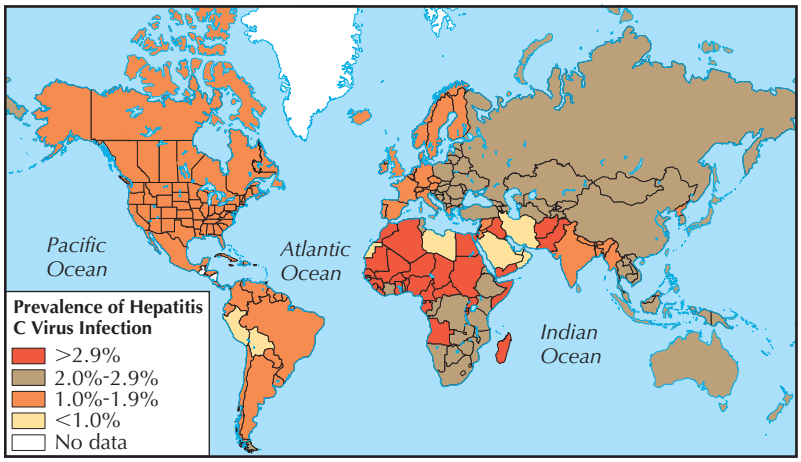

Figure 67-3 Global prevalence of hepatitis C virus infection. *(From the Centers for Disease Control and Prevention (CDC):* CDC Health information for international travel 2010, *Atlanta, 2009, U.S. Department of Health and Human Services, Public Health Service.)*

Hepatitis D

Epidemiologic features of HDV infection strongly parallel those of HBV, as would be expected from its status as a hepatitis B–dependent virus. HDV shares with HBV similar reservoirs of infection and transmission pathways. Worldwide prevalence of HDV infection tends to parallel that of HBV, being highest in nations or subpopulations with highest HBV prevalence. In the United States the most important routes of transmission for HDV are through injection drug use and sexual contact, although HDV is less efficiently transmitted than HBV in these settings. The importance of perinatal transmission of HDV appears minimal in contrast to its central role in HBV transmission. Individuals at highest risk for chronic co-infection are those who originate from endemic areas such as the Mediterranean, selected Pacific islands, Greenland, the Middle East, subtropical Africa, and South America.

Hepatitis E

HEV is transmitted via the fecal-oral route, with contaminated water being the most common source of infection. HEV is the single most important cause of acute clinical hepatitis in adults throughout Central and Southeast Asia and the second most important cause, behind HBV, throughout the Middle East and North Africa. In contrast, HEV is responsible for a very small number of cases in the United States and other industrialized countries, which are usually associated with travelers returning from endemic areas. In contrast to the geographic incidence of HEV disease, the geographic prevalence of antibody to HEV is worldwide; although the highest prevalences have been found in countries where the disease is highly endemic, prevalences of up to 20% have been found in countries such as the United States, where there are virtually no clinical cases (Figure 67-4).

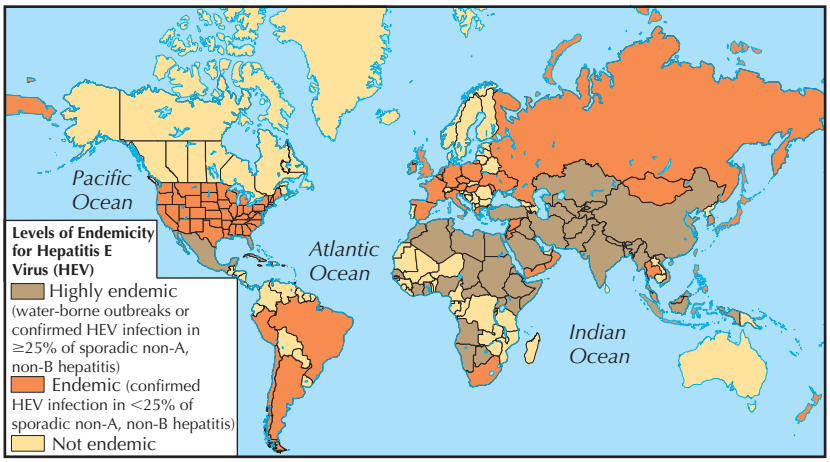

Figure 67-4 Global endemicity of hepatitis E virus. *(From the Centers for Disease Control and Prevention (CDC):* CDC Health information for international travel 2010, *Atlanta, 2009, U.S. Department of Health and Human Services, Public Health Service.)*

There is a growing body of evidence that HEV is a zoonotic infection and that animals, particularly swine, may be the source of most endemic HEV infections in countries such as the United States, where there are few clinical cases. Unlike the virulent strains of HEV responsible for widespread outbreaks of hepatitis E (from contaminated water) in developing countries, the HEV strains circulating in industrialized countries are more benign. These less virulent strains have been recovered from both swine and humans in the same regions and are responsible for the occasional case of clinical HEV in these settings. This suggests that the relatively high prevalence of anti-HEV in industrialized countries may result from inapparent infections with attenuated strains of HEV derived from swine or other domestic or wild animals and that the strains rarely cause clinical disease. Unlike other enterically transmitted infections, HEV is rarely spread to household contacts, and infection rates are low in infants and young children.

HEPATITIS A

Clinical Illness

HAV, a 27-nm ribonucleic acid (RNA) agent classified as a picornavirus, can produce either asymptomatic or symptomatic infection in humans after an average incubation period of 28 days (range 15 to 50 days). Illness caused by HAV infection typically has an abrupt onset that can include fever, malaise, anorexia, nausea, abdominal discomfort, dark urine, and jaundice. The likelihood of having symptoms with HAV infection is related to age. In children younger than age 6 years, 70% of infections are asymptomatic; if illness does occur, it is typically not accompanied by jaundice. Among older children and adults, infection typically is symptomatic, with jaundice occurring in more than 70% of patients. Signs and symptoms typically last less than 2 months, although 10% to 15% of symptomatic persons have prolonged or relapsing disease lasting up to 6 months (Figure 67-5). However, persistent infections with HAV are not well documented and may never occur. The overall case-fatality ratio among reported cases in the United States is approximately 0.3% to 0.6% but reaches 1.8% among adults older than age 50 years; persons with chronic liver disease are at increased risk of acute liver failure.

Diagnosis

HAV cannot be differentiated from other types of viral hepatitis on the basis of clinical or epidemiologic features alone. Two serologic tests are licensed for the detection of antibodies to HAV: (1) immunoglobulin M antibody to HAV (IgM anti-HAV) and (2) total anti-HAV (i.e., IgM and IgG anti-HAV). Serologic testing to detect IgM anti-HAV is required to confirm a diagnosis of acute HAV. In the majority of persons, serum IgM anti-HAV becomes detectable 5 to 10 days before onset of symptoms and declines to undetectable levels less than 6 months after infection. IgG anti-HAV, which appears early in the course of infection, remains detectable for the person's lifetime and provides lifelong protection against the disease.

Treatment

HAV does not cause persistent infection and rarely causes hepatic failure. Supportive care is the mainstay of treatment for HAV infections. Individuals with acute HAV with altered mental status or severe dehydration from nausea and vomiting require hospitalization. Laboratory results revealing increased international normalized ratio (INR) and/or reduced albumin may indicate synthetic dysfunction that requires consultation with a hepatologist. If hepatic encephalopathy develops, liver transplantation may be indicated. Patients with minimal symptoms can be managed on an outpatient basis.

Prevention

Depending on conditions, HAV can be stable in the environment for months. Heating foods at temperatures greater than 185° F (85° C) for 1 minute or disinfecting surfaces with a 1 : 100 dilution of sodium hypochlorite (i.e., household bleach) in tap water is necessary to inactivate HAV. HAV can be prevented by

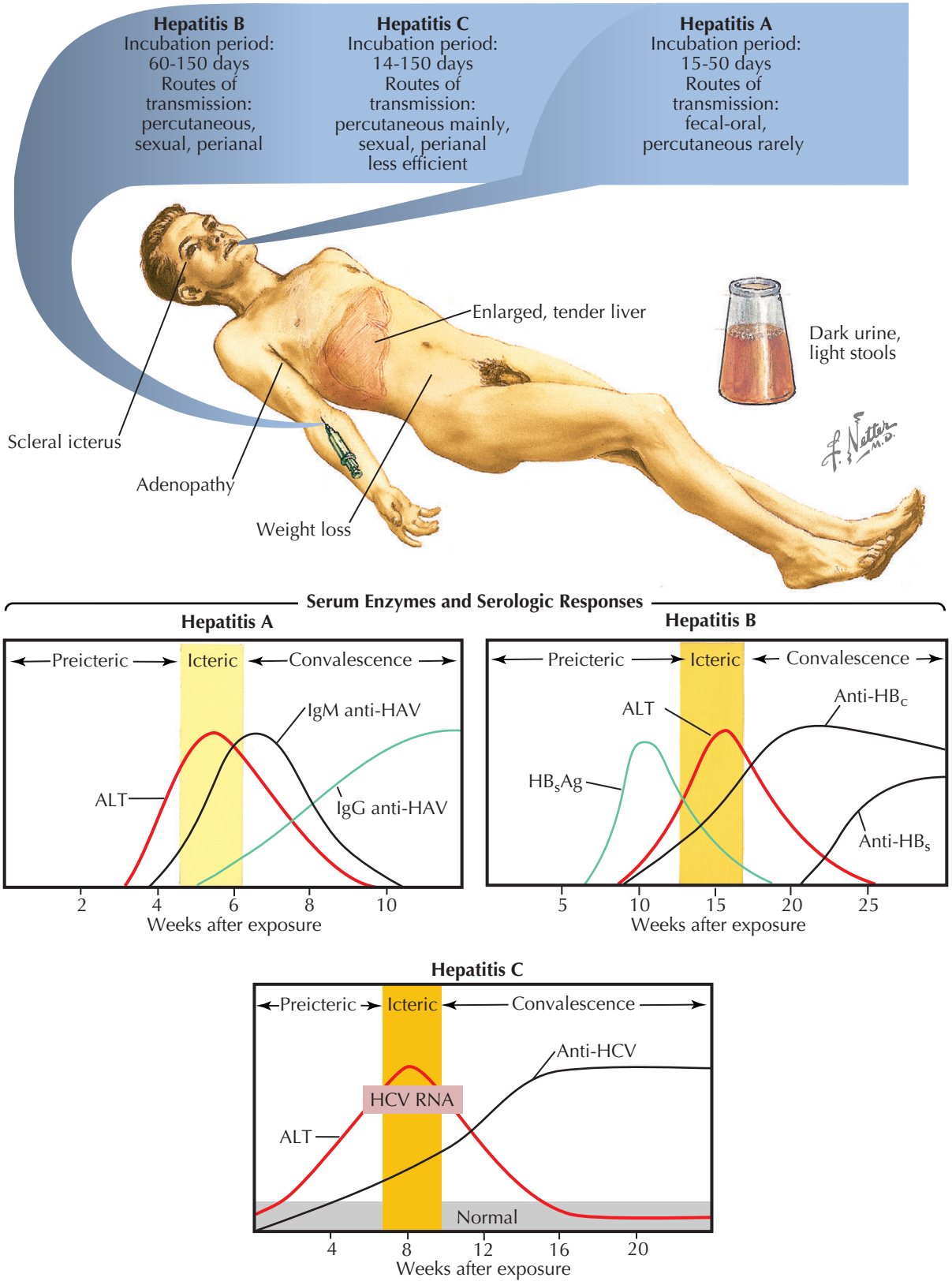

Figure 67-5 Acute viral hepatitis: clinical course, pathology, and diagnosis.

(1) general measures of good personal hygiene, particularly hand washing, provision of safe drinking water, and proper disposal of sanitary waste; (2) preexposure or postexposure immunization with HAV vaccine; and (3) preexposure or postexposure immunization with immunoglobulin. In the United States, preexposure administration of HAV vaccine is recommended for all children 1 year of age and older, international travelers, men who have sex with men, injection and noninjection illicit drug users, and individuals with chronic liver disease.

HEPATITIS B

Clinical Presentation

HBV is a 42-nm DNA virus classified in the family Hepadnaviridae. HBV infection can produce either asymptomatic or symptomatic infection. The average incubation period is 90 days (range 60 to 150 days) from exposure to onset of jaundice, 60 days (range 40 to 90 days) from exposure to onset of abnormal serum alanine aminotransferase (ALT) levels, and 30 days (range 6 to 60 days) from exposure to detection of HBsAg. The onset of acute disease is usually insidious. Infants, young children, and immunosuppressed adults with newly acquired HBV infection are typically asymptomatic. When present, clinical symptoms and signs might include anorexia, malaise, nausea, vomiting, abdominal pain, and jaundice (see Figure 67-5). Extrahepatic manifestations of disease include skin rashes, arthralgias, and arthritis. The case-fatality rate for acute HBV is 0.5% to 1%.

Most (≥95%) primary infections in adults with normal immune status are self-limited, with elimination of virus from blood and development of lasting immunity to reinfection. In contrast, primary infection develops into chronic infection in 30% of children younger than age 5 years and 80% to 90% of infants, with continuing viral replication in the liver and persistent viremia (Figure 67-6). Although the consequences of acute HBV can be severe, most of the serious sequelae associated with the disease occur in chronically infected persons, who are at increased risk for developing cirrhosis, decompensated liver disease, and primary HCC. Host and viral risk factors associated with disease progression include older age (longer duration of infection), high levels of HBV deoxyribonucleic acid (DNA), habitual alcohol consumption, and concurrent infection with HCV, HDV, or human immunodeficiency virus (HIV). Persons with chronic infection also serve as the reservoir for continued HBV transmission. Extrahepatic manifestations related to chronic HBV infection include immune complex–mediated diseases such as membranoproliferative glomerulonephritis.

Diagnosis

Although there are eight serologic markers associated with HBV infection, only four of these are necessary for diagnosis and screening (Table 67-2). The presence of HBsAg is indicative of ongoing HBV infection, and all HBsAg-positive persons should be considered potentially infectious. In newly infected persons, HBsAg is the only serologic marker detected during the first 3 to 5 weeks after exposure, and it persists for variable periods. Antibody to hepatitis B core antigen (anti-HBc) develops in all HBV infections, appearing at the onset of symptoms or liver test abnormalities in acute HBV infection, rising rapidly to high levels, and persisting for life. Acute or recently acquired infection can be distinguished by the presence of the IgM class of anti-HBc, which is detected at the onset of acute HBV and persists for approximately 6 months.

In persons who recover from HBV infection, HBsAg is eliminated from the blood, usually in 2 to 3 months, and anti-HBs develops during convalescence, indicating immunity from HBV infection. Most persons who recover from natural infection will be positive for both anti-HBs and anti-HBc, whereas persons who are successfully vaccinated against hepatitis B develop only anti-HBs. In persons who do not recover from HBV infection and who become chronically infected, HBsAg and anti-HBc persist, usually for life.

Other markers associated with HBV infection include hepatitis B e antigen (HBeAg) (and its corresponding antibody) and HBV DNA, both of which correlate with viral replication and high levels of virus and can be detected in the serum of persons

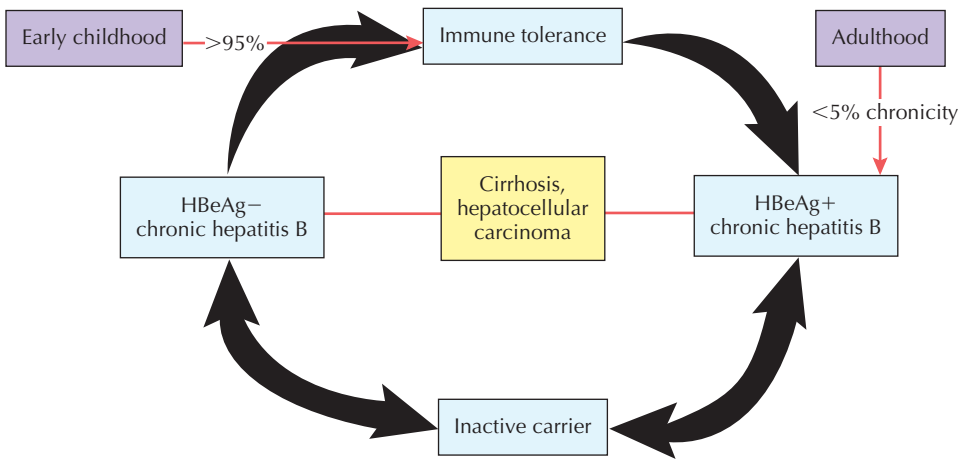

Figure 67-6 Age-related risk of persistent hepatitis B virus infection.

Table 67-2 Interpretation of Serologic Test Results for Diagnosis of Hepatitis B (HBV) Infection

Serologic Marker				
HBSAG[a]	**TOTAL ANTI-HBC[b]**	**IGM[c] ANTI-HBC**	**ANTI-HBS[d]**	**INTERPRETATION**
–	–	–	–	Susceptible; never infected
+[e]	–	–	–	Early acute infection
+	+	+	–	Acute infection
–	+	+	–	Acute resolving infection
–	+	–	+	Past infection; recovered and immune
+	+	–	–	Chronic infection
–	+	–	–	False positive (i.e., susceptible); past infection; "low-level" chronic infection[f]; passive transfer to infant born to HBV-infected mother
–	–	–	+	Immune if titer is ≥10 mIU/mL[g]

[a]Hepatitis B surface antigen.
[b]Antibody to hepatitis B core antigen.
[c]Immunoglobulin M.
[d]Antibody to hepatitis B surface antigen.
[e]To ensure that an HBsAg-positive test result is not a false positive, samples with repeatedly reactive HBsAg results should be tested with a licensed neutralizing confirmatory test.
[f]Persons positive for only anti-HBc are unlikely to be infectious except under unusual circumstances involving direct percutaneous exposure to large quantities of blood (e.g., blood transfusion).
[g]mIU = milli–international units per milliliter.

with acute or chronic HBV infection. The results of testing for these markers are most useful for monitoring chronically infected patients who are treated with antiviral drugs.

Treatment

The primary goal of HBV treatment is suppression of viral replication. Indications of response include return of liver enzymes to normal, suppression of HBV DNA levels, and serologic conversion of HBeAg to anti-HBe. Antiviral treatment algorithms change regularly owing to newly implemented agents, and consultation with a hepatologist is recommended before initiation of antiviral therapy. Pegylated interferon therapy, possessing both antiviral and immunomodulatory properties, is commonly used for its suppression of viral replication. The treatment course is a once-weekly subcutaneous injection for 12 months.

Another class of HBV antivirals includes the nucleoside and nucleotide analogues. Included in this class are lamivudine, adefovir, tenofovir, entecavir, and telbivudine. The main focus of this class is disruption of HBV DNA synthesis either by DNA chain termination or direct inhibition of DNA polymerase. Initial sustained response rates range from 50% to 70% with therapy, but long-term response is affected by adherence to the treatment course and development of resistance.

Combination therapy has been proven to be more effective than monotherapy in HBV infections in producing sustained response. Advantages to combination therapy include possible antiviral synergy and/or delayed resistance, but this type of therapy may lead to drug interactions, increased cost, and drug side effects. Typical HBV treatment combinations include pegylated interferon and lamivudine, lamivudine and adefovir, and lamivudine and telbivudine. Other promising therapies under investigation include emtricitabine, clevudine, tenofovir and emtricitabine (Truvada), and thymosin.

With recent advances in HBV treatment and detection of liver cancer, identification of an HBV-infected person permits the implementation of important interventions to reduce liver disease–related morbidity and mortality. Persons who are most likely to be actively infected with HBV should be tested for chronic HBV infection. These include persons born in geographic regions with HBsAg prevalence ≥2% (see Figure 67-2), persons with unexplained elevations in liver enzymes, persons infected with HIV, and persons undergoing immunosuppressive therapy.

Prevention

Immunization with hepatitis B vaccine is the most effective measure to prevent HBV infection and its consequences. During the past 15 years the incidence of acute hepatitis B in the United States has declined by 70%. The most significant decline (94%) has occurred among children and adolescents, coincident with an increase in HBV vaccine coverage. Although acceptance of vaccination is high among adults offered vaccination, the rates of HBV vaccine coverage among most adults are low. The low coverage is attributed to missed opportunities by healthcare professionals to offer HBV vaccine to high-risk adults seeking care in general medical care settings.

Screening of individuals at risk of acquiring HBV (as well as those most likely to be infected) should occur in primary care settings (e.g., physician's offices, community health centers, travel clinics, occupational health programs) and high-risk settings (sexually transmitted disease [STD] and drug treatment facilities). Information should be provided to all adults regarding risk factors for HBV transmission and persons for whom the vaccine is recommended (Table 67-3). Focused history tailored around these factors will increase identification of the at-risk population. Also, HBV vaccine should be readily available to anyone requesting vaccination.

Table 67-3 Hepatitis B Vaccination Recommendations for Adults by Risk Category

Sexual exposure	Partners of HBsAg-positive partners
	Sexually active with multiple partners
	Homosexual males
	Individuals seeking treatment for STDs
Percutaneous exposure	Injection drug users (past or present use)
	Residents and staff of institutions for mentally disabled persons
	Healthcare and public safety workers
	Household contacts of HBsAg-positive individuals
	Individuals with end-stage renal disease and hemodialysis patients
Other high-risk groups	Travelers to endemic regions
	Individuals with chronic liver disease
	HIV-positive individuals
	Individuals interested in vaccination

Data from Mast EE, Weinbaum CM, Fiore AE, et al: A comprehensive immunization strategy to eliminate transmission of hepatitis B virus infection in the United States: recommendations of the Advisory Committee on Immunization Practices (ACIP). Part II: immunization of adults, MMWR Recomm Rep *55:1-33, 2006.*
HBsAg, Hepatitis B surface antigen; *HIV,* human immunodeficiency virus; *STD,* sexually transmitted disease.

A complete primary HBV vaccination series for adults includes three doses over a 6-month period. The vaccine has a 95% response rate in healthy persons younger than 40 years old; in older persons, rates may be lower. Postvaccination testing is recommended for individuals who need to know their immune status, such as healthcare workers. Nonresponders to vaccination should undergo a second three-dose regimen, which is successful in conferring immunity in 70%. Postexposure prophylaxis is achieved with hepatitis B immunoglobulin and hepatitis B vaccine. Hepatitis B immunoglobulin is effective in preventing infection, but vaccination is recommended for sustained immunity. The estimated window for postexposure prophylaxis is ≤7 days for needlestick injury and ≤14 days for sexual exposure.

HEPATITIS C

Clinical Presentation

HCV, a single-stranded RNA agent, is a member of the Flaviviridae family. HCV strains show extraordinary genetic diversity. There are six major genotypes and more than 100 subtypes. The most common genotype in the United States is genotype 1 (70%), followed by genotypes 2 and 3 (30%). HCV genotype has no impact on disease progression; genotype 1 is associated with antiviral resistance.

HCV has a mean incubation period of 50 days (range 14 to 180 days). Although 70% to 80% of acute infections are asymptomatic, biochemical evidence of hepatitis, such as elevated ALT levels, is observed in most patients, and some patients demonstrate acute viral hepatitis–associated malaise, nausea, and right upper quadrant pain, followed by dark urine and jaundice. Such cases are indistinguishable from acute hepatitis A or B without the results of specific diagnostic tests (see the section on diagnosis). Chronic infection develops in about 70% to 85% of persons with HCV. They are at risk for developing clinically significant liver disease, including steatosis, progressive fibrosis, cirrhosis, and HCC (Figure 67-7). Factors associated with more rapid disease progression include alcohol use, male gender, age older than 40 years at infection, and HIV co-infection. Extrahepatic manifestations associated with persistent HCV infection include cryoglobulinemia, glomerulonephritis, porphyria cutanea tarda, and possibly diabetes mellitus, lichen planus, and B-cell lymphoma.

Table 67-4 Interpretation of Serologic Test Results for Diagnosis of Hepatitis C Virus (HCV) Infection

ANTI-HCV	HCV RNA	DIAGNOSIS
Positive	Positive	Acute or chronic HCV infection
Positive	Negative	Resolution of HCV infection or false-positive antibody
Negative	Positive	Early acute HCV infection, HCV in immunocompromised patients, false-positive nucleic acid test result
Negative	Negative	Negative for HCV infection

Diagnosis

Testing for HCV infection is performed for (1) clinical diagnosis of patients with signs, symptoms, or abnormal laboratory test results indicative of liver disease; (2) management of patients with chronic HCV during therapy; and (3) screening of asymptomatic persons to identify those infected with HCV. Serologic and virologic markers that are clinically useful include IgG antibody (anti-HCV), a marker of past or present HCV infection; HCV RNA, a direct indicator of ongoing HCV replication; and HCV genotype, for determining a treatment regimen. In clinical practice the usual approach is to test initially for anti-HCV, and if results are positive, for HCV RNA to document viremia (Table 67-4). If HCV RNA test results are positive, active HCV infection is confirmed. If HCV RNA test results are negative, additional testing with a supplemental antibody assay is necessary to verify the anti-HCV result and determine the need for additional follow-up. Although a confirmed anti-HCV–positive result does not distinguish between current or past infection, it does indicate the need for serial determinations of HCV RNA and ALT activity. In addition, liver biopsy is also used for diagnosis of chronic hepatitis and cirrhosis but only with confirmed diagnosis.

Treatment

Evaluation and treatment of patients with hepatitis C should be carried out in consultation with a hepatologist. Acute hepatitis

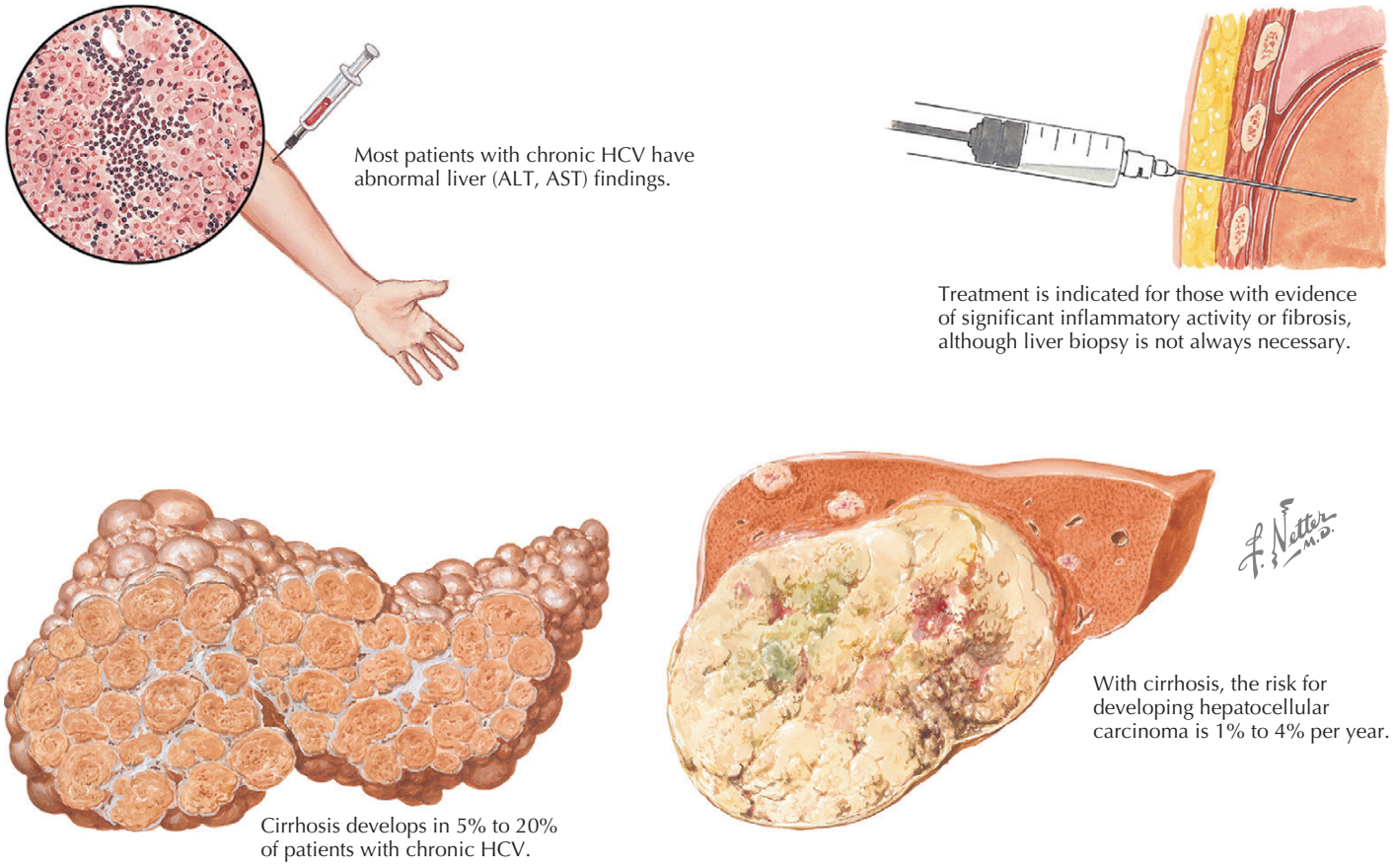

Figure 67-7 Progression of hepatitis C virus disease.

C is usually asymptomatic, and diagnosis of acute infection is uncommon. If infection is identified early, therapy with interferon within 3 to 6 months of infection can prevent development of chronic infection in 85% to 90% of patients. Most patients identified as HCV-positive have established chronic infection and should be vaccinated against HAV and HBV. Treatment is indicated for those with evidence of significant inflammatory activity or fibrosis, although liver biopsy is not always necessary. Length of treatment differs by genotype; response is defined as being negative for HCV RNA in serum 6 months after stopping treatment.

The use of pegylated interferon, injected subcutaneously once per week, plus oral ribavirin taken twice daily for 1 year results in sustained virologic response in 56% of patients infected with genotype 1. The same regimen for 6 months results in sustained virologic response in 75% to 85% of patients infected with genotypes 2 or 3. Side effects include neutropenia, thrombocytopenia, hemolytic anemia, depression, and thyroid dysfunction. Treatment is contraindicated for those with significant depression, cardiac disease, or decompensated liver disease. Co-infection with HIV causes rapid progression from primary HCV infection to end-stage liver disease. Combination antiviral therapy for HCV in HIV-positive individuals is recommended with early or mild disease. The decision to treat an HIV-positive patient with HCV is dependent on the current HIV regimen and stage of disease. Ribavirin has well-documented interactions with antiretroviral medications and thus can interfere with proper HIV therapy.

Of patients treated with pegylated interferon and ribavirin, 20% to 50% do not respond; retreatment with the same regimen is ineffective in most such patients. New therapeutic agents are under development, such as telaprevir, a protease inhibitor. Phase II trials have shown that treatment with telaprevir in combination with peginterferon and ribavirin substantially improves sustained virologic response rates in both naïve and previously treated patients with genotype 1; however, discontinuation rates resulting from side effects are higher.

Prevention

Because there is no vaccine and no postexposure prophylaxis for HCV, the prevention of new infections worldwide requires procedures to ensure a safe blood supply, implementation of effective infection control and safe injection practices in healthcare and other settings, establishment of expanded harm-reduction and treatment programs for injection drug users, and development of educational programs to prevent initiation of high-risk drug and sexual behaviors.

In countries with more developed economic, medical, and public health infrastructures, efforts to minimize morbidity and complications from chronic HCV need to start with the identification of persons already infected with HCV so they can be

provided with appropriate counseling and medical management. In the United States, HCV screening is recommended for those at highest risk of being infected. These include persons who have ever injected illegal drugs; who received blood transfusions before 1992; who received clotting factors before 1985; who have unexplained abnormal ALT levels; or who are HIV positive. For the purpose of medical management after a known exposure, HCV screening also is recommended for children born to HCV-infected mothers, healthcare workers after needlestick injury, and current sexual partners of HCV-infected individuals.

HEPATITIS D

Clinical Illness

HDV is a defective RNA virus that is dependent on the presence of HBV to cause infection and disease and greatly augments the severity of both acute and chronic liver disease in the HBV- and HDV-infected host. The incubation period and clinical presentation parallel those of HBV. HDV can cause infection in two ways: (1) by co-infection with HBV of an HBV-susceptible host, and (2) by superinfection of an HBV chronic carrier. Co-infection with HDV can lead to accelerated fulminant hepatic failure, and the vast majority of HDV-superinfected carriers develop progressive hepatitis.

Diagnosis

Accurate diagnosis of HDV infection in persons with acute hepatitis requires use of serologic tests for HBV (HBsAg and lgM anti-HBc) and HDV (anti-HDVand IgM anti-HDV). Acute HBV-HDV co-infection is diagnosed in persons with positive IgM anti-HBc (indicative of acute HBV infection) and a positive marker for HDV. Clinically, acute HDV superinfection often appears as a severe acute hepatitis that may run a fulminant course. It may manifest as an exacerbation of preexisting HBV disease or as new hepatitis in a previously asymptomatic HBsAg carrier. The correct diagnosis is indicated by a negative result of a test for IgM anti-HBc and is confirmed by the detection of HDV markers in persons who are chronically infected with HBV (HBsAg and total anti-HBc positive but IgM anti-HBc negative).

Treatment

HDV infection can be treated with interferon for 12 months, but therapy rarely leads to clearance of the infection. Lamivudine, a nucleoside analogue, has been used as monotherapy or in combination with interferon for treatment of HBV, but it does not suppress HDV infection. Therefore many of the medications used in the treatment of HBV are ineffective against HDV.

Prevention

The single most important tool in the prevention of HBV-HDV co-infection in HBV-susceptible individuals is immunization with HBV vaccine. Sexually active young adults and new initiates of injection drug use are at highest risk, and efforts to vaccinate them need to be strengthened. The prevention of HDV superinfection must rely on awareness of HBV carrier status and counseling on modification of high-risk behaviors.

HEPATITIS E

Clinical Illness

HEV is a small nonenveloped RNA virus that causes disease indistinguishable from that caused by HAV without serologic testing. However, HEV differs from HAV in a few respects: the incubation period of HEV is, on average, 10 days longer, with a mean of 40 days (range 14 to 60 days), and its overall mortality rate is higher (1% to 4%) but not age dependent. Similar to HAV, HEV causes an acute, self-limiting infection that may vary in severity from unapparent to fulminant and is not known to progress to chronicity, except in the rare event of infection of the immunologically compromised host.

A unique feature of HEV is an approximate 20% mortality rate among pregnant women, particularly in the third trimester. The exact cause of this phenomenon is uncertain, although hormonal and/or immunologic factors have been implicated. HEV infection during pregnancy is associated with low birth weight, prematurity, and increased perinatal mortality.

Diagnosis

HEV can be diagnosed by the demonstration of IgM anti-HEV in the serum (generally present when the patient is first seen by a physician) or by detection of viral RNA in the serum or feces by nested or real-time PCR. Although the anti-HEV assay is commercially available, it is not U.S. Food and Drug Administration (FDA) approved. Unfortunately, both serologic tests and molecular tests vary greatly in sensitivity, making diagnosis, and especially seroprevalence studies, less reliable than for the other human hepatitis viruses.

Treatment

There is no specific treatment for acute HEV. The mainstay of treatment is supportive care with fluids, rest, and avoidance of medications and alcohol, which may exacerbate liver damage.

Prevention

In developing countries, preventive measures are aimed at proper treatment and disposal of human waste and purification of water in addition to improved personal hygiene. During epidemics, boiling and/or chlorination of water has been an effective means of prevention. Travelers to such countries should observe protective measures against all enterically transmitted infections. Serum immunoglobulin does not appear to protect against HEV. At least one vaccine has been shown to be safe and effective in protecting humans against HEV, but it is not in production. The potential market in industrialized countries is quite small, and such a vaccine may be cost-prohibitive for developing countries.

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McHutchison JG, Everson GT, Gordon SC, et al: Telaprevir with peginterferon and ribavirin for chronic HCV genotype 1 infection, *N Engl J Med* 360(18):1827-1838, 2009. *Telaprevir, a protease inhibitor, combined with peginterferon and ribavirin, rapidly reduced HCV RNA levels and substantially increased sustained virologic response in patients infected with genotype 1.*

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ADDITIONAL RESOURCES

American Association for the Study of Liver Diseases: *Your liver*. Available at: www.aasld.org/patients/Pages/default.aspx. *Basic information about the liver, common diseases, and physician referral service.*

Centers for Disease Control and Prevention (CDC): V*iral hepatitis – Resource Center.* Available at: http://www.cdc.gov/hepatitis/Resources/index.htm. *For healthcare professionals, published recommendations and evidence for screening, vaccination, and preexposure and postexposure prophylaxis. For the public, patient education materials with general information about all types of viral hepatitis.*

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Rabies

Kis Robertson, Nina Marano, and Katherine J. Johnson

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ABSTRACT

Rabies has been recognized as a source of great human suffering and fear since ancient times. Characterized by a near-100% case-fatality rate, it is among the deadliest infectious diseases known to man. The rabies virus is present in the saliva of clinically ill mammals and is typically transmitted to humans through a bite. The incubation period is usually 1 to 3 months. After entering the central nervous system (CNS), the virus causes an acute, progressive encephalomyelitis. Although treatment options for rabies are currently limited, the disease is highly preventable with proper administration of rabies postexposure prophylaxis (PEP).

GEOGRAPHIC DISTRIBUTION

Africa and Asia

Of the estimated 35,000 to 55,000 rabies casualties every year, more than 95% occur as a result of dog bites in the developing countries of Africa and Asia. Exposure risk is highest in rural areas where free-roaming dogs are commonplace. Poor usage, accessibility, and affordability of medical care and rabies biologics are additional factors associated with human incidence. Children younger than age 15 years old are disproportionately infected owing to the high incidence of dog bites in this demographic group. Rabies and rabies-related viruses have also been isolated from African and Asian wildlife, including bats, mongooses, jackals, foxes, raccoon dogs, and other species. Travelers to rabies-endemic countries who anticipate prolonged stays in rural areas and extensive outdoor activities should consider preexposure immunization before travel (Figure 68-1).

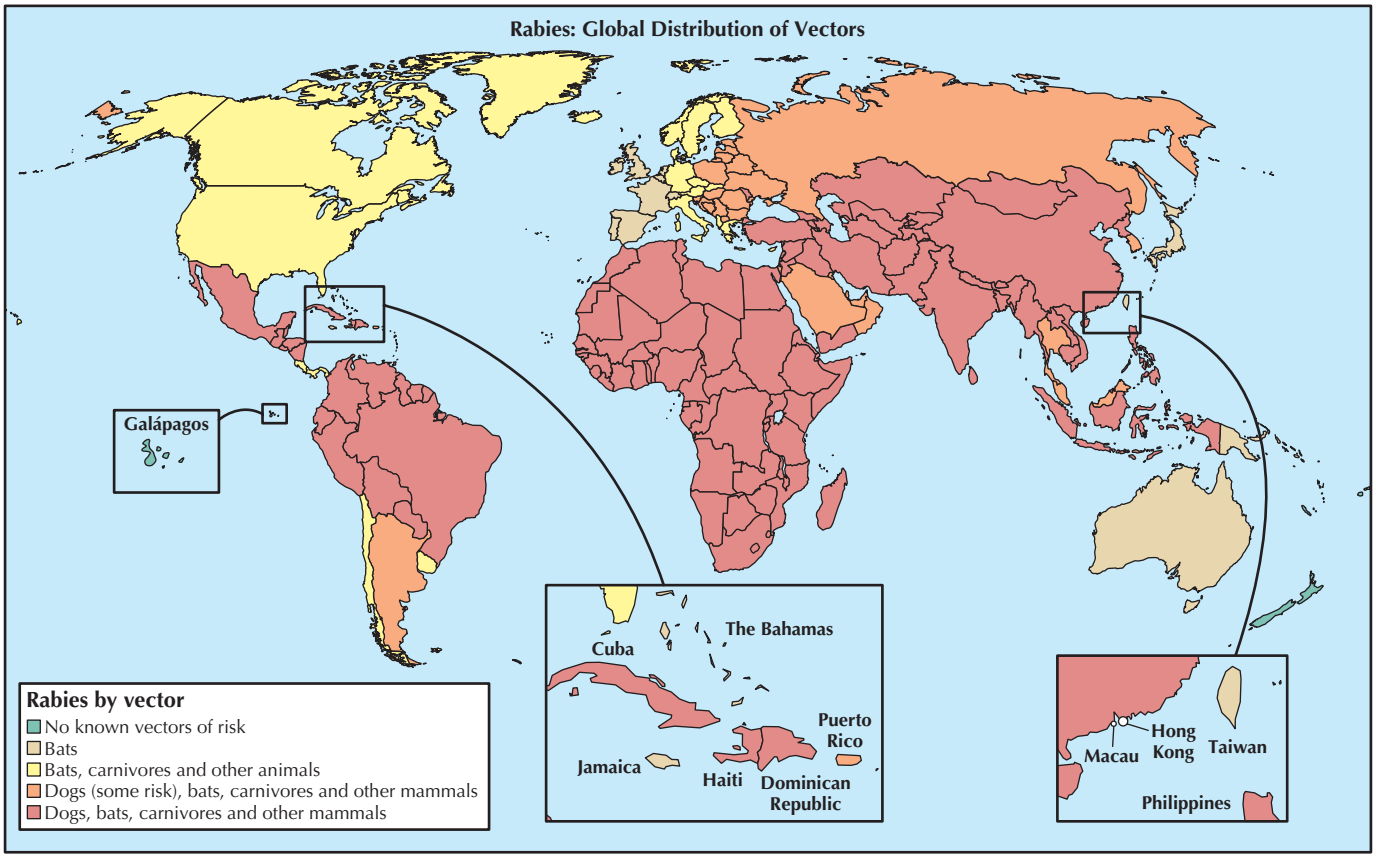
Latin America and the Caribbean

In many Latin American and Caribbean countries, human rabies has declined in recent years as canine vaccination rates and use of rabies PEP have risen. From 1993 to 2002, dogs were implicated in 65% of human cases reported in the region; in 2004, 22% were attributed to dogs. In spite of this overall trend, canine rabies remains a concern in many places throughout the region. A growing proportion of human cases are also mediated by hematophagous (vampire) bats. Notable outbreaks caused by these animals have occurred in Brazil, Peru, and Columbia. Rabid vampire bats are particularly a threat to human and cattle populations in remote tropical areas within the Amazon. Although rabies is also present in nonhematophagous bats in the region, a complete understanding of their contribution to human disease is lacking because of the absence of taxonomic specificity when bats are identified and reported as a source of exposure, in addition to other surveillance limitations. In multiple instances, human rabies has been linked to monkeys, skunks, foxes, raccoons, and livestock. Domestic cats have also served as an important source of infection, with 3% of reported human cases in 1993 to 2002 attributed to these animals. Travelers who come in contact with animals—particularly wild or stray animals—should be mindful of rabies risks and take steps to avoid bites and other exposures.

Europe, Canada, and the United States

In Europe and temperate North America, human rabies is rare. From 1980 to 2008, an average of two people a year died from rabies in the United States, and in that time there were five human rabies deaths reported in Canada. Europe currently averages approximately nine reported cases a year, with most cases occurring in eastern Europe. The widespread availability of rabies vaccines and rabies immune globulin (RIG), a well-immunized dog population, and effective antistray programs are credited with the low human rabies incidence seen in most developed countries. Wildlife has the highest burden of rabies in North America and Europe. Most human cases in the United States and Canada are associated with insectivorous bats, whereas in eastern Europe rabies transmission is largely driven by the red fox, with dogs playing an important role as victims of fox-associated spillover infections. Insectivorous bats in Europe also serve as important reservoirs of European bat lyssaviruses (EBLs), which causes rabies in humans. Foreign-acquired rabies represents a significant portion of human cases reported in North America and western Europe, which are typically associated with dog exposures in rabies-endemic countries (Figure 68-2). From 1980 to 2008, 28% of cases reported in the United States and Canada were imported.

More than 65% of animal rabies reported in the United States is found in wild terrestrial carnivores such as raccoons, skunks, and foxes. However, insectivorous bats are considered higher risk vectors to humans because lesions inflicted by these mammals tend to be less conspicuous, less easily recognized, and/or taken less seriously and therefore are less likely to be treated than are bites and scratches from rabid carnivores. A majority of bat-associated human cases in the United States and Canada have been attributed to so-called *cryptic bat exposures*—characterized by the absence of an elicited bite or scratch history—which most often involve rabies virus variants associated with the silver-haired bat *(Lasionycteris noctivagans)* and the eastern pipistrelle bat *(Pipistrellus subflavus)*. Because of the risks associated with undetected bat bites, the U.S Advisory Committee on Immunization Practices (ACIP) recommends that any suspected contact with a bat be evaluated for possible rabies virus exposure if a bite cannot be reasonably excluded.



Recommendations for Pre-Exposure Immunization for Travelers

Exposure	Vaccine recommended for:
No known risk	No recommendation
• Bats	• Travelers with high occupational risks such as wildlife professionals, researchers, veterinarians • Adventure travelers visiting areas where vectors commonly found
• Bats • Carnivores and other mammals	
• Bats • Dogs (some risk) • Carnivores and other mammals	All of the above, plus • Long-term travelers • Expatriates
• Bats • Dogs • Carnivores and other mammals • High-risk activities explicitly identified	All of the above, plus • Travelers spending a lot of time outdoors • Travelers to rural areas • Travelers involved in activities like bicycling, camping, hiking • Children

Figure 68-1 Rabies distribution and immunization recommendations. *(Courtesy Nancy Gallagher and Kevin Liske, Division of Global Migration and Quarantine, Centers for Disease Control and Prevention.)*

Australia

In Australia, the emergence of Australian bat lyssaviruses (ABLs) in 1996 has elevated public health concerns in a country that historically has enjoyed "rabies-free" status. These bat-associated viruses—like the EBLs seen in Europe and the Lagos bat and Duvenhage viruses seen in African bats—although phylogenetically distinct from the classic rabies virus seen in the New World and most of the Old, produce a fatal encephalomyelitis indistinguishable from that caused by the rabies virus. In the late 1990s, two people acquired rabies after incurring bites from ABL-infected bats. Variants of the virus have been isolated from both frugivorous and insectivorous bats. Exposures to these animals should therefore be regarded the same way they would be in countries where bat rabies is present.

Rabies-Free Countries

The World Health Organization (WHO) may designate a country as "rabies free" if there have been no reports of

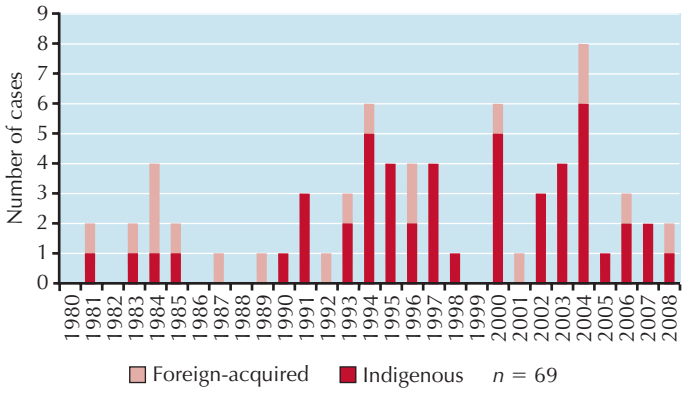


Figure 68-2 Human rabies cases in the United States, Puerto Rico, and Canada, 1980 to 2008. Four cases occurring in 2004 were the result of organ or tissue transplants from an infected donor, which accounts for the elevated count during this year. Of the indigenous cases, all but five were linked to bats either historically or through variant typing. Two indigenous U.S. cases occurring in 1991 and 1994 were associated with coyote or dog variants, and a skunk and a raccoon were linked to cases occurring in 1981 and 2003, respectively. In 2003, a man died from rabies in Puerto Rico as a result of a dog bite.

indigenous cases in at least 2 consecutive years based on surveillance that is considered sufficiently sensitive. However, travelers should be aware that because surveillance for rabies often involves underreporting, an animal exposure may carry transmission risks even if the exposing animal is from a country considered "rabies free."

ETIOLOGY

The rabies and rabies-related viruses belong to the Rhabdoviridae family as members of the *Lyssavirus* genus. Lyssaviruses are neurotropic, single-stranded ribonucleic acid (RNA) viruses characterized by a bullet-shaped morphology, a tightly coiled nucleocapsid, and five structural proteins. In keeping with other nonsegmented RNA viruses that have negative-sense polarity, genome replication and protein synthesis occur within the cytoplasm of infected cells under the direction of an RNA-dependent viral polymerase.

There are eleven recognized species of lyssaviruses that cause rabies, but only one species is formally called the *rabies virus*. Each species is further subdivided into phylogenetically distinct variants that are host-adapted to the mammalian reservoirs in which they circulate. The phenomenon known as *spillover* occurs when a variant adapted to one host species (such as the dog) infects another species (e.g., human) to which it is not adapted. Although disease in the newly infected host may result, spillover infrequently leads to sustained propagation of the variant in a new host population. Humans are poor conduits of disease transmission (naturally occurring human-to-human transmission has yet to be definitively established) and thus are considered dead-end hosts.

PATHOPHYSIOLOGY

Rabies transmission usually occurs through the percutaneous bite of a rabid mammal shedding the virus in its saliva (Figure 68-3). Nonbite exposures such as scratches and licks can also lead to rabies infection, although less frequently than bites. Under atypical conditions, transmission may also occur through inhalation of highly concentrated aerosolized viral particles. Access to the nervous system is granted either through inoculation directly into peripheral nerves or via infection of surrounding tissue (e.g., muscle cells) with subsequent nerve entry at the neuromuscular junction (see Figure 68-3).

After peripheral nerve invasion, the rabies virus reaches the CNS via retrograde axoplasmic transport. Once the virus infects the ventral horn of the spinal cord and/or the dorsal root ganglia, viral amplification leads to rapid dissemination of the virus in the rostral gray matter of the spinal cord. Progression to the brain is achieved through axoplasmic transport within several ascending and descending fiber tracts, leading to early placement in the brainstem followed by retrograde diffusion into the rest of the brain. Resulting neurologic signs are considered to be primarily a product of nerve cell dysfunction as opposed to necrosis or apoptosis; however, the exact functional impairment involved is unclear.

Viral migration from the brain into peripheral sites such as the salivary glands provides a gateway for virus particles to escape from the body and invade a new host. After infection of brainstem nuclei, the facial and glossopharyngeal cranial nerves convey virus to the salivary glands via their associated ganglia. Subsequent infection of glandular epithelia results in considerable viral shedding into salivary secretions. Virions are also dispatched to ocular structures such as the cornea and retina and deposited in organs and tissues serviced by parasympathetic and sympathetic nerves, including the heart, kidneys, and liver. The iatrogenic implications of this latter phenomenon were demonstrated in 2004, when four people contracted rabies after receiving transplanted material from a then-undiagnosed rabies-infected organ donor. Rabies transmission via corneal transplants has also occurred on several occasions. Because the virus frequently accumulates in the free sensory nerve endings of nuchal tactile hair, a skin biopsy sample from this area is used as a standard diagnostic specimen.

CLINICAL FEATURES

Onset of symptoms for most rabies patients occurs 3 to 12 weeks postexposure; however, incubation periods far outside of this timeframe do occur. Multiple bite wounds, severe wounds, and bite wounds to the head, face, and neck are associated with shorter incubation times and should therefore be considered when assessing the urgency of the need for PEP. Incubation periods a year or more have been described in a few cases of human infection, and therefore rabies PEP should be reasonably considered regardless of the amount of time that has elapsed since an exposure occurred.

Rabies has two clinical manifestations: the encephalitic form (or furious rabies) and the paralytic form (or dumb rabies). Encephalitic rabies is the most common form overall, although the majority of patients infected by vampire bats exhibit the

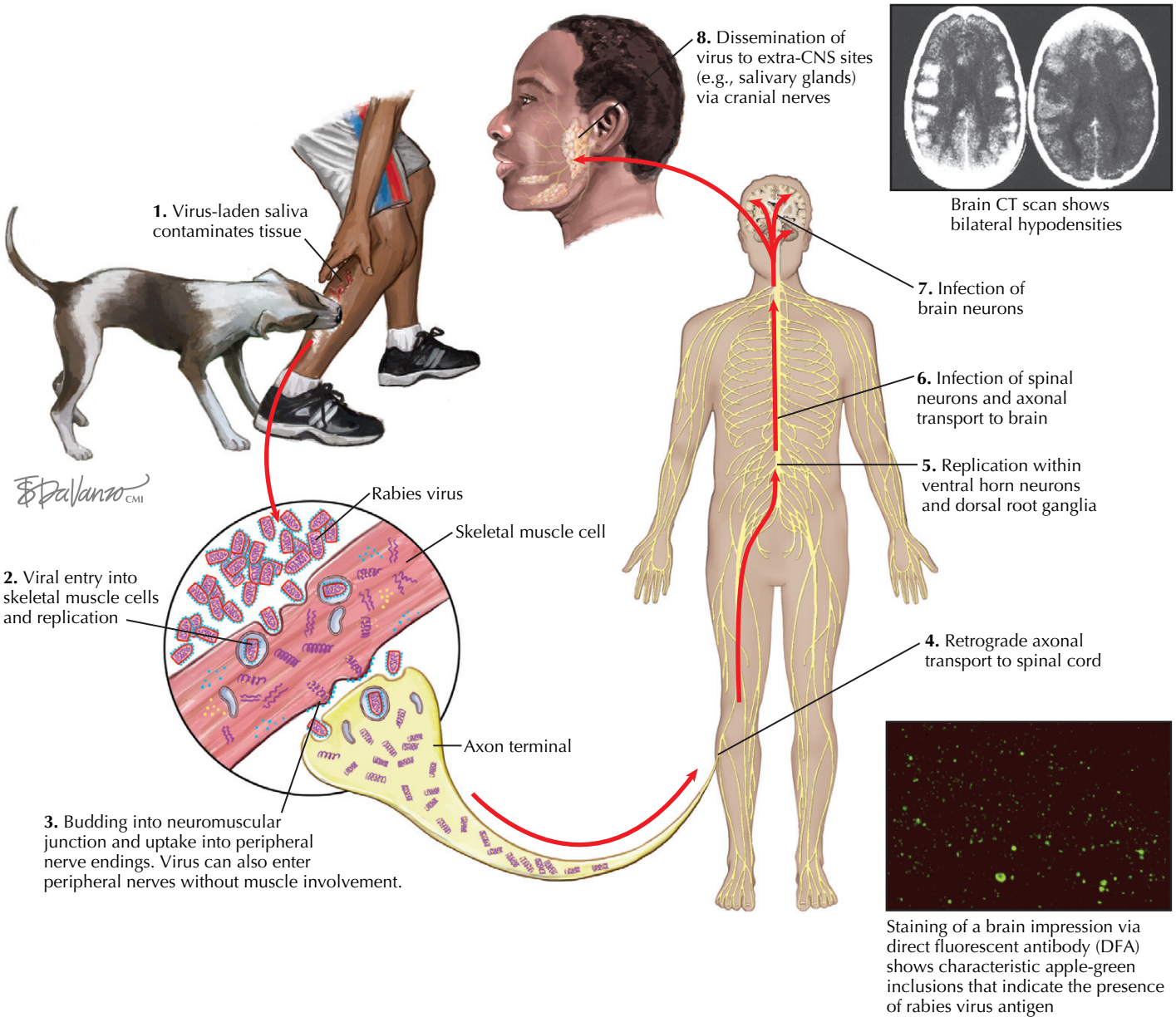


Figure 68-3 Pathophysiology of rabies. *(Computed tomography and direct fluorescent antibody courtesy Centers for Disease Control and Prevention.)*

paralytic form for reasons that remain unknown. Prodromal signs and symptoms for both are nonspecific and include fever, chills, malaise, and headache. Paresthesias on the part of the body that received the bite and pain and/or pruritus at the site of the bite wound that is unrelated to the injury itself are also common features.

Encephalitic rabies is characterized by altered mental status, agitation, hyperreactivity to sensory stimuli, intermittent consciousness, myoclonus, and muscle tremors. Also featured are signs indicative of autonomic neuropathy that include hypersalivation, mydriasis, and excessive lacrimation. Dysphagia and hydrophobia are cardinal sequelae; affected patients often react fearfully when offered water and exhibit inspiratory laryngeal spasms. Aerophobia is also frequently observed, as reflected by an exaggerated response to air currents passing over the skin (commonly referred to as the "fan test"). Seizures may occur but are not typical. Paralysis leading to coma usually occurs within 10 to 14 days, with death ensuing shortly thereafter and frequently precipitated by multiple organ failure.

In paralytic rabies, patients initially develop ascending muscle weakness that rapidly progresses to flaccid paralysis. Mental status is often unremarkable at the onset, hydrophobic spasms are less likely to be present, and patients may be unable to speak because of laryngeal muscle weakness—an occurrence that can interfere with obtaining an animal bite history and therefore complicate a clinical diagnosis. Peripheral neuropathy may be

the cause of the muscle weakness seen in this form. Patients with the paralytic form overall tend to have longer periods of survival than patients exhibiting encephalitic rabies.

DIFFERENTIAL DIAGNOSIS

Viral encephalitides produce preliminary laboratory findings and clinical signs consistent with rabies. In particular, neuroinvasive arboviral diseases including those caused by California serogroup, equine encephalitis, and West Nile viruses are important differential diagnoses for rabies. Occurrence of these illnesses increases in late summer, which slightly resembles the seasonal pattern seen in bat-associated rabies in the United States. Serologic testing to rule out these diseases before testing for rabies (antemortem) is especially indicated if an encephalitic patient is older than age 50 years, lacks an animal exposure history, and resides in or has recently traveled to an area where West Nile disease and other mosquito-borne encephalitides are endemic.

Other acute neurologic diseases may be mistaken for rabies because of their epidemiologic link to animal exposures. Tetanus, which occurs secondarily to animal bites and other contaminated wounds, causes sustained muscle rigidity that differs from the spasms expressed in encephalitic rabies and the flaccidity expressed in paralytic rabies. In addition, altered mental status is not a typical feature of tetanus. Herpes B infection usually is the result of bites or scratches from macaque monkeys, and skin vesicles at the bite wound are a common manifestation. Incubation periods for both tetanus and herpes B are generally shorter than for rabies. Severe forms of brucellosis, leptospirosis, and toxoplasmosis are other zoonoses associated with encephalopathy but usually produce systemic sequelae that rabies does not.

Another differential diagnosis is acute disseminated encephalomyelitis (ADEM), which is an immune-mediated disease triggered by exanthematous viral and bacterial infections including measles, varicella-zoster, herpes simplex, and Rocky Mountain spotted fever. Less frequently, ADEM also occurs in association with certain vaccines, including those against rabies, smallpox, and measles. Signs of ADEM generally arise 1 to 20 days after a preceding illness or 1 to 3 weeks after vaccination is initiated. Rabies vaccines derived from neural tissue carry a higher risk for causing ADEM than do rabies cell-culture vaccines. Magnetic resonance imaging (MRI) findings suggestive of diffuse or multifocal demyelination in the CNS along with cortical signs such as aphasia, cortical blindness, and seizures are more characteristic of ADEM than rabies.

A condition that clinically mirrors paralytic rabies is Guillain-Barré syndrome (GBS). Demyelination of peripheral nerves and axonal degeneration are features of both. As with ADEM, patients with GBS usually have a recent history of vaccination or febrile illness. Patients with postinfection GBS may exhibit signs associated with the precipitating infection (e.g., gastroenteritis), whereas localized pruritus and pain occurring in the prodromal phase favor a rabies diagnosis.

A psychosomatic condition termed *rabies hysteria* has been ascribed to individuals whose belief in having the disease leads them to exhibit rabieslike signs of aggression, swallowing difficulty, and other behavioral patterns. Objective evidence, such as fever and cerebrospinal fluid pleocytosis, that points to an encephalomyelitic infection is usually absent in these patients, as is the steady progressiveness that exemplifies the clinical course of rabies disease.

DIAGNOSTIC APPROACH

Rabies should be suspected in any person with an animal exposure history who has an unexplained encephalitis or myelitis. It should be noted that the lack of an elicited exposure history should not preclude suspicion, because absent exposure histories are common in rabies patients. Recent travel to or emigration from a rabies-endemic area should also elevate suspicion. Progressive worsening of neurologic signs over a period of days is an important positive indicator of disease.

Facilities capable of conducting human rabies testing are limited to a few reference laboratories. Most human rabies testing in the United States and Canada is conducted by the rabies laboratories at the Centers for Disease Control and Prevention (CDC) and the Canadian Food Inspection Agency, respectively. Once rabies is suspected, consultation with state or provincial health departments is advisable. Other, more likely causes should be ruled out before resources are expended in rabies testing. However, laboratory testing should be pursued soon after the disease is suspected to ensure that persons potentially exposed to infectious material can take appropriate actions and safeguards.

For antemortem diagnosis, specimens used to confirm rabies include serum, cerebrospinal fluid, saliva, and neck skin biopsy specimen. A brain biopsy specimen may also be used for antemortem diagnosis; however, its collection is not recommended because its diagnostic value is outweighed by associated risks to the patient. Serum and cerebrospinal fluid are examined for the presence of rabies virus antibody via indirect fluorescent antibody and virus neutralization tests. Detection of viral antigen in a neck skin biopsy specimen is achieved through direct fluorescent antibody testing, and reverse transcription–polymerase chain reaction (RT-PCR) is used to detect the presence of viral RNA in both saliva and skin. Repeat testing may be necessary to rule out rabies if negative laboratory findings exist in the presence of strong clinical and epidemiologic evidence.

In deceased patients, brain tissue is the standard specimen for diagnosis. Direct fluorescent antibody testing is used to detect viral antigen in the brainstem, cerebellum, and hippocampus.

TREATMENT

There is no standard treatment for rabies besides palliative support, which includes appropriately applied analgesia, sedation, and assisted ventilation. Given the poor prognosis, careful consideration should be given before pursuing aggressive treatment measures. Experimental therapeutic approaches have been used to treat human cases, including one patient in Wisconsin who successfully recovered from the disease. Treatment for this patient included antiviral therapy using ribavirin and coma induction using benzodiazepines and barbiturates, with ketamine and amantadine used to prevent excitotoxicity. Neither rabies immunoglobulin nor vaccine was administered before or after illness. To date, this patient is the only documented

survivor of rabies who had not received PEP or been previously vaccinated against rabies.

PREVENTION

Rabies in humans and animals is highly preventable through vaccination and, when applicable, passive immunization. There are currently two U.S. Food and Drug (FDA)–approved rabies vaccines available in North America: the human diploid cell vaccine (HDCV) and purified chick embryo cell vaccine (PCECV). These biologics are used for both preexposure prophylaxis and PEP.

Preexposure Prophylaxis

In areas where terrestrial animal rabies is present, occupational groups with frequent exposure to animals (e.g., veterinarians, wildlife workers, animal rehabilitators), or individuals engaged in activities that put them at risk of wildlife animal contact (e.g., ecotourists, cavers) should be vaccinated preventively, as should laboratory workers who work closely with the agent. Travelers who plan long-term travel to enzootic areas (e.g., expatriates and their young children) should also consider preexposure immunization. This recommendation also applies to travelers who are planning activities in settings where bats are abundant. Tiered recommendations for preexposure immunization for travelers are based on the global distribution of the principal reservoirs and vectors of rabies (see Figure 68-1).

For preexposure immunization, a 1-mL dose of rabies vaccine (either HDCV or PCECV) should be injected intramuscularly (IM) in the deltoid (or outer thigh, in children) on days 0, 7, and 21 (or 28). After primary immunization, boosters may be later indicated for individuals continuously or frequently at risk for inapparent rabies exposures, such as those encountered by rabies laboratory workers or bat handlers. For such occupational groups, antibody titers should be monitored using the rapid fluorescent focus inhibition test (RFFIT) every 6 months or 2 years depending on the individual's risk category; a 1-mL booster is indicated if tested serum fails to exhibit complete virus neutralization at the 1:5 dilution. Periodic titer checks and booster shots are not recommended for individuals who are infrequently exposed to rabies and have a high likelihood of being aware of such exposures when they occur.

During 2007 to 2009, the supply of HDCV and PCEC was limited owing to production constraints. As a result, preexposure rabies vaccination was restricted for most people in the United States and Canada, including overseas travelers. Exceptions included high-risk occupational groups such as animal control officers and rabies laboratorians. However, vaccine remained available for PEP for individuals possibly exposed to rabies. For the latest update on availability and access to rabies vaccine, consult www.cdc.gov/rabies/news/RabVaxupdate.html.

Postexposure Prophylaxis

To appropriately manage a potential rabies exposure, the risk of infection should be thoroughly assessed. Administration of rabies PEP is generally considered a medical urgency, not a medical emergency. When feasible, rabies transmission should be ruled out by having the exposing animal either euthanized and tested for rabies or—in the case of dogs, cats, and ferrets—confined and observed for any neurologic signs that appear within 10 days. In the absence of a negative animal rabies diagnosis, any patient that has been bitten by a wild terrestrial carnivore (e.g. raccoons, skunks, foxes) should be suspected of rabies virus exposure and managed accordingly. State or local public health authorities can facilitate animal rabies testing and assist in conducting exposure risk assessments.

Travelers potentially exposed to rabies should contact local health authorities immediately for advice about the local availability of rabies PEP. Because RIG and/or rabies vaccine may not be available in the destination country, before travel the individual should have a strategy in place for responding to a possible exposure. This strategy may require the traveler to fly to a different country to obtain the appropriate care.

Any mammalian bite or scratch should receive prompt local first aid by thorough cleansing of the wound with copious amounts of soap, water, and a virucidal agent such as povidone iodine. Wound cleansing is considered an important component of rabies PEP, as it reduces tissue contact with infectious material. In unvaccinated patients with severe wounds, suturing should be delayed to allow infiltration of the wound with RIG and to prevent further dissemination of the virus throughout the traumatized tissue. The recommended protocol for PEP in immunized and nonimmunized patients differs (Figure 68-4).

POSTEXPOSURE PROPHYLAXIS FOR PREVIOUSLY IMMUNIZED PATIENTS

PEP is indicated regardless of prior vaccination history. For patients who have previously recieved a full course of PreP or PEP with PCECV, HDCV, or a comparable vaccine, PEP consists of two booster doses of rabies vaccine each given IM in the deltoid on days 0 and 3 in addition to wound cleansing. RIG should not be administered to previously vaccinated patients. Patients that were last vaccinated before the year 1980 (when lower-potency rabies vaccines were used) may not have adequate immunity against the virus to safely qualify for a 2-dose course of PEP vaccination. In the absence of a documented history of an adequate antibody titer, it is advisable to manage this subset of patients identically to previously unvaccinated patients.

POSTEXPOSURE PROPHYLAXIS FOR NONIMMUNIZED PATIENTS

In previously unvaccinated patients, recommended PEP consists of one dose of human RIG (HRIG) (20 IU/kg body weight) given on day 0 and a series of four 1-mL injections of vaccine given IM on days 0, 3, 7, and 14 (see Figure 68-4). HRIG should be infiltrated in and around the wound(s), with any remaining volume given IM at a site distant to vaccine administration. The deltoid is the recommended injection site for vaccine; in children, the vastus lateralis is another acceptable location. Neither adults nor children should be given vaccine in the gluteus, and RIG and vaccine should not be administered in the same deltoid. The window for administering RIG can be extended up to day

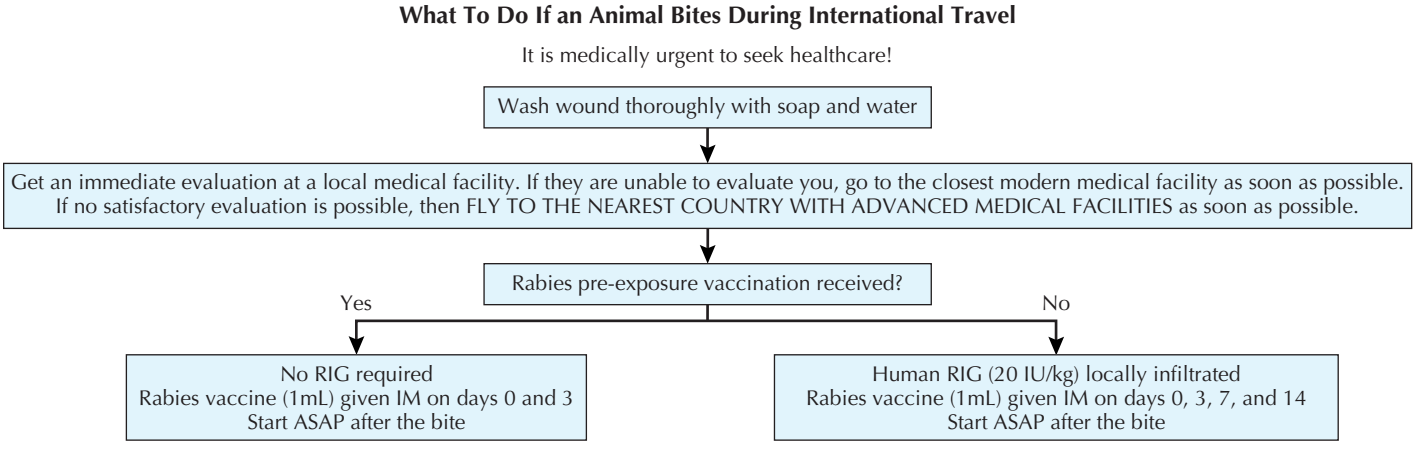


Figure 68-4 Algorithm for rabies postexposure management of travelers. *(Adapted from Keystone J, Kozarsky P, Freedman D, et al, eds:* Travel medicine, *ed 2, Philadelphia, 2008, Elsevier.)*

7 if not given when vaccination was initiated, but after that time RIG is not indicated owing to its likely interference with active immunity. Minor deviations of the vaccine schedule have not been shown to adversely influence the effectiveness of prophylaxis; however, adherence to the recommended schedule is advised whenever possible. If substantial schedule deviations have occurred, serologic testing using the RFFIT 7 to 14 days after the last dose is indicated to ensure that an adequate antibody titer has been reached.

Immunocompromised patients should receive, in addition to RIG and wound cleansing, a 5-dose series of rabies vaccination on days 0, 3, 7, 14, and 28. Individuals that have HIV/AIDS or recipients of chemotherapy, antimalarials, and other immunosuppressive medications are included in this group. Postvaccination serological testing should be performed on these patients 7 to 14 days after the day 28 vaccine dose, to verify an adequate antibody response. Placement of RIG and vaccine in these patients is the same as it is in healthy patients.

POSTEXPOSURE PROPHYLAXIS OVERSEAS

The first vaccines against rabies were derived from viruses extracted from the brains and spinal cords of infected animals. Some of these vaccines, also known as *Semple rabies vaccines*, are still in use in developing countries because of their low production costs relative to modern cell-culture vaccines. Therefore persons exposed to rabies while abroad may receive PEP with biologics that are not approved for use in the United States and Canada. Neural tissue vaccines are often administered in daily injections over a period of 14 to 21 days in the subcutaneous tissue overlying the stomach or upper back. Doses may be relatively high in volume (5-mL) and somewhat uncomfortable to receive. These vaccines pose a greater risk of vaccine-associated adverse events and are of lower potency than cell-culture vaccines. All attempts should be made to obtain modern cell-culture vaccines before accepting prophylaxis with these neural tissue vaccines. Other cell-culture–derived vaccines, including purified duck embryo and Vero cell vaccines, are also frequently used abroad, but they are not licensed for use in the United States. Purified equine RIG (ERIG) is frequently used in places where HRIG is unavailable. The frequency of reported adverse reactions associated with ERIG administration has been relatively low (0.8% to 6.0%), and most reactions reported are minor. Unpurified antirabies serum of equine origin may still be used in some countries where neither HRIG nor ERIG is available. More severe adverse reactions, including anaphylaxis, after antirabies serum administration have been reported.

If PEP is initiated with nonapproved biologics or regimens, a patient may require additional prophylaxis. State or provincial or local health departments should be contacted for specific advice in such cases. Serologic testing using the RFFIT may be indicated to determine whether the patient's neutralizing antibody level precludes the need for additional vaccination.

Failure to prevent rabies in PEP recipients has not occurred in the United States since cell-culture vaccines and RIG have been in routine use; however, failures have occurred abroad when biologics of low potency were used, when some deviation occurred from the recommended PEP protocol, or when RIG was not administered, was administered in insufficient amounts, or was improperly administered. Inadequate wound cleansing or administration of vaccine at incorrect anatomic sites (e.g., the gluteal area) may also be associated with ineffective PEP. In addition, substantial delays between exposure and PEP initiation increase the likelihood that disease will occur before an adequate immune response has developed.

Adverse Reactions

Patients receiving preexposure prophylaxis or PEP should be advised that they may experience local reactions after vaccination, such as pain, erythema, swelling, or itching at the injection site, or mild systemic reactions, such as headache, nausea, abdominal pain, muscle aches, and dizziness. Approximately 6% of persons receiving booster vaccinations with HDCV have reported an immune complex–like reaction characterized by urticaria, pruritus, and malaise. Fewer adverse events have

been reported in association with PCECV. If exposure to the rabies virus is a valid concern, rabies PEP should not be interrupted or discontinued because of local or mild systemic reactions to rabies vaccine.

Precautions and Contraindications

Pregnancy or age status are not contraindications for PEP. Known allergies to substances present in a particular vaccine (such as egg protein in the case of PCECV) may necessitate switching the vaccine to another type.

In immunocompromised individuals, rabies vaccination may fail to generate an adequate immune response. Such patients should postpone preexposure vaccinations and consider avoiding activities for which rabies preexposure prophylaxis is indicated. If preexposure prophylaxis and/or PEP must be administered to a person of poor immune status, serology is indicated to determine whether the patient obtained an adequate rabies virus neutralizing antibody titer. In the event that no acceptable antibody response is detected, the patient should be managed in consultation with his or her physician and appropriate public health officials.

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ADDITIONAL RESOURCES

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Arboviruses of Medical Importance

Theodore F. Tsai

69

ABSTRACT

Arboviruses (arthropod-borne viruses) and related zoonotic viral infections transmitted from animals to humans without the intermediate infection of a vector are important endemic causes of morbidity and mortality among residents of developed as well as developing countries, and a risk for travelers of all ages—not only in tropical locations but also in temperate locations, where they may be transmitted seasonally. More than 150 arboviruses are known to infect humans, but only a small number have been recognized to pose a significant medical and public health burden. Healthcare providers who attend international travelers will find it worthwhile to familiarize themselves with the most common of these infections for pretravel consultations, because the risk of their acquisition can be mitigated by appropriate counseling about avoiding exposure and because several are vaccine-preventable, and for posttravel consultations, because they must be considered in the differential diagnosis of travel-acquired clinical syndromes. Moreover, returned travelers infected with dengue, chikungunya, and other viruses that produce a viremia lasting several days potentially could become a source of mosquito-borne or parenteral infections that could pose a nosocomial and local public health risk.

CLINICAL SYNDROMES AND GEOGRAPHIC DISTRIBUTION

Arboviral infections can be divided arbitrarily into those causing simple febrile illnesses (with or without rash), a syndrome of prominent polyarthritis or polyarthralgias, neurologic infection, or hemorrhagic fever. Features of selected medically important or prevalent infections are described in Table 69-1 by their most common presentation; like other infections, however, their clinical spectrum may be far broader. For example, dengue and chikungunya cases may be complicated by encephalopathy or encephalitis, and both also have been associated with hemorrhagic manifestations. On the other hand, despite its name, Venezuelan equine encephalitis (VEE) develops into encephalitis in only approximately 1 in 10,000 adult cases; the majority of infections are a self-limited albeit incapacitating, even unbearable, grippelike illness.

VEE (transmitted in various subtypes in Florida and Central and South America) and Oropouche viruses, along with dengue, are responsible for a significant fraction of the febrile illnesses presenting for clinical consultation in areas of South America. Because dengue and chikungunya viruses both are transmitted in *Aedes aegypti* or *Aedes albopictus* mosquito-human (anthroponotic) epidemic cycles and share similar clinical features of acute fever and musculoskeletal symptoms, individual cases and even outbreaks of one have been mistaken for the other. But chikungunya, along with infections caused by closely related Ross River, Barmah Forest, and Mayaro (transmitted in the Caribbean and Central and South America) viruses, leads to excruciating joint pain, swelling, and immobilization, whereas intense myalgias and musculoskeletal pain characterize dengue, accounting for its colloquial name of "breakbone fever."

Sindbis virus, an alphavirus more distantly related to chikungunya virus, causes a similar if less intense polyarthritis and is an important seasonal disease of berry pickers, mushroom hunters, and other springtime trampers in the Northern European and Scandinavian woods, as well as being a common cause of sporadic febrile illnesses throughout the Middle East, Africa, and Asia.

The antigenically related flaviviruses in the Japanese encephalitis (JE) virus complex—West Nile (WN) virus, St Louis encephalitis (StLE) virus (transmitted in North and South America), and Murray Valley encephalitis virus (transmitted in Australia)—share important clinical features of a low case: infection ratio (approximately 1 : 300) and a sharply higher risk of symptomatic illness and neurologic infection with advanced age, so that elders are at greatly increased risk of severe illness and death after infection. It is important to note that the clinical presentation of WN virus infection is protean, so although the majority of cases manifest as a self-limited illness with fever and rash, hepatitis, myocarditis, pancreatitis, and retinitis also may complicate the illness.

In contrast to these mosquito-borne infections, Toscana virus is spread by phlebotomine sandflies, much smaller insects that are not excluded by conventional netting and screens and that are prevalent through the Mediterranean littoral where the virus circulates. Related phleboviruses in the same region cause a 2- to 3-day febrile illness, sandfly fever, and Toscana virus also can produce a neurologic infection. In areas of Italy, Toscana virus rivals the enteroviruses as a cause of summertime aseptic meningitis necessitating hospitalization. More detailed clinical descriptions of these and other arboviral infections can be found in infectious disease or tropical medicine texts.

RISK FACTORS

Arboviruses are transmitted within specific vector-host cycles (e.g., mosquito-bird, tick-mammal) (Figure 69-1), so the geographic and specific ecologic locations where the infections are transmitted, their seasonality, and individual host and behavioral risk factors—including even the time of day of activities—all are relevant to the risk of infection. Consequently, travelers can be counseled to avoid those particular circumstances when and where infections are more likely to occur. For example, the location that poses the greatest risk for acquiring JE virus during travel to Asia is a rural location because the principal viral vector, *Culex tritaeniorhyncus*, uses flooded ground pools such as

Table 69-1 Selected Medically Important Arboviruses

CLINICAL SYNDROME*	VIRUS/ TAXONOMIC FAMILY	GEOGRAPHIC DISTRIBUTION	TRANSMISSION†	INCUBATION PERIOD
Febrile illness	Dengue 1-4/Flaviviridae	Tropical and subtropical Central and South America, Africa, Asia, Australia, Oceania	Mosquito–anthroponotic‡: urban, peridomestic	2-7 days
	Oropouche/Bunyaviridae	Central and South America	Mosquito and midge–vertebrates, anthroponotic: sylvatic, periurban	
Polyarthritis	Sindbis/Togaviridae	Europe, Africa, Asia, Australia	Mosquito–bird: sylvatic	2-7 days
	Chikungunya/Togaviridae	Africa, Asia, Europe	Mosquito–anthroponotic: urban, peridomestic	2-10 days
	Ross River/Togaviridae	Australia, Oceania	Mosquito–mammal: sylvatic, suburban	3-21 days
Neurologic infection	Tick-borne encephalitis/ Flaviviridae	Europe, Asia	Tick–mammal, bird: sylvatic Oral: milk products	3-7 days
	West Nile/Flaviviridae	Cosmopolitan	Mosquito–bird: sylvatic, periurban	3-10 days
	Japanese encephalitis/ Flaviviridae	Asia, Australia, Oceania	Mosquito–vertebrate: rural	4-14 days
	Toscana/Bunyaviridae	Europe, Africa	Sandfly–vertebrate: periurban	2-7 days
Hemorrhagic fever	Yellow fever/Flaviviridae	Central and South America, Africa	Mosquito–mammal, anthroponotic: rural, urban	3-6 days
	Rift Valley Fever/ Bunyaviridae	Middle East, Africa	Mosquito–vertebrate, anthroponotic: rural, periurban	3-5 days

*The diseases listed are displayed by their principal clinical presentation; other manifestations or complications may occur.
†Reports have included nosocomial transmission by needlestick, blood transfusion (dengue, West Nile viruses), or transplantation (West Nile virus); transmission by direct contact with infected animals or meat (tick-borne encephalitis, Rift Valley Fever viruses); transmission through breastfeeding (yellow fever virus); and vertical transmission to the fetus (dengue, Japanese encephalitis, West Nile, Western equine encephalitis viruses, and possibly Colorado tick fever and Ross River viruses).
‡Transmitted from human to human by the vector.

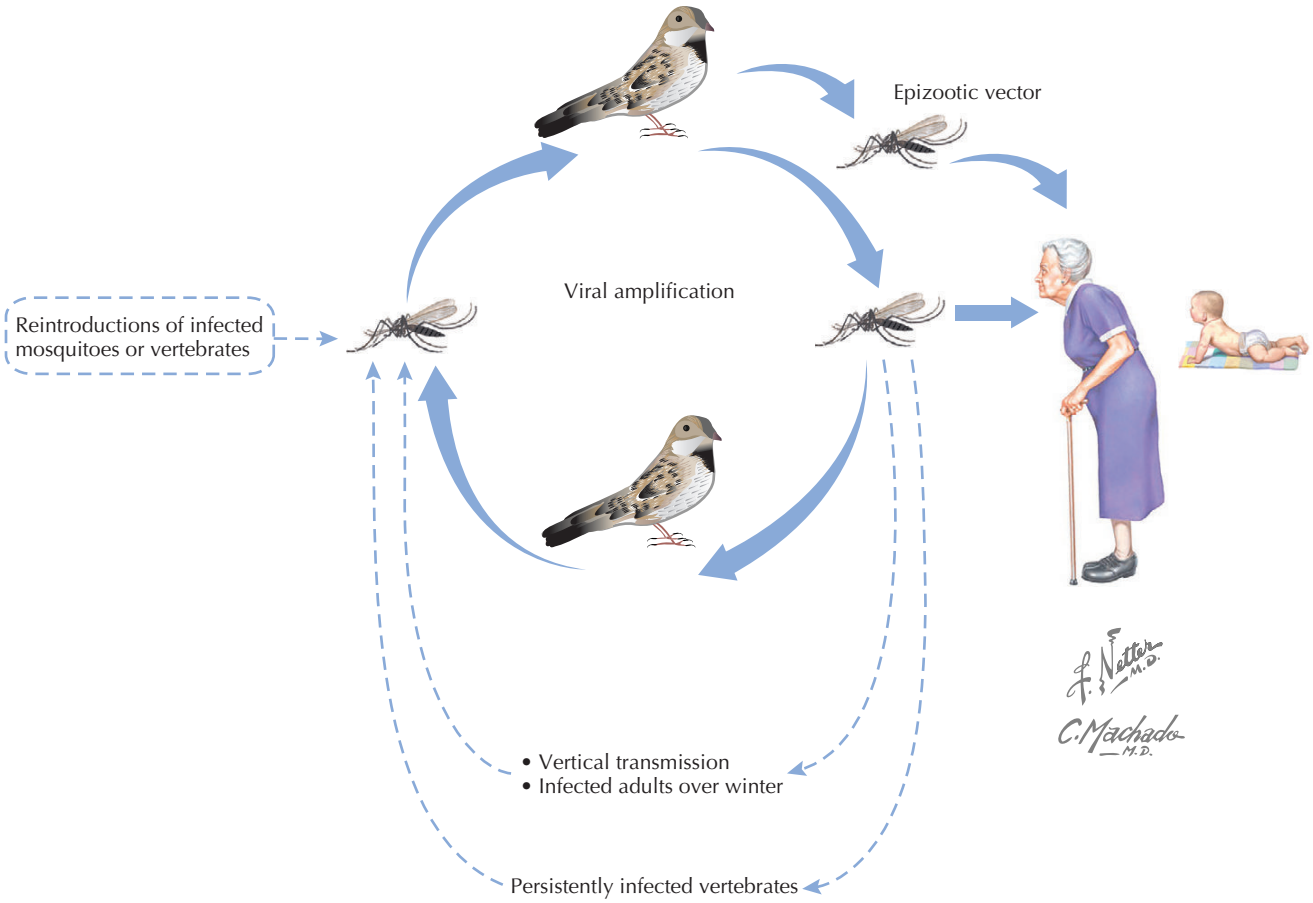
rice paddies in its breeding cycle and because it feeds on pigs and aquatic birds that function as viral amplifying hosts. The mosquito vector is most active at twilight and outdoors, so avoiding rural areas and outdoor activities in the early evening can greatly reduce the risk of acquiring infection. Furthermore, because JE is transmitted seasonally in temperate areas of Asia, traveling outside the summer months can effectively eliminate any risk of acquiring the infection.

In contrast, dengue virus is transmitted between humans by tropical and subtropical *Ae. aegypti* mosquitoes, which lays eggs in small collections of clean water such as flower dishes and discarded containers that can hold rainwater. Consequently the vectors are abundant in the peridomestic and urban environments, and dengue outbreaks in tropical cities are common. Because the mosquito feeds most actively during the day and also indoors—even in modern hotels—infection is more difficult to avoid.

Providers would do well to beware the nuances of local transmission when consulting maps and descriptions defining transmission risk. In particular, tick-borne diseases have been described as "diseases of place," meaning that they usually are transmitted in highly specific locations within a region (e.g., below certain elevations and where temperature and humidity provide a suitable microclimate, often at forest ecotones). General recommendations, such as references to rural and urban locations, can provide only a rough guide. For example, although tick-borne encephalitis (TBE) virus is spread by ticks in wooded locations and vaccination is recommended mainly for hikers, campers, and others visiting sylvatic locations, cases have been acquired in the Vienna Woods, the city being an otherwise urban destination (see Chapter 72). Maps and other descriptions of areas with enzootic transmission often rely on old vector surveys or serosurveys or passive surveillance, and although they may forewarn risk, their revision usually follows reports of human cases in new areas. Moreover, the emergence of arboviral outbreaks in specific locations within their geographic range is unpredictable.

Besides the particularities and changeability of locations where arboviruses outbreaks occur, the intensity of their transmission and disease incidence can fluctuate significantly from year to year. In addition, some viruses, exemplified by chikungunya and the related alphavirus, o'nyong-nyong virus, exhibit years- or even decades-long intervals of obscurity—to the point that they seem to have vanished, probably into cryptic enzootic cycles—followed by emergence with epidemic spread. These short- and longer-term fluctuations are perhaps understandable in view of the complex transmission cycles of arboviruses and their dependence on the biology of vectors, intermediate vertebrate hosts, and human factors and, in turn, the impact of climate and weather on those elements. A number of models have been developed to identify climatic and weather phenomena that predict hyperendemic or epidemic transmission to aid arboviral control programs.

Both innate and acquired host factors have been characterized as risk factors for individual arboviral diseases. Among innate factors, observations from epidemics indicate a lower risk for



In a typical arboviral transmission cycle, the virus is amplified among vertebrates, frequently birds, and infected enzootic vectors also infect humans. In the transmission cycle of some viruses, an epizootic vector is required to bridge the amplification cycle to humans; this circumstance applies when the enzootic vector does not feed on humans, necessitating other species with more catholic feeding habits to acquire the infection from the vertebrate amplifying host and, on a subsequent feeding, to infect humans (e.g., eastern equine encephalitis). A number of mechanisms allow viruses to survive periods when they are not actively amplified. Some viruses are transmitted vertically in infected mosquito eggs; infected adults can survive in protected settings over extended periods, including winters in temperate climates; persistently infected vertebrates (e.g., bats) can re-enter the virus amplification cycle locally; or the virus can be re-introduced from a distance by windblown vectors or migratory viremic vertebrates.

Figure 69-1 Generic arbovirus transmission cycle.

dengue hemorrhagic fever and for yellow fever (YF) in persons of African descent compared with Caucasians; the proportion of alphavirus infections leading to arthritis typically is higher in females than in males; and a deletion mutation of *CCR5* increases risk of severe illness from WN virus and possibly other flaviviruses, but not risk of infection itself. Age is a major determinant of risk for neurologic infection; infants are at increased risk for encephalitis caused by eastern equine encephalitis, western equine encephalitis, and VEE viruses and from JE-related flaviviruses (e.g., StLE, WN viruses). These infections also have a strikingly higher risk in persons of advanced age. Human immunodeficiency virus (HIV) infection has been associated anecdotally with increased severity of YF; however, in the Western Hemisphere and in Southeast Asian locations where both dengue and HIV infections are epidemic, HIV infection has not been identified as a risk factor for more severe dengue or hemorrhagic fever. On the contrary, laboratory evidence that flaviviruses (including GB virus [GBV-C]) can modulate expression of CD4 suggests that these concurrent infections could inhibit HIV replication. Chronic diseases in general, however, have been associated with an increased risk for developing neurologic disease after infection with WN or StLE virus. Poor nutrition has been a protective factor against risk of hemorrhagic fever associated with dengue, supporting the role of a host immunopathologic response in the severity of disease.

CLINICAL FEATURES AND DIAGNOSTIC APPROACH

Although establishing a specific diagnosis of an arboviral infection may help to guide appropriate therapy of other infections, no approved antivirals or immunotherapies are approved for any arboviral infection, and therapy relies on supportive and symptomatic care.

The clinical course of most arboviral infections is monophasic; however, a number are associated with a recurrence of symptoms after an initial defervescence or may exhibit a relapsing course (Table 69-2). Recognition of such symptoms as delayed

Table 69-2 Delayed Manifestations of Selected Arboviral Infections

DISEASE	DELAYED OR RELAPSING MANIFESTATION*	INTERVAL AFTER INITIAL DEFERVESCENCE
Tick-borne encephalitis, louping ill	Meningitis, encephalitis, polyneuritis	1-20 days
Russian spring-summer encephalitis	Chronic progressive encephalitis	Months to years
Kyasanur Forest disease	Meningoencephalitis	9-21 days
Omsk hemorrhagic fever	Meningismus, hemorrhages	3-18 days
Rift Valley fever	Retinitis, uveitis, optic atrophy, meningoencephalitis	1-3 weeks
Alphaviral polyarthropathy	Polyarthralgias, polyarthritis	Months to years

*As distinct from sequelae of illness.

manifestations of an earlier illness may be important in returned travelers.

The clinical features of illness in the returning traveler mapped against the places visited and activities during travel can reduce the number of agents to be included in a differential diagnosis and that can be confirmed by laboratory tests. Few exhibit pathognomonic clinical features; however, the differential diagnosis of dengue among other systemic febrile illnesses can be aided by features such as rash, retroorbital pain, myalgia, and leukopenia and thrombocytopenia, although the rash may be difficult to detect in persons with darker skin pigmentation. Even entire outbreaks of dengue have been mistaken for measles epidemics. The differential diagnosis of the alphavirus-associated polyarthritis syndrome includes rubella, parvovirus B19, hepatitis B, and mycoplasma infections that also may be acquired outside the context of travel. JE and related flaviviruses produce a frequently severe but not distinctive panencephalitis with vomiting, an altered state of consciousness, and various pyramidal and extrapyramidal motor abnormalities; radiologic imaging frequently shows thalamic lesions. However, it is likely that only the most severe neurologic infections are identified among returned travelers, and more aggressive laboratory testing of ill travelers would identify others.

Because of the long time interval between acquisition of illness and posttravel consultation in most cases, viral isolation or specific diagnosis by polymerase chain reaction (PCR) may be fruitless, and serologic testing usually is the best option to achieve a specific diagnosis. Nevertheless, PCR assays are available for most important arboviral infections, and blood, cerebrospinal fluid from patients with neurologic infection, and biopsy specimens or other tissues can be examined for evidence of viral genomic material. In the United States, specimens should be sent to state health departments, who may refer certain specimens to the Centers for Disease Control and Prevention (CDC) for special testing. Immunoglobulin M (IgM) determination by capture enzyme-linked immunosorbent assay (ELISA) is the preferred serologic assay and usually yields a specific result. Prior related infections, however, can obfuscate the diagnosis of flaviviral infections, and more specific neutralization tests may be needed.

PREVENTION AND CONTROL

Routine childhood vaccination with YF and JE vaccines is a cornerstone of prevention in regions where the diseases are transmitted in an endemic pattern. Development of a quadrivalent dengue vaccine has been delayed because of technical difficulties, but several are in clinical development. In addition, other experimental arboviral vaccines for use in laboratory workers have been produced by the U.S. military.

For most other arboviral infections, epidemics have been too unpredictable in their size, location, and frequency to have justified vaccine development, and public health prevention has focused on controlling vectors by source reduction, larviciding, and routine and emergency adulticiding.

YF, dengue, chikungunya, and certain other viruses can be spread anthroponotically because viremias are sustained at a high enough level and for a sufficient interval that feeding mosquitoes have chance to become infected during the incubation period or early in the illness. Viremic returning travelers can initiate local chains of transmission if bitten by vectors that are capable of spreading the infection, so it is imperative that cases be reported to public health authorities. In the United States, dengue outbreaks from imported cases have occurred on Maui, in Key West, and along the Texas-Mexico border; in Northern Queensland, Australia and in Taiwan, recurring dengue outbreaks are a consequence of the high volume of travel to neighboring areas with endemic transmission; and, in Europe, local chikungunya virus transmission in Italy most likely was initiated by a returning viremic traveler. It has been speculated that WN virus may have been introduced to the United States in this way. Consequently, patients who are acutely ill (and potentially viremic) with these infections should be protected from mosquito bites, blood-borne pathogen precautions should be followed in their care, and cases should be reported at the earliest suspicion to local health authorities.

During pretravel counseling, consideration of a hierarchy of avoidance—cancelling or delaying travel, altering an itinerary, and changing behavior—is more likely to be important for travelers with special circumstances (e.g., pregnancy, immunocompromising conditions, older age) that might place them at risk of more serious disease should they become infected, but others also may take pause when considering travel into an area with an ongoing epidemic. Epidemics of YF, chikungunya, dengue, Oropouche virus infection, Rift Valley fever, and others may occur with sufficiently high attack rates that ordinary travelers may choose to alter their plans to avoid that elevated risk. Travel health advisors can access current reports of epidemic activity at a number of websites, listed later.

Travelers can mitigate their risk of exposure by sleeping under mosquito netting, wearing long-sleeved shirts and long pants to reduce mosquito bites, wearing light-colored clothing

that will facilitate the removal of ticks, wearing hats, and overlapping socks over pants to prevent tick attachment. Visitors to areas that are tick infested should check themselves frequently to remove ticks.

Repellents

Repellents provide another important means of preventing bites and infection. Permethrin, a synthetic pyrethroid insecticide and acaricide (kills mites and ticks), sprayed onto clothing and equipment according to package directions can reduce mosquito and tick bites, and if all in a travel group wear permethrin-impregnated clothing, a "herd effect" can be achieved. Although field trials have demonstrated that insecticide-impregnated mosquito nets have been effective against malaria, their impact on reducing arboviral infections has not been shown as conclusively (as only nocturnally active, indoor biting vectors would be affected). Permethrin is available for topical use in a 5% cream formulation intended to treat scabies. In that formulation, it is poorly absorbed through the skin, is rapidly eliminated, and has been used in infants as young as 2 months of age. However, it is indicated only for one or two applications for scabies treatment and is not recommended currently to reduce insect or tick exposure.

Recommendations for the use of various repellents are available from a number of sources. Picaridin and N,N-diethyl-*m*-toluamide (DEET) are the most commonly recommended repellents applied to skin. Whereas DEET has been effectively used as a repellent for decades, concerns about neurotoxicity have led to caution in its use, especially in children. Various organizations have issued guidelines on use of DEET in children to minimize any hypothetical risk, including selecting products with lower concentrations of active ingredient (e.g., 10%) and avoiding use in infants younger than 2 months old. One assessment concluded that the risks of subacute or chronic use of 25% DEET and 15% picaridin in children younger than 12 years old were similar. Complicating recommendations, oxybenzone, a common ingredient in sunscreen that may be used concurrently with repellents, increases percutaneous absorption of DEET but inhibits absorption of picaridin. Oil of lemon eucalyptus oil, a popular herbal repellent, also has shown activity similar to low concentrations of DEET for some mosquito species. This illustrates the often overlooked point that repellent activity against individual arthropod species varies. Recommendations for the use of various repellents are available from a number of sources.

Vaccination

Short of avoidance, vaccination is the most reliable means for preventing travel-associated arboviral infections. Vaccines are licensed internationally for YF, JE, and TBE, and others are produced locally (e.g., Kyasanar Forest disease in India) or are available on a compassionate, experimental use basis (e.g., VEE).

YF vaccine is a live-attenuated virus grown in embryonated eggs. A single subcutaneous dose is highly immunogenic, has been efficacious in preventing the disease in epidemic settings, and provides immunity at protective levels for decades, although by World Health Organization Health (WHO) international health regulations, vaccination must be renewed every 10 years. The vaccine is indicated for travelers to areas with risk for endemic or epidemic transmission in Central and South America and in Africa; furthermore, certain countries (mainly in Asia) require an International Certificate of Vaccination or Prophylaxis for travelers coming from an area where the virus is transmitted, even if in transit. The vaccine can cause severe, even fatal, adverse events (see Chapter 64 for details).

Inactivated JE virus vaccines made from infected mouse brain tissue or from cell cultures are licensed internationally. The cell culture–derived vaccine was licensed in 2007 on the basis of accepted immunologic criteria and is more immunogenic after two doses than three doses of the mouse brain–derived vaccine. As important, whereas the mouse brain–derived vaccine is associated with severe hypersensitivity reactions, including facial angioedema, and also has been linked to a risk of acute disseminated encephalomyelitis, the cell culture–derived vaccine is significantly less reactogenic, and no safety signals have emerged thus far from the clinical trials or limited commercial experience. The largest manufacturer of the mouse brain–derived vaccine has stopped production, but stockpiled doses remain. Until a pediatric indication is approved, the cell culture–derived vaccine is indicated only for adults older than 17 years of age; therefore many practitioners have reserved available mouse brain–derived vaccine doses for use in children.

Because JE is a prevalent and serious neurologic infection in Asia, leading to a fatal outcome in one third of cases and neurologic sequelae in another third, routine pediatric vaccination is a component of public health programs in countries that can afford the vaccine. GAVI recently has advanced the vaccine's introduction to several countries. Because JE has been an uncommon yet potentially devastating disease of travelers, risk assessments differ and recommendations for vaccination of travelers vary by country. In general, vaccination is recommended for expatriates, persons with extended itineraries (e.g., longer than 1 month), or persons with itineraries that place them at greater risk of infection (e.g., travel to rural areas and outdoor activities). In deciding whether to use the vaccine, travelers and their advisors face the difficult and highly individual decision regarding whether it is worthwhile to prevent a low-risk event that may have extreme consequences. Clinical trials showed that 1 week after receiving the second dose of the cell culture–derived vaccine, 97% of vaccinees developed a seroprotective response, whereas approximately 40% achieved protective antibody titers 1 month after the first dose. Protective antibody levels are maintained for at least 1 year, and boosters are recommended at 12- to 24-month intervals. A clinical study showed that the cell culture–derived vaccine may be given concurrently with hepatitis A vaccine without affecting the efficacy of either vaccine.

Two TBE vaccines are licensed in Europe to prevent locally acquired infections in Central and Western Europe and in Scandinavia. Like infection with other flaviviruses, the majority of TBE viral infections are asymptomatic, and the risk for neurologic infection (e.g., meningoencephalitis, cranial or peripheral mononeuritis or polyneuritis) increases with age. The tick vector, *Ixodes ricinus*, also transmits agents of Lyme disease, anaplasmosis, and babesiosis, as well as several other pathogenic arboviruses, and the relatively high level of awareness

surrounding TBE and associated infections has resulted in routine TBE vaccine uptake exceeding 70% in some Central European countries. WHO and authorities in certain European countries where the disease is not endemic (e.g., Spain) recommend vaccination of travelers to Central Europe whose activities place them at increased risk (e.g., camping, hiking). One of the European-licensed vaccines is available in Canada on a compassionate-use basis, but neither vaccine is licensed in the United States. Expatriates and certain travelers with a high risk of exposure can seek the vaccine locally in Europe (see Chapter 72 for details).

EVIDENCE

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Centers for Disease Control and Prevention (CDC): *Travelers' health.* Available at: wwwnc.cdc.gov/travel/default.aspx. *General, up-to-date advice on travel-associated risks and their prevention.*

Centers for Disease Control and Prevention (CDC): *Travelers' health—yellow book.* Available at: wwwnc.cdc.gov/travel/content/yellowbook/home-2010.aspx. *A standby and "bible" of travel medicine information and advice. Available in print or online. Written by CDC experts.*

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Lanciotti R, Tsai TF: Arboviruses. In Murray PR, Baron EJ, Pfaller MA, et al, eds: *Manual of clinical microbiology*, ed 10, Washington DC, American Society for Microbiology (in press). *Provides a table of all medically important arboviruses, showing geographic distribution, mode of vector spread, clinical presentation, and detailed approaches to laboratory diagnosis.*

United States Environmental Protection Agency (EPA): *New pesticide fact sheet.* Available at: www.epa.gov/opprd001/factsheets/picaridin.pdf. *The EPA regulates the use of repellents—agency information on picaridin.*

World Health Organization (WHO): *International travel and health, 2010 edition.* Available at: www.who.int/ith/en/. *Official WHO travel medicine recommendations—along with CDC Yellow Book, reflects an informed standard of practice.*

Leptospirosis

Vernon Ansdell

70

ABSTRACT

Leptospirosis is the most common zoonosis worldwide and has recently emerged as an important travel-related infection, particularly in adventure travelers to the tropics and subtropics. Characteristic symptoms may include fever, headache, myalgias, jaundice, and conjunctival suffusion, but it often manifests as a nonspecific febrile illness. Because it has a wide range of signs and symptoms, a high index of suspicion is necessary for clinicians to make an accurate diagnosis. Early treatment with an antibiotic such as doxycycline, amoxicillin, penicillin, or ceftriaxone before waiting for confirmation of the diagnosis is very important. Most cases are relatively mild and self-limited, but 5% to 10% of affected patients develop a severe, potentially life-threatening illness characterized by fever, jaundice, renal failure, bleeding, or severe pulmonary hemorrhage.

TRANSMISSION AND RISK OF INFECTION

Leptospirosis *(Leptospira interrogans)* is a spirochete infection that occurs worldwide except in polar regions. The organism survives best in warm, humid conditions and is most common in the tropics and subtropics, with many wild and domestic animal reservoirs including rats, mice, dogs, pigs, and cattle (Figure 70-1). After infection, animals may shed the organism in the urine for months or even years. Organisms proliferate in fresh water, damp soil, vegetation, and mud and survive for weeks to months.

Infection in humans occurs after exposure to animal urine, either by direct contact or, more commonly, as the result of indirect exposure to contaminated mud or water in rivers, lakes, and streams. Infection is acquired through damaged skin or via exposed mucous membranes of the nose, mouth, or eyes. Contaminated drinking water may also be a significant source of infection.

Traditionally, leptospirosis was an occupational illness (e.g., farmers, sewage workers, and miners). Recently, however, recreational exposure (e.g., of hikers, white water rafters, and triathletes) has been recognized as an important exposure risk. Leptospirosis has recently been identified as an important emerging disease in adventure travelers to the tropics and subtropics, and it is an important cause of fever in returned travelers. The majority of reported cases have been linked with travel to southeast Asia. Outbreaks of leptospirosis are becoming increasingly recognized after periods of heavy rainfall or flooding such as from hurricanes.

CLINICAL FEATURES

Leptospirosis

The incubation period is usually 5 to 14 days (range 2 to 30 days). Some human cases are probably completely asymptomatic, and over 90% of symptomatic cases are relatively mild and self-limited. The remaining cases may be severe and potentially life-threatening, however, and associated with jaundice, hemorrhage, renal failure, and myocarditis (Weil disease) or massive pulmonary hemorrhage.

The illness may be biphasic. The first or leptospiremic phase typically lasts 3 to 7 days and represents the period when organisms are present in the blood. The second or immune phase may be clinically silent or last for 4 to 30 days or longer. This phase coincides with the formation of circulating immunoglobulin M (IgM) antibodies. Aseptic meningitis (with or without symptoms) is characteristic of the immune phase and may occur in over 50% of cases (Figure 70-2).

In the milder form of leptospirosis there may be a clinically apparent, symptom-free interval of 1 to 3 days between the first and second phases. In severe cases, however, the distinction between these two phases is usually not apparent.

The acute leptospiremic phase begins abruptly with high fever (often >39° C), chills, and a severe frontal headache. Patients often report one of the worst headaches they have ever experienced. Severe muscle pain and tenderness are common, typically involving the muscles of the calves, thighs, and lower back. Conjunctival suffusion (dilatation of conjunctival vessels without inflammation or purulent discharge) is virtually pathognomonic of leptospirosis but must be distinguished from conjunctivitis. It usually appears on the third or fourth day of illness and is probably very common, although it may be mild and easily overlooked. Subconjunctival hemorrhages are often present.

A wide range of other symptoms are common and may confuse the diagnosis. Gastrointestinal symptoms include abdominal pain, anorexia, nausea, vomiting, and diarrhea. Early respiratory symptoms may include sore throat, cough, dyspnea, and chest pains. The disease often manifests as a flulike illness without the typical upper respiratory symptoms associated with influenza or other respiratory viruses. A variety of rashes are present in up to 10% to 30% of patients during the first week of illness: they may be erythematous macular, maculopapular, urticarial, petechial, or purpuric. Less common physical signs during this phase include lymphadenopathy, hepatomegaly, and splenomegaly.

The second or immune phase is characterized by aseptic meningitis and symptoms such low-grade fever, headache, neck

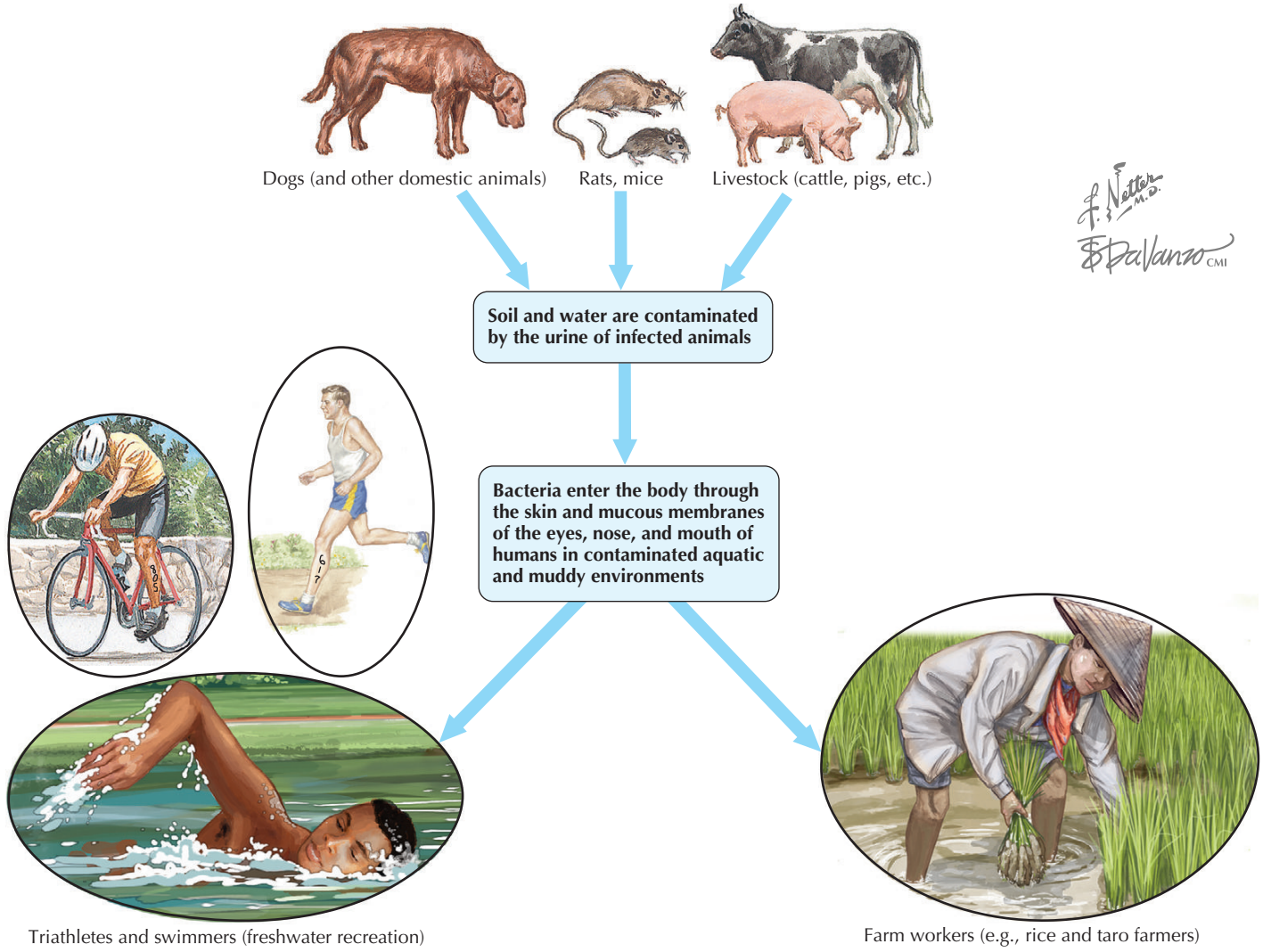

Figure 70-1 Transmission of leptospirosis.

stiffness, nausea, vomiting, and photophobia. Other clinical features during this phase may include jaundice, renal insufficiency, cardiac arrhythmias, and various pulmonary symptoms. Unilateral or bilateral uveitis characterized by iritis, iridocyclitis, and chorioretinitis may develop up to 18 months after acute infection and persist for several years.

Severe Leptospirosis

Approximately 10% of patients develop a severe, life-threatening form of the disease. Historically this was characterized by jaundice, hemorrhage, renal failure, and myocarditis and often referred to as *Weil's disease*. More recently, however, another severe form of the disease characterized by pulmonary hemorrhage has been increasingly recognized: severe pulmonary hemorrhage syndrome (SPHS). Frank hemoptysis may occur, but hemorrhage may not be apparent until after patients are intubated. It is therefore very important to suspect SPHS in patients with respiratory distress even if they do not have hemoptysis. Rapid progression to acute respiratory distress syndrome (ARDS) and high mortality are not uncommon.

The onset of severe illness is usually indistinguishable from the milder form of leptospirosis, but after 4 to 9 days there is progression to a severe, life-threatening form of the disease. Jaundice typically appears between the fifth and ninth days of illness and may last for several weeks. Bilirubin levels may be very high, but liver failure is extremely rare because severe hepatocellular damage is very unusual. Tender hepatomegaly and splenomegaly may be present. Renal insufficiency is evident within 3 to 4 days of onset. Important factors in the pathogenesis include hypovolemia, hypotension, and acute tubular necrosis. Oliguric or nonoliguric renal failure usually occurs during the second week of illness. Hemorrhagic manifestations are common in severe illness and are thought to be related to severe vasculitis with endothelial damage resulting in capillary injury. Thrombocytopenia and abnormal clotting factors serve to increase the risk of bleeding. Clinically there may be petechial and purpuric rashes, bleeding gums, epistaxis, hemoptysis, gastrointestinal

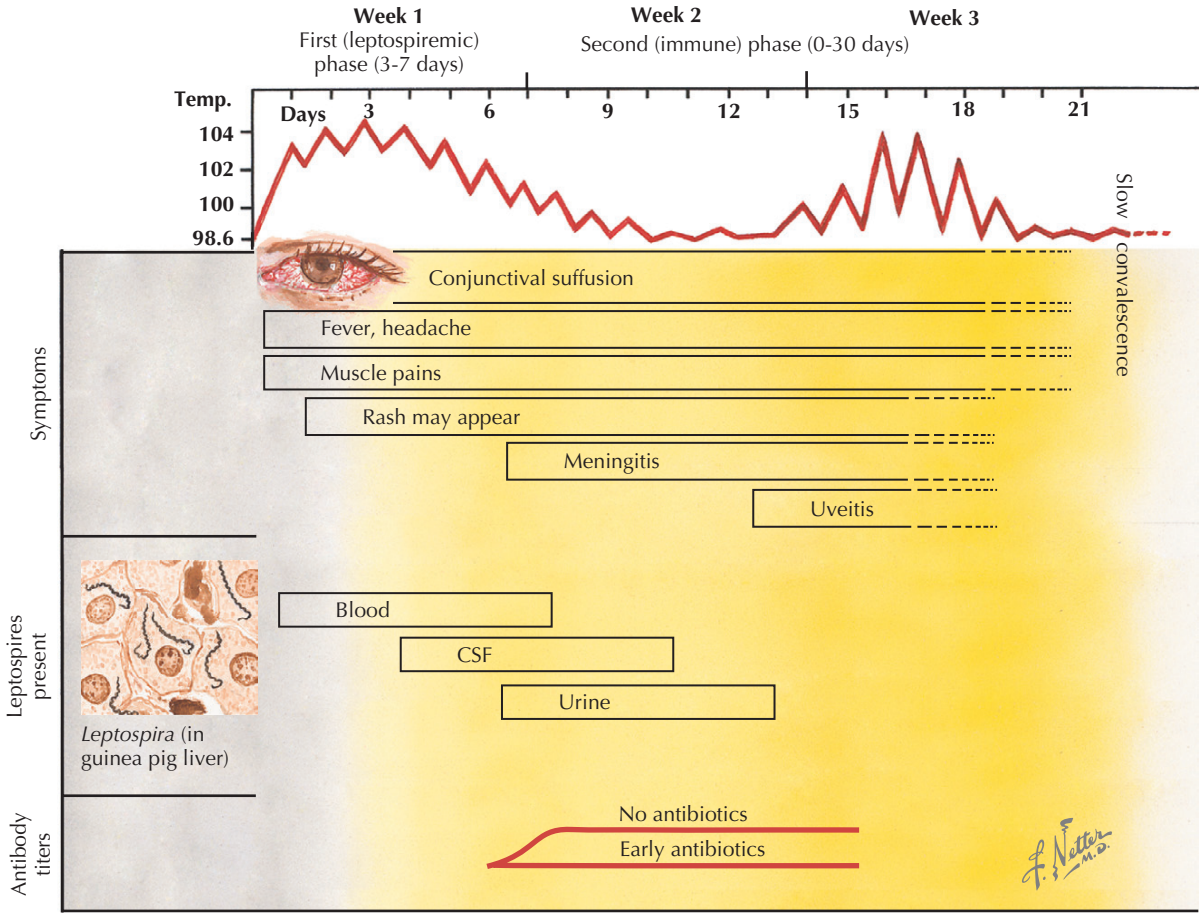

Figure 70-2 Clinical course of leptospirosis.

hemorrhage, and, rarely, subarachnoid or adrenal hemorrhage. Cardiac involvement may result in myocarditis or pericarditis and arrhythmias such as atrial fibrillation, atrial flutter, and a variety of conduction disturbances. Congestive heart failure and myocarditis are common in fatal cases (Figure 70-3).

DIAGNOSTIC APPROACH

Leptospirosis has protean manifestations and is often confused with other infectious diseases (Box 70-1). This is particularly common in returned travelers from the tropics. A high index of suspicion is often needed to make the diagnosis, and a number of diagnostic "red flags" may help to alert clinicians (Box 70-2).

Immunodiagnosis

Antibodies usually appear in the second week of illness. The gold standard for immunodiagnosis remains the microscopic agglutination test (MAT), and paired sera should be obtained 14 to 28 days apart for testing. Diagnosis is usually based on demonstrating a fourfold rise in titer or a single MAT titer of at least 1 in 200. Rapid screening tests (e.g., enzyme-linked immunosorbent assay [ELISA], indirect hemagglutination assay [IHA]) may also be available. Early use of antibiotics may delay or blunt the appearance of antibodies (see Figures 70-2 and 70-3).

Culture

Cultures should be attempted whenever possible, and specimens should be obtained before antibiotics are started. Blood, cerebrospinal fluid (CSF), urine, and peritoneal dialysis fluid may all be cultured. Specimens should be inoculated as soon as possible using special media. It may take as long as 6 weeks or more for cultures to become positive.

The total white blood cell count is variable but is usually elevated in severe disease. A neutrophil leukocytosis with a shift to the left is common (in contrast to viral hepatitis). A mild to moderate thrombocytopenia (platelet counts 50,000 to 120,000/mm^3) is common. Platelet counts of less than 50,000/mm^3 are less common but may be seen in severe disease. Prothrombin time may be prolonged in Weil's disease but can be corrected with vitamin K. Erythrocyte sedimentation rate (ESR) is very commonly elevated, often greater than 50 mm/hr. Liver function abnormalities include elevated bilirubin (up to 20 mg/dL or higher) with a relatively mild increase in transaminase and alkaline phosphatase levels. Elevated serum amylase and lipase levels may occur but are not necessarily associated with clinical evidence of pancreatitis. Creatine kinase levels are elevated in the majority of patients during the first week of illness, and this may help to differentiate leptospirosis from viral hepatitis. Hyponatremia is relatively common. Nonoliguric hypokalemia

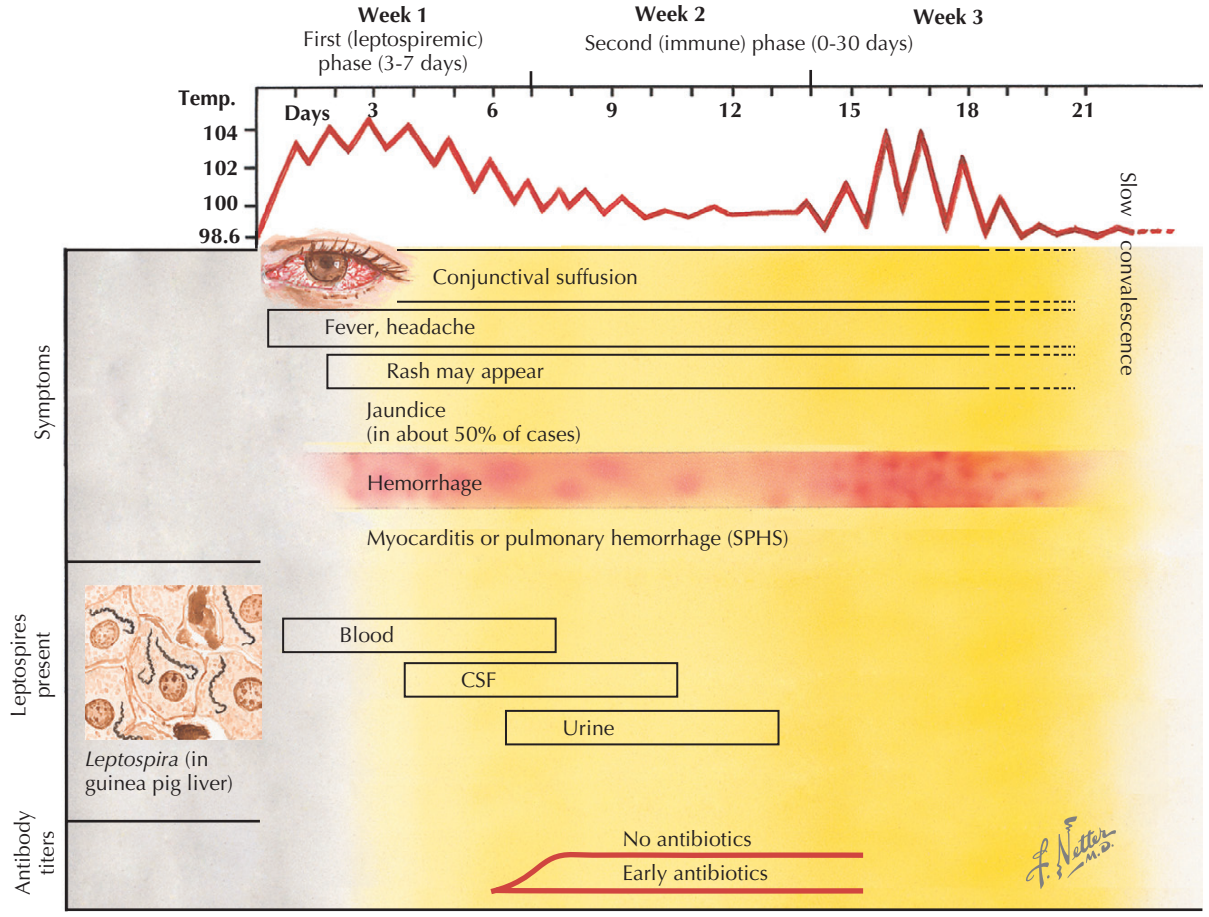

Figure 70-3 Clinical course of severe leptospirosis.

Box 70-1 Differential Diagnosis of Leptospirosis

- Influenza
- Aseptic meningitis
- Brucellosis
- Dengue fever
- Rickettsial diseases (e.g., typhus, Q fever)
- Streptococcal pharyngitis
- Acute human immunodeficiency virus (HIV) infection
- Toxoplasmosis
- Malaria
- Viral hemorrhagic fever
- Viral hepatitis
- Legionnaires' disease
- Hantavirus
- Typhoid fever
- Relapsing fevers

Box 70-2 Leptospirosis Diagnostic "Red Flags"

- History of contact with fresh water or mud
- History of contact with animals
- History of cuts or abrasions
- Abrupt onset of severe headache
- Severe myalgias (calves, thighs, lower back)
- Conjunctival suffusion
- Fever and new-onset atrial fibrillation
- Jaundice and relatively mild transaminase elevation
- Fever, jaundice, and thrombocytopenia
- Hepatitis and neutrophil leukocytosis with left shift
- Fever and elevated creatine kinase levels
- Fever and elevated amylase or lipase levels

is an early feature of renal insufficiency. Urinalysis findings are frequently abnormal and may show proteinuria, pyuria, hyaline or granular casts, and hematuria.

During the second (immune) phase of illness, CSF typically shows features of aseptic meningitis. The CSF cell count is usually less than 500/mm^3 with a lymphocytic pleocytosis. CSF protein is moderately elevated, but CSF glucose is normal.

Chest x-ray abnormalities may include small nodular densities, patchy alveolar infiltrates, areas of consolidation, pleural effusions, or the typical changes associated with ARDS.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Early antibiotic treatment has been shown to reduce the duration and severity of illness, and antimicrobials should be started as soon as the diagnosis is suspected. Antibiotics are usually given for 7 to 10 days. The organism is sensitive to a wide range of antibiotics including penicillin, amoxicillin, doxycycline, erythromycin, macrolides (e.g., azithromycin and clarithromycin), third-generation cephalosporins (e.g., ceftriaxone

Box 70-3 Antibiotics Used for Treatment of Leptospirosis (7 to 10 Days, Administration in Adults)

- Doxycycline 100 mg PO bid
- Amoxicillin-clavulanate potassium PO 875-125 mg bid
- Azithromycin 1000 mg PO, then 500 mg × 3 days
- Penicillin G 1.5 MU IV q6h
- Amoxicillin 500 mg PO tid
- Erythromycin 500 mg PO qid
- Clarithromycin
- Ceftriaxone 1-2 g IV or IM q24h

IM, Intramuscularly; *IV*, intravenously; *PO*, orally.

and cefotaxime), and some fluoroquinolones (Box 70-3). The organism may be resistant to chloramphenicol, vancomycin, aminoglycosides, and first-generation cephalosporins. Jarisch-Herxheimer reactions after penicillin treatment occur less frequently than with other spirochetal infections. Supportive care, if necessary in an intensive care unit, is very important, and meticulous attention to fluid and electrolyte balance is essential. Renal failure is an important cause of death, and prompt initiation of hemodialysis or peritoneal dialysis helps to limit mortality.

PROGNOSIS

Over 90% of cases of leptospirosis are mild and self-limited. In severe cases of Weil disease, however, mortality may be as high as 20%, and in SPHS mortality of up to 50% has been reported. Mortality tends to increase with age and in association with underlying disease.

PREVENTION AND CONTROL

Preventive measures include avoiding potentially contaminated fresh water, damp soil, or mud whenever possible, wearing protective clothing, and covering cuts and abrasions with waterproof dressings. Submersion should be avoided, because the organism can enter via the mucous membranes of the eyes, nose, and mouth. Potentially contaminated drinking water should be boiled or treated with iodine or chlorine. Simple filtration may not provide adequate protection.

Chemoprophylaxis may be indicated in short-term, high-risk situations. Doxycycline, 200 mg once *weekly*, beginning before the first exposure and ending after the last possible exposure, appears to be effective. Travelers to malaria-endemic areas who are also at risk of leptospirosis may be protected against both infections by taking doxycycline, 100 mg *daily*, one of the chemoprophylaxis regimens recommended against chloroquine-resistant malaria (CRPF) (see Chapter 63). Azithromycin may also be effective for prevention of leptospirosis in situations where doxycycline is contraindicated.

Preventive measures are particularly important in situations that are associated with increased risk of infection—for example, white water rafting and adventure racing such as triathlons, particularly after heavy rainfall or flooding. Vaccines for human use are generally not available.

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Trevejo RT, Rigua-Pérez JG, Ashford DA, et al: Epidemic leptospirosis, associated with pulmonary hemorrhage-Nicaragua, 1995, *J Infect Dis* 178:1457-1463, 1998. *One of the first papers to highlight the importance of severe pulmonary hemorrhage in leptospirosis. Since then, pulmonary hemorrhage has become increasingly recognized as an important cause of severe illness and death in leptospirosis.*

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Sejvar J, Bancroft E, Winthrop K, et al: Leptospirosis in "Eco-Challenge" athletes, Malaysian Borneo, *Emerg Infect Dis* 9:702-707, 2000. *This article emphasizes the importance of adventure travel and adventure racing in the epidemiology of leptospirosis.*

Victoriano AFB, Smythe LD, Gloriani-Barzaga N, et al: Leptospirosis in the Asia Pacific region, *BMC Infect Dis* 9:147, 2009. *An excellent review of leptospirosis in the Asia Pacific region by an internationally recognized group of experts. The article describes current trends in the epidemiology of leptospirosis, existing surveillance programs, and some of the prevention control programs in the region.*

Lyme Disease

Christopher Sanford

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ABSTRACT

Lyme disease, caused by infection with spirochetes of the *Borrelia burgdorferi* complex, is the most common arthropod-borne infection in the United States. The spirochetes are transmitted to humans by bites of infected ticks of the *Ixodes ricinus* complex, which are also known as *black-legged deer ticks*. As many as 90% of patients have a characteristic rash, erythema migrans (EM); other manifestations of early disease include lymphadenopathy, myalgias, and low-grade fever. If left untreated, the disease may progress to further systemic symptoms, including those involving the nervous and cardiac systems. Doxycycline appears to be a highly effective treatment for eradicating the infection when used in postexposure treatment of high-risk tick exposures, and in cases of early localized (stage 1) and early disseminated (stage 2) Lyme disease, thus preventing systemic complications of long-term infection. Reinfection of persons living in Lyme-disease hyperendemic areas may complicate the assessment of treatment efficacy. Clinicians practicing in high-risk geographic areas should consider Lyme disease not only in patients with a history of tick exposure or a rash suggestive of EM but also in patients with a viral-like illness without a rash.

GEOGRAPHIC DISTRIBUTION

Within the United States, Lyme disease is most commonly transmitted in the northeastern coastal region, although transmission in the north central and Pacific coastal regions also occurs (Figure 71-1). Although Connecticut is the state with the highest prevalence of Lyme disease, between 1997 and 2006 the three counties in the United States with the highest rates of Lyme disease were Nantucket County, Massachusetts, and Columbia and Dutchess Counties, both in New York.

In 1999, approximately 90% of the 13,306 cases of Lyme disease reported by state health departments occurred in Maryland through Maine, 2.8% in Wisconsin and Minnesota, and 1.1% in Oregon and California (most cases reported in California were from northern California). In general, reported incidence has increased since the early 1990s, in part because of improved surveillance systems and the continued expansion of human settlement into deer habitats. In 2007, 27,444 cases of Lyme disease were reported in the United States. Because early cases of Lyme disease are treated without laboratory testing and not all cases of Lyme disease are recognized by medical personnel, official numbers probably markedly underestimate the actual number of cases.

Outside of the United States, Lyme disease is transmitted in the temperate forested regions of Europe and Asia, but it is not known to be transmitted in the tropics.

TICK LIFE CYCLE

Ixodes ticks are born as larval ticks in the summer; they feed only once, their preferred host being the white-footed mouse. In the following spring the larval ticks transform into nymphs and again feed only once, their preferred host again being the white-footed mouse. In the fall, the nymphs become adults and feed again, the preferred host being the white-tailed deer. Neither mice nor deer develop illness from *B. burgdorferi*. Only ticks that have fed on an infected animal can infect humans. Eighty-five percent of human infections are caused by nymphs in the spring and summer; 15% are caused by adult ticks in the fall.

In endemic areas, as many as 50% of ticks may be infected, but the risk of acquiring Lyme disease from a single tick bite is at most 3.5%, even in highly endemic areas. The time of year during which humans are at greatest risk of infection is mid-spring through late fall, which is when tick populations, particularly biting nymphs, are at their greatest levels; this is also when people in endemic areas have their highest level of outdoor exposure. A minimum of 36 to 48 hours of tick attachment is required for effective transmission to humans (Figure 71-2).

RISK FACTORS

People engaged in outdoor activities (e.g., hiking, gardening) are at highest risk for Lyme disease. Those with occupational exposure to brush, such as forest rangers and landscapers, are also at elevated risk. The age groups with the highest risk of infection are 5 to 19 years, and those older than age 30 years. June and July are the peak months of infection in humans. There is no difference in risk of infection between the genders.

CLINICAL FEATURES

For surveillance purposes, the clinical case definition of Lyme disease is used, as follows:

- EM of 5 cm (2 inches) or greater, or
- At least one late manifestation of neurologic, cardiovascular, or musculoskeletal disease, and laboratory confirmation of infection with *B. burgdorferi*

Of patients with Lyme disease, 70% to 85% have early localized disease (stage 1) at presentation. The incubation period between the bite of an infected tick and the appearance of the characteristic rash ranges from a few days to 1 month. The EM rash (formerly termed *erythema chronicum migrans*) usually, but not always, occurs at the site of the tick bite. This large annular rash, which occurs in up to 90% of patients with Lyme disease, is the single best clinical indicator of Lyme disease. Although it is sometimes described as a "bull's-eye" rash, it often consists of

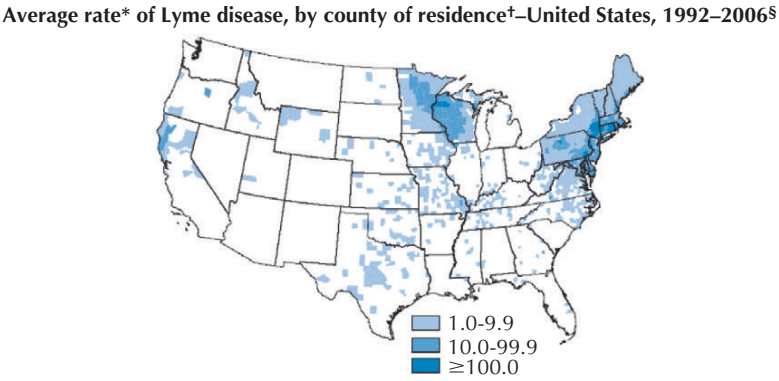

Figure 71-1 Tick distribution in the United States. *(From Bacon RM, Kugeler KJ, Mead PS; Centers for Disease Control and Prevention [CDC]: Surveillance for Lyme disease—United States, 1992-2006,* MMWR Surveill Summ *57:1-9, 2008.)*

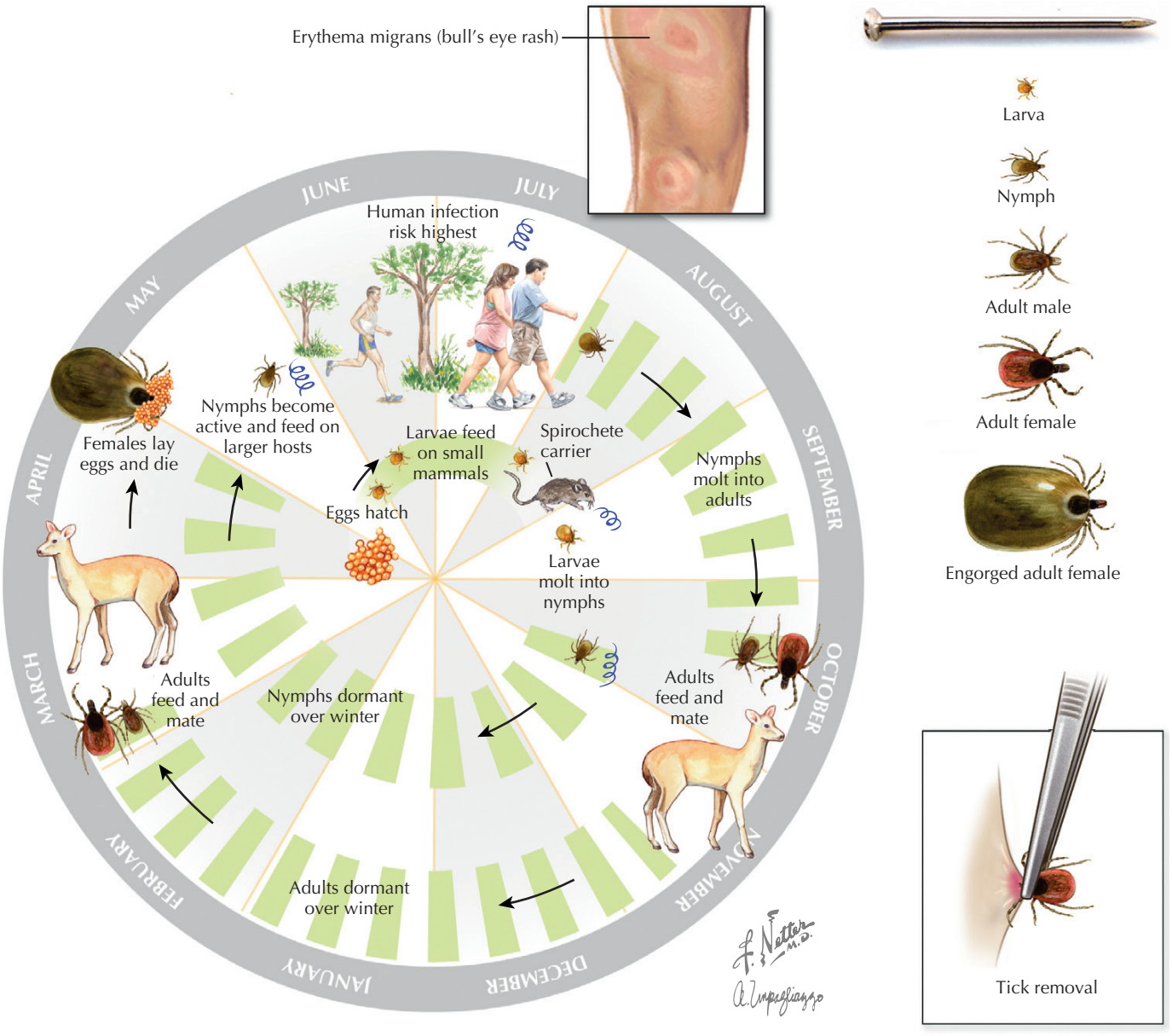

Figure 71-2 Transmission of Lyme disease.

confluent erythema that expands (hence its name). Untreated, it persists for 2 to 3 weeks. Other manifestations of early localized disease include mild lymphadenopathy (23%), low-grade fever (19% to 39%), mild fatigue and malaise (54%), neck stiffness (35%), and mild arthralgias and myalgia (44%); headache is also a common stage 1 symptom.

In the absence of appropriate treatment, infection may progress to early disseminated disease (stage 2). Symptoms of stage 2 illness are dermatologic (disseminated EM), neurologic (meningitis, encephalitis), gastrointestinal (hepatitis, abdominal pain), cardiac (atrioventricular [AV] block, myopericarditis), and rheumatologic (monoarticular arthritis). Late disease (stage 3) manifestations are dermatologic (acrodermatitis chronica atrophicans), rheumatologic (arthralgias, oligoarthritis), and neurologic (cranial nerve palsy, ataxia, spastic paresis, encephalomyelitis). Unlike syphilis, another disease caused by a spirochete infection, stage 3 illness may occur within 1 year of initial infection.

The Centers for Disease Control and Prevention (CDC) data collected from 1992 to 2004 shows that EM was the most common presenting sign, with 68% of those with Lyme disease demonstrating this finding. Thirty-three percent of patients with Lyme disease had arthritis, 8% had facial palsy, 4% had radiculopathy, 1% had meningitis or encephalitis, and 1% had heart block at presentation.

Clinical manifestations of Lyme disease differ between the United States and Europe. Those infected with *B. burgdorferi* in Europe have a higher rate of remaining asymptomatic relative to patients in the United States. Two dermatologic manifestations occur in some patients in Europe with Lyme disease but are apparently absent in North American patients: borrelial lymphocytoma, a purplish nodular swelling usually occurring on the earlobe or nipple in stage 2 disease, and acrodermatitis chronica atrophicans, which occurs over extensor surfaces of the extremities. Meningopolyradiculitis (Bannwarth's syndrome), a manifestation of stage 2 neuroborreliosis, which is characterized by severe radicular pain, occurs much more frequently in Europe than in the United States. The clinical course of EM, arthritis, neuroborreliosis, and other manifestations also may differ between patients in the United States and those in Europe. The differences are probably a result of illness being caused by different strains of *Borrelia.* Isolates from the east coast of the United States are termed *B. burgdorferi* sensu stricto. The European isolate *Borrelia garinii* is associated with neurologic symptoms, whereas *Borrelia afzelii*, also found in Europe, is associated with acrodermatitis chronica atrophicans.

DIAGNOSTIC APPROACH

The diagnosis of Lyme disease is based primarily on clinical findings. Any patient with a history of potential exposure to ticks who manifests EM should be presumed to have early localized disease and should be treated accordingly; resolution of symptoms with a course of antibiotics confirms the diagnosis.

Culturing the organism *B. burgdorferi* is limited to research settings. An enzyme-linked immunosorbent assay (ELISA) that tests for immunoglobulin M (IgM) and IgG antibodies to *B. burgdorferi* is available. However, in patients with Lyme disease, several weeks may elapse before an IgM response can be detected. Early antibiotic treatment may cause the antibody response to remain undetectable.

The IgM response, once positive, can remain positive for over a year; hence it indicates exposure but does not confirm recent infection. The IgG antibody response occurs 4 to 8 weeks after infection. A false-positive antibody response can be caused by several conditions and situations, including viral infections, rheumatoid arthritis, other autoimmune diseases, and healthy persons living in endemic areas (5% to 10% of those living in Lyme disease–endemic regions have positive antibody results with no history of symptoms). Hence laboratory studies in and of themselves, in the absence of clinical findings and exposure history, are insufficient to confirm or exclude the diagnosis of Lyme disease.

A Western blot test is also available for Lyme disease. The CDC recommends a two-step sequence of testing, in which positive or equivocal ELISA findings are confirmed via Western blot testing for IgM and IgG bands specific to Lyme disease. The IgM Western blot has a high rate of false-positive results and should be performed only in patients with less than 1 month of symptoms. The test is read as positive if two of three Lyme disease–specific bands are present; the IgG test is considered positive if at least 5 of 10 Lyme disease–specific bands are positive.

Deoxyribonucleic acid (DNA) detection of *B. burgdorferi* by polymerase chain reaction (PCR) is problematic, with lack of standardization, poor sensitivity, and risk of contamination all contributing to limit its usefulness. One role of PCR may be in confirming active Lyme disease in synovial fluid.

In 2005 the CDC issued a warning regarding commercial laboratories that represent themselves as specializing in Lyme disease diagnosis. Many of these labs use unproven techniques for diagnosis, including immunofluorescent staining of blood for *B. burgdorferi*, DNA PCR tests on blood or urine, and Western blot testing via unvalidated criteria. If in doubt, healthcare providers and patients should inquire whether or not these labs use Food and Drug Administration (FDA)–approved tests for Lyme disease.

DIFFERENTIAL DIAGNOSIS

When EM is present in a patient with known or suspected exposure to ticks in an area endemic for Lyme disease, diagnosis is straightforward. EM may initially be mistakenly diagnosed as cellulitis, allergic dermatitis, or contact dermatitis in response to a plant such as poison oak or poison ivy. Manifestations other than EM have extensive differential diagnoses, and determining the presence of Lyme disease in the absence of EM may be difficult. The initial febrile illness, when occurring without EM, can resemble influenza, viral gastroenteritis, infectious mononucleosis, and other acute febrile infections. Because the *Ixodes scapularis* and *Ixodes pacificus* ticks also may transmit the infective agents causing human granulocytic anaplasmosis (*Anaplasma phagocytophilum*, a small gram-negative bacterium) and babesiosis (*Babesia microti*, an intraerythrocytic protozoan parasite) in some of the same geographic areas as Lyme disease transmission, these tick-borne infections should also be considered in the differential diagnosis of a febrile illness without EM after a tick bite. The differential diagnosis may also include, depending

on presenting symptoms, fibromyalgia, reactive arthritis, rheumatoid arthritis, systemic lupus erythematosus, and aseptic meningitis.

TREATMENT

Lyme disease can usually be cured by an appropriate course of antibiotics. Doxycycline is the drug of choice in stage 1 disease; amoxicillin can be used in children younger than age 8 years and in pregnant or lactating women. Another option is oral cefuroxime. For stage 2 and 3 disease, treatment is intravenous antibiotics: ceftriaxone, cefotaxime, or penicillin G. Treatment regimens and drug doses are given in Table 71-1. With appropriate early treatment, prognosis is excellent. There is no demonstrated benefit to following serial serologies. Infection does not provide immunity from future infections.

POSTEXPOSURE PROPHYLAXIS

In Lyme-endemic regions, when an attached tick is large (suggesting a prolonged attachment time), a single dose of doxycycline 200 mg in those older than the age of 8 years will prevent infection. This strategy appears to be less effective in Europe.

PREVENTION

Deer do not become infected with the spirochete that causes Lyme disease; however, they do serve as the primary source of blood on which the adult ticks reproduce. Measures aimed at reducing deer populations have been shown to reduce the population of ticks. However, the amount of tick population reduction requisite to affect the transmission of Lyme disease has not been established.

Wearing long sleeves and long pants is of benefit, and tucking pants into boots or socks and tucking shirts into pants will help to keep ticks on the outside of clothing. Ticks are easier to see on light-colored clothing. Applying permethrin to clothing offers significant protection; applying *N,N*-diethyl-*meta*-toluamide (DEET) to exposed skin is less helpful. Avoiding thickly wooded and bushy areas and areas with high grass and large quantities of leaf litter may be of benefit, particularly during the months of May, June, and July when transmission of Lyme disease is most intense.

After outdoor activities, a head-to-toe tick check with the aid of a mirror or close friend will reduce risk. *Ixodes* ticks are small and may be difficult to detect. Ticks attached to the skin should be removed immediately with fine-tipped tweezers (see Figure 71-2). If a tick has been attached for less than 24 hours, the risk of transmission of Lyme disease is extremely small.

An effective vaccine against Lyme disease (*B. burgdorferi* outer surface membrane protein A or OspA) was available in the United States for a limited time but was withdrawn from the market by the manufacturer in 2002 owing to alleged adverse effects and low usage.

Table 71-1 Antibiotic Treatment Regimens for Lyme Disease

CLINICAL STAGE	ANTIBIOTIC REGIMEN (ADULT)
Exposure or presumed exposure to nymphal deer tick in an endemic area	Doxycycline,* 200 mg orally once with food
Early local (erythema migrans) or Early disseminated	*One of the following, taken for 14-21 days:* Doxycycline, 100 mg orally twice daily, *or* Amoxicillin, 500 mg orally three times a day, *or* Cefuroxime axetil, 500 mg orally twice daily, *or* Erythromycin, 250 mg orally four times a day, if none of the above drugs are tolerated
Carditis	*One of the following, taken for 14-21 days:* Ceftriaxone, 2 g IV once daily, *or* Cefotaxime, 2 g IV every 8 hours, *or* Penicillin G, 24 million units IV per day divided every 4 hours
Facial nerve paralysis (isolated finding, early)	*One of the following, taken for 14-21 days:* Doxycycline, 100 mg orally twice a day, *or* Amoxicillin, 500 mg orally three times a day, *or* Ceftriaxone, 2 g IV once daily
Meningitis, encephalitis	*One of the following, taken for 14-28 days:* Ceftriaxone, 2 g IV once daily, *or* Penicillin G, 20 million units IV per day divided every 4 hours, *or* Cefotaxime, 2 g IV every 8 hours
Arthritis	*One of the following, taken for 30-60 days:* Doxycycline, 100 mg orally once daily, *or* Amoxicillin, 500 mg orally three times a day, *or* *One of the following, taken for 14-28 days:* Ceftriaxone, 2 g IV once daily, *or* Penicillin G, 20-24 million units IV per day divided every 4 hours

Adapted from Gilbert DN, Moellering RC, Eliopoulos GM, et al: The Sanford guide to antimicrobial therapy 2009, *ed 39, Sperryville, Va., 2009, Antimicrobial Therapy.*

*Avoid use of doxycycline in pregnant women and in children younger than 8 years old.

IV, Intravenously.

EVIDENCE

Aucott J, Morrison C, Munoz B, et al: Diagnostic challenges of early Lyme disease: lessons from a community case series, *BMC Infect Dis* 9:79-87, 2009. Available at: www.biomedcentral.com/1471-2334/9/79. Accessed February 17, 2010. *Community-based case series shows that primary care providers need to improve their clinical recognition of early Lyme disease, consider atypical presentations, and become familiar with appropriate antibiotic regimens.*

Centers for Disease Control and Prevention (CDC): Surveillance for Lyme Disease—United States, 1992-2006. *MMWR Surveillance Summaries* 57 (SS10):1-9, 2008. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5710a1.htm. Accessed February 20, 2011. *Detailed summary of official surveillance data on Lyme disease cases reported in the U.S.*

Kowalski TJ, Tata S, Berth W, et al: Antibiotic treatment duration and long-term outcomes of patients with early Lyme disease from a Lyme disease–hyperendemic area, *Clin Infect Dis* 50:512-520, 2010. *This article discusses findings from a retrospective cohort study of 607 patients in a Lyme disease–hyperendemic area who had early localized disease or early disseminated disease, and demonstrates that 10 days of doxycycline is as effective as longer treatment regimens for eradication of early Lyme disease.*

ADDITIONAL RESOURCES

Baker CD, Charini WA, Duray PH, et al: *Final report of the Lyme Disease Review Panel of the Infectious Diseases Society of America (IDSA).* Available at: http://www.idsociety.org/Content.aspx?id=16499 Accessed February 21, 2011. *The Review Panel reaffirmed the recommendations of the 2006 guidelines and concluded that in the case of Lyme disease, there is no evidence to support long-term antibiotic therapy beyond 1 month. This report is a valuable resource to clinicians seeking evidence-based guidelines on Lyme disease and its treatment in the United States.*

Centers for Disease Control and Prevention (CDC): Notice to readers: caution regarding testing for Lyme disease, *MMWR Morb Mortal Wkly Rep* 54:125, 2005. *Reminder that some commercial laboratories may offer tests for Lyme disease diagnosis that are inadequately validated. U.S. providers should seek laboratory tests cleared by the FDA. Caution is advised in Canada and Europe, where some laboratories also use inadequately validated tests.*

Gilbert DN, Moellering RC, Eliopoulos GM, et al: *The Sanford guide to antimicrobial therapy 2010*, ed 40, Sperryville, Va, 2009, Antimicrobial Therapy. *A clinical guide for current usage of antimicrobial drugs in the United States; incorporates evidence-based medical practices and includes citations, updated annually.*

Halperin JJ, Shapiro ED, Logigian E, et al: Practice parameter: treatment of nervous system Lyme disease (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology, *Neurology* 69:91-102, 2007. *A clinical practice guideline for nervous system Lyme disease.*

Mygland A, Ljøstad U, Fingerle V, et al: EFNS guidelines on the diagnosis and management of European Lyme neuroborreliosis, *Eur J Neurol* 17:8-16, 2010. *A clinical practice guideline for European Lyme neuroborreliosis.*

Stafford KC: *Tick management handbook*, rev ed, New Haven, 2007, Connecticut Agricultural Experiment Station. Available at: www.ct.gov/caes. Accessed February 17, 2010. *A comprehensive handbook covering all aspects of tick-borne diseases including epidemiology, transmission, diagnosis, treatment, and prevention, as well as environmental controls. The handbook is illustrated with many photographs of tick vectors and habitats and integrates information from many sources. This is an essential reference for public health officers and clinical practitioners in tick-endemic areas.*

Wormser GP, Dattwyler RJ, Shapiro ED, et al: The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the Infectious Diseases Society of America, *Clin Infect Dis* 43:1089-1134, 2006. *A clinical practice guideline on Lyme disease developed by the Infectious Diseases Society of America. Published in 2006, the IDSA's 2006 Lyme disease guidelines underwent review by a special independent Review Panel. The Review Panel's final report, published on April 22, 2010, validated the 2006 Lyme disease guidelines and offered some additional advice.*

Tick-Borne Encephalitis

Martin Haditsch

72

ABSTRACT

For a long time, tick-borne encephalitis (TBE) was perceived as a risk only for the local population living in endemic areas. There was very little specific awareness and hardly any knowledge about this viral disease among doctors outside the endemic areas. Thus TBE has been a neglected travel-associated health risk.

World Tourism Organization statistics show that the European continent continues to be the main travel destination for international travelers. Considerable parts of this continent, especially those with the highest recent increases in international tourism (i.e., the Baltic States) as well as parts of Asia are proven TBE endemic areas (Figures 72-1 and 72-2). Thus it is increasingly important to provide travelers to these areas with current information on the risk of disease transmission and the possibilities of prophylaxis in general, and vaccination options in detail.

TBE is known under a variety of names, synonyms being spring-summer-encephalitis, Central European encephalitis, Far-East Russian encephalitis, Taiga encephalitis, Russian spring-summer encephalitis, bi-undulating meningoencephalitis, diphasic milk fever, Kumlinge disease, Schneider's disease, and, in German-speaking areas, Früh-Sommer-Meningo-Encephalitis (FSME) or early-summer meningoencephalitis—a description that might be misleading, as will be shown later.

In its most severe course, the infection affects the central nervous system (CNS), mostly as a meningoencephalitis leading to persistent sequelae in up to 58% of patients. Prophylaxis is focused on the avoidance of exposure and on vaccination. Because many of the TBE endemic areas are (increasingly) popular tourist destinations, it seems of utmost importance to raise awareness among travelers and their health advisors, primary care medicine practitioners, and infectious disease specialists.

THE PATHOGEN

TBE is caused by a single-stranded ribonucleic acid (RNA) virus that belongs to the family of the Flaviviridae and therefore shows some similarities with other viruses in this family (e.g., West Nile virus and Japanese encephalitis [JE] virus). The TBE virus is fairly homogenous in endemic areas of Europe (European subtype). There are two additional subtypes within the same group with few genetic differences: the recently identified Siberian subtype (which genetically is quite closely linked to the European subtype) and the Far Eastern subtype.

VECTOR AND TRANSMISSION

TBE is transmitted by hard ticks and via consumption of raw milk. By far the most frequent way of transmission to humans is by bites of certain species of hard ticks (i.e., *Ixodes ricinus* and *Ixodes persulcatus*) that previously have fed on infected reservoir hosts (Figure 72-3). With some areas of overlap, *I. ricinus* (the common castor-bean tick) mostly inhabits the western part, and *I. persulcatus* ("Taiga tick") mainly is found in the eastern part of the endemic area that roughly stretches from the Alsace region of France in the West to Hokkaido Island, Japan, in the East, and from Scandinavia in the North to Italy, Albania, and Greece in the South. According to old published data, the TBE virus prevalence in the tick population in endemic areas may be as low as 0.05% in Italy and 0.07% in Finland and as high as 26.6% in some regions of Latvia.

One phenomenon contributing to an increasing prevalence of TBE-infected tick populations is the fact that a vertical or transovarian transmission (i.e., a TBE-infected female tick infects her eggs before oviposition) takes place as well as from an infected animal to a tick during a bite (or even from tick to tick by cofeeding on the same blood pool). In contrast to other blood-feeding insect vectors, ticks do not directly puncture blood vessels but feed from a "feeding pool" produced by vasoactive mediators and coagulation inhibitors released via the tick's saliva. The blood meal of an adult female and immature blood-sucking nymphs may last up to 5 days, resulting in an approximately 120-fold increase of the volume of an adult female tick. Male ticks do not feed on blood at all but may repeatedly feed on a small amount of tissue fluid during a relatively short feeding period, which nevertheless may be sufficient for the transmission of the TBE virus.

In addition to tick bites, another way of transmission is by consumption of raw milk and products made from it. This mode of transmission used to occur quite frequently in the Baltic States (e.g., in Lithuania) and in Slovakia, but in 2008 there were some cases of alimentary infection reported for the first time in Austria. Another risk of exposure is laboratory work with this virus.

EPIDEMIOLOGY

In the past, at least in central Europe, most cases were seen in early summer. Later on, two peaks of this disease were described, with the recognition of an additional peak in late summer. Tick biting activity appears to be increased by humidity and temperature. Owing to recent climate changes observed in the whole

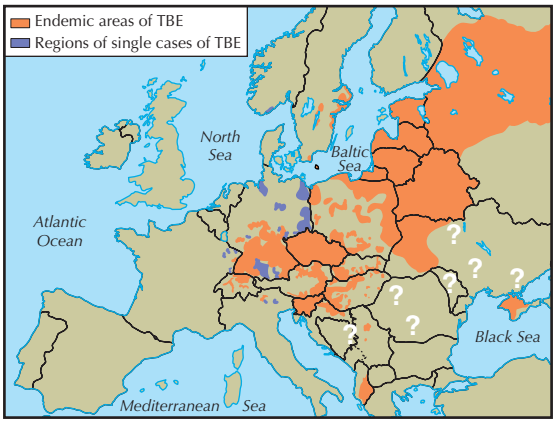

Figure 72-1 Geographic distribution of tick-borne encephalitis. *(Data from the International Prevention Initiative on Tick-Borne Encephalitis. Available at: www.tbe-prevention.info/m-6870.php.)*

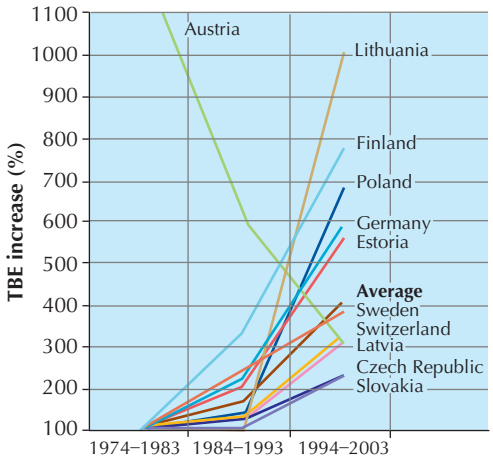

Figure 72-2 Tick-borne encephalitis cases reported in Europe, 1974 to 2003. (*Data from Kunze U, Baumhackl U, Bretschneider R, et al: The golden agers and tick-borne encephalitis. Conference report and position paper of the International Scientific Working Group on Tick-Borne Encephalitis*, Wien Med Wochenschr *155 [11-12]:289-94, 2005.)*

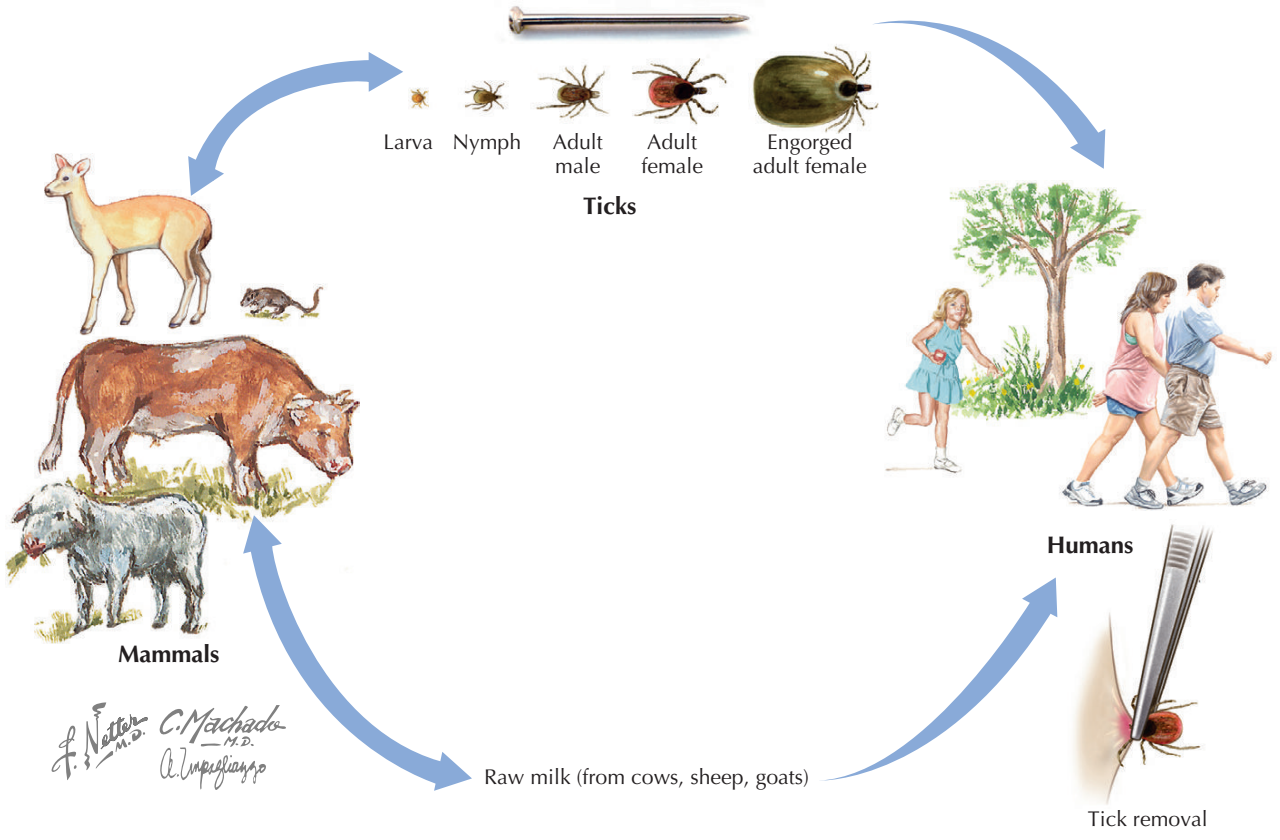

Figure 72-3 Transmission of tick-borne encephalitis virus.

region, currently at least five new phenomena have been observed:

- In addition to the steady growth of the geographic risk area at the same latitude accompanied by a confluence of scattered foci to bigger endemic regions, there has been movement of the TBE endemic area boundary northward, with the eruption of highly active foci in Scandinavia, for instance. In addition, the areas of risk include higher altitudes.
- In some areas the two peaks of reported clinical cases have merged into one broader peak occurring in July and August.
- In some areas, most likely as a result of warmer temperatures, the typical seasonal pattern with transmission-free intervals has vanished. Transmission seasons have expanded, and, in some regions, year-round transmission is occurring.
- The tick populations in some areas have substantially increased, probably because of climate changes that have caused increased rain, warm winters, and moist springs. As a consequence, the tick bite season starts earlier, and the development of the different stages is quicker. Tick activity starts with a soil temperature of about 7° C, and the relative humidity of at least 92% necessary for the ticks' survival is provided by more frequent episodes of rainfall.
- In most TBE-endemic countries, people have achieved better living conditions. They have more leisure time, which, at least during the warm season, contributes to an increase of exposure-prone outdoor activities. Furthermore, many families have shifted from living in apartments to having their own house with a garden, bushes, and trees, associated with an increased risk of tick bites.

These factors contribute to a higher risk of exposure to ticks. In most regions, the risk of exposure to TBE has shifted from being mainly an occupational risk (forestry workers, farmers) to that of being a health risk among people spending leisure time outdoors (e.g., collecting mushrooms, playing golf, camping and picnicking, Nordic walking, hiking, trekking). This particularly is true for older and retired people, who, if they acquire a TBE infection, tend to develop more severe symptoms.

As is the case with other infections, epidemiologic data reported officially depend on a variety of factors including the awareness within the healthcare system caring for a patient, the availability of adequate diagnostic tools, the notification systems of regional, national, and international health authorities, and the adherence of those who should report. The low awareness of TBE in nonendemic countries is likely to result in an underdiagnosis of clinical cases, and this is the most probable explanation for the difference between the estimated attack rates in tourists and the numbers reported.

On a person-based calculation, the highest incidence published (98 per 100,000) is that of forestry workers in Austria. As with other infectious diseases, not every infection results in specific clinical symptoms. The risk of symptomatic disease after a single tick bite in an endemic area varies from 1:200 to 1:1000. Actual epidemiologic data underline the importance of the vaccination of travelers going to endemic areas, the risk of acquiring TBE in an endemic area being about the same as for typhoid fever in nonvaccinated travelers going to India.

CLINICAL FEATURES

TBE typically is a biphasic disease. About 1 week (2 to 28 days) after an infectious tick bite, most patients develop an influenza-like illness (ILI) for a few days (2 to 8 days) caused by the viremia (Figure 72-4). For many patients, this remains the one and only symptomatic period. After an asymptomatic interval of about 1 more week (1 to 20 days), some patients develop a sudden increase in temperature that marks the beginning of the second stage. In this context, it seems noteworthy that TBE patients tend to have higher temperatures than patients with other forms of viral meningitis or meningoencephalitis.

The second phase is that of CNS involvement. The symptoms are most frequently caused by meningoencephalitis: stiff

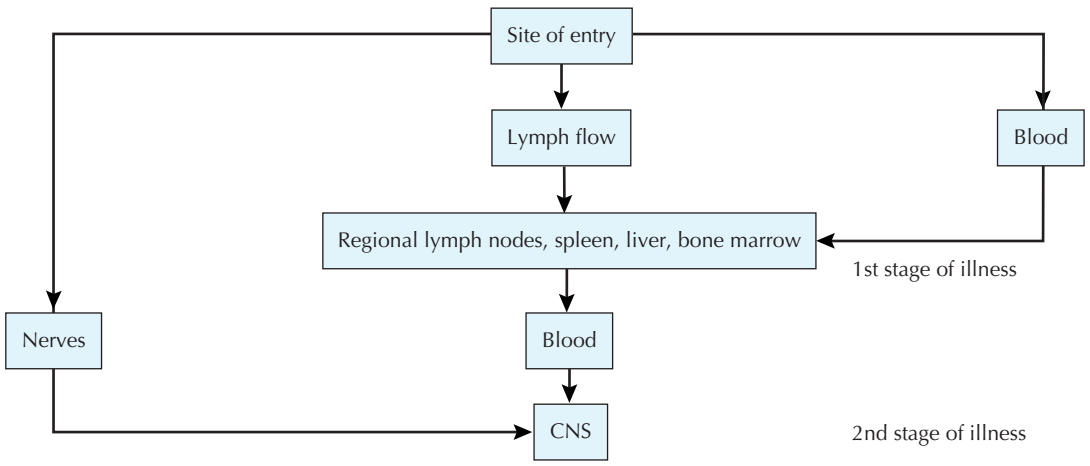

Figure 72-4 Spread of tick-borne encephalitis virus in the body. *(Data from Kaiser R: Tick-borne encephalitis in Germany and clinical course of the disease,* Int J Med Microbiol *291[suppl 33]:58-61, 2002.)*

neck, fever, headache, nausea, vomiting, photophobia, and impairment of CNS functions (Figure 72-5). These result from either direct destruction of CNS tissue (irreversible) or from an inflammatory edema (reversible). The amount of CNS involved, the mass of destruction, and its location determine the severity of the clinical course. Some factors, such as the presence of underlying diseases or conditions and older age are associated with increased severity of the disease. In its most severe form, TBE might involve all parts of the CNS—that is, causing meningoencephalomyeloradiculitis.

Compared with some other vector-borne flaviviral infections, there is no impairment of the clotting system, and symptoms of a viral hemorrhagic fever have never been proven in a case of TBE in Western Europe. According to incidence figures, cases in travelers from nonendemic countries are likely to stay undiagnosed or misdiagnosed, showing that the doctors responsible for the workup of these cases lack awareness of and experience in diagnosing this disease. The features of differential diagnosis between TBE and Lyme disease are given in Table 72-1.

DIAGNOSTIC APPROACH

Typically, a patient will not seek medical care until the second stage of the disease—that is, with the onset of neurologic signs. As in other cases of meningoencephalitis, diagnostics usually include a neurologic examination, serologic tests (paired samples: blood and cerebrospinal fluid [CSF]), radiology (computed tomography [CT] and magnetic resonance imaging [MRI]), and general laboratory screening tests (including a differential blood count and general inflammation parameters). The typical results are as follows:

- Besides specific neurologic signs attributable to the cerebral region involved, patients show unspecific neurologic symptoms such as headache, stiffness of the neck, photophobia, nausea with or without vomiting, and fever. The area most frequently affected in terms of paralysis is the shoulder girdle.
- The radiologic examination (CT or MRI) shows signs of meningitis and randomly spread foci in the CNS tissue

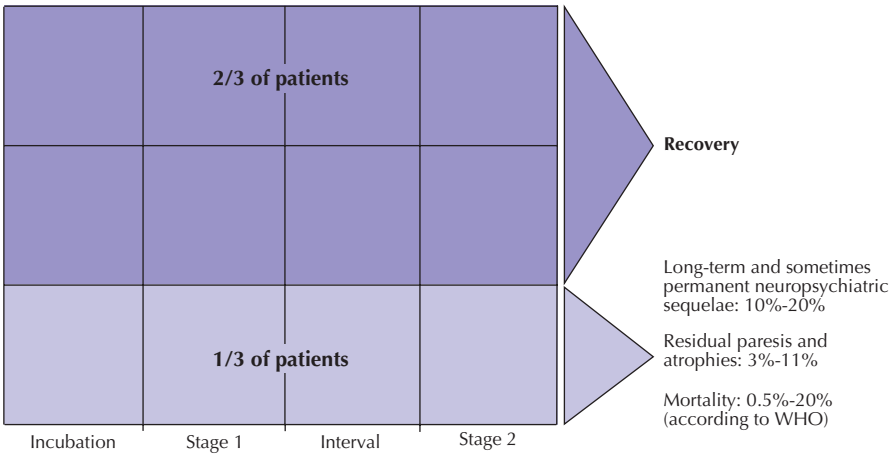

Figure 72-5 Clinical course of tick-borne encephalitis infection. *(Data from Kaiser R: Tick-borne encephalitis in Germany and clinical course of the disease,* Int J Med Microbiol *291[suppl 33]:58-61, 2002.)*

Table 72-1 Differential Diagnosis of Tick-Borne Encephalitis and Lyme Disease

	TICK-BORNE ENCEPHALITIS (TBE)	LYME DISEASE
Pathogen	TBE virus	*Borrelia burgdorferi* (bacterium)
Clinical Picture		
Phase 1	Temperature ≤38° C Uncharacteristic influenza-like signs and symptoms	Red rash (usually round or oval, erythema chronicum migrans) Uncharacteristic influenza-like signs and symptoms Lymphadenosis benigna cutis (rare form of benign recurrent tumor)
Phase 2	Fever (temperature ≥40° C) Meningitis Meningoencephalitis Meningomyelitis Meningoencephalomyelitis	Meningopolyneuritis (Garin-Bujadoux-Bannwarth) Facial paresis Cardiac arrhythmia Myocarditis
Phase 3		Acrodermatitis chronica atrophicans Arthritis

(encephalitis). Some of these abnormal signals are caused by destruction, others by perifocal edema.

- In the differential blood count at this stage there is a shift toward mononuclear cells in a usually decreased white blood cell (WBC) count. C-reactive protein CRP and procalcitonin PCT levels are low; lactate dehydrogenase (LDH) levels may be elevated (in accordance with CNS tissue destruction).
- CSF examination shows the typical picture of a viral meningitis—that is, elevated cell count (mononuclear cells) and protein, with a normal glucose level. The protein elevation is partly a result of unspecific inflammatory proteins and partly of the autochthonous production of TBE-specific immunoglobulin (Ig).
- When checking paired samples serologically, the first result indicating a recent infection is the detection of specific anti–TBE-virus IgM antibodies both in the serum and in the CSF. These antibodies are often present at the time of hospital admission, which, as mentioned previously, usually is triggered by the appearance of neurologic signs (i.e., in the second phase). The tests routinely used are based on the enzyme-linked immunosorbent assay (ELISA) technique. It is important to note that TBE antibodies may cross-react with other flaviviruses in these test systems, which is important particularly among travelers returning from endemic areas of JE and dengue fever, or those previously vaccinated against JE and/or yellow fever (YF). In case of inconclusive results, there are additional options such as the neutralization test (NT) or polymerase chain reaction (PCR) assays (which usually are limited to specialized laboratories).

TREATMENT

As with most other viral diseases, there is no specific therapy available. Treatment therefore is symptomatic only and focused on managing inflammation, pain, fever, and nausea as well as convulsions in serious infections. The most severe TBE cases may require intensive care, including parenteral nutrition and auxiliary ventilation. The availability of a high-quality standard of care may reduce the incidence and the amount of neurologic sequelae and affects the survival rate. This should be recognized, especially by nonvaccinated travelers heading to remote areas within an endemic region.

PROGNOSIS

The outcome of the disease depends on the amount, location, and function of the CNS structures destroyed. TBE viruses are known to have a particular predilection for anterior horn cells of the cervical spinal cord, thus leading to paresis of the upper limbs, the shoulder girdle, and the head levator muscles and having the potential to involve the respiratory muscles. The incidence rate of sequelae after TBE varies from 35% to 58%. The case-fatality rate (CFR) in central Europe is about 1% to 2%, whereas the CFR of the Siberian subtype (the Taiga strain, which is closely related to the Far Eastern form) is said to be as high as 20%, but there are doubts about whether this figure is correct; it might be biased by the fact that only people who are severely sick go to hospitals. On the other hand, there are investigations that show a higher virulence of the Siberian subtype in mice compared with the other Far Eastern strains.

After an infection (whether symptomatic or asymptomatic) TBE always leads to lifelong immunity.

PREVENTION

There is no chemoprophylaxis against TBE, so only the two other methods of prevention are left: avoidance of exposure and vaccination. In contrast to widespread beliefs, ticks do not primarily live on trees, nor do they jump down on their victims. Their usual habitats are areas with grass, meadows, bushes, and small trees. The ticks increase their chances to attach to warm-blooded animals (and humans) by sitting at the tips of the plants analyzing their surroundings with a very complex organ (so-called *organ of Haller*, located at their first pair of legs). Although it is not understood in detail, temperature, CO_2, and butyric acid (which is also responsible for the smell of sweat) seem to attract ticks and to trigger the attachment of ticks to the skin, facilitated by a contact time of not more than 0.1 second.

Because ticks in TBE-endemic areas might also transmit other diseases (Lyme borreliosis being the most common), the avoidance of all tick exposure is crucial. This includes avoidance of running or walking through high grasses or on narrow paths with repeated unavoidable contact with grass and bushes, and the use of insect repellents on exposed skin surfaces and impregnating outer clothing. Products containing the chemical *N,N*-diethyl-*meta*-toluamide (DEET) (in higher concentrations, preferably >20%) are considered to be effective skin repellents against ticks (and other arachnids, as well as insects). An insecticide containing permethrin is recommended for the impregnation of clothing. Several products are commercially available at sporting goods stores, to be used according to package directions. Another consideration is the fact that the color of the clothes has substantial impact on the attraction of ticks, light-colored clothing being significantly less attractive than dark-colored clothing. A summary of recommendations is provided in Table 72-2.

First Aid

After an infected tick is attached to the skin, some time is required until the transmission of a specific pathogen takes place. The process involves the time it takes for the tick to select the location for its bite, the penetration of the skin, the production of a "feeding pool" in the case of the blood-sucking nymph stages and adult females (adult males feed on tissue fluid only), and the time for the influx of a sufficient amount of tick saliva and/or regurgitated sucked blood to reach the minimal infectious dose in the human host. Therefore it makes sense to remove a tick as soon as possible to avoid an infection—even if the bug is already firmly attached to the skin.

To be able to remove attached ticks in a timely fashion, the whole body should be examined after outdoor activities. A thorough inspection usually necessitates the help of a second person (e.g., *before* showering or bathing). The removal of an attached tick should be as atraumatic as possible. This can be managed

Table 72-2 General Preventive Measures

INTERVENTION	MEASURE	COMMENT
Behavior	Avoid tick-infested areas	Whenever possible
Clothing	Light-colored clothing that covers arm and legs (long-sleeved shirts, tight at the wrists; long pants, tight at the ankles and tucked into the socks), shoes covering the entire foot	Dark clothing is more attractive for ticks (which in addition are more difficult to identify against a dark background)
Use of repellents	Apply adequate repellent (with proven activity against ticks) to exposed skin and to outer clothing	DEET* in higher concentrations and permethrin are proven to act against ticks; allow clothing to dry before wearing
Early detection	Adults should check daily, children should be checked more frequently (i.e., after each episode of potential exposure [could result in two or three checks per day])	The checks should especially focus on waistbands, sock tops, underarms, other moist areas (in children: check the head and behind the ears); even adults may need the help of a second person to check the whole body
Early removal of ticks	Remove tick as soon as possible by using fine tipped tweezers or special cards (resembling carved credit cards); grasp the tick firmly as close to the skin as possible and simply tear it out without squeezing or rotating the tick	Don't suffocate the tick (do not use oil, cream, nail polish, water); don't burn the tick; don't apply "traditional recipes"; don't wait for medical services when not promptly available—remove the tick yourself

*DEET, *N*,*N*-diethyl-*meta*-toluamide.

by using a pair of fine-tipped tweezers. The recommended method for tick removal is to pick the part of the tick closest to the skin and to tear it off without rotation and without squeezing the body, which could result in an increased influx of pathogens (see Figure 72-3). The tick should also not be drowned (e.g., by bathing), suffocated (by putting a drop of glue, nail polish, or oil on the tick), or burned (with a match or a cigarette), because an increased burden of infectious particles may be released into the bite wound while the tick is struggling. Another misconception is that if a black dot remains in the wound, it is the head; rather, it is some part of the biting apparatus only. Because of the anatomy of the tick, the salivary glands containing the TBE virus are removed by removing the body as described here, and any remaining mouth parts are of no significant contribution to the time span of possible virus transmission.

Vaccination

In former times, postexposure prophylaxis (PEP) by using TBE hyperimmune globulin within 96 hours for passive immunization after a tick bite was practiced. However, TBE hyperimmune globulin is no longer available, and standard lots of commercially available human immune globulin are untested as PEP and unlikely to contain a sufficient level of specific antibodies to protect against this infection.

Immunization against TBE before exposure is advised for persons living in or traveling to TBE-endemic areas, and the vaccine is currently available year round without any seasonal restrictions in many countries (but is not yet licensed in the United States).

The vaccine products that are registered in some western countries are branded as FSME-IMMUN and Ticovac (Baxter; originally developed by the Immuno AG, Vienna, Austria) and Encepur (Novartis; originally developed by the Chiron Behring GmbH and Company KG, Marburg, Germany). Both vaccines use very closely related inactivated TBE virus strains as antigens that elicit protective antibodies against all known subtypes of the TBE virus and are registered for intramuscular administration. Reported adverse events are mainly local side effects, with the likelihood of serious side effects such as neuritis being extremely low (neuritis occurs in less than 1 : 1,000,000 vaccinees). Neurologic disorders in general did not occur more often in the vaccinees than in the unvaccinated population. Standard and rapid immunization schedules are established, and virtually all lead to a strong immune response.

The topic of the booster dose interval is controversial. The intervals recommended by the companies are not always identical to those recommended by national vaccination boards or those listed on Internet websites (frequently used by travelers as a basic source of information). In case of a history of a probable TBE infection or irregular vaccination schemes, serologic testing to check or prove immunity should be stressed.

Data from 2004 show that about 60 million travelers visit TBE-endemic parts of Europe each year. Among these travelers, according to World Tourism Organization (WTO) data, there is an increasing trend to travel to those countries with an exceptionally high risk of TBE. Calculations show that for nonvaccinated travelers, the risk of acquiring TBE in a highly endemic area is not less than the risk of contracting typhoid fever in India (and typhoid fever vaccination on a regular basis for travelers heading to this destination is recommended).

Travelers tend to explore and enjoy their destinations, which usually includes some outdoor exposure. Furthermore, the curiosity to sample authentic regional food in some areas might expose travelers to TBE via raw milk and dairy products. In addition to advice for recreational travelers whose stated purpose in going to a TBE-endemic area is to participate in outdoor activities, education about the risks of TBE and prevention of transmission and discussion about the availability of vaccines to prevent disease should be offered by healthcare practitioners to families, scout groups, school classes, and students on exchange programs.

ACKNOWLEDGMENTS

I want to thank the companies of Baxter and Novartis for providing information material including data and graphics. In particular, Dr. Dieter Gniel was very helpful in sharing his vast experience on TBE.

EVIDENCE

Centers for Disease Control and Prevention (CDC): Tick-borne encephalitis among U.S. travelers to Europe and Asia—2000-2009, *Morb Mortal Wkly Rep* 26:59(11):335-338, 2010. *A review of all 2000-2009 laboratory records was conducted to identify cases of TBE among U.S. travelers. Five cases were identified by IgM serum antibodies and confirmed as TBE by plaque-reduction neutralization tests: four patients had traveled to Europe or Russia and had a biphasic illness followed by nearly complete recoveries. The fifth patient had traveled to China and had a monophasic illness with severe encephalitis and neurologic sequelae.*

Czupryna P, Moniuszko A, Pancewicz SA, et al: Tick-borne encephalitis in Poland in years 1993-2008—epidemiology and clinical presentation: a retrospective study of 687 patients, *Eur J Neurol* Dec 12, 2010. 10.1111/j.1468-1331.2010.03278.x. [Epub ahead of print]. *The epidemiology and clinical features of TBE in this region of Europe were analyzed. In this group of patients, the initial disease presented with meningitis in 41%, meningoencephalitis in 51%, and meningoencephalomylelitis in 8%. Ataxia in 14% and pareses in 9% were the most common neurological abnormalities that developed. Upon discharge, 23% had neurological and 44% had psychiatric sequelae.*

Schoendorf I, Ternak G, Oroszlan G, et al: Tick-born encephalitis (TBE) vaccination in children: advantage of the rapid immunization schedule (i.e., days 0, 7, 21). *Hum Vaccin* 4:42-47, 2007. *A clinical study involving 294 children aged 1-11 years old vaccinated with a pediatric formulation of TBE vaccine (Encepur children) according to the conventional schedule on days 0, 28, and 300, the modified conventional schedule on days 0, 21, and 300, or the rapid schedule on days 0, 7, and 21. The rapid immunization schedule in children stimulated rapid protection and stable titers for at least 300 days after vaccination.*

Weinberger B, Keller M, Fischer KH, et al: Decreased antibody titers and booster responses in tick-borne encephalitis vaccinees aged 50-90 years. *Vaccine* 28:3511-3515, 2010. *Cases of vaccine failures (clinical and serological evidence of TBE infection despite adequate immunization) have been reported predominantly in older persons. The immune-responsiveness to TBE vaccinations for age groups 50-59, 60-69, and >69 years were compared to a control group aged below 30 years. The antibody titers and booster responses measured for each group suggest that responsiveness of the immune system to vaccination is already impaired at the age of 50 compared to the control group. Booster intervals of 3 years are currently recommended for persons = or >60 years in Austria, but might be beneficially applied to persons = to or >50 years.*

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): *Tick-borne encephalitis.* Available at: www.cdc.gov/ncidod/dvrd/spb/mnpages/dispages/TBE.htm. *Good basic information on many aspects of this infectious disease.*

Centers for Disease Control and Prevention (CDC): *Travelers' health.* Available at: www.cdc.gov/travel/yellowbook/2010/chapter-5/tick-borne-encephalitis.aspx. *One of the reference sites on infectious diseases for U.S. doctors.*

International Scientific Working Group on Tick-Borne Encephalitis: *Prevention information.* Available at: www.tbe-prevention.info. *Site providing information focused on tick bite and TBE prevention.*

International Scientific Working Group on Tick-Borne Encephalitis: *Tick victims information.* Available at: www.tick-victims.info. *Information on the disease focused on clinical aspects provided by tick victims as well as by people working with TBE patients (including the so-called "self-help group of tick victims").*

International Scientific Working Group on Tick-Borne Encephalitis website. Available at: www.isw-tbe.info. *Information on TBE by the International Scientific Working Group on Tick-Borne Encephalitis.*

World Health Organization (WHO): *The vector-borne human infections of Europe: their distribution and burden on public health.* Available at: www.euro.who.int/__data/assets/pdf_file/0008/98765/e82481.pdf. *A WHO Internet site dedicated to European infectious diseases.*

World Health Organization (WHO): *Tick-borne encephalitis.* Available at: www.who.int/immunization/topics/tick_encephalitis/en/. *WHO site explaining prophylaxis and vaccination.*

World Health Organization (WHO): *Tick-borne encephalitis vaccine.* Available at: www.who.int/biologicals/areas/vaccines/tick_encephalitis/en/. *WHO site explaining prophylaxis and vaccination.*

Zuckerman JN, Jong EC, eds: *Travelers vaccines*, ed 2, Shelton, Conn., 2010, Peoples Medical Publishing House. *This book includes a chapter on TBE, mostly focused on travel medicine aspects.*

Primary Amebic Meningoencephalitis

Govinda S. Visvesvara, Jonathan S. Yoder, and Michael J. Beach

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ABSTRACT

Primary amebic meningoencephalitis (PAM) is caused by *Naegleria fowleri*, a mitochondria-bearing aerobic protist that normally completes its life cycle in the environment as a free-living organism. Occasionally, however, amebae invade the central nervous system (CNS) of humans and other animals, survive within the brain tissue, and cause an acute and fulminant infection, PAM. *N. fowleri* is also called *amphizoic amebae*.

Among the more than 40 species included in the genus *Naegleria*, *N. fowleri* is the only species that causes human infection. *N. fowleri* was previously classified under phylum Protozoa, subphylum Sarcodina, superclass Rhizopoda, class Lobosea, order Schizopyrenida, and family Vahlkampfiidae. However, the International Society of Protozoologists replaced the older classical taxonomic classification with a newer system based on modern morphologic approaches, biochemical pathways, and molecular phylogenetics. According to this new system, all eukaryotes including the amebae have been classified into six clusters or "supergroups," namely Amoebozoa, Opisthokonta, Rhizaria, Archaeplastida, Chromalveolata, and Excavata. *N. fowleri* is now included under supergroup Excavata: Heterolobosea: Vahlkampfiidae.

N. fowleri has three life-cycle stages: a feeding and reproducing trophozoite, a transitory flagellate, and a resistant cyst. Because it has a transitory flagellate stage in its life cycle, it is also called an *ameboflagellate*. The trophozoite is a sluglike ameba, feeds on gram-negative bacteria, and reproduces by binary fission. It moves sinuously by producing, usually from the anterior end, hemispherical bulges called *lobopodia*. The posterior end is sticky, often has several trailing filaments, and is called the *uroid*. The trophozoite measures 10 to 25 mcm and contains a single vesicular nucleus with a prominent, centrally placed nucleolus that stains densely with chromatic dyes. The cytoplasm contains numerous mitochondria, ribosomes, food vacuoles, and a contractile vacuole.

The trophozoite transforms into a flagellate stage when the ionic concentration of the surrounding environment changes as a result of rainfall. The flagellate reverts back to the trophic stage when favorable conditions return. It is possible to induce the trophozoites to transform into flagellates by suspending them in distilled water. The trophozoites begin to convert to flagellates within 10 minutes, and more than 50% will have differentiated into flagellates within a couple of hours. The flagellate has a single nucleus with a large nucleolus and usually has two flagella, but three or four flagella may also be seen occasionally. The flagellate has no cytostomes and hence cannot feed. It ranges in length from 10 to 16 mcm.

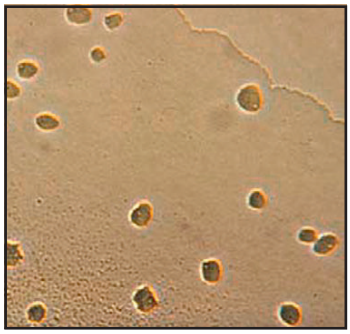
During adverse conditions (e.g., when the food supply becomes scarce or the environmental niche dries up), the trophozoite transforms into the resistant cyst. The cyst is usually spherical, measures 8 to 12 mcm, and is double-walled with a thick endocyst and a closely apposed thinner ectocyst. The cyst wall has pores, although they are difficult to see. The cyst has a single nucleus with a prominent nucleolus (Figure 73-1).

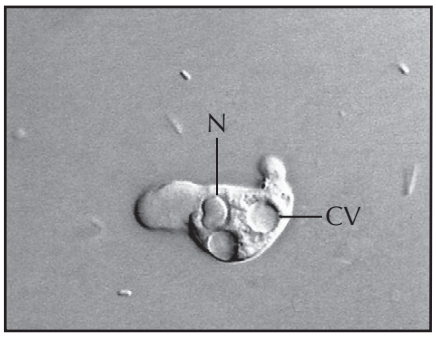
N. fowleri feeds on gram-negative bacteria such as *Escherichia coli* or *Enterobacter aerogenes*. It can therefore be easily maintained in the laboratory on nonnutrient agar plates coated with bacteria. It can also be grown on mammalian cell cultures like monkey kidney (E6) and human lung fibroblast (HLF) monolayers.

EPIDEMIOLOGY OF *NAEGLERIA FOWLERI* AND PRIMARY AMEBIC MENINGOENCEPHALITIS

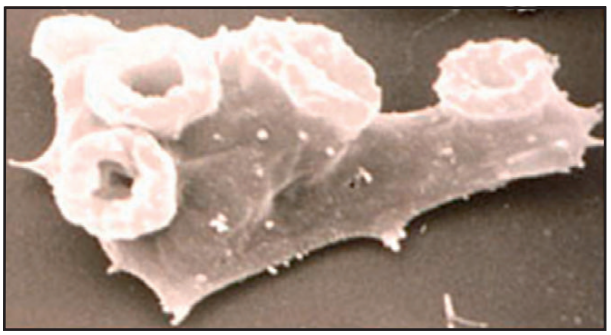
N. fowleri occurs worldwide and has been isolated from fresh water, thermal discharge of power plants, improperly disinfected heated swimming pools, hot springs, hydrotherapy pools, aquaria, sewage, and even nasal passages and throats of healthy individuals. *N. fowleri* can tolerate high temperatures, even up to 45° C. Therefore these amebae proliferate during summer months when the ambient temperature is likely to be high. Environmental sampling done in warm water lakes suggests that the amebae likely inhabit most warm fresh water habitats in southern-tier states in the United States. Typically, cases of PAM occur in the hot summer months when large numbers of people engage in aquatic activities in lakes, ponds, swimming pools, and other warm freshwater bodies that may harbor these amebae (Figure 73-2). Persons participating in aquatic activities, including swimming, diving, and water skiing, might come in contact with the amebae in water, resulting in infection. The portal of entry into the CNS is the olfactory neuroepithelium. The amebae that enter the nasal passages pass through the sievelike cribriform plate of the ethmoid bone, penetrate into the subarachnoid space, and enter the brain parenchyma. The incubation period from exposure to the ameba to disease may vary from 1 to 7 days (average 5 days), depending on the inoculum size. The disease progresses rapidly and leads to death within a week of symptom onset. PAM has also been diagnosed in the South American tapir and domestic cattle.

From 1962 to 2008, 111 PAM cases were reported in the United States (Figure 73-3). An additional 11 cases dating back to 1937 were identified through a retrospective examination of autopsy samples in Virginia. The median age of the 111 cases was 12 years (range 8 months to 66 years). Among the 111 cases, 88 (79.3%) involved male patients. Exposure occurred primarily in untreated, warm freshwater lakes or rivers in 15 warm-weather southern-tier states (Figure 73-4). Among the 100 cases for which the month of exposure was known, 87 (87%) occurred during July through September. Case patients were

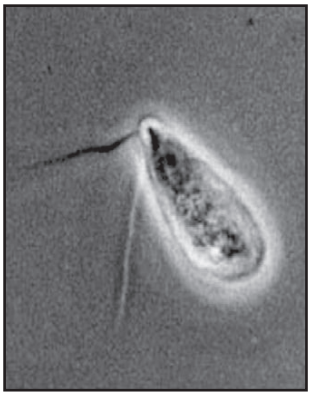

Trophozoite on agar



Trophozoite, differential interference contrast
(N = Nucleus; CV = Contractile vacuole)


Trophozoite, scanning electron microscopy


Cyst, phase contrast


Flagellate, phase contrast

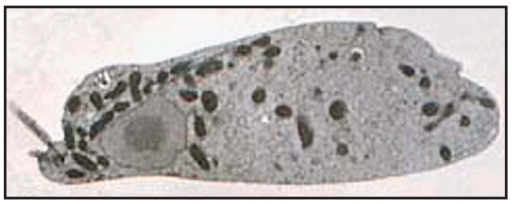

Flagellate, transmission electron microscopy

Figure 73-1 Morphology of the three life stages of *Naegleria fowleri*. *(Courtesy Centers for Disease Control and Prevention.)*

described as engaging in water-related activities including diving or jumping into the water, swimming, or other water sports before illness onset.

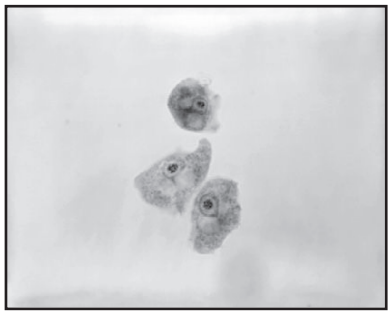
CLINICAL FEATURES

Symptoms and/or clinical features of PAM include sudden onset of bifrontal or bitemporal headaches, high fever, nuchal rigidity, nausea, vomiting, irritability, and restlessness, which are similar to meningoencephalitis caused by bacteria or viruses. As the infection progresses, other signs and symptoms such as photophobia, lethargy, seizures, confusion, coma, diplopia, or bizarre behavior may occur, and death occurs within a week.

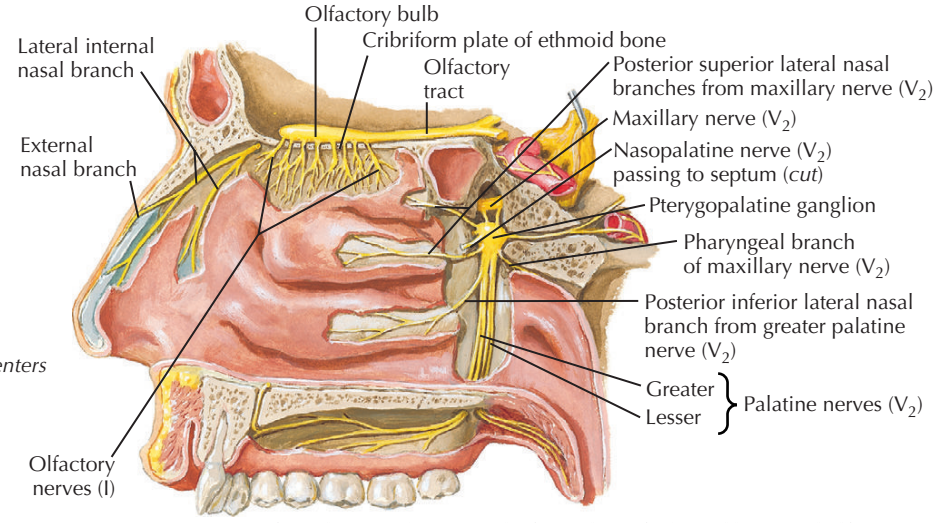
DIFFERENTIAL DIAGNOSIS

Because the clinical presentation is nonspecific and may be present in other bacterial or viral meningeal infections, it is difficult to differentiate PAM caused by *N. fowleri* from pyogenic or bacterial meningitis. Therefore PAM should be suspected in symptomatic young adults and children with recent exposure to fresh waters during summer, especially in the southern tier of the United States. The cerebrospinal fluid (CSF), obtained by lumbar puncture, may have low to normal glucose, high protein, and elevated pressure. CSF is usually pleocytotic with a preponderance of polymorphonuclear leukocytes and no bacteria. Microscopic examination of CSF smears may reveal the presence of actively moving amebae or in rare cases flagellates. Giemsa or trichrome staining of CSF smears will demonstrate the presence of amebae with a characteristically large nucleolus within the nucleus of the amebae and thus facilitate in differentiating amebae from the neutrophils (Figure 73-5). Amebae in the CSF smears can be identified as *N. fowleri* by using a monoclonal antibody specific for *N. fowleri* by a direct immunofluorescent antibody (IFA) technique.

The amebae can also be cultured from samples of CSF or from brain tissue obtained postmortem, by placing macerated brain tissue onto an agar plate coated with bacteria into axenic growth medium, or by inoculating the brain tissue, or onto tissue culture monolayers. The ameba feeds voraciously on the cell culture and destroys the confluent layers within 2 to 3 days. *N. fowleri* can also be grown in cell-free axenic medium as well as in a chemically defined medium. Molecular techniques such as polymerase chain reaction (PCR) and nested PCR assays have been developed for the specific identification of *N. fowleri* in cultured amebae from the CSF and brain tissue of patients, and the environment. In addition, specific genotypes that are present in the United States can be identified by sequencing the 5.8S ribosomal ribonucleic acid (rRNA) gene and the internal transcribed spacers 1 and 2 (*ITS1* and *ITS2*) of *N. fowleri.* Based on the analysis of such sequencing it was shown that the two strains of *N. fowleri*, isolated from two PAM patients who visited the same hot spring in California but at different times, belonged to the same genotype, type II. A real-time multiplex PCR assay developed at the Centers for Disease Control and Prevention (CDC) can identify deoxyribonucleic acid (DNA) of *N. fowleri*



Amebae proliferate during the summer months in warm freshwater *(Courtesy Centers for Disease Control and Prevention)*



Cross section of nasal cavity showing cribriform plate of ethmoid bone and olfactory nerves. Amebae enter the brain parenchyma through the cribriform plate

Healthy young individuals swimming, diving, and engaging in other aquatic activities in warm freshwater bodies that may harbor *N. fowleri* are at risk for infection

Figure 73-2 Environmental exposure leading to infection with *Naegleria fowleri.*

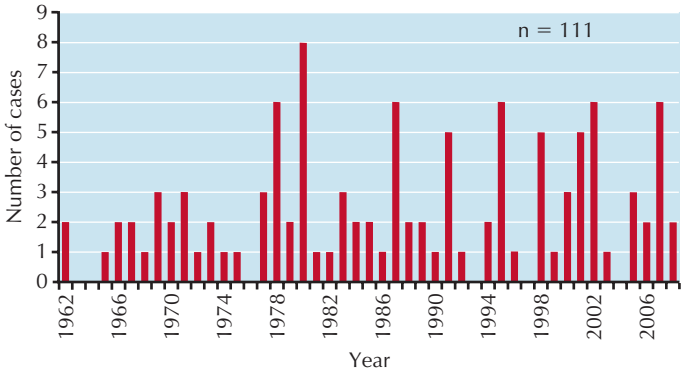


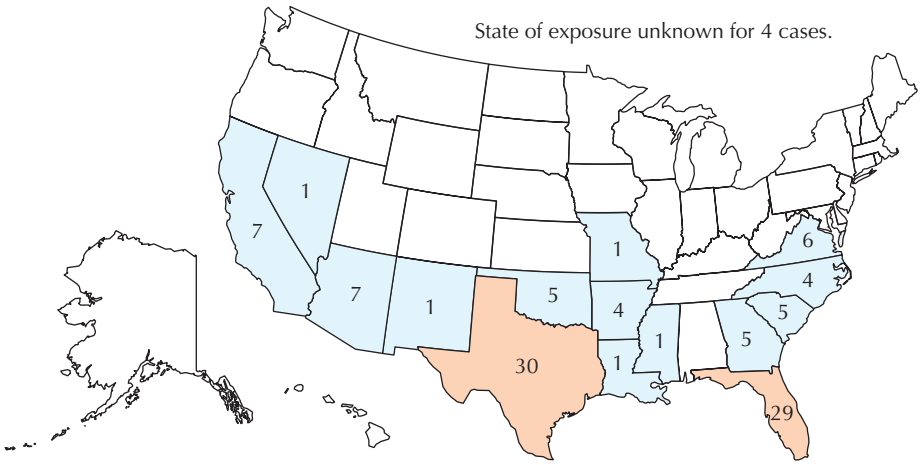
Figure 73-3 Number of *Naegleria fowleri* infections by year—United States, 1962 to 2006. *(Courtesy Centers for Disease Control and Prevention.)*

in the CSF in about 5 hours, illustrating that this test is invaluable for the rapid antemortem detection of *N. fowleri* so that treatment can be instituted.

PATHOPHYSIOLOGY

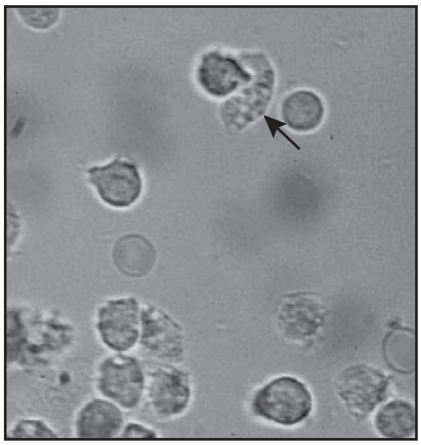
The olfactory bulbs demonstrate severe hemorrhagic necrosis and are usually surrounded by purulent exudate. Cerebral hemispheres are usually soft, markedly swollen, edematous, and severely congested. The leptomeninges (arachnoid and pia mater) also are severely congested, hyperemic, and opaque, with limited purulent exudate within sulci, the base of the brain, the brainstem, and the cerebellum. Numerous superficial hemorrhagic areas are also seen in the cortex. Lesions are also found in and around the base of the orbitofrontal and temporal lobes, base of the brain, hypothalamus, midbrain, pons, medulla oblongata, and upper portion of the spinal cord.

Microscopically, the purulent leptomeningeal exudate consists of predominantly polymorphonuclear neutrophils (PMNs),

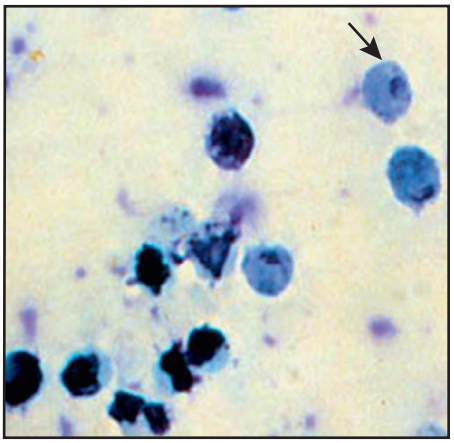


State	# of Cases
Arizona	7
Arkansas	4
California	7
Florida	29
Georgia	5
Louisiana	1
Mississippi	1
Missouri	1
Nevada	1
New Mexico	1
North Carolina	4
Oklahoma	5
South Carolina	5
Texas	30
Unknown	4
Virginia	6
Total	**111**

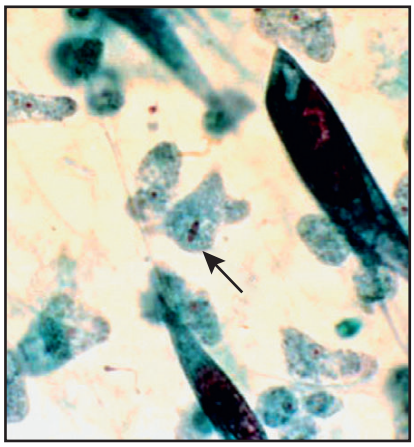
Figure 73-4 Number of cases of primary amebic meningoencephalitis caused by *Naegleria fowleri* by state of exposure—United States, 1962 to 2008.



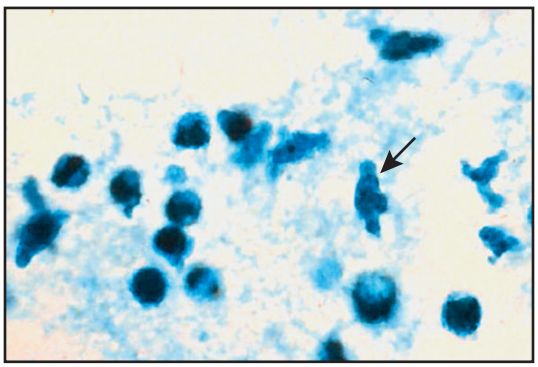
CSF smear showing an ameba *(arrow)*



CSF smear stained with Giemsa showing an ameba *(arrow)*



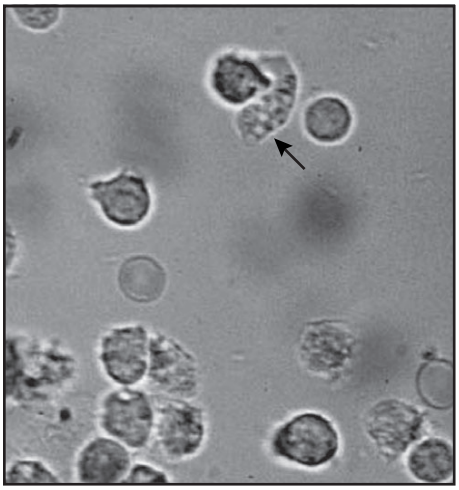
Amebae *(arrow)* growing in human lung fibroblast cell culture



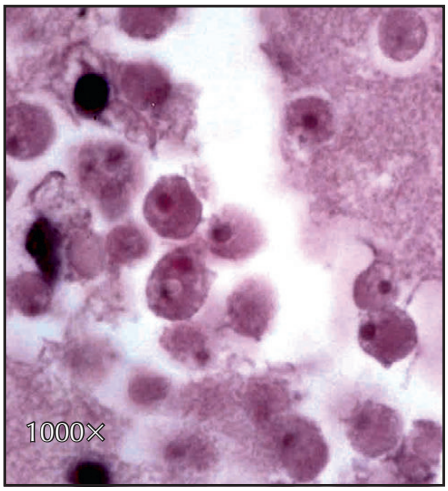
CSF smear stained with trichrome showing an ameba *(arrow)*

Figure 73-5 *Naegleria fowleri* in the cerebrospinal fluid and in cell culture. *(Courtesy Centers for Disease Control and Prevention.)*

few eosinophils, few macrophages, and some lymphocytes. Large numbers of *N. fowleri* trophozoites but no cysts without the presence of PMNs are seen, usually in pockets, within edematous and necrotic neural tissue. Amebic trophozoites ranging in size from 8 to 12 μm are also seen deep in Virchow-Robin spaces, usually around blood vessels with no inflammatory response (Figures 73-5 and 73-6). Scanning electron microscopic images have shown the presence of suckerlike structures, amebostomes, on the surface of the trophozoites, and it is believed that the amebostomes nibble away bits and pieces of the brain tissue. The trophozoites can be specifically identified as *N. fowleri* by polyclonal or monoclonal antibody staining.



N. fowleri ameboid trophozoite in cerebrospinal fluid, wet mount



N. fowleri trophozoites in brain section, hematoxylin and eosin (H&E) stain

Figure 73-6 Pathologic manifestation of primary amebic meningoencephalitis. *(Courtesy Centers for Disease Control and Prevention.)*

Computed tomography (CT) scans reveals the destruction of the cisternae around the midbrain and the subarachnoid space over the cerebral hemispheres.

MECHANISMS OF PATHOGENESIS

PAM can be produced in laboratory mice by instilling as few as 100 amebae into the nostrils. Mice develop the disease and usually die within a week, depending on the virulence of the strain of *N. fowleri*. In addition, when *N. fowleri* is inoculated onto mammalian cell cultures, it destroys the cell cultures within a week. It is believed that the amebae, in addition to ingesting bits and pieces of the brain tissue and/or the cell cultures, may also produce (1) phospholipase A and B activity or a cytolytic factor, causing destruction of cell membranes; (2) neuraminidase or elastase activity facilitating destruction of tissue culture cells; (3) presence of a perforin-like, pore-forming protein that lyses target cells; and (4) cytopathic protein that triggers the apoptosis pathway in susceptible tissue culture cells.

SEROLOGIC TESTS

A specific antibody response to *N. fowleri* in a California patient who recovered from this disease was documented. However, because most PAM patients die within a short time (2 to 15 days) after infection, there is usually insufficient time to mount a detectable immune response before death; hence the usefulness of serologic tests in the diagnosis of PAM is limited. Therefore previous attempts to detect an antibody response to *N. fowleri* using IFA have been largely unsuccessful. Serologic studies have shown that domesticated as well as wild mammals including raccoons, muskrats, squirrels, and rabbits, as well as humans, develop antibodies to *Naegleria* amebae.

THERAPY AND PROGNOSIS

According to published reports, only a few patients have survived PAM; 1 of 111 reported patients in the United States has survived documented PAM. Amphotericin B, an antifungal drug, is very active in vitro against *N. fowleri*, and treatment with this drug early in the process of infection may be beneficial. One survivor was aggressively treated with intravenous and intrathecal amphotericin B, intravenous and intrathecal miconazole, and oral rifampin. Over a 4-year follow-up, she remained completely healthy and free of any neurologic deficits. Although miconazole is no longer available in a parenteral form in the United States, treatment with amphotericin B alone may be beneficial because it is 100 times more active against *N. fowleri* than miconazole in vitro. However, use of amphotericin B monotherapy in cases since the published report of the survivor who received combination treatment has not, to date, proven effective. Whether these treatment failures were a result of therapy being administered too late in the progression of the disease is unknown.

PREVENTION AND CONTROL

Because *N. fowleri* is a thermophilic ameba, it can proliferate in water when the ambient temperature increases (particularly above 30° C), especially during summer months in the southern tier of the United States. Although the impact of global climate change on this organism is unclear, it is possible that rising temperatures will lead to cases of *N. fowleri* infection in countries or northern states where it has not been recorded. Chlorine (one part per million) can kill both *N. fowleri* trophozoites and cysts, so proliferation of this ameba can be prevented by adequate maintenance and disinfection of swimming pools and drinking water supplies, especially during summer months.

Inadequate chlorination may allow the growth of *N. fowleri*, resulting in colonization of pools and drinking water systems, proliferation of the ameba, and increased potential for infection and death of swimmers or people getting contaminated water up their noses. In former Czechoslovakia, 16 deaths from PAM occurred over a 3-year period and were traced to a swimming pool with low free-chlorine concentration. In Arizona, two children contracted PAM and died after putting their heads under the water in an in-home tub and a partially filled, untreated swimming pool that was filled with untreated, thermally heated

groundwater from the neighborhood drinking water supply. *N. fowleri* was subsequently identified in the drinking water by nested PCR analysis. This was the first time that drinking water was implicated as the source of *N. fowleri* infection in the United States. However, drinking water, carried overland in pipes warmed by the sun, was identified as a source of infection in Australia during the 1970s. Because of a cluster of cases of PAM involving children and adults in South Australia, the South Australia High Commission issued warnings to children, young adults, and swimmers not to immerse their heads in tap water.

No data validating prevention methods exist for this rare but severe disease. As a result, the only certain way to prevent *N. fowleri* infection is for swimmers to refrain from water-related activities in bodies of untreated fresh water, particularly in southern-tier states in the United States where the ameba is known to proliferate. However, some unproven measures that might reduce risk by limiting the chance of contaminated water going up the nose include (1) avoiding water that might be expected to contain the amoeba (e.g., warm freshwater, hot springs, and thermally polluted water such as water around power plants); (2) avoiding water-related activities in warm freshwater during periods of high water temperature and low water volume; (3) holding the nose shut or using nose clips when taking part in water-related activities in bodies of warm fresh water such as lakes, rivers, and hot springs; and 4) avoiding digging in or stirring up the sediment while taking part in water-related activities in shallow, warm freshwater areas. Messages regarding the risks associated with swimming in these locations should be routinely disseminated to the public, along with other messages about water safety and risks.

CONCLUSIONS

Although *N. fowleri* infection is rare, it is of major concern because of the severity of the disease, its nearly 100% fatality rate, and the disproportionate impact on children. Because PAM is a rare disease and signs and symptoms of infection are clinically similar to those of bacterial or viral meningitis, health professionals might not have a high index of suspicion. The low index of suspicion for PAM is likely to lead to a delay in appropriate diagnostic testing and initiation of treatment. As a result, it is likely that many cases occur that go undiagnosed and unreported on a global scale.

EVIDENCE

Centers for Disease Control and Prevention (CDC): Primary amebic meningoencephalitis caused by *Naegleria fowleri*—Arizona, Florida, and Texas, 2007, *MMWR Morb Mortal Wkly Rep* 57:573-577, 2008. *An important publication that describes the infection, primary amebic meningoencephalitis, caused by* Naegleria fowleri *in 2007 in the three southern States (Arizona, Florida, and Texas) of the United States.*

Seidel JS, Harmatz P, Visvesvara GS, et al: Successful treatment of primary amebic meningoencephalitis, *N Engl J Med* 306:346-348, 1982. *Case report of the only known treated survivor of PAM.*

Yoder JS, Eddy BA, Visvesvara GS, et al: The epidemiology of primary amoebic meningoencephalitis in the USA, 1962-2008, *Epidemiol Infect* 22:1-8, 2009. *Comprehensive report emphasizes an urgent need for the development of science-based risk reduction messages and strategies needed to prevent infections caused by* Naegleria fowleri.

ADDITIONAL RESOURCES

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Schuster FL, Visvesvara GS: Opportunistic amoebae: challenges in prophylaxis and treatment, *Drug Resist Updat* 7:41-51, 2004. *An excellent review of the various drugs that have shown promise in vitro and those that can be used in the treatment of infections caused by* Acanthamoeba *spp.*, Balamuthia mandrillaris *and* Naegleria fowleri.

Visvesvara GS, Moura H, Schuster FL: Pathogenic and opportunistic free-living amoebae: *Acanthamoeba* spp., *Balamuthia mandrillaris*, *Naegleria fowleri*, and *Sappinia diploidea*, *FEMS Immunol Med Microbiol* 50:1-26, 2007. *A detailed review highlighting the morphology of the amebae (*Acanthamoeba, Balamuthia mandrillaris, Naegleria fowleri *and* Sappinia*) their taxonomic status, ecology, clinical manifestations of diseases caused by the amebae, pathologic features, epidemiology, and treatment modalities.*

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SECTION VIII

Edited by Elaine C. Jong

Parasitic Diseases

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Introduction to Parasitic Diseases

74

Elaine C. Jong

Parasitic diseases that contribute a large share to the global burden of infectious diseases are featured in this section. Most people living in urban and suburban communities in industrialized nations tend to be insulated from the parasitic diseases that commonly affect the lives of millions of people living in rural tropical areas under impoverished circumstances where clean water, safe food, and adequate sanitation are lacking. Limited access to health services further amplifies the impact of parasitic diseases on the health of populations at risk, especially children residing in tropical developing countries. Human and fiscal resources for surveillance, diagnosis, treatment, and prevention of parasitic diseases are often insufficient in the areas of greatest need; thus many parasitic infections fall into the category of diseases referred to as *neglected tropical diseases* (NTDs).

Current trends in international travel and global migration contribute to the growing incidence of parasitic infections that come to medical attention in nonendemic areas. Silently incubating protozoan and helminthic (worm) infections acquired in endemic geographic locations abroad may be subsequently imported by returned international travelers and immigrants. High-risk exposures in endemic areas may have included insect bites (malaria, filariasis, Chagas disease); ingestion of contaminated water (giardiasis, amebiasis); ingestion of ethnic specialties prepared by cooking and preservation techniques insufficient to kill parasites contained in certain meats, fish, and seafood (trichinellosis, cestodes, food-borne trematodes); eating raw or inadequately cooked vegetables (soil-transmitted helminths [STHs], food-borne trematodes [FBTs]); skin contact with damp sandy ground (hookworm, strongyloidiasis); intimate contact with other humans (strongyloidiasis, amebiasis); and swimming in freshwater lakes, rivers, or streams in endemic regions (schistosomiasis).

Parasite transmission in industrialized countries may occur through blood-borne transmission (malaria, Chagas disease), pica (STHs), and poor hygiene among food handlers (amebiasis, giardiasis, cysticercosis). Eating inadequately cooked meat from wild game has been identified as a special risk factor for trichinellosis. Incursion into urban environments by wild animals such as coyotes and foxes has been recognized as a risk factor for transmission of alveolar echinococcosis in urban areas. The emergence of a global food market, where food items may be sold in locations across national borders far away from the place of origin, contributes to the dispersion of parasitic infections outside of regions where they are considered endemic and creates challenges for the recognition and epidemiologic analysis of single cases as well as mass outbreaks of food-borne illness caused by parasites.

Malaria is considered the most important parasitic disease in terms of global morbidity and mortality from an infectious agent, because its toll on human health is of a magnitude second only to tuberculosis. According to World Health Organization (WHO) statistics, there are 300 to 500 million cases of and 1 to 2 million deaths from malaria infections annually. Over 90% of the disease burden is in sub-Saharan Africa, where malaria (mostly *Plasmodium falciparum*) is the leading cause of mortality in children younger than 5 years of age. An estimated 25,000 travelers from developed countries acquire malaria each year, resulting in approximately 150 deaths.

Although helminth infections affect larger numbers of people than malaria and although helminth infections can be serious, the usual time period it takes for fatal pathology to develop is relatively indolent compared with that of *P. falciparum* malaria, in which death may occur within 72 hours after onset of clinical disease if the patient is not promptly diagnosed and treated with efficacious drugs (Table 74-1). With regard to helminth infections, the severity of disease is usually related to the worm burden, with heavily infected persons experiencing more health consequences than lightly infected persons. Preschool and school-age children in endemic areas tend to carry heavy worm burdens and are commonly co-infected by multiple parasite species. The consequences of living in "this wormy world," as described by American parasitologist Norman Stoll in a 1946 address, are not only limited to stunting of physical growth and development: multiple field studies have shown cognitive impairment among school-age children infected with schistosomiasis and intestinal worms. Measurable improvements in cognitive function as well as decreased rates of absenteeism were seen in children after school-based mass deworming programs.

The spectrum of parasites constituting the burden of parasitic disease varies from region to region, and detailed data about the geographic prevalence and incidence of parasite infections are needed to accurately assess the health of populations, target resources and interventions toward those in greatest need, and measure outcomes. Modern mapping technologies have been developed over the past decade that can be used to identify and quantify the magnitude of risk for specific parasite infections in specific geographic regions and integrate these data along with environmental factors. Such complex applications have been made possible by technologic advances in immunodiagnostic testing, remote sensing, and information processing. Examples of new mapping programs that illustrate the global distribution and disease burden of malaria and of STHs and schistosomiasis may be accessed at www.map.ox.ac.uk and www.thiswormyworld.org, respectively.

Although the greatest burden of parasitic disease affects populations in developing tropical countries, such infections lurk invisibly beneath the veneer of modern urban civilization. Returned international travelers, international adoptees, immigrants, migrant workers, and residents of rural agricultural communities in temperate-zone countries may harbor parasite infections that could become more widely transmissible given

Table 74-1 Estimates of Global Morbidity Resulting from Human Parasitic Infections

PARASITE	NUMBER OF INFECTIONS
Malaria	300-500 million
Ascaris (intestinal roundworm), *Enterobius* (pinworm)	1 billion each
Trichuris (whipworm), hookworm	500-900 million each
Schistosomiasis (blood fluke)	200 million
Filariasis, lymphatic *(Wuchereria bancrofti)*	115 million
Strongyloides	50-100 million
Paragonimus (lung fluke)	21 million
Onchocerciasis	17.8 million
Loa loa	3-13 million
Opisthorchis (liver fluke)	10 million
Clonorchis (liver fluke)	7 million
Fasciola hepatica (liver fluke)	2 million

appropriate circumstances of environment, vector, and proximity. Among debilitated and immunocompromised hosts, when the normal host-parasite relationship becomes unbalanced, serious hyperinfection syndromes may develop from latent parasitic infections—as seen, for example, in patients with strongyloidiasis.

Parasitic diseases are important health concerns at individual, community, and regional levels. Knowledge of the epidemiology, clinical presentations, diagnostic tests, and treatments is essential for detecting human parasites and preventing progression of early infections into serious conditions in affected individuals. Facilitating higher levels of personal hygiene and environmental sanitation among populations at risk and revitalizing vector control programs, as well as expanding surveillance and mass treatment programs (using new antiparasitic drugs and new drug combination therapies), are important actions for control at community and regional levels. Ultimately the development of vaccines against the most serious parasite infections will be a major step toward future parasitic disease control and prevention.

ADDITIONAL RESOURCES

Brooker S, Hotez PJ, Bundy DAP: The global atlas of helminth infection: mapping the way forward in neglected tropical disease control, *PLoS Negl Trop Dis* 4:e779, 2010. *Improved diagnostic tests and new technology for surveillance have enabled the development of new evidence-based maps that show the areas where there is the greatest prevalence and morbidity related to helminth infections—that is, oil-transmitted helminth infections, schistosomiasis, onchocerciasis,* Wuchereria bancrofti, *and others. The maps produced to date are accessible online at www.thiswormyworld.org. Continuing data collection will support efforts to implement and assess various control strategies, such as mass drug administration, in the control of targeted helminth infections.*

Hay SI, Okiro EA, Gething PW, et al: Estimating the global clinical burden of *Plasmodium falciparum* malaria in 2007, *PLoS Med* 7:e1000290, 2010. *This article describes a new cartographic technique and its application for deriving global clinical burden estimates of* P. falciparum *malaria for 2007, comparing these estimates with those derived under surveillance-based approaches. The article provides the rationale and detailed methodology used for the development of the Oxford University website www.map.ox.ac.uk.*

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Na-Bangchang K, Congpuong K: Current malaria status and distribution of drug resistance in East and Southeast Asia with special focus to Thailand, *Tohoku J Exp Med* 211:99-113, 2007. *An invited review of the malaria status in Asia reporting the distribution of confirmed foci and areas of chloroquine-, sulfadoxine-pyrimethamine–, and mefloquine-resistant* P. falciparum *malaria in Southeast Asia.*

Stoll NR: This wormy world, *J Parasitol* 33:1-18, 1947. *Landmark paper addressing the quantification of the global burden of helminth infections.*

World Health Organization (WHO): Preventive chemotherapy in human helminthiasis: coordinated use of anthelmintic drugs in control interventions: a manual for health professionals and programme managers, Geneva, 2006, Preventive Chemotherapy and Transmission Control, Department of Control of Neglected Tropical Diseases, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland. *An essential guide for health professionals and program managers planning to implement preventive chemotherapy programs.*

Amebiasis

Martin S. Wolfe

75

ABSTRACT

Infection with *Entamoeba histolytica* is a leading parasitic cause of death in developing nations and is an important health risk to travelers. Amebiasis is transmitted by parasite cysts via fecal-oral contamination from infected individuals or from contaminated food or water. *E. histolytica* infections may be noninvasive and asymptomatic or may cause varying degrees of symptoms through tissue invasion.

The first description of *E. histolytica* was by Lösch in 1875 from a case of acute dysentery. The cause of amebiasis is the protozoan parasite *E. histolytica*, which occurs in both cyst and motile trophozoite forms. A morphologically identical species, *Entamoeba dispar*, is considered a nonpathogenic parasite not requiring treatment and must be differentiated from potentially pathogenic *E. histolytica* by means of a stool enzyme-linked immunosorbent assay (ELISA) antigen test. Another species, *Entamoeba hartmanni* (formerly known as *small-race* E. histolytica), is now considered a separate nonpathogenic ameba. It is morphologically identical to *E. histolytica* and can best be distinguished by the small size of *E. hartmanni* cysts, which are less than 10 microns in size.

ETIOLOGIC AGENT

E. histolytica has trophozoite, precyst, and cyst stages (Figure 75-1). The cyst is the infective stage and is ingested orally from contaminated food, water, or fingers. Ingested cysts pass through the stomach, and excystation occurs in the lower small bowel; four small metacystic trophozoites are formed, which grow to full size. Trophozoites generally measure 12 to 40 microns and contain a single characteristic nucleus with a diameter of 2.8 to 4.5 microns and a small central karyosome with peripheral chromatin granules uniformly arranged along the nuclear membrane. Trophozoites are motile and move unidirectionally by rapidly thrusting out large, blunt, transparent pseudopodia. They pass along the intestinal canal until conditions favorable for colonization are found. This can occur anywhere in the large bowel but is more frequent in the cecal area. Multiplication is by rapid and repeated binary fission. Depending on various parasite and host factors, trophozoites may invade the tissue of the large intestine, primarily by lytic means, and may also metastasize to the liver and other extraintestinal sites. Invading trophozoites may contain ingested red blood cells. As the trophozoites are carried toward the rectum they eliminate food vacuoles and other cytoplasmic inclusions and become precysts. Precysts are rounded or oval with a cyst wall and contain a mass of glycogen vacuoles and large chromatoidal bars with rounded ends and a single nucleus. The precyst matures by two nuclear divisions to form a quadrinucleate cyst.

Mature cysts generally measure 10 to 14 microns and are round with a protective tough cyst wall. The four nuclei have the same characteristics as the nucleus of the trophozoite. Within the cyst are one or more oval bars known as chromatoid bodies, and in the early stages cysts contain glycogen. Cysts form only in the large intestinal lumen, and they exit the body in the feces. Cysts are relatively hardy and can survive outside the body long enough to be ingested and thus are the vehicles of transmission. Cysts are quite sensitive to desiccation and to temperatures above 40° C or below −5° C. They are killed almost immediately by boiling. Cysts are relatively resistant to chlorine and are not destroyed by concentrations used for water purification. Motile trophozoites passed in the feces of infected persons with diarrhea or dysentery can survive for only a brief time outside the body and do not develop into cysts; therefore trophozoites do not play a role in transmission.

EPIDEMIOLOGY

Amebiasis has a worldwide distribution but is most common in the developing world. In underdeveloped areas where drinking water is obtained from fecally contaminated water sources and contaminated water or sewage is used to grow or freshen vegetables, amebiasis has high incidence. Animal reservoirs of *E. histolytica* include monkeys, dogs, and pigs, but these animals play a minor role in transmission in comparison to humans, who are the principal reservoir of infection. Infection usually occurs by either direct person-to-person transmission of cysts or by cysts contaminating food or water. Frequent transmission is recognized in institutionalized groups and daycare centers for young children. Homosexuals, particularly males, are very commonly infected with the nonpathogenic *E. dispar* species and are asymptomatic.

CLINICAL FEATURES

E. histolytica is unique among the amebae parasitizing humans because of its ability to invade tissue. The fundamental pathology of *E. histolytica* is the trophozoite's lytic effect on the large bowel mucosa, leading to penetration of the host's tissue, necrosis of tissue cells, and formation of ulcers. Undermining of the ulcer margin and confluence of one or more ulcers lead to sloughing of the mucosa and development of broad ulcers with irregular outlines (Figure 75-2). Host factors, including nutritional deficiencies and other variables associated with poor socioeconomic and environmental conditions, appear to promote the more invasive nature of amebiasis observed in the developing world.

There is a variable clinical response to *E. histolytica* infection. Invasive amebiasis leading to dysentery, liver abscess, pleuropulmonary involvement, or, less commonly, involvement of other

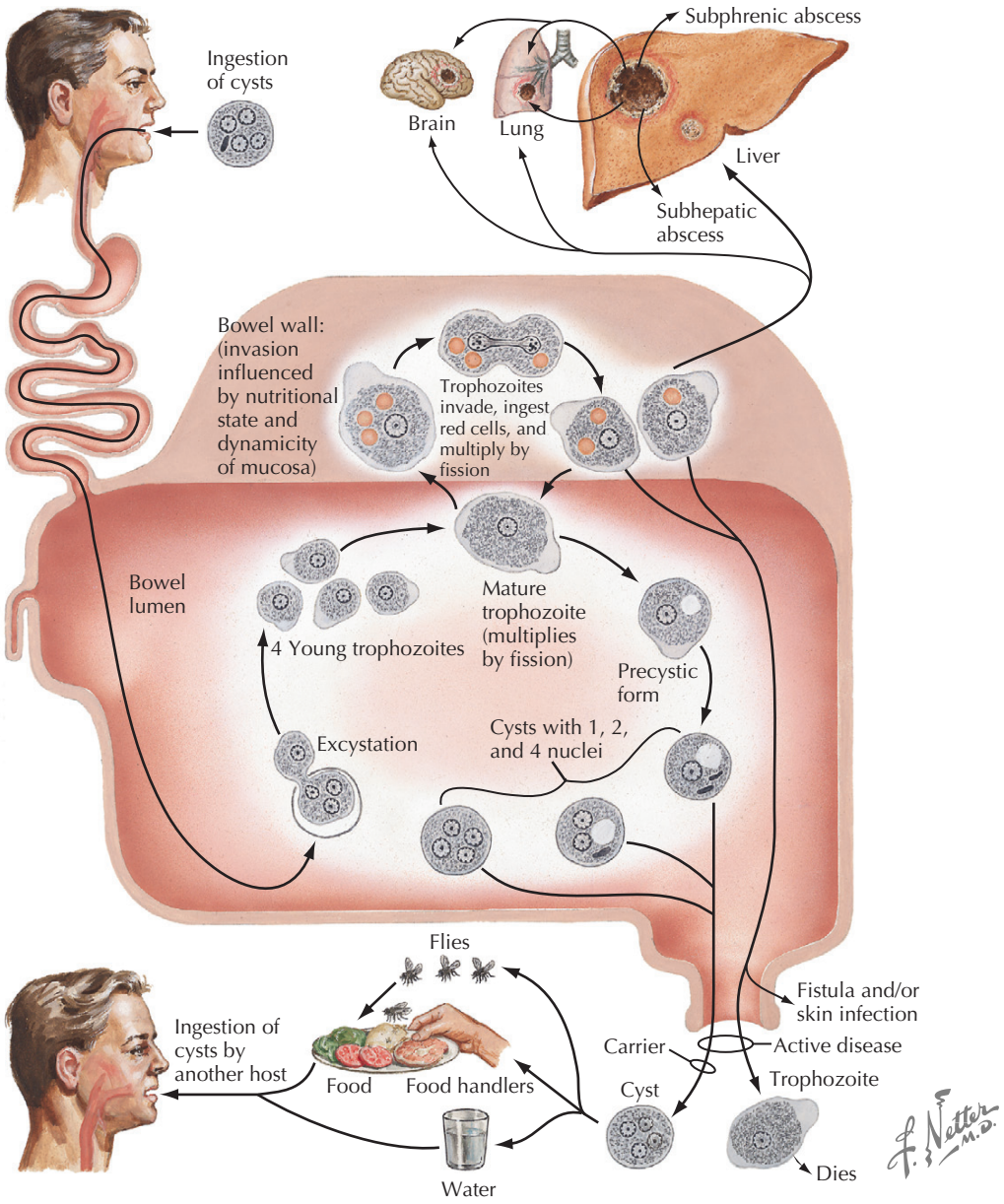


Figure 75-1 Amebiasis: clinical features and epidemiology.

organs occurs in the minority of infections. The majority of cases have either nondysenteric intestinal amebiasis with mild to moderate symptoms or are asymptomatic cyst passers.

Amebic dysentery, or acute amebic colitis, usually has an incubation of about 8 to 10 days, and onset is often sudden. Acute dysenteric symptoms may also develop in individuals with longstanding mild symptoms or who have been asymptomatic cyst passers. Typical acute symptoms and signs include severe abdominal cramps, chills, fever, nausea, headache, and tenesmus. The stools are liquid and contain bloody mucus. The white blood cell count may be elevated, with a polymorphonuclear leukocytosis. In very severe fulminant cases, extensive colonic involvement may lead to massive destruction of the mucosa, hemorrhage and perforation, and peritonitis. These complications can be fatal. The differential diagnosis of acute amebic dysentery includes bacillary dysentery, *Campylobacter* infection, and inflammatory bowel disease.

In nondysenteric intestinal amebiasis a spectrum of symptoms can be seen, ranging from totally asymptomatic individuals to those with mild symptoms: increased numbers of soft nonbloody stools, intermittent constipation, excessive intestinal distention and non-foul flatus, and increased fatigue. Those more severely infected may develop localized small ulcers in the large bowel and have very frequent mushy stools, lower abdominal cramps (often localized over the cecum or sigmoid), weight loss, anorexia and nausea, marked asthenia, and occasional urticaria. The differential diagnosis of nondysenteric intestinal amebiasis includes giardiasis, *Dientamoeba fragilis* infection, strongyloidiasis, *Schistosoma mansoni* infection, low-level inflammatory bowel disease, diverticulitis, and irritable bowel syndrome.

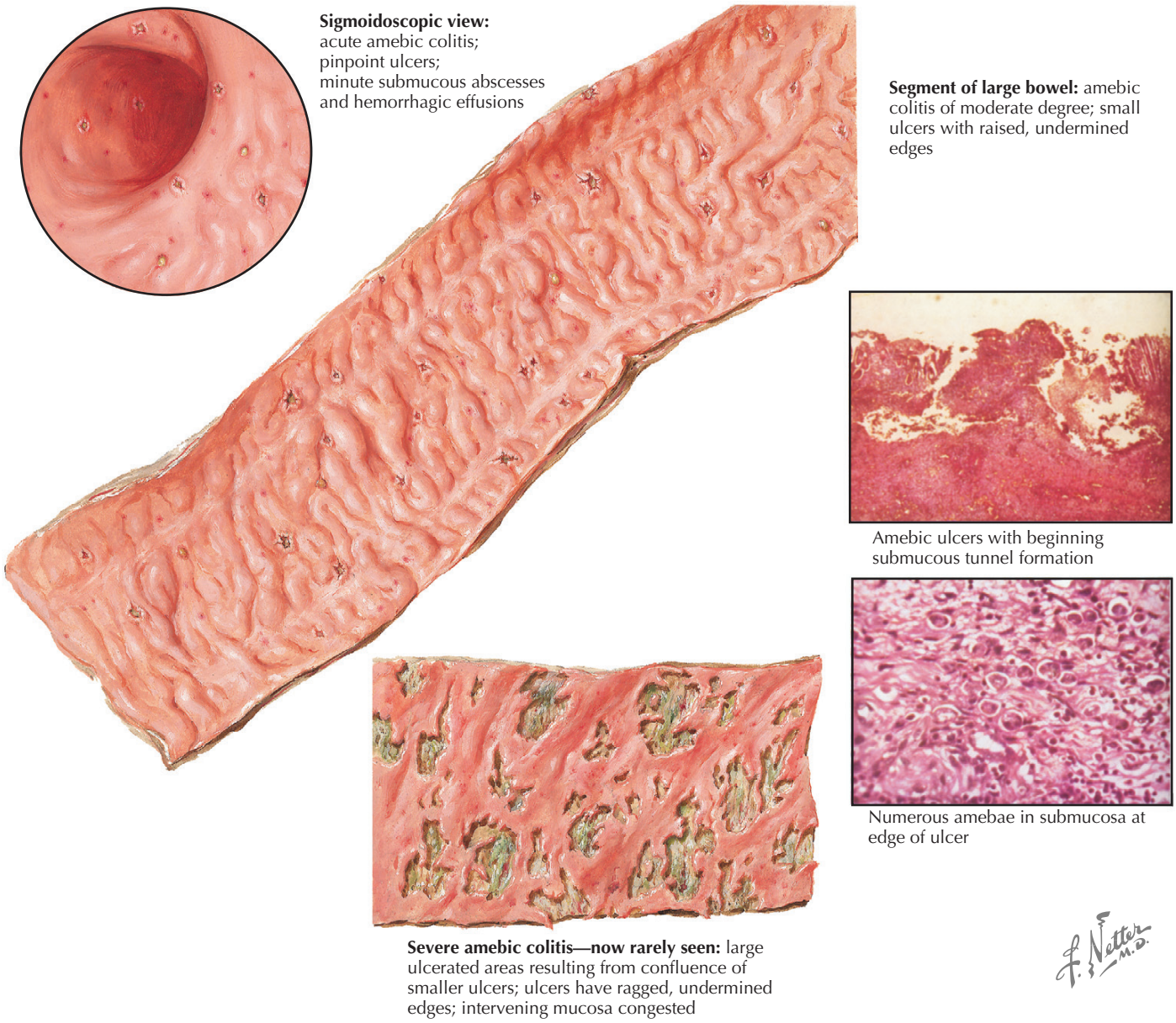
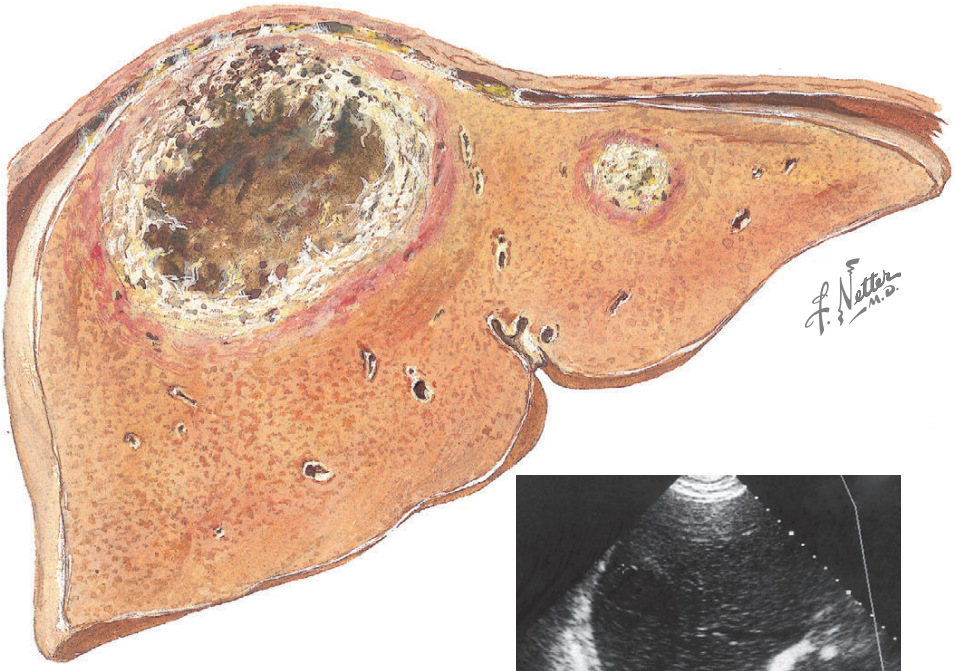


Figure 75-2 Amebiasis: pathologic findings.

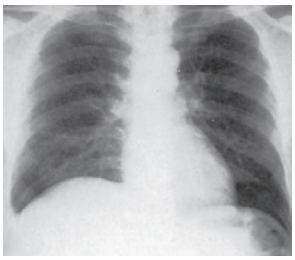
Asymptomatic cyst passers make up the majority of amebic infections seen in temperate climates. Both *E. histolytica* and nonpathogenic *E. dispar* may be present. *E. histolytica* infections may remain asymptomatic but also could potentially develop at a later date into symptomatic or invasive infections and could be the source of infection for others.

Amebic liver abscess may occur in the presence or absence of intestinal symptoms. Often it develops after a latent period following an earlier diarrhea episode or other intestinal disorders. No more than 20% of patients with amebic liver abscess have *E. histolytica* organisms present on stool examinations. The right liver lobe is much more commonly affected then the left lobe. Dissemination of *E. histolytica* trophozoites through the circulation to the liver lead to small microabscesses that coalesce into amebic liver abscess, which is usually single. The clinical picture may be variable, but typically there is high fever, pain over the right lower area of the chest or right hypochondrium, marked tenderness over an enlarged liver, and a moderate leukocytosis. Chills and profuse sweats may be present. Jaundice occurs only with very large abscesses and is a poor prognostic sign. Other signs may include referred pain to the right shoulder, a visible mass with a large abscess, and a nonproductive cough. In many cases, abscesses extend upward to involve the diaphragm, leading to diaphragmatic elevation and immobility and compression of the right lower lobe of the lung. An abscess may rupture into the lung or peritoneum (Figure 75-3). Differential diagnosis includes bacterial abscess of the liver, acute cholecystitis or cholangitis, infected hydatid cyst, acute

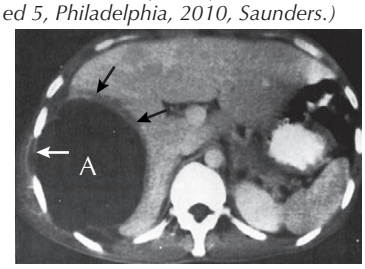


Large amebic abscess about to rupture through diaphragm; early-stage abscess in left lobe of liver

Typical ultrasound of an amebic hepatic abscess. Note the peripheral location, rounded shape with poor rim, and internal echoes. *(From Blumgart LH, Fong Y, eds:* Surgery of the Liver and Biliary Tract, *London, 2000, WB Saunders.)*



Chest x-ray of a 39-year-old Chinese man with a documented amebic liver abscess showing elevated right hemidiaphragm and a small right pleural effusion. *(From Mason RJ, Broaddus VC, Martin TR, et al:* Murray and Nadel's Textbook of Respiratory Medicine, *ed 5, Philadelphia, 2010, Saunders.)*



CT scan of amebic abscess. The lesion is peripherally located and round. The rim is nonenhancing but shows peripheral edema *(black arrows)*. Note the extension into the intercostal space *(white arrow)*. *(From Townsend CM, Beauchamp RD, Evers BM, et al:* Sabiston Textbook of Surgery, *ed 18, Philadelphia, 2008, Saunders.)*

Figure 75-3 Amebic liver abscess.

hepatitis, malaria, subphrenic abscess, and carcinoma of the liver. There is no entity of amebic hepatitis. The preferred term for liver involvement is hepatic amebiasis.

Pleuropulmonary amebiasis usually results from an extension of a hepatic abscess through the diaphragm, leading to pleural and pulmonary involvement. Pain occurs in the lower right area of the chest, and there may be a nonproductive cough.

Amebic pericarditis is an uncommon complication of an amebic liver abscess, usually resulting from extension of a left lobe liver abscess through the diaphragm into the pericardium.

Amebic brain abscess is a rare but generally fatal occurrence. It usually follows from amebic involvement of the liver and lungs. The most common symptoms are headache, fever, and convulsions.

DIAGNOSIS

Definitive diagnosis of intestinal amebiasis is by demonstrating *E. histolytica* parasites in the stool and requires accurate stool examinations. *E. histolytica* and morphologically identical *E. dispar* parasites must be differentiated by means of a two-step stool ELISA amebic antigen test described later. *E. histolytica* must also be differentiated from certain other similar-appearing, mainly nonpathogenic, intestinal protozoa (see Figure 77-1).

E. histolytica and other protozoal cysts may remain viable for some time in unpreserved formed stools, but trophozoites that are seen in dysenteric and diarrheal stool specimens are labile and may disappear from the stool within 30 minutes of passage. Specimens should preferably be collected with use of commercial stool collection kits containing a preservative. These preserved stools can then be examined without any time constraints with direct smear, concentration, and stained slide procedures.

Because protozoal cysts and trophozoites may be passed intermittently, three stool specimens should be collected on alternate days over a 6-day period. A negative result with a single or even three specimens does not totally rule out infection. As a more sensitive adjunct to stool examination procedures, and to differentiate *E. histolytica* and *E. dispar* cysts identified with standard procedures, a stool amebic antigen test can be performed. This cannot be done currently on a preserved stool specimen and requires freshly passed unpreserved stool. This is a two-stage ELISA that first identifies the presence or absence of breakdown products of *E. histolytica* and *E. dispar*. With a positive finding, a second *E. histolytica* test designed to specifically detect *E. histolytica* in stool specimens is performed.

Antibiotic and antiparasitic drugs, antacids, kaolin products, enema products, oily laxatives, and barium can cause masking or disappearance of protozoa in the stool or interfere with their recognition.

Charcot-Leyden crystals may be found in the stools of patients with amebiasis but are not pathognomonic. Unlike stools in acute bacterial dysentery, in which sheets of white blood cells are usually seen, stools in amebic dysentery seldom contain more then few leukocytes.

If diagnosis from stool examinations and ELISA is not possible in a patient in whom amebiasis is suspected, proctoscopic or colonoscopic examination allows visualization of typical ulcerated lesions from which scrapings or biopsies may be taken.

Various serologic techniques to detect invasive amebiasis are available. A positive result usually indicates an amebic cause, and conversely a negative result virtually rules out an amebic liver abscess and makes a diagnosis of amebic colitis highly unlikely. Indirect hemagglutination antiamebic antibodies can remain elevated for years after invasive infection.

Amebic liver abscess should be suspected in a patient with right upper quadrant pain, a tender liver, and fever. Liver function test results are often normal except for elevated alkaline phosphatase. Demonstration of a filling defect in the liver on computed tomography, magnetic resonance imaging, or sonogram examination, followed by a positive serum amebic antibody test result allows for definitive diagnosis (see Figure 75-3). Serologic studies may be negative in patients with an acute presentation of less than 7 days. A repeat examination 5 to 7 days later should then be positive.

TREATMENT

The nitromidazoles, metronidazole, and the related tinidazole are tissue amebicides that act on both invasive bowel and liver amebiasis. Paromomycin, iodoquinol, and diloxanide furoate are poorly absorbed luminal drugs that act primarily on the bowel lumen to eliminate cysts.

For amebic dysentery, moderate nondysenteric amebiasis, and invasive liver or other organ involvement, a tissue amebicide should be given, followed by a course of a luminal drug to prevent a later relapse (Table 75-1 lists treatment regimens).

Metronidazole comes as a 250-mg tablet and as an intravenous preparation. Tinidazole comes as a 500-mg tablet. Whichever of these drugs is used for moderately symptomatic or invasive amebiasis, it should always be followed by one of the poorly absorbed luminal drugs, which are more effective in clearing the bowel of *E. histolytica* cysts, in order to prevent later relapses of intestinal amebiasis or development of an amebic liver abscess.

Surgery may be necessary in patients with acute bowel perforation with localized abscess formation, perforation with peritonitis, or fulminating amebic colitis not responding to chemotherapy.

It is essential to attempt to differentiate amebic colitis from ulcerative colitis before administering corticosteroids, because amebic infection may be worsened by corticosteroids.

Mildly symptomatic nondysenteric infection may be treated as with moderately severe nondysenteric amebiasis with a nitroimidazole followed by a luminal drug. Alternatively, a luminal drug may be given initially; if this fails, a more vigorous combined treatment can be given.

Differences of opinion exist concerning the need to treat asymptomatic *E. histolytica* cyst passes. With the nonpathogenic *E. dispar*; treatment is not indicated: *E. dispar*–infected individuals spontaneously clear the parasite in 8 to 12 months. An asymptomatic *E. histolytica* cyst passer is a potential infector of others, and long-term carriage of this parasite could possibly lead to later active intestinal disease or amebic liver abscess.

With typical symptoms and signs of liver abscess, a scan or sonogram positive for a filling defect in the liver, and a positive serologic test for amebiasis, drug treatment is indicated. As with acute amebic dysentery, similar treatment with a nitroimidazole followed by a luminal drug should be administered. If satisfactory clinical improvement is not obtained after 3 days of the nitroimidazole treatment, aspiration of the abscess should be performed. It is a generally acceptable practice to percutaneously aspirate large pointing abscesses not responding to drugs alone or that may potentially rupture. Open surgical drainage may be necessary in certain situations. Serial liver scans have shown that most amebic abscesses heal gradually over 2 to 4 months after successful treatment. Occasionally the resolution time may be longer.

Table 75-1 Drug Therapy for Amebiasis

DRUG	ADULT DOSE	PEDIATRIC DOSE
Asymptomatic Cyst Passer		
Paromomycin	500 mg tid PO × 7 days	30 mg/kg/day in three divided doses PO × 7 days
Iodoquinol	650 mg tid PO × 20 days	30-40 mg/kg/day (max 2 g) in three doses × 20 days
Diloxanide furoate*	500 mg tid PO × 10 days	20 mg/kg/day PO in three doses × 10 days
Mild to Moderate Intestinal Disease		
Either metronidazole or tinidazole followed by one of the luminal drugs used for asymptomatic cyst passers above		
Metronidazole	500 mg tid PO × 10 days	35 mg/kg/day in three divided doses PO × 10 days
Tinidazole	2 g once PO × 3 days	>3 yr: 50 mg/kg/day (max 2 g) in one dose PO × 3 days
Amebic Dysentery, Amebic Liver Abscess, and Other Extraintestinal Infection		
Either metronidazole or tinidazole followed by one of the luminal drugs used for asymptomatic cyst passers above		
Metronidazole	750 mg tid PO × 10 days	45 mg/kg/day in three divided doses × 10 days
Tinidazole	2 g once PO × 5 days	>3 yr: 50 mg/kg/day (max 2 g) in one dose PO × 5 days

*Not available commercially. May be obtained through a compounding pharmacy such as Panorama Compounding Pharmacy (800-292-6773).
PO, Orally; *tid,* three times a day.

After treatment of intestinal amebiasis, follow-up stool examinations and/or an ELISA amebic antigen test should be performed about 4 weeks later as a check for cure.

PREVENTION

Preventive measures are similar to those for other enteric pathogens and should be directed toward education concerning means of transmission of amebiasis and methods of avoiding infection. Infected food handlers should be identified and treated, as should infected individuals in institutions and children in daycare centers. Contamination of food by flies may be prevented by screening and use of insecticides. Food handlers should wash their hands and have appropriate sanitary facilities. In endemic areas it is important to avoid cold foods and salads prepared from raw vegetables possibly infected from "night soil," sewage, or contaminated water. Community water sources should be protected from fecal contamination and made safe by filtration, sedimentation, and chlorination. Boiling of water destroys amebic cysts immediately. Iodine water purification tablets or portable water filters using a filter and iodination are more effective than chlorine tablets. Only ice prepared from treated water should be used. Asymptomatic *E. histolytica* cyst passers should be treated to avoid possible transmission to others.

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Giardiasis

Martin S. Wolfe

76

ABSTRACT

Giardia lamblia was first discovered in 1681 by Antoine van Leeuwenhoek, who found the parasite in his own stool. For many years thereafter, *G. lamblia* was considered to be of doubtful pathogenicity. Increased awareness of this parasite and appreciation for its clinical significance occurred in the early 1970s with its recognition in large numbers of visitors to the Soviet Union who returned with symptomatic giardiasis. Giardiasis caused by *G. lamblia* is now recognized as a leading disease of travelers to and natives of the developing world. In the United States, *G. lamblia* causes intestinal disease in persons who drink contaminated water, in children who attend daycare centers and their families, and in men who have sex with men. This parasite is also one of the most frequently identified pathogens in waterborne outbreaks in the United States and elsewhere.

ETIOLOGIC AGENT

G. lamblia is a flagellate and has both trophozoite and cyst stages in its life cycle. The trophozoite is pear-shaped and dorsally convex and has a shallow ventral concave sucking disk. The trophozoite attaches to the small intestinal mucosal surface by the sucking disk. The trophozoite measures 9.5 to 21 µm long by 5 to 15 µm wide and has two nuclei and four pairs of flagella. Trophozoites divide by longitudinal binary fission, and cysts develop as liquid feces gradually dehydrate in transiting the large bowel.

Cysts are oval with a tough hyaline cyst wall and measure 8 to 10 µm long by 7 to 10 µm wide. The mature cysts contain four nuclei, usually situated at one end; curved median bodies; and linear axonemes. The cysts can survive if kept cool and damp and can persist in water for up to 3 months. They can also survive standard concentrations of chlorine used in water purification systems. Infection is transmitted by ingestion of cysts in contaminated water or food or from unwashed hands; cysts pass through the stomach unharmed.

Excystation occurs in the duodenum, and two trophozoites from each mature cyst establish themselves among the intestinal villi of the duodenum and upper jejunum. Trophozoites firmly attach to the intestinal microvillous surface with their sucking disks or move about free in the lumen; actual invasion of the mucosa and submucosa has been infrequently documented. The trophozoites are most often found in liquid or soft stools, and the more resistant, infective cysts are seen in more formed stools (Figure 76-1).

EPIDEMIOLOGY

Giardiasis occurs worldwide with higher prevalence where sanitation is poor. Persons of all ages are affected, though in endemic areas infection is more frequent in infants. Specific areas of recognized increased risk for travelers include Russia, Southeast and South Asia, tropical Africa, Mexico, and western South America. *G. lamblia* is the most commonly reported pathogenic protozoan infection in the United States.

Infection is spread directly from person to person by fecal-oral contamination with cysts or indirectly by transmission from water or food. In the United States, most infections are sporadic, especially in campers, hikers, or returned travelers who drink untreated stream or other water. Infections occur in outbreak or endemic forms in nursery centers or other institutional settings and among family members of infected children. Transmission also occurs among male homosexuals and others engaging in oral-anal sexual practices. Ingestion of 100 or more cysts is required to ensure infection in humans, but ingestion of as few as 10 cysts has resulted in infection in volunteers.

Humans are the main reservoir of the parasite, but a variety of animals carry *Giardia* species similar to those infecting humans. *Giardia duodenalis* (which includes *G. lamblia*) naturally infects humans, beavers, coyotes, cats, and dogs and can experimentally infect certain other animals. Another distinct species, *Giardia muris*, infects primarily mice and rats. Community water supplies or streams can be contaminated by *G. duodenalis* cysts from infected beavers, which have been infective for humans experimentally. There is little confirmed evidence of transmission from infected dogs to humans.

Both humoral and cellular immune responses to *G. lamblia* infection are generated by the host. Secreted immunoglobulin A (IgA) and IgM antibodies play a role in eradicating parasites. Deficiency of IgA can lead to difficult-to-eradicate, long-lasting infection.

CLINICAL FEATURES

Symptomatology differs from person to person, depending on such factors as inoculum size, duration of infection, and individual host and perhaps parasite factors. The incubation period generally varies from about 8 to 15 days. The acute stage usually begins with a feeling of intestinal uneasiness, followed by nausea and anorexia. Low-grade fever and chills may also be early symptoms. Subsequent symptoms may include explosive, watery, foul-smelling diarrhea; marked abdominal distention and gurgling associated with increased passage of foul gas; and perhaps belching with foul taste. Upper or middle epigastric cramps or pain may also occur. Blood or mucus in the stool is rare. The acute stage, which usually lasts about 3 or 4 days, can resemble travelers' diarrhea from other causes and may not be recognized as resulting from giardiasis. Whereas most patients experience diarrhea during this time, some of the other symptoms may occur less frequently.

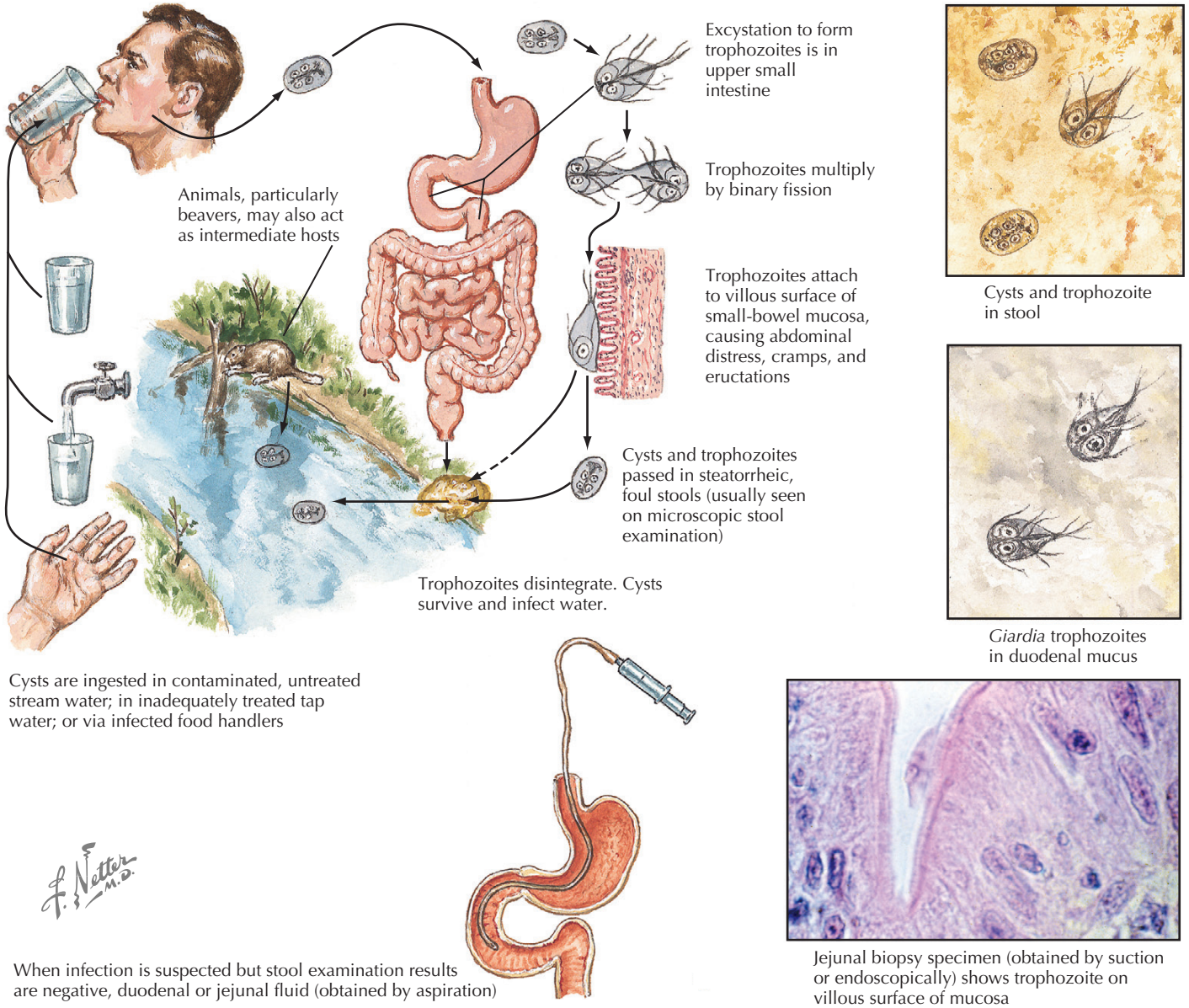

Figure 76-1 Giardiasis.

Some acute infections may clear spontaneously, but not infrequently a more long-standing subacute or chronic infection lasting for months to years may develop. In persons returning from endemic areas, the acute stage may not be remembered, and these patients can experience persistent or recurrent mild to moderate symptoms. Lassitude, headache, anorexia, malabsorption with weight loss, foul diarrhea and gas, bloating, and gurgling may occur (Table 76-1). Chronic infection in small children can cause failure to thrive. Urticaria can occur with giardiasis, and rarely cholecystitis and pancreatitis have been reported with *G. lamblia* infection. Uncommon associated symptoms including arthritis and retinal arteritis and iridocyclitis have responded to specific anti-*Giardia* treatment. As stated by an experienced clinician working on giardiasis, "the symptomatology of giardiasis is rich and unpredictable; individual variability and the intermittent nature and changing of the symptoms are characteristic."

Many infections disappear after variable periods of time. About 13% of infected adults and up to 50% of infected young children may remain asymptomatic. The duration of the asymptomatic cyst-passing state has not been determined.

Malabsorption of fat, glucose, lactose, xylose, vitamin A, and vitamin B_{12} has been reported in some patients. Lactose intolerance, frequently present during infection, may persist for variable periods of time after apparent eradication of giardiasis with specific treatment. Symptoms of lactose intolerance such as loose stools, bloating, and increased gas that persist after treatment must be differentiated from similar symptoms caused by continuing infection.

The differential diagnosis can include peptic ulcer disease or gastritis, hiatal hernia, gallbladder disease, lactose intolerance, irritable bowel syndrome (including postinfectious irritable bowel), celiac disease, and other causes of malabsorption, and certain other intestinal protozoa.

Table 76-1 Clinical Features of 32 Patients with Proven Giardiasis Recently Returned from the Former Soviet Union* Compared with 105 State Department Cases with Undetermined Duration of Proven Infection

	Percent with Symptom	
SYMPTOM	**STATE DEPARTMENT (105)**	**USSR (32)**
Flatulence	46.7	56.5
Foul stool	44.8	52.2
Cramps	32.4	59.4
Distention	31.4	0
Anorexia	20.0	56.2
Nausea	20.0	0
Weight loss	18.1	30.4
Belching	15.2	30.4
Heartburn	14.3	0
Headache	11.4	0
Constipation	11.4	0
Vomiting	4.8	34.4
Fever	3.8	17.4
Chills	2.9	0
Diarrhea	62.9	71.9
Blood in stool	0	0
Mucus in stool	3.8	87.5
Fatigue	28.6	87.5

*Data from Walzer PD, Wolfe MS, Schultz ME: Giardiasis in travelers, *J Infect Dis* 124:235-237, 1971.
USSR, Union of Soviet Socialist Republics.

Table 76-2 Possible Problems Preventing Identification of *Giardia lamblia*

PROBLEM	COMMENT
Medication administration	Antibiotics may cause organism distortion, or organisms may be present in very low numbers; antacids, antidiarrheal preparations, and laxatives may cause organism distortion or may mask the presence of organisms.
Diagnostic procedures	Enemas may cause organism distortion.
Radiographic examination	Barium may cause organism distortion and mask the presence of organisms.
Intermittent shedding	Organism numbers in stool fluctuate widely. Even if a series of three stool specimens is examined correctly, the organisms may not be recovered and identified.
Laboratory techniques	Use of concentration techniques and permanent stained fecal smears are mandatory for complete stool workup.
Specimen examination	Trained personnel required for accuracy.
Failure to obtain additional specimen types	Duodenal-jejunal aspirates and biopsy; enzyme immunoassay technique to detect fecal antigen.

DIAGNOSIS

Many, but not all, cases of giardiasis can be confirmed by stool examination. A series of three stools, one collected on alternate days, should be examined by direct smear, after concentration, and on a stained slide. It must be recognized that *G. lamblia* cysts and trophozoites are shed in the stool on a periodic basis, and even examination of a series of six or more stools may not reveal the organism. Continued negative stool examinations do not rule out *G. lamblia* as a causative agent.

A more sensitive method of confirming the presence of *G. lamblia* is with a *Giardia* stool enzyme immunoassay (EIA) cyst antigen test. A number of comparable commercial test kits are available. Stool immunofluorescence (IF) test kits are also available to identify *G. lamblia* cysts in stool. One of these tests should always be performed when *G. lamblia* is suspected. Stool specimens preserved in merthiolate-formalin (MF), 10% buffered formalin, or sodium acetate formalin (SAF) can be used for the EIA technique. Direct smear, concentration, and stained slide examinations of stool can also be performed on preserved stool specimens.

In some cryptic cases unable to be confirmed by stool examinations, fluid obtained by endoscopy in the area of the duodenal-jejunal junction may reveal *G. lamblia* trophozoites. Reports on the value of upper intestinal fluid examination are mixed; some workers report it to be more reliable than stool examinations, whereas others have shown that stools may be positive when intestinal fluid and biopsy specimens are negative. In an occasional case of giardiasis that cannot be confirmed by the methods previously described, diagnosis may be made by small intestinal biopsy in the area of the duodenal-jejunal junction, or preferably of multiple duodenal or jejunal sites. Imprint smears for Giemsa staining should be prepared from the biopsy specimens before they are submitted for histologic examination. *G. lamblia* is rarely recognized as a mucosal invader; parasites (trophozoite stage) are more likely to be found on the microvillous border, particularly in the crypts.

There are several possible reasons for the failure to diagnose *G. lamblia* (Table 76-2). Different workers have had various rates of success with the diagnostic methods cited. In part, these differences are related to technical expertise, the care used in performing the tests, and the quality of reagents. It must be appreciated that no single method or even combination of methods can detect all *G. lamblia* infections. In patients with strong clinical and epidemiologic evidence of giardiasis, marked improvement and apparent cure may follow empirical treatment with specific anti-*Giardia* drugs, despite negative diagnostic test results.

TREATMENT

A number of drugs are available for treatment of giardiasis, including the nitroimidazoles (metronidazole and tinidazole), quinacrine, nitazoxanide, furazolidone, and albendazole (Table 76-3). To prevent person-to-person spread, it is important to treat all those infected, even if asymptomatic.

Table 76-3 Drugs Used in the Treatment of *Giardia lamblia*

DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Metronidazole (Flagyl)	250 mg PO tid × 7 days	5 mg/kg PO tid × 7 days
Tinidazole (Tindamax)	2 g PO once	50 mg/kg PO once (max 2 g)
Nitazoxanide (Alinia)	500 mg PO bid × 3 days	1-3 yr 100 mg PO q12h × 3 days 4-11 yr: 200 mg PO q12h × 3 days >12 yr: 500 mg PO q12h × 3 days
Quinacrine (Atabrine)*	100 mg PO tid × 5 days	2 mg/kg PO tid × 5 days (max 300 mg/day)
Alternatives		
Albendazole (Albenza)	400 mg/day PO × 5 days	10 mg/kg/day PO × 5 days
Paromomycin (Humatin)	30 mg/kg/day PO in three doses × 7 days	—
Furazolidone (Furoxone)*	100 mg PO qid × 7 days	6 mg/kg/day PO in four doses × 7 days

*Not available commercially. May be obtained through compounding pharmacy such as Panorama Compounding Pharmacy (800-292-6773).
bid, Twice per day; *PO,* by mouth; *qid,* four times per day; *tid,* three times per day.

A frequently used initial therapeutic agent is a nitroimidazole. Metronidazole (Flagyl) is given in an adult dose of 250 mg three times a day for 7 days and 5 mg/kg three times a day for children. Cure rates range from 80% to 90%. Tinidazole (Tindamax) is given in a single adult dose of 2 g orally and 50 mg/kg orally once (max 2 g) for children. Tinidazole has only recently been marketed in the United States and there is less experience with it than with metronidazole. However, very good results, simplicity of use, and good tolerance have been reported from abroad, and it is considered by some to be the treatment of choice. These drugs should be taken after food, and alcohol should be withheld when taking them. Side effects can include a metallic taste, dark urine, and gastrointestinal symptoms. Questions regarding potential carcinogenic and mutagenic effects of nitroimidazoles have arisen, but careful observation and follow-up of treated patients have shown no increased risk. A nitroimidazole can be used when a pregnant woman is symptomatic.

The most effective drug, with cure rates of 90% to 95%, is quinacrine (Atabrine). However, its increased effectiveness in comparison with the nitroimidazoles and other drugs must be weighed against the increased risk of troublesome side effects, tempering enthusiasm for its use as the treatment of choice. Also, quinacrine is not commercially available and must be obtained from certain compounding pharmacists who provide quinacrine powder in a gelatin capsule. Dosages are 100 mg three times a day for 5 days for adults and 2 mg/kg three times a day for 5 days for children. Common side effects can include intestinal upset, headache, and yellow urine. Nausea, vomiting, diarrhea, abdominal cramps, and skin rash are less common side effects that may necessitate discontinuation of the drug. A toxic psychosis with depression, excitation, or anxiety can occur in less than 1% of those taking quinacrine. It is prudent not to give quinacrine to persons with a history of depression or excitation.

Nitazoxanide (Alinia) is available as a tablet for adults and in a liquid formulation for children. The adult dosage is 500 mg orally twice daily for 3 days, with food. Children aged 12 to 47 months old take 100 mg (5 mL) of the liquid preparation twice daily for 3 days, and children 4 to 11 years old take 200 mg (10 mL) twice daily for 3 days, again with food. Nitazoxanide is generally well tolerated, with the most common adverse events being abdominal pain, diarrhea, vomiting, and headache. However, these adverse events are comparable to those occurring with placebo. Cure rates appear to be no more than 80%.

Furazolidone (Furoxone) had been the only liquid treatment for young children until the availability of nitazoxanide. The dosage for children is 1.25 mg/kg four times a day for 7 days and for adults is 100 mg four times a day for 7 days. Cure rates are in the 70% to 80% range. Adverse reactions can include gastrointestinal symptoms, fever, rash, urticaria and brown urine. Patients with G-6PD deficiency can develop hemolysis, and an Antabuse-like reaction can occur with alcohol ingestion (as with nitroimidazoles and quinacrine). Because of the relatively low cure rate and higher propensity for troublesome side effects, furazolidone has little current indication for use in giardiasis.

Albendazole (Albenza), which is primarily an anthelmintic drug, has been shown to have effect against giardiasis. Mixed results have been obtained when albendazole is used alone in an adult dose of 400 mg per day single dose for 5 days and 10 mg/kg single dose for 5 days in children. Albendazole combined with standard doses of metronidazole or quinacrine for 21 days has been effective in a small number of refractory infections. A combination of standard doses of metronidazole and quinacrine for 21 days has also shown effectiveness in some refractory infections.

Although none of the drugs just described can be used with totally assured safety in pregnancy, when treatment during pregnancy is necessary, quinacrine or a nitroimidazole could be used. Reports describing treatment of giardiasis with the poorly absorbed antibiotic paromomycin have shown mixed results, but in one study the drug was shown to be useful when administered to a few pregnant women with symptomatic giardiasis. Paromomycin should be the initial treatment of choice in the first semester.

As a check for cure, a series of three stool examinations and a *Giardia* stool antigen test should be performed approximately 4 weeks after completion of treatment. With treatment failures, retreatment with a different drug should be attempted.

PREVENTION

To prevent community outbreaks of waterborne giardiasis, conventional water treatment plants that use coagulation-sedimentation-filtration methods are needed. Although chlorination alone is often effective in killing most enteric organisms, *G. lamblia* cysts may require higher nonpalatable concentrations of chlorine and longer contact time to be inactivated, particularly in cold water. For individual protection, bringing water to a rolling boil for 1 minute destroys *Giardia* cysts. If boiling is not possible, two to four drops of household bleach or 0.5 mL of 2% tincture of iodine can be added to each liter of water, and the water can be held for 60 minutes before drinking. Iodine water purification tablets are available. *G. lamblia* and all other enteric organisms can be eliminated by using one of a number of commercially available personal water filters that eliminate waterborne bacteria and viruses; remove pathogenic cysts such as *Giardia* with a cyst filter; and remove sediment and improve taste with a carbon prefilter. Eating hot, cooked foods helps to prevent ingestion of viable cysts from foods contaminated by infected water or fingers.

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Other Intestinal Protozoa

77

Martin S. Wolfe

ABSTRACT

A number of less common intestinal protozoa are proven pathogens for humans, and some other nonpathogenic protozoa must be morphologically differentiated from those of medical significance (Figure 77-1). Identification of specific protozoa is based on certain characteristics of the cyst and trophozoite. These features are best demonstrated by permanently stained fecal smears. Treatment of infection with pathogenic protozoa varies by parasite (Table 77-1).

BALANTIDIUM COLI (BALANTIDIASIS)

Balantidium coli is a large pathogenic ciliated protozoan that in rare instances infects humans and produces intestinal symptoms. *B. coli* has a worldwide distribution, and prevalence is highest in areas of poor hygiene and nutrition and where pigs and humans have close contact. Infection in and transmission to humans from pigs is the most usual mode of infection. Cysts are the infective stage and may remain viable for weeks in moist feces. Excystation occurs in the bowel, and the trophozoites live in the large intestine, where they either remain in the lumen or invade the bowel mucosa and produce necrosis and ulceration. As in amebiasis, symptomatology ranges from the asymptomatic carrier state; to chronic symptoms with intermittent diarrhea and constipation, abdominal pain, and weight loss; to a dysenteric form with blood and mucus in the stool and tenderness over the colon. Diagnosis depends on demonstrating *B. coli* in the stool by direct or concentration examinations. Large trophozoites have been found in about 90% if cases, with cysts being seen only infrequently. Treatments of choice include tetracycline, iodoquinol, and metronidazole.

ISOSPORA BELLI (ISOSPORIASIS)

Isosporiasis is caused by *Isospora belli* of the subphylum Sporozoa, which has alternating generations, one sexual (sporogony) and one asexual (schizogony), in the small bowel mucosa. *Isospora hominis*, formerly grouped together with *I. belli*, is now recognized as a *Sarcocystis* species. *I. belli* has a worldwide distribution but is rarely reported in humans. In recent years, *I. belli* has been recognized as an opportunistic infection causing chronic diarrhea in patients with acquired immunodeficiency syndrome (AIDS). Infection occurs from oral ingestion of ripe oocysts, which have matured within 48 hours after evacuation in the stool into the infective stage. The mechanism by which the invading parasites produce small bowel mucosal lesions is unclear. Some *I. belli* infections are asymptomatic, but others may lead to significant signs and symptoms; these include diarrhea, abdominal colic, flatulence, malaise, and weight loss. The clinical picture resembles giardiasis or cryptosporidiosis, and in patients with AIDS the symptoms can last for months or years. Unlike in most protozoal infections, peripheral eosinophilia may be present. Oocysts are usually scanty in the stool. Flotation methods are the most sensitive stool concentration techniques. Duodenal aspiration or intestinal biopsy may detect infections not found by stool examinations. It is often necessary to examine multiple serial biopsy sections to find organisms, which may be in both sexual and asexual stages. The treatment of choice is one trimethoprim-sulfamethoxazole double-strength (DS) tablet every 12 hours for 10 days.

SARCOCYSTIS SPECIES (SARCOSPORIDIOSIS)

The organisms that cause human intestinal sarcosporidiosis are *Sarcocystis cruzi*, with cattle as intermediate hosts, and *Sarcocystis suihominis*, with pigs as intermediate hosts. Human intestinal *Sarcocystis* infection has been rarely recognized, and despite the high incidence in beef and pork, clinical reports of intestinal symptoms in people have been few. Infection follows ingestion of raw beef or pork; meat heated to 60° F or higher is noninfective. Diagnosis is difficult, and concentration tests may be required to confirm infection. There is no specific drug therapy. Most infections appear to be self-limited.

DIENTAMOEBA FRAGILIS

Dientamoeba fragilis, formerly thought to be an ameba and occurring only in a labile trophozoite form, has been reclassified as an amoeba-like flagellate. *D. fragilis* has a worldwide distribution. Its prevalence is higher in surveys employing preserved stool specimens, permanently stained fecal smears, and multiple daily stool examinations. The mode of transmission by the labile trophozoite remains uncertain. There is some epidemiologic evidence of waterborne and person-to-person transmission. In some reports, a close correlation has been found between the incidence of *Enterobius vermicularis* (the pinworm) and *D. fragilis* infection, and it has been postulated that pinworm eggs or larvae may be a transmitting agent of *D. fragilis*. The ability of *D. fragilis* to invade the host has not been demonstrated; it appears that irritation of the large bowel intestinal mucosa is the most likely cause of symptoms. *D. fragilis* has been considered a nonpathogen by some, and many of those infected may be asymptomatic. Signs and symptoms present in others include intermittent diarrhea, abdominal pain, flatulence, anorexia, and fatigue. A number of others have reported a low-grade eosinophilia in infected individuals in the absence of associated pinworm or other helminthic infections. *D. fragilis* is diagnosed by finding trophozoites in the stool, which can be missed if only fresh stool specimens are examined. Collection into various preservatives immediately on passage of stool and the

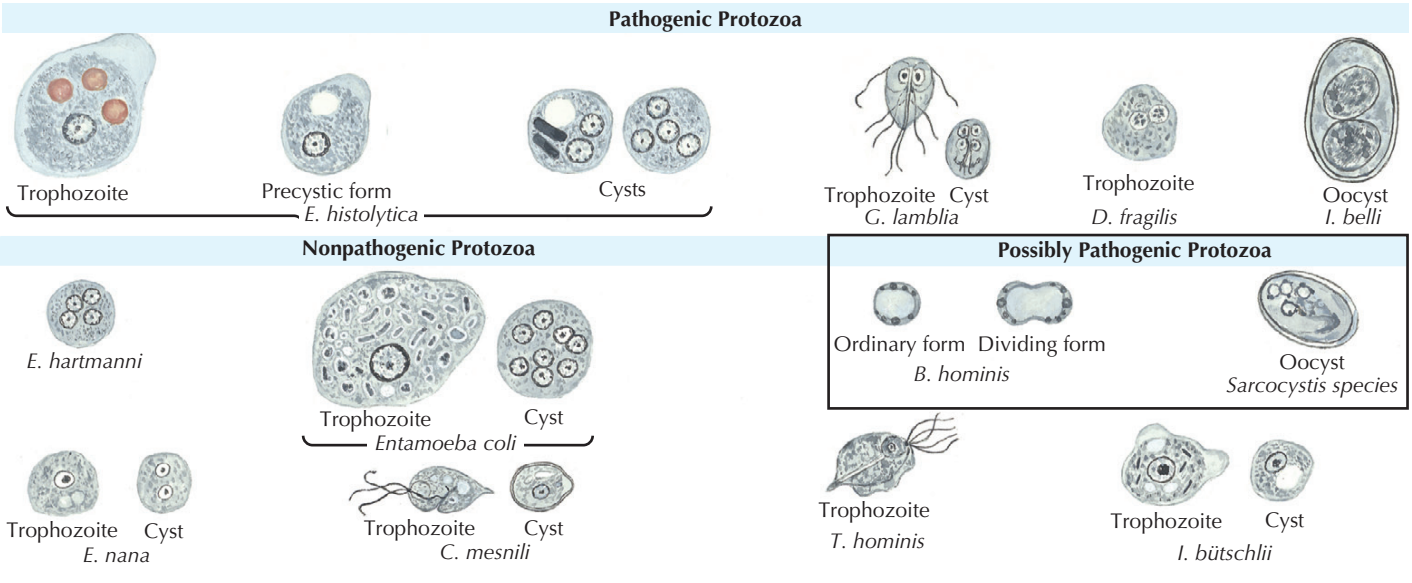

Figure 77-1 Intestinal protozoa and helminths affecting travelers.

Table 77-1 Drug Therapies for Other Intestinal Protozoa

PARASITE	DRUG	ADULT DOSAGE	PEDIATRIC DOSAGE
Balantidium coli	Tetracycline	500 mg PO qid × 10 days	40 mg/kg/day (max 2 g) PO in four doses × 10 days
	Iodoquinol	650 mg PO tid × 20 days	35 mg/kg/day (max 2 g) PO in three doses × 20 days
	Metronidazole	750 mg PO tid × 5 days	40 mg/kg/day (max 2 g) PO in three doses × 5 days
Isospora belli	Trimethoprim-sulfamethoxazole (TMP-SMX)	TMP 160 mg/SMX 800 mg (1 DS tab) PO bid × 10 days	TMP 5 mg/kg/day/SMX 25 mg/kg/day PO in two doses × 10 days
Dientamoeba fragilis	Paromomycin	500 mg tid × 7 days	30 mg/kg/day PO in three doses × 7 days
	Iodoquinol	As per *B. coli*	As per *B. coli*
Cryptosporidium	Nitazoxanide	500 mg PO bid × 3 days	1-3 yr: 100 mg PO bid × 3 days 4-11 yr: 200 mg PO bid × 3 days >12 yr: 500 mg PO bid × 3 days
Cyclospora	TMP-SMX	As per *I. belli*	As per *I. belli*

bid, Twice per day; *DS,* double strength; *PO,* by mouth; *qid,* four times per day; *tid,* three times per day.

preparation and careful examination of stained fecal smears will lead to higher recovery rates. Examination of multiple specimens passed on alternate days has been found useful, because the excretion of parasites may fluctuate markedly from day to day. Paromomycin, iodoquinol, and tetracycline have been used for treatment.

CRYPTOSPORIDIUM (CRYPTOSPORIDIOSIS)

Early reported cases of *Cryptosporidium* species were primarily in persons positive for human immunodeficiency virus (HIV) and other conditions causing immunosuppression. In these individuals, infection usually results in severe, irreversible, lethal diarrhea. In persons with normal immunologic functions, signs and symptoms include watery diarrhea, cramps, and headaches; infection is usually self-limited in about 7 to 14 days. Cases have been recognized in daycare centers and recreational and drinking water outbreaks in the United States, and in surveys of children and adults in the developing world. Diagnosis is by finding 5- to 6-micron oocysts in the feces that can be distinguished by acid-fast staining. A stool antigen enzyme-linked immunosorbent assay (ELISA) is also available. The drug of choice for non–HIV-infected persons is nitazoxanide. No drug has been demonstrated to be effective in HIV-infected individuals with chronic diarrhea, though nitazoxanide may be tried to decrease diarrhea.

CYCLOSPORA (CYCLOSPORIASIS)

Cyclospora is a coccidian parasite that causes diarrhea and other gastrointestinal symptoms in humans worldwide. *Cyclospora* oocysts in freshly passed stool are noninfectious, making direct

person-to-person transmission through fecal exposure very unlikely. Oocysts must sporulate in the environment to become infectious, usually taking at least 1 week. The incubation period after ingestion of sporulated oocysts averages 7 days. Signs and symptoms include watery diarrhea, abdominal bloating and flatulence, cramping, anorexia, weight loss, and marked fatigue. In untreated nonimmunosuppressed individuals, infection is self-limited in about 6 to 8 weeks. Effective treatment is with trimethoprim-sulfamethoxazole, one DS tablet twice daily for 7 to 10 days. HIV-infected individuals may need higher dosage and long-term maintenance. A number of food-borne multistate outbreaks have occurred in the United States.

BLASTOCYSTIS HOMINIS

Blastocystis hominis is a common inhabitant of the human intestinal tract. For many years it was regarded as a harmless yeast, but it is now considered by most to be a protozoan. The potential for *B. hominis* as a pathogen is a subject of debate. Reported symptoms associated with heavy *B. hominis* infection in the absence of other recognized pathogenic organisms include mild diarrhea, nausea, anorexia, and fatigue. It remains uncertain whether *B. hominis* itself is the cause of symptoms or if it is only a marker of some other unidentified pathogen. Markell and Udkow have given an interesting and compelling perspective to this controversy. In 32 symptomatic subjects initially found with *B. hominis* alone or in combination with nonpathogenic protozoa, an additional series of stool specimens (up to six) were rigorously examined. In 27 of those 32 patients, at least one known pathogenic protozoa in addition to *B. hominis* was found. *B. hominis* persisted, but symptoms improved in all 27 patients treated specifically for these other pathogenic protozoa. It was concluded that *B. hominis* is not a pathogen, that treatment with common antiprotozoal drugs may not eliminate it from the stool, and that "symptomatic blastocystosis" was attributable to either an undetected parasite or parasites in some patients or functional bowel problems in others.

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Soil-Transmitted Helminths and Other Intestinal Roundworms

78

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ABSTRACT

Infections with soil-transmitted helminths (STHs) affect the health of millions of people around the world. Individuals of all ages may be infected with the common roundworm *(Ascaris lumbricoides)*, whipworm *(Trichuris trichiura)*, and hookworm (*Ancylostoma duodenale* and *Necator americanus*), although school-aged children living in resource-poor endemic areas are more likely to be infected with heavy worm burdens that contribute to significant malnutrition, delayed physical growth, cognitive impairment, serious illness, and even death. Chronic infections with hookworm and whipworm are associated with the development of iron-deficiency anemia owing to daily blood loss in the stools. Light worm infections are usually asymptomatic; however, when such infections are diagnosed among returning travelers and immigrants from endemic areas, there is usually a strong personal desire to be free from worms whether symptomatic or asymptomatic.

Two other nematode (roundworm) infections also are considered in this chapter: those caused by pinworm and *Strongyloides stercoralis*. Pinworm *(Enterobius vermicularis)* infections are a ubiquitous scourge among children and the households that they live in, usually causing perianal itching but occasionally producing more serious pathology. *S. stercoralis* can cause chronic infections in humans that last decades because of parasite autoinfection, and may be associated with skin rashes and hypereosinophilia as well as fatal hyperinfections in immune-compromised hosts—for example, persons on immunosuppressive drugs, persons infected with human immunodeficiency virus (HIV), and persons with cancer or various other immune-compromising conditions.

There are many geographic areas where a high risk of STH transmission overlaps with high rates of HIV infections and acquired immunodeficiency syndrome (AIDS) among resident populations. Some studies have postulated that helminthic infections in persons co-infected with HIV may adversely affect HIV-1 progression, as measured by changes in CD4 count, viral load (measured by HIV-1 ribonucleic acid [RNA]), and/or clinical disease progression. Diagnosis of latent worm infections and appropriate treatment of HIV-1 co-infected persons and others with immunocompromised status are strongly recommended for those who live or have lived in high-risk geographic areas for STH transmission.

GEOGRAPHIC DISTRIBUTION

Ascaris is probably the most common helminthic infection, with a global prevalence of approximately 1.3 billion persons infected. The majority (over 70%) of *Ascaris* infections occur in China, India, and Southeast Asia, followed by countries in Latin America and the Caribbean region (approximately 13%), and in sub-Saharan Africa (approximately 8%). It is estimated that whipworm and hookworm each are responsible for 500 to 900 million infections worldwide. Whipworm has a similar geographic distribution as *Ascaris*, whereas hookworm is highly prevalent in sub-Saharan Africa and south Asia. Transmission of STHs also occurs in developed countries; it has been reported in persons living or working in resource-poor rural farming communities in the southern United States and southern Europe. Transmission of *Strongyloides* and pinworm occurs in urban as well as rural locales, because there is not an obligatory life-cycle developmental stage in soil.

RISK FACTORS

STHs are transmitted in human populations in tropical and temperate climates where poverty and poor sanitation result in fecal contamination of the environment. Parasite eggs of *Ascaris*, whipworm, and hookworm have an obligatory developmental period of several weeks in the soil before the larvae contained in the eggs become mature and infective for humans. Humans usually acquire worm infections by fecal-oral transmission from contaminated fingers and food (*Ascaris*, whipworm, pinworm) or by direct skin contact with fecally contaminated soil (hookworm, *Strongyloides*). In addition, direct person-to-person transmission of *Strongyloides* and pinworm is possible among those having close personal contact with infected persons, and autoinfections are also possible (see later).

CLINICAL FEATURES

Clinical signs and symptoms reflect the life-cycle stages of each parasite within the human host (Table 78-1). Larval penetration of intact skin often elicits a pruritic skin rash (hookworm, *Strongyloides*). When immature larval parasite forms are migrating through the lungs and other host tissues during natural life-cycle stages, elevated peripheral blood eosinophils may occur. As the larvae of *Ascaris*, hookworm, and *Strongyloides* migrate through the lungs as a part of their life cycle in the human host, a cough may develop and transient infiltrates may be seen on chest radiographs. During *Strongyloides* hyperinfection, larvae may be found in specimens of the blood-tinged sputum. Persons with light STH infections may have few specific signs or symptoms, and many are undiagnosed. Because worm infections do not elicit a protective immune response, persons (especially children) residing in areas of transmission can acquire heavy worm burdens over time and manifest serious consequences of infection.

Table 78-1 Summary of Parasite Life Cycles

PARASITE	TRANSMISSION	INCUBATION	ADULT HABITAT	LIFESPAN	CLINICAL FEATURES
Ascaris lumbricoides (common roundworm)	Ingestion of eggs	2-3 months	Small intestine	1-2 years	Pulmonary larval migration (cough and eosinophilia) Intestinal discomfort Obstruction of a viscus, or intestinal perforation Ova in stools Spontaneous passage of adult worms per rectum, mouth, or nose
Trichuris trichiuris (whipworm)	Ingestion of eggs	1-3 months	Large intestine in the cecum; gravid females migrate to the rectum	3-8 years	Diarrhea, cramps Blood in stools Anemia Tenesmus, rectal prolapse Ova and occasional adults in stools
Ancylostoma duodenale, Necator americanus (hookworm)	Skin penetration by infective larvae after contact with contaminated soil	2 or more weeks	Small intestine in the duodenum and upper jejunum	1 year	Skin rash at site of infection ("ground itch") Pulmonary larval migration (cough and eosinophilia) Diarrhea, abdominal discomfort Anemia Hypoproteinemia Occult blood and ova in stools
Strongyloides stercoralis	Skin penetration by infective larvae after contact with contaminated soil; autoinfection; skin-to-skin contact	3 weeks	Small intestine	May persist up to 35 years through autoinfections	Skin rash at site of infection Pulmonary larval migration (cough and eosinophilia) Diarrhea, abdominal discomfort Persistent eosinophilia Larvae in stools Autoinfective cycle Hyperinfection syndrome
Enterobius vermicularis (pinworm)	Ingestion of eggs	2-4 weeks	Large intestine in the cecum	Gravid females, 3-6 weeks; males, 1-2 weeks	Anal and/or vulvar pruritus Rare cause of appendicitis Self-infection from fecal-oral contamination

Common Roundworm: Ascaris lumbricoides

Infected persons may be asymptomatic or complain of vague abdominal symptoms. *Ascaris* worms become hyperactive when irritated by fever, starvation, or medications in the human host: a worm may ascend from normal residence in the lumen of the small intestine through the stomach and esophagus, exiting through the mouth or nose; or a worm may pass without symptoms per rectum, shocking the host who finds a spontaneously expelled gross specimen. Infection with only a single *Ascaris* worm can cause morbidity owing to their relatively large size: a worm may migrate to ectopic locations such as the appendix or common bile duct, causing obstruction and inflammation. *Ascaris* is capable of perforating the intestines, resulting in fecal spillage and the development of peritonitis. In heavily infected children, small bowel obstruction may result from a bolus of worms and may necessitate emergency laparotomy. Taking all these possible scenarios into account, *Ascaris* infections should be treated when detected (Figure 78-1).

Whipworm: Trichuris trichiura

Whipworm is a parasite infection with worldwide distribution, and although persons of any age may be infected, children account for the majority of reported cases. Whipworm infections are chronic and relatively silent, but moderate to severe infections (from around 200 to 1000 adult worms or more) are associated with iron-deficiency anemia, growth retardation, and chronic bloody mucoid diarrhea. The adult worms inhabit the human colon, from the cecum to the rectum, with the mouthpart of each worm firmly embedded in the bowel epithelium, and the thicker posterior bodies of the worms moving freely in the bowel lumen. In heavy whipworm infections, rectal prolapse is thought to be associated with both physical factors and inflammatory changes caused by infection in the bowel wall: peristaltic contractions of the bowel push the worm bodies in the rectum toward the anus while the anterior ends remain firmly attached to the chronically inflamed bowel wall, and rectal prolapse may occur (Figure 78-2).

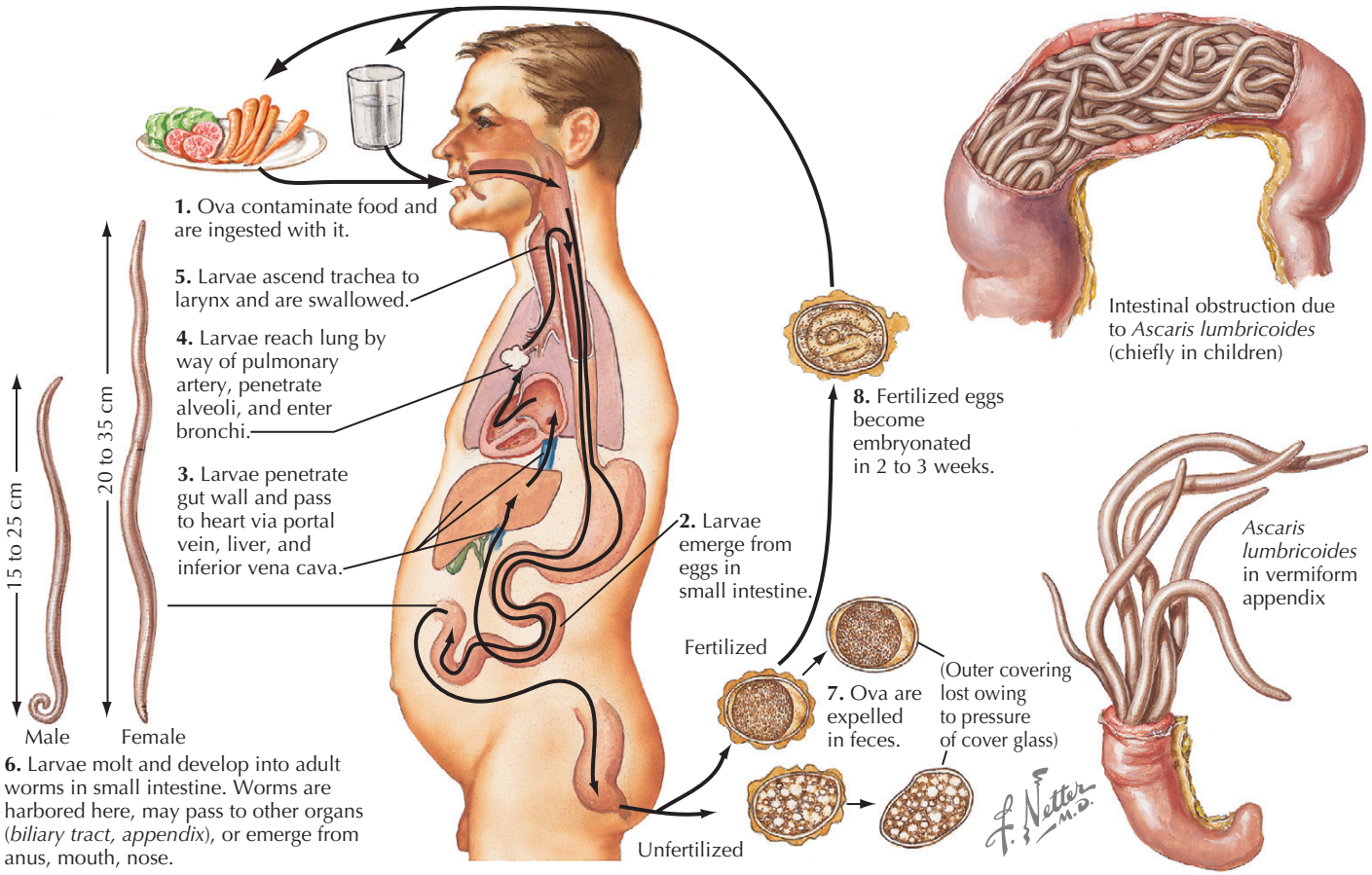


Figure 78-1 *Ascaris* infection.

Hookworm: Ancylostoma duodenale *and* Necator americanus

A. duodenale and *N. americanus* were commonly known as "Old World" and "New World" hookworm, respectively. However, after recognition that infections with both species are transmitted in both the Eastern and Western hemispheres, the geographic designations have decreased in usage. Infections with *A. duodenale* are potentially more harmful than infections with *N. americanus; A. duodenale* worms attach to the intestinal mucosa and suck blood at a rate of 0.15 to 0.26 mL/day per worm compared with *N. americanus* with a rate of 0.03 mL/day per worm. Thus blood loss is greater with *A. duodenale* for a comparable level of infection. Additional blood loss occurs from the multiple points of attachment and detachment of the adult hookworms in the duodenum and jejunum. When the worms bite into the mucosa to attach and feed, an anticoagulant is released into the local tissue, and bleeding from these sites into the lumen of the small intestine persists after the worms detach and move on to fresh areas of mucosa. Although the two species can be distinguished by the morphology of the mouth parts and the copulatory bursae of the adult worms, the eggs of the two are indistinguishable. Once the diagnosis of hookworm is made, drug treatment is the same regardless of species (Figure 78-3).

Strongyloidiasis: Strongyloides stercoralis

In the soil-transmitted cycle of *Strongyloides*, adult female worms developing in the submucosa of the small intestine lay eggs that mature within in a few hours to produce rhabditiform larvae that enter the fecal stream in the lumen of the bowel. *Strongyloides* rhabditiform larvae exiting the body in feces that are deposited in moist soil develop into infective stage filariform larvae (through asexual or sexual free-living cycles). Filariform larvae are capable of penetrating intact human skin, and new infections occur when skin comes into direct contact with the contaminated soil.

Alternatively, the immature rhabditiform larvae in the fecal stream may rapidly develop into infective filariform larvae while still in the intestines. The filariform larvae in the fecal stream may penetrate either the intestinal mucosa or the perianal skin and migrate to blood vessels, completing their life cycle without leaving the human host through a process of autoinfection. The pruritic, serpiginous erythematous skin rash on the buttocks elicited by this autoinfection is called *cutaneous larva currens*, because the tracklike rash caused by the migrating subcutaneous larvae can extend at a rate of 5 to 10 cm an hour. Strongyloidiasis is a sexually transmitted infection when intimate skin-to-skin contact occurs while infective filariform larvae are present in the rectum and on the perianal skin.

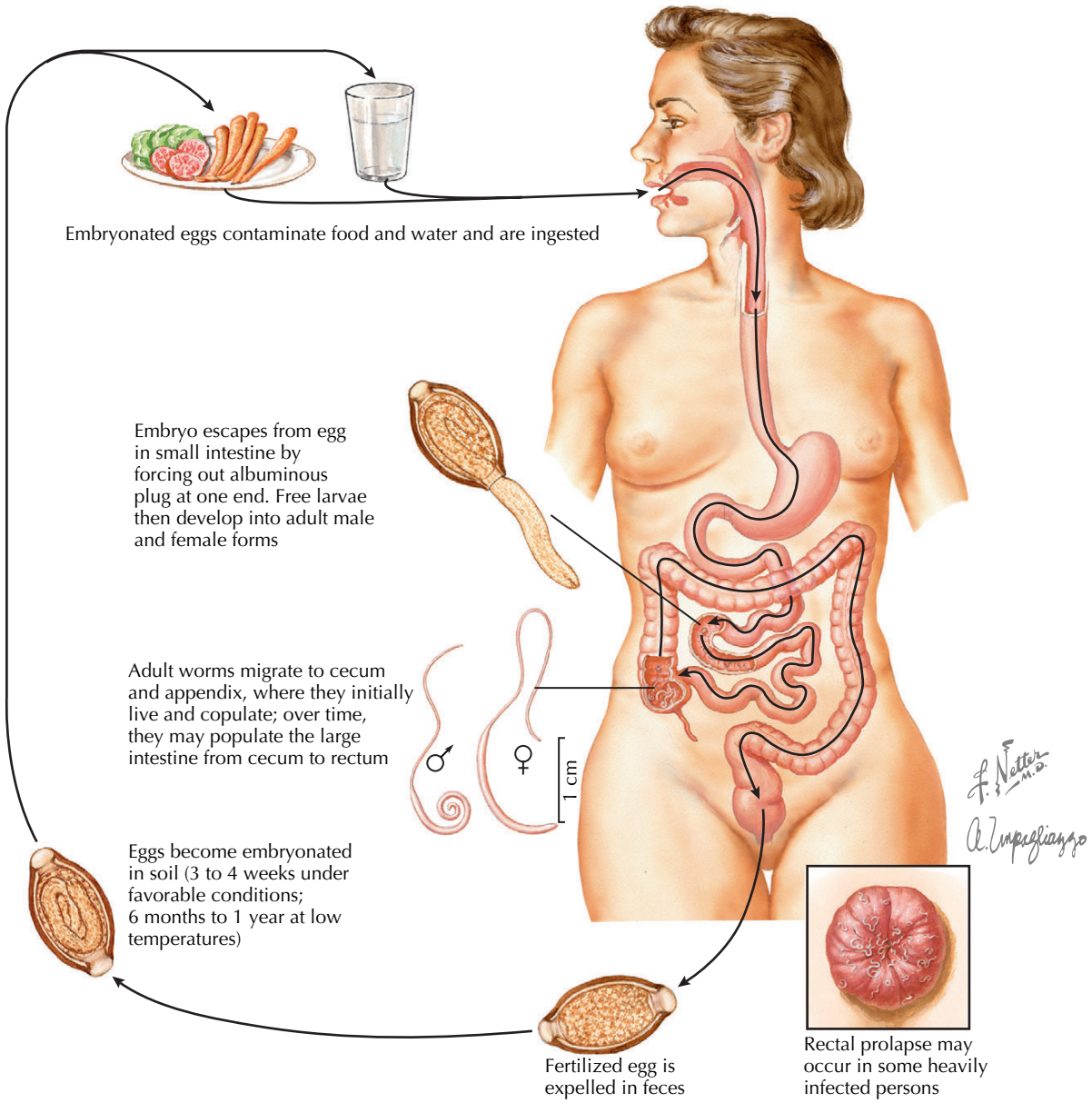


Figure 78-2 Whipworm infection.

Chronic *Strongyloides* infections are often silent, although some patients complain of transient skin rashes and itching associated with the autoinfective cycle. Elevation of the peripheral blood eosinophils may be noted as an incidental finding on routine laboratory studies and may trigger a clinical investigation for occult parasite infection. Serious disease results if the infected host becomes immunocompromised; then, *Strongyloides* hyperinfection with dissemination of the parasites to all internal organs precipitates local inflammatory changes and severe enteritis, pneumonitis, and microabscesses as well as other life-threatening secondary complications (Figure 78-4).

Pinworm: Enterobius vermicularis

Perianal itching in children is the hallmark of pinworm infections. However, there are rare reports of appendicitis, peritonitis, and salpingitis in which ectopic pinworms or ova were associated with inflammatory reactions in the tissue. Usually, adult pinworms inhabit the cecum, and gravid females migrate to the rectal area at night to deposit eggs on the perianal skin. The embryonated eggs mature after 4 to 6 hours of oxygenation outside the intestine. Fingers and fingernails touching or scratching the perianal area are easily contaminated and may reinfect the original host when the contaminated fingers or

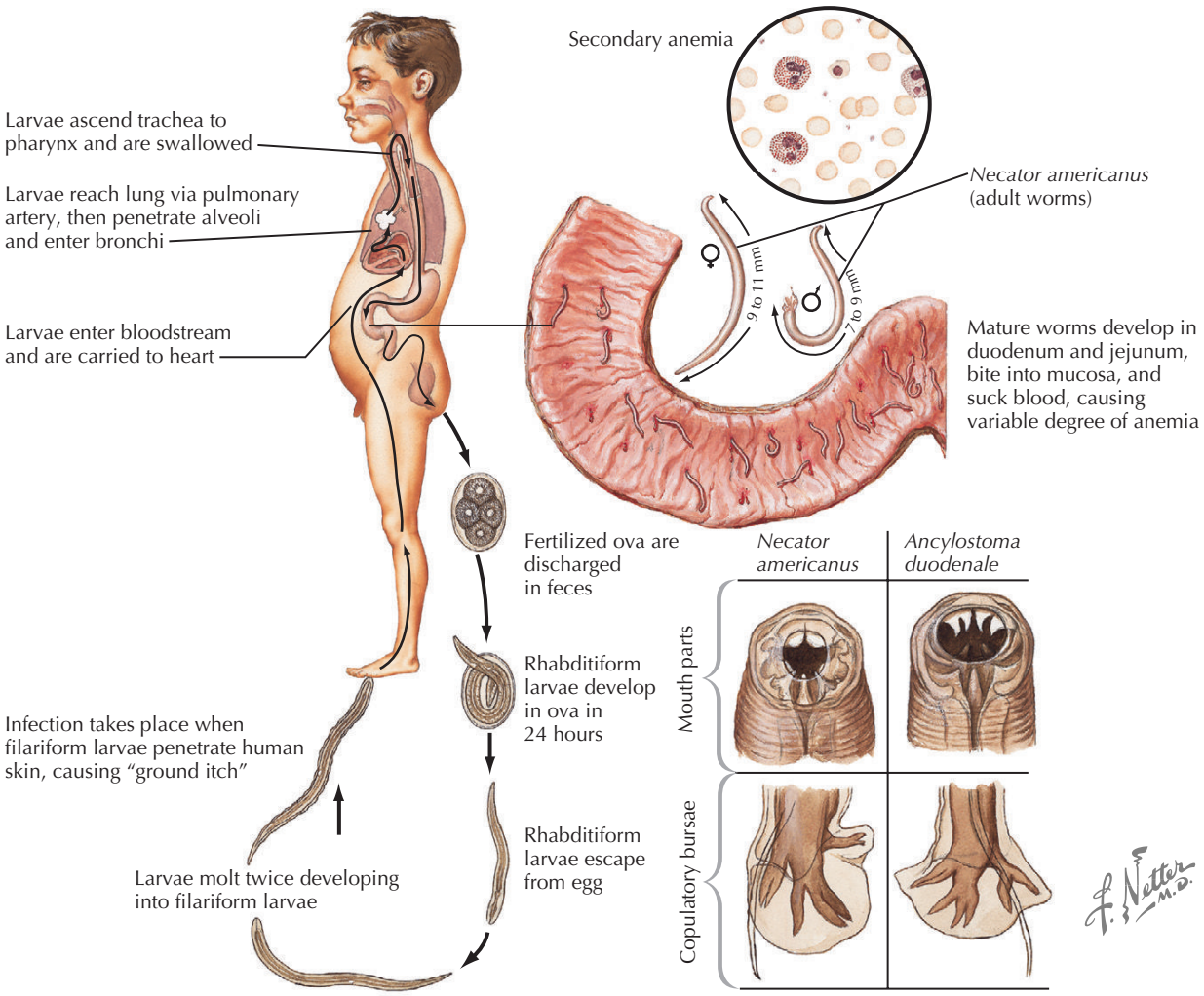


Figure 78-3 Hookworm infection.

objects touched by the fingers are put in the mouth. Contamination of the household environment (e.g., blankets, sheets, clothing, dust) results from eggs shed from the skin, and infections are easily spread to other persons as a consequence of close household or personal contact (Figure 78-5).

DIAGNOSTIC APPROACH

Definitive diagnosis of helminthic infection depends on morphologic identification of the characteristic eggs (ova), larvae, and/or even adult forms in fecal samples, tissue biopsy specimens, or sputum. Identifying unique parasite ova and larval forms in submitted stool specimens by microscopic examination is the most common way of making the diagnosis. However, microscopic diagnosis and estimation of the worm burden by quantitative egg counts in the stool are challenging, because parasite eggs may not be shed uniformly into the fecal stream on a daily basis and may be unevenly dispersed within a given stool specimen. Therefore when resources allow, the examination of three stool specimens from the given individual, each collected on a different day, yields a more comprehensive profile of potential parasite infections and allows a more accurate estimation of the parasite burden compared with examination of a single stool specimen. Owing to their relatively large size, diagnosis of *Ascaris* infections can be made by visual inspection of adult worms that are spontaneously passed through one of the body orifices (per rectum, mouth, or nose), contained in surgical specimens, or observed during radiologic imaging studies. Pinworm eggs can be recovered from suspected cases by pressing the sticky side of clear adhesive tape on the perianal skin first thing in the morning. *Strongyloides* eggs are rarely seen in stool specimens, and special laboratory techniques are usually required to visualize the larval forms. Serologic tests for diagnosis of *Strongyloides* are available from state public health and commercial reference laboratories.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Drug therapy is usually directed by the parasite diagnosis. The therapeutic goal of anthelmintic parasitic drug treatment is to eradicate or significantly lower the worm burden in infected individuals—except for *Strongyloides*-infected individuals, who

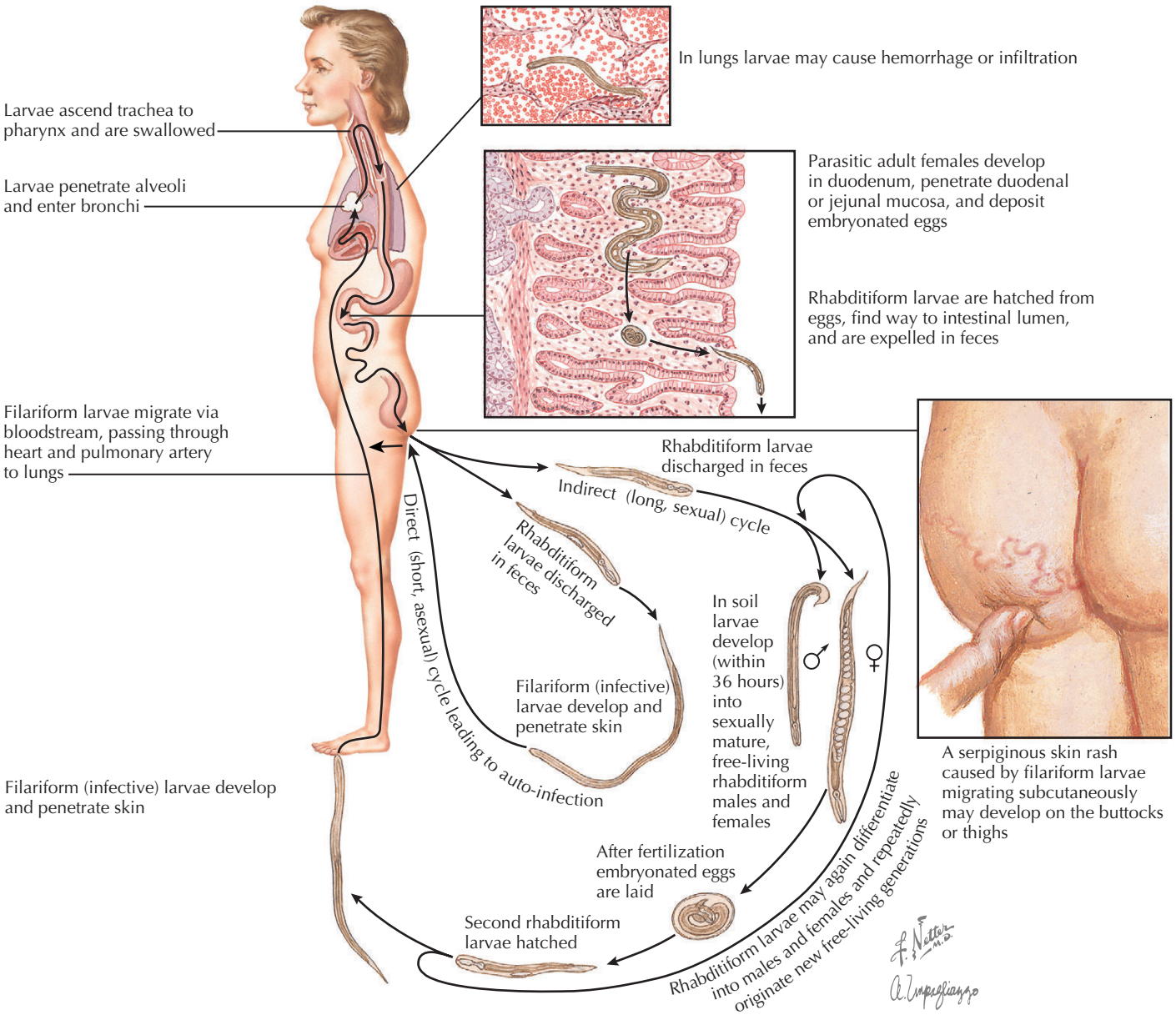


Figure 78-4 *Strongyloides* infection.

should be treated until a total cure is achieved. The parasites have varying degrees of susceptibility to the anthelmintic drugs, and some of the drugs have a broad spectrum, a useful property for treating mixed infections. Single-dose drug treatment protocols (Tables 78-2 and 78-3) have been studied because of their utility in mass treatment programs. Published studies conducted in Africa, South America, and Asia have demonstrated that periodic mass treatment programs conducted with broad-spectrum anthelmintic drugs in school-aged children in endemic areas resulted in catch-up and accelerated physical growth, as well as improved cognitive performance measurable in the months following treatment.

Recommended drug treatment may feature a single-dose regimen or a longer duration of treatment with a given drug to ensure optimal cure rates for a given parasite. Pyrantel pamoate is widely used and relatively inexpensive in developing countries. The drug is a tetrahydropyrimidine derivative, which is thought to inhibit neuromuscular transmission in the helminth, causing spastic paralysis of the worm that promotes subsequent expulsion of the worm from the host's intestine. Pyrantel pamoate is poorly absorbed from the gastrointestinal tract, is generally well tolerated with few reported adverse side effects, and is not efficacious in the treatment of *Trichuris* and *Strongyloides*.

The anthelmintic drugs albendazole, mebendazole, and thiabendazole were developed as the result of research on the benzimidazole ring, an integral part of the chemical structure of vitamin B_{12}. Anthelmintic benzimidazole drugs are thought to preferentially bind with the cytoskeletal protein tubulin in parasite cells, impairing microtubule formation, and also appear

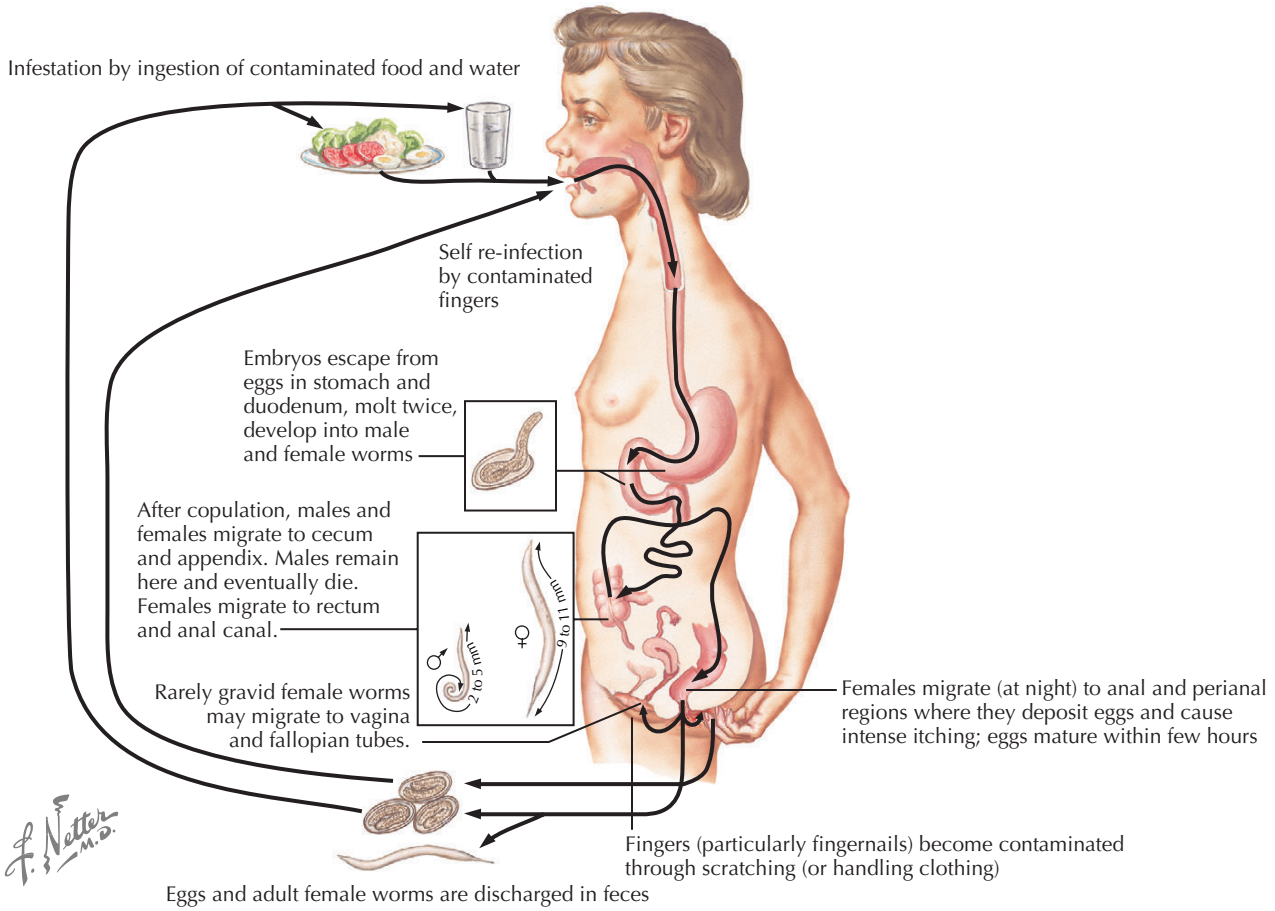


Figure 78-5 Pinworm infection.

Table 78-2 Summary of Overall Cure Rate (%) in Studies Reporting the Use of Single-Dose Oral Albendazole, Mebendazole, and Pyrantel Pamoate

	Treatment Regimen		
PARASITE	**ALBENDAZOLE (400 mg)**	**MEBENDAZOLE (500 mg)**	**PYRANTEL PAMOATE (10 g/kg)**
Ascaris lumbricoides	93.9%	96.5%	87.9%
Trichuris trichiura	43.6%	23.0%	28.1%
Hookworm	78.4%	22.9%	87.9%

Data from Keiser J, Utzinger J: Efficacy of current drugs against soil-transmitted helminth infections. Systemic review and meta-analysis, JAMA *299:1937-1948, 2008.*

to interfere with parasitic glucose uptake. The benzimidazole drugs are not efficiently absorbed from the gastrointestinal tract, although the amounts absorbed during oral treatment appear sufficient to affect some tissue-phase parasites.

Thiabendazole was discovered in 1961 and was the first anthelmintic benzimidazole drug introduced into clinical medicine. Although highly effective against several helminths, its usage has been limited by predictable unpleasant side effects (including anorexia, nausea, vomiting, vertigo, and headache) and toxicity, notably erythema multiforme. Thiabendazole remains the drug of choice for treatment of serious *Strongyloides* and *Trichinella* infections (Chapter 83).

Mebendazole became widely used in clinical medicine in the 1970s and is a highly efficacious drug against several intestinal parasite infections. In the United States the drug is indicated for treatment of *Ascaris*, whipworm, hookworm, and pinworm infections. Mebendazole has few adverse side effects (infrequently reported mild nausea, vomiting, abdominal discomfort) when used in the low-dose, short-term treatment schedules recommended for intestinal nematode infections.

Albendazole was introduced into clinical medicine in 1979, although it was not licensed in the United States until the mid-1990s. Albendazole's broad spectrum of activity and low profile of adverse reactions make it invaluable for the treatment

Table 78-3 Drugs and Treatment Regimens for Selected Helminths

	Treatment Regimens			
	ALBENDAZOLE (200-mg TABLET; 100-mg/5-mL ORAL SUSPENSION)	**MEBENDAZOLE (100-mg CHEWABLE TABLET)**	**PYRANTEL PAMOATE (50-mg/mL ORAL SUSPENSION)**	**THIABENDAZOLE (500-MG CHEWABLE TABLET OR 500-mg/5-mL ORAL SUSPENSION)**
Ascaris lumbricoides	400 mg as a single dose for adults and children over 2 years of age; 200 mg as a single dose in children 1-2 years old	100 mg twice daily × 3 days for adults and children over 2 years of age	11 mg/kg in a single oral dose not to exceed a maximum dose of 1 g for adults and children over 2 years of age	Not recommended (drug toxicity concerns)
Whipworm *(Trichuris trichiura)*	400 mg daily × 1 or 2 days	100 mg twice daily × 3 or 4 days	Not recommended (low cure rates)	Not recommended (drug toxicity concerns)
Hookworm (*Ancylostoma duodenale* and *Necator americanus*)	400 mg daily × 1 or 2 days	100 mg twice daily × 3 or 4 days	11 mg/kg in a single oral dose not to exceed a maximum dose of 1 g for adults and children over 2 years of age × 3 days	Not recommended (drug toxicity concerns)
Pinworm *(Enterobius vermicularis)*	400 mg as a single dose for adults and children over 2 years of age; 200 mg as a single dose in children 1-2 years old; repeat the dose after 2 weeks	100 mg as a single dose for adults and children over 2 years of age; repeat the dose after 2 weeks	11 mg/kg in a single oral dose not to exceed a maximum dose of 1 g for adults and children over 2 years of age; repeat the dose after 2 weeks	Not recommended (drug toxicity concerns)
Strongyloides stercoralis—intestinal infection	400 mg daily × 3 days for adults and children over 2 years of age*	Not recommended (low cure rates)	Not recommended (low cure rates)	25 mg/kg twice daily (not to exceed 1.5 g twice daily) × 2 or 3 days
Strongyloides stercoralis—hyperinfection syndrome	400 mg daily × 15 days for adults and children over 2 years of age	Not recommended (low cure rates)	Not recommended (low cure rates)	25 mg/kg twice daily (not to exceed 1.5 g twice daily) × 10-15 days

*See text for use of ivermectin drug therapy for treatment of intestinal strongyloidiasis.

of individuals as well as a favored drug in mass treatment programs.

Ivermectin, a semisynthetic anthelmintic drug derived from the avermectins, antiparasitic agents isolated from the fermentation products of *Streptomyces avermitilis*, is indicated for the treatment of uncomplicated (intestinal) *S. stercoralis* infections. The drug acts by binding selectively to glutamate-gated chloride ion channels present in nerve and muscle cells of the parasite. Subsequent hyperpolarization of these cells owing to chloride ion influx leads to paralysis and death of the parasite. The drug is active only against intestinal larval stages of *Strongyloides* and is not indicated for treatment of disseminated tissue infections (hyperinfection syndrome). The test of cure for intestinal *Strongyloides* infections is the absence of larvae in three or more follow-up stool samples collected over the period beginning 3 or 4 weeks after completion of therapy to 3 months afterward. Clinical studies suggest that ivermectin administered as a single oral dose of 170 to 200 mcg/kg may be more effective than albendazole therapy (200 mg twice a day for 3 days) against intestinal strongyloidiasis. Other studies show that ivermectin (200 mcg/kg given once daily for 1 or 2 days) had a comparable cure rate with fewer reported side effects than thiabendazole (25 mg/kg twice a day for 3 days) against intestinal strongyloidiasis.

PREVENTION AND CONTROL

Prevention and control of STH requires a multipronged approach involving public health measures, personal hygiene, and drug treatment of infected persons. Improved levels of sanitation, especially implementation of programs for collection and decontamination of human fecal wastes, are essential in regions with high rates of STH transmission, but such improvements require administrative infrastructure and resources over the course of years. Mass drug treatment programs targeting school-aged children and other high-risk groups have been shown to yield short-term improvements in affected populations, but these also depend on administrative infrastructure and continued availability of affordable, efficacious drugs. Personal prevention measures include wearing shoes and avoiding direct skin

contact with moist ground in areas where there is known transmission of hookworm and *Strongyloides;* school-aged children should be taught good personal hygiene practices. Challenges to current control efforts include varying degrees of inherent parasite susceptibility to the commonly used anthelmintic drugs and the possibility of accelerated emergence of drug-resistance as a consequence of repeated mass chemotherapy programs in endemic areas.

EVIDENCE

Igual-Adell R, Oltra-Alcaraz C, Soler-Company E, et al: Efficacy and safety of ivermectin and thiabendazole in the treatment of strongyloidiasis, *Expert Opin Pharamacother* 5:2615-2619, 2004. *A retrospective review of 88 adult cases of chronic strongyloidiasis treated with either thiabendazole or ivermectin, from 1999 to 2002, in Valencia, Spain. Noncure after drug treatment was associated with continued eosinophilia.*

Kirwan P, Asaolu SO, Molloy SF, et al: Patterns of soil-transmitted helminth infection and impact of four-monthly albendazole treatments in preschool children from semi-urban communities in Nigeria: a double-blind placebo-controlled randomised trial, *BMC Infect Dis* 9:20, 2009. *This placebo-controlled field study among Nigerian preschool children aged 1 to 4 years found that more than 50% of the preschool children were infected by one or more helminths.* A. lumbricoides *was the most prevalent infection (47.6%). Results of the study suggest that systematic treatment programs using a broad-spectrum anthelmintic drug are necessary to reduce the prevalence and intensity of STH infection among preschool children in a population characterized by moderate prevalence and low intensity.*

Sasaki J, Seidel JS: Ascariasis mimicking an acute abdomen, *Ann Emerg Med* 21:217-219, 1992. *Ascariasis is a common childhood infection worldwide. Whereas most* Ascaris *infections are benign, the two pediatric cases presented in this report illustrate that such infections are in the differential diagnosis of pediatric acute abdomen. Children at risk include immigrants and those with a history of travel to foreign countries, but cases of ascariasis have been reported in children who have not traveled outside the United States.*

Stephenson LS, Latham MC, Kurz KM, et al: Treatment with a single dose of albendazole improves growth of Kenyan schoolchildren with hookworm, *Trichuris trichiura*, and *Ascaris lumbricoides* infections, *Am J Trop Med Hyg* 41:78-87, 1989. *This placebo-controlled field study of Kenyan schoolchildren studied the association between infections with one or more intestinal helminths and poor child growth. The study reports that measurable improvements in growth could be seen on reexamination 6 months after a single oral dose of albendazole, despite the children's continued exposure to reinfection.*

ADDITIONAL RESOURCES

Keiser J, Utzinger J: Efficacy of current drugs against soil-transmitted helminth infections: systemic review and meta-analysis, *JAMA* 299:1937-1948, 2008. *A comprehensive review and meta-analysis of published studies assessing the efficacy of single-dose albendazole, mebendazole, levamisole, and pyrantel pamoate against* A. lumbricoides, *hookworm, and* T. trichiura *infections. The authors conclude that additional data from "well-designed, adequately powered and rigorously implemented trials" are needed regarding efficacy of current drugs with regard to both cure and egg reduction rates, and that benchmarks are needed for monitoring subsequent drug resistance.*

Watson JL, Herrin BR, John-Stewart G: Deworming helminth co-infected individuals for delaying HIV disease progression, *Cochrane Database Syst Rev* 3:CD006419, 2009. *A review and meta-analysis of published studies evaluating the effects of deworming on markers of HIV-1 disease progression in helminth and HIV-1 co-infected individuals. They conclude that there is evidence of significant benefit in attenuating or reducing plasma viral load and/or increasing CD4 counts after deworming. Further trials are necessary to further evaluate species-specific effects and to document long-term clinical outcomes.*

Intestinal Cestodes (Tapeworms)

Douglas William MacPherson

79

ABSTRACT

The relationship between humans and intestinal cestodes (tapeworms) goes well beyond the essential biologic interaction between host and parasite. Over time, tapeworms and tapeworm stories have contributed to human culture, literature, and dietary practices. In the late nineteenth century, part of the popular folklore was that a tapeworm infection could help make one thin, and tapeworm eggs were actually advertised commercially as a weight reduction aid. On the other hand, one of the well-known clinical manifestations of intestinal tapeworm infection is the passing of grossly visible ribbons or tapes (strobilae) of worm segments (proglottids), often alive and wriggling, from the anus of the human host, leading to considerable reaction in the infected person.

Human tapeworm infections usually result from food-borne transmission when raw, smoked, pickled, or undercooked pork, beef, or fish infected with larval stages of tapeworms is ingested. Pork *(Taenia solium)*, beef *(Taenia saginata)*, and fish *(Diphyllobothrium latum)* tapeworms account for the majority of human infections, but human infections with the rodent tapeworms *Hymenolepis nana* and *Hymenolepis diminuta* and the dog tapeworm *Dipylidium caninum* may occur after inadvertent ingestion of contaminated insect intermediate hosts. Invasive systemic diseases in humans caused by tapeworm infections such as cysticercosis (caused by *T. solium*), and cystic and multilocular echinococcosis (caused by *Echinococcus granulosus* and *Echinococcus multilocularis*, respectively) are addressed in separate chapters (see Chapters 45 and 82).

Intestinal tapeworm infections are rare in the general population of economically advanced countries but cause significant human morbidity and economic losses in the meat industry in regions where personal and environmental hygienic practices and regulatory controls are insufficient. Recently, however, with the emergence of a global food market, salmon aquaculture has been associated with transmission of fish tapeworm infections thousands of miles beyond the region of original fish production. Similarly, it is possible that international meat markets could contribute to food-borne beef and pork tapeworm infections outside of known endemic regions, especially if breakdowns occur in regulatory infrastructure or meat inspection procedures.

CLINICAL PRESENTATION AND MANIFESTATIONS

Patients with the chief complaint of "passing a tapeworm" or with signs and symptoms of heavy worm burdens (vague abdominal discomfort, perianal irritation, anorexia, eosinophilia) are uncommon in most developed countries unless there is a history of specific risk, such as international travel, dietary exposures, migration, occupation, or certain circumstances of socioeconomic deprivation. Table 79-1 summarizes the geographic distribution and usual clinical features of the tapeworms infecting humans.

Humans serve as definitive hosts for beef and pork tapeworms; ingested larvae mature to sexually mature adult forms, and parasite eggs are produced in the small intestine. The eggs are excreted in the feces of the human host. Intermediate hosts ingest the eggs when human waste is deposited indiscriminately in the environment. On ingestion, the eggs develop into infective larvae in the tissues of the intermediate host. The reproductive life cycle is completed when humans ingest the infected intermediate hosts (Figures 79-1 and 80-1). In the case of *Diphyllobothrium* species, larval stages in two intermediate hosts are involved. The interdependence of the parasite on human definitive hosts and nonhuman intermediate hosts is complex (Figure 79-2).

The rodent tapeworm infection caused by *H. nana* (Figure 79-3) deserves special attention. It is one of very few helminthic (worm) infections of humans that can complete its entire life cycle in the human host without an obligate life stage in an intermediate host. Thus *H. nana* can cause autoinfections, resulting in a persistently infected state, heavy worm burdens in a given individual, and the possibility of direct human-to-human infections. Other important helminthic infections with a potential autoinfective cycle are the nematodes *Strongyloides stercoralis* (see Chapter 78), *Enterobius vermicularis* (see Chapter 78), and *Capillaria philippinensis*. *H. nana* infections are most commonly found in children living in dire socioeconomic conditions where rodent feces contaminate the environment and foodstuffs, leading to inadvertent oral exposure. The usual life cycle involves an infected rodent (definitive host) excreting eggs that are ingested by a beetle (intermediate host) where the larval forms develop; when a rodent eats the infected beetle, the larvae mature to adults, and ultimately infective eggs are excreted into the environment, thus reestablishing an infection in another beetle. Neither the usual definitive hosts nor intermediate hosts are obligate requirements for the completion of this life cycle. On ingestion of infected rodent feces, humans can serve as an inadvertent definitive host without the requirement of the intermediate beetle host, or humans can become reinfected by swallowing *H. nana* eggs passed in their own feces.

Intestinal infections with other animal tapeworms *D. caninum* or *H. diminuta* are sporadically detected in otherwise healthy persons. Infection occurs after inadvertent ingestion of infected fleas (*D. caninum*) or grain beetles (*H. diminuta*) (see Table 79-1).

Most human intestinal tapeworm infections are asymptomatic until a proglottid, a longer chain of proglottid segments (strobila), or the entire adult tapeworm is passed out of the bowel. Each of these living worm components can be motile;

Table 79-1 Distribution and Usual Clinical Significance of Tapeworms Affecting Humans

PARASITE NAME	ENDEMIC GEOGRAPHIC PARASITE DISTRIBUTION	COMMON CLINICAL SIGNIFICANCE
Tapeworms with Humans as the Definitive Host (Sexual Reproduction of the Parasite)		
Taenia saginata	The beef tapeworm is common in cattle-breeding regions worldwide. Humans are the definitive host and cattle the intermediate host. Areas with the highest (i.e., >10%) prevalence are central Asia, Near East Asia, and Central and Eastern Africa. Areas with low (i.e., 1%) prevalence are Southeast Asia, Europe, and Central and South America. *Prepatent period: 3-5 months* *Lifespan: up to 25 years* *Length of worms: 4-8 m*	Adult tapeworms live in the gastrointestinal tract of the human host. Eggs are excreted in the stools, and motile tapeworm segments can also be expelled from the bowels. The beef tapeworm does not cause invasive disease in humans but must be distinguished from the pork tapeworm, which does cause tissue infections in people, in regions where their distribution overlaps. People of all ages and races and both genders are susceptible to infection, which is acquired by eating larvae-infected undercooked beef meat.
Taenia solium	The pork tapeworm is endemic in Central and South America, Southeast Asia, India, the Philippines, Africa, Eastern Europe, and China, with humans being a definitive host and pigs the intermediate host. Areas of highest prevalence include Latin America and Africa. In some regions of Mexico, prevalence of infection may reach 3.6% of the general population. *Prepatent period: 3-5 months* *Lifespan: up to 25 years* *Length of worms: 3-5 m*	Adult tapeworms live in the gastrointestinal tract of the human host. Eggs are excreted in the stools, and motile tapeworm segments can also be expelled from the bowels. In humans the pork tapeworm causes invasive disease affecting soft tissues and the brain (cysticercosis). People of all ages and races and both genders are susceptible to infection, which is acquired by eating larvae-infected undercooked pork meat or by ingesting pork tapeworm eggs.
Diphyllobothrium latum	In North America, fish tapeworm infections have been previously reported in fish from the Great Lakes. There are six *Diphyllobothrium* species known to reside in Alaskan lakes and rivers, and some saltwater species may also be seen in North America. *Diphyllobothrium* infections are not species specific, and widespread reports describe infection in North American fish-eating birds and mammals. Humans are a definitive host, and crustaceans followed by fish are intermediate hosts. The incidence in the United States has been declining recently. Pike, perch, and salmon are among the fish most commonly infected. Reports are commonly made of *D. latum* infection in humans residing in Europe, Africa, and the Far East. *Prepatent period: 3-5 weeks* *Lifespan: up to 25 years* *Length of worms: 4-10 m*	Adult tapeworms live in the gastrointestinal tract of the human host. Eggs are excreted in the stools, and motile tapeworm segments can also be expelled from the bowels. The fish tapeworm does not cause invasive disease but, because of its length and potential to interfere with vitamin B_{12} absorption, can cause a number of nonspecific symptoms. People of all ages and races and both genders are susceptible to infection, which is acquired by eating undercooked, infected fish flesh. People preparing fresh fish, implements used to prepare fish (e.g., knives and cutting boards), and raw or undercooked fish meals (e.g., sushi, sashimi, ceviche) may be associated with a higher risk of infection.
Tapeworms with Humans as Inadvertent or Unnatural Hosts (Sexual Reproduction of the Parasite Normally Occurs in Another Animal Species)		
Hymenolepis nana	*H. nana* (dwarf tapeworm) is a cosmopolitan intestinal tapeworm usually infecting rodents, mice, or rats. The intermediate host, a beetle, is not required to complete its life cycle in definitive hosts. Ingestion of tapeworm eggs by a definitive host, including humans, can reestablish an adult tapeworm infection. *Prepatent period: 2-3 weeks* *Lifespan of infection: many years because of autoinfection.* *Length of worms: 2.5-4 cm*	Often associated with environments with poor sanitation, the dwarf tapeworm causes few clinical problems; signs and symptoms include nonspecific abdominal complaints, loosening of the stools, perianal irritation, and the possible presence of small motile segments visible in the stool or on undergarments.

Table 79-1 Distribution and Usual Clinical Significance of Tapeworms Affecting Humans—cont'd

PARASITE NAME	ENDEMIC GEOGRAPHIC PARASITE DISTRIBUTION	COMMON CLINICAL SIGNIFICANCE
Dipylidium caninum	*D. caninum* is a cosmopolitan tapeworm infection of dogs, with inadvertent human infections occurring through ingestion of the intermediate host, a flea that has fed on the tapeworm eggs contaminating the animal's fur or dog feces. Human infections have been reported in Europe, the Philippines, China, Japan, Argentina, and North America. *Prepatent period: 3-4 weeks* *Lifespan: Less than 1 year.* *Length of worms: 10-70 cm*	Adult tapeworms live in the gastrointestinal tract of the inadvertent human host, usually a child. Perianal irritation may occur, with the passage of motile segments of the tapeworm or small "grain of rice"—like motile segments that may be seen in the stools. The proglottids are motile when passed and may be mistaken for maggots or fly larvae.
Hymenolepis diminuta	The rat tapeworm requires a grain beetle as an intermediate host, so it is most common in grain-producing areas of the world or where grain or other dry foods are stored. Human infections are uncommon. *Prepatent period: 3 weeks* *Lifespan: less than 1 year* *Length of worms: 20-60 cm*	Often associated with environments with poor sanitation, the rat tapeworm rarely infects humans and causes few clinical problems; these include nonspecific abdominal complaints, loosening of the stools, and perianal irritation and the possible presence of small motile segments visible in the stool or on undergarments.

Adapted from MacPherson DW, McQueen R: Cestodes: intestinal and extra-intestinal tapeworm infections, including echinococcosis and cystercercosis. In Jong EC, Sanford CS, eds: The travel and tropical medicine manual, *ed 4, Philadelphia, 2008, Saunders, pp 597-610.*

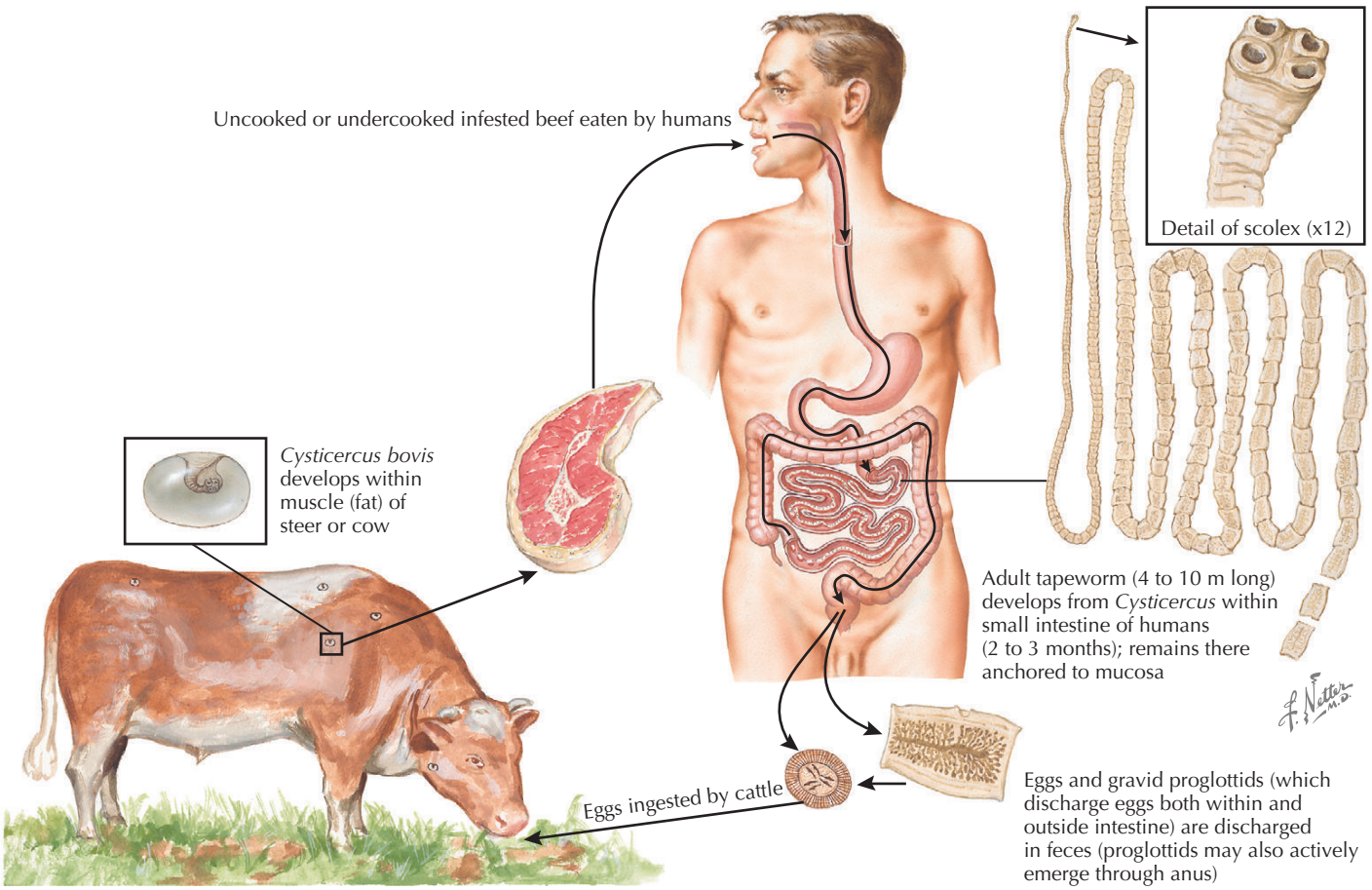


Figure 79-1 *Taenia saginata.*

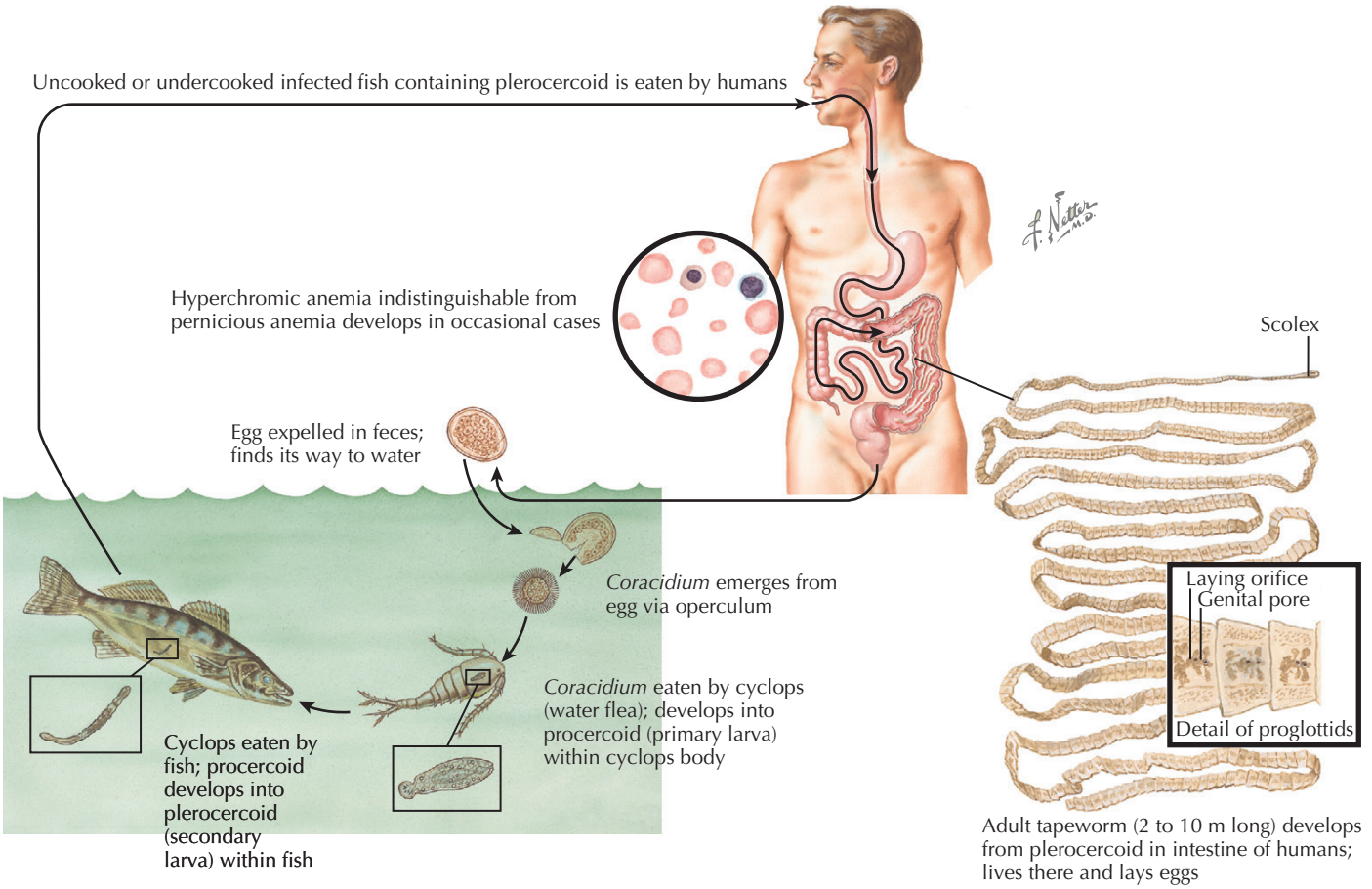


Figure 79-2 *Diphyllobothrium latum.*

thus the presence of the tapeworm is often manifested by a patient's complaint of the sensation of wriggling in the perianal region or undergarments. Pernicious anemia caused by vitamin B_{12} deficiency is a rare complication of fish tapeworm infections. Complications of tissue invasion with larval forms of tapeworms are addressed elsewhere (see Chapters 80 and 82). Multiple adult tapeworm infections and infections with multiple species of intestinal tapeworms in a single individual at the same time are uncommon clinical phenomenon.

DIAGNOSIS AND MANAGEMENT

A tapeworm infection can often be diagnosed by the description given by the patient of passing a single segment or a chain of proglottids per rectum and gross inspection of the specimen. A species-specific diagnosis requires examination of a specimen in a parasitology laboratory. Ova and parasite (O&P) stool examination can be used to detect both eggs and proglottids (segments) of tapeworms if present in the feces. *Taenia* species eggs cannot be distinguished as pork or beef tapeworm eggs on routine laboratory examination. In these cases, the morphology of the uterine branches in a proglottid is diagnostic. The head (scolex) of each tapeworm species is also distinctive, but rarely is an entire, intact worm available for laboratory examination. Serologic examination and other tests can confirm invasive pork tapeworm disease (see Chapter 80).

Except for *H. nana*, which can autoinfect its human host, all adult tapeworms have a limited lifespan in humans, although some can live for years. Specific management and treatment with antiparasitic drugs is indicated for a personal sense of well-being as well as for public health considerations (Table 79-2).

PREVENTION

In general, tapeworm infections can be prevented by food precautions, meticulous personal and environmental hygiene, and improved sanitary practices in animal husbandry and fish farming. At the individual level, persons should avoid eating raw, pickled, or undercooked meat and fish, especially in regions where food safety regulations are not likely to be strictly enforced. Food preparers should wash their hands before food preparation and again before eating, and avoid "snacking" on the unprocessed flesh during preparation,. At the public health and farm industry level, human wastes should be collected, contained, and processed: untreated sewer sludge should not be spread on cattle grazing lands, and piggeries should avoid feeding raw garbage to swine. Raw sewage should not be released

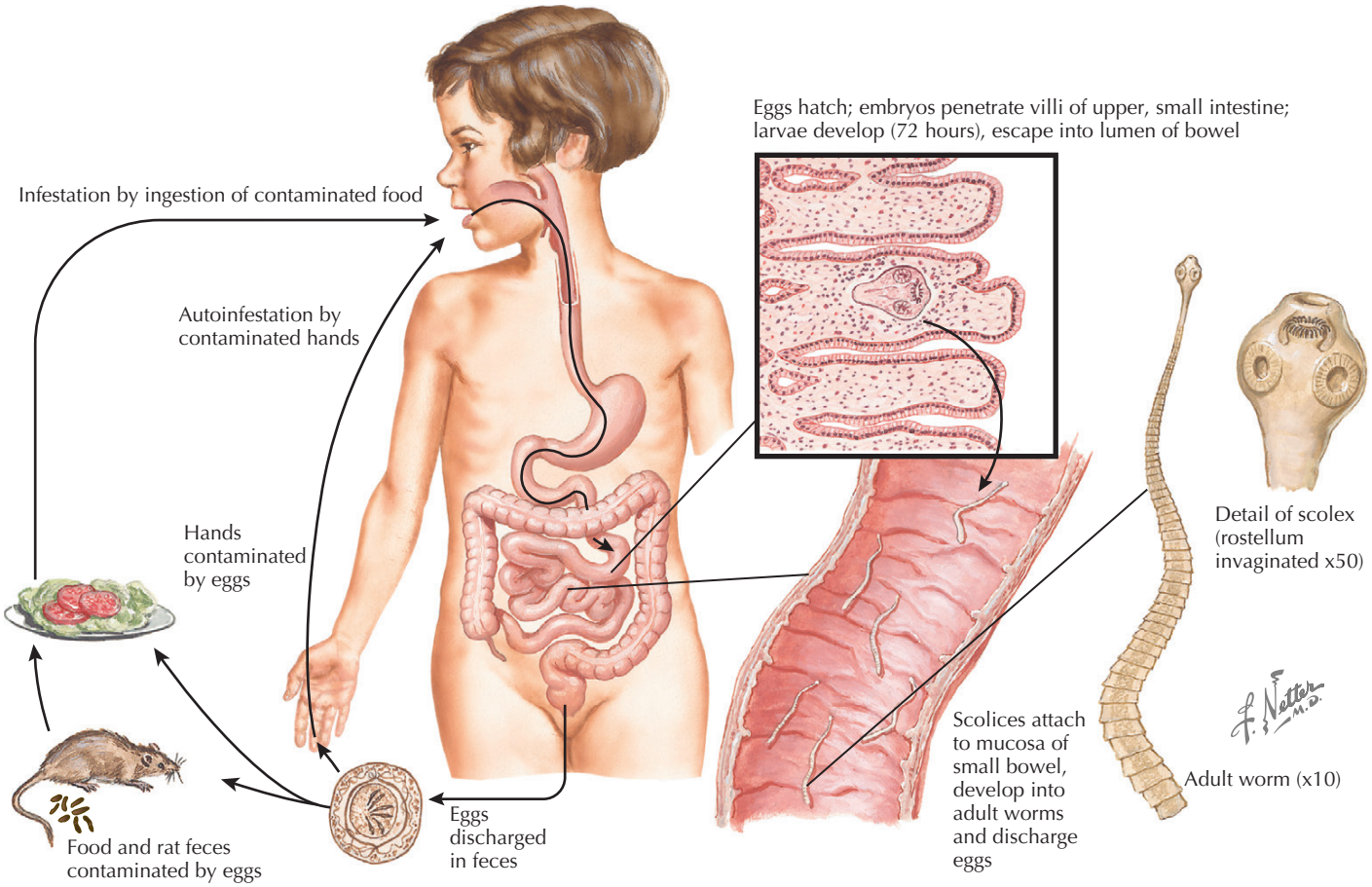


Figure 79-3 *Hymenolepis nana.*

Table 79-2 Treatment for Human Tapeworm Infections

PARASITE	DRUG	DOSAGE
Taenia saginata	Praziquantel	Single dose of 5-10 mg/kg
	Alternative: niclosamide	2.0 g once (50 mg/kg once)
Taenia solium (intestinal)	Praziquantel	Single dose of 5-10 mg/kg
	Alternative: niclosamide	2.0 g once (50 mg/kg once)
Diphyllobothrium latum	Praziquantel	Single dose of 5-10 mg/kg
	Alternative: niclosamide	2.0 g once (50 mg/kg once)
Dipylidium caninum	Praziquantel	Single dose of 5-10 mg/kg
	Alternative: niclosamide	2.0 g once (50 mg/kg once)
Hymenolepis nana	Praziquantel	*Adults and children:* Single dose of 25 mg/kg
	Alternative: nitazoxanide	500 mg × 3 days (1-3 years old: 100 mg bid × 3 days; 4-11 years old: 200 mg bid × 3 days)
Hymenolepis diminuta	Praziquantel or nitazoxanide	*Adults and children:* Single dose of 25 mg/kg 500 mg × 3 days (1-3 years old: 100 mg bid × 3 days; 4-11 years old: 200 mg bid × 3 days)

Adapted from MacPherson DW, McQueen R: Cestodes: intestinal and extra-intestinal tapeworm infections, including echinococcosis and cystercercosis. In Jong EC, Sanford CS, eds: The travel and tropical medicine manual, *ed 4, Philadelphia, 2008, Saunders, pp 597-610.*
bid, Twice per day.

into fresh water lakes or streams where copepods serving as intermediate hosts of the fish tapeworm can become infected and subsequently transmit the infection to fish, which in turn may be ingested by humans.

Cosmopolitan palates that cannot eschew sushi, sashimi, steak tartare, and other raw, smoked, pickled, or fermented meat and fish products, as well as enthusiastic home cooks who taste their culinary creations before adequate cooking need to entertain the possibility of tapeworm disease. The increasing use of gamma irradiation to process raw meat and seafood products may increase food safety in the future, especially in regions where ingestion of raw, smoked, pickled, fermented, or undercooked meat and/or fish is culturally ingrained.

EVIDENCE

Rodriguez-Canul R, Argaez-Rodriguez F, Pacheco de la Gala D, et al: *Taenia solium* metacestode viability in infected pork after preparation with salt pickling or cooking methods common in Yucatan, Mexico, *J Food Prot* 65:666-669, 2002. *Study showing that some traditional Mexican cooking methods may be sufficient to kill tapeworm larvae in infected pork.*

ADDITIONAL RESOURCES

Cabello FC: Salmon aquaculture and transmission of the fish tapeworm, *Emerg Infect Dis* 13:169-171, 2007. *Summary of epidemiologic studies associating human outbreaks of fish tapeworm in Brazil with salmon shipped from Chile, and implications for future outbreaks in other regions. Parasite destruction by various fish preparation methods is reviewed.*

Desowitz RS: New guinea tapeworms and Jewish grandmothers. In *New Guinea tapeworms and Jewish Grandmothers: tales of parasites and people*, New York, 1987, WW Norton and Company, pp 36-45. *Entertaining account of cultural practices and tapeworm transmission among two very different ethnic groups.*

International Consultative Group on Food Irradiation (ICGFI): *Facts about food irradiation*, Vienna, Austria, 1999, ICGFI, pp 1-45. Available at: www.iaea.org/icgfi. Accessed January 27, 2009. *Basic introduction to the process of food irradiation and its impact on food-borne infections, including parasites.*

MacPherson DW: Intestinal parasites. In Rakel RE, Bope ET, eds: *Conn's current therapy*, Philadelphia, 2008, Saunders, pp 558-564. *Succinct overview of intestinal parasites and treatment.*

MacPherson DW, McQueen R: Cestodes: intestinal and extra-intestinal tapeworm infections, including echinococcosis and cystercercosis. In Jong EC, Sanford CS, eds: *The travel and tropical medicine manual*, ed 4, Philadelphia, 2008, Saunders, pp 597-610. *Aspects of clinical diagnosis and treatment of tapeworm infections presented in detail for the healthcare provider.*

Cysticercosis

Raul E. Isturiz and Hector H. Garcia

80

ABSTRACT

Cysticercosis is the infection caused by *Cysticercus cellulosae*, the larval stage of the cestode *Taenia solium*, the pork tapeworm. The clinically significant helminthic invasion to central nervous system (CNS) structures and the resulting spectrum of neurologic illness define neurocysticercosis (NCC).

With the more extensive use of computed tomography (CT) and magnetic resonance (MRI) neuroimaging and the availability of accurate serologic testing, NCC has been increasingly diagnosed not only in less developed countries where pigs are raised, but also in industrialized countries with large immigrant populations originating from endemic areas. NCC is presently recognized as the most common parasitic infection of the CNS.

GEOGRAPHIC DISTRIBUTION

T. solium is found worldwide. The pig is the obligate intermediate host, and thus completion of the life cycle occurs in areas where humans live in close contact with free-roaming pigs and eat undercooked pork, typically in rural villages.

Conservative worldwide estimates suggest there are at least 50 million people infected with cysticercosis and 50,000 die per year. Endemicity has been demonstrated in Latin America, Eastern Europe, and non-Muslim populations of Africa, India, and other Asian countries.

NCC is the most important cause of acquired epilepsy in developing countries and is becoming more common in industrialized countries owing to immigration and travel of tapeworm carriers and cysticercosis-infected individuals from endemic regions. Approximately 1000 cases are diagnosed in the United States every year; Europe increasingly reports cases, but no reliable continental statistics exist. In industrialized countries, the incidence is highest in major urban centers with large immigrant populations.

The incidence of epilepsy per 100,000 population ranges from 30 to 50 in industrialized countries and 90 to 122 in developing countries; in cysticercosis-endemic areas, the overall epilepsy incidence rate measured per 100,000 person-years can be as high as 162.3, and for epileptic seizures, as high as 216.6. In endemic areas, an important proportion of seizure cases is associated with NCC.

TRANSMISSION AND RISK FACTORS

Humans are the definitive host for the *T. solium* adult and become infected by ingesting cysticerci in undercooked contaminated pork. The resulting pork tapeworm infection, taeniasis, and consequent stool shedding of eggs and proglottids are associated with few or no symptoms; thus infected carriers are not routinely detected (Figure 80-1). Human (and porcine) cysticercosis follows ingestion of excreted gravid proglottids or embryonated ova from a tapeworm carrier by fecal-oral transmission; however, autoinfection from larvae released in the intestinal tract may occur.

That pork ingestion or direct contact with pigs is not required for the transmission of human cysticercosis is exemplified by reported cases of the disease that have occurred among members of an Orthodox Jewish community in the United States and among vegetarians in India.

CLINICAL FEATURES

When they invade the CNS, the larvae encyst (vesicular or cystic stage) and actively evade or modulate the human host immune response by using various strategies. After a period of months to years, the cysts are recognized and attacked by a complex array of host inflammatory mechanisms. The result is the degeneration and death of the parasite (colloidal and granular stages) and development of inflammation of surrounding tissues. The inflammatory response, which is transitory, is believed to be responsible for most symptoms. Calcification eventually occurs (calcific stage).

NCC induces neurologic syndromes that vary from an asymptomatic infestation to sudden death, but seizures and hydrocephalus (headache) are the most important clinical presentations. Seizures may be focal but more commonly are generalized, or focal with generalization. Cognitive impairment and focal neurologic deficits are common. Individual clinical presentation and clinical course are contingent on the type, stage, location, and number of parasites in the nervous system, as well as the host's immune response (Figure 80-2).

Parenchymal Disease

Active parenchymal cysticercosis is the most common presentation of the disease. Because viable intact (vesicular) cysts are frequently asymptomatic, most patients with symptoms have CT or MRI evidence of cyst degeneration (colloidal and granular) or inflammation (contrast enhancement or brain edema) surrounding the parasite.

Cysts can be single or multiple, and the surrounding parenchymal inflammation explains the seizures and most other clinical findings. A range of parenchymal cystic lesions can be found. For example, in India and in the United States, radiographic images of most patients show a single degenerating cysticercus, whereas in Latin America and China they commonly are consistent with multiple viable cysts.

Cysticercotic encephalitis is the uncommon presence of large numbers of cysts and generalized cerebral edema associated with seizures and abnormal mental status.

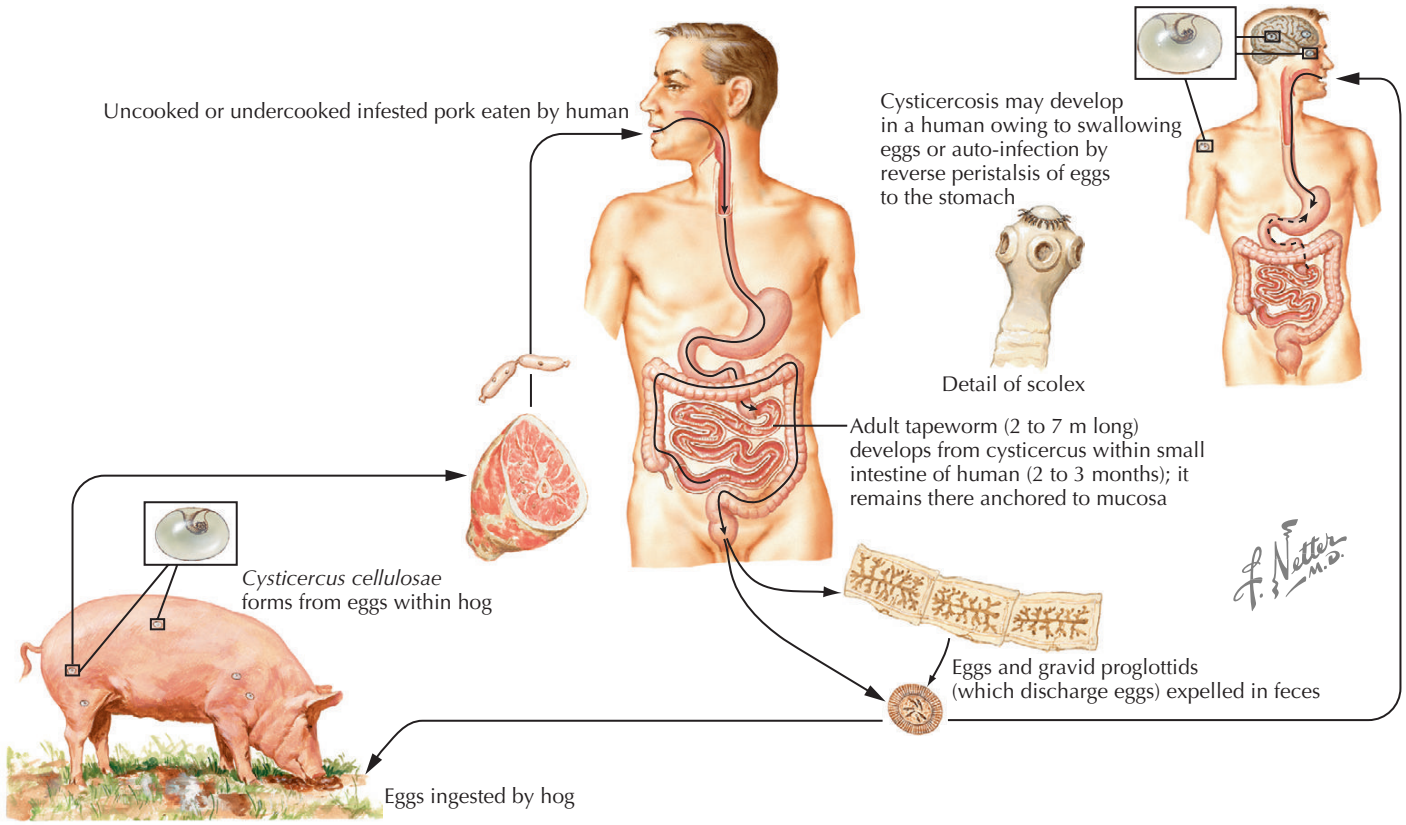


Figure 80-1 *Taenia solium (Cysticercus cellulosae).*

Calcified lesions on CT are the hallmark of inactive parenchymal cysticercosis, and patients usually experience seizures that are believed to be caused by disruption of calcified granulomas and cerebral inflammation secondary to antigen exposure.

Extraparenchymal Disease

Extraparenchymal NCC can be found alone or in combination with parenchymal disease. Cysticerci lodged in the convexity of the cerebral hemispheres tend to be larger but produce similar clinical manifestations as intraparenchymal cysts. Cysticerci may also be localized inside the ventricles, in the basal subarachnoid space, or in the sylvian fissure. Intracranial hypertension results from mechanical factors or arachnoiditis.

Ventricular NCC is not uncommon, and the cysts, which may be found in any ventricle and be difficult to detect by neuroimaging, may cause hydrocephalus by obstructing the normal flow of cerebrospinal fluid (CSF). The clinical manifestations depend on the parasitized ventricle involved and the degree of obstruction.

Active subarachnoid NCC occurs when cysts lodge outside of the brain. They tend to occupy the sylvian fissure or the basal cisterns, where more space is available. In those areas, cysts may be numerous; tend to grow larger and disordered; and induce a severe inflammatory response, which may be evident in CSF examination and induce stroke secondary to vasculitis. Even inactive NCC of this area can cause CSF flow obstruction and hydrocephalus.

Other Manifestations

Sellar NCC mimics pituitary adenoma; spinal NCC causes level-related sensory and motor manifestations; and ophthalmic cysticercosis is usually retinal or vitreous.

DIAGNOSTIC APPROACH

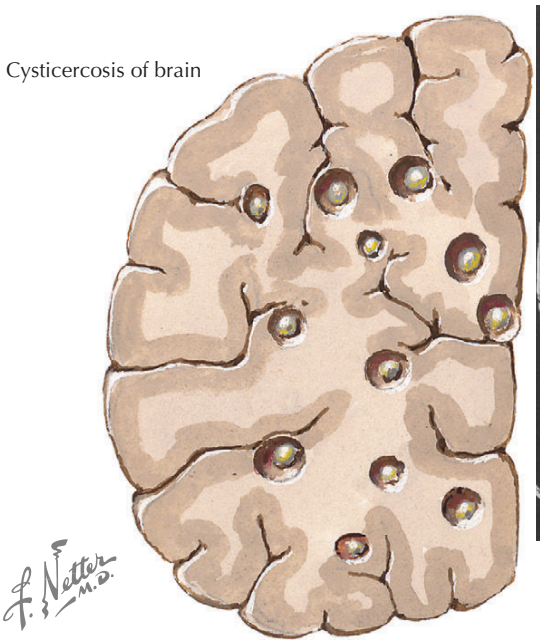
Details of the clinical presentation in patients with suspected NCC are relatively helpful but not definitive, because many different neurologic manifestations can be caused by the diverse location, number, size, and stage of the parasites, as well as the varying intensity of the inflammatory response of individual human hosts. However, in endemic regions, late-onset seizures and intracranial hypertension are suggestive, and NCC should be high on the list of differential diagnoses.

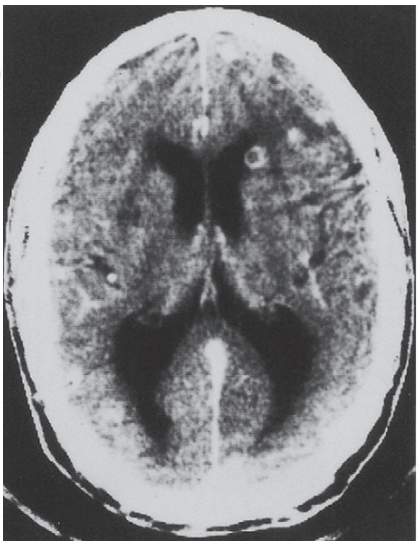
The current approach to the diagnosis of NCC rests on neuroimaging, with serology providing confirmatory support. Brain imaging can be performed using either CT or MRI, and each imaging technique has advantages and disadvantages. CT is more frequently available in developing countries and is less expensive (extremely important considering that NCC is a disease of poverty). A good CT scan will diagnose most cases of NCC. Conversely, old machines that produce bad images are of poor help in making the diagnosis. MRI, in turn, gives better images as well as images in different planes. Definition of small lesions, intraventricular lesions, and lesions close to the bone is much better with MRI than with CT. MRI's diverse imaging protocols allow also a better definition of the perilesional

Ovum of *Taenia solium* (pork tapeworm); indistinguishable from that of *T. saginata* (beef tapeworm)

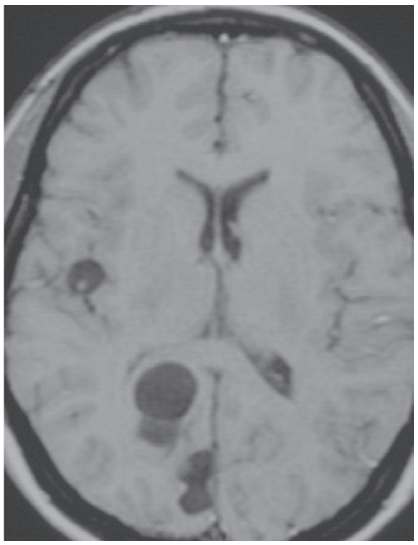
Cysticercus (larval stage) of pork tapeworm; fluid-filled sac (bladder) containing scolex (head) of worm

T. solium ova hatch after ingestion by hogs; embryos migrate to hog tissues and form cysticerci. When humans eat infested pork, intestinal tapeworms develop. However, if humans ingest ova instead of larvae, or if ova reach the stomach by reverse peristalsis after release from intestinal worms, human cysticercosis may occur.





CT scan: punctate calcifications, cystic lesions (some with ring enhancement) and noncystic areas, which enhance in areas of inflammation



MRI T1-weighted image with multiple cystic masses, one with eccentric intradural signal region (seen as calcification on CT, representing calcification of dead larvae)

Figure 80-2 Cysticercosis.

inflammation. As a drawback, MRI imaging of calcifications is suboptimal, and often they are missed.

Serologic diagnosis of cysticercosis improved greatly with the introduction of the enzyme-linked immunoelectrotransfer blot assay (EITB, western blot) with purified glycoprotein antigens in 1989. Previous assays including the enzyme-linked immunosorbent assay (ELISA) had low sensitivity and incomplete specificity. EITB can reach a level of 98% sensitivity in patients with more than one viable cyst, dropping to 70% in patients with a single degenerating parasite. Recently, assays aimed to detect specific circulating parasite antigens on ELISA using monoclonal antibodies have been revisited. Their diagnostic sensitivity is lower than that of the antibody-detecting EITB. However, antigen detection assays seem better at differentiating infections with viable parasites, as well as being very useful for monitoring disease evolution in complicated cases of basal subarachnoid NCC.

TREATMENT

The long-lasting controversy in the medical literature about whether or not to use antiparasitic drugs in the treatment of NCC has distracted physicians' attention from two key points in NCC management: (1) it should be approached differentially according to the type of NCC, and (2) symptomatic management is crucial. The pleomorphic nature of NCC involves different stages (patients with viable, degenerating, and/or calcified cysts) as well as different sizes (from punctuate calcifications to giant cysts in the sylvian fissure); different localizations (intraparenchymal, intraventricular, subarachnoid); and, of course, the different numbers of lesions that are present and the variable inflammatory response of the host.

The principles of treatment of NCC involve as a first step appropriate use of symptomatic medication to control seizures, headache, or intracranial hypertension, followed by a decision on the specific measures targeted to destroy or inactivate the parasitic lesions.

Symptomatic treatment includes management of intracranial hypertension with steroids and mannitol, and in cases in which NCC obstructs CSF flow, surgical removal of large cysts and cyst masses may be required. Other common therapies include analgesics, and antiepileptic drug therapy to manage the underlying seizure disorder. Seizures associated with NCC usually respond well to first-line antiepileptic drugs. Carbamazepine and phenytoin are the most commonly used drugs in endemic regions.

Specific management of the parasitic lesions involves the use of cysticidal antiparasitic drugs, either albendazole (ABZ) or

praziquantel (PZQ), and, less frequently, surgery. ABZ is used at 15 mg/kg/day for 7 to 15 days, and PZQ is used at 50 mg/kg/day for 15 days, although a single-day scheme has been reported. Steroids are given concomitantly with ABZ or PZQ to decrease the inflammation resulting from exposure to antigens released from degenerating cysts. Analysis of the existing literature suggests that treatment with cysticidal antiparasitic drugs is of benefit in most cases of NCC with viable (vesicular) or degenerating (colloidal) cysts. Of note, subarachnoid NCC would probably require antiparasitic drug treatment for long periods and repeated courses. On the other hand, in patients with cysticercotic encephalitis (many small intraparenchymal cysts with a heavy and diffuse inflammatory response) the use of antiparasitic medications is contraindicated because it could boost the inflammatory response and lead to fatal intracranial hypertension.

The role of surgery is restricted to the excision of bulky cysts or cyst clumps leading to mass effect, or to neuroendoscopic excision of intraventricular parasites.

PREVENTION

The elimination of taeniasis and cysticercosis in Europe by sanitation efforts suggests that the disease can be eliminated on a global scale. All steps in the life cycle of *T. solium* can be targeted. Improved animal husbandry and effective porcine meat inspection are effective but difficult to implement in developing areas of the world.

Better detection and treatment of tapeworm carriers could effectively interrupt human transmission. A porcine vaccine is available. An effective human vaccine seems promising but has received low priority.

EVIDENCE

Abba K, Ramaratnam S, Ranganathan LN: Anthelmintics for people with neurocysticercosis, *Cochrane Database Syst Rev* 1:CD000215, 2010. *Randomized controlled trials comparing albendazole (ABZ) with placebo, no anthelmintic, or another anthelmintic regimen in subjects with NCC were reviewed to assess the effectiveness and safety of anthelmintic treatment. In adults with NCC with viable lesions, ABZ treatment may reduce the number of lesions, but there was no difference in the rate of seizure recurrence compared with no treatment. In children with NCC with nonviable lesions, ABZ treatment substantially lowered seizure recurrence compared with no treatment, although no differences were detected in persistence of lesions at follow-up. Limited evidence suggested reduction in the occurrence of headache when corticosteroids were co-administered with ABZ, but further research is needed.*

Del Brutto OH, Roos KL, Coffey CS, García HH: Meta-analysis: Cysticidal drugs for neurocysticercosis: albendazole and praziquantel, *Ann Intern Med* 145:43-51, 2006. *This review presents a meta-analysis of randomized trials assessing the effect of cysticidal drugs (ABZ or PZQ) on neuroimaging and clinical outcomes of patients with NCC. Six trials randomly assigned 464 patients with cystic lesions (vesicular cysticerci, viable parasites), and five trials randomly assigned 478 patients with enhancing lesions (colloidal cysticerci, degenerating parasites) met the study's inclusion criteria. The authors conclude that the evidence shows that cysticidal drug therapy results in better resolution of both colloidal and vesicular cysticerci, lower risk for recurrence of seizures in patients with colloidal cysticerci, and a reduction in the rate of generalized seizures in patients with vesicular cysticerci. The evidence favors ABZ over PZQ, and larger courses of ABZ may be needed for treatment of patients with more than a few cystic lesions.*

Manuel V, Villarán SM, Montano GG, Gonzalvez G, et al: Epilepsy and neurocysticercosis: an incidence study in a Peruvian rural population, *Neuroepidemiology* 33:25-31, 2009. *This study of the incidence of seizures in rural Peru demonstrates that NCC accounts for a significant proportion of the reported seizure cases in this setting and that measures to control transmission of* T. solium *infections would contribute to improved individual and community health.*

Parija SC, Gireesh AR: A serological study of cysticercosis in patients with HIV, *Rev Inst Med Trop Sao Paulo* 51:185-189, 2009. *A report on the prevalence of cysticercosis among human immunodeficiency virus (HIV)–infected persons living in Puducherry, India, and neighboring areas, based on serologic screening. One hundred HIV-positive sera were tested for anti-*T. solium *larval stage antibodies using EITB and ELISA tests, and* T. solium *larval stage antigens using the coagglutination (Co-A) test. The overall seropositivity for* T. solium *larvae detected by all methods was 5%. Two of the samples were positive for parasite antibody by EITB and four were positive by ELISA, with only one sample positive by both tests; no sample tested positive for parasite antigen. Further studies are needed to correlate serologic findings, neuroimaging results, and status of infection in study populations of HIV-infected persons with NCC co-infection.*

Praet N, Speybroeck N, Rodriguez-Hidalgo R, et al: Age-related infection and transmission patterns of human cysticercosis, *Int J Parasitol* 40:85-90, 2010. *This investigation of* T. solium *transmission dynamics in a south Ecuadorian rural population correlates serologic evidence (antibodies and antigens) of* T. solium *cysticerci with host age and status of infection. Immunosenescence is suggested to account for the finding that an increasing proportion of people older than 60 years of age had presence of circulating parasite antigens, indicative of viable cysticerci.*

Rangel-Castilla L, Serpa JA, Gopinath SP, et al: Contemporary neurosurgical approaches to neurocysticercosis, *Am J Trop Med Hyg* 280:373-378, 2009. *This article presents a retrospective analysis of the outcomes in 31 patients with NCC that had neurosurgical evaluations at a Houston, Texas, hospital from 1997 to 2005. Two patients were treated with medical therapy, and 29 were treated with a variety of neurosurgical procedures (shunts, craniotomy, and endoscopy). A high rate of shunt failure was observed, and neuroendoscopy seemed to be associated with a higher success rate.*

Schantz PM, Moore AC, Munoz JL: Neurocysticercosis in an Orthodox Jewish community in New York City, *N Engl J Med* 327:692-695, 1992. *A fascinating account of NCC transmission in a U.S. community that does not eat pork.*

Singhi P, Singhi S: Neurocysticercosis in children, *Indian J Pediatr* 76:537-545, 2009. *A comprehensive analysis of NCC in children with the diagnosis made by either CT or MRI. More than 80% of children demonstrated seizures, particularly partial seizures, and about one third complained of headache and vomiting. Children with single lesions were reported to have a good outcome and low recurrence of seizures after cysticidal therapy, whereas children with multiple lesions tended to have recurrent seizures.*

ADDITIONAL RESOURCES

Carabin H, Cowan L, Nash T, et al: Estimating the global burden of cysticercosis. Bellagio, 2006. Available at: www.who.int./entity/foodsafety/foodborne_disease/cysticercosis2.pdf (accessed 02/27/2011) *Presentation from meeting of WHO expert consultants that provides a global overview and suggests strategic steps and economic considerations for decreasing the risk of cysticercosis in the global food supply*.

Centers for Disease Control and Prevention (CDC): Web site: www.cdc.gov/parasites/cysticercosis/index.html. *Portal to multiple resources for information on cysticercosis, including epidemiology, clinical signs and symptoms, diagnosis and treatment, public health considerations, patient education materials, and guidance for health professionals*.

Food-Borne Trematodes: Liver, Lung, and Intestinal Flukes

Elaine C. Jong

81

ABSTRACT

Liver, lung, and intestinal flukes usually infect humans through the ingestion of freshwater plants, fish, and crustaceans contaminated by encysted forms of the parasite infective-stage metacercariae; thus these organisms are referred to as food-borne trematodes (FBTs). FBT infections are prevalent in Asia, Southeast Asia, and the Western Pacific, and transmission is fostered by local culinary preferences for raw or undercooked foods, presence of freshwater snails in the environment serving as obligatory intermediate hosts in the parasite life cycle, and contamination of surface water by untreated fecal wastes from infected human and nonhuman mammalian hosts. Because of current patterns of human migration and the growth of aquaculture with produce that reaches a global marketplace, cases of FBT infection may be reported among immigrants to nonendemic areas who acquired infections in their country of origin before migration, and among residents of nonendemic areas who may have inadvertently eaten contaminated freshwater fish imported from endemic areas or contaminated foods while traveling. Fluke infections are associated with gastrointestinal symptoms and local inflammation, fibrosis, obstruction, and in some cases cancer in the anatomic structures where the adult flukes and their eggs are localized within the human body.

GEOGRAPHIC DISTRIBUTION

Liver flukes are transmitted in rural agricultural communities throughout the world. At a workshop convened by the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) in 2002, it was estimated that more than 40 million people may be infected with FBTs throughout the world. The burden of disease actually may be higher, because accurate data on prevalence and geographic distribution of FBT infections depend on sufficiently staffed and funded public heath surveillance programs—often lacking in some highly endemic areas. The time-consuming work of diagnosing infections by identifying trematode eggs in stool and/or sputum samples from individuals with suspected infections requires that local access to primary health care providers who are trained in clinical diagnosis and appropriate treatment must be available.

RISK FACTORS

Humans and animals may become infected with FBTs when they ingest raw or undercooked freshwater plants, crustaceans, and/or fish contaminated with the encysted metacercariae of the flukes, and serve as definitive hosts, meaning that the parasites become sexually mature adults within the body of the host. The parasite ova (eggs) produced by liver and intestinal flukes exit the body in the fecal stream. In the case of lung flukes the eggs may be expectorated in the sputum or swallowed and then excreted in the stools. The life cycle of the intestinal fluke *Heterophyes*, a fish-borne trematode, is shown in Figure 81-1 and serves as a model for understanding transmission of the other fish-borne transmitted flukes: *Metagonimus yokogawai*, *Clonorchis sinensis*, and *Opisthorchis viverrini*. After contamination of freshwater environments by feces from infected mammalian hosts, *Heterophyes* eggs are taken up by suitable snail hosts (the first intermediate host) and hatch, with the emergence of parasite forms called *miracidia*. After going through further developmental stages in the snail gut with both parasite maturation and multiplication, free-swimming parasite forms called *cercariae* are shed by the snails into the water. The cercariae attach and penetrate fish (the second intermediate host), transforming into encysted metacercariae in the flesh of the fish. The metacercariae are the parasite stage infectious for mammalian hosts, and after infected fish are eaten by humans or other fish-eating mammals or birds, the metacercariae excyst and develop into adults in the small intestine.

After ingestion of fish containing encysted metacercariae of *C. sinensis* and *O. viverrini*, the parasites excyst and there is a larval migration through the duodenum, the ampulla of Vater, and the extrahepatic bile ducts, with the larvae eventually reaching the intrahepatic bile ducts, where they mature into adults.

In the life cycle of the liver flukes *Fasciola gigantica* and *Fasciola hepatica* and the intestinal fluke *Fasciolopsis buski*, the cercariae shed by the snails attach to freshwater plants and become encysted metacercariae. After ingestion, larvae of *F. gigantica* and *F. hepatica* excyst in the duodenum, penetrate the intestinal wall to reach the peritoneal cavity, penetrate Glisson's capsule, migrate through the liver parenchyma, and finally reach the bile ducts, where the flukes mature and live for many years. After excystation, the larvae of *F. buski* attach to the walls of the duodenum and jejunum and remain firmly attached as they develop into adults.

Freshwater crabs and crayfish serve as the second intermediate host in the lung fluke *(Paragonimus)* life cycle. After ingestion, viable metacercariae excyst in the small intestine, and the larvae penetrate the intestinal wall, migrate through the peritoneal cavity, pass through the diaphragm into the pleural space, and eventually migrate into the lung parenchyma, where the parasites mature into adults and produce eggs. The eggs are expectorated in the sputum or are swallowed and passed in the stool.

The risk of infection by FBTs can be reduced if freshwater plants, crustaceans, and fish are thoroughly cooked before being eaten. Freezing at 120° C for 7 days kills encysted metacercariae in fish. However, in many of the locales where FBTs are prevalent, there are cultural preferences and social practices that involve eating raw or undercooked vegetables, crabs, and fish.

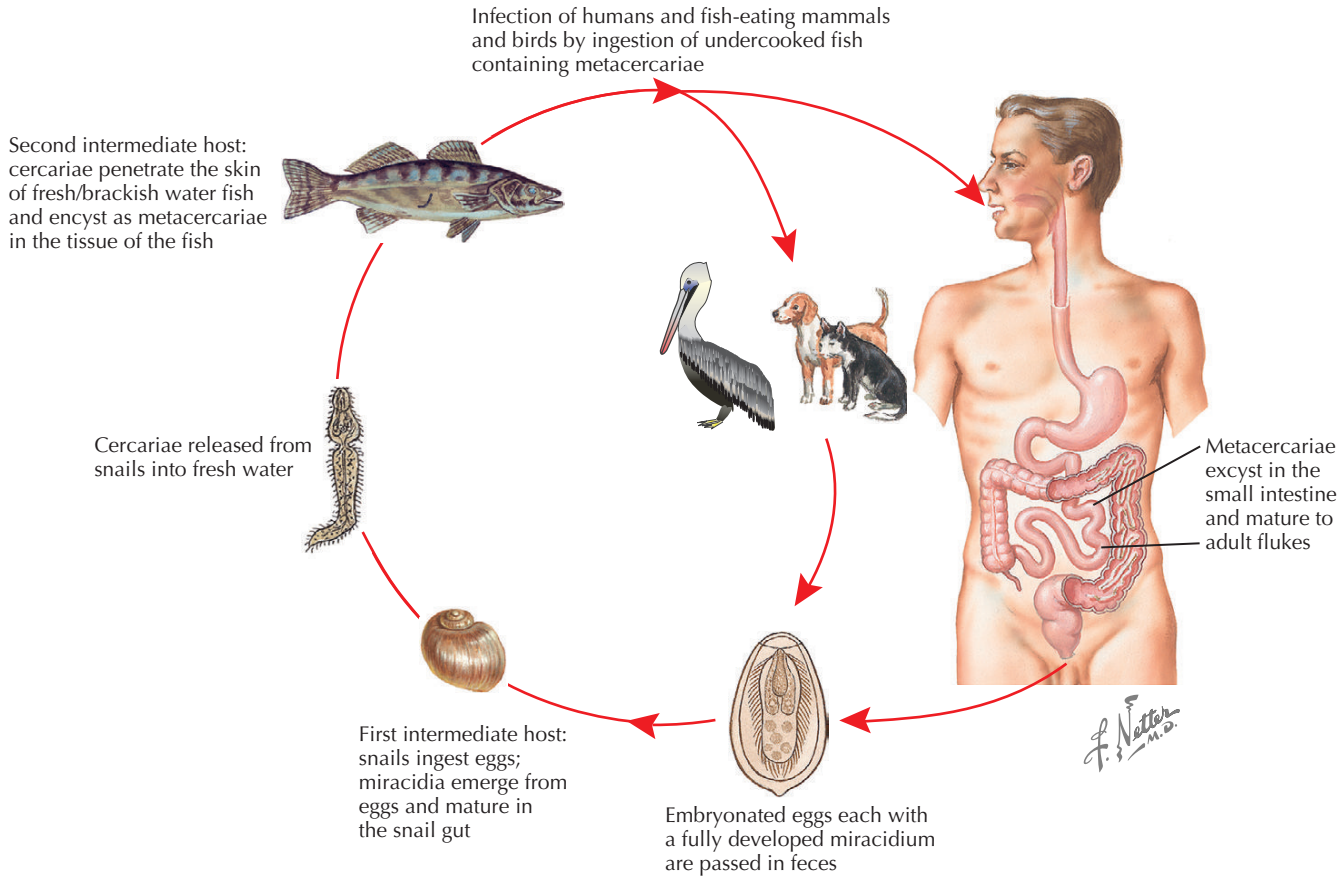


Figure 81-1 Life cycle of *Heterophyes*.

CLINICAL FEATURES AND DIAGNOSTIC APPROACH

Among the numerous FBTs that may cause animal infections, about 100 species are known to infect humans. The features of eight FBTs of medical importance and public health significance are summarized in Table 81-1. Finding parasite eggs in stool specimens may be an incidental finding in persons with light infections, who tend to be asymptomatic. The heavier parasite burdens seen among persons living in endemic regions are usually the result of repeated exposures, and such individuals may eventually manifest a variety of symptoms and end-organ disease owing to the chronic inflammation and fibrosis induced by the flukes and eggs retained in the tissues. Given the longevity of certain flukes that may live in infected human hosts for a decade or more, immigrants who were infected in their country of origin and moved to a nonendemic area may experience disease manifestations many years after resettlement.

Diagnosis of infections is based on finding and identifying trematode eggs in submitted stool samples, or in sputum and/or stool samples in the case of *Paragonimus*. Morphologic diagnosis can be challenging, as the number of eggs passed may vary from day to day, and in some cases of chronic infection few eggs, if any, may be passed. The trematode eggs of one species cannot be easily differentiated from the eggs of another species based on morphology, and some of the eggs are relatively small (Figure 81-2). Specific serodiagnostic tests and imaging studies might help improve diagnosis but may not be readily available in community primary care. Specimen send-out to a reference or research laboratory and patient referral to a regional medical center for examination by an experienced radiologist might be required for ultimate diagnosis.

TREATMENT

Prompt treatment of diagnosed infections may prevent some of the serious sequelae of FBT infections. Praziquantel (PZQ) is the drug of choice for the treatment of most FBTs, with the exception of fascioliasis. Triclabendazole (TCZ) has selective activity against immature and mature trematodes and is used for treatment of fascioliasis and paragonimiasis. Treatment regimens are given in Table 81-2.

PZQ also is used in the treatment of schistosomiasis and has activity against cestodes. Thus in areas co-endemic for cysticercosis, ocular cysticercosis must be ruled out before initiation of treatment with PZQ. Common adverse effects include abdominal discomfort, nausea and vomiting, malaise, headache, dizziness, and drowsiness. Safety in pregnancy has not been established, and as a precaution, breastfeeding should be avoided during treatment and for 72 hours afterward.

Table 81-1 Selected Food-Borne Trematodes of Medical Importance

COMMON NAME	GENUS AND SPECIES	ANIMAL RESERVOIR HOSTS	SOURCE OF HUMAN INFECTION	LOCATION IN HUMAN BODY	DISEASE MANIFESTATIONS
Liver flukes	*Fasciola gigantica*	Cattle, buffalo	Freshwater plants	Liver and biliary system	*Fascioliasis:* abdominal pain, anorexia and weight loss, mild intermittent fever, hepatosplenomegaly, jaundice, biliary abnormalities, necrotic lesions in hepatic tissue, fibrosis of biliary ducts.
	Fasciola hepatica	Sheep	Freshwater plants, especially watercress	Liver and biliary system	
	Clonorchis sinensis	Dogs and cats	Freshwater fish	Liver, biliary system, and pancreatic duct	*Clonorchiasis:* anorexia, indigestion, abdominal pain, weakness and weight loss, gastrointestinal bleeding, formation of gallstones; invasion of pancreatic duct, cholangitis, cholecystitis and gallstones in severe infections. Increased risk of cholangiocarcinoma.
	Opisthorchis viverrini	Dogs, cats, and pigs	Freshwater fish, especially grass carp	Biliary system	*Opisthorchiasis:* similar to clonorchiasis; enlarged gallbladder, cholecystitis, cholangitis, liver abscess and gallstones in chronic heavy infections. Increased risk of cholangiocarcinoma.
Lung flukes	*Paragonimus* species complex	Pigs, dogs, and a wide variety of felines	Freshwater crabs and crayfish	Pleural cavity and lungs; occasional brain invasion	*Paragonimiasis:* chest pain, cough with rust-colored sputum, fatigue, fever, focal hemorrhagic pneumonia, granuloma formation and fibrotic encapsulation in the lungs; possible larval migration to ectopic sites (e.g., brain, abdomen, groin, skin, heart). Misdiagnosis of pulmonary tuberculosis or lung cancer.
Intestinal flukes	*Fasciolopsis buski*	Farm animals such as pigs, dogs and cats	Freshwater plants: water caltrops, water chestnuts, bamboo shoots	Small intestine	*Fasciolopsiasis:* epigastric pain, facial edema, urticarial skin lesions, nausea and vomiting, diarrhea.
	Heterophyes heterophyes	Dogs, cats, and fish-eating birds	Freshwater fish, especially mullet	Mucosa of small intestine	*Heterophyiasis:* abdominal pain, diarrhea, lethargy.
	Metagonimus yokogawai	Dogs and cats	Freshwater fish	Mucosa of small intestine	*Metagonimiasis:* similar to heterophyiasis.

Data from the World Health Organization (WHO) Regional Office for the Western Pacific: Joint WHO/FAO Workshop on Foodborne Trematode Infections in Asia, WHO Regional Office for the Western Pacific, Manila, Philippines, 2004. Available at: http://www.wpro.who.int/internet/resources.ashx/MVP/FBT.pdf.

TCZ is a drug with a long history of use in veterinary medicine for treating fascioliasis in sheep and cattle and subsequently has become available for use in human trematode infections. Common adverse effects include gastrointestinal discomfort and headache.

In the treatment of paragonimiasis with either PZQ or TCZ, initiating treatment in the hospital is recommended because of the possibility of central nervous system (CNS) involvement and the possibility of inducing local hypersensitivity reactions, accompanied by edema, to drug-damaged parasites in the confined anatomic spaces of the CNS.

PREVENTION AND CONTROL

Prevention and control of FBTs require a multipronged approach: drug treatment of infected human populations, periodic mass treatment of nonhuman reservoir hosts when feasible, improved sanitation, control of intermediate hosts, and cooking freshwater fish, crustaceans, and vegetation before human consumption.

Detection and treatment of newly acquired human infections can prevent the morbidity and mortality associated with chronic heavy infections and contribute to the interruption

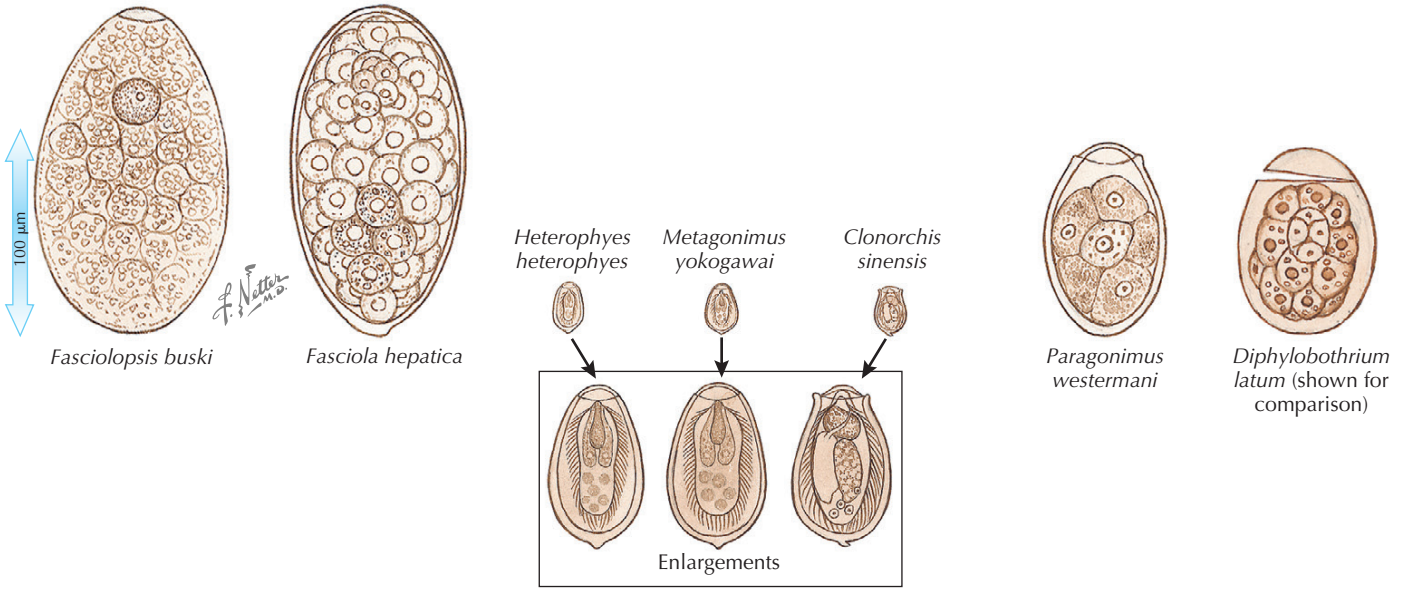


Figure 81-2 Ova of selected food-borne trematodes.

Table 81-2 Drug Regimens for Treatment of Food-Borne Trematodes

TREMATODE	PRAZIQUANTEL, 600-mg TABLET: ADULTS AND CHILDREN OVER 4 YEARS OF AGE*	TRICLABENDAZOLE, 250-mg TABLET: ADULTS AND CHILDREN OVER 4 YEARS OF AGE*
Liver flukes (excluding fascioliasis)	25 mg/kg by mouth three times a day for 2 consecutive days, *or* 40 mg/kg by mouth as a single dose	Praziquantel is the drug of choice
Liver flukes (for fascioliasis)	Praziquantel efficacy is considered unsatisfactory for this infection	10 mg/kg by mouth as a single dose
Lung flukes	25 mg/kg by mouth three times a day for 2 consecutive days, *or* 40 mg/kg by mouth as a single dose Note: Treatment may need to be extended for up to 3-5 days	20 mg/kg by mouth given in two divided doses in 1 day
Intestinal flukes	25 mg/kg by mouth as a single dose	Praziquantel is the drug of choice

Data from Stuart MC, Kouimtzi M, Hill SR: WHO Model Formulary 2008, *Geneva, 2009, World Health Organization. Available at: www.who.int/selection_medicines/list/WMF2008.pdf.*
*See text for adverse side effects, warnings, and contraindications.

of transmission through contaminated human feces. Similarly, chemotherapy of infected livestock would contribute to decreased environmental contamination with infected feces.

On a larger scale, agricultural communities in endemic areas need improved procedures for collecting and processing human and animal wastes and must avoid using raw sewage as fertilizer for crops, because runoff from farms eventually contaminates human-made and natural freshwater bodies, where the intermediate hosts dwell. Water velocity, water temperature, and sunlight may be manipulated at sites of aquaculture and contribute to control of the snails, intermediate hosts, and aquatic vegetation.

Populations at risk can be educated about the benefits of cooking aquatic products and that smoking and pickling raw seafood may not destroy encysted parasites—but changing human behavior with regard to traditional culinary practices and preferences is very difficult. Food inspection and regulation of exported foods may influence the techniques used in commercial aquaculture ventures but have little impact on the rural farmer raising fish for his own consumption and that of the local community.

EVIDENCE

Trung Dung D, Van De N, Waikagul J, et al: Fishborne zoonotic intestinal trematodes, Vietnam, *Emerg Infect Dis* 13:1828-1833, 2007. Available at: www.cdc.gov/eid. *A study that documents an extremely high infection rate with intestinal trematodes as well as other parasites among 615 persons living in rural Vietnamese farming communities where the traditional cuisine includes raw fish*.

Yossepowitch O, Gotesman T, Assous M, et al: Opisthorchiasis from imported raw fish, *Emerg Infect Dis* 10:2122-2126, 2004. Available at: www.cdc.gov/eid. *Interesting account of a familial outbreak of liver fluke infection in Israel transmitted by illegally imported smoked carp from Siberia*.

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): *Domestic intestinal parasite guidelines.* Available at: www.cdc.gov/immigrantrefugeehealth/guidelines/domestic/intestinal-parasites-domestic.html. (Accessed 02/28/2011). *The CDC guidelines for evaluating refugee populations after arrival in the United States for intestinal and tissue-invasive parasite infections. Addresses special considerations for young children, pregnant women, and immunocompromised hosts*.

Centers for Disease Control and Prevention (CDC): *Refugee health guidelines: intestinal parasites overseas guidelines. Recommendations for overseas presumptive treatment of intestinal parasites for refugees destined for the United States.* Available at: www.cdc.gov/immigrantrefugeehealth/pdf/intestinal-parasites-overseas.pdf. Accessed August 2010. *The CDC guidelines suggest an approach based on geographic exposures to screening for and treating infections with intestinal parasites among immigrants and refugees before arrival in the U.S*.

Keiser J, Utzinger J: Emerging foodborne trematodiasis, *Emerg Infect Dis* 11:1507-1514, 2005. Available at: www.cdc.gov/eid. *Review of trematode infections related to the expansion of aquaculture for production of freshwater fish and crustaceans, especially in trematode-endemic areas in the Far East. Improved transportation and distribution systems to bring these aquatic foods to local and international markets and global migration suggest that trematodiasis will be more frequently seen among populations in nonendemic areas*.

Echinococcosis: Cystic and Alveolar Disease

Christina M. Coyle

82

ABSTRACT

Within the genus *Echinococcus*, there are four species recognized: *Echinococcus granulosus*, *Echinococcus multilocularis*, *Echinococcus vogeli*, and *Echinococcus oligarthrus*. The larval cestodes of all four species can develop in the human host and can cause various forms of hydatid disease. A fifth species, *Echinococcus shiquicus*, a tapeworm of Tibetan foxes, has recently been described, but there have been no infections reported in humans. Recent mitochondrial DNA studies have identified *Echinococcus felidis* as a distinct species. The adult worm resides in the African lion and the larval form is believed to occur in wild ungulates. To date, no cases have been reported in humans. This chapter focuses on disease caused by cystic echinococcus (CE) caused by *E. granulosus* and alveolar echinococcus (AE) caused by *E. multilocularis*.

E. granulosus is made up of a number of biologically and genetically distinct entities that have been referred to as *strains* or *subspecies*. Classic CE is caused by the adult worm, *E. granulosus*, that resides in the jejunum of dogs and other canines (definitive hosts) and produces eggs that are passed in the stool. Eggs ingested by cows, sheep, moose, caribou, or humans (intermediate hosts) liberate an embryo in the duodenum, which passes through the intestinal mucosa to enter the portal circulation. Over 85% are filtered by the liver and lungs, where they lodge and develop into hydatid cysts.

AE disease results from infection by *E. multilocularis*. Transmission to humans is usually through accidental ingestion of parasite eggs shed by dogs that had previously eaten an infected rodent. In humans, the metacestode (larval) form develops in the liver, proliferating indefinitely by exogenous budding, and invades the surrounding tissue, mimicking a malignancy.

INFECTION WITH *ECHINOCOCCUS GRANULOSUS* (CYSTIC ECHINOCOCCUS, OR HYDATID CYST)

Life Cycle

E. granulosus is a small tapeworm of canids (measuring approximately 2 to 7 mm), which are the definitive hosts. The adult tapeworm lives in the gut of the definitive host, attached by the scolex to the mucosa of the small bowel. The mature worm has an average of three proglottids: immature, mature, and gravid (Figure 82-1). The terminal gravid proglottid contains eggs that are released into the feces. The eggs contain the true larval or hexacanth stage, which is accidently ingested by the intermediate host. Cows, sheep, moose, caribou, or humans can act as the intermediate host. Once an egg is ingested by a suitable intermediate host, the oncosphere is released from its protective coat and penetrates the intestinal wall using its larval hooks. The majority of oncospheres are deposited in the liver after migration through the portal circulation, and those that escape the hepatic filter will enter the pulmonary circulation, where they may be trapped. A small number escape the pulmonary sieve and are distributed systemically. Once deposited in an organ, the oncosphere begins to develop into a metacestode or a hydatid cyst. The cycle is completed when the cyst is ingested by a canine carnivore. The cyst contains protoscolices that are released into the gut of the canid, where they form new adult worms (Figure 82-1).

Epidemiology

The distribution of *E. granulosus* is worldwide, with only a few areas such as Iceland, Ireland, and Greenland free of autochthonous human CE. The greatest prevalence of CE occurs in countries of the temperate zones, including South America, the entire Mediterranean littoral, the southern and central areas of the former Soviet Union, Central Asia, Australia, and areas of Africa. Most cases in the United States and Central and Western Europe are imported. In many parts of the world, CE is considered an emerging disease. For example, CE has been on a dramatic increase in the former Soviet Union and Eastern Europe in recent years (see Figure 45-4).

Consistently, the highest prevalence is found among populations involved with sheep raising. People of both sexes and all ages appear susceptible. Socioeconomic and cultural characteristics are among the best-defined risk factors for human infection: dogs living closely with people, uncontrolled slaughter of livestock, and unsanitary living conditions. There may be as many as 40,000 tapeworms in a heavily infected dog, and each tapeworm sheds approximately 1000 eggs every 2 weeks. Dogs infected with *Echinococcus* pass eggs in their stools, which adhere to hairs around the anus and around the muzzle. Eggs are accidently ingested through intimate contact, usually with children. In addition, soil and vegetables can become contaminated, providing another route of infection. When dogs at risk of infection are maintained close to the family home, all members of the family may be exposed.

Clinical Manifestations

CE may occur in persons younger than 1 year to over 75 years of age. In areas of endemic infection, most hospital cases are recorded among those 21 to 40 years of age, but severe morbidity may also occur in younger individuals.

The incubation of human hydatid disease is highly variable and often prolonged for several years. Many individuals will remain asymptomatic, and hydatid cysts are frequently observed

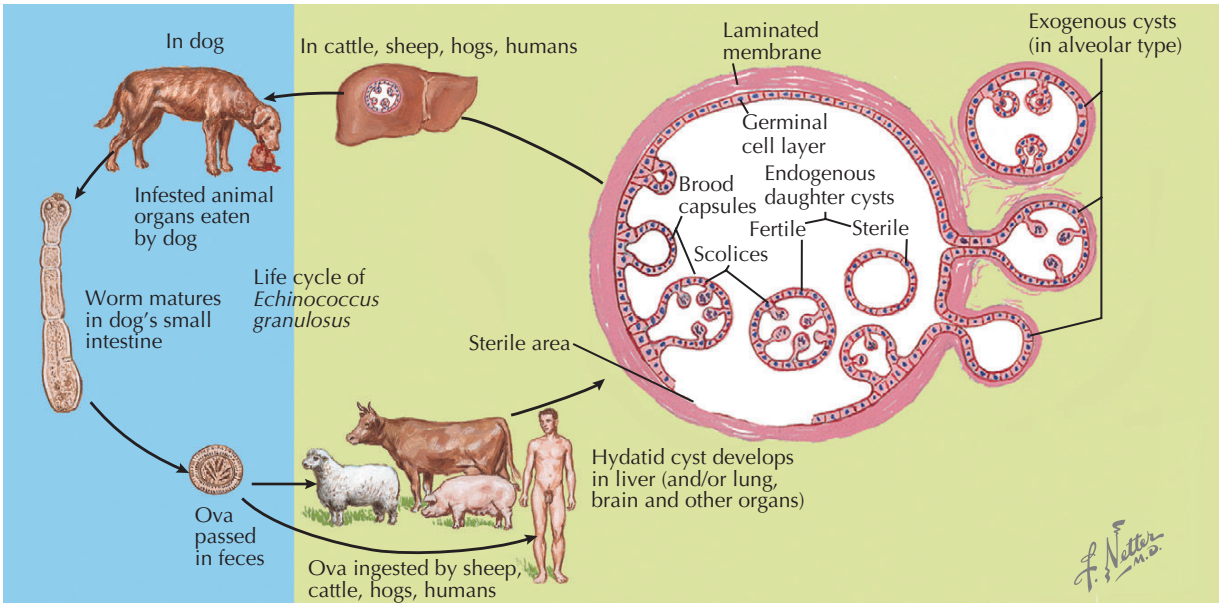


Figure 82-1 Life cycle of *E. granulosus*, with detail showing development of endogenous daughter cysts from a primary cyst in the liver. Although the life cycle of *E. multilocularis* is not shown, the formation of exogenous cysts by evagination of the primary cyst wall is illustrated to show the difference in cyst formation (the hydatid daughter cysts lack the pericyst layer, whereas the alveolar cysts retain this membrane layer).

as incidental findings at autopsy or detected by abdominal ultrasound screening, at rates much higher than the reported local morbidity rates. The liver is the most common site of cyst localization (65%), followed by the lungs (25%). Hydatid cysts are less frequently seen in the spleen, kidneys, heart, bone, and central nervous system. The clinical manifestations of CE are diverse and determined by the site of the cyst, its size, and its stage. Hence intracerebral, cardiac, bone, and ocular cysts may be very small (less than 2 cm) when clinical effects manifest. In contrast, lung and liver cysts may grow asymptomatically to very large sizes (larger than 40 cm) for many years before clinical signs develop. Most asymptomatic liver hydatid cases (75%) remain symptom-free for more than 10 years, regardless of cyst size or type. Single cysts are most common; however, 20% to 40% of patients have multiple cysts or multiple organ involvement. Therefore all patients with hepatic cysts need a full radiographic evaluation of the pelvis and lung for extrahepatic cysts. In secondary echinococcosis, new cysts develop from released protoscolices after spontaneous or trauma-induced cyst rupture or during surgical treatment.

HEPATIC DISEASE

Owing to the distensible nature of the liver, hepatic cysts may grow for years before becoming symptomatic. Solitary cysts are most common and the right lobe is affected more often than the left lobe. The size of the cyst is variable, ranging from 1 to 15 cm. Hepatic cysts can cause pain in the upper abdominal region secondary to pressure from an enlarging cyst. Within the liver, the maturing cyst form of *E. granulosus* consists of an internal germinal layer surrounded by an acellular, parasite-derived laminated layer; together they form the endocyst. The endocyst is surrounded by the pericyst, or adventitial layer, and is largely derived from host tissue. By 3 weeks of development, the cyst is approximately 250 μm in size and by 20 weeks, approximately 1 cm in size. The central cavity of *E. granulosus* cysts is filled with hydatid fluid, which is similar in composition to the interstitial fluid. Intracystic pressure increases as the cyst grows and reaches maturity.

As the cyst grows, cells bud from the germinal layer. They develop stalks, becoming "brood" capsules in the central cystic cavity. From the wall of the brood capsule, a protoscolex develops. The protoscolex is able to develop into a daughter or secondary cyst if accidently spilled or into a mature worm in the definitive host if ingested. As the primary cyst matures the brood capsule detaches from the germinal layer and ultimately will degenerate, releasing protoscolices into the hydatid cyst fluid, forming the so-called "hydatid sand" characteristically found in older cysts. Daughter cysts, a pathognomonic feature of *Echinococcus*, resemble the primary cyst with the exception that the pericyst is not present (see Figure 82-1 and also see Figure 45-1).

Communication with and rupture of hepatic cysts into the biliary tree are well described and can result in cholangitis and cholestasis. With frank intrabiliary rupture, the daughter vesicle and germinative membrane pass into the main biliary ducts, resulting in obstructive jaundice. In these instances, patients experience epigastric pain and right upper quadrant pain. The pain can be intermittent, mimicking gallstone disease, if smaller membranes are passed. These cysts are considered complicated, and patients should be treated surgically; if cysts are left untreated, cholangitis can occur, with resultant bacterial superinfection of the cyst cavity and abscess formation. The cyst contents are under high pressure, and communication with the biliary tree occurs in 3.2% to 17% of cases without evidence of frank rupture. This is termed *occult intrabiliary rupture;* the

symptomatology is less severe, and presenting symptoms usually include vague abdominal pain. Making the diagnosis of a cystobiliary communication preoperatively is important because sclerosing agents should be avoided owing to the risk of sclerosing the biliary tree. Less commonly, portal hypertension can complicate hepatic CE by extrinsic compression of the liver or by obstruction of the inferior vena cava and hepatic outflow tract. Rarely, parasitic emboli may result from rupture of a cyst into the hepatic vein or inferior cava. Rupture or leakage can result in acute or intermittent allergic manifestations and secondary CE.

Thoracic complications of hepatic hydatid cysts are seen in approximately 2% to 11% of cases. The diagnosis is based on clinical findings, chest radiography, ultrasonography, or computed tomography (CT) scans. Although bile-stained sputum and particularly hydatidoptysis (expectoration with daughter cysts, sometimes bile stained) are pathognomonic, these symptoms are infrequently reported. Cysts may rupture into the peritoneal cavity, usually secondary to trauma, with resultant anaphylaxis or secondary CE. Mild to severe anaphylactoid reactions (and occasionally death) may follow the sudden massive release of cyst fluid.

Cysts are dynamic and change over time, going through stages that have both clinical and therapeutic implications. Two commonly used imaging-based classification systems correlate individual hepatic cyst stage with natural progression of hepatic cysts and predict biologic activity of the cyst. They are the World Health Organization (WHO) Informal Working Group on Echinococcosis (IWGE) and the Gharbi classification systems; both are very similar, and this chapter will refer to the WHO classification system. WHO breaks down the stages into active versus inactive and transitional. This is very helpful when choosing therapeutic options. Table 82-1 summarizes the stratified approach to treatment based on cyst stages. CE1 is a unilocular anechoic cystic lesion with a double sign. CE2 is a multiseptated, "rosette-like" "honeycomb" cyst. Both CE1 and CE2 are considered active, usually fertile cysts containing viable protoscolices. CE3a is a cyst with detached membranes ("water lily" sign), whereas CE3b has daughter cysts in a solid matrix. These are considered cysts in the transitional stage, where the integrity of the cyst has been compromised either by the host or by chemotherapy. A cyst with heterogeneous hypoechoic or hyperechoic contents and no daughter cysts is the CE4 stage, and calcified cysts are considered CE5. CE types 4 and 5, which are inactive, have normally lost their fertility and are degenerative. The WHO IWGE classification stages CE1 through CE 5 correspond to type I through type V in the Gharbi system. When considering what is the best modality of treatment for a patient with hepatic CE, the physician must take into consideration the staging of the cyst.

PULMONARY DISEASE

Pulmonary hydatid disease has been reported in up to 30% of cases of hydatidosis in some series and can be either primary or secondary. The most common presenting symptoms include hemoptysis (25% to 69%), cough (25% to 60%), and dyspnea (2% to 56%). Fever is uncommon and present in less than 35% of cases at presentation. The hydatid cyst can occur anywhere in the lung, but it settles more often on the right side and has a predilection for the lower lobes. It generally is a single cyst, and in up to 25% of cases there is a coexisting hepatic cyst. Pulmonary cysts may be multiple and/or bilateral in approximately 30% of cases. Typically, cysts grow at an average rate of 1 cm in diameter per year. However, growth rates of up to 5 cm per year have been noted. Because the period of initial cyst growth is frequently asymptomatic, pulmonary hydatid disease most frequently manifests in the second to third decade of life. Cysts may be entirely asymptomatic in 75% of cases at initial detection, and asymptomatic pulmonary cysts are more likely to be found in areas of the world where chest radiographs are taken for mass tuberculosis screening programs.

Pulmonary hydatid cysts have a two-layer wall; the outer layer (exocyst), white and fragile, is made up of concentric sheets of hyaline, and the inner layer is the germinal layer, or the endocyst. Unlike with hepatic cysts, daughter cysts are rarely seen. The content is liquid, with some solid elements that constitute the so-called "hydatid sand," made up of hooklets and scolices. In "closed" cysts the fluid resembles water. It contains antigenic elements that are responsible for the anaphylactic phenomenon that may appear when the cyst ruptures.

As with hepatic lesions, the adventitia (pericyst) is the result of the inflammatory response of the organ in which the parasite settles. It consists of three layers: an inner layer, which is smooth and glossy; a middle layer, which is of a fibrous nature; and an outer layer, with active inflammation. Atelectasis is seen around the adventitia, but more extensive alterations such as bronchiectasis and interstitial sclerosis can be seen.

When pulmonary cysts rupture into neighboring bronchi with formation of cystobronchial fistulas, a typical "salty water and grape skin" expectoration may occur. Cysts may also become infected in this setting. A large pulmonary cyst can cause stenosis and occlusion of the bronchi. Pleural effusion may develop in 30% of the cases and may occur secondary to cyst rupture into the pleural space. Rupture can lead to severe complications, such as massive hemoptysis and tension pneumothorax.

In contrast to perforation into a bronchus, rupture of a hydatid cyst into the pleural cavity usually causes pneumothorax, pleural effusion, or empyema. Cyst rupture into the pleural cavity can also result in tension pneumothorax. Rupture of a cyst into the pleural cavity or rupture into the bronchial tree may also lead to secondary larval spread or to allergic and anaphylactic reaction. Although extrapulmonary hydatid cyst rupture may cause fatal anaphylaxis, the incidence of this phenomenon is low in association with pulmonary cysts.

The typical radiographic appearance of pulmonary hydatid disease is that of one or more homogeneous round or oval masses with smooth borders surrounded by normal lung tissue (Figure 82-2). Large cysts can shift the mediastinum, induce a pleural reaction, or cause atelectasis of the surrounding parenchyma. Pulmonary cysts rarely calcify, and the contents of the cyst are usually homogeneous, with a density close to that of water. The introduction of air between the pericyst and exocyst produces the appearance on imaging of a thin layer around the exocyst, which is referred to as the *crescent*, or *meniscus sign*. If the ruptured cyst communicates with the tracheobronchial tree, evacuation of the contents of the cyst results in an air-fluid level. The endocyst may appear to float in the remaining fluid,

Table 82-1 Treatment Modalities for Uncomplicated Cystic Echinococcosis Stratified by Cyst Stage

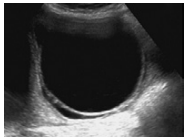
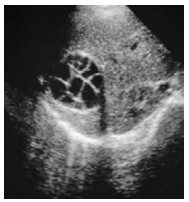
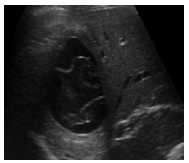
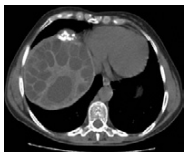
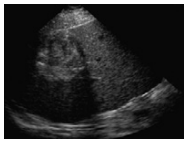
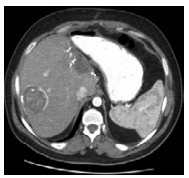
WORLD HEALTH ORGANIZATION CLASSIFICATION, 2001	RADIOGRAPHIC IMAGE		*Current Practice*			
			SURGERY	PERCUTANEOUS TECHNIQUES	MEDICAL TREATMENT	SUGGESTED*
CE1		Hepatic unilocular anechoic cystic lesion with a double sign (ultrasound)	Practiced	Practiced	Practiced	PAIR + ABZ if >5 cm ABZ alone if <5 cm
CE2		Multiseptated, "rosette-like" or "honeycomb" cyst in the liver (ultrasound)	Practiced	Rarely practiced	Practiced	Non-PAIR PT + ABZ Surgery + ABZ
CE3a		Hepatic cyst with detached membranes ("water lily" sign) (ultrasound)	Practiced	Practiced	Practiced	PAIR + ABZ if >5 cm ABZ alone if <5 cm
CE3b		Hepatic cyst showing daughter cysts in solid matrix (CT scan)	Practiced	Rarely practiced	Practiced	Non-PAIR PT + ABZ Surgery + ABZ
CE4		Hepatic cyst showing heterogeneous hypoechoic or hyperechoic contents and no daughter cysts (ultrasound)	Regard as inactive; unless complicated, they should not be treated Watch and wait			
CE5		Calcified hepatic cyst (CT scan)				

Image for CE1 courtesy Prof. P. Kern, Division of Infection Diseases and Clinical Immunology, Comprehensive Infectious Diseases Center, University Hospitals, Ulm, Germany; images for CE2 and CE3b courtesy Prof. C. Coyle, Department of Medicine, Division of Infectious Diseases, Albert Einstein College of Medicine, New York; image for CE3a courtesy Prof. E. Brunetti, Division of Infectious and Tropical Diseases, University of Pavia, IRCCS S. Matteo Hospital Foundation, Pavia, Italy; images for CE4 and CE5 courtesy Prof. B. Gottstein, Institute of Parasitology, University of Bern, Bern, Switzerland.

*See text for discussion.

ABZ, Albendazole; *CE,* cystic echinococcus; *CT,* computed tomography; *PAIR,* percutaneous aspiration-injection-reaspiration; *PT,* percutaneous treatment.

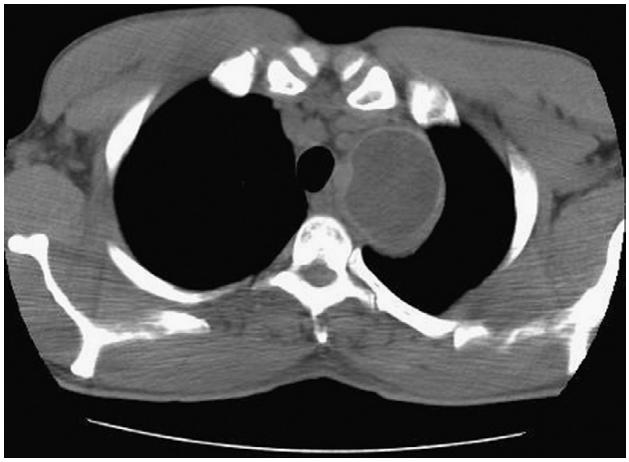


Figure 82-2 Computed tomographic appearance of pulmonary cystic echinococcosis. *(Courtesy Prof. C. Coyle, Department of Medicine, Division of Infectious Diseases, Albert Einstein College of Medicine, New York.)*

producing a characteristic radiographic feature known as the *water-lily sign.*

BONE DISEASE

Hydatid disease of the bone is rare and accounts for only 0.5% to 4% of echinococcus disease in humans. The spine is the most common site, accounting for 50% of cases, followed by the pelvis and hip. Other osseous sites for infection include the femur, tibia, fibula, ribs, scapula, clavicle, and tarsal bones. Patients experience pain, swelling, and occasionally pathologic fracture when the condition occurs in the long bones or neural compromise when it occurs in the spine.

In cases involving the spine, radiographs show pedicle erosion and loss of vertebral body height. Plain radiograph findings include multilocular osteolysis and reactive sclerosis of a honeycomb nature. CT scan demonstrates erosions of the body, pedicle, and lamina of the cancellous bone without a subperiosteal reaction. Magnetic resonance imaging (MRI) is superior to CT scanning in evaluating the extent of disease preoperatively and can also be helpful for evaluating recurrence. Successful treatment of vertebral hydatidosis represents a challenge because of its invasive features. Surgery is the treatment of choice, but adjuvant anthelmintic chemotherapy is essential to control the disease locally, avoid systemic spread, and prevent recurrences. Wide surgical excision is particularly difficult to achieve in the spine and the pelvis, but medical therapy alone is not appropriate.

HYDATID DISEASE OF THE BRAIN

Hydatid cysts of the brain are uncommon, accounting for 2% to 3.6% of all intracranial space-occupying lesions in endemic areas. Children are much more frequently affected than adults; 50% to 93% of intracranial cysts are found in children younger than 17 years of age. Associated extracranial cysts are common, making a thorough radiologic evaluation of the patient, with chest radiographs and abdominal ultrasound or CT scan, mandatory. Furthermore, cardiac ultrasound is indicated, especially in children, when the occurrence of primary cerebral hydatid cysts may imply a communication between the right and left sides of the heart.

Cerebral hydatidosis manifests differently in children and adults. Signs of increased intracranial pressure with papilledema dominate in the younger age group, whereas focal findings such as hemiparesis, speech disorders, and hemianopsia, sometimes associated with epileptic seizures, are more prevalent in the older age group.

Cerebral hydatid cysts are usually unilocular on neuroimaging. They are most often supratentorially localized in the distribution of the terminal branches of the middle cerebral artery, usually temporo-parieto-occipitally. The definitive treatment is surgical removal.

Diagnosis

The diagnosis of CE in individual patients is based on identification of cyst structures by imaging techniques, predominantly ultrasound and CT, and confirmation by detection of specific serum antibodies on immunodiagnostic tests. For clinical practice it should be noted that confirmation via enzyme-linked immunosorbent assay (ELISA) using crude hydatid cyst fluid ranges from 85% to 98% for liver cysts, 50% to 60% for lung cysts, and 90% to 100% for multiple organ cysts. Specificity is limited by cross-reactions because of other cestode infections, some helminths, malignancy, cirrhosis, and presence of anti-P1 antibodies. Confirmatory tests must be used (arc-5 test; Antigen B [AgB] 8kDa/12kDa subunits or EgAgB8/1 immunoblotting) in cases that are doubtful. Cysts in the brain, bone, or eye and calcified cysts often induce no or low antibody responses. In routine laboratory practice, at least two different tests are used to improve accuracy.

Treatment

Three therapeutic modalities exist to treat hepatic CE: chemotherapy, surgery, and percutaneous drainage. For many years, surgery was the only treatment available for CE. Percutaneous drainage (consisting of percutaneous aspiration-injection-reaspiration [PAIR]) of hepatic hydatid cysts is now accepted as an alternative to surgery in the appropriate group of patients. Medical therapy is usually used in conjunction with surgery and PAIR but can be used alone if the patient is not a candidate for either surgery or PAIR.

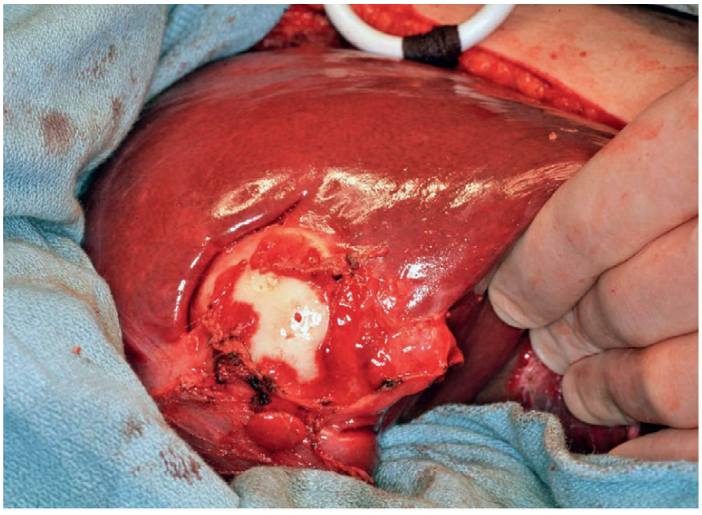
SURGERY

Surgery has been the mainstay of therapy. In uncomplicated CE1 and CE3a liver cysts, surgery is increasingly being replaced by alternative therapies. In patients with complicated cysts (rupture, cystobiliary or most cases of cystobronchial fistulas, compression of vital organs and vessels, hemorrhage, secondary bacterial infection), surgery remains the treatment of choice (see Chapter 45).

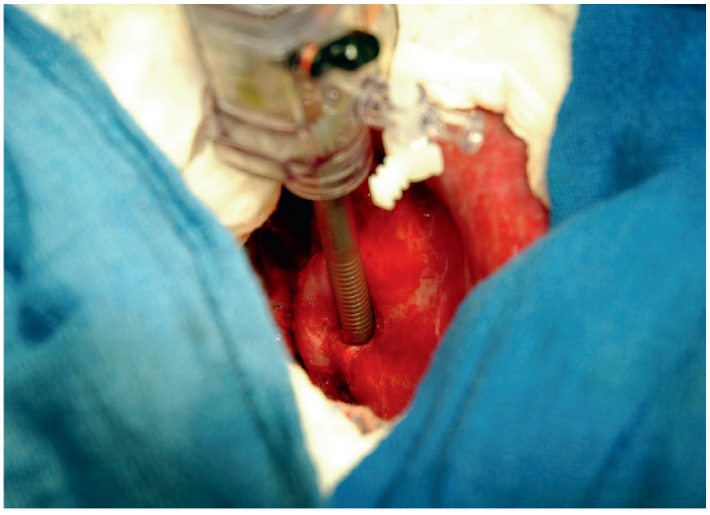
Surgical procedures can be divided into conservative and radical. Conservative procedures aim at sterilization and

evacuation of cyst content, including the hydatid membrane (hydatidectomy), and partial removal of the cyst. The cyst is punctured and partially aspirated and then a scolicidal agent is injected, followed by total aspiration (Figure 82-3). The risks are anaphylactic shock and chemical cholangitis or alveolar or bronchial damage if the cyst communicates with the biliary or bronchial tree, respectively. Other risks include spillage and secondary CE, with relapse rates of up to 20% being reported after surgery for liver cysts and up to 11.3% for lung cysts. After partial removal of the cyst, a residual cavity remains, which is at risk of secondary bacterial infection and abscess formation. The goal of a radical procedure is to remove the cyst completely. This can be achieved with or without hepatic or lung resection. There is greater intraoperative risk with a radical procedure, but fewer postoperative complications and relapses. Conservative procedures are preferred in pulmonary hydatid disease.

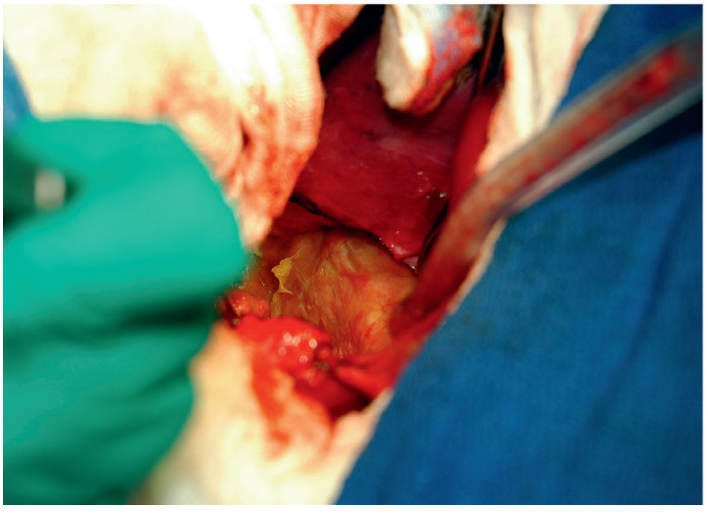
Efforts to avoid spillage are imperative, and during surgery the surgical fields should be protected with pads soaked with scolicidal agents. At present, 20% hypertonic saline is recommended, and when injected into the cyst it should be in contact with the germinal layer for at least 15 minutes for optimal efficacy. To avoid the risk of chemically induced sclerosing cholangitis, the possibility of a cystobiliary fistula should be ruled out before introduction of hypertonic saline into a hepatic cyst. This can be done before surgery with endoscopic retrograde cholangiopancreatography (ERCP) or intraoperatively, by checking for bile staining in the fluid aspirated from the cyst. If necessary, an anterograde cholangiography can be performed. Similarly, the surgeon should avoid injecting a scolicidal agent into the bronchial tree if there is a cystobronchial fistula. Albendazole should be started at least 1 day to a week before surgery and then continued up to 1 to 3 months after surgery to prevent



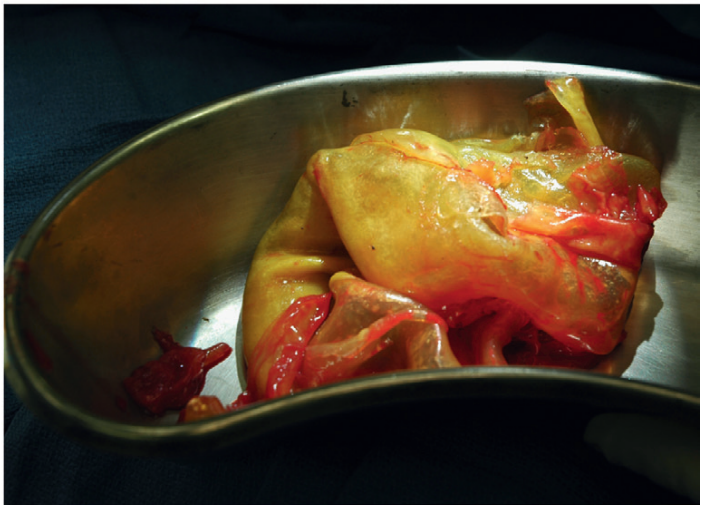
Exposure of large hepatic cyst wall



Aspiration of cyst contents



Residual hepatic cavity with deflated cyst



Excised cyst capsule

Figure 82-3 Surgical management of hepatic cystic echinococcosis. *(Courtesy Prof. C. Coyle, Department of Medicine, Division of Infectious Diseases, Albert Einstein College of Medicine, New York.)*

secondary CE and relapse. The length of adjunctive albendazole therapy has never been formally evaluated.

Surgery should be carefully evaluated and is the first choice for complicated cysts. In the liver, it is indicated for removal of large CE2 to CE3b cysts with multiple daughter cysts, cysts communicating with the biliary tree, and cysts exerting pressure on vital organs.

PAIR

Percutaneous treatment of abdominal CE was introduced in the mid-1980s and currently is accepted as an alternative to surgery in the appropriate patient. The original descriptions involved puncture of the cyst, aspiration of the cyst fluid, injection of a scolicidal agent for at least 15 minutes, and reaspiration of the cyst content (PAIR). In the literature, PAIR is as effective as open surgical drainage with fewer complications and lower cost. Long-term follow-up to assess the long-term relapse rate is lacking.

Khuroo et al (1997) reported that, in comparison with patients who underwent surgical intervention (cystectomy), patients treated by PAIR followed by 8 weeks of albendazole chemotherapy had comparable rates of cyst disappearance (88% to 72%) but had a reduced hospital stay (4 versus 13 days) and reduced risk of complications (32% versus 84%). A recent paper from Turkey, reporting a single-center experience with surgery, laparoscopic surgery, and percutaneous treatments over a 10-year period in 355 patients, concluded that PAIR is a safe and effective option for treatment of hydatid disease.

Smego and Sebanego (2005) conducted a meta-analysis of 21 studies with 769 patients having 1072 hepatic cysts undergoing PAIR, and compared the findings with 952 era-matched surgically treated historical controls. They claimed that the rate of clinical and parasitologic response was greater in patients receiving PAIR plus chemotherapy than in those receiving surgery. Disease recurrence, major complications (anaphylaxis, biliary fistulas, cyst infections, liver and intraabdominal abscesses, and sepsis), minor complications, and death occurred more frequently among patients treated with surgery than among patients treated with PAIR. The mean durations of hospital stay was 2.4 days for patients treated with PAIR and 15 days for the surgical control group. PAIR is indicated for patients with single or multiple cysts in the liver, abdominal cavity, spleen, and kidney. For hepatic cysts, with which there is the greatest experience, staging of the cyst is critical for choosing the appropriate treatment. The optimal stage for PAIR is CE1 or CE3a (a cyst with detached membrane or water lily sign). Recent data suggest that PAIR of multivesiculated cysts does not allow complete healing (solidification, i.e., progression to stage CE4 or CE5) and in 30% of cases resulted in an intracystic recurrence that required up to four repeat procedures. For this reason, CE2 and CE3b cysts are now preferably treated with cutting devices and large-bore catheters in centers that have a large percutaneous treatment experience.

PAIR is contraindicated for inaccessible or superficially located liver cysts, CE2 cysts and CE3b cysts, inactive or calcified cystic lesions, complicated cysts, and cysts with biliary communication. In addition, PAIR is also contraindicated in lung cysts. To avoid sclerosing cholangitis, this procedure must not be performed in patients whose cysts have biliary communication. Therefore cyst fluid should be tested for the presence of bile after it is aspirated and before instillation of a scolicidal agent. Protoscolicides used in PAIR are mainly 20% NaCl and 95% ethanol. If the patient has symptoms suggestive of communication, ERCP should be performed before PAIR. Complications have included secondary infection of the cavity, acute allergic reactions, and recurrence; however, these have been managed successfully.

Allergic reactions are possible, and the radiologist should be prepared to treat an allergic reaction in the event that this should occur. Prophylaxis with albendazole 4 hours before and 1 month after the PAIR procedure is mandatory.

PAIR is indicated for inoperable patients and those who refuse surgery, in cases of relapse after surgery, or if benzimidazole treatment alone fails to elicit a response. Best results with PAIR + benzimidazoles are achieved in CE1 and CE3a cysts that are larger than 5 cm.

CHEMOTHERAPY

Treatment of hepatic cystic echinococcosis with mebendazole or albendazole alone is not as effective as a combined chemotherapy-drainage approach. Mebendazole (MBZ) was the first benzimidazole carbamate agent found to have in vivo activity in hydatid disease. The drug interferes with mechanisms of glucose absorption through the wall of the parasite, leading to glycogen depletion and subsequent degenerative changes in the mitochondria and endoplasmic reticulum of the germinal cells. Both albendazole, 10 to 15 mg/kg body weight per day, and mebendazole, 40 to 50 mg/kg body weight per day, for 3 to 6 months have demonstrated efficacy. Albendazole (ABZ) is more active in vitro than mebendazole and has improved gastrointestinal absorption and bioavailability as well as reportedly better clinical results.

Benzimidazoles (BMZ) are indicated for inoperable patients with liver or lung CE, patients with multiple cysts in two or more organs, and patients with peritoneal cysts. Smaller cysts (<5 cm) with little adventitial reaction seem to respond best to medical therapy. Cysts with multiple daughter cysts (CE2) are more likely to recur with medical treatment, and older cysts with a thick or calcified surrounding adventitial reaction are likely to be refractory to treatment. With treatments for less than 3 months (i.e., one or two cycles), fewer patients respond, and a slightly smaller proportion are cured. Franchi and colleagues treated 448 patients with 3- to 6-month cycles of either albendazole or mebendazole. Among 882 evaluable cysts, 74% showed degenerative changes on imaging; the efficacy of albendazole (82%) was superior to that of mebendazole (56%). However, 25% of subjects showed evidence of relapse, most commonly within the first 2 years after ending therapy, and occurring more frequently in CE2 cysts of the liver. Of note, further chemotherapy cycles induced degenerative changes in more than 90% of relapsed cysts.

The optimal treatment duration has not been established. Clearly duration of treatment of less than 3 months produces a less than optimal response, whereas results of extension beyond 6 months need to be evaluated. It has been suggested that further improvement might be gained by using strategies to

increase absorption of ABZ, such as ingestion with fatty food, which is currently recommended. Adverse effects of BMZ include hepatotoxicity, severe leukopenia, thrombocytopenia, and alopecia.

The role of praziquantel in hydatid disease has not been defined, although there is some evidence to support a role for the use of praziquantel (40 mg/kg) once a week in combination with albendazole as chemotherapy before and after surgery or percutaneous procedures. Combined therapy is more protoscolicidal in this setting and may reduce the risk of disease recurrence and intraperitoneal seeding of infection that could develop via cyst rupture and spillage, but studies are small and nonrandomized. Currently there are no data to support the addition of praziquantel in disseminated disease or in cases that are treated medically, and further studies are needed to evaluate this recommendation.

Mebendazole and albendazole have been used in pulmonary hydatid disease. Cure rates are only 25% to 30%. Most experience with medical treatment of pulmonary hydatidosis is in children. In a 16-year retrospective of 36 children with pulmonary disease treated medically, complications were more likely in cysts with a mean diameter of 6 cm at the beginning of medical therapy. There are some suggestions that anthelmintics weaken the cyst wall and increase the risk of cyst rupture in pulmonary disease. Wen and Yank found a 77.3% incidence of cyst rupture in 21 patients with hydatid disease who were treated with albendazole.

WATCH AND WAIT

A recent review by Junghanss and others (2008) introduces the idea of leaving certain cyst types untreated and monitoring them over time. CE4 and CE5 cysts are consolidating and calcifying or have become calcified (completely inactive). Cysts that have reached this stage and behave quietly (i.e., do not compromise organ functions or cause discomfort) seem to remain like this or stabilize even further. These cysts can be probably be watched. This concept underscores the importance of staging cysts with ultrasound examination when patients are being evaluated for treatment regimens. If one chooses to watch and wait, the patient should be monitored with long-term ultrasonographic follow-up care. A period of 10 years seems to be an adequate time frame.

CE is difficult to treat and cure, but a full knowledge of staging and complications can help the clinician choose the best treatment options for his or her patient.

Prevention

The main risks for transmission of CE to humans are present in locales where sheep raising is predominant, and *E. granulosus* is established in a dog-sheep-dog cycle, with dogs serving as the definitive host and the sheep serving as the intermediate host. The sheep are infected from eating grass and vegetation contaminated with feces (containing eggs) from infected wild canids or infected domestic dogs. During sheep slaughtering, dogs eat infected viscera of sheep and new infections may occur. Prevention of human disease is highly dependent on increased awareness among the shepherds and their family members, meat processers, and veterinarians and their willingness to change behaviors. Avoiding close personal contact with dogs and washing hands thoroughly after working with or handling animals is basic but difficult to do in the high-risk areas. Humans also should avoid ingestion of water and raw vegetables that may be fecally contaminated. Blocking access of dogs to slaughterhouses and periodically treating dogs with anthelmintic drugs will help to lower the prevalence of infection in the canine environment.

INFECTION WITH *ECHINOCOCCUS MULTILOCULARIS* (ALVEOLAR ECHINOCOCCUS)

Life Cycle

E. multilocularis is a microscopic tapeworm of foxes (mainly Arctic and red foxes) characterized by its small size (length of up to 4.5 mm) that causes rare but serious infections of humans when the eggs are accidentally ingested. Transmission of *E. multilocularis* occurs in a sylvatic (natural) cycle when foxes or other wild canids—such as coyotes, raccoons, dogs, and wolves—or wild cats, which can serve as definitive hosts, eat infected rodents and other small mammals that serve as intermediate hosts, harboring the metacestode (larval) stage in the liver.

After an infected rodent is eaten, the larvae mature into adults in the gastrointestinal tract of the definitive host, and eggs are passed in the feces. Environmental contamination of soil, grass, berries, and other ground vegetation thus results. The ova are ingested then by foraging rodents, which serve as intermediate hosts, and the natural life cycle is completed when the rodents are eaten by their predators. Humans serve as accidental intermediate hosts and inadvertently become infected by hand-to-mouth transmission through close association with dogs or cats that have eaten infected rodents and are passing eggs. Some of the eggs passed in the fecal stream stick to the perianal fur and contaminate human hands. Accidental ingestion of eggs may also occur when humans drink water contaminated by fox feces or eat unwashed vegetables and berries from the ground.

Once the *E. multilocularis* eggs are ingested, embryos (oncospheres) are released, penetrate through the small intestinal mucosa, and are carried in the portal blood flow to the liver where the larvae (metacestodes) begin to develop. The larval mass develops into an alveolar lesion, infiltrating the liver parenchyma, destroying the surrounding tissue, and resembling a malignancy in both its appearance and behavior. There is contiguous extension of AE from the liver to other organs, and the infection may metastasize to the brain and lung by hematogenous routes.

Epidemiology

AE has been reported in parts of central Europe, much of Russia, the Central Asian republics, western China, the northwestern portion of Canada, and western Alaska. The annual incidence in endemic areas of Europe has increased from a mean of 0.10 per 100,000 during 1993 to 2000 to a mean of 0.26 per 100,000 during 2001 to 2005. There is evidence of parasites spreading from endemic to previously nonendemic areas in North America

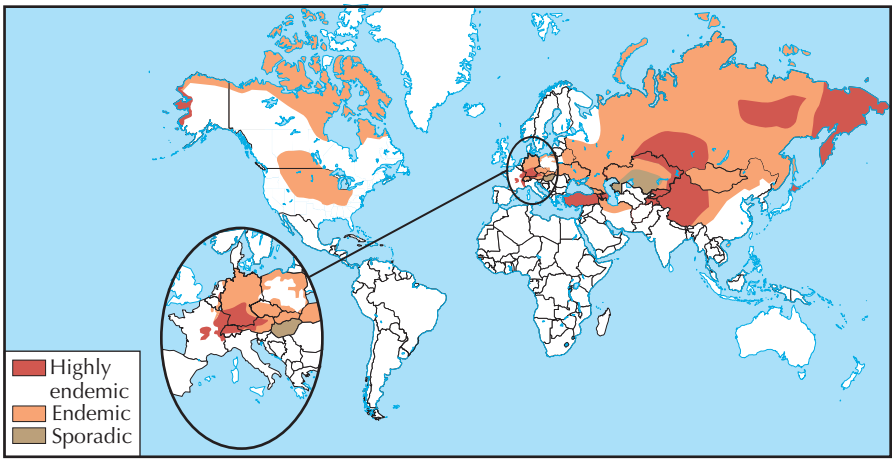


Figure 82-4 Global geographic distribution of alveolar echinococcosis. *(Data from Torgerson PR, Keller K, Magnotta M, Ragland N: The global burden of alveolar echinococcosis,* PLoS Negl Trop Dis *4:e722, 2010.)*

and North Island, Hokkaido, Japan, principally because of the movement or relocation of the fox (Figure 82-4). Hunters, trappers, and persons who work with fox fur are at risk of exposure. Hyperendemic foci have been described in some Eskimo villages of the North American tundra and in western China, where dogs feed on infected rodents.

Clinical Manifestations

In humans, the initial phase of AE infection is usually asymptomatic. Estimates of the incubation period vary from less than 5 to up to 15 years. The reported ages of patients at diagnosis ranges from 5 to 89 years, with a mean of 45 ± 15 years.

The metacestode stage of *E. multilocularis* is characterized by an alveolar structure composed of numerous small vesicles (<1 mm to 3 cm in diameter). The lesions grow slowly and can grow to diameters of 15 to 20 cm. Most patients become symptomatic in the progressive phase, when the metacestode has infiltrated large parts of the liver. Symptoms include abdominal pain, jaundice, hepatomegaly, sometimes fever and anemia, weight loss, and pleural pain.

Mature lesions consist of a central necrotic cavity filled with white amorphous material that is covered with a thin peripheral layer of dense fibrous tissue. Focal areas of calcification occur, and extensive infiltration by proliferating vesicles can be seen. Initially the metacestodes establish infections in the liver, but over time they can spread by extension to adjacent organs or hematogenously to distant sites (e.g., lungs, brain, bones).

The advanced stage is characterized by severe hepatic dysfunction, often associated with portal hypertension. The duration of the disease is variable from weeks to years. Mortality rates in untreated or inadequately treated AE patients can be high; in several published studies, the average survival rate 10 years after diagnosis was 29% (range, 0% to 23%), and the survival rate after 15 years was 0%.

Diagnosis

Ultrasonography is the method of choice for screening; it is usually complemented by CT, which detects the large number of lesions and characteristic calcifications (Figure 82-5). MRI may facilitate the diagnosis in some cases.

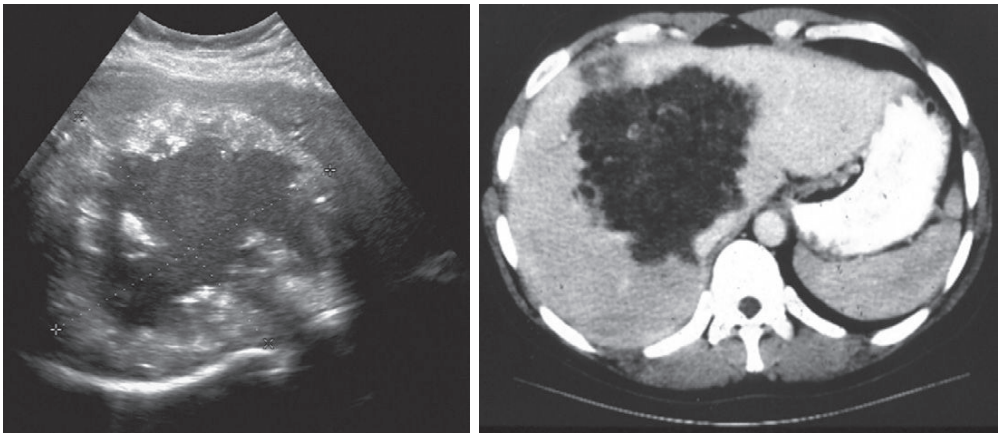
The diagnosis can be confirmed by parasite identification in surgical or biopsy material. In most cases, histologic examination is sufficient, but recognition of characteristic structures in fine-needle biopsy specimens or calcified samples may be difficult or impossible. In these cases polymerase chain reaction (PCR) is used mainly for the direct detection of parasite nucleic acid in biologic specimens. The Em2plus-ELISA is a diagnostic test that employs a mixture of affinity-purified *E. multilocularis* metacestode antigens and has been used successfully for the serologic differentiation of AE and CE. The *E. multilocularis* protoscolex-derived Em18 antigen has also been used to differentiate AE and CE. ELISA and western blot tests based on the Em18 show sensitivities and specificities in the ranges of 91% to 100% and 77% to 97%, respectively.

Treatment

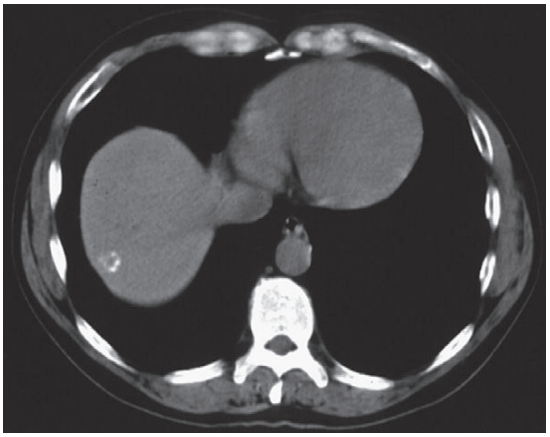
Surgery is the mainstay of treatment of AE, and radical resection of the lesion from the liver or affected organs is the goal of surgery. Radical surgery is possible in virtually all cases diagnosed at an early stage but in only 20% to 40% of the advanced cases. It may lead to complete cure, but resection is often incomplete because of diffuse and undetected parasite infiltration into host tissues. Therefore postsurgical chemotherapy should be carried out for at least 2 years with evaluation using positron emission tomography (PET) scans and MRI scans, with monitoring of the patients for a minimum of 10 years for possible recurrence.

For chemotherapy of AE in humans, mebendazole is given at daily doses of 50 mg/kg in three divided doses, or albendazole is given at daily doses of 15 mg/kg in two divided doses. Cyclic or continuous treatment is practiced. In a Swiss study, therapy for nonresectable AE with mebendazole or albendazole resulted in a significantly increased 10-year survival rate.

Liver transplantation has been used successfully in otherwise terminal cases. For patients who have incomplete resection or undergo liver transplant chemotherapy a benzimidazole is recommended for many years to life.



Conventional and active alveolar echinococcosis lesions in ultrasound (left) and CT images (right), showing typical findings in patients presenting with symptoms and requiring treatment



CT scan showing an inactive calcified alveolar echinococcosis lesion, typical of an "abortive" course of infection that is dying out spontaneously and will not require treatment

Figure 82-5 Alveolar echinococcosis lesions in the liver. *(Ultrasound courtesy Prof. Peter Kern, Division of Infectious Diseases and Clinical Immunology, Comprehensive Infectious Diseases Center, University Hospitals, Ulm, Germany; CT scans courtesy Prof. Bruno Gottstein, Institute of Parasitology, University of Bern, Bern, Switzerland.)*

Prevention

The primary intervention for preventing AE is to interrupt the hand-to-mouth transmission of *E. multilocularis* eggs from animal to man. Hunters, trappers, and people who work with fox fur should wear protective gloves when handling animals and their byproducts. People should try to prevent their domestic dogs and cats from eating rodents that might be infected and should always wash their hands after petting, grooming, or handling animals with potential exposure to contaminated feces.

Environmental efforts to control the sylvatic cycle have included baiting wild foxes with bait containing scolicidal (anthelmintic) drugs. However, given the scale of the problem and the expense of such programs, this is likely to be practical only for targeted regions, such as urban areas where control is a high priority.

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Trichinellosis

Zvi Shimoni and Paul Froom

83

ABSTRACT

Trichinellosis (trichinosis) is a parasitic infection caused by a roundworm of the *Trichinella* species. There are eight known species, and all are capable of causing human disease. The most common infections are caused by *Trichinella spiralis*, which can be found in pigs, rodents, horses, bears, and foxes. Another common species is *Trichinella nativa*, which infects humans after ingestion of infected bear or dog meat. Humans are incidental hosts. Reservoir hosts include carnivorous animals such as rats, mice, and foxes.

GEOGRAPHIC DISTRIBUTION

The disease has a worldwide geographic distribution, causing a major public health problem in many parts of the world. *T. spiralis* is found primarily in the United States, South America, Europe, and South Asia, whereas *T. nativa*, when associated with ingestion of bear meat, is found more often in Canada and Northern Asia.

Trichinellosis is common in Thailand and in developing countries, where many outbreaks are reported each year as a result of consumption of undercooked pork or wild animals. Although the disease is rare in the western world, outbreaks are reported in Europe and the United States, especially among immigrants who continue to eat undercooked meat or when there are breakdowns of veterinary services. Most infections are caused by ingestion of wild or domestic pork, but cases have been reported after ingestion of infected meat from other animals including horses, bears, walruses, rodents, dogs, lions, panthers, and crocodiles. Game animals as sources of infection have increased greatly in both developing and developed countries; in the United States, game animal–associated cases now exceed pork-associated cases.

LIFE CYCLE

The life cycle includes enteral and parenteral phases (Figure 83-1).

Enteral Phase

Humans are infected after eating encysted *Trichinella* larvae present in raw or inadequately cooked meat. The cyst walls are digested by acid-pepsin digestion in the stomach, larvae are released and pass into the small intestine. The larvae invade the small intestine epithelial wall, molt four times, and develop into adult worms. The males die after copulation, and the females produce 500 to 1500 newborn larvae that are deposited into the mucosa of the duodenal wall over a 2- to 3-week period before their expulsion in the fecal stream.

Parenteral Phase

Newborn larvae enter the bloodstream and seed various organs including myocardium, lungs, brain, pancreas, and lymph nodes, but only the larvae that invade the skeletal muscle survive. The individual muscle fibers invaded by the *Trichinella* larvae show degeneration and necrosis and heavy infiltration with lymphocytes and eosinophils. The larvae are encysted within a few weeks, and the cyst wall may calcify over time.

CLINICAL FEATURES

Many infections are thought to be asymptomatic, yet in outbreaks, attack rates can approach 100%. Factors affecting the manifestation of clinical disease are the number of living larvae ingested, species involved, and host factors including age, sex, ethnic group, and immune status. There are two distinct phases. During the first week after ingestion, symptoms are consistent with those of gastroenteritis from other causes and include diarrhea, vomiting, and abdominal discomfort. This acute, enteric phase can be delayed if the infective dose is low. The second, parenteral phase corresponds to the invasion of the skeletal muscles and occurs 8 to 42 days after infected meat is eaten. The most common symptom at this stage is muscular pain, and the most distinctive physical finding is periorbital edema. Systemic symptoms such as fever, headache, and rashes are common. Rarely, death may occur from myocarditis, encephalitis, or pneumonitis.

DIAGNOSTIC APPROACH

In the enteric phase, a history of ingesting raw or undercooked meat is helpful in differentiating parasitic infection from other causes of gastroenteritis. Still, the diagnosis of an individual case in the enteric phase and early into the parenteral phase can be difficult because diagnostic antibody test results are commonly not positive until 3 to 5 weeks after infection. Also, the sensitivity of a muscle biopsy to identify diagnostic encysted *Trichinella* larvae in infected muscle will be dependent on the degree of muscle involvement and choice of the area for biopsy.

Serologic tests (enzyme immunoassays [EIAs]) for *Trichinella* using excretory-secretory (ES) antigens are usually available from commercial clinical laboratories, as well as through the public health department. During the parenteral phase, even with negative *Trichinella* antibody test results, a febrile illness accompanied by headache, periorbital and facial edema, and myalgias is suggestive of trichinellosis in persons with a compatible food history. Elevated blood levels of muscle enzymes such as creatine phosphokinase (CPK) as well as elevated eosinophil counts in the peripheral blood increase the probability even further.

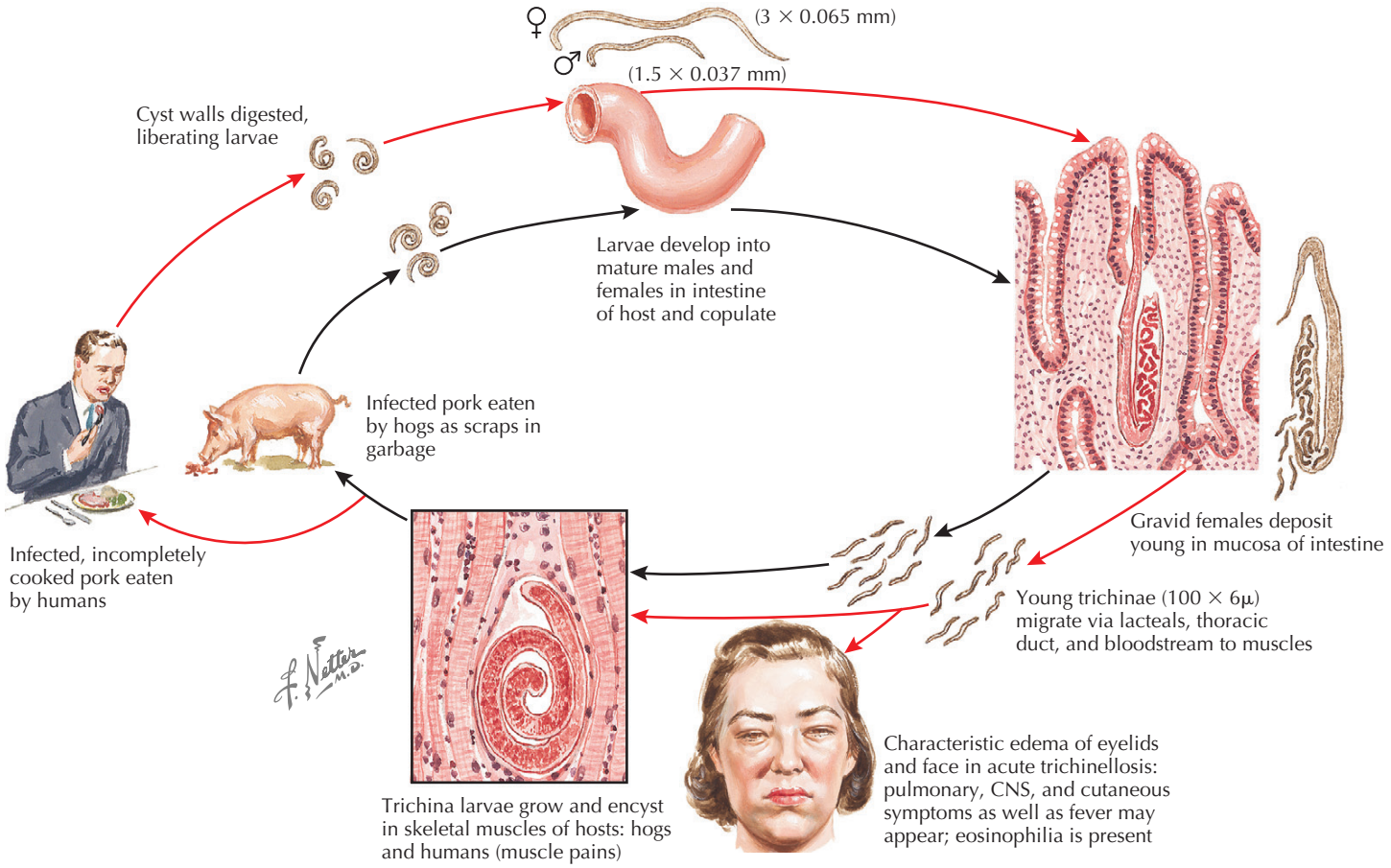


Figure 83-1 Trichinellosis.

In an outbreak, however, the most important diagnostic information is a history of ingestion of undercooked or raw meat with multiple symptomatic patients. Because of the relative insensitivity of the serologic tests for diagnosis of acute trichinellosis, the following case definition is used by the U.S. Centers for Disease Control and Prevention (CDC):

1. A positive muscle biopsy or positive serologic test result in a patient with symptoms compatible with trichinellosis.
   or
2. At least one person with a positive serologic test result or muscle biopsy; associated cases are defined by compatible symptoms in persons who shared the epidemiologically implicated meal or implicated meat product. This is important because 50% or more of infected persons early in the course of the disease will not have positive serology.

TREATMENT

Although treatment is still controversial, most experts recommend albendazole 400 mg orally twice a day for 8 to 14 days as standard therapy and concomitant prednisone 40 to 60 mg for an unspecified number of days. There are other, alternative antiparasitic drugs that can be substituted for albendazole. A recent observational study suggested that prednisone is particularly important in the prevention of systemic symptoms that can occur after treatment with albendazole. The optimum dose of prednisone is uncertain, but 1 mg/kg for 5 days without tapering is probably sufficient. Aggressive supportive treatment and perhaps higher doses of steroids are warranted in those with life-threatening complications such as myocarditis, encephalitis, or pneumonitis.

PREVENTION

The two ways to prevent the disease are first, to prevent infected meat from reaching the consumer, and second, to educate people on the importance of proper handling and cooking of potentially high-risk meats. Commercial producers of pork are required, in many countries, not to feed swine garbage (which could contain infected meat scraps) and to prevent swine ingestion of small mammals potentially infected with *Trichinella*, including rodents, raccoon, skunks, and opossums. Commercial producers of pork products such as hams, sausage, and jerky are required to follow brining, smoking, and cooking guidelines that will kill *Trichinella* larvae in pork. However, even with effective commercial standards, the risk of trichinellosis remains with meat from swine raised on small noncommercial farms, specialty meat products (sausage, jerky, and so on) from small-scale meat processing concerns, and wild game meat, often home butchered.

Cooking is the most reliable method of destroying *Trichinella* in any type of meat, and a temperature of 170° F (77° C) is above the thermal death point. This temperature is usually achieved if the meat is no longer pink, but the most accurate way of measuring temperature during cooking is with a rapid-read cooking thermometer. *T. spiralis* in pork can be killed at a temperature of 160° F (71° C) for 2 minutes (Table 83-1). Microwaving meat is not recommended as a method of cooking to eradicate parasites, because uniform temperatures are not obtained throughout the meat. *T. spiralis* in pork cuts that are less than 6 inches thick are killed by freezing at –20° F (–29° C) for 6 days (see Table 83-1). However, freezing may not kill *Trichinella* larvae in game meats, which are relatively resistant to low temperatures.

Table 83-1 Consumer Processing Guidelines to Kill *Trichinella spiralis* Larvae in Pork

MEAT	PROCESS	TEMPERATURE† FAHRENHEIT	TEMPERATURE‡ CENTIGRADE	DURATION
Fresh pork	Cooking	160° F	71° C	2 minutes
Fresh pork	Cooking	140° F	60° C	6 minutes
Fresh pork*	Freezing	–20° F	–29° C	6 days
Fresh pork*	Freezing	–10° F	–23° C	10 days
Fresh pork*	Freezing	–5° F	–17° C	20 days

*Applies to pork cut less than 6 inches thick.
†Refers to minimal internal temperature achieved
‡*Guidelines for killing* Trichinella *species in pork may not apply to* Trichinella *larvae in other meats, which may be more resistant to both cooking temperatures and freezing temperatures effective for processing pork.*

EVIDENCE

Bouree P, Bouvier JB, Passeron J, et al: Outbreak of trichinosis near Paris, *BMJ* 1:1047-1049, 1979. *Description of clinical and laboratory data in 125 cases, including cases in 30 children, associated with ingestion of horsemeat.*

Jansen E, Schoneberg I, Stark K, Nockler K: Epidemiology of trichinellosis in Germany, 1996-2006, *Vector Borne Zoonotic Dis* 8:189-196, 2008. *Domestic pigs are practically free from infection with* Trichinella *species. The highest mean incidence of trichinellosis infections was found in immigrants from southeast European countries. Risk factors were consumption of imported pork and indigenous and imported wild boar meat.*

Kaewpitoon N, Kaewpitoon SJ, Pengsaa P: Food-borne parasitic zoonosis: distribution of trichinosis in Thailand, *World J Gastroenterol* 14:3471-3475, 2008. Trichinella *is a common food-borne parasite in Thailand and is associated with ingestion of raw and undercooked domestic pork and/or wild animals.*

Ortega-Pierres MG, Arriaga C, Yepez-Mulia L: Epidemiology of trichinellosis in Mexico, Central and South America, *Vet Parasitol* 93:201-225, 2000. *Most of the outbreaks of trichinellosis reported in Mexico, Argentina, and Chile have been associated with consumption of undercooked pork or pork products. The true prevalence of the infection in this region is probably underestimated, and improvements in meat inspection and pig production are needed.*

Roy SL, Lopez AS, Schantz PM: Trichinellosis surveillance, United States, 1997-2001, *MMWR Surveill Summ* 52:1-8, 2003. *Comprehensive review of recent epidemiology, laboratory diagnosis, and control measures for trichinellosis in the United States. Reported human cases of trichinellosis associated with consumption of wild game meat now outnumber cases associated with pork in the United States.*

Schellenberg RS, Tan BJK, Irvine ID, et al: An outbreak of trichinellosis due to consumption of bear meat infected with *Trichinella nativa* in 2 northern Saskatchewan communities, *J Infect Dis* 188:835-843, 2003. *Report of an outbreak involving 78 cases associated with ingestion of inadequately cooked bear meat contaminated with* T. nativa.

Shimoni Z, Klein Z, Weiner P, et al: The use of prednisone in the treatment of trichinellosis, *Isr Med Assoc J* 9:537-539, 2007. *Description of clinical and laboratory data in 30 cases associated with ingestion of pork that occurred in immigrants, and comparison of clinical outcomes when the patients were treated with antiparasitic drugs plus prednisone or antiparasitic drugs alone.*

Takahashi Y, Mingyyuan L, Wikagul J: Epidemiology of trichinellosis in Asia and the Pacific Rim, *Vet Parasitol* 93:227-239, 2000. *Major outbreaks of disease have been reported primarily in China and Thailand, with fewer outbreaks reported from Japan. Although* Trichinella *appears to be prevalent throughout the region, some outbreaks of disease may be underreported owing to limited public health resources for reporting systems.*

ADDITIONAL RESOURCES

Centers for Disease Control and Prevention (CDC): www.cdc.gov/parasites/trichinellosis (Accessed 02/28/11). *Web portal for information on trichinellosis, including epidemiology, disease, diagnosis and treatment, prevention and control; includes patient education materials and resources for health care professionals.*

Gilbert DN, Moellering RC, Eliopoulos GM, Sande MA, eds: *The Stanford guide to antimicrobial therapy*, ed 36, Hyde Park, Vt, 2006, Antimicrobial Therapy, p 101. *Clinical guidelines for use of albendazole in the treatment of trichinellosis.*

Filarial Diseases

Jan Agosti

84

ABSTRACT

The filarial parasites covered in this chapter constitute a group of tissue-dwelling filarial nematodes that persist in the human host for years, causing damage to the lymphatic system leading to elephantiasis and genital hydroceles (lymphatic filariasis) and marked inflammatory reactions in the skin and eyes leading to blindness (onchocerciasis). Global elimination efforts are scaling up to address their significant global burden, using annual or biannual mass drug administration of donated anthelmintic drugs and vector-control measures. Significant progress has been made, particularly on onchocerciasis elimination from the Americas. A remaining challenge is to develop a treatment strategy to use in areas of Africa co-endemic for *Loa loa* and lymphatic filariasis or onchocerciasis—where the existing drug regimens can precipitate significant adverse side effects. Another challenge is developing more effective macrofilaricide treatments to kill adult worms in order to shorten the duration of elimination programs.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Lymphatic filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)

Lymphatic filariasis is a leading cause of permanent and long-term disability worldwide. *W. bancrofti* is responsible for the vast majority of cases and is found throughout the tropics and in some subtropical areas worldwide (Figure 84-1; Table 84-1). *B. malayi* is present in South, Southeast, and East Asia. *B. timori* is restricted to the island of Timor and its environs. The global burden of lymphatic filariasis is not well defined, but it is known to be endemic in over 80 countries, placing 1 billion persons at risk, with the World Health Organization (WHO) most recently estimating 120 million people to be currently infected—2% of the world's population. Of these, 44 million have clinical manifestations such as lymphedema, elephantiasis, hydrocele, lymphangitis, chyluria, and renal disease. The remaining infected individuals often have subclinical lymphatic or renal injury. In addition to the disease burden, there is a significant social, psychological, and economic burden owing to physical stigmata and inability to work. The current estimates are that 4.6 million disability-adjusted life years (DALYs) are lost each year to this disease.

Onchocerciasis (Onchocerca volvulus)

Onchocerciasis, commonly called *river blindness*, is caused by the filarial parasite *O. volvulus* and is one of the most common infectious causes of blindness worldwide, second only to trachoma. There are an estimated 37.2 million infected individuals in 37 countries, primarily in Africa but also Yemen and six countries of the Americas, with 123 million living in endemic areas and at risk of infection (Figure 84-2). Of those infected, an estimated 270,000 individuals are blind and another 500,000 are severely visually impaired. Each year, 1,990,000 DALYs are lost to onchocerciasis; of those, approximately 40% are a result of eye disease and 60% of severe skin manifestations. This disability affects not only the infected patients but also the children who are often assigned to escort blind individuals, preventing them from attending school. Fertile riverine areas needed for agricultural development are abandoned because of risk of this disease, which has devastating socioeconomic consequences.

Loiasis (Loa loa)

Loiasis occurs only in rainforest and swamp forest areas of Central and West Africa, as its distribution is primarily restricted by its transmission vector (see Figure 84-2). Its primary significance is its co-endemicity in areas of Africa with lymphatic filariasis and onchocerciasis, because patients with *L. loa* co-infection cannot be treated with the usual antimicrofilarial regimens used in mass drug administration programs owing to side effects from high levels of dying *L. loa* microfilariae in the circulation and tissues.

RISK FACTORS

Lymphatic Filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)

Risk factors for acquisition of the vector-borne filarial parasites *W. bancrofti*, *B. malayi*, and *B. timori* include living in endemic areas with exposure to a broad range of potential vectors that promote human-to-human spread (see Figure 84-1). For lymphatic filariasis, the mosquito vectors are diverse and include *Anopheles* species, *Culex* species, *Aedes* species, and *Mansonia* species. Infants, children, and adults are exposed to mosquitoes carrying infective larvae (Figure 84-3). There is no natural animal reservoir for *W. bancrofti* or *B. timori*, but a very small percentage (under 5%) of *B. malayi* may be found in domestic and wild animals such as monkeys and cats. Urbanization in endemic areas may be contributing to an increased risk of lymphatic filariasis because infected and susceptible individuals may then live in close proximity to each other and stagnant, contaminated water that provides a breeding ground for the *Culex* vector. Irrigation projects may further increase risk.

Onchocerciasis (Onchocerca volvulus)

Onchocerciasis is termed *river blindness* because the vector, the *Simulium* species black fly, breeds along rivers in fast-flowing

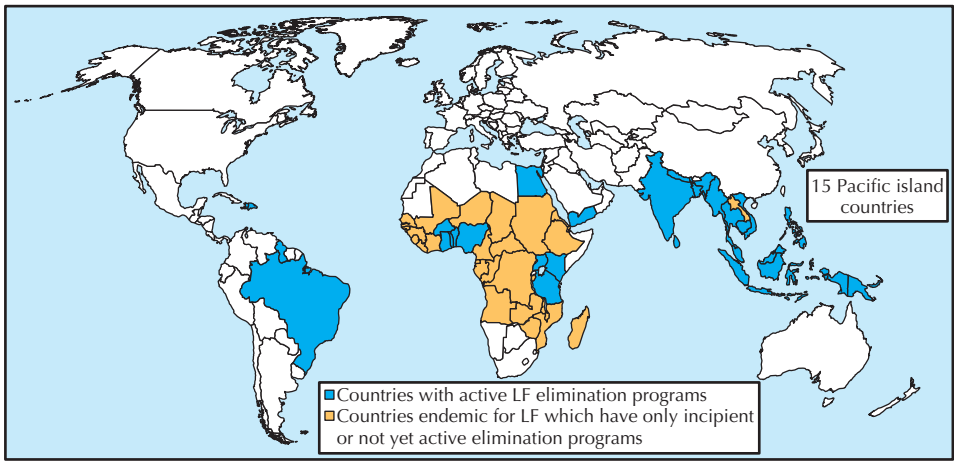


Figure 84-1 Countries with lymphatic filariasis elimination programs. *(Data from Global Alliance to Eliminate Lymphatic Filariasis. Available at:* www.filariasis.org.*)*

Table 84-1 Filarial Nematode Characteristics and Clinical Manifestations

PARASITE SPECIES (DISEASE NAME)	DISTRIBUTION	VECTOR	ADULT LOCATION	MICROFILARIAE LOCATION	CLINICAL FEATURES
Wuchereria bancrofti (bancroftian lymphatic filariasis)	Tropical regions	*Anopheles, Aedes,* and *Culex* species	Lymphatics	Blood	Lymphangitis Elephantiasis Hydrocele Chyluria
Brugia malayi (brugian lymphatic filariasis)	South, East, and Southeast Asia	*Mansonia, Anopheles,* and *Aedes* species	Lymphatics	Blood	Lymphangitis Elephantiasis
Brugia timori (brugian lymphatic filariasis)	Indonesia	*Anopheles* species	Lymphatics	Blood	Lymphangitis Elephantiasis
Onchocerca volvulus (onchocerciasis, river blindness)	Africa, Central and South America	*Simulium* species	Skin	Skin	Dermatitis Nodules Eye lesions Visual impairment
Loa loa (loiasis)	Central and West Africa	*Chrysops* species	Connective tissue	Blood	Calabar swellings Subconjunctival eye worm

water where its larvae can filter feed. Residents along rivers are at highest risk, but the fly has also been carried by monsoon winds for hundreds of kilometers, reinfecting areas that have previously eradicated the fly vector. There is no animal reservoir for onchocerciasis, and transmission is human to human (see Figure 84-4). The severity of ocular disease varies considerably among geographic zones, possibly based on the different vector-parasite complexes. The disease in the West African savanna is responsible for the most severe ocular disease; in the most affected villages, more than 10% of the population may be blind.

Loiasis (Loa loa)

L. loa is transmitted by the day-biting tabanid deer flies of the genus *Chrysops*, which rest in the forest canopy and lay eggs in mud, so transmission is primarily in the rainy season. The flies become infected during a blood meal taken from an infected human and transmit the infective microfilariae (larvae) during subsequent human bites.

CLINICAL FEATURES

Lymphatic filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)

Subclinical infection with the threadlike worms of *W. bancrofti*, *B. malayi*, and *B. timori* may persist for decades but is not benign because there is significant subclinical damage to lymphatics, tissue, and kidneys (see Figure 84-3). Ultrasound and lymphoscintigraphy have shown marked lymphatic dilatation with collateral channels even at this occult stage. There are two distinct pathologic processes involved in progression: the first is acute dermatolymphangioadenitis (ADLA), in which there is cutaneous or subcutaneous inflammation with ascending lymphangitis and regional adenitis probably caused by secondary bacterial infection. There may be accompanying fever and chills. Recurrent episodes are an important cause of chronic lymphedema. The other is acute filarial lymphangitis (AFL), caused by an inflammatory response to the dying adult worms as a result of immunity or drug treatment, which manifests as a well-circumscribed nodule or cord with or without lymphadenitis

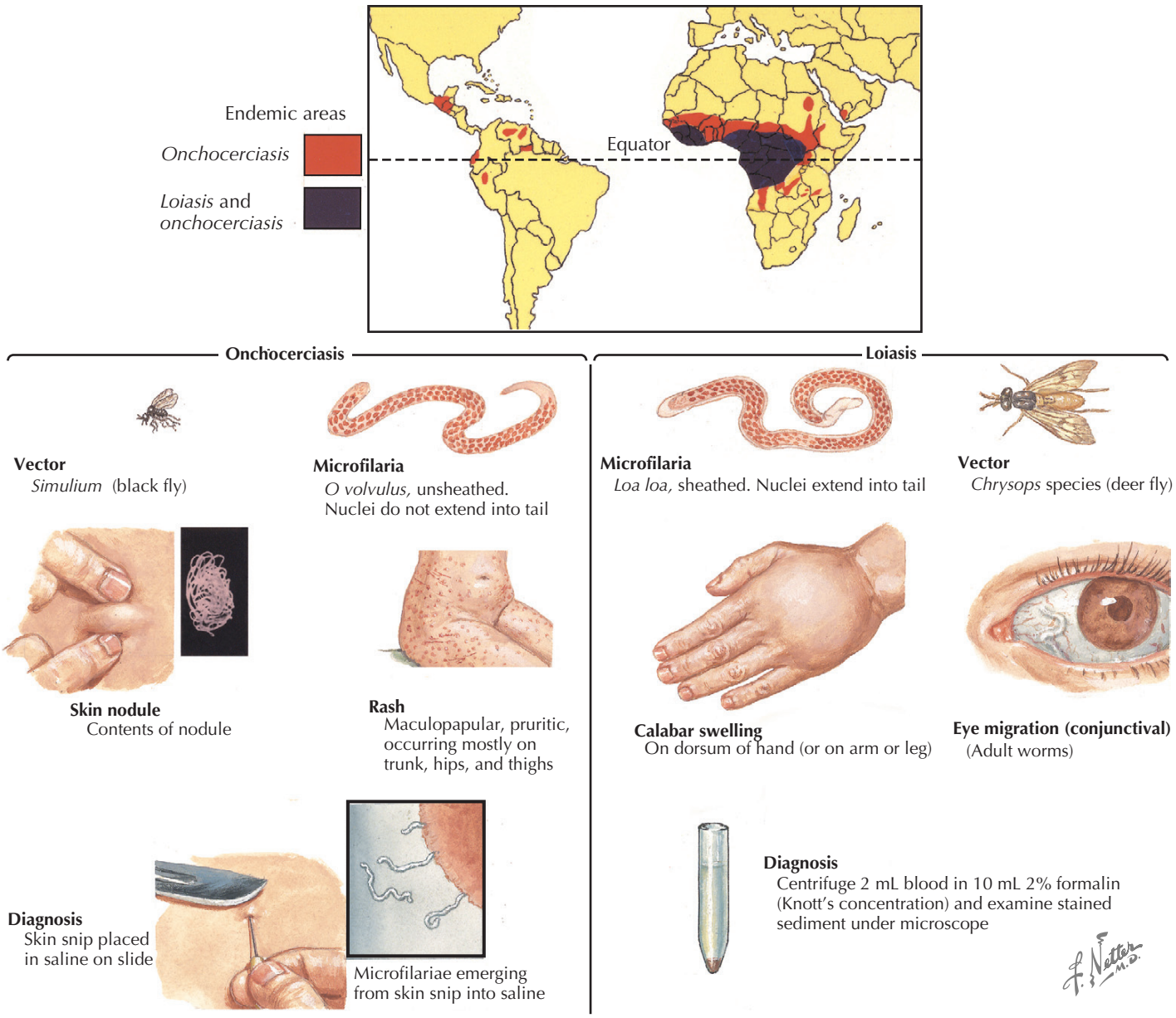


Figure 84-2 Filariasis: onchocerciasis and loiasis.

and lymphangitis and without fever. If lymphangitis is present, it may spread in a descending (centrifugal) manner. AFL rarely causes residual lymphedema, but these episodes damage the lymphatics and lead to the other recurrent infection-lymphedema syndrome.

The disease may progress to brawny lymphedema that can involve the limbs and breasts and may lead to hydroceles of the scrotum and vagina (Figure 84-5). Further progression leads to the chronic state known as *elephantiasis*, in which the skin becomes thick, roughened, hyperkeratotic, and fissured (see Figure 84-5). Radionuclide lymphoscintigraphic imaging shows lymphatic tortuosity, dermal backflow, obstruction, stasis, and poor regional lymph node visualization. Superinfection of these tissues becomes a problem at this stage. Hydroceles can become grossly enlarged to the degree that they become disabling. If there is obstruction of the retroperitoneal lymphatics, renal lymphatic pressure can increase to the point that they rupture, causing chyluria. Hydroceles, genital lesions, chyluria, and elephantiasis of the upper leg are seen with bancroftian filariasis but not with *B. malayi* or *B. timori* infection, presumably because of localization of the given parasite within the body.

Renal manifestations such as hematuria, proteinuria, nephrotic syndrome, and glomerulonephritis have all been reported. Other reported manifestations include tropical pulmonary eosinophilia (paroxysmal cough, wheezing, hypereosinophilia), monoarthritis, polymyositis, urethral obstruction, fibrosing mediastinitis, and bladder pseudotumors.

Onchocerciasis (Onchocerca volvulus)

Clinical manifestations of onchocerciasis include ocular lesions that can cause visual loss, and skin lesions including disfiguring

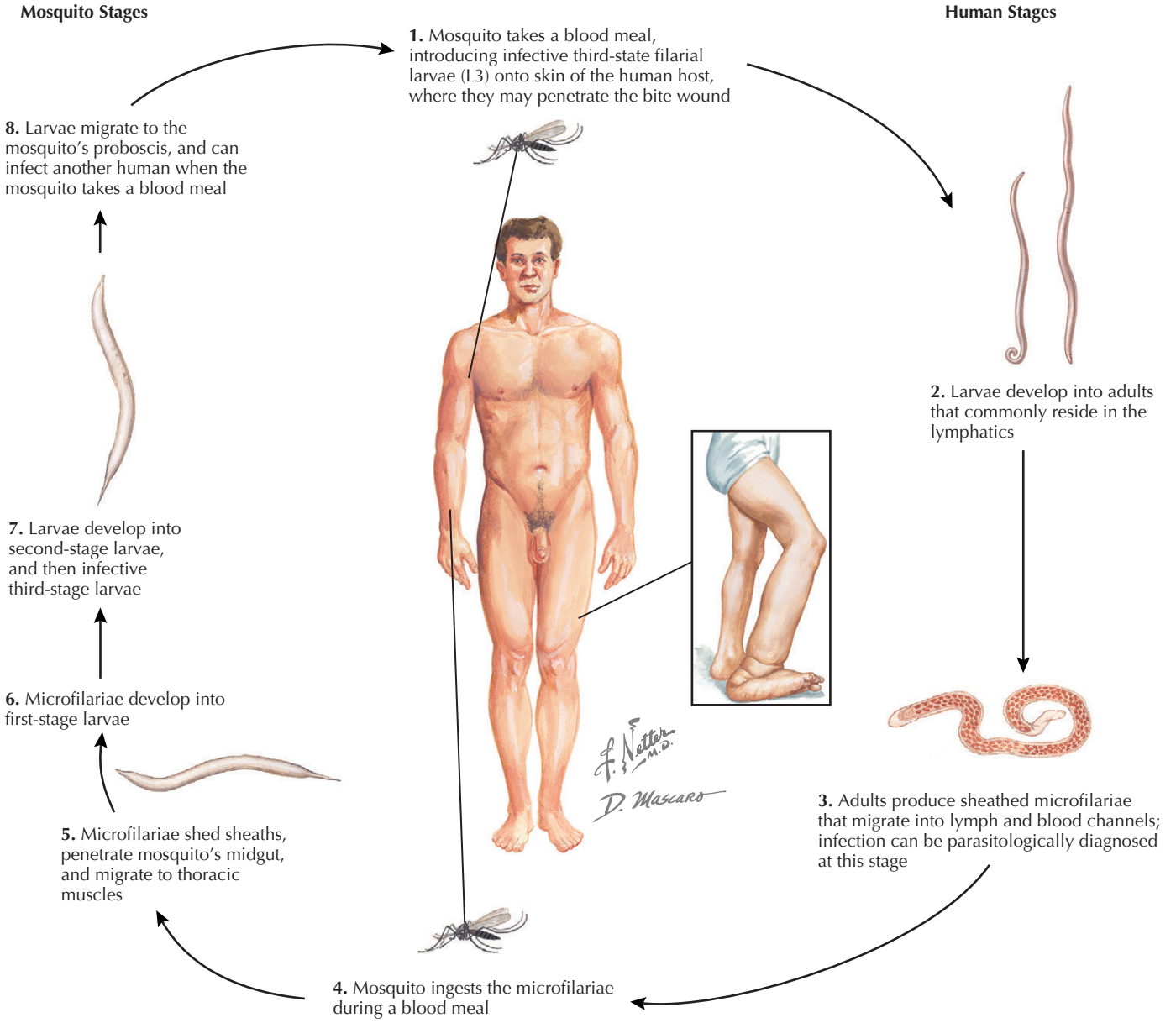


Figure 84-3 Life cycle of *Wuchereria bancrofti*.

skin changes and subcutaneous nodules (see Figure 84-2). The adult worms typically entwine in subcutaneous nodules where they produce millions of microfilariae that migrate to the skin, eyes, and other organs, where many die spontaneously, producing local tissue inflammation. Inflammation in the eyes leads to irreversible ocular lesions, resulting first in impaired vision and finally total blindness. Characteristic lesions include punctate keratitis (snowflake opacities), sclerosing keratitis, iridocyclitis, synechiae, optic nerve atrophy, and choroidoretinitis. The death of microfilariae in the skin causes intense itching, dermatitis, atrophy, and depigmentation of the skin, the last sometimes termed "leopard skin." Secondary infection from scratching is common; lymphadenitis is less common. Subcutaneous granulomas resulting from tissue reaction around adult worms are not symptomatic but are useful for rapid community surveys to identify disease burden.

Loiasis (Loa loa)

Loiasis is often present as an asymptomatic infection that is recognized only after the adult worm migrates across the subconjunctiva ("eye worm"). This is generally benign and should not be confused with the inflammatory response to intraocular microfilariae that leads to blindness in onchocerciasis. Another manifestation of loiasis is the Calabar swelling, which is an evanescent localized skin lesion consisting of erythema and angioedema, particularly on the extremities (see Figure 84-2). Nephropathy, encephalopathy, and cardiomyopathy are rare

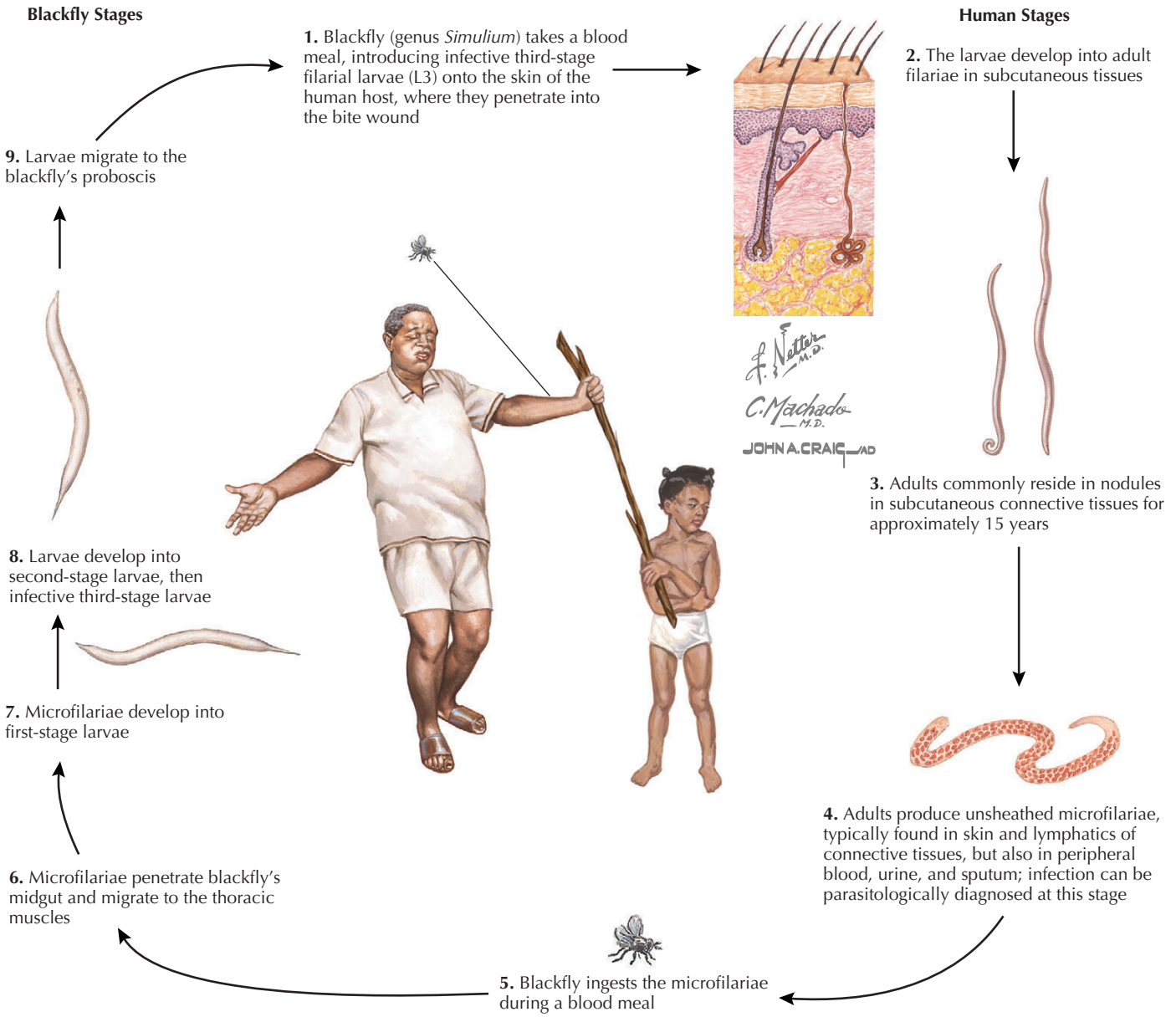


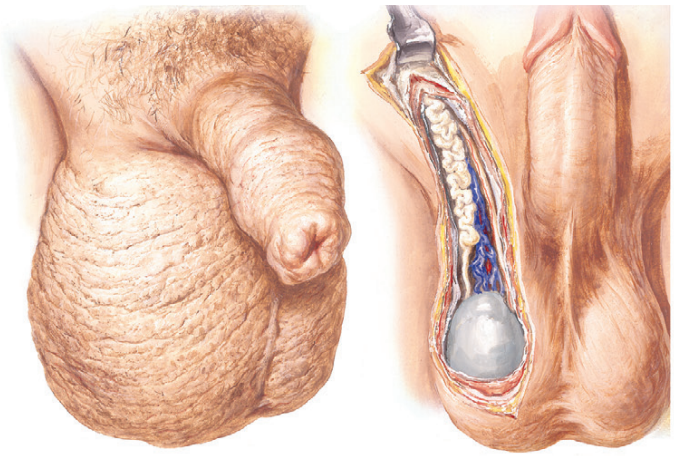
Figure 84-4 Life cycle of *Onchocerca volvulus*.

manifestations. Nonresidents of endemic areas may have more pronounced Calabar swellings and extreme eosinophilia.

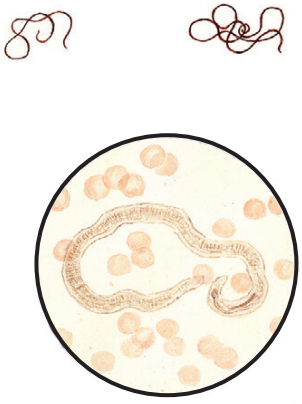
DIAGNOSTIC APPROACH

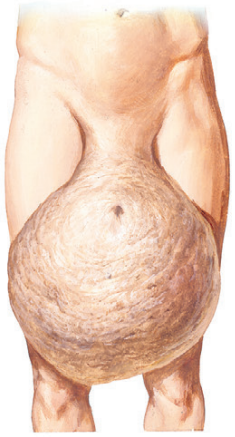
Lymphatic Filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)

The simplest method for detection is a thick blood film of capillary blood stained with Giemsa, although it must be collected around midnight or midday depending on local periodicity of the microfilaremia. Concentration techniques improve the sensitivity of detection and include filtration of blood samples through a 3-micron pore polycarbonate filter or Knott's concentration technique with 2% formalin. For detecting *W. bancrofti* infections, lymphatic filarial antigen tests have replaced this method, because blood can be drawn at any time and because infection can be detected in patients without circulating microfilariae. The enzyme-lined immunosorbent assay (ELISA) based on the Og4C3 monoclonal antibody or the rapid immunochromatographic test (ICT) based on the monoclonal antibody AD12 is the preferred method for antigen detection. Antifilarial immunoglobulin G4 (IgG4) antibody detection assays provide an index of exposure and can be used for early detection of resurgent transmission after mass drug administration programs have stopped. Polymerase chain reaction (PCR) methods for detection of *W. bancrofti* or *Brugia* deoxyribonucleic acid (DNA) can also be used to detect microfilaremia effectively. Doppler ultrasonography can detect moving adult worms ("filarial dance sign") in the scrotum and breast particularly.

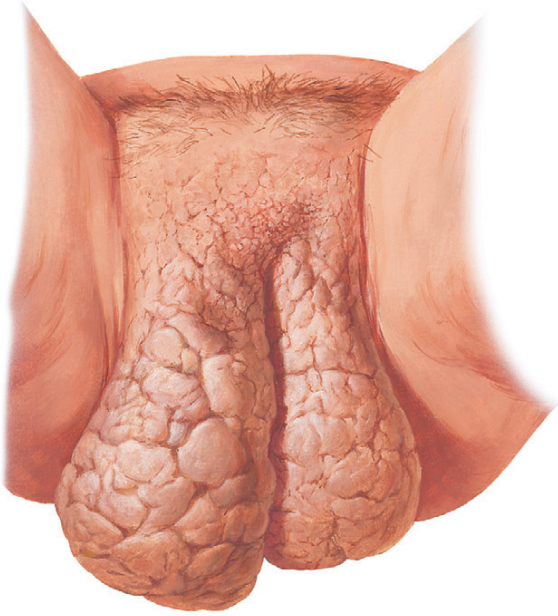


Hydrocele due to lymphatic filariasis
(*Wuchereria bancrofti*)





Elephantiasis of the scrotum
(lymphatic filariasis)



Elephantiasis of the vulva
(lymphatic filariasis)

Figure 84-5 Lymphatic filariasis *(Wuchereria bancrofti).*

Onchocerciasis (Onchocerca volvulus)

Skin snips are immersed in isotonic saline, and the microfilariae that have emerged after 0.5 to 24 hours are counted by microscopy. Microfilariae of *O. volvulus* are 270 to 320 mcm long, unsheathed, and have a characteristic head and a pointed tail. They must be differentiated from the smaller skin-dwelling microfilariae of *Mansonella streptocerca* in Africa and *Mansonella ozzardi* in South America, as well as other rarer microfilariae. A patch test using topical diethylcarbamazine (DEC) has also been developed but is not completely reliable. Serologic detection of IgG4 antibody to the onchocerciasis recombinant antigen OV16 is sensitive and specific even in the rapid-format card test. Antibodies to OV16 often can be detected significantly before the appearance of microfilariae in skin snips. This is an exposure assay only and does not distinguish between prior and current infection. Microfilariae may be visible in the anterior chamber of the eye or the cornea on slit-lamp examination. Xenomonitoring for ongoing transmission is done by collecting pools of *Simulium* flies and screening with PCR for the larvae of *O. volvulus.* Humans are still used to attract flies to the monitoring traps, and because this potentially exposes them to disease, efforts are underway to develop an attractant-baited flytrap to use for monitoring and possibly vector control.

Loiasis (Loa loa)

In order to diagnose loiasis, blood needs to be drawn usually between noon and 2 PM owing to diurnal periodicity of the microfilariae in the blood. Blood smears for parasite visualization are specific, quantitative, and of low cost but are not scalable upward for use in community screening programs. PCR tests are specific, scalable, and quantitative but costly. Serologic assays to detect antiparasite antibodies are scalable but nonspecific and not quantitative.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Lymphatic Filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)

For ADLA, supportive treatment with rest, postural drainage, cold compresses, antipyretics, and analgesics is recommended.

Treatment with antifilarial drugs is not recommended during the acute episode because it may provoke additional inflammatory response to the dying worms. After the acute episode has resolved, a single dose of two drugs—DEC (Hetrazan, Banocide, Notezine) and albendazole (Albenza, Eskazole, Zentel), or ivermectin (Mectizan, Stromectol) and albendazole—will kill the microfilariae and a proportion of the macrofilarial adults (Table 84-2). Corticosteroid pretreatment may decrease the severity of adverse side effects associated with drug treatment of patients with heavy microfilaremia. Retreatment is usually required after 6 to 12 months as indicated by blood smear or antigen testing. Severe reactions to DEC may occur in persons co-infected with *O. volvulus* or *L. loa*, so care must be taken to screen for co-infection in areas where these infections occur. DEC will also treat intestinal *Ascaris* in the patient.

Ivermectin is a potent microfilaricide but does not have a macrofilaricidal effect. Ivermectin will also treat *Ascaris* infection and scabies.

Once lymphatic filariasis is established, twice-daily washing of affected parts with soap and water; raising the affected limb at night; performing regular exercise of the limb to promote lymph flow; keeping the nails clean; wearing shoes; using antibiotic or antiseptic cream to treat small wounds or abrasions; and possibly wearing elastic bandages, can slow the onset of elephantiasis and reverse some disease manifestations. Before surgery for hydroceles, treatment with one of the regimens in Table 84-2 is recommended.

Mass drug administration given to interrupt disease transmission in communities in which there is a high prevalence of infection also helps individuals with disease by markedly reducing the incidence of filarial fevers, and one country reported a decrease in the incidence of hydrocele (Table 84-3).

Onchocerciasis (Onchocerca volvulus)

A single dose of ivermectin causes a rapid elimination of microfilaremia from the skin, which is maintained over several months and then gradually increases (see Table 84-2). Retreatment may be necessary at 3-, 6-, or 12-month intervals. Treatment is contraindicated in pregnant women or children under the age of 5 years. Head nodules may be excised because they may increase the risk of blindness, but otherwise excision of nodules does not provide benefit.

Loiasis (Loa loa)

DEC rapidly eliminates microfilariae but must be used with caution when microfilaremia is present (see Table 84-2). It has some inhibitory effect on adult worms but usually requires repeated therapy. Heavily microfilaremic individuals (>2000 microfilariae per milliliter of blood) should not be treated except with careful observation and possible management with corticosteroids.

Table 84-2 Drugs and Treatment Regimens for Patients with Filarial Nematodes

PARASITE	TREATMENT REGIMENS	WARNINGS
Wuchereria bancrofti, Brugia malayi, Brugia timori	Diethylcarbamazine (DEC) 6 mg/kg orally as a single dose plus albendazole 400 mg orally as a single dose. Alternatively, ivermectin 200-400 mcg/kg orally as a single dose plus albendazole 400 mg orally as a single dose.	DEC is unsafe in patients who have co-infection with onchocerciasis or loiasis. Mazzotti reactions (headache, fever, rash, pruritus, lymphadenopathy, lymphedema, occasionally postural hypotension) from dying microfilariae may be managed with antipyretics, analgesics, antihistamines, and, if necessary, systemic corticosteroids. Corticosteroid pretreatment and gradual dose introduction may be needed for heavy microfilaremia.
Onchocerca volvulus	Ivermectin 150-200 mcg/kg orally as a single dose; repeat every 3, 6, or 12 months as symptoms (pruritus, rash) recur.	If microfilariae are present in the eye, administer prednisone orally for 1 day before and 2 days after ivermectin. Mazzotti reactions (headache, fever, rash, pruritus, lymphadenopathy, occasionally postural hypotension) from dying microfilariae may be managed with antipyretics, analgesics, antihistamines, and, if necessary, systemic corticosteroids.
Loa loa	DEC 6-8 mg/kg/day orally divided into three doses after food for 3 weeks; may require repeat treatment. Do not use in patients with microfilaremia greater than 2000/mcL (drawn at time of day for peak parasitemia) because of lysis of microfilariae leading to risk of encephalitis or death.	For patients with microfilaremia, strongly consider expert referral. Ivermectin results in slower lysis of microfilariae but may still result in encephalitis or death.

Table 84-3 Drug Recommendations and Approaches for Community Mass Drug Administration Control Programs

TREATMENT REGIMENS	DIETHYLCARBAMAZINE CITRATE (DEC) (50-mg OR 100-mg TABLET)	IVERMECTIN* (3-mg TABLET)	ALBENDAZOLE (400-mg TABLET; 100-mg/5 mL ORAL SUSPENSION)	VECTOR CONTROL
Lymphatic filariasis, if not *Onchocerca* co-endemic	6 mg/kg given as a single oral dose every 12 months. Used in combination with albendazole.	Effective in combination with albendazole, but drug donations not available unless onchocerciasis is coendemic.	400 mg as a single oral dose for adults and children over 2 years of age; 200 mg as a single oral dose in children 1-2 years old. Repeat every 12 months. Used in combination with DEC.	Indoor residual spraying, insecticide-treated nets (for *Anopheles* species); breeding site reduction (for *Culex* species)
Lymphatic filariasis, if *Onchocerca* co-endemic	Not recommended because of adverse reactions from dying microfilariae, including potential blindness.	150-200 mcg/kg as a single oral dose every 12 months. Used in combination with albendazole.	400 mg as a single oral dose for adults and children over 2 years of age; 200 mg as a single oral dose in children 1-2 years old. Repeat every 12 months. Used in combination with ivermectin.	Indoor residual spraying, insecticide-treated nets for *Anopheles* species)
Lymphatic filariasis, if *Onchocerca* and *Loa* co-endemic	Not recommended because of adverse reactions from dying microfilariae, including potential blindness and encephalitis.	Use only with extreme caution owing to the potential for adverse reactions from dying microfilariae, including potential microhemorrhagic encephalitis.	400 mg as a single oral dose for adults and children over 2 years of age; 200 mg as a single oral dose in children 1-2 years old. Repeat every 12 months.	Indoor residual spraying, insecticide-treated nets (for *Anopheles* species)
Onchocerciasis	Not recommended because of adverse reactions from dying microfilariae, including potential blindness.	150-200 mcg/kg orally given as a single dose. Retreat every 6-12 months for lifespan of adult worm.	Not applicable	Aerial spraying

*Except sick and infirm, children <90 cm, pregnant and lactating women 1 week postpartum.

PROGNOSIS

Lymphatic Filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)

If disease is detected early, treatment can be effective at preventing disease progression. Once the infection is established, morbidity from chronic disease causes lifelong disability.

Onchocerciasis (Onchocerca volvulus)

Repeated ivermectin has been reported to cause regression of early lesions of the anterior segment, including iridocyclitis and sclerosing keratitis, and of optic nerve disease and visual field loss, but not of chorioretinitis. Visual loss from onchocerciasis is not reversible once established.

Loiasis (Loa loa)

Calabar swellings are usually self-limited and last for a few hours to several days. They may recur at irregular intervals for years, even after the patient leaves the endemic area. Transocular migration of the worm does not result in impaired vision.

PREVENTION AND CONTROL

Lymphatic Filariasis (Wuchereria bancrofti, Brugia malayi, Brugia timori)

The Global Alliance to Eliminate Lymphatic Filariasis and the World Health Assembly have established the goal of eliminating lymphatic filariasis disease. Lymphatic filariasis has been further designated as potentially eradicable by the International Task Force for Disease Eradication, but this will require sustained national and international commitment. Despite some interesting research, there is no filarial vaccine, so control efforts focus on interrupting transmission by mass drug administration programs and vector control through insecticides and bed nets. Long-lasting insecticide–treated bed nets have been shown to significantly decrease lymphatic filariasis microfilaremia in community-based studies of integration with malaria control. The mainstay of control is annual, mass, community-wide drug administration programs, excluding children under age 2 years and pregnant and lactating women (see Table 84-3). In areas primarily outside of Africa where there is no co-endemicity with onchocerciasis, DEC 6 mg/kg and albendazole 400 mg are given together, each as a single dose annually. Where feasible,

DEC-fortified salt as the only source of domestic salt for at least 6 months a year would be an alternative strategy to mass drug administration. In areas where there is co-endemicity with onchocerciasis, DEC is not used because of the possibility of severe ocular reactions. Instead, the regimen is albendazole 400 mg plus ivermectin 150 to 200 mcg/kg. Albendazole has the additional benefit of treating intestinal helminths *Ascaris lumbricoides*, *Trichuris trichiura*, and hookworm, with resultant benefits to growth in children. Ivermectin, in addition to treating *Ascaris* and *Trichuris*, is effective against scabies. These programs depend on donations of drugs from the pharmaceutical companies GlaxoSmithKline (albendazole) and Merck & Co. (ivermectin), as well as support from other donors.

Although the previously described regimens are effective at reducing microfilarial burden for a prolonged period, their effect on adult macrofilariae is less complete. Mass drug administration needs to be repeated annually for the lifespan of the adult worm, which can be 5 to 7 years for lymphatic filariasis. Higher doses and increased frequency of administration of ivermectin plus albendazole, or DEC plus albendazole, are being evaluated for their potential to decrease the survival of the adult macrofilariae and shorten the duration of mass drug administration programs. Ivermectin may cause severe reactions in areas co-endemic for *L. loa* and so should be used only with great caution in those areas. Defining a mass drug administration regimen for *L. loa* co-endemic areas is a current challenge.

Another potentially promising approach for a macrofilaricide is antibiotic therapy targeted against the *Wolbachia* rickettsial endosymbiont that the macrofilariae require for growth and development. Tetracycline, doxycycline, and rifamycin, which kill *Wolbachia* organisms, have been shown to cause death of the *Onchocerca* adult worm and presumably kill adult lymphatic filariae as well. The challenge of these regimens is that they require weeks of treatment, which is difficult for mass drug administration programs, which usually rely on drugs that require only a single dose. *L. loa* do not contain *Wolbachia* organisms, so the anti-*Wolbachia* approach is of potential use in co-endemic areas. Other new potential macrofilaricides being evaluated include moxidectin and oxaboroles.

Onchocerciasis (Onchocerca volvulus)

Mass drug administration of ivermectin prevents the eye and skin disease and may even interrupt transmission, depending on the frequency of treatment and the geographic extent of the distribution program. With ivermectin, the mass drug administration regimen kills primarily the microfilariae and not the adult worm; therefore the treatment must be continued until the adult worms die of natural causes. The estimated lifespan of the adult onchocercal worm is 14 to 17 years. DEC is considered contraindicated in onchocerciasis because of ocular side effects.

The distinction between control and elimination programs of mass drug administration is important. In the former, ivermectin distribution will likely need to continue indefinitely because transmission persists. Sustainability under this strategic approach is critical, and therefore it is important to integrate with other control activities such as vitamin A distribution, treatment of intestinal helminths, and malaria bed net distribution. In the case of elimination, ivermectin is used more intensively (semiannually or quarterly) so that it can eventually be halted when surveillance shows the parasite population has disappeared. Development of a potent macrofilaricide would greatly improve the feasibility of elimination because it would decrease the need to conduct mass drug administration annually for the entire lifespan of the adult worm, 13 to 17 years.

Significant progress has been made toward elimination in the Americas, where transmission has been interrupted or suppressed in all but five of the thirteen foci through semiannual ivermectin treatment of at least 85% of the eligible population and vector control. Colombia was the first of the affected countries to achieve countrywide interruption of transmission of the parasite. Active eye disease attributable to onchocerciasis (defined as a greater than 1% prevalence of microfilariae in the cornea or anterior chamber of the eye) was found only in Brazil and Venezuela; there has been no incident onchocercal blindness in the region since 1995. A Pan American Health Organization resolution in 2008 called for elimination of the ocular disease and interruption of transmission by 2012.

In the Americas, onchocerciasis is found in limited foci; migration of infected human and fly populations is not a major problem, and most black fly species are inefficient vectors. In contrast, onchocerciasis in Africa covers extensive areas and is associated with large human and fly population migrations as well as very efficient black fly vectors. Black flies can travel hundreds of kilometers on monsoon and harmattan winds. Incompatibility in savannah and forest vector-parasite complexes seems to work to limit the infection. Vector control—aerial spraying of black fly breeding sites with larvicides—was effectively applied in the Onchocerciasis Control Program in West Africa from 1974 to 2002 with strong results, interrupting transmission in most of the program areas and maintaining this result for up to 12 years with no additional control effort in an area that had been sprayed for 14 years.

Ivermectin has been effective at controlling onchocerciasis as a public health problem in all areas; however, its potential for interruption of transmission is more promising in hypoendemic and mesoendemic areas. The African Programme for Onchocerciasis Control, which now supports control in endemic countries of Africa, uses ivermectin donated by the pharmaceutical firm Merck & Co. as its principal control tool in communities determined to be at high risk by rapid epidemiological mapping of onchocerciasis (REMO; identifies communities with an onchocercal nodule prevalence ≥20%) and Geographic Information Systems (GISs). Their strategy of community-directed treatment with ivermectin empowers communities to make their own decisions regarding the distribution process, such as selection and remuneration of distributors, time of distribution, method of distribution, and so on. This approach has now also recently been demonstrated to be effective at interrupting transmission in focal areas of Africa.

There is no documented resistance to ivermectin in onchocerciasis, although high-grade resistance emerged in intestinal trichostrongylid nematodes of sheep, cattle, and goats but not horses and dogs. A report from Ghana of human poor responders (defined as microfilariae counts >10 microfilariae per snip after nine or more rounds of ivermectin) is being followed.

Indirect evidence for the needed duration of control programs comes from Guinea Bissau where civil unrest resulted in

suspension of a quarterly ivermectin treatment program in place for 5 years. Despite prevalence levels having dropped to near zero, recrudescence occurred, and it is likely that transmission will resume if interventions are halted before the entire duration of the lifespan of the adult *O. volvulus* (about 14 to 17 years).

Loiasis (Loa loa)

The disease burden from loiasis is not significant enough to merit an elimination program, but its primary significance is that its coendemicity impedes use of ivermectin needed for control programs directed toward lymphatic filariasis and onchocerciasis in Africa. Because of the profound levels of microfilaremia in loiasis and the side effects from rapid microfilarial death, use of ivermectin should be considered contraindicated in areas of significant co-infection with *L. loa*. Residents of areas coendemic for onchocerciasis or lymphatic filariasis who receive ivermectin as part of mass drug administration programs are at increased risk of adverse events, including encephalopathy, coma, and death, particularly if microfilarial burden is greater than 8000 microfilariae per microliter. The pathogenesis includes microfilarial emboli and microvascular hemorrhages. Subconjunctival hemorrhage is considered an early sign of treatment reaction. Corticosteroids do not prevent cerebral reactions and are even harmful once a reaction has occurred.

For individuals, DEC 300 mg orally once a week can be used to prevent infection. Using insect repellents (including permethrin-impregnated clothing) and covering the extremities may reduce the number of bites from infected flies. The flies are day biting, so insecticide-treated bed nets do not help, but other vector-control measures are being explored.

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Schistosomiasis

Elaine C. Jong

85

ABSTRACT

Schistosomiasis is a disease caused by infection with one of the species of *Schistosoma*, helminthic flatworms known as *flukes* belonging to the class Trematoda of the phylum Platyhelminthes. Schistosomiasis is second only to malaria as a human parasitic disease causing significant morbidity and premature mortality in populations living in tropical endemic areas, negatively affecting both individual health and socioeconomic development of communities. It is currently estimated that over 200 million persons worldwide are infected with schistosomiasis, with significant numbers experiencing severe disease manifestations. Visitors to endemic areas become infected in the course of occupational or recreational contact with bodies of fresh water inhabited by infected snails and return home to temperate nonendemic regions, where acute disease manifestations are often not recognized.

There are three main species of *Schistosoma* associated with human disease: *Schistosoma mansoni* and *Schistosoma japonicum* cause intestinal schistosomiasis, and *Schistosoma haematobium* causes genitourinary schistosomiasis. Other *Schistosoma* species have been recognized less commonly as agents of intestinal schistosomiasis in humans, reported only from specific areas and having limited transmission: *Schistosoma mekongi* (part of the *S. japonicum* complex) in Southeast Asia and *Schistosoma intercalatum* and *Schistosoma guineensis* in Africa.

A serious illness accompanied by high fever may be seen in acute schistosomiasis several weeks after initial infection with *S. mansoni*, *S. japonicum*, or *S. haematobium*, and appears to be caused by host immune responses to the release of soluble parasite antigens associated with maturation into the circulation (Katayama fever). Local tissue injury resulting from the passage of parasite eggs through the walls of the intestines to the bowel lumen is associated with abdominal pain and bloody stools in intestinal schistosomiasis, and passage of parasite eggs through the urinary bladder wall to the bladder lumen may result in grossly bloody urine in genitourinary schistosomiasis. Light infections may be asymptomatic and go unnoticed.

Chronic schistosomiasis is the consequence of parasite eggs becoming trapped in the tissues, with resulting granulomatous reactions to the eggs. Egg granulomas in the walls of the intestine and bladder eventually may disrupt function and cause obstruction. In intestinal schistosomiasis, eggs swept back to the liver in the portal circulation lead to chronic inflammation and fibrosis of the portal triads, eventually resulting in cirrhosis, portal hypertension, splenomegaly, and bleeding esophageal varices. In genitourinary schistosomiasis, egg granulomas in the bladder wall lead to impaired bladder emptying, recurrent bacterial urinary tract infections, obstruction of the ureters with the development of hydroureter and hydronephrosis, and, ultimately, renal failure. Involvement of the female genital organs can result in dyspareunia and impaired fertility. Eggs shunted to the systemic circulation may end up in ectopic locations such as the brain (seizures), heart (acute myocarditis, heart block), spinal cord (transverse myelitis, pain, paralysis), and skin ("egg dermatitis" rash).

GEOGRAPHIC DISTRIBUTION

Schistosomiasis is prevalent in tropical and subtropical areas of Africa, the Middle East, South America, Southeast Asia, and the southern provinces of the People's Republic of China. Surveillance data are incomplete but indicate that approximately 85% of infected persons live in sub-Saharan Africa. In the past the parasite was also transmitted in some islands in the Caribbean, the Philippines, and in Japan, but control programs appear to have been successful in eradicating the disease in these areas.

Humans serve as the definitive host where sexual reproduction of the parasite takes place. Each *Schistosoma* species has a specific snail intermediate host necessary for completion of asexual life-cycle stages (Table 85-1). The geographic range of disease transmission is actually determined by the geographic distribution of the requisite snails, and expansion of areas where schistosomiasis is transmitted has been associated with new habitats for snails created by the development of water resources: dams, irrigation waterways, streams, and ponds and the concurrent migration of infected human populations into the new habitats (Figure 85-1). Snails spread to new areas not only by migration along contiguous waterways, but also by introduction into new bodies of fresh water on the feet of aquatic birds.

Schistosomiasis is transmitted to humans by infective parasite larvae called *cercariae* that are released into fresh water by infected aquatic snails. The cercariae are free-swimming and capable of penetrating intact wet human skin. On skin penetration, the cercaria sheds its motile forked tail section, and the tail-less body, called a *schistosomulum*, accesses the circulation and migrates to the hepatic vasculature where maturation takes place. After the schistosomula mature into male and female adults, the adults pair up and mate and migrate to the mesenteric veins of the intestine (intestinal schistosomiasis) or to the venous plexus of the urinary bladder (genitourinary schistosomiasis). Eggs are deposited on the peritoneal surface of the intestine or bladder, and the eggs work their way through the walls of the intestine or bladder to the viscus cavity, and exit the body in the fecal stream or in the urine, respectively.

The transmission cycle begins anew when untreated human feces and urine containing parasite ova (eggs) contaminate the freshwater aquatic environment. On appropriate conditions of light and temperature, the schistosome eggs burst open in the water, releasing free-swimming parasite larvae called *miracidia*. The miracidia are infective only for the species-specific snail

Table 85-1 Parasite Species and Geographic Distribution of Schistosomiasis

DISEASE DESCRIPTION	SPECIES	SNAIL HOST	GEOGRAPHIC DISTRIBUTION
Intestinal schistosomiasis	*Schistosoma mansoni*	*Biomphalaria* species	Africa, the Middle East, the Caribbean, Brazil, Venezuela, Suriname
	Schistosoma japonicum	*Oncomelania* species	China, Indonesia, the Philippines
	Schistosoma mekongi	*Neotricula* species	Several districts of Cambodia and the Lao People's Democratic Republic
	Schistosoma intercalatum	*Bulinus* species	Rain forest areas of central Africa
	Schistosoma guineensis	*Bulinus forskalii*	West Africa
Urogenital schistosomiasis	*Schistosoma haematobium*	*Bulinus* species	Africa, the Middle East

Adapted from World Health Organization (WHO): Schistosomiasis. *WHO Fact Sheet No. 115, February 2010. Available at: www.who.org. Accessed March 15, 2010.*

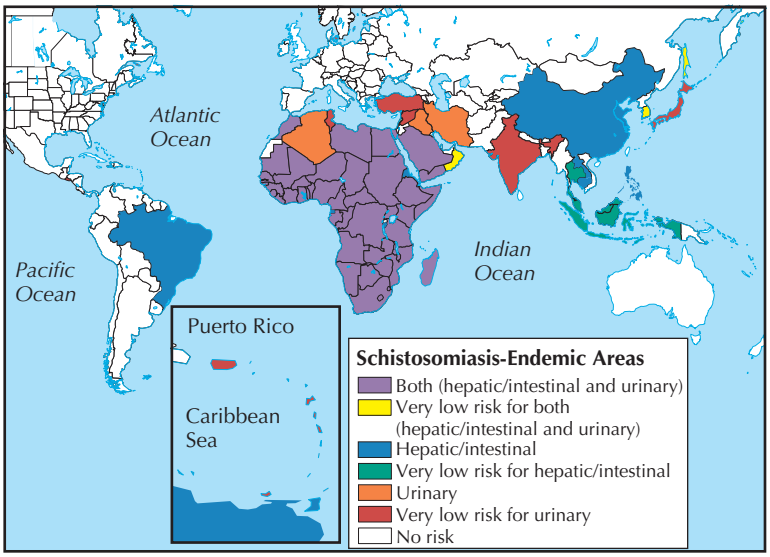

Figure 85-1 Map showing global distribution of schistosomiasis. *(From Centers for Disease Control and Prevention [CDC]:* Health information for international travel 2010, *Atlanta: U.S. Department of Health and Human Services, Public Health Service, 2009.)*

host. If the snails become infected, they will release cercariae, the parasite larval stage that is infective for humans, after a week or so, starting the cycle all over again (Figures 85-2 and 85-3).

RISK FACTORS

The burden of infection is directly related to the period of time persons living in endemic regions are immersed in or wading in bodies of water containing infected snails. Established infections do not stimulate protective host immunity, so new schistosome infections may be acquired during every instance of contact with infected-snail–contaminated water. The snails tend to live close to the shoreline among vegetation and to shed infective cercariae during the middle of the day when the sun is shining brightly. This is the time of day when residents in endemic areas are most likely to be in the water: fishing, boating, farming, bathing, washing clothes, gathering water, swimming, and engaging in other water activities. Males in the population seem to acquire heavier parasite burdens from childhood onward and experience more severe disease manifestations than females, ascribed to longer periods of water exposure of males through occupational and recreational activities. Visitors to endemic areas have acquired schistosomiasis while living and working among resident populations or while participating in recreational activities such as swimming, snorkeling, and kayaking in contaminated bodies of fresh water.

CLINICAL FEATURES

Within hours after cercarial penetration of the skin, with transformation of the cercarial stage parasite into a schistosomula, some individuals develop a pruritic skin rash (cercarial dermatitis, also known as "swimmer's itch") at each point of parasite entry. The rash may last for a few days, and itching can be relieved by antihistamines.

The infection is then followed by an asymptomatic incubation period lasting approximately 4 to 8 weeks, during which time the schistosomula migrate to the hepatic circulation, mature to adult male and female worms, mate, and migrate against the direction of portal blood flow to the mesenteric

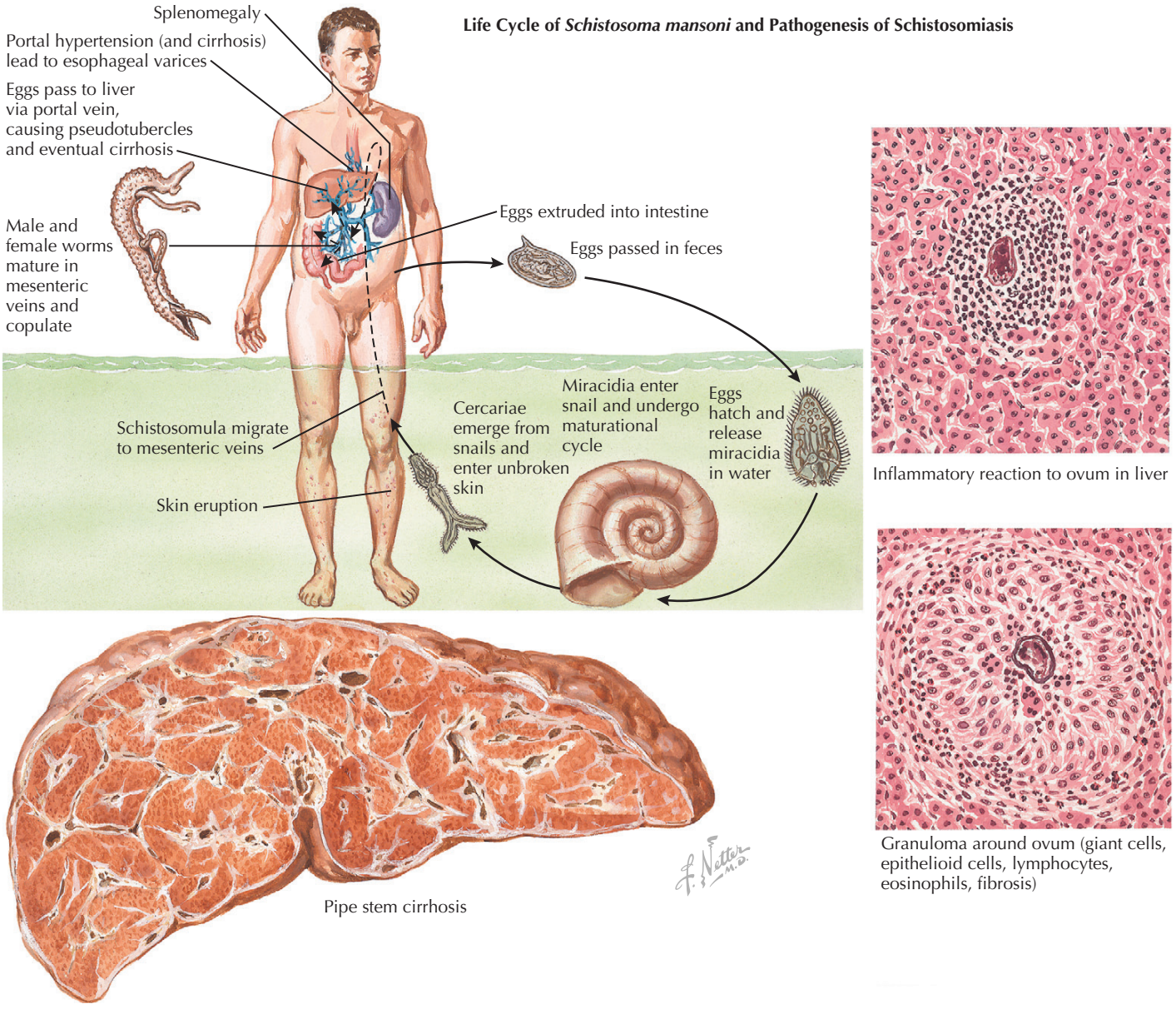

Figure 85-2 Life cycle of *Schistosoma mansoni*.

veins or the venous plexus surrounding the bladder, depending on species. After copulation, the female migrates to the terminal venules and deposits eggs onto the peritoneal surface of the intestines or the bladder. With the aid of intrinsic mechanical movements of the egg and egg secretions, the eggs transit the walls of the viscus and break through the mucosa on the luminal side, exiting the body in the fecal stream in intestinal schistosomiasis or in the urine in genitourinary schistosomiasis.

Onset of egg laying may be marked by abdominal pain and bloody diarrhea. A severe illness may occur 4-8 weeks after initial infection, probably a pronounced hypersensitivity reaction to a variety of circulating parasite antigens. The illness is characterized in most cases by a high fever and may be accompanied by cough and urticaria. A peripheral blood eosinophilia is often present. This illness was first described in association with *S. japonicum* infections in the district of Katayama near Hiroshima, Japan, and was called *Katayama fever;* a similar illness may occur in acute schistosomiasis caused by *S. mansoni* and has been reported recently in some cases of *S. haematobium* infection. Acute schistosomiasis may be misdiagnosed as malaria, as results of definitive diagnostic tests may be negative in both acute febrile illnesses acquired in the tropics.

Adult schistosomes may live in humans for decades, persisting long after the initial infective episode(s) with prolonged production of eggs by the female worms. In intestinal schistosomiasis, the intestinal walls become scarred by egg granulomas over time, leading to further entrapment of parasite eggs in the tissues. Eggs that do not penetrate the walls are passively swept away in the direction of the portal blood flow and become trapped in the portal triads of the liver, where granulomatous reactions around the eggs lead to fibrosis (see Figure 85-2). Bridging pipestem fibrosis of the liver is the hallmark of chronic

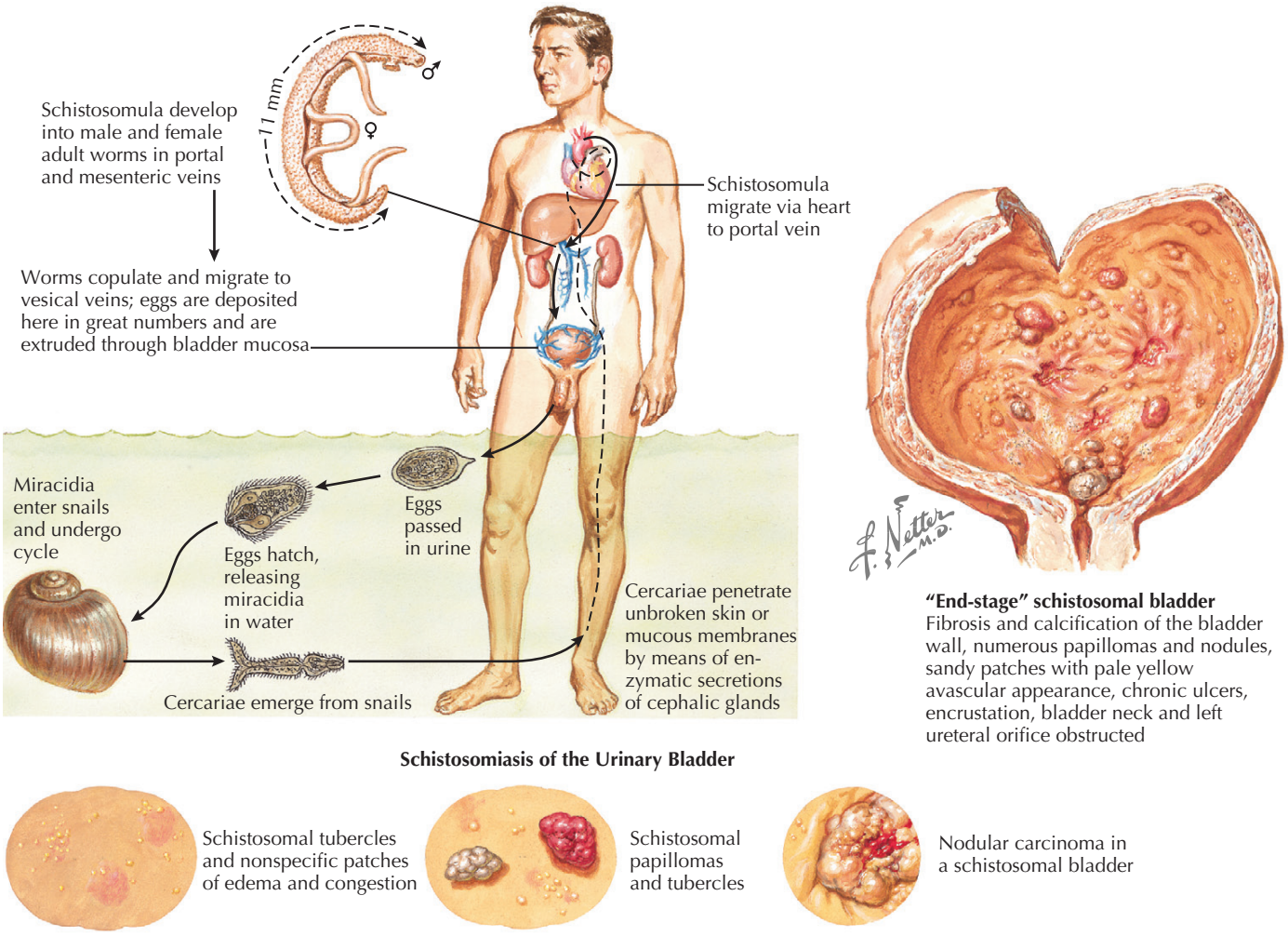

Figure 85-3 Life cycle of *Schistosoma haematobium.*

severe infection with *S. mansoni.* Cirrhosis, portal hypertension, splenomegaly, and esophageal varices represent late stages of chronic intestinal schistosomiasis, and bleeding esophageal varices are a common cause of premature death of infected adults in their second or third decade of life.

In genitourinary schistosomiasis, egg granulomas in the bladder wall may cause ureteral obstruction, leading to hydronephrosis and eventually renal failure (see Figure 85-3). Impaired bladder function leading to incomplete urinary voiding is accompanied by recurrent urinary tract infections. Chronic inflammation of the bladder wall caused by egg granulomas is linked epidemiologically to an increased risk of bladder cancer in *S. haematobium*–infected persons. Dispersion of *S. haematobium* eggs to ectopic locations outside the bladder occurs because of the complex anatomy of the vesicle venous plexus, which allows loose eggs to gain access to other parts of the circulation with egg entrapment in a variety of end-organ tissues.

DIAGNOSTIC APPROACH

The standard for diagnosis of schistosomiasis is the morphologic identification of the characteristic eggs in stool, urine, or tissue specimens (Figure 85-4). The *S. mansoni* egg is relatively large and characterized by a prominent hooklike lateral spine. The *S. haematobium* egg is characterized by a prominent terminal spine. The *S. japonicum* egg is relatively small and has a small inconspicuous lateral knob; it may traverse smaller blood vessels than the eggs of other species before becoming lodged and trapped in end-organ tissues. In endemic areas of Asia, *S. japonicum* eggs that reach the brain are a leading cause of seizures.

In light infections the ova and parasite examinations of stool and urine specimens may not yield the diagnostic forms, even if egg concentration methods are used. Serologic tests (Falcon assay screening test–enzyme-linked immunosorbent assay [FAST-ELISA] based on *S. mansoni* adult microsomal antigen; Western blot for confirmation and species) available at the Centers for Disease Control and Prevention (CDC) and at other reference laboratories (soluble egg antigen ELISA, not species specific) may help with diagnosis, if at least 8 to 10 weeks have elapsed since presumed exposure to infection.

In persons with a strong history of possible exposure to intestinal schistosomiasis, diagnosis of *S. mansoni* and *S. intercalatum* by identification of characteristic eggs in wet mounts of rectal mucosal snips is another way to make the diagnosis

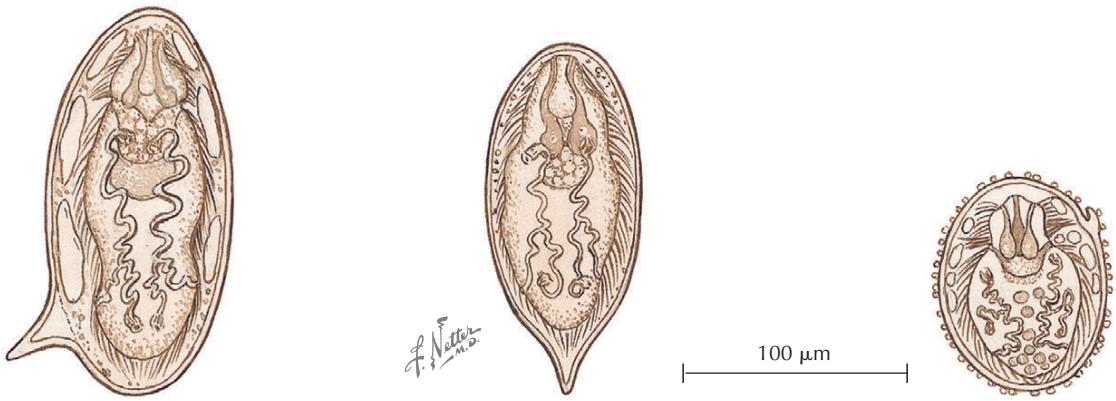

Figure 85-4 Schistosoma ova.

when stool samples are negative. Schistosomiasis may also be diagnosed from tissue biopsy samples taken during colonoscopy, cystoscopy, or surgical procedures in more seriously ill patients. Typical findings seen during cystoscopy of patients with advanced genitourinary disease are shown in Figure 85-3.

CLINICAL MANAGEMENT AND DRUG TREATMENT

At the present time, praziquantel is the most widely used antiparasitic drug for individual therapy and mass treatment programs against schistosomiasis because it is highly efficacious against all *Schistosoma* species. Oxamniquine is an oral antiparasitic drug that was used for treatment of *S. mansoni* only, and metrifonate was used for treatment of *S. haematobium* before praziquantel became widely available. Artemether appears to have activity against juvenile parasite stages in animal models, but its role in the treatment of human schistosomiasis needs further research.

Praziquantel is an oral drug that is manufactured as 600-mg tablets, scored into four segments of 150 mg each. An oral dose of 60 mg/kg/day given in three divided doses for one day, each dose separated by 4 to 6 hours, is indicated for the treatment of schistosomiasis in the official package insert. Adverse side effects are not serious but include nausea, dizziness, and abdominal discomfort. Praziquantel may be used in patients 4 years of age and older, but safety in pregnant and lactating women has not been established, and caution is advised for use in persons with impaired renal function, as drug elimination from the body is mainly through renal excretion. Praziquantel is thought to interfere with the adult parasite's calcium ion influx, but the molecular basis of activity has not been completely defined.

Because of economic constraints in the countries most affected by endemic schistosomiasis, clinical studies have investigated alternate dosage regimens and duration of treatment for praziquantel drug therapy. Praziquantel at a dose of 40 mg/kg given once for treatment of *S. haematobium* has been shown to be highly efficacious and is currently considered standard. Other treatment protocols employing the praziquantel package insert dose of 60 mg/kg/day given in three divided doses for durations longer than 1 day have been investigated for treatment of *S. mansoni* infections.

If acute schistosomiasis involves the central nervous system, praziquantel treatment may be deferred to avoid drug-induced disintegration of parasite eggs and worsening local inflammatory reactions. If respiratory manifestations of acute schistosomiasis are prominent, therapy with corticosteroids may be implemented prior to initiation of antiparasitic treatment. When praziquantel is used for treatment of acute schistosomiasis, a second dose given approximately 3 months after the initial exposure is recommended to eradicate any remaining adult flukes.

PREVENTION AND CONTROL

Travelers can be instructed to take personal precautionary measures to prevent schistosomiasis infection, such as not swimming or wading in bodies of fresh water when visiting endemic areas, and toweling the skin off immediately if drops of water from contaminated sources are splashed onto bare skin. Avoiding personal contact with contaminated water is impractical advice for residents who live in endemic areas under impoverished conditions: their livelihood and activities of daily living largely center around the local water supply.

Current research on vaccines against schistosomiasis shows that an irradiated cercarial vaccine may partially protect laboratory animals against infection. Other vaccine development strategies employ integral membrane proteins (tetraspanins) and excretory-secretory products (ESP) specific to schistosomulum-stage and adult schistosomes. At this time, no human schistosomiasis vaccine appears close to commercial development.

A three-pronged approach to prevent and control schistosomiasis in endemic areas involves environmental interventions to destroy snail habitats by use of herbicides and destruction of the snails themselves by use of molluscicides; interval mass drug treatment programs targeting all local residents presumed to be infected; and improved sanitation systems to prevent raw sewage from contaminating bodies of fresh water.

EVIDENCE

Danso-Appiah A, Utzinger J, Liu J, Olliaro P: Drugs for treating urinary schistosomiasis, *Cochrane Database Syst Rev* 3:CD000053, 2008. *Praziquantel given at a standard dose of 40 mg/kg body weight once in one day had equivalent efficacy compared with metrifonate 10 mg/kg given three times at 4-month intervals in the treatment of* S. haematobium *infection. Efficacy of praziquantel given at doses of 20 mg/kg twice, 30 mg/kg once, and 20 mg/kg once in 1 day were not significantly different from that of the standard dose. Based on limited data, the combination of artesunate and praziquantel was not superior to treatment with praziquantel alone.*

Ferrari ML, Coelho PM, Antunes CM, et al: Efficacy of oxamniquine and praziquantel in the treatment of *Schistosoma mansoni* infection: a controlled trial, *Bull World Health Organ* 81:190-196, 2003. *Praziquantel given at a dose of 60 mg/kg body weight in three divided doses per day for 3 consecutive days was more efficacious than two daily doses of 10 mg of oxamniquine per kilogram in eradicating infection as measured by quantitative egg counts.*

Meltzer E, Artom G, Marva E, et al: Schistosomiasis among travelers: new aspects of an old disease, *Emerg Infect Dis* 12:1696-1700, 2006. Available at: www.cdc.gov/eid. Accessed March 15, 2010. *Well-written analysis of the clinical presentation and disease parameters among 137 Israeli travelers, most returning from trips to sub-Saharan Africa, in whom the diagnosis of schistosomiasis was made; 42.5% of the patients were asymptomatic. Serologic tests were more helpful in making the diagnosis in 87.6% of patients with acute schistosomiasis than traditional ova and parasite examinations. Diagnosis was made in 26.9% of the patients by finding ova in submitted urine, semen, or stool specimens; these patients tended to have chronic schistosomiasis.*

ADDITIONAL RESOURCE

World Health Organization (WHO): Schistosomiasis. Available at: www.who.int/diseases/schisto/default.htm. Accessed March 15, 2010. *Useful portal for accessing current information on global epidemiology, treatment trials, and prevention and control projects.*

Chagas Disease

Fabiana Simão Machado and Herbert B. Tanowitz

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ABSTRACT

Chagas disease is caused by infection with the protozoan parasite *Trypanosoma cruzi*. It is endemic in many areas of Latin America, where it remains an important cause of morbidity and mortality. It is an important cause of heart disease and gastrointestinal (GI) dysfunction such as megacolon and megaesophagus. There has been increased immigration from endemic areas to North America and Europe, where Chagas disease is recognized with increased frequency as an imported infection. Chagas disease is also an opportunistic infection in immunocompromised individuals, including those with human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS). The diagnosis of acute infection is based on finding trypomastigotes in the blood, and chronic Chagas disease is suggested by serologic testing. The antiparasitic drugs benznidazole and nifurtimox are used to treat acute infection, but antiparasitic treatment in the chronic phase is not uniformly recommended. The management of chronic chagasic cardiomyopathy is similar to that of cardiomyopathies from other causes. The management of the GI complications generally involves both medical and surgical interventions.

GEOGRAPHIC DISTRIBUTION AND EPIDEMIOLOGY

Chagas disease is present in Latin America (Mexico, Central and South America) with the exception of the Caribbean countries. Vector-borne transmission of the *T. cruzi* parasite usually occurs in individuals living in primitive houses in areas where the sylvatic cycle is active. Living quarters are often invaded by infected vectors (triatome or reduviid bugs), which become domiciliary and feed at night on people, dogs, and other mammals that live in and around the household area. The parasite has a complex life cycle (Figure 86-1). During a blood meal from an infected mammalian host, the insect vector ingests blood-form trypomastigotes, which undergo transformation, and after 3 to 4 weeks, infective, nondividing metacyclic trypomastigotes are present in the hindgut of the vector. These forms are deposited with the feces of the vector during subsequent blood meals. Transmission to the new host occurs when the parasite-laden feces contaminate oral or nasal mucous membranes, the conjunctiva, or insect-bite wounds. When trypomastigotes (Figure 86-2, *A*) enter a host cell, they transform into intracellular amastigotes, which multiply by binary fission (Figure 86-2, *B*) and then transform to trypomastigotes, which are released as the host cell ruptures. Trypomastigotes infect adjacent uninfected cells or disseminate through the lymphatics and the bloodstream (Figure 86-2, *A*) to infect new cells in distant tissues. Although any nucleated mammalian cell can be parasitized, the cells of the cardiovascular, reticuloendothelial, nervous, and muscle systems, as well as adipose tissue, appear to be favored. Other modes of transmission include blood transfusion, organ donation, congenital transmission, breast milk, ingestion of contaminated food or drink, and laboratory accidents.

In recent years there has been increased immigration of infected, usually asymptomatic, individuals from endemic areas to nonendemic areas such as North America and Europe, and thus Chagas disease is being recognized with increasing frequency worldwide. In the United States there have been a handful of autochthonous cases of Chagas disease. The immigration into the United States of potentially chronically infected individuals has led to screening of blood donors to identify people who are asymptomatic but have the potential to transmit the infection via blood transfusion.

CLINICAL AND LABORATORY MANIFESTATIONS

Individuals who are serologically positive for Chagas disease usually do not recall having acute infection. In addition, they often do not know that they are chronically infected with *T. cruzi*. This is because vector-borne acute Chagas disease is usually mild. After an incubation period of 1 to 2 weeks a newly infected individual may develop fever, chills, nausea, vomiting, diarrhea, rash, and meningeal irritation. A raised inflammatory lesion at the site of parasite entry (a chagoma), unilateral periorbital edema (Romaña sign), conjunctivitis, lymphadenopathy, and hepatosplenomegaly have been observed in acute infection. During acute infection, anemia, thrombocytopenia, and elevated liver enzymes may be present. Blood-form trypomastigotes can be observed in wet preparations of blood and cerebrospinal fluid in many patients. Results of serologic tests for *T. cruzi*–specific immunoglobulin G (IgG) are often negative during acute infection.

Myocarditis, cardiomegaly, vasculitis, and congestive heart failure (CHF) develop in a small percentage of acutely infected patients. The presence of arrhythmias is usually a poor prognostic finding. The mortality rate of acutely naturally infected patients, often children, is less than 2%, and the common mode of death is acute myocarditis and/or meningoencephalitis. In most patients an immune response develops, the parasitemia wanes, and signs and symptoms resolve completely in 2 to 4 months. These individuals then enter the indeterminate phase of infection, which is characterized by a positive serology but the absence of clinical manifestations. This phase may last from months to an entire lifetime, and, as noted, most chronically infected persons never develop clinical manifestations attributable to the persistence of the parasites.

Most experts believe that 15% to 30% of infected individuals develop chronic Chagas disease. Chronic Chagas disease is

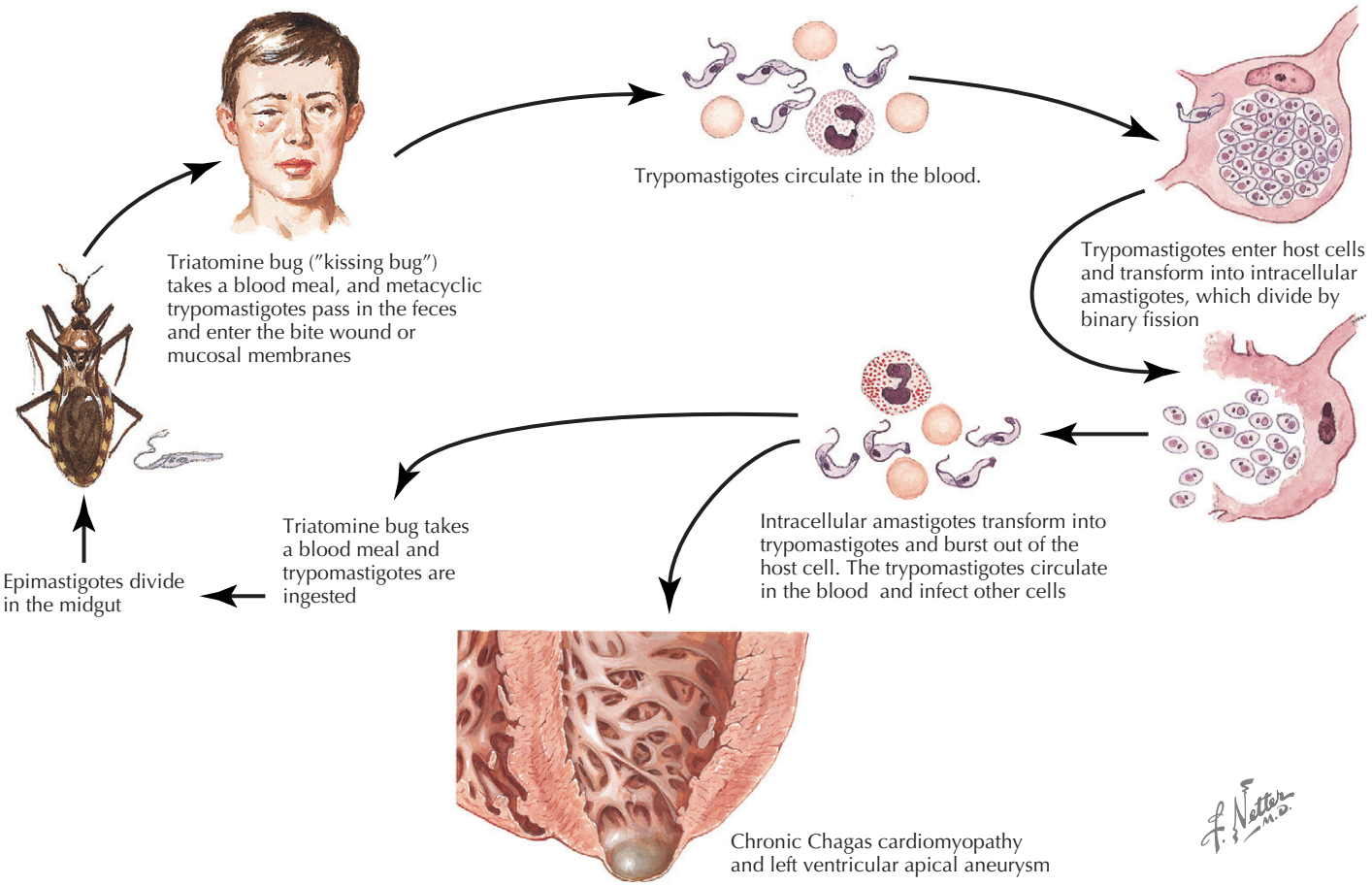

Figure 86-1 Life cycle of Chagas disease.

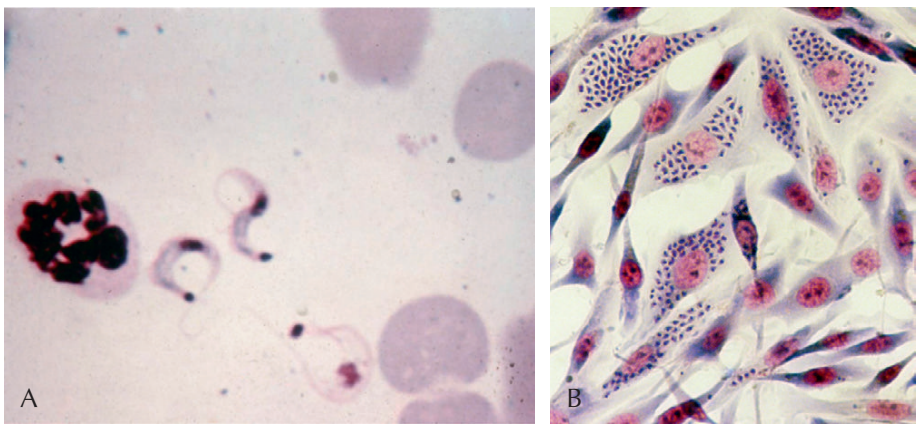

Figure 86-2 **A,** Trypomastigotes of *Trypanosoma cruzi* in a peripheral blood smear. Image of trypomastigotes. **B,** Intracellular amastigotes of *Trypanosoma cruzi* in a culture of myoblasts. (***A*** *From Zaiman H:* Pictorial presentation of parasites, *American Society of Tropical Medicine and Hygiene.)*

usually divided into cardiac and GI manifestations. The cardiac manifestations usually predominate, although in some geographic areas GI alterations are most important. The GI manifestations of chronic Chagas disease are part of the so-called *megasyndrome* complex.

Chronic chagasic heart disease may manifest insidiously as CHF or abruptly with arrhythmias and/or thromboembolic events such as stroke. Dilated congestive cardiomyopathy is an important manifestation and usually occurs years or even decades after a person first became infected (Figure 86-3).

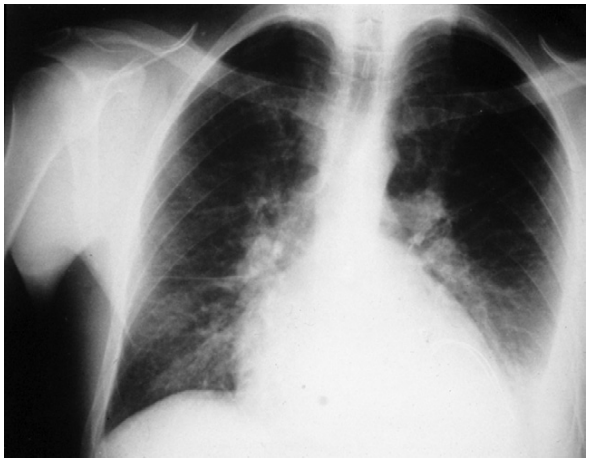

Figure 86-3 Chest radiograph of a patient with chronic Chagas disease and cardiomyopathy. The patient has congestive heart failure, and pacemaker wires are visible. *(From Tanowitz HB, Kirchhoff LV, Simon D, et al: Chagas' disease,* Clin Microbiol Rev *5:400-419, 1992.)*

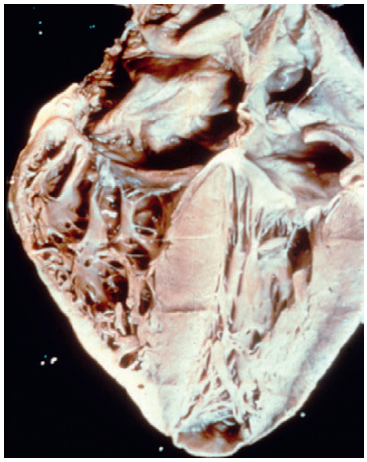

Figure 86-4 Autopsy specimen of a heart that is dilated and hypertrophied and has an apical aneurysm. *(Courtesy Armed Forces Institute of Pathology.)*

Apical aneurysm of the left ventricle is one of the hallmarks of chronic chagasic cardiomyopathy and is observed by cardiac imaging and at autopsy (Figure 86-4). Histology of cardiac tissue from these patients reveals chronic inflammation and fibrosis. The destruction of conduction tissue results in atrioventricular and intraventricular conduction abnormalities. The most common electrocardiographic abnormality is a right bundle branch block, which may also be associated with an anterior fascicular block. Conduction defects may necessitate the placement of a pacemaker. Increases in levels of brain natriuretic peptide (BNP) have been demonstrated to be important in the evaluation of patients with chronic chagasic heart disease. Echocardiography and cardiac magnetic resonance imaging are often useful is assessing severity of disease.

The GI dysfunction that may accompany chronic Chagas disease is likely the result of injury to the enteric nervous system. Affected individuals may develop dilatation of portions of the GI tract. Although megacolon and megaesophagus are most common, megastomach, megaduodenum, megajejunum, megagallbladder, and megacholedochus have all been described (Figure 86-5). Other associated dysfunctions include achalasia and aspiration pneumonia, disturbances of gastric emptying, alterations in intestinal transit, and motility disorders of the colon and gallbladder. Patients may develop GI and/or cardiac dysfunction or both. Imaging studies of the GI tract such as computed tomography and ultrasound scans as well as pressure and motility studies are useful in assessing the extent of damage. These should be performed in conjunction with radiologists and GI specialists.

LABORATORY DIAGNOSIS OF CHAGAS DISEASE

The diagnosis of acute *T. cruzi* infection is usually made by the detection of parasites in wet mounts of blood or cerebrospinal fluid and in Giemsa-stained slides (see Figure 86-2, *A*). Testing for anti–*T. cruzi* IgM antibodies is not useful. Inoculation of blood samples into a special medium or into mice may be required to demonstrate the parasite, but these culture methods lack sensitivity because parasites may not be seen for several weeks. Parasites may at times be observed in other sites, such as pericardial fluid, bone marrow, brain, skin, and lymph nodes. If acute Chagas disease is suspected in an immunocompromised patient, an examination of other samples may be useful. Polymerase chain reaction (PCR) technology is thought to be the most sensitive method for detecting acute *T. cruzi* infection but is not widely available. PCR-based tests have been used in the diagnosis of congenital Chagas disease immediately after birth.

The diagnosis of chronic Chagas disease is usually based on detecting specific antibodies. Several serologic assays are employed, including indirect immunofluorescence (IFA) and enzyme-linked immunosorbent assay (ELISA). Serologic assays are used widely for clinical diagnosis and for screening of donated blood, as well as in epidemiologic studies. An immunoprecipitation assay based on iodinated *T. cruzi* proteins (RIPA) is specific and sensitive and is being used as the confirmatory assay to test all donor samples that are positive in the screening test.

CLINICAL MANAGEMENT

The treatment of Chagas disease must be considered at two levels: parasite-specific therapy and adjunctive therapy for the management of the clinical manifestations. The treatment of *T. cruzi* is not satisfactory. There are two drugs available: nifurtimox (Lampit, Bayer 2502) and benznidazole (Rochagan, Roche 7-1051). They are available from the Centers for Disease Control and Prevention (CDC) Drug Service (www.cdc.gov/ncidod/srp/drugs/drug-service.html; 404-639-3670). The drugs lack efficacy, must be taken for extended periods, and have severe side effects. These drugs appear to reduce the severity of acute infection, and the general consensus is that parasitologic cure is achieved in approximately 70% of persons with acute infection with a full course of either drug, but there are no large

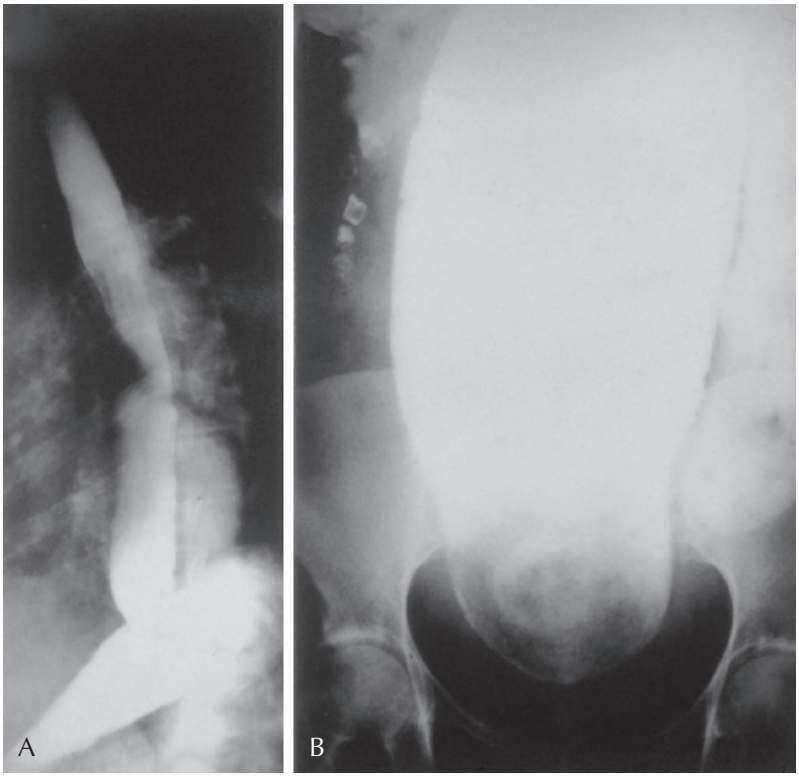

Figure 86-5 Gastrointestinal manifestations of Chagas disease. A 48-year-old woman came to the United States 10 years previously. She complained of difficulty swallowing and constipation. **A,** Barium swallow revealed a megaesophagus. **B,** A flat plate of the abdomen revealed megacolon and retained barium. The patient had undergone a barium enema 7 months previously. *(From Tanowitz HB, Simon D, Gumprecht JP, et al: Gastrointestinal manifestations of Chagas' disease. In Rustgi VK, ed:* Gastrointestinal infections in the tropics, *Basel, 1990, Karger, p 64.)*

studies that support these data. This cure rate is thought to decrease as a function of the time patients have been infected, and perhaps less than 10% of individuals with longstanding chronic infection can be cured.

There are no data at this time to state that treatment with either drug is beneficial in individuals with longstanding infections. Some experts recommend antiparasitic treatment only for patients with acute and congenital infections and for chronically infected children and young adults. Antiparasitic therapy for adults assumed to have longstanding infections is not generally recommended, regardless of clinical status, although many do get treatment. For example, the question often arises as to whether to use antiparasitic therapy in individuals who are seropositive in a blood donation screen. Regardless of age, a seropositive person should be removed from the blood donation pool, and some have suggested that individuals 50 years of age or younger should be given the option of treatment. A large clinical trial designed to address the efficacy of benznidazole treatment in this situation is underway. Allopurinol and several antifungal azoles have been shown to have anti–*T. cruzi* activity in vitro and in animal models.

The medical management of patients with chagasic heart disease is similar to the management of patients with CHF and cardiomyopathy from other causes and should be instituted in conjunction with cardiologists who specialize in CHF. Digoxin is useful in the treatment of CHF but should be used with caution in individuals with extensive fibrosis to avoid conduction disturbances. Angiotensin-converting enzyme (ACE) inhibitors and β-adrenergic blockers have also been successfully employed. Individuals with conduction disturbances may require the placement of a pacemaker. The use of anticoagulation therapy in patients with chagasic cardiomyopathy is controversial and should not be undertaken without consultation with a cardiologist.

Persons with severe chronic chagasic heart disease with dilated cardiomyopathy and severe CHF may benefit from heart transplantation. A major concern in the heart transplant recipient would be the consequences of long-term immunosuppressive therapy after transplant—including the possible reactivation of *T. cruzi* infection from other tissue sites in the body. Stem cell transplantation currently is being evaluated in patients with severe CHF and chagasic heart disease.

Individuals with GI disturbances such as megaesophagus and megacolon are initially managed conservatively but may require surgery. These patients should be managed with GI specialists and surgeons familiar with these conditions.

PREVENTION AND CONTROL

Improved housing, socioeconomic standards, and vector control have all been instrumental in reducing the spread of Chagas disease. The screening of blood and organ donors has also played an important role in reducing transmission.

SUMMARY

Chagas disease should be considered in any individual who comes from an endemic area and manifests cardiac or GI dysfunction, and serology for Chagas disease should be obtained. If the serology is positive, the patient should be referred to an infectious disease or tropical disease specialist. Blood donors with a positive serology for Chagas disease should also be evaluated clinically for consideration of possible treatment.

ADDITIONAL RESOURCES

Bern C, Montgomery SP, Herwaldt BL, et al: Evaluation and treatment of Chagas disease in the United States: a systematic review, *JAMA* 298:2171-2181, 2007. *A detailed description of the current epidemiology of Chagas disease in the United States, and the approach to diagnosis and treatment when Chagas disease is suspected in immigrants or returned travelers from endemic areas.*

Biolo A, Ribeiro AL, Clausell N: Chagas cardiomyopathy—where do we stand after a hundred years? *Prog Cardiovasc Dis* 52:300-316, 2010. *Clinical perspective on Chagas cardiomyopathy and its management.*

Centers for Disease Control and Prevention (CDC): *What happens to blood donors who test positive for Chagas disease?* Available at: www.cdc.gov/chagas. Accessed May 18, 2010. *Fact sheet that provides information for healthcare providers and blood donors and CDC contacts for physician consultation, testing, and treatment. The CDC estimates that 300,000 or more* T. cruzi*–infected individuals of Hispanic origin currently live in the United States. Only approximately 11% of Chagas-seropositive blood donors or their physicians have contacted the CDC for consultation regarding treatment, according to the fact sheet.*

Gascon J, Bern C, Pinazo MJ: Chagas disease in Spain, the United States and other non-endemic countries, *Acta Trop* 115:22-27, 2010. *Current epidemiology of Chagas disease in nonendemic countries.*

Tanowitz HB, Machado FS, Jelicks LA, et al: Perspectives on *Trypanosoma cruzi*–induced heart disease (Chagas disease), *Prog Cardiovasc Dis* 51:524-539, 2009. *Up-to-date review on the pathogenesis and pathology of* T. cruzi*–induced heart disease.*

SECTION
IX

Edited by Jo Hofmann

Emerging Infectious Diseases and Pandemics

87 *Introduction to Emerging Infectious Diseases and Pandemics*
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Introduction to Emerging Infectious Diseases and Pandemics

Jo Hofmann

87

Plagues have been described since humans began to recall their history. Despite the development of antimicrobials, vaccines, and other technologic advances, infection is a leading cause of death in the developing world, and outbreaks of infectious diseases continue to influence global events, even in the twenty-first century. The appearance of emerging infectious diseases (those caused by a newly recognized agent) and reemerging infectious diseases (those caused by a known agent that has developed enhanced pathogenicity or dramatically increased in incidence) may be due to multiple factors, but perhaps the most important are the alteration of human and nonhuman ecology and environmental change. Despite the devastating effect that unrecognized and unanticipated diseases may have on the human population, the concept of "emerging infections" did not coalesce until the 1990s. In 1992, the Institute of Medicine (IOM) of the National Academy of Sciences published a report that called for the establishment of programs to effectively identify, monitor, and respond to all infectious agents, including newly recognized pathogens such as human immunodeficiency virus (HIV) and antimicrobial-resistant bacteria. The 1992 IOM report recommended strengthening communicable disease surveillance in the United States at the local, state, and federal levels; establishing a comprehensive global network for infectious disease surveillance; and supporting research to improve infectious disease detection and response. In 2003, the IOM evaluated the progress of efforts to implement their recommendations and reported that the global infrastructure to support response to emerging and reemerging infections continued to be neglected, particularly in developing regions, where many previously unrecognized human infections first appear.

Much has happened in the United States and globally since the publication of that 1992 IOM report: burgeoning antimicrobial resistance, the North American emergence of West Nile virus (WNV), the intentional distribution of *Bacillus anthracis*, and a vaccine campaign for a vanquished disease (smallpox) rumored to be the next weapon of mass destruction. More recently, widespread outbreaks of severe acute respiratory syndrome (SARS) and avian influenza, both initially thought to portend the next pandemic, were upstaged when a novel swine influenza caused the first pandemic of the twenty-first century.

The confluence of human and nonhuman ecology and environmental disturbance sets the stage for the prototypical emerging or reemerging infectious disease: a zoonosis, or disease caused by an agent that typically infects another species but has made an evolutionary transition that enables it to infect humans. Two recent reports that reviewed trends in emerging infections identified several patterns of association: emerging infectious diseases of temperate regions tend to be associated with domesticated animals, advanced agriculture, and healthcare technologies, whereas those originating in tropical regions are more typically linked to human interaction with wild animals or exposure to insect vectors. Both reports called for renewed efforts to establish programs for surveillance and investigation of emerging infections that focus on these associations, allocating resources to detect novel or reemerging infections in developing regions with the greatest biodiversity and interaction between wildlife and humans.

Even a partial list of emerging and remerging infections of the last 30 years includes pathogens too numerous for all to be covered in this section: HIV, hepatitis C (formerly non-A, non-B hepatitis) virus, avian and swine influenza A viruses, the SARS coronavirus, Sin Nombre virus, WNV, dengue viruses, and the agent of variant Creutzfeldt-Jakob disease; *B. anthracis*, *Escherichia coli O157:H7* and other enterohemorrhagic *E. coli*, *Francisella tularensis*, *Vibrio cholerae* O139, and *Yersinia pestis;* and *Cryptosporidium parvum* and *Cyclospora cayetanensis*. In addition, a number of pathogens have developed significant resistance to antimicrobials: *Neisseria gonorrhoeae*, *Salmonella* and *Shigella* species, *Staphylococcus* species, *Streptococcus pneumoniae*, *Mycobacterium tuberculosis*, bacterial species responsible for healthcare-associated infections, and *Plasmodium falciparum* and *Plasmodium vivax*.

The chapters chosen for this section are excellent reviews of the epidemiology of several of these infections. In addition, they outline the diagnostic approach to each disease, discuss the clinical management of patients, and describe public health interventions to prevent and control the infections.

Bacillus anthracis is a zoonosis that occurs globally but is extremely rare in North America and Europe. *B. anthracis* is easily transmissible, is highly lethal if untreated, and has great potential to cause social disruption, as evidenced by the 2001 bioterrorist attack. For this reason, anthrax is an excellent example of a Category A Select Agent, as designated by the Centers for Disease Control and Prevention.

The influenza A virus is the prototypical reemerging zoonosis and an agent with great pandemic potential. Although influenza A virus has infected mammals and birds for millennia, changes in the viral genetic structure may enable a novel influenza A virus to cause widespread human disease. Each novel virus's pathogenicity is unpredictable, and several influenza A pandemics of varying severity have occurred since the devastating pandemic of 1918.

SARS is caused by a coronavirus (SARS-CoV) that was first recognized during a widespread but brief global outbreak that began in November 2002 and rapidly evaporated in July 2003. Coronaviruses very closely related to SARS-CoV have been isolated from bats and other mammals (notably, those traded in live animal markets as food), and SARS is most likely a zoonotic infection. The rapid, extensive global response to SARS reflects the enormous public health resources required to deal with a rapidly emerging infection.

Worldwide, more than 2 billion people are infected with *M. tuberculosis*. Drug-resistant tuberculosis is emerging as a significant threat to developing regions of the world, places already being devastated by the HIV pandemic. Where resources are most limited, the potential public health burden, morbidity, and mortality from drug-resistant tuberculosis and HIV are staggering.

Finally, two infections exemplify the impact of environmental change on human disease: tularemia and WNV disease. Tularemia is classically associated with rural hunting activities and typically manifests as oculoglandular disease; however, an increasing number of cases of inhalational tularemia have been reported in suburban lawn-mowing residents of Martha's Vineyard, Massachusetts, where infected rabbits were imported by hunting clubs in the 1920s and 1930s. Until 1999, WNV did not occur in the Americas;, however, since the virus's apparent introduction into New York City in 1999, it has spread rapidly across the United States and Canada to become the most common arthropod-borne viral disease in North America.

ADDITIONAL RESOURCES

Jones KE, Patel NG, Levy MA, et al: Global trends in emerging infectious diseases, *Nature* 451:990-993, 2008. *A fascinating report by a multidisciplinary group that evaluates emerging infectious disease "events" over the past several decades. The authors identify factors that could more effectively target resource allocation in the global effort to investigate and monitor emerging infections.*

Lederberg J, Shope RE, Oaks SC Jr: *Emerging infections: microbial threats to health in the United States*, Washington, DC, 1992, Institute of Medicine, National Academy Press. *One of the first publications to outline the concept of "emerging infections," and an excellent introduction to the subject. Table 2-1 (which lists emerging and reemerging pathogens) is of interest in light of which agents subsequently became significant public health problems.*

Smolinski MS, Hamburg MA, Lederberg J: *Microbial threats to health: emergence, detection, and response*, Washington, DC, 2003, Institute of Medicine, National Academies Press. *The IOM revisits its original 1992 report and evaluates the progress of response to emerging infectious diseases.*

Wolfe ND, Dunavan CP, Diamond J: Origins of major human infectious diseases, *Nature* 447:279-283, 2007. *The authors define five stages in a pathogen's transition from animal to human hosts and discuss the factors associated with this transition; they recommend prioritization of future directions in emerging infections research based on these factors.*

Novel Influenza

Jo Hofmann

88

ABSTRACT

Influenza virus is a cosmopolitan ribonucleic acid (RNA) virus that infects birds and mammals worldwide. When an influenza A virus subtype that usually affects birds or animals mutates into a novel strain able to infect people, lack of immunity in human populations may cause widespread and serious influenza or other syndromes. Three worldwide influenza epidemics, or pandemics, of the twentieth century were caused by novel influenza A viruses of avian (bird) origin, including the devastating pandemic of 1918, and a novel influenza A virus of pig (swine) origin, H1N1, caused the first twenty-first–century pandemic. The potential for novel influenza A viruses to infect humans, cause severe disease, and spread efficiently from person to person is a worldwide public health concern. This chapter focuses on novel influenza A virus subtypes with pandemic potential.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Influenza is an RNA orthomyxovirus that occurs worldwide and is capable of infecting a variety of bird and mammal species, including humans. Influenza viruses include types A, B, and C; however, most human influenza is caused by influenza virus types A and B. In temperate regions, influenza types A and B circulate year-round, but illness and outbreaks of influenza peak during the colder months (the "influenza season"). Although the severity and rates of influenza in the United States vary from year to year, the Centers for Disease Control and Prevention (CDC) estimates that in an average year, 5% to 20% of the U.S. population will be infected with influenza, more than 200,000 people are hospitalized with complications of influenza, and about 36,000 people will die from influenza-related causes.

The influenza virus is composed of a lipid envelope, matrix proteins, and a nuclear core that contains the eight-segment single-stranded RNA genome. Embedded in the viral envelope are glycoprotein spikes, known as *hemagglutinin* (H) and *neuraminidase* (N) antigens; these antigens, especially H, are the primary targets for the human antibody response against influenza (Figure 88-1). There are 16 H and 9 N antigens that vary from strain to strain and are used to identify influenza A subtypes—for example, the influenza A virus responsible for the 1918 pandemic ("Spanish flu") was an H1N1 strain, whereas H2N2 was associated with the 1957 pandemic ("Asian flu") and H3N2 with the 1968 pandemic ("Hong Kong flu").

Influenza A is of particular concern because the virus causes infection in a wide variety of birds and mammals and can mutate quickly—two characteristics that provide the virus ample opportunity to mix genomic material. Influenza A viruses change through genetic mutation and sharing of segments of their genome; a small change in a viral strain is known as *genetic drift*, whereas a less frequent but more significant change resulting from genetic reassortment (mixing of genomic material between different influenza viruses infecting the same host) is called *genetic shift*. The reassortment of H antigen genomic segments from avian or animal influenza A and those from influenza viruses in a human host can result in a completely novel virus—one against which human populations have little or no immunity. If a novel influenza A virus is capable of infecting humans, spreading rapidly, and causing severe infection, it has the potential to cause a particularly lethal global epidemic (pandemic), because most of the world's human population will lack antibodies against its unique H antigen (Figure 88-2).

Avian- or animal-origin influenza A viruses that have adapted to humans have been responsible for numerous localized and worldwide outbreaks of influenza. Swine influenza was first described in 1918, and an influenza A (H1N1) virus was first isolated from pigs in 1930. Influenza A H1N1 virus has caused periodic outbreaks in the North American pig population and probably circulated as a relatively stable strain from 1930 through the 1990s. Recent studies of the 2009 pandemic H1N1 viral genome have suggested that since about 1998 the viruses that circulate in North American swine have undergone a series of reassortments that have incorporated genetic segments from avian, swine, and, possibly, human influenza A viruses.

Although the exact origin of the 2009 pandemic H1N1 strain is unknown, one theory is that it arose from Mexican swine populations and infected humans working with pigs early in 2009. The first documented H1N1 infections appeared in the Mexican state of Veracruz in March 2009. Influenza was subsequently identified across Mexico and then reached the United States and Canada via travelers from Mexico. The H1N1 outbreak spread globally, and a pandemic was declared by the World Health Organization (WHO) in June 2009. By April 2010 the pandemic had affected 214 countries and caused nearly 18,000 deaths worldwide. In the United States, the CDC estimates that 59 million people were infected with H1N1 from April 2009 to April 2010, with 265,000 hospitalizations and 12,000 deaths.

Avian-origin influenza A H5N1 virus was first detected in domestic fowl in China in 1996, and 18 human H5N1 infections (six of them fatal) were reported from Hong Kong in 1997. The virus likely circulated in bird populations at low levels for several years but resurfaced in 2003, when H5N1 infections were reported among birds and animals in South Korea, China, Hong Kong, and Thailand. The following year, infected birds were identified in numerous East Asian countries (Cambodia, China, Hong Kong, Indonesia, Japan, Laos, Malaysia, Thailand, and Vietnam), and H5N1 was confirmed to be the cause of an outbreak of severe human respiratory disease in Vietnam. From

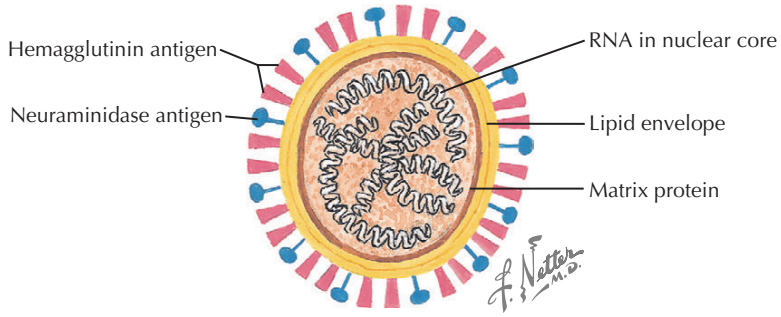


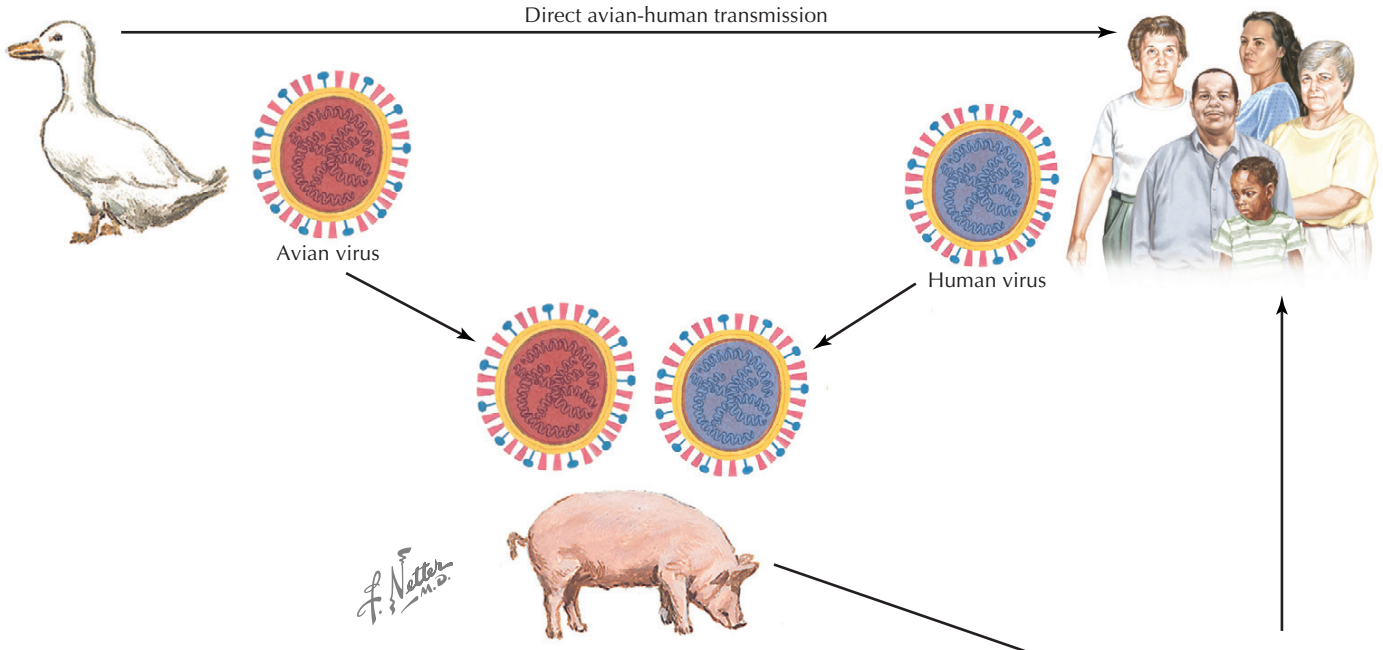
Figure 88-1 Structure of the influenza A virus.

The influenza A virus is composed of a lipid envelope, matrix proteins, and a nuclear core that contains the single-stranded ribonucleic acid (RNA) genome. Embedded in the viral envelope are glycoprotein spikes, known as hemagglutinin and neuraminidase antigens. These antigens are the primary targets for human antibody response against influenza.

2004 through 2010, several strains (or clades) of H5N1 continued to spread among domestic and wild birds, causing avian and human influenza in 61 countries in Asia, Africa, the Mideast, and Europe. By April 2010, 495 laboratory-confirmed human H5N1 infections had been reported from 15 countries in Asia, Eurasia, the Mideast, and Africa; these infections resulted in 292 deaths (case-fatality rate, 59%). The occurrence of human H5N1 infection in an unaffected country (e.g., the United States) would constitute a public health emergency, and human H5N1 virus infection is reportable to most local and state health departments as well as to the CDC and WHO.

RISK FACTORS

Transmission of influenza viruses to humans occurs primarily through inhalation of small, contaminated respiratory droplets or by contact of the virus with mucous membranes such as those of the nasopharynx, oropharynx, or the conjunctivae. Mucosal exposure to the virus can occur by droplets produced when someone with influenza coughs or sneezes, or via a contaminated fomite. In general, all modes of transmission (except fomite) require close contact (i.e., within 6 feet or in an enclosed, small space) with an ill person.



Reassortment of influenza A virus genes can occur when a single host is infected by several viruses, all of different strains. Pigs are likely "mixing vessels" for reassortment because they can be infected with influenza A viruses from birds, humans, and pigs. If an avian virus (red RNA) and a human virus (blue RNA) infect a pig at the same time, reassortment could occur, resulting in a novel influenza virus (red and blue RNA). If a novel virus can infect humans, cause serious illness, and spread from person to person, a pandemic may ensue.

Figure 88-2 Generation of a potentially pandemic strain of influenza A through reassortment.

Before the 2009 pandemic, influenza A viruses of swine origin were reported to cause human disease, but infections were isolated, and human-to-human transmission was limited. A 2007 review of 37 human infections with swine-origin influenza found that 61% of individuals reported contact with pigs (typically work on a farm with swine) before the onset of their illness. Although genetic evidence points to swine origin for the influenza A H1N1 virus responsible for the 2009-2010 pandemic, the virus was not detected in pigs until after recognition of H1N1 influenza in humans. There is no evidence that H1N1 can be transmitted to humans from properly prepared and cooked pork, ham, or other pig products. The modes of human-to-human transmission of the H1N1 virus are presumed to be similar to those of other subtypes of influenza A, with droplet inhalation and contamination of mucous membranes being the primary modes.

According to CDC data, younger age appears to be a risk for infection with H1N1, with the highest rates of disease in persons younger than 25 years of age, especially children younger than 5 years of age. This finding may be related to partial immunity among older individuals, who may have been exposed to an H1N1 virus before 1958. The rate of hospitalization has a bimodal distribution: the highest rates occur among children and young adults younger than 25 years of age and adults 50 to 64 years of age. Many hospitalized patients (24% to 50%) have asthma or chronic obstructive pulmonary disease. With the exception of age over 65 years, the risk factors associated with more severe influenza appear to be the same as those for seasonal disease (Table 88-1). Among hospitalized persons, 30% had at least one underlying medical condition typically associated with complications of seasonal influenza (see Table 88-1). Deaths occur at the highest rate among persons 25 to 64 years of age, in contrast to seasonal influenza, in which more than 90% of fatalities occur among persons 65 years of age or older.

Thus far, essentially all human H5N1 infections have been acquired in areas experiencing the H5N1 epizootic (an epidemic affecting animals or birds), via direct contact with infected domestic birds or their contaminated environments. Human exposure usually occurs during farming, slaughtering, marketing, or preparing poultry in the 14 days before illness onset. Human H5N1 infection has been reported after the consumption of raw poultry products; however, properly cooked poultry does not pose a risk for infection. As of this writing, no infections have been reported in short-term travelers to areas where the avian H5N1 epizootic is occurring.

The median age of patients with H5N1 is 18 years; 90% are 40 years of age or younger, and the case-fatality rate is greatest among persons 10 to 19 years of age. Although human H5N1 infection may occur year-round, more cases are reported during winter months, a pattern also seen in avian H5N1 infections. Despite a widespread epizootic that has affected millions of birds in 61 countries since 1996, fewer than 500 humans have been infected with H5N1, suggesting that bird-to-human transmission is relatively rare. Human-to-human transmission of H5N1 virus is even less frequent; however, clusters of influenza among family members have been reported from several countries, suggesting possible genetic determinants of viral susceptibility and/or spread of the virus by close human contact.

Table 88-1 Risk Factors for Severe or Complicated Infection with 2009 Influenza A Virus (H1N1)

RISK FACTOR	COMMENT
Age <5 years	Risk increases with decreasing age; hospitalization rate highest among children <12 months of age
Age ≥65 years	Highest rate of mortality but lowest risk of infection
Chronic cardiovascular disease	Congestive heart failure, atherosclerosis
Chronic lung disease	Asthma, cystic fibrosis, chronic obstructive pulmonary disease
Chronic renal disease	Dialysis or transplantation
Chronic hepatic disease	Cirrhosis
Metabolic disease	Diabetes
Neurologic disease	Neuromuscular, cognitive, or seizure disorder
Hemoglobinopathies	Sickle cell anemia
Immunosuppression	Human immunodeficiency virus (HIV) infection; malnutrition; receipt of organ transplant, chemotherapy, or long-term corticosteroids
Long-term aspirin therapy in children	Salicylate use in children with influenza is associated with Reye's syndrome and should be avoided
Pregnancy	Increased risk for hospitalization, especially in third trimester
Long-term smoking	Possible independent risk factor
Morbid obesity (body mass index ≥40)	Possible independent risk factor for hospitalization, critical illness, and death

Adapted from Writing Committee of the WHO Consultation on Clinical Aspects of Pandemic (H1N1) 2009 Influenza, Bautista E, Chotpitayasunondh T, et al: Clinical aspects of pandemic 2009 influenza A (H1N1) virus infection, N Engl J Med *362:1708-1719, 2010.*

CLINICAL FEATURES

The incubation period for human infections caused by influenza A H1N1 virus is similar to that of seasonal influenza, about 2 days (range 1.5 to 7 days). Infection with H1N1 displays a wide spectrum of disease: individuals may seroconvert without evidence of illness or may succumb to fulminant viral pneumonia. A mild influenza-like illness is reported in many (8% to 32%) patients, with cough, fever, sore throat, and rhinorrhea. Less than 2% of patients report dyspnea or symptoms of pneumonia. In contrast to seasonal influenza, gastrointestinal symptoms are more common, especially among adults: vomiting and diarrhea are seen in about 24%. The mean duration of illness is 5 days (range 0 to 23 days).

Rates of hospitalization vary by country, age group, and presence of underlying conditions; the highest rates in the United States are seen in children younger than 5 years of age and children and adults with conditions that put them at risk for complications of seasonal influenza (see Table 88-1).

Hospitalized patients typically have viral pneumonia with hypoxemia and acute respiratory distress syndrome (ARDS). Many patients with severe or fatal infections will develop secondary bacterial pneumonia, most commonly caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, or *Staphylococcus aureus*, and rarely myositis, rhabdomyolysis, myocarditis, or neurologic syndromes. Chest radiographs commonly show diffuse, mixed interstitial and alveolar infiltrates, but focal or multifocal consolidation can occur, especially with secondary bacterial infection. Chest computed tomography may show multifocal lower lobe ground-glass opacities, air bronchograms, and alveolar consolidation. Common laboratory findings include leukopenia, lymphocytopenia, and elevated serum aminotransferases, lactate dehydrogenase, creatine kinase, and creatinine.

The incubation period of human H5N1 infection appears to be 2 to 5 days, but incubation as long as 9 days has been reported. The infectious period (duration of shedding of H5N1 virus) is unknown; however, shedding of seasonal influenza virus begins the day before illness onset and lasts 5 to 7 days, with a peak of viral shedding during the first 2 to 3 days of illness. Some patients may shed virus longer, particularly young children and severely immunocompromised persons. Most patients demonstrate fever, dyspnea, cough, and signs of viral pneumonia. The majority have abnormal chest radiographic findings at presentation, including multifocal consolidation or interstitial infiltrates that may be focal or lobar and unilateral or bilateral; serious infections rapidly progress to ARDS, showing bilateral ground-glass opacities. Common laboratory abnormalities include leukopenia, lymphocytopenia, thrombocytopenia, and elevated serum aminotransferases. Atypical symptoms include diarrhea, headache, and, rarely, syndromes in which gastrointestinal or neurologic symptoms predominate. The time from onset to death in fatal infections is about 10 days; death is usually caused by primary viral pneumonia, secondary bacterial pneumonia, and multiorgan dysfunction. Less serious upper respiratory infection without pneumonia has been reported in children; however, serosurveys of poultry workers indicate that asymptomatic infections are uncommon (3% to 10%).

DIAGNOSTIC APPROACH

Unfortunately, both seasonal and novel influenza viruses can cause a nonspecific illness; depending on the geographic region or a patient's recent travel, community-acquired bacterial or viral respiratory infection, dengue, leptospirosis, typhoid, tuberculosis, malaria, or other causes of acute systemic or respiratory illnesses may be included in the differential diagnosis. As the influenza A H1N1 virus continues to circulate, any patient with an influenza-like illness should be suspected of being infected with this virus.

Human H5N1 infections are most likely to be encountered in persons who have had contact with domestic birds in areas currently experiencing the H5N1 avian epizootic. Clinicians in the United States and other unaffected countries should be alert for possible human H5N1 infections in persons who develop a serious febrile respiratory illness of unknown cause within 7 days of leaving an affected area. These patients should receive rapid laboratory diagnosis and be managed with appropriate infection control precautions; public health authorities should be notified of the suspected diagnosis immediately (see the discussion of prevention and control later in this chapter).

Commercial tests for diagnosis of seasonal influenza include rapid antigen detection assays and viral isolation from respiratory tract secretions, serum antibody assays, and polymerase chain reaction (PCR) assays. Rapid antigen detection assays lack the sensitivity and specificity to detect or distinguish influenza A subtypes (e.g., H5 versus H1 or H2), and isolation of novel influenza viruses can take several days and may necessitate use of biosafety practices not available in most laboratories. Paired acute and convalescent serum influenza antibody assays are useful for research purposes but do not provide rapid diagnosis for influenza. Currently the most rapid and accurate method for detection of influenza A H5N1 and H1N1 viruses are real-time reverse transcription–PCR (RT-PCR) assays capable of detecting viral RNA in respiratory secretions.

Every effort should be made to obtain diagnostic specimens as quickly as possible, as viral shedding decreases with time and may be affected by treatment with antiviral medication. Oropharyngeal or nasopharyngeal specimens are generally acceptable for outpatients with suspected H1N1, whereas oropharyngeal specimens are preferred for suspected H5N1. In moderately to severely ill patients with lower respiratory tract disease, specimens obtained by bronchoalveolar lavage or tracheal aspirate have the highest yield, as both viruses replicate most efficiently in the lower respiratory tract.

If a novel influenza virus infection is highly suspected, a negative RT-PCR assay result does not rule out infection, and multiple specimens obtained over several days may further increase the yield. These specimens should be obtained using a plastic or aluminum swab tipped with synthetic material (polyethylene or Dacron), and the swab should be placed directly into sterile viral transport media. The PCR assay can also be performed on tissue samples, but formalin fixation may interfere with viral RNA extraction. A PCR assay that specifically detects influenza A H5 and H1 viruses is available at most state public health laboratories and at the CDC viral diagnostic laboratory in Atlanta.

Note that all diagnostic procedures should be performed using appropriate infection control and personal protective equipment (PPE) (see discussion of prevention and control) for the respective novel viruses. Whereas influenza A H1N1 may be isolated using Biosafety Level 2 protocols, isolation of H5N1 virus requires a Biosafety Level 3 laboratory, as the live virus is considered to be a significant biohazard. This high level of biocontainment is available at a few North American laboratories, including the CDC. For additional information on influenza viral diagnostics or isolation methods, contact your local or state health department.

CLINICAL MANAGEMENT AND DRUG TREATMENT

The presentation of influenza is variable, and the management is determined by the severity of disease, not necessarily by the specific virus subtype. In general, mild illness is limited to symptoms of an upper respiratory infection with possible gastrointestinal involvement. Moderate illness may include signs and symptoms of lower respiratory tract involvement (e.g., dyspnea,

chest pain, or labored breathing), myalgias, headache, and prostration and may be accompanied by exacerbation of underlying medical conditions. Severe illness is characterized by respiratory distress and prolonged or recurrent fever and may progress to respiratory failure, secondary bacterial pneumonia, and multiorgan failure.

Most mild to moderate influenza in healthy individuals can be managed symptomatically; however, patients infected with confirmed or suspected influenza A H5N1 and those with H1N1 who require hospitalization, exhibit signs of progressive infection, or are at risk for complications of influenza should receive empirical antiviral therapy as quickly as possible (see Table 88-1). More than 50% of patients with influenza A H5N1 virus infections develop progressive respiratory failure and require intensive care and mechanical ventilation. Therefore ventilatory support and prevention of nosocomial complications are frequently key elements of clinical management for severe influenza.

Two classes of drugs are effective for the treatment of influenza A virus infections: adamantines (i.e., rimantadine and amantadine) and neuraminidase inhibitors (e.g., zanamivir and oseltamivir). Influenza A viral subtypes and strains may vary in their susceptibility to these antivirals. In the United States, resistance to adamantines or oseltamivir has been found in seasonal influenza A viruses and the H5N1 and H1N1 viruses. Although the adamantine resistance is significant enough to warrant exclusive use of neuraminidase inhibitors for H5N1 and H1N1, oseltamivir resistance appears to be sporadic.

Antiviral treatment should begin as soon as possible after the onset of symptoms, and as mentioned earlier, the neuraminidase inhibitors are the preferred drugs for therapy. Oseltamivir is available in tablet and suspension formulations for oral use and is approved for patients 12 months of age or older; it is available for younger children under a U.S. Food and Drug Administration (FDA) Emergency Use Authorization. Inhaled zanamivir is approved for use in patients older than 6 years of age. In addition, intravenous zanamivir and peramivir are available for life-threatening influenza H1N1 by Emergency Use Authorization for both adults and children who require intravenous therapy or in whom therapy with other neuraminidase inhibitors has failed. The recommended duration of therapy for H1N1 infection is 5 days.

WHO recommends early initiation of treatment with oseltamivir for H5N1 infections, based on the results of several uncontrolled clinical trials that demonstrated a significant survival benefit from prompt oral oseltamivir therapy. However, the optimal dose and duration of oseltamivir therapy for H5N1 are not yet known. WHO suggests that it may be reasonable to use a high dose of oseltamivir (adults, 150 mg orally twice daily) for a 10-day course. Combination therapy with amantadine may be considered in areas where the clades are susceptible, although published data to support this approach are limited to animal models; in addition, the efficacy of zanamivir or peramivir in human influenza A H5N1 virus infections is unknown.

Based on limited data, the use of corticosteroids or other immunomodulators has not demonstrated effectiveness in improving outcome in patients with influenza A virus infections; therefore routine use of these drugs is not recommended.

PROGNOSIS

For infections with influenza A H1N1 virus, a poor prognosis is associated with moderate to severe illness with thrombocytopenia, metabolic acidosis, and elevated creatine kinase, creatinine, and lactate dehydrogenase. Case-fatality rates have been highest in children younger than 5 years of age, pregnant women, and persons 65 years of age and older. Overall estimates of the case-fatality rate for H1N1 are less than 0.5%—significantly lower than that associated with seasonal influenza.

Most patients with influenza A H5N1 virus infections develop serious illness, and many will experience complications including secondary bacterial pneumonia and respiratory, renal, cardiac, and other organ dysfunction. Overall the case-fatality rate for human influenza A H5N1 virus infection is high: 62%, with a range of 33% to 82% (based on case-fatality rates among countries reporting more than 10 cases). The impact of regional variations in viral clade predominance, medical practices, or resources may account for some regional variations in case-fatality rates. As noted previously, early initiation of antiviral therapy with oseltamivir appears to confer a significant survival benefit.

PREVENTION AND CONTROL

Overview

Reducing the burden of human influenza A virus infections relies on preventing disease through immunization and chemoprophylaxis and minimizing the risk of disease transmission with appropriate infection control measures and community interventions (e.g., school closure, cancellation of large crowd events, voluntary isolation [“social distancing”], and quarantine).

For influenza A associated with animals, primary prevention of associated human disease relies on reducing infections among animals and decreasing opportunities for spread of influenza A virus from animals to humans. For example, controlling avian influenza A H5N1 in epizootic countries has focused on the most common sources of human infection in these areas: domestic birds and the poultry industry. Prevention and control recommendations are available for poultry and agriculture workers, wildlife workers, farmers, hunters, travelers to epizootic areas, and others at risk for contact with infected birds. In the United States, where influenza A H5N1 virus infections are expected to arrive among travelers from epizootic regions, it is hoped that early recognition of initial infections by astute clinicians, implementation of effective infection control practices, and rapid notification of public health authorities will facilitate prevention and control of person-to-person spread of H5N1. The use of chemoprophylaxis and vaccines that effectively provide protection against the influenza A H5N1 virus in humans will also play a role.

Infection Control

The characteristics of novel influenza A viruses are highly variable and difficult to predict. Individual strains of influenza A virus may differ in their ability to spread from person-to-person. Estimates of the secondary attack rate for influenza A H1N1 virus range from 4% to 28%, depending on the circumstances;

the basic reproduction number (the mean number of secondary infections transmitted by a single primary case in a susceptible population) ranges from 1.3 to 1.7 according to the setting, similar to or slightly higher than the estimates for seasonal influenza. Nosocomial spread of both seasonal and H1N1 viruses has been reported. Person-to-person transmission of influenza A H5N1 virus appears to be limited, without well-documented nosocomial transmission in the absence of additional disease risk factors. However, the influenza A H5N1 virus has the potential, through reassortment, to acquire the capability to easily spread among humans.

In general, CDC and WHO recommendations for infection control for influenza A focus on immunization of healthcare workers and reducing the risk of respiratory droplet transmission (the presumed primary mode of person-to-person spread of influenza A viruses). Specific recommendations for any individual viral strain may vary, depending on the availability of effective vaccines and the degree of infectivity of a particular novel influenza A virus.

The CDC emphasizes the following fundamental measures for the prevention of influenza transmission in healthcare settings: promoting and administering seasonal influenza vaccine, minimizing potential influenza A exposures in healthcare settings, managing healthcare workers with suspected or confirmed influenza appropriately, and using effective infection control measures. Due to the rapidly changing nature of influenza epidemiology, the details of specific infection control recommendations are beyond the scope of this chapter; however, comprehensive and updated recommendations for prevention and control of influenza are available from the many agencies (see Box 88-1).

Public Health Measures

One aspect of disease prevention and control that may be overlooked is the importance of reporting suspected communicable diseases to public health authorities. In the case of novel influenza A viruses, which may cause widespread, serious illness, it is extremely important that clinicians report any suspected novel influenza A virus infections to their local or state health department. Public health personnel can assist in the evaluation of the patient and facilitate diagnostic and confirmatory laboratory testing. They can also assist in the identification of any persons with whom the patient may have been in contact during the infectious period and can provide indicated chemoprophylaxis for influenza for those contacts. In addition, early in a looming pandemic, voluntary isolation of sick patients and quarantine of exposed contacts, combined with the suspension of certain social activities, may decrease the spread of disease. A coordinated effort by local and national public health authorities will be needed to effectively limit the spread of a novel influenza A virus in the United States.

Box 88-1 Infection Control Recommendations for Influenza A

CDC: Prevention Strategies for Seasonal Influenza in Healthcare Settings http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm

WHO: Infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses http://www.who.int/csr/resources/publications/cp150_2009_1612_ipc_interim_guidance_h1n1.pdf

WHO: Infection control recommendations for avian influenza in health care facilities http://www.who.int/csr/disease/avian_influenza/guidelines/EPR_AM1_E5.pdf

Chemoprophylaxis

Events of previous pandemics and mathematical modeling studies suggest that early, targeted mass antiviral chemoprophylaxis, combined with interventions to limit social interactions, may arrest or delay the onset of an influenza pandemic. Neuraminidase inhibitors are the preferred agents for chemoprophylaxis for influenza A H1N1 or H5N1 virus infections. WHO and the CDC have developed plans that address the priorities for distribution and use of stockpiles of these drugs; these priorities may differ depending on the severity of the pandemic and supplies of the drugs. The indiscriminate use of chemoprophylaxis during a pandemic may be problematic as supplies dwindle or as the pandemic virus develops resistance to available chemoprophylaxis agents.

Immunization

The H1 and N1 antigens in the viral envelope characterize the influenza A virus and are used to determine the antigenic composition of influenza vaccines. In 2007, the FDA licensed the first human monovalent H5N1 vaccine in the United States for persons 18 through 64 years of age, and the vaccine is part of the National Pharmaceutical Stockpile. After the development of a safe and effective monovalent vaccine for H1N1 in 2009, the CDC Advisory Committee on Immunization Practices recommended that the 2009 pandemic strain be included in the 2010-2011 trivalent seasonal influenza vaccine; they also expanded their recommendations for influenza vaccination to include all persons 6 months of age and older. However, existing techniques for influenza vaccine development are time- and work-intensive and impractical for the rapid, large-scale production needed to supply sufficient quantities of vaccine in the event of a severe pandemic. Future directions in influenza vaccine research will focus on production methods, modes of delivery, adjuvants, and how changes in influenza antigens may affect vaccine immunogenicity.

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Severe Acute Respiratory Syndrome (SARS)

Eileen Schneider

89

ABSTRACT

Severe acute respiratory syndrome (SARS) first appeared in November 2002 and ultimately resulted in 8096 probable human infections and 774 deaths worldwide. By July 2003, the global outbreak was declared over. A new coronavirus, SARS-associated coronavirus (SARS-CoV), was identified as the causative agent; this virus appeared to have a zoonotic origin, as genetically similar coronaviruses have been identified in several animal species. The global response to the outbreak was extensive. Within a short period, the pathogen had been identified, new diagnostic tests were developed, surveillance systems were created, infection control and prevention measures were instituted, and transmission among humans stopped. It is unclear if and when person-to-person SARS-CoV transmission will reappear. However, procedures have been established by public health organizations, including the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC), to help guide diagnosis, reporting, surveillance, and prevention.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Background

In 2002 and 2003, a previously unknown infectious agent caused a widespread, global outbreak of life-threatening respiratory infections. The illness was called *severe acute respiratory syndrome (SARS)* and was one of the first emerging infections in recent history to test the global public health response. Strategies used to prevent and control SARS helped to shape future public health response to infectious disease emergencies such as the 2009 H1N1 influenza pandemic. SARS emerged in Guangdong Province, China, in mid-November 2002 and was first officially reported to WHO in February 2003. In mid-March 2003, WHO issued an alert calling attention to several outbreaks of severe atypical pneumonia in Hong Kong, Hanoi, and Singapore. Many of the initial SARS infections were traced to a guest staying at a Hong Kong hotel, and global spread occurred quickly with multiple outbreaks reported in China, Southeast Asia, Europe, and North America. By mid-April 2003, the causative agent was identified as a new coronavirus, SARS-CoV. An unprecedented global outbreak response (including the implementation of surveillance systems, epidemiologic studies, appropriate infection control measures, and development of laboratory diagnostics) was swiftly initiated. In July 2003, WHO announced that the SARS outbreak was over. Although a few laboratory-associated SARS infections were reported in Asia after the outbreak was declared over, no infections have been reported worldwide since early 2004. Almost all persons with SARS were reported from China, Hong Kong, Taiwan, Singapore, or Toronto, but overall, as of December 2003, WHO had received reports of SARS from 29 countries and regions: 8096 persons with probable SARS, resulting in 774 deaths, a case-fatality rate of 9.6%. In the United States, eight infections were documented by laboratory testing, and an additional 19 probable infections were reported. The syndrome arose and vanished within several months, and it is unclear when or if SARS will return.

Coronaviruses

Coronaviruses are enveloped, single-stranded positive strand ribonucleic acid (RNA) viruses that infect a wide spectrum of mammals and birds. There are three coronavirus groups: groups I and II affect mammals and group III affects birds. In humans, coronaviruses are primarily associated with upper respiratory infections. During the 2002-2003 SARS outbreak, several strains of a coronavirus unrelated to previously described coronaviruses were identified and isolated from clinical samples, including respiratory secretions, urine, and autopsy tissues. This new virus was identified as a novel group II coronavirus and named *SARS-associated coronavirus;* of all coronaviruses, it is responsible for causing the most severe human disease.

Bats have been identified as natural reservoirs of SARS-CoV–like viruses and are most likely the natural reservoirs for SARS-CoV; therefore SARS is a zoonosis. Studies of animal ecology and virus evolution have revealed that SARS-CoV–like viruses are also present in other animals, including those commonly traded at live animal markets in southern China (e.g., masked palm civet, raccoon dog, red fox). At this time, it is unclear if these animals are susceptible hosts or carriers of SARS-CoV, but recent research indicates that the masked palm civet probably served as intermediate host between bats and humans during the 2002-2003 outbreak. Sequence analyses of SARS-CoV have shown that SARS-CoV–like viruses that infect masked palm civets are very similar (genome identity >99.6%) to the SARS-CoV that infected humans in the 2002-2003 SARS outbreak, suggesting that the virus had only recently circulated in the masked palm civet. The increased prevalence of SARS-CoV immunoglobulin G (IgG) antibodies among animal traders compared with a control group (13% versus 1% to 3%) further supports this theory. In addition, the absence of SARS-CoV antibodies in the general population without clinical evidence of SARS suggests that SARS-CoV did not widely circulate before the 2002-2003 SARS outbreak.

Transmission

The estimated incubation period for SARS is 2 to 10 days (median 5 to 6 days). The virus is detected at low levels in

respiratory secretions during the initial days after the onset of illness, and peak viral levels occur during the second week of illness (e.g., 10 days). This viral replication phase is followed by the immune hyperreactive phase, which occurs when disease severity increases and viral load decreases. Disease progression is variable, and not all patients progress to the final pulmonary destruction phase.

The primary route of SARS-CoV transmission is via the respiratory tract; during close contact with an infected patient, respiratory droplets may come into contact with mucous membranes either directly or indirectly through contaminated fomites. Studies have determined that SARS-CoV can remain stable on environmental surfaces for several days, although the virus can be easily inactivated by disinfectants. The virus has been isolated from respiratory secretions, saliva, tears, urine, and stool. Viral shedding generally does not persist beyond 4 weeks, except in stool, in which the virus can be detected by reverse transcription-polymerase chain reaction (RT-PCR) for longer than a month. Isolation of the virus more than a month after the onset of illness is rare. Virus detection in nasopharyngeal specimens using quantitative RT-PCR found that the level typically peaks during the second week of illness, often when severely ill patients are seeking medical care. As patients improve clinically and the viral load decreases, transmission of the virus also decreases. Unlike other respiratory viral infections, such as influenza, transmission before symptom onset has not been reported. During the recent SARS outbreak, transmission occurred primarily in hospitals, less so within households, and to an even lesser extent within communities.

RISK FACTORS

In the 2002-2003 outbreak, the primary risk factor was contact with a person who was infected with SARS-CoV. Twenty-one percent of all reported SARS-CoV infections occurred among healthcare workers. Nosocomial transmission of SARS-CoV was common early in the outbreak but subsequently decreased significantly as a result of early diagnosis and reinforcement of infection control practices. Nosocomial spread is theorized to occur via aerosolization during patient procedures, such as intubation and bronchoscopy. Transmission has also been documented on an airplane, in an apartment complex (probably secondary to faulty plumbing and aerosolization of fecal matter), and among laboratory workers handling SARS-CoV. Transmission of the virus has not been not reported via food-borne or waterborne sources, nor from an infected patient whose fever had resolved more than 14 days previously.

As seen with other infectious diseases, environmental and host factors influence the risk of transmission. Although the virus was initially thought to be highly infectious, the rate of secondary transmission of SARS-CoV is estimated to be low to moderate. Transmission modeling studies have estimated that each patient will infect an average of three persons. However, some SARS-infected patients designated as "superspreaders" have been documented to have very high secondary transmission rates (infecting an average of 36 contacts [range 11 to 74 contacts]), a phenomenon not unique to SARS. Transmission of SARS-CoV by superspreaders primarily occurred in hospital settings and was associated with a greater number of close contacts, delayed diagnosis, older age, more severe illness, and poor infection control practices.

CLINICAL FEATURES

Severity of disease among SARS patients varies from asymptomatic infection to fatal acute respiratory distress syndrome (ARDS) (Figure 89-1). Seroprevalence surveys have documented asymptomatic infection, especially among animal traders in Guangdong, China, but overall, asymptomatic or mild disease is relatively uncommon (<1%).

SARS affects persons of all ages; however, most infections occur among adults (median age approximately 42 to 57 years). Infections among children, especially those younger than 12 years of age, are uncommon. Compared with adults, the disease is considerably less severe among children, and the outcome is much more favorable. Infections during pregnancy have been documented, with an increased risk of spontaneous abortion, preterm labor, severe pulmonary disease, and death. No reports of perinatal transmission have been noted.

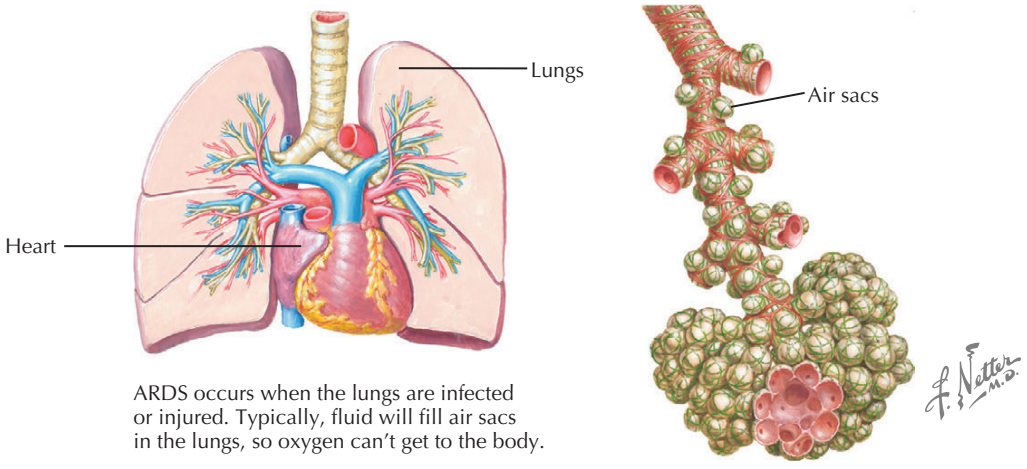
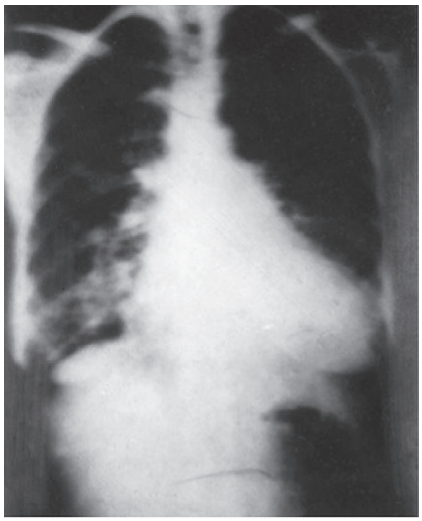


Figure 89-1 Mechanism of acute respiratory distress syndrome.

Early SARS symptoms are similar to other respiratory infections and include headache, chills, myalgia, and fever, typically seen in the first week following onset. This is followed by cough and shortness of breath, which typically appear in the second week



Chest radiographs can provide valuable information. Typical early findings include a ground glass appearance and focal opacities or consolidations in the peripheral lower lung fields, which often progress to bilateral patchy consolidations

Figure 89-2 Symptoms of severe acute respiratory syndrome.

The initial symptoms of SARS are nonspecific and consistent with an influenza-like illness. A prodrome that includes fever, headache, chills, rigors, malaise, and myalgias occurs approximately 1 to 2 days after exposure (Figure 89-2). Nearly all patients report fever (with temperatures frequently exceeding 101° F), which typically precedes other prodromal symptoms but can also occur after the prodrome. The elderly and those with a history of chronic comorbid conditions, such as diabetes mellitus or chronic renal failure, may have atypical presentations (e.g., lack of fever).

Although SARS primarily affects the pulmonary system, respiratory symptoms (typically including nonproductive cough and shortness of breath) appear more often during the second week of illness. In one reported patient series, gastrointestinal symptoms, primarily diarrhea, were prominent (73%), with high-volume diarrhea occurring in the second week of illness. In a separate report, diarrhea, nausea, and vomiting were less common (<25%). Mucus and blood in stool are uncommon, and the diarrhea is often self-limiting. Lymphadenopathy, rhinorrhea, sore throat, rash, and purpura are unusual.

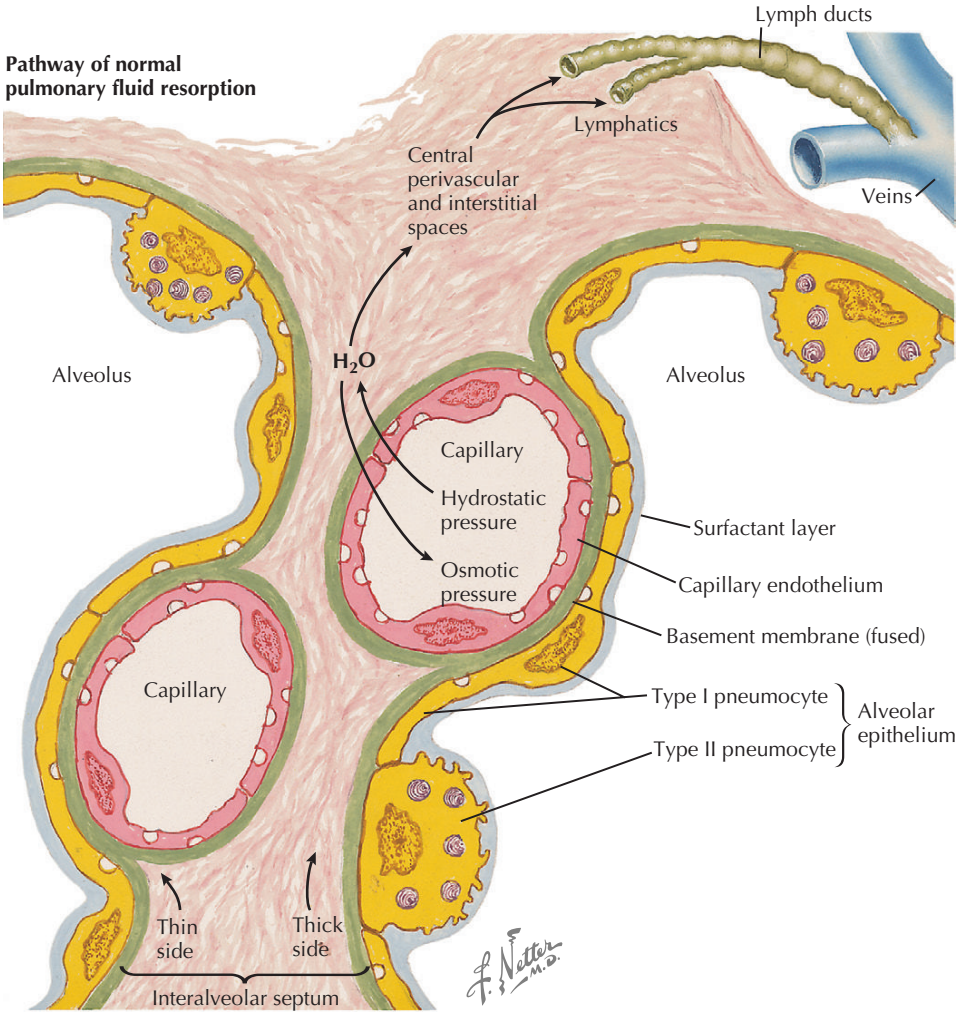
In persons with SARS, inspiratory crackles at the lung bases and, less commonly, wheezing may be noted on auscultatory examination. Initially a consistent finding is the paucity of auscultatory findings relative to the degree of abnormalities displayed on chest radiographs. By the second week of illness, clinical deterioration may occur, with pneumonia and hypoxemia that necessitate hospitalization. During the 2002-2003 outbreak, respiratory failure and ARDS were the most common reasons for admission to an intensive care unit (ICU). In several studies, approximately 20% to 30% of patients hospitalized with SARS were admitted to an ICU; about 75% of ICU patients required mechanical ventilation.

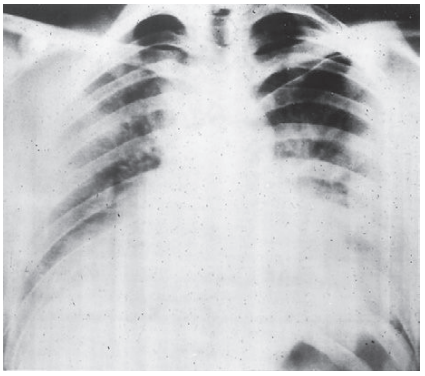
Initial chest radiographic findings may be unremarkable or indistinguishable from those of other causes of infectious pneumonia in up to 30% of patients. However, serial chest radiographs and high-resolution computed tomography (CT) scans may offer valuable information during evaluation of a patient with suspected SARS, as abnormalities appear in a large proportion of patients by day 7 to 10 of illness. Typical chest radiographs have a ground glass appearance with focal opacities or consolidation in the peripheral lower lung fields; these focal findings often progress to bilateral patchy consolidation (Figure 89-2). Peripheral lung involvement was a very common finding in most case studies of the 2002-2003 outbreak, and pulmonary cavitation, hilar lymphadenopathy, nodular infiltrates, and pleural effusion were unusual (Figure 89-3).

Evidence of extrapulmonary dissemination of SARS-CoV can be found by laboratory and pathologic diagnostic methods. The virus has been detected in several extrapulmonary organs, including the gastrointestinal tract, kidneys, liver, and spleen. Studies to improve our understanding of SARS pathogenesis and immune response are ongoing.

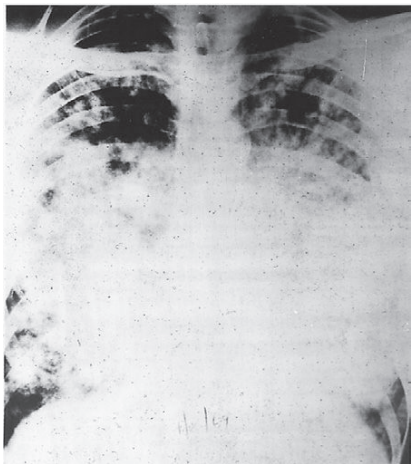
LABORATORY FINDINGS

Common laboratory findings in patients with SARS include moderate lymphocytopenia with a low to normal white blood cell count (primarily caused by a decrease in T-cell lineages); mild thrombocytopenia; increased serum lactate dehydrogenase (i.e., more than three to five times the upper limit of normal); and elevated serum hepatic transaminases. Decreased CD4 and CD8 T-cell counts can be significant: up to 30% of infected patients have a CD4 T-cell count of <200 cells/mm^3. Elevated serum creatinine phosphokinase (noncardiac) and electrolyte





Early pulmonary edema. Hazy opacification chiefly in central lung areas (butterfly pattern)



Advanced pulmonary edema. Patchy consolidation distributed chiefly in lower parts of both lungs

Figure 89-3 SARS is a cause of noncardiac pulmonary edema. The infection causes the lung's capillaries to leak more fluid than normal into the air sacs (alveoli).

abnormalities, including hypocalcemia, hypokalemia, hypomagnesemia, and hypophosphatemia, are also commonly seen in SARS.

DIAGNOSTIC APPROACH

It is important to note that since 2004 there has been a worldwide absence of human-to-human transmission of SARS-CoV. As a result, resources for the laboratory diagnosis of SARS infection are limited, and testing is reserved for situations in which a high level of suspicion exists for possible SARS-CoV infection. In the United States, the CDC has developed guidelines for the clinical and public health management of SARS, including specific criteria and algorithms for laboratory testing (see the section on prevention and control for a detailed explanation).

In response to the SARS outbreak, laboratory diagnostics were rapidly developed to detect the newly identified coronavirus. Methods of choice currently include detection of SARS-CoV–specific antibodies in serum using enzyme immunoassays (EIAs) or immunofluorescence assays (IFAs) and detection of SARS-CoV RNA in clinical specimens using real-time RT-PCR. Other diagnostic methods, such as virus isolation, electron microscopy, and immunohistology, are also available but are not routinely used because of specific technologic requirements and safety issues (e.g., virus isolation requires a Biosafety Level 3 laboratory).

The virus that causes SARS can be detected from a number of clinical specimens including respiratory fluids and tissue (i.e., nasopharyngeal and oropharyngeal [NP/OP] swab, nasal aspirate, sputum, bronchoalveolar lavage [BAL] specimen or lung tissue) and from serum, stool, urine, and hepatic tissue. To optimize laboratory diagnosis, the type of specimen obtained and the timing of specimen collection relative to illness onset are important. In the 2002-2003 SARS outbreak, rapid detection of SARS was initially hampered by several factors: diagnostic assays had to be developed, high-level biosafety was required for working with the live virus, and low viral load in clinical specimens and the time required by a host to mount antibody limited the sensitivity of assays to detect early SARS-CoV infection.

During the outbreak, studies of the first-generation quantitative RT-PCR assay for detection of virus levels in respiratory specimens found that SARS-CoV RNA was detected in less than

50% of specimens obtained in the first 4 to 5 days of illness and that viral load peaked by about 10 to 12 days before gradually declining. Additional studies confirmed that after 7 to 10 days, RNA was detectable by RT-PCR in the majority of both respiratory and stool specimens. Second generation RT-PCR assays, developed after the outbreak ended, can detect SARS-CoV RNA in more than 80% of respiratory specimens within the first 3 days of symptom onset. When upper respiratory tract specimens are negative, sputum and BAL specimens may be useful for diagnosis, as viral loads may be greater in the lower respiratory tract. In stool, RT-PCR assays are able to detect SARS-CoV RNA for more than 4 weeks after illness onset; however, virus has not been isolated from stool after the third week.

Serologic testing is a useful tool for diagnosis because it permits detection of anti-SARS antibodies, as well as helping to confirm or exclude a SARS diagnosis and better characterize the SARS immune response. Host immune response includes the development of IgG and IgM SARS-CoV–specific antibodies as well as anti–SARS-CoV neutralizing antibodies. Longitudinal studies conducted after the 2002-2003 outbreak using IFA and/or EIA on specimens obtained from outbreak-related SARS patients showed that in the first 7 days of illness, only about 15% had detectable anti–SARS-CoV IgG or IgM. However, by the second week of illness, IgG was detected in approximately 40% to 50% of patients and IgM in about 40% to 65%. More than 90% of patients had detectable anti–SARS-CoV IgG by day 28 after illness onset. This milestone is important because an undetectable anti-SARS antibody in a serum specimen obtained more than 28 days after onset of illness is one of three exclusion criteria recommended by the CDC when defining an infection as a probable SARS case. A 3-year study that followed the progression of antibody titers in 56 patients with SARS found that levels of anti–SARS-CoV IgG peaked 4 months after onset of illness, then decreased; 3 years after infection, IgG was still detectable in 26% of patients. Second-generation immunoassays are being developed, some focusing on recombinant SARS-CoV nucleoprotein antigens. However, cross-reactive antigenic epitopes between SARS-CoV and other human coronaviruses (some of which are newly discovered and also cause respiratory illness) may complicate serologic test results and merit continued investigation.

A diagnosis of SARS should not be based on a single reactive laboratory test. Any reactive result should be confirmed by a laboratory that participates in the WHO SARS International Reference and Verification Laboratory Network. Because of apparent lack of circulating SARS-CoV in humans, a single reactive serologic test may support a diagnosis, but the positive predictive value of serologic testing is low, and confirmation by an experienced laboratory is still recommended. Test results that suggest a diagnosis of SARS must be evaluated in the context of clinical findings, exposure risk factors, and epidemiologic data. The positive predictive value of a laboratory diagnosis increases with the collection and testing of multiple and different specimen types.

CLINICAL MANAGEMENT AND DRUG TREATMENT

The clinical management of SARS primarily relies on providing supportive care for the acute respiratory illness and its complications and preventing and treating secondary bacterial infections. During the 2002-2003 SARS outbreak, ribavirin and corticosteroids were used with little apparent success. The effectiveness of other therapeutic options, such as interferon, intravenous immunoglobulin, and antiviral drugs is poorly understood. Several laboratories worldwide are conducting research on SARS-CoV to improve our understanding of the virus and its pathogenesis, which may lead to possible future treatment options. Currently no effective vaccine exists.

PROGNOSIS

Approximately 30% of patients with SARS clinically improve within a week or two of the onset of their illness, whereas 70% develop persistent fever and worsening respiratory symptoms and may require hospitalization; some will be admitted to an ICU. The length of hospital stays has varied, but several studies have reported a median length of stay of approximately 2 weeks.

In hospitalized patients, common complications of SARS include cardiovascular abnormalities (e.g., hypotension, tachycardia) and hepatic dysfunction. Deep vein thrombosis (DVT) has been less common, but in one Singapore case series 30% of hospitalized patients had evidence of a DVT. Disseminated intravascular coagulation, acute renal failure, and neurologic and other complications are uncommon.

In the 2002-2003 SARS outbreak, poor outcome was associated with increasing age and the presence of comorbid conditions (e.g., diabetes mellitus, hypertension, cardiovascular disease, chronic renal disease). Overall crude mortality rates ranged from about 4% to 15%, with age-specific mortality rates highest among older adults. Mortality rates were higher in those aged 60 years or older (43%) as compared with those younger than 60 years of age (13%). Most SARS patients who survive have a complete, sometimes prolonged recovery, but some severely ill patients have reported long-term decreased pulmonary function.

PREVENTION AND CONTROL

It is unclear when or if the world will experience another SARS epidemic. In the absence of person-to-person SARS-CoV transmission worldwide, recommendations have been published by several public health organizations, including WHO and the CDC. In the United States, the CDC has developed several documents that provide guidance on surveillance, clinical and laboratory evaluation, and reporting of suspected SARS infections (www.cdc.gov/ncidod/sars). Being familiar with the clinical features of SARS-CoV disease, assessing travel history and exposure risk, and recognizing unusual clusters of unexplained pneumonia can help maximize early detection. In the absence of person-to-person transmission, public health and healthcare personnel should be aware of specific settings that should raise suspicion for SARS-CoV infection (www.cdc.gov/ncidod/sars/absenceofsars.htm). These situations include persons who are hospitalized for radiographically confirmed pneumonia or ARDS without an identifiable cause and who have one of the following three risk factors in the 10 days before the onset of illness:

- Travel to mainland China, Hong Kong, or Taiwan, or close contact with an ill person with a history of recent travel to one of these areas
- Employment in an occupation associated with a risk for SARS-CoV exposure (e.g., healthcare worker, worker in a laboratory that contains SARS-CoV)
- Illness in association with a cluster of cases of atypical pneumonia without an alternative diagnosis

Clinicians evaluating patients who fit one of these three criteria should implement appropriate infection control measures, contact the local or state health department, and continue with a diagnostic evaluation. This evaluation should include testing for other respiratory pathogens (e.g., influenza, respiratory syncytial virus, *Streptococcus pneumoniae*, *Legionella* species). If no alternative diagnosis has been made after 72 hours or if a high index of suspicion for SARS exists, the clinician and health department should consider SARS-CoV testing and contact the CDC for consultation. Currently, laboratory-acquired SARS infection remains a possible scenario but a remote one, as adherence to strict biosafety and laboratory policies has significantly reduced this risk. The CDC is available for consultation and testing and has made guidelines for laboratory personnel working with SARS-CoV available (www.cdc.gov/ncidod/sars/guidance/f/pdf/app6.pdf).

Globally, SARS is one of a select few conditions that has been designated as immediately reportable by International Health Regulations. The local or state health department should be promptly notified if a suspected SARS case is identified. Prompt case detection, implementation of infection control measures including patient isolation and standard and droplet precautions (www.cdc.gov/ncidod/sars/guidance/i/pdf/i.pdf), and contact tracing have been shown to reduce transmission. Additional infection control measures should be instituted depending on the setting (e.g., healthcare, home, community) (www.cdc.gov/ncidod/sars/guidance/i/pdf/i.pdf).

One critical lesson learned from the 2002-2003 SARS outbreak is the apparent need for prompt collaboration and open communication among local, national, and international health agencies. Early diagnosis, timely reporting, implementation of infection control measures, and continued research, including research regarding treatment and vaccine development, will help identify and control possible future SARS outbreaks.

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Multidrug-Resistant Tuberculosis

Christopher Edward Spitters

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ABSTRACT

The World Health Organization (WHO) estimates that more than 2 billion people are infected with *Mycobacterium tuberculosis* worldwide; most of these infections occur in low-income areas where tuberculosis is a leading cause of death among persons affected by the human immunodeficiency virus (HIV) pandemic. The global control of tuberculosis is a major public health challenge, and the emergence of drug-resistant strains of *M. tuberculosis* (particularly strains resistant to multiple antituberculosis drugs) presents a significant threat to efforts to address this challenge. Although resources for the diagnosis and effective treatment of multidrug-resistant and extensively drug-resistant *M. tuberculosis* are available in most high resource settings, these resources are lacking in regions where the burden of tuberculosis is the greatest. Advances in diagnostics and therapeutics, effective implementation of disease surveillance and control programs, and general strengthening of health care systems are needed to control the global threat of multidrug-resistant tuberculosis.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Tuberculosis occurs in virtually every corner of the globe. WHO has estimated that more than 2 billion people worldwide have tuberculosis, and most cases occur in resource-poor areas where tuberculosis is a leading cause of death among persons affected by the HIV pandemic (Figures 90-1 and 90-2). The global prevalence of drug-resistant strains of tuberculosis varies greatly, but overall about 5% of all infections are resistant to multiple drugs, with approximately 500,000 new cases worldwide each year (Figure 90-3). In the United States, where approximately 15,000 cases of tuberculosis are reported each year, about 10% to 15% are isoniazid resistant, 1% to 2% are resistant to multiple drugs, and 10% of multidrug-resistant infections are extensively drug resistant (i.e., 10 to 20 cases per year).

RISK FACTORS

Tuberculosis in humans is caused by a closely related group of acid-fast bacilli that includes *M. tuberculosis*, *Mycobacterium bovis*, *M. bovis BCG*, *Mycobacterium africanum*, *Mycobacterium microti*, *Mycobacterium canetti*, *and Mycobacterium pinipedii*. *M. tuberculosis* and *M. bovis* are the most common causes of human tuberculosis worldwide. Mycobacteria are typically transmitted through the air by respiratory particles 1 to 5 μm in diameter (droplet nuclei); these particles are produced when a person with active, infectious respiratory (including laryngeal) tuberculosis coughs, sneezes, speaks, or sings. Infection occurs when the particles are inhaled; the mycobacteria are ingested by macrophages and in most cases are killed or sequestered in granulomata. Some organisms, though, traverse the pulmonary lymphatics to the right side of the heart, where they can disseminate via the bloodstream to the lungs and other organs. Ingestion of infectious organisms, particularly of *M. bovis* via unpasteurized dairy products, accounts for a small proportion of cases.

In the vast majority of cases (approximately 90% to 95%), primary tuberculosis infection is controlled by the immune system, and no disease occurs either at the time of infection or later in life. In 5% to 10% of infections, however, either the primary infection progresses or latent infection reactivates to produce active disease either in the lungs or in extrapulmonary sites. The risk of developing tuberculosis disease after infection is increased by immunosupression (e.g., HIV, tumor necrosis factor-α blockers, certain malignancies), diabetes mellitus, tobacco smoking, end-stage renal disease, silicosis, gastrectomy, and various forms of malnutrition and malabsorption.

In the United States, tuberculosis is most commonly caused by *M. tuberculosis*, and active disease is initially treated with a combination of four different first-line agents (i.e., isoniazid, rifampin, pyrazinamide, and ethambutol or streptomycin) to avoid the development of resistance to any single drug (Table 90-1). Drug resistance occurs when isolates of *M. tuberculosis* are less susceptible to antituberculosis agents, a spontaneous event driven by genomic mutations that affect the cellular targets of these drugs (Table 90-2). Resistance to rifampin (which inhibits ribonucleic acid [RNA] polymerase) is conferred by a highly conserved mutation in the gene for RNA polymerase, whereas isoniazid resistance can be caused by mutations at multiple sites in the genome.

Drug resistance can emerge when treatment is incorrectly prescribed or administered or when the drugs fail to reach the affected site in adequate concentrations. The average frequency of a drug-resistance mutation is about 1 in 10^6 to 10^8 mycobacteria; therefore the greater the mycobacterial burden, the greater the opportunity for development of resistance mutations (see Table 90-2).

Typical pulmonary tuberculosis with a cavitary lesion results in a total mycobacterial burden of about 10^9 organisms; therefore a patient with cavitary disease may harbor 10 to 1000 organisms resistant to a given drug (Figure 90-4). Consequently, patients with visible acid-fast bacilli from a sputum specimen and those with cavitary lesions on chest radiography carry the highest risk for the emergence of drug resistance if treated inappropriately or if adherence is poor. If adherence to initial therapy was good and a relapse of drug susceptible tuberculosis occurs, the mycobacteria typically remain fully susceptible; however, relapses of previously drug-resistant disease often show development of further resistance to previously effective drugs. If an individual with fully susceptible tuberculosis receives isoniazid

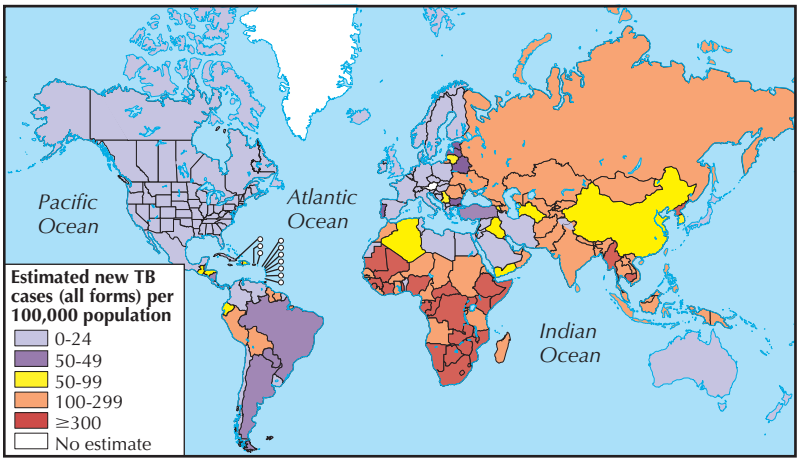


Figure 90-1 Estimated new tuberculosis infections per 100,000 population, 2008. *(From World Health Organization [WHO]:* Global tuberculosis control: a short update to the 2009 report, *Geneva, Switzerland, 2009, WHO Press.)*

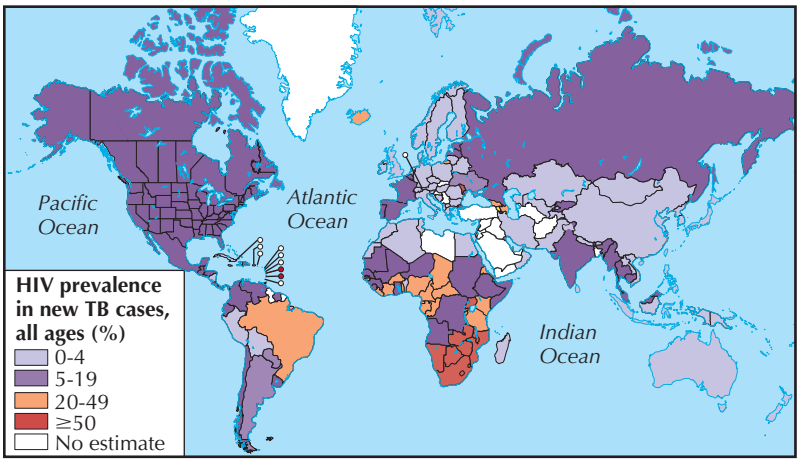
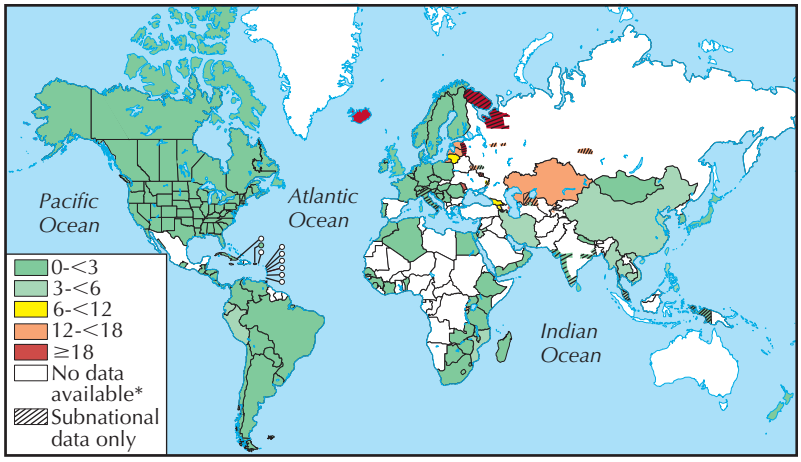


Figure 90-2 Estimated HIV prevalence in new tuberculosis infections, 2008. *(From World Health Organization [WHO]:* Global tuberculosis control: a short update to the 2009 report, *Geneva, Switzerland, 2009, WHO Press.)*



*Australia, Democratic Republic of the Congo, Fiji, Guam, New Caledonia, Solomon Islands and Qatar reported data on combined new and previously treated cases.

Figure 90-3 Proportion of multidrug-resistant tuberculosis among new tuberculosis infections, 1994-2009. *(From World Health Organization [WHO]:* Multidrug and extensively drug-resistant TB [M/XDR-TB]: 2010 global report on surveillance and response, *Geneva, Switzerland, 2010, WHO Press.)*

Table 90-1 First-line Antimycobacterial Agents

	Dosing			
	Adult		Pediatric	
AGENT	DAILY (MAXIMUM DOSE)	INTERMITTENT (MAXIMUM DOSE)	DAILY (MAXIMUM DOSE)	INTERMITTENT (MAXIMUM DOSE)
Isoniazid	5 mg/kg (300 mg)	15 mg/kg BIW or TIW (900 mg)	10-20 mg/kg (300 mg)	20-40 mg/kg (900 mg)
Rifampin	10 mg/kg (600 mg)	10 mg/kg BIW or TIW (900 mg)	10 mg/kg (600 mg)	10 mg/kg BIW or TIW (900 mg)
Pyrazinamide	15-30 mg/kg (2000 mg)	50 mg/kg BIW (4000 mg) or 30 mg/kg TIW (3000 mg)	15-30 mg/kg (2000 mg)	50 mg/kg BIW (4000 mg) or 30 mg/kg TIW (3000 mg)
Ethambutol	15-25 mg/kg (1600 mg)	50 mg/kg BIW (4000 mg) or 30 mg/kg TIW (3000 mg)	15-30 mg/kg (2000 mg)	50 mg/kg BIW (4000 mg) or 30 mg/kg TIW (3000 mg)
Streptomycin	12-15 mg/kg (1 g)*	12-15 mg/kg (1 g)*	12-15 mg/kg (1 g)	12-15 mg/kg (1 g)

*Consider lowering maximum dose in patients >65 years of age to 750 mg
BIW, Twice weekly; *TIW,* three times weekly.

Table 90-2 Mechanism of Action and Frequency of Resistance Mutations in *Mycobacterium tuberculosis*

AGENT	TARGET	COMMON RESISTANCE MUTATIONS	FREQUENCY
Isoniazid	Mycolic acid synthesis	*katG* *inhA* Others	10^{-6}
Rifamycins	RNA-dependent RNA polymerase	*rpoB*	10^{-8}
Pyrazinamide	Mycolic acid synthesis	*pncA*	10^{-6}
Ethambutol	Mycolic acid synthesis	*embB*	10^{-5}
Streptomycin	Ribosome; protein synthesis	*rpsL* *rrs*	10^{-6}
Amikacin and kanamycin	Ribosome; protein synthesis	*Rrs*	
Ethionamide	Mycolic acid synthesis	*inhA*	
Fluoroquinolones	DNA-gyrase	*gyrA*	

Adapted from Centers for Disease Control and Prevention (CDC): Tuberculosis training module 3. Drug resistance.

monotherapy, mycobacteria expressing isoniazid-resistant mutations proliferate; among those isoniazid-resistant mutants, 1 in 10^6 to 10^8 will also be resistant to rifampin. If such a patient is subsequently treated with rifampin alone, then mutants resistant to isoniazid and rifampin will be selected, generating multidrug-resistant mycobacteria.

Multidrug resistance is defined as resistance to at least isoniazid and rifampin; extensive drug resistance occurs when *M. tuberculosis* is resistant not only to isoniazid and rifampin, but also to fluoroquinolones and one or more of the second-line injectable agents (i.e., amikacin, kanamycin, capreomycin). This definition was chosen because the highest rate of tuberculosis treatment failures and mortality has been observed in patients infected with *M. tuberculosis* having this drug susceptibility profile.

Multidrug-resistant tuberculosis can be acquired through transmission of an already resistant organism ("primary" multidrug resistance) or through inappropriate treatment of a previously acquired, susceptible organism ("secondary" multidrug resistance). In evaluating a patient with suspected or confirmed tuberculosis, it is important to elicit any history of factors that may contribute to the acquisition of drug resistance (Table 90-3). These factors include the following:

- Exposure to someone with documented drug-resistant disease, or exposure in an area or setting with a high prevalence of drug resistance
- Prior treatment for tuberculosis, especially with extensive disease; or if the treatment was not directly observed, potentially inappropriately prescribed, interrupted, or if patient adherence is questionable
- Poor or no improvement with therapy
- Treatment for latent infection when active tuberculosis was present
- Prolonged use of multiple drugs, fluoroquinolones, or an injectable drug for an unspecified pulmonary process

At the clinical level, failure to improve with initial standard four-drug therapy is suggestive of drug resistance, misdiagnosis, drug malabsorption, nonadherence, or overwhelming infection. In low resource settings, clinical management protocols prompt suspicion of drug resistance if sputum smears are still positive after 2 months of therapy.

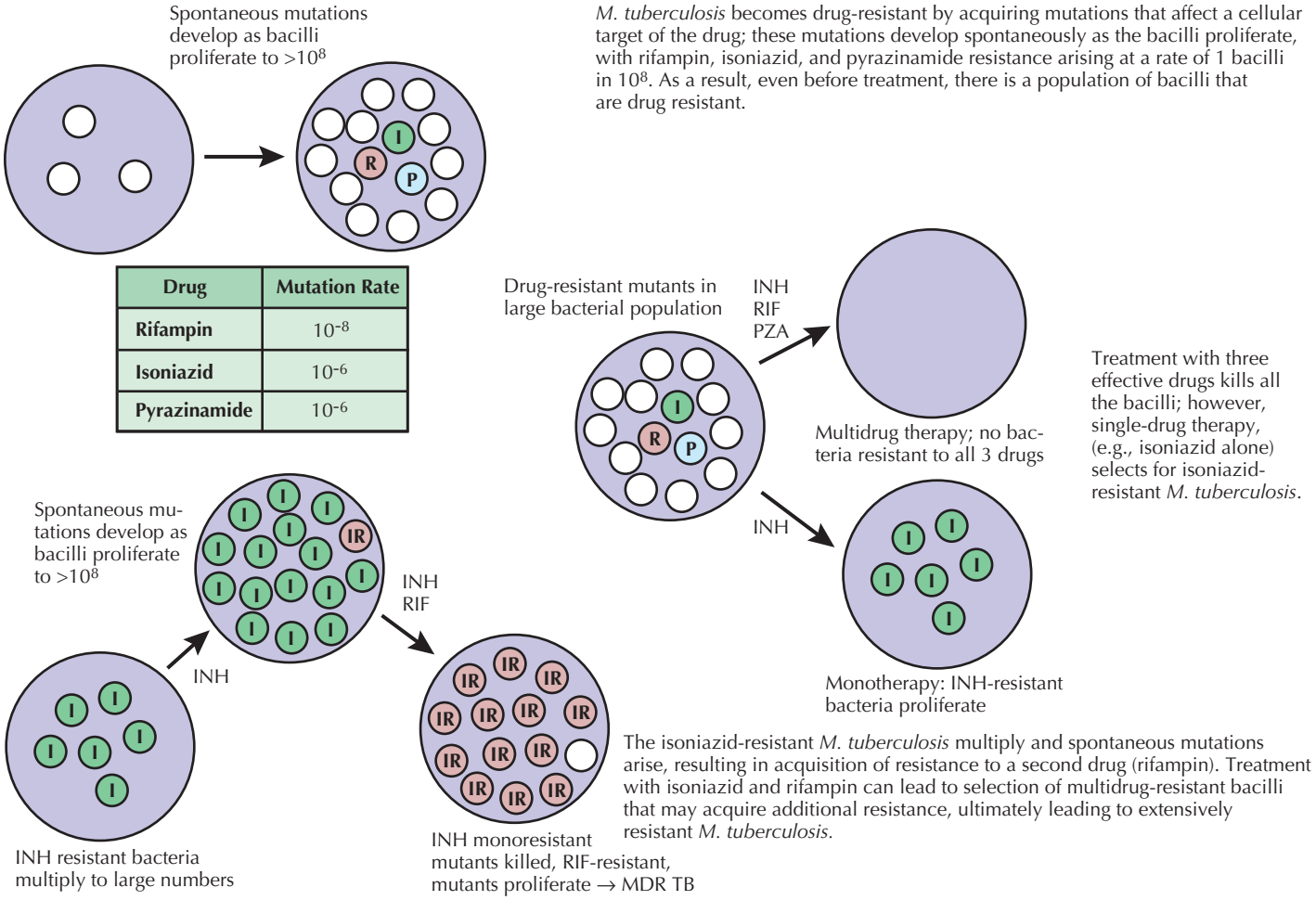


Figure 90-4 Schematic mechanism of emergence of drug resistance in *Mycobacterium tuberculosis*.

Table 90-3 Risk Factors for Drug Resistance in Tuberculosis

History of tuberculosis (TB)	Large bacillary load with extensive disease
	Lack of conversion of cultures to negative during therapy
	No or little improvement or worsening of symptoms
	Nonadherence or intermittent ingestion or absorption of regimen
	No or poorly supervised directly observed therapy
	History of an inappropriate treatment regimen
No history of tuberculosis	Exposure to a person with documented drug-resistant TB
	Residence in or travel to a region with high rates of drug-resistant TB
	Residence or work in a setting in which drug-resistant TB is documented
	Treatment of pulmonary disease with a prolonged course of multiple medicines, fluoroquinolone, or an injectable agent for more than a few weeks
	Previous treatment for latent TB infection when signs of active TB disease were not recognized

CLINICAL PRESENTATION

The initial clinical presentation of multidrug-resistant tuberculosis is largely indistinguishable from that of infection with drug-susceptible *M. tuberculosis*. Tuberculosis may manifest as an organ-specific or systemic disease, and the diagnosis is based on a constellation of clinical, radiographic, and mycobacteriologic findings. Pulmonary involvement, which is present in 70% to 80% of patients in most settings, is characterized by a productive cough, fever, night sweats, fatigue, anorexia, and weight loss (constitutional symptoms). Chest pain, dyspnea, and hemoptysis are also common features. Clinical manifestations of extrapulmonary tuberculosis include constitutional symptoms and pain or dysfunction corresponding with the affected site; about one third of individuals with extrapulmonary infection have concurrent pulmonary involvement.

Physical findings can include cachexia, cervical or regional lymphadenopathy, abnormal auscultatory findings corresponding to lung consolidation or pleural effusion, pulsus paradoxus, hepatosplenomegaly, peritonitis, spinal tenderness or gross gibbus deformity, meningismus, and neurologic deficits.

Suggestive standard chest radiographic findings include single or multiple areas of upper zone consolidation, upper zone fibronodular opacities, cavitation, mediastinal and/or hilar adenopathy, and pleural effusion, occurring alone or in

combination. Computed tomography (CT) is more sensitive for characterizing pleural abnormalities and detecting pulmonary infiltrates, cavitation, and lymphadenopathy. Imaging for extrapulmonary tuberculosis includes CT or magnetic resonance imaging (MRI) with contrast, depending on the suspected site of infection. Typical findings include ring-enhancing lesions in lymph nodes, brain, or other tissues; multiple hypodense lesions in liver and/or spleen; fluid collections (e.g., paraspinous abscess, ascites, basilar meningitis); bone destruction; and obstructive lesions (e.g., bronchial compression, lateral ventricular enlargement, hydronephrosis). Whereas radiographic studies (standard chest radiography, CT, and MRI) may be useful in identifying the site and extent of disease, these technologies may be limited or unavailable in low resource settings.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for tuberculosis is broad: pulmonary tuberculosis may mimic an acute or chronic pneumonic process caused by bacteria, viruses, fungi, nontuberculous mycobacteria, malignancy, sarcoidosis, or rheumatologic disease. Tuberculosis should be considered in the evaluation of fever of unknown origin and in chronic inflammation of unknown cause (e.g., meningitis, peritonitis, and osteomyelitis). In the absence of mycobacteriologic or molecular evidence of tuberculosis, it is generally wise to consider further studies to reasonably exclude these non-TB diagnoses before committing to empirical antituberculosis therapy.

DIAGNOSTIC APPROACH

The laboratory diagnosis of pulmonary tuberculosis relies mainly on the demonstration of acid-fast bacilli on smear and culture of sputum. The sensitivity of sputum smear examination is enhanced by the use of concentrated specimens and fluorochrome staining. Smear results are generally available within 24 hours, whereas cultures typically require 2 to 4 weeks to demonstrate growth of bacilli, which is typically confirmed as *M. tuberculosis* complex using nucleic acid hyridization. Of all infections ultimately confirmed as pulmonary tuberculosis, about 90% will have *M. tuberculosis* isolated or identified from culture of a respiratory specimen. In the United States, 33% to 50% of patients with culture-confirmed pulmonary tuberculosis will have negative sputum smears. Therefore when clinical suspicion for tuberculosis is high and alternative diagnoses are reasonably excluded or deemed unlikely, the absence of acid-fast bacilli on sputum smear should not dissuade the initiation of empiric treatment. Some settings may have *M. tuberculosis* nucleic acid amplification testing for sputum specimens, with a sensitivity exceeding 90% in smear-positive specimens and approaching 70% in smear-negative specimens. Consequently, these tests are most useful for excluding the diagnosis in smear-positive patients in whom infection with nontuberculous mycobacteria is suspected.

The diagnosis of extrapulmonary tuberculosis uses the collection of relevant fluids or tissues for pathologic examination and mycobacterial studies. The histopathologic hallmark of tuberculosis is the presence of necrotizing granulomata. For fluid or tissue from extrapulmonary sites, the sensitivities of acid-fast bacilli smear (25% to 50%) and culture (50% to 70%) are relatively low. Consequently, the diagnosis of extrapulmonary tuberculosis often hinges on exclusion of other diagnoses, the patient's epidemiologic risks, clinical presentation, histopathologic results, and response to therapy.

Drug resistance is determined by cultivation of *M. tuberculosis*, followed by drug susceptibility testing using liquid and/or solid media. Growth occurs more rapidly in liquid media, but solid media can quantify the in vitro degree of drug resistance. Most laboratories in high resource settings use liquid media for growth of *M. tuberculosis* and initial screening for resistance to first-line drugs (see Table 90-1). To confirm and quantify drug resistance and to screen for resistance to second-line drugs, specimens are inoculated onto solid media plates impregnated with clinically relevant concentrations of single drugs. This technology is slowly becoming available in parts of the developing world where the need is greatest, but the vast majority of multidrug-resistant infections are primarily diagnosed by clinical recognition of treatment failure and persistence of visible acid-fast bacilli on serial specimens of expectorated sputum.

Nucleic acid amplification techniques that identify mutations highly correlated with phenotypic resistance have become available for testing on initial growth or even on patient specimens. Using such assays, it is possible to identify *M. tuberculosis* and detect rifampin resistance within a single working day. Because rifampin monoresistance is extremely unusual, detection of rifampin resistance mutations is highly suggestive of multidrug resistance. These techniques have been adapted for use in low resource settings where they can accelerate the detection of drug resistance before the availability of phenotypic drug susceptibility results.

MANAGEMENT AND THERAPY

In the United States and other areas where the rates of antituberculosis drug resistance are low to moderate, standard treatment of fully susceptible tuberculosis consists of an initial daily regimen of isoniazid, rifampin, pyrazinamide, and ethambutol. As soon as drug susceptibilities are available and the *M. tuberculosis* is shown to be susceptible to isoniazid and rifampin, ethambutol can be discontinued. After 8 weeks of therapy, pyrazinamide is discontinued, and isoniazid and rifampin are continued to complete 6 months (26 weeks) of therapy. Treatment can be administered daily, thrice weekly, or twice weekly (with appropriate dosage adjustments) after the initial 2 weeks of therapy. However, some studies show increased rates of relapse when intermittent therapy is used during the initial phase in infections with heavy bacillary load. Treatment is extended to 9 months if cavitary disease is present and sputum cultures are still positive at 8 weeks; up to 9 months for bone and joint disease; and from 9 to 12 months for central nervous system or meningeal involvement.

Treatment for drug-resistant tuberculosis varies depending on the resistance patterns. For isolated isoniazid resistance, treatment options include the following:

- Rifampin, pyrazinamide, and ethambutol for 6 months *or*
- Rifampin and ethambutol (with or without a fluoroquinolone) for 12 months

For isolated pyrazinamide resistance (or for any course of treatment using only isoniazid and rifampin), therapy should be

extended to 9 months. Resistance to rifampin alone is extremely rare, but when present the standard approach is to give isoniazid, pyrazinamide, and ethambutol for 2 months, followed by isoniazid and ethambutol for 16 months.

Regimens for Multidrug Resistance

The treatment of multidrug-resistant tuberculosis involves prolonged use of less proven and more toxic drugs. Clinical trials in this area are limited, and treatment recommendations are drawn from observational studies and expert opinion. The standard approach to treatment of laboratory confirmed drug resistance includes the following:

- Always treating drug-resistant tuberculosis in consultation with an expert in the field
- Never adding fewer than two drugs to a failing regimen
- Continuing any first-line drug to which the *M. tuberculosis* is susceptible
- Adding an injectable to which the isolate is susceptible
- Adding a fluoroquinolone (e.g., moxifloxacin, levofloxacin)
- Adding cycloserine, ethionamide, and/or para-aminosalicylate as necessary to achieve a five- or six-drug regimen
- Considering use of linezolid, amoxicillin-clavulanate, clofazimine, and/or imipenem if the drug-resistance profile (or patient drug intolerance) is extensive enough to exclude an adequate regimen using the previously mentioned drugs
- Administering an injectable for 6 months and oral agents for 18 to 24 months after sputum culture becomes negative

In general, a drug to which *M. tuberculosis* shows decreased susceptibility is discontinued. Some experts, however, may still use high-dose daily or intermittent isoniazid or continue ethambutol on a daily or intermittent basis even when initial findings indicate resistance. In such cases, the drugs are only stopped when final susceptibility results indicate high-level resistance or the patient is intolerant of the treatment regimen. If an isolate shows decreased susceptibility to all injectable agents or fluoroquinolones, many experts would proceed with the injectable and fluoroquinolone agents to which the isolate shows the greatest susceptibility.

Adjunctive Corticosteroids

For tuberculosis involving the pericardium, meninges, or central nervous system, systemic corticosteroids are routinely recommended during the initial 1 to 2 months of therapy; corticosteroids can also be considered if an inflammatory mass compromises vital structures. Although their use should be limited to conditions for which there is objective evidence of benefit, systemic corticosteroids need not be inappropriately feared in the setting of tuberculosis treatment when concurrent effective therapy is being administered.

Drug Adverse Effects

Compared with therapy for other bacterial infections, treatment of multidrug-resistant tuberculosis with multiple potentially toxic agents over the course of months to years resembles cancer chemotherapy more than it does treatment of an acute infectious disease. Adverse drug reactions necessitating alteration of treatment occur in about 20% of patients with fully susceptible tuberculosis.

Although the adverse effects associated with individual antituberculosis drugs have been extensively described (Table 90-4), the frequency of adverse effects related to treatment with regimens primarily consisting of second-line agents for multidrug-resistant disease has not been well documented. Despite the lack of reports, the incidence of adverse effects in this setting is likely to be high, and the options for regimen alteration are limited. Consequently, knowledge of the nature, cause, and management of adverse effects of first- and second-line antituberculosis drugs is essential for successful management of tuberculosis, particularly in the setting of multidrug resistance.

Another key principle in evaluation of reported adverse effects is to discriminate between nuisance and dangerous effects. The former generally do not merit regimen alteration, whereas the latter generally do. Finally, when an adverse effect has multiple agents as its potential cause (e.g., liver injury in the setting of standard first-line regimens, rash with any drug), it is often wisest to stop all agents and then subsequently reintroduce them serially once the effect has improved or resolved. In some instances (e.g., severe disease) it may be necessary to impose an alternative holding regimen while the former process is undertaken (e.g., streptomycin, ethambutol, and moxifloxacin in the setting of liver injury).

Adjunctive Surgical Therapy

Surgical excision of focal disease (e.g., lung nodules, affected lobe or lymph nodes) can reduce bacillary load and subsequent chances of treatment failure or relapse. Surgery is often considered as adjunctive therapy when the benefit of a procedure (e.g., wedge resection or lobectomy) outweighs the risks (e.g., intraoperative mortality, bronchopleural fistula or reduced lung capacity). Surgical management of multidrug-resistant tuberculosis should generally be referred to or conducted in consultation with a center with significant experience and expertise in this practice.

Monitoring Treatment

Although a meta-analysis of randomized clinical trials on directly observed therapy (DOT) has shown no significant impact of DOT on treatment outcomes, historical case series suggest that programmatic implementation is associated with increased treatment completion and decreased drug resistance in communities. While work remains to be done to better specify the elements of treatment support that are most important for good clinical and public health outcomes, DOT remains a public health standard of care for treatment of tuberculosis, especially in the setting of multidrug resistance. DOT not only ensures administration of prescribed therapy for the benefit of community disease control but also provides a regular venue for detecting adverse effects, assessing response to therapy, and encouraging perseverance with drug regimens that are typically difficult to tolerate.

Table 90-4 Adverse Effects of Antituberculosis Drugs

SYSTEM	EFFECT	*Typical Causative Agents* FIRST LINE	SECOND LINE	MANAGEMENT OPTIONS
Gastrointestinal	Gastritis, nausea, vomiting	PZA RIF INH	Ethionamide PAS FQN	Small predose snack or meal Proton pump inhibitor If severe, discontinuation
		—	Linezolid	Antiemetic or motility agent
	Liver injury	PZA INH RIF	Ethionamide	Interrupt therapy if transaminases >3 times ULN with symptoms or >5 times ULN without symptoms Follow resolution with serial challenge
Central nervous system	Paresthesias	INH	Ethionamide	Increase pyridoxine dose Consider discontinuation if severe
	Asthenia	INH	Any	Reassurance Time dose for later in the day
	Depression	—	Cycloserine	Antidepressant medication Discontinuation if severe
	Sleep disturbance, agitation, tremulousness	—	FQN	Discontinuation if severe
	Development or worsening of movement disorders	INH	—	Discontinuation if severe
	Seizures	INH	Cycloserine Ethionamide	High-dose pyridoxine, antiseizure medication, discontinuation
	Vision changes	EMB INH	—	Interruption and ophthalmologic examination with observation for recovery
	Hearing and/or vestibular changes	—	Streptomycin Amikacin Kanamycin Capreomycin	Discontinuation Can progress despite interruption and can be irreversible Consider a different injectable agent if treatment options are limited
	Psychosis	INH	Cycloserine	Discontinuation and consult a psychiatrist
Renal	Uremia	—	Streptomycin	Discontinuation
	Interstitial nephritis	RIF INH	—	Discontinuation
Integument	Noninflammatory pruritus	INH	—	Diphenhydramine
	Urticaria	Any	Any	Discontinuation and diphenhydramine
	Acneiform rash	INH RIF	Cycloserine	Topical therapy Consider discontinuation if severe
	Maculopapular rash	Any	Any	Discontinue, follow resolution with serial drug challenge
Endocrine	Hypothyroidism	—	Ethionamide PAS	Levothyroxine

EMB, Ethambutol; *FQN,* fluoroquinolone; *INH,* isoniazid; *PAS,* para-aminosalicylate; *PZA,* pyrazinamide; *RIF,* rifampin; *ULN,* upper limit of normal.

Standard monitoring for tolerance and response to therapy beyond DOT should include monthly standardized symptom evaluation, weight check, comprehensive metabolic panel and complete blood count, thyroid-stimulating hormone and/or thyroxine levels (if the patient is receiving ethionamide or para-aminosalicylate), assessment of visual acuity and color discrimination (if receiving ethambutol), audiogram and vestibular assessment (while receiving injectable agents), and periodic (e.g., quarterly) radiographic examination. For patients with pulmonary disease, serial sputum examinations should be conducted (e.g., weekly until smear negative, then monthly through the end of treatment). For extrapulmonary tuberculosis, mycobacteriologic monitoring is not feasible, warranting greater attention to clinical and radiographic responses to therapy. Experts disagree on the benefit of routine pharmacokinetic studies to evaluate drug absorption and targeted blood levels, but there is greater support for its use in the context of treatment failure. In practice, these studies tend to be limited to patients with suspected malabsorption (e.g., HIV enteropathy, inflammatory bowel disease, diabetic enteropathy), drug-drug interactions that result in suboptimal serum levels of antituberculosis drugs, treatment failure in the absence of drug resistance, and use of particular agents (e.g., cycloserine).

In low resource settings, routine culture, bloodwork, and radiography are often eliminated from monitoring protocols and tests to detect serum drug levels are not available.

Prognosis and Posttreatment Follow-Up

Published studies vary widely in reported rates of case fatality, treatment response, and cure. High-income nations with full access to second-line drugs, DOT, and, if appropriate, surgical

therapy show long-term cure rates that approach 90% to 95%. In less developed settings where drug resistance may be extensive, treatment resources limited, and HIV co-infection more common, case-fatality rates can exceed 50% and long-term cure rates vary from 25% to 75%. In a South African outbreak of extensively drug-resistant tuberculosis among HIV-infected individuals, the case-fatality rate was 98%; contributing factors included delays in diagnosis, immunosuppression, and lack of access to effective drugs. Efforts to provide sustainable community-based treatment for multidrug-resistant tuberculosis in high-burden settings (e.g., Peru) appear to show early success, with cure rates approaching those seen in high-income, low-burden countries.

Posttreatment surveillance for fully susceptible tuberculosis is generally not conducted, given the high probability of cure (95% to 98%) and low probability (2% to 5%) of relapse. Relapse usually occurs within 12 to 24 months of completion of treatment. Failure and relapse rates following treatment for multidrug resistance vary by setting, being as low as 10% to 20% in high resource settings and as high as 25% to 50% in low resource settings. Because of these higher relapse rates, experts in high resource settings generally favor active follow-up after completion of treatment for multidrug resistant tuberculosis. Typically, follow-up for pulmonary disease includes serial symptom evaluation, standard chest radiography, and sputum examination during the period when relapse is most likely to occur (e.g., at 4, 8, 12, 18, and 24 months after treatment completion).

Co-infection with HIV

An HIV test should be a standard component of every baseline evaluation for active tuberculosis in all patients not previously known to be co-infected. A comprehensive review of the management of co-infection with multidrug-resistant tuberculosis and HIV is beyond the scope of this text. However, several key principles should be noted when evaluating or treating any HIV-infected patient for tuberculosis:

- The presentation of pulmonary tuberculosis can be atypical, particularly with severe immunosuppression (e.g., CD4 <200):
  - On standard chest radiography, hilar and mediastinal adenopathy, lower zone opacities, and diffuse micronodular (miliary) opacities are more common in severely immunosuppressed patients.
  - Acid-fast bacilli smears of sputum are more likely to be negative.
  - Extrapulmonary disease is more common.
  - Rifampin resistance may be present in patients previously treated with rifabutin for prophylaxis of *Mycobacterium avium* complex and in patients previously treated for TB with intermittent rifamycin administration.
  - The toxicities and interactions associated with antiretroviral therapy and prophylaxis for opportunistic infections may overlap with those associated with antituberculosis drugs.
  - Regimens should be tailored with potential drug-drug interactions between rifamycins and anti-retrovirals in mind. Drug-drug interactions between rifabutin and azoles or macrolides should also be anticipated and managed in patients being considered for use of this rifamycin.
  - Immune reconstitution inflammatory syndrome, caused by an exuberant immune response to mycobacterial antigens, may occur during tuberculosis treatment. Immune reconstitution is most often characterized by the return of constitutional symptoms and apparent worsening of disease. Although this syndrome may occur in persons not infected with HIV, it is seen most commonly several weeks following initiation of antiretroviral therapy in severely immunosuppressed, HIV-infected individuals being treated for tuberculosis.

PREVENTION AND CONTROL

Isolation

Although isolation for pulmonary tuberculosis is unusual in low resource settings, in the United States, isolation of patients for suspected pulmonary tuberculosis is standard and generally discontinued once the patient has adhered to at least 2 weeks of medication, has demonstrated clinical improvement, and shows no or decreased bacilli on sputum smears. In multidrug-resistant pulmonary tuberculosis, the goal is to eliminate rather than control disease transmission; therefore affected patients typically remain in isolation until sputum cultures demonstrate no growth of *M. tuberculosis*. Patients with extrapulmonary disease in whom pulmonary tuberculosis has been reasonably excluded do not merit isolation unless they are undergoing an invasive procedure that is likely to aerosolize organisms.

Management of Exposed Contacts

About 30% of household contacts to an individual with infectious pulmonary tuberculosis will become infected. In the absence of intervention, about 5% to 10% of those exposed will develop active tuberculosis in their lifetime. Latent infections can be detected by a tuberculin skin test (TST) or interferon-γ release assay (IGRA); a positive TST or IGRA result in a person exposed to tuberculosis is associated with an increased risk of subsequent active tuberculosis.

Latent infections are usually treated to prevent progression to active tuberculosis, and persons known to have been exposed to someone with infectious pulmonary tuberculosis are usually evaluated for latent tuberculosis infection (LTBI) and treated if they are infected. However, in the setting of a possible exposure to multidrug-resistant tuberculosis, no clinical trials or observational studies have assessed the benefits of LTBI treatment. For contacts of multidrug-resistant tuberculosis with LTBI, all efforts should be made to recover information regarding prior evaluations for tuberculosis in order to assess the likelihood of a prior infection with a susceptible organism as compared with recent acquisition of infection from exposure to multidrug-resistant disease. For contacts of a patient with multidrug-resistant tuberculosis, United States–born individuals with a new diagnosis of LTBI, children (especially under 5 years of age), or individuals with a newly positive TST or IGRA are more likely to have multidrug-resistant LTBI. Conversely, a positive TST or IGRA result in previously untested older patients who were born in, or lived for extended periods

in, tuberculosis-endemic regions is much less likely to reprsent multidrug-resistant LTBI. And finally, immunocompetent contacts of individuals with multidrug-resistant disease with positive TST or IGRA results prior to exposure are at negligible risk for multidrug-resistant LTBI. Nevertheless, once a decision has been made that multidrug-resistant LTBI is likely, most experts recommend using the two most effective oral drugs (typically, two of the following three drugs: pyrazinamide, ethambutol, and moxifloxacin) to which the organism is susceptible. Recommended duration of therapy is 6 to 12 months, and some experts will consider a 6- to 12-month course of moxifloxacin alone if the source is infected with *M. tuberculosis* resistant to (or the contact is intolerant of) pyrazinamide or ethambutol. In the United States, many experts recommend frequent surveillance of contacts of individuals with multidrug-resistant tuberculosis using symptom evaluation and standard chest radiography for 24 months (e.g., 4, 8, 12, 18, and 24 months after exposure was interrupted). Evaluation of close contacts of individuals with tuberculosis should be conducted in collaboration with the local public health agency responsible for tuberculosis control.

FUTURE DIRECTIONS

Previously, multidrug-resistant tuberculosis tended to occur in regions where access to first-line drugs was sufficient but control programs were too poorly funded or insufficiently strong to ensure adherence to therapy and standardized practices. Generally, these have been low- to middle-income countries (e.g., former Soviet Republics, Argentina), where treatment practices vary widely and treatment frequently occurs within the private medical sector (e.g., India) (see Figure 90-2). More recently, the spread of multidrug and extensive drug resistance has been fueled by HIV-associated immunosuppression and consequently plays an increasing role in tuberculosis morbidity in sub-Saharan Africa.

Over the past decade, WHO and its international partners have increased emphasis on identifying, treating, and controlling transmission of multidrug-resistant tuberculosis as part of an overall strategy for global tuberculosis control. A strategic element of this global plan to STOP TB is known as "DOTS", a program that calls for the commitment of political and financial resources; use of quality mycobacteriology for TB diagnosis; use of standardized treatment regimens with appropriate supervision and support for adherence; ensurance of an adequate supply of antituberculosis drugs; and program monitoring and evaluation. Challenges toward this end include developing a sustainable capacity for sputum culture and drug susceptibility testing; ensuring access to high-quality first- and second-line drugs and adequate infection control for healthcare workers and HIV-infected patients; and avoiding pitfalls associated with potential amplification of drug resistance by use of standardized retreatment protocols in the absence of drug susceptibility testing.

Significant barriers to the overall control of tuberculosis include the following:

- Inadequate infrastructure for implementing existing technology, especially in low resource settings
- Long duration of regimens for treatment for latent and active infections
- Limitations of existing tools for diagnosis and evaluation of treatment (radiography, sputum smear and culture, TST)
- Limited efficacy of bacille Calmette-Guérin (BCG) vaccine (used in infants to prevent disseminated and meningeal disease in most high incidence countries)
- Impact of HIV infection on transmission and progression to active disease

Consequently, strategies that would benefit efforts to control tuberculosis and prevent further emergence of drug resistance include the following:

- Ensuring infrastructure that supports cost-effective control methods by expanding the DOTS coverage
- Preventing HIV transmission and mitigating the associated population-level immunosuppression, especially in tuberculosis-endemic regions
- Addressing the needs of other special groups (e.g., incarcerated, indigenous)
- Strengthening health systems infrastructure
- Engaging the private sector in implementation of international standards for TB care
- Promoting advocacy, community involvement, and social mobilization surrounding TB prevention, treatment, and control
- Developing and implementing simple, robust, and affordable assays for detection of tuberculosis and drug resistance
- Discovering, testing, and implementing safe, new drug regimens that will effectively treat both drug-susceptible and drug-resistant strains
- Developing more effective vaccines that protect against acquisition of infection and/or progression to active disease

Such efforts form the key elements of the Global Plan to STOP TB. This initiative will require the commitment of political will and financial and human resources at global, regional, and local levels, as well as cooperation among aid and nongovernmental organizations, national governments, and the academic and private biomedical sectors.

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West Nile Virus Disease

Grant L. Campbell, J. Erin Staples, James J. Sejvar, and Marc Fischer

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ABSTRACT

Before 1999, West Nile virus (WNV) received little attention outside Africa, Asia, and Europe, where WNV is an endemic, mosquito-borne cause of febrile illness and sporadic encephalitis. After the dramatic emergence of WNV in New York City in 1999, the virus spread westward across the United States, resulting in the largest outbreaks of serious WNV disease ever reported. From 1999 through 2009, 29,681 cases of WNV disease were reported in the United States, including 12,208 infections affecting the central nervous system (neuroinvasive disease) and 1,167 deaths. Over the past decade, much has been learned about the virology, ecology, transmission, epidemiology, and clinical manifestations of WNV. This review highlights these new developments, which provide a platform for further research into the prevention and control of WNV disease.

ETIOLOGY AND TRANSMISSION

WNV is a ribonucleic acid (RNA) flavivirus that is related antigenically to St. Louis encephalitis and Japanese encephalitis viruses. WNV is transmitted to humans primarily through the bite of infected mosquitoes (Figure 91-1). The predominant vectors worldwide are *Culex* mosquitoes, which feed primarily from dusk to dawn and breed mostly in peridomestic standing water or pools created by irrigation or rainfall. Mosquitoes become infected with WNV by feeding on a host that can sustain infectious levels of viremia, serving to amplify the virus. Birds are the most important amplifying hosts of WNV; they infect feeding mosquitoes, which then transmit the virus to humans and other mammals during subsequent feeding. Viremia usually lasts fewer than 7 days in immunocompetent persons, and WNV concentrations in human blood are generally too low to infect mosquitoes, making humans incidental or "dead-end" hosts. However, person-to-person transmission can occur through blood transfusion and organ transplantation. Intrauterine transmission and probable transmission via human milk also have been described but appear to be uncommon. Percutaneous infection and aerosol infection have occurred in laboratory workers, and an outbreak of WNV infection among turkey handlers also raised the possibility of aerosol transmission (Figure 91-2).

GEOGRAPHIC DISTRIBUTION

WNV activity has been reported in Europe and the Middle East, Africa, India, parts of Asia, and Australia (in the form of Kunjin virus, a WNV subtype) (Figure 91-3). WNV was first detected in North America in 1999, after which it rapidly spread across the United States and northward into Canada. In the United States, WNV activity in mosquitoes, birds, or other animals has been reported in all states except Alaska and Hawaii. The highest incidence of WNV disease is in the western mountain and plains states (Figure 91-4). In more recent years the virus also has been detected in the Caribbean and Central and South America.

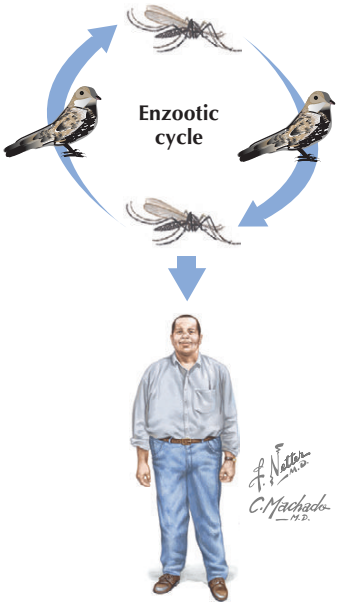
PUBLIC HEALTH IMPORTANCE

WNV is the most common cause of arthropod-borne viral (arboviral) disease in the United States and Canada. Most human WNV infections are asymptomatic. Approximately 20% of infected people develop an acute systemic febrile illness (WNV fever), and less than 1% develop neuroinvasive WNV disease (i.e., encephalitis, meningitis, or acute flaccid paralysis) (Figure 91-5). In the United States, WNV surveillance data are reported to the Centers for Disease Control and Prevention (CDC) through ArboNET, an Internet-based arbovirus surveillance system managed by the CDC and state health departments. From 1999 through 2009, 29,681 cases of WNV disease were reported to ArboNET, including 12,208 (41%) cases of neuroinvasive WNV disease and 17,473 (59%) cases of WNV non-neuroinvasive disease; there were 1,167 (4%) associated deaths. Reports of neuroinvasive WNV disease are considered the most accurate indicator of WNV activity in humans, owing to the substantial associated morbidity and mortality and the presumed completeness of reporting by clinicians and laboratories. In contrast, WNV fever likely is underdiagnosed and underreported, as people with mild illness may not seek medical care, or clinicians may not suspect or confirm WNV disease. Assuming that there were 140 human WNV infections for each reported neuroinvasive WNV disease case, an estimated 1.7 million human WNV infections occurred in the United States from 1999 through 2009, including approximately 340,000 cases of WNV non-neuroinvasive disease.

RISK FACTORS

In endemic areas of the northern hemisphere, the risk of WNV infection is higher during the warmer months when mosquitoes are active and more abundant, typically July through October (Figure 91-6). Although people of all age groups appear to be equally susceptible to WNV infection, the risk of neuroinvasive WNV disease increases with age (Table 91-1). In addition, among patients with neuroinvasive WNV disease, adults 50 years of age or older have substantially higher case-fatality rates and are more likely to be reported as having encephalitis or meningoencephalitis, compared with children or younger adults (18 to 49 years of age).

Solid organ transplant recipients also are at significantly higher risk of severe illness. With the exception of increased age



West Nile virus (WNV) is transmitted in an enzootic cycle between *Culex* mosquitoes and amplifying vertebrate hosts, primarily birds. WNV concentrations in human blood are generally too low to infect mosquitoes, making humans incidental or "dead-end" hosts.

Figure 91-1 West Nile virus transmission cycle.

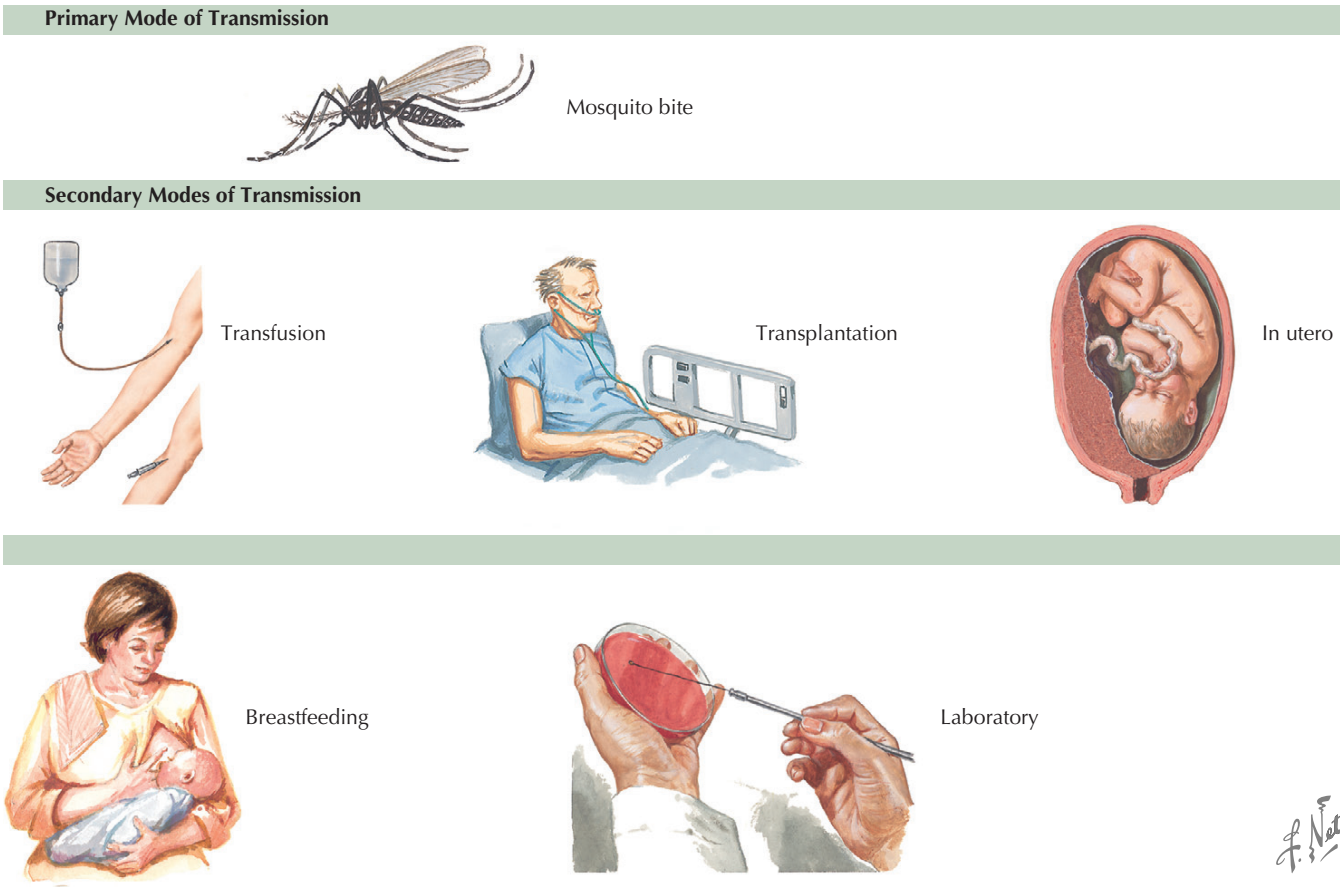


Figure 91-2 West Nile virus transmission to humans.

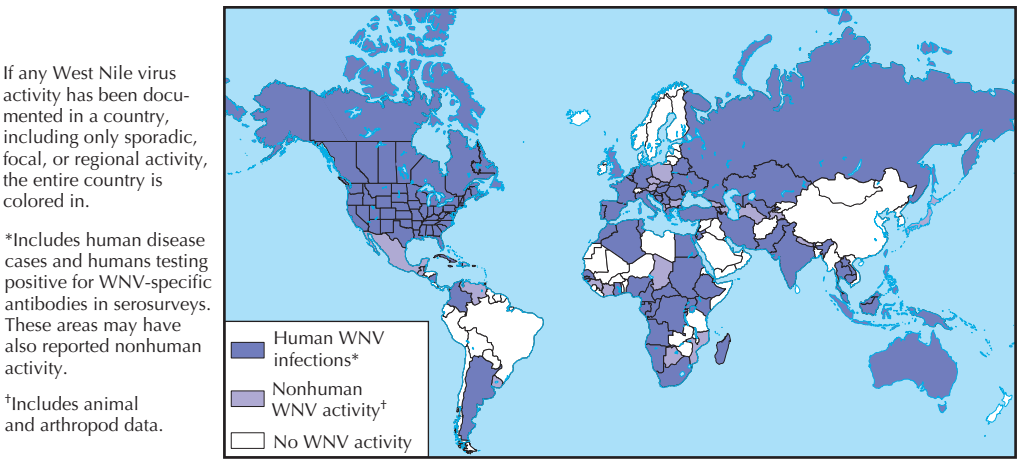


Figure 91-3 Reported West Nile virus activity by country* as of 2009.

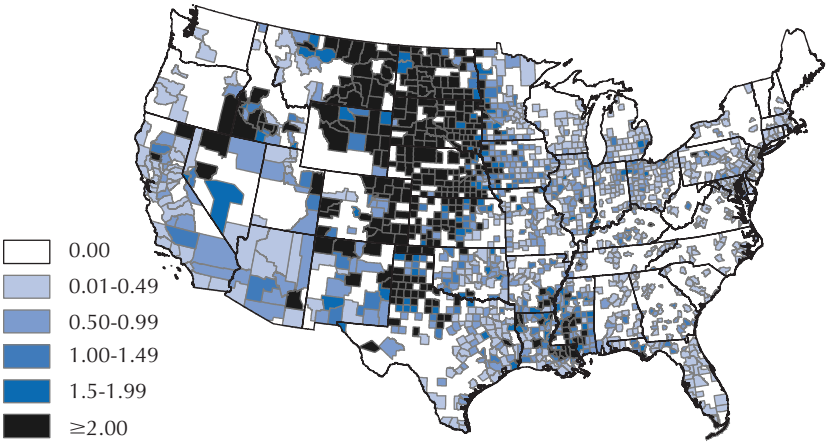


Figure 91-4 Average annual incidence per 100,000 population of West Nile virus neuroinvasive disease by county of residence, United States, 1999 to 2008. *(Adapted from Lindsey NP, Staples JE, Lehman JA, Fischer M: Surveillance for human West Nile virus disease—United States, 1999-2008, Centers for Disease Control and Prevention Surveillance Summaries, April 2, 2010.* MMWR *2010;59 (No. 55-2.)*

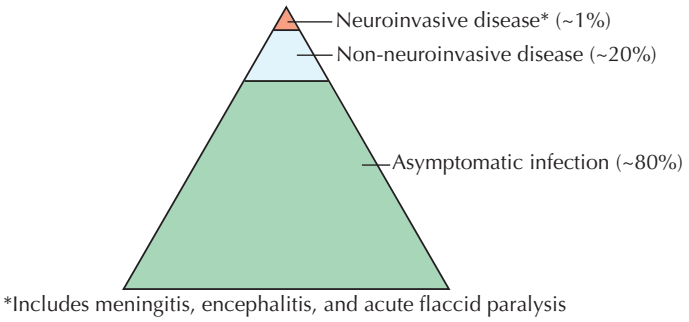


Figure 91-5 Clinical spectrum of West Nile virus disease in humans. *(Courtesy Centers for Disease Control and Prevention.)*

and organ transplantation, risk factors for severe disease in persons infected with WNV have not been well defined. Severe WNV disease has been described in persons with malignancies, but the relative risk from these or other immunocompromising conditions remains unclear. Hypertension, cerebrovascular disease, chronic renal disease, and diabetes mellitus also have been identified as possible risk factors for severe WNV disease, but further research is warranted.

CLINICAL FEATURES

The incubation period for WNV disease is typically 2 to 6 days but ranges from 2 to 14 days and can be up to 21 days in immunocompromised people. Patients with WNV non-neuroinvasive disease typically have an abrupt onset of fever, headache, myalgia, weakness, and often abdominal pain, nausea, vomiting, or diarrhea. Some patients have a transient maculopapular rash. The acute phase of illness usually resolves within several days, but fatigue, malaise, and weakness can linger for weeks. Patients with neuroinvasive WNV disease may develop signs and symptoms of aseptic meningitis, encephalitis, and/or acute flaccid paralysis. WNV meningitis is generally indistinguishable from viral meningitis from other causes and typically manifests with fever, headache, and neck stiffness. WNV encephalitis is a more severe clinical syndrome characterized by fever and altered mental status, seizures, focal neurologic deficits, or movement disorders such as tremor or parkinsonism. Acute flaccid paralysis associated with WNV infection has been attributed to WNV poliomyelitis, Guillain-Barré syndrome, and radiculitis. WNV poliomyelitis typically manifests as isolated limb paresis or paralysis and can occur without fever or apparent viral prodrome. It is clinically and pathologically identical to poliomyelitis caused by poliovirus, with

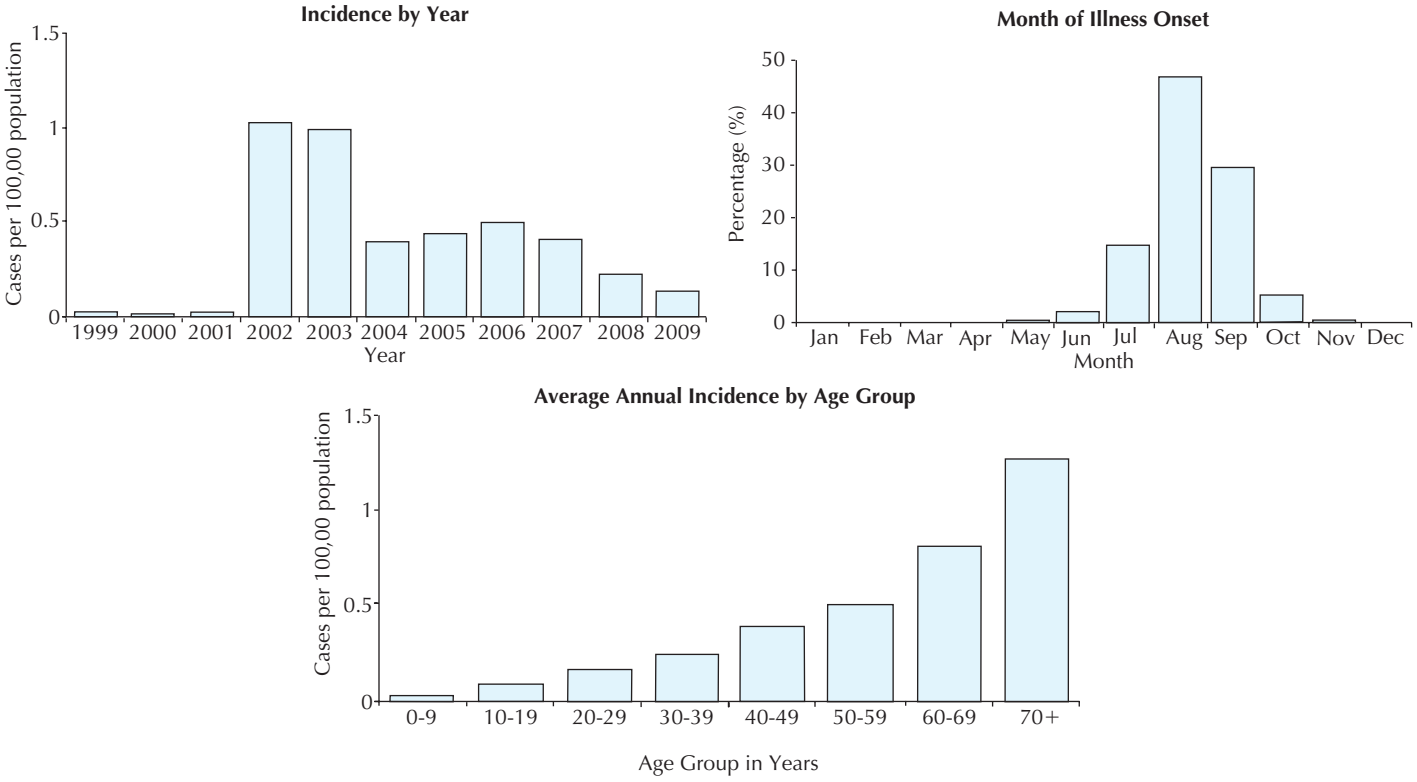


Figure 91-6 Epidemiologic characteristics of West Nile virus neuroinvasive disease in the United States, 1999 to 2009. *(Adapted from Lindsey NP, Staples JE, Lehman JA, Fischer M: Surveillance for human West Nile virus disease—United States, 1999-2008, Centers for Disease Control and Prevention Surveillance Summaries, April 2, 2010.* MMWR *2010;59 (No. 55-2) and West Nile Virus Activity—United States, 2009.* MMWR *2010;59:769-772.)*

Table 91-1 Epidemiologic Features of West Nile Virus Neuroinvasive Disease Cases Reported in Children and Adults, 1999 to 2007*

	CHILDREN (<18 YR OLD) N = 443		ADULTS (18-49 YR OLD) N = 3634		ADULTS (≥50 YR OLD) N = 7004	
Median cases per year (range)	49	(1-137)	377	(4-1057)	826	(15-1879)
Median incidence† per year (range)	0.07	(0.00-0.19)	0.28	(<0.01-0.78)	0.92	(0.02-2.32)
Clinical syndrome (%)						
Encephalitis or meningoencephalitis	163	(37)	1230	(34)	4160	(59)
Meningitis	208	(47)	1847	(51)	1640	(23)
Acute flaccid paralysis‡	5	(1)	23	(<1)	37	(<1)
Unspecified neuroinvasive disease	67	(15)	534	(15)	1167	(17)
Fatality (%)	3	(1)	48	(1)	949	(14)
Hospitalized§ (%)	166/206	(81)	1255/1585	(79)	2941/3344	(88)

*Includes cases reported as encephalitis, meningoencephalitis, meningitis, and/or acute flaccid paralysis (AFP) with age data.
†Incidence per 100,000 persons.
‡Includes cases reported as AFP only (not those reported as encephalitis or meningitis with AFP). Data available only from 2004 to 2007.
§Includes data from 2004 to 2007 only.

damage of anterior horn cells, and may progress to respiratory muscle paralysis, necessitating mechanical ventilation. Guillain-Barré syndrome can be distinguished from anterior horn cell disease by clinical manifestations and electrophysiologic testing. Rarely, cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, chorioretinitis, orchitis, pancreatitis, and hepatitis have been described in patients with WNV disease.

Most women known to have been infected with WNV during pregnancy have delivered infants without evidence of infection or clinical abnormalities. In the best-documented, confirmed congenital WNV infection, the mother developed neuroinvasive WNV disease during the twenty-seventh week of gestation, and her neonate was born with cystic lesions in brain tissue and chorioretinitis. One infant who apparently acquired WNV infection through breastfeeding remained asymptomatic.

DIAGNOSTIC APPROACH

WNV disease should be considered in any person with a febrile or acute neurologic illness who has had recent exposure to mosquitoes, blood transfusion, or organ transplantation, especially during the summer months in areas where WNV activity has been reported in birds, animals, mosquitoes, or humans. The diagnosis of WNV disease should also be considered in any infant born to a mother infected with WNV during pregnancy or while breastfeeding. Guidelines for the evaluation of fetal and neonatal WNV infections are available at www.cdc.gov/mmwr/preview/mmwrhtml/mm5307a4.htm. In a patient with suspected neuroinvasive WNV disease, other arboviruses (e.g., La Crosse, St. Louis encephalitis, eastern equine encephalitis, and Powassan viruses) also should be considered in the differential diagnosis.

Routine clinical laboratory studies are generally nonspecific in WNV disease. In patients with neuroinvasive WNV disease, cerebrospinal fluid (CSF) examination generally shows lymphocytic pleocytosis, but neutrophils may predominate early in the course of illness. Brain magnetic resonance imaging scans are frequently normal, but signal abnormalities in the basal ganglia, thalamus, and brainstem may be seen in patients with WNV encephalitis. Abnormalities may also be observed in the anterior spinal cord in patients with WNV poliomyelitis. Clinical features and electrodiagnostics can help differentiate WNV poliomyelitis from WNV-associated Guillain-Barré syndrome.

Serology continues to be the cornerstone of the laboratory diagnosis of WNV infection. Serum and, if indicated, CSF should be tested for WNV-specific immunoglobulin M (IgM) antibody. If serum is collected within 8 days of illness onset, the absence of detectable WNV-specific IgM does not rule out the diagnosis of WNV infection, and the test may need to be repeated on a later sample. Enzyme immunoassays for WNV-specific IgM currently are available commercially and through local or state public health laboratories. The presence of WNV-specific IgM in blood or CSF provides good evidence of recent WNV infection but may also result from cross-reactive antibodies after infection with other flaviviruses. Plaque-reduction neutralization tests performed in reference laboratories, including some state public health laboratories and the CDC, can help determine the specific infecting flavivirus and can confirm acute WNV infection by demonstrating a fourfold or greater change in WNV-specific neutralizing antibody titer between acute- and convalescent-phase serum samples collected 2 to 3 weeks apart. Because WNV-specific IgM can persist in some patients' serum for more than 1 year, the presence of WNV IgM occasionally may reflect past rather than recent WNV infection.

Viral cultures and nucleic-acid amplification tests (NATs) for WNV RNA can be performed on serum, CSF, and tissue specimens that are collected early in the course of illness and, if results are positive, can confirm WNV infection. Immunohistochemistry (IHC) can detect WNV antigen in formalin-fixed tissue. Negative results of these tests do not rule out WNV infection. Viral culture, NAT, and IHC can be requested through state public health laboratories or the CDC.

CLINICAL MANAGEMENT

Management of WNV disease is supportive. Patients with severe meningeal symptoms often require pain control for headaches and antiemetic therapy and rehydration for associated nausea and vomiting. Patients with WNV encephalitis require close monitoring for the development of elevated intracranial pressure and seizures, and patients with WNV encephalitis or poliomyelitis should be monitored for inability to protect their airway. Acute neuromuscular respiratory failure may develop rapidly, particularly in patients with prominent bulbar signs, and prolonged ventilatory support may be required. In patients hospitalized with WNV disease, standard infection control precautions are recommended. Although various drugs have been evaluated or empirically used for WNV disease, none has shown specific benefit to date. Information regarding ongoing clinical trials for treating WNV disease can be found at www.cdc.gov/ncidod/dvbid/westnile/clinicaltrials.htm.

PROGNOSIS

Most patients who develop WNV fever or meningitis recover completely, although some experience prolonged fatigue and other nonspecific symptoms. Patients who recover from WNV encephalitis or poliomyelitis often have residual neurologic deficits. Among patients with neuroinvasive WNV disease, the overall case-fatality rate is approximately 10%, but it is significantly higher in WNV encephalitis and poliomyelitis than in WNV meningitis or fever, in which case-fatality rates are very low.

PREVENTION AND CONTROL

WNV infection can be prevented by avoiding exposure to WNV-infected mosquitoes and by systematic screening of blood donors for WNV infection. Coordinated mosquito-control programs in areas with enzootic WNV transmission can reduce the abundance of mosquito vectors. People who live in areas with WNV-infected mosquitoes should apply insect repellent to skin and clothes and avoid being outdoors during peak mosquito-feeding times (usually dusk to dawn for WNV vectors). The most effective repellents for use on the skin are *N,N*-diethyl-*methyl*-toluamide (DEET) and picaridin. Products containing DEET or permethrin also can be applied to clothing. The American Academy of Pediatrics recommends using formulations of no more than 30% DEET on infants and children and not using DEET on infants younger than 2 months of age. In the United States, systematic screening of the blood supply for WNV infection was implemented in 2003. Nevertheless, healthcare providers should remain vigilant for possible WNV transmission through blood transfusion or organ transplantation. Any suspected WNV infections temporally associated with blood transfusion or organ transplantation should be reported promptly to public health authorities.

Pregnant women should take the aforementioned precautions to avoid mosquito bites. Products containing DEET can

be used in pregnancy without adverse effects. Although WNV probably has been transmitted through human milk, such transmission appears rare, and no adverse effects on infants have been described.

Several vaccines against WNV are licensed for use in horses. Human WNV vaccines are not yet available, but several candidate vaccines are being evaluated.

EVIDENCE

Bode AV, Sejvar JJ, Pape WJ, et al: West Nile virus disease: a descriptive study of 228 patients hospitalized in a 4-county region of Colorado in 2003, *Clin Infect Dis* 42:1234-1240, 2006. *The authors reported the results of the largest study to date of patients hospitalized with WNV disease, including neuroinvasive disease and WNV fever. Older age, diabetes mellitus, and alcoholism were associated with an increased risk of development of WNV encephalitis. Older age, encephalitis, immunosuppression, a need for mechanical ventilation, and a history of stroke were associated with fatal outcome.*

Hayes EB, Sejvar JJ, Zaki SR, et al: Virology, pathology, and clinical manifestations of West Nile virus disease, *Emerg Infect Dis* 11:1174-1179, 2005. *This concise review of WNV disease focused on clinical features, pathogenesis, pathology, laboratory diagnosis, clinical management, prognosis, vaccine development, and future prospects.*

Iwamoto M, Jernigan DB, Guasch A, et al: Transmission of West Nile virus from an organ donor to four transplant recipients, *N Engl J Med* 348:2196-2203, 2003. *This landmark article described the first four recognized cases of WNV transmission via solid organ transplantation. The sole organ donor, a trauma victim, probably acquired the infection via transfusion of WNV-infected blood products, a conclusion that prompted the issuance of national guidelines concerning surveillance for blood donors with possible WNV viremia.*

Lindsey NP, Hayes EB, Staples JE, Fischer M: West Nile virus disease in children, United States, 1999-2007, *Pediatrics* 123:e1084-e1089, 2009. *The authors described the epidemiologic features of pediatric WNV disease cases reported to the CDC from 1999 through 2007 and compared features of pediatric and adult neuroinvasive WNV disease. The clinical syndromes and severity of reported cases of pediatric neuroinvasive WNV disease were similar to those reported for cases in young adults (aged 18 to 49 years). In contrast, a larger proportion of cases in older adults (aged 50 years or older) were classified as neuroinvasive WNV disease, cases of neuroinvasive WNV disease were more often reported as encephalitis or meningoencephalitis, and the case-fatality rate was substantially higher.*

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Centers for Disease Control and Prevention (CDC): West Nile virus: information and guidance for clinicians. Available at: www.cdc.gov/ncidod/dvbid/westnile/clinicians. Accessed February 24, 2010. *A concise online summary, including information on epidemiology, clinical features, diagnostic testing, prevention, surveillance, and public health reporting, with links to state and some local public health department websites.*

Centers for Disease Control and Prevention (CDC): West Nile virus: updated information regarding insect repellents. Available at: www.cdc.gov/ncidod/dvbid/westnile/repellentupdates.htm. Accessed February 24, 2010. *A brief, information-rich summary of the current state-of-the-art of repellent use in the prevention of mosquito-borne diseases; includes links to several additional useful resources.*

Anthrax

Benjamin D. Moser, Sean V. Shadomy, and Theresa L. Smith

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ABSTRACT

Anthrax, caused by *Bacillus anthracis*, is a devastating disease for both humans and animals. Naturally occurring anthrax occurs worldwide; however, it no longer causes substantial disease in humans and animals in the United States. Anthrax most often manifests as cutaneous, inhalation, or gastrointestinal disease. The three forms of anthrax have different clinical presentations associated with the route of infection and the organism's effect on the affected organ system. Once diagnosed, anthrax is aggressively treated with an antimicrobial regimen consisting primarily of ciprofloxacin or doxycycline, often as part of a multidrug antimicrobial regimen, and appropriate supportive care. Prognosis for survival is relatively high for treated anthrax in both cutaneous (<1% mortality when treated) and gastrointestinal forms (0% to 29% mortality); however, inhalation anthrax, even when treated early and aggressively, has a lower survival rate (55% in 2001). Prevention and mitigation of this disease depends on the control of anthrax in animal populations, the restriction or decontamination of animal products, and the response of public health authorities to bioterrorism events.

GEOGRAPHIC DISTRIBUTION

Anthrax is a zoonotic disease that has been reported worldwide. Epizootic in many African, Asian, and Central American countries and sporadically reported in southern and eastern Europe, anthrax is responsible for major losses of livestock in endemic areas such as Iran, Iraq, Turkey, Pakistan, South America, and sub-Saharan Africa. Anthrax is relatively uncommon or not present in the countries of North America and northern Europe; however, sporadic epizootic outbreaks are still reported in livestock and wild herbivores and remain potential threats to human health.

DISEASE BURDEN

Anthrax cases in humans are typically related to animal anthrax outbreaks. True disease burden, however, is impeded by underdiagnosis and underreporting of both human and animal cases, especially in the developing world. In Zimbabwe, as a result of political instability and armed conflict that impeded anthrax control initiatives, an estimated 10,000 human cases occurred from 1978 to 1987. In countries with significant epizootic anthrax, several hundred cases occur yearly.

Human cases of anthrax in the United States are rare. From 1951 to 2000, 410 cases of anthrax were identified, and a majority of these cases were cutaneous. Total disease burden drastically declined from the later half of the 1950s (125 cutaneous, six inhalation) to the 1990s (one cutaneous; no inhalation) because of advancements in industry, agriculture, and laboratory risk-prevention practices. In 2001, a surge of cases in the United States occurred surrounding bioterrorist attacks (11 cutaneous, 11 inhalation).

RISK FACTORS

Anthrax infection in humans occurs naturally secondary to infection in animals. However, anthrax resulting from bioterrorist activities has increased the potential risk of anthrax occurring in individuals previously not at risk.

Worldwide, anthrax results from contact with infected animals or animal products, including those of animal origin such as leather drumheads, brushes, or yarn. Cutaneous and gastrointestinal anthrax outbreaks typically result from butchering, slaughtering, or handling infected animals or from the consumption of undercooked meat.

Anthrax may also be an occupational disease affecting veterinarians and farmers likely to contact or handle infected animals or their carcasses. Laboratory workers are also at increased risk when working with samples containing anthrax spores. Industrial anthrax exposures leading to inhalation anthrax result from the inhalation of spores aerosolized by processing of animal hides, hair, and wool. In the 1950s and 1960s, 80% of U.S. anthrax cases were related to the production of textiles with imported goat hair. Inhalation anthrax, or woolsorter's disease, decreased after improvements in industrial hygiene, immunization, proper disinfection of imported materials, and the decline in the importation of contaminated raw materials.

Sporadic cases of inhalation and cutaneous anthrax occurred from 2006 to 2008 in persons using contaminated imported animal hides for drum making. This included two cases of cutaneous anthrax in a drum maker and a family member. Both cutaneous and inhalation anthrax have been associated with the playing or handling of goatskin drums containing *B. anthracis* spores.

B. anthracis is a Centers for Disease Control and Prevention (CDC) category A select agent and is considered to be one of the most serious biowarfare or bioterrorism agents. It was used by the Germans during World War I against livestock and the Japanese during World War II in Manchuria. The United States and Britain conducted research on weaponized anthrax during and after World War II, and nations such as the Soviet Union and Iraq continued research into more recent decades. Anthrax poses a threat as a bioterrorist weapon because of its ability to be easily disseminated or transmitted into the environment, its resulting high mortality rate, its potential for causing social disruption, and the demands it places on public health preparedness.

CLINICAL FEATURES

Microbiology

B. anthracis, the causative agent of anthrax, is a large, gram-positive, nonmotile, spore-forming, rod-shaped bacterium. It grows optimally at 37° C on many culture media. The virulence of *B. anthracis* depends on three plasmid-mediated factors: edema toxin, lethal toxin, and a poly-D-glutamic acid capsule. The pX01 plasmid encodes for the three exotoxin components: edema factor, lethal factor, and protective antigen (PA); and the pX02 plasmid encodes the antiphagocytic poly-D-glutamic acid capsule. Edema factor combines with PA to form edema toxin, causing edema and inhibiting neutrophil function. Lethal factor combines with PA to form lethal toxin, which causes macrophage apoptosis, disrupts cytokine signaling, and causes shock and death. The combined effects of edema toxin and lethal toxin include local necrosis and edema in cutaneous anthrax, and hemorrhagic mediastinal necrosis, hypoxic insult, and pleural edema in inhalation anthrax. *B. anthracis* is susceptible to a variety of antimicrobial agents including penicillin, chloramphenicol, tetracycline, erythromycin, streptomycin, and the fluoroquinolones (see treatment section).

Clinical Presentation

Human anthrax has three major clinical forms; cutaneous, inhalation, and gastrointestinal (Figure 92-1). Cutaneous anthrax is a result of introduction of spores via the skin, inhalation anthrax via the respiratory tract, and gastrointestinal anthrax via ingestion through the gastrointestinal tract. Cutaneous anthrax is the most common naturally occurring infection caused by *B. anthracis*.

CUTANEOUS ANTHRAX

Cutaneous anthrax develops after transcutaneous introduction of *B. anthracis* spores. Over 90% of cutaneous anthrax lesions occur in exposed areas such as the face, neck, arms, and hands. The lesion begins as a small, painless, but often pruritic papule, developing 5 to 7 days after infection (range 1 to 12 days) and enlarging to create a central vesicle or bulla. The vesicle ruptures or erodes, leaving an underlying necrotic ulcer over which the characteristic black eschar develops. Satellite vesicles and ulcers may also form. Edematous swelling of the surrounding tissues is present, often with regional lymphadenopathy and

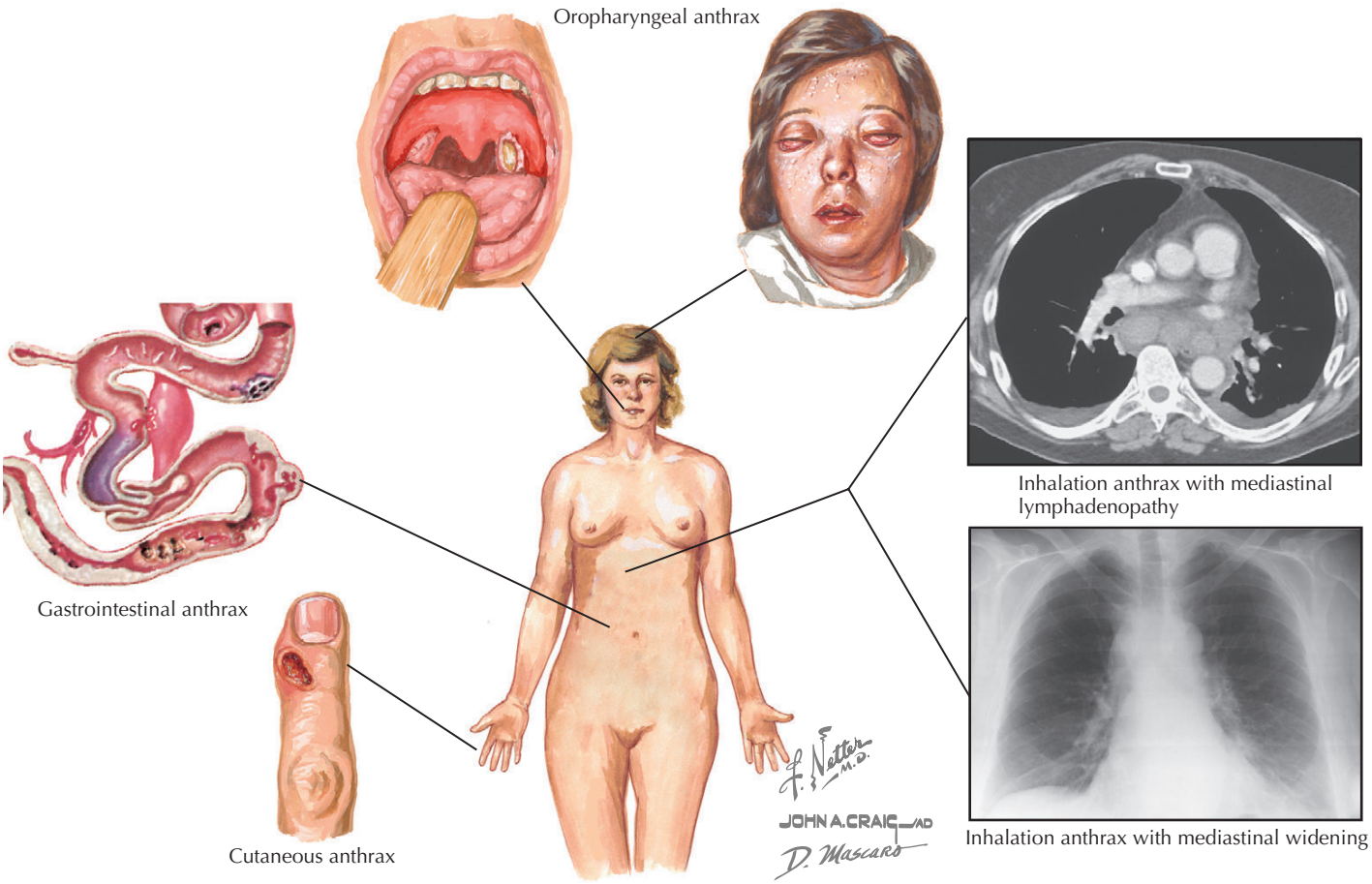

Figure 92-1 Clinical forms of anthrax.

lymphangitis. Systemic symptoms, including fever, malaise, and headache, can accompany the cutaneous lesion.

INHALATION ANTHRAX

Inhalation anthrax develops after the inhalation of anthrax spores. Alveolar macrophages phagocytize the spores and transport them to mediastinal lymph nodes, where the spores germinate, multiply, and release toxins, resulting in hemorrhagic necrosis of the thoracic lymph nodes and hemorrhagic mediastinitis (Figure 92-2). Necrotizing pneumonia may also develop. The incubation period for inhalation anthrax is generally estimated to be 1 to 7 days but was reported to be as long as 42 days in the 1979 outbreak in Sverdlovsk, and inhalation anthrax has developed up to 58 days and 98 days after experimental aerosol exposure in nonhuman primates.

The course of inhalation anthrax may be biphasic. First-stage clinical signs and symptoms are nonspecific and include low-grade fever, malaise, fatigue, myalgia, and nonproductive cough. The condition may mimic other illnesses such as influenza. The second stage of acute illness begins 2 to 3 days later with sudden onset of severe dyspnea and hypoxemia. Patients become hypotensive, diaphoretic, and cyanotic.

GASTROINTESTINAL ANTHRAX

Gastrointestinal anthrax develops after the consumption of undercooked meat contaminated with *B. anthracis*. There are two clinical forms of gastrointestinal anthrax: oropharyngeal and intestinal. The oropharyngeal form develops after infection of the oropharyngeal epithelium. Edematous lesions occur on the epithelium and progress to necrotic ulcers with a pseudomembrane. Profound edema develops in the oropharynx and neck. Pharyngitis, cervical lymphadenopathy, and fever follow. The intestinal form develops after infection of the gastric or intestinal mucosa. The infected intestinal segments become edematous, lesions may become necrotic and ulcerated, and draining mesenteric lymph nodes become infected and enlarged. The incubation period of gastrointestinal anthrax is estimated to be 1 to 6 days.

Patients may present with fever, nausea and vomiting, anorexia, or abdominal pain; symptoms may progress to hematemesis and bloody diarrhea, and patients may develop abdominal swelling as a result of voluminous, hemorrhagic ascites. In less severe cases, only mild diarrhea and abdominal pain develop.

BACTEREMIC DISSEMINATION AND MENINGITIS

After infection at the primary site of infection, the disease may progress with bacteremia, toxemia, and dissemination to other organ systems, resulting in shock and death. Anthrax meningitis may develop after initial infection with any of the three primary forms of disease and has been rarely reported in the absence of any other associated primary form of the disease.

DIAGNOSTIC APPROACH

Diagnosis of anthrax currently depends on culture and isolation of *B. anthracis*, which remains the gold standard for laboratory

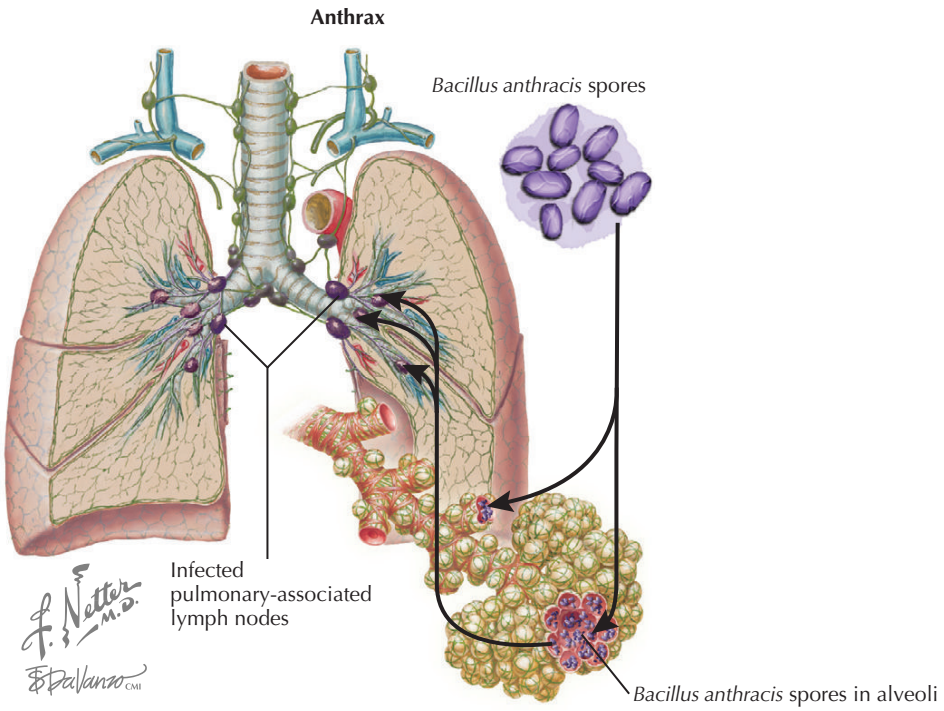

Figure 92-2 Inhalation anthrax.

confirmation of the diagnosis, or the detection of *B. anthracis* deoxyribonucleic acid (DNA) or antigens or of antibody responses against *B. anthracis*. Serologic diagnosis is possible through use of an enzyme-linked immunosorbent assay (ELISA) to detect immunoglobulin (IgG) antibodies against PA and also through the detection of capsule-specific antibodies, which has been used successfully for retrospective confirmation of anthrax in humans. Use of serology requires paired acute and convalescent sera. Diagnostic specimens, especially for culture, should be obtained before initiation of antimicrobial therapy, as the organisms may be rapidly cleared once effective antimicrobial therapy has been initiated.

In the United States, the Laboratory Response Network (LRN), established by the Association of Public Health Laboratories and the CDC, provides laboratory capacity for confirmatory diagnosis of anthrax.

DIFFERENTIAL DIAGNOSIS

Cutaneous Anthrax

In an appropriate epidemiologic setting, the presence of an eschar with extensive edema disproportionate to the size of the lesion and the presence of gram-positive rods and few polymorphonuclear leukocytes on Gram stain are strongly suggestive of cutaneous anthrax. The following diagnostic tests should be performed on patients with suspected cutaneous anthrax:

- For vesicular lesions, two swabs of vesicular fluid from an unopened vesicle—one for Gram stain and culture, the second for polymerase chain reaction (PCR)
- For eschars, the edge should be lifted and two swab samples rotated underneath and submitted—one for Gram stain and culture, the second for PCR
- For ulcers, the base of the lesion should be sampled with two saline-moistened swabs and submitted—one for Gram stain and culture, the second for PCR

In addition, a full-thickness punch biopsy of a papule or vesicle including adjacent skin should be submitted in 10% formalin for histopathology and immunohistochemical staining. In patients not undergoing antimicrobial therapy or who have been undergoing therapy for less than 24 hours, a second biopsy specimen should be submitted for Gram stain, culture, and PCR. Box 92-1 lists the diseases that should be considered in the differential diagnosis of a blackened eschar lesion.

Box 92-1 Differential Diagnoses of Cutaneous Anthrax

Toxin-Related
- Brown recluse spider bite

Bacterial
- Rickettsial pox
- Syphilis
- Ecthyma gangrenosum
- Ulceroglandular tularemia
- Tularemia
- Tropical ulcer
- Plague
- Typhus
- Glanders
- Rat-bite fever
- Leprosy
- Staphylococcal cellulitis
- Streptococcal cellulitis
- Cutaneous tuberculosis
- Atypical mycobacteria
- Cat-scratch disease

Drug-Induced
- Heparin or Coumadin necrosis

Autoimmune Disorders
- Antiphospholipid syndrome
- Pyoderma gangrenosum

Viral
- Varicella zoster
- Orf and milker's nodules
- Herpes simplex
- Vaccinia

Fungal
- Aspergillosis
- Mucormycosis

Protozoa
- Cutaneous leishmaniasis

Tumor
- Melanoma
- Squamous cell carcinoma
- Basal cell carcinoma

Other
- Eczema
- Trauma
- Burns

Inhalation Anthrax

Confirmatory testing should be performed on specimens from patients being evaluated for inhalation anthrax including patients with a known exposure or clear epidemiologic link to exposure who are manifesting symptoms of inhalation anthrax (see discussion of prevention and control). Because the window of opportunity for successful treatment is narrow once symptoms appear, it is important to distinguish potential inhalation anthrax cases from more common disorders such as community-acquired pneumonia (CAP), influenza, and influenza-like illnesses (ILIs). Analysis of the clinical characteristics predictive of inhalation anthrax using data from 47 historical cases of inhalation anthrax compared with 376 controls with CAP or ILI revealed the following:

- The most accurate predictors of inhalation anthrax were mediastinal widening or pleural effusion on chest x-ray examination, and one or both of these findings were 100% sensitive for inhalation anthrax and 72% and 96% specific when compared with CAP or ILI controls, respectively.
- Clinical signs more frequently associated with inhalation anthrax than with CAP or ILI included shortness of breath, nausea, vomiting, altered mental status, pallor or cyanosis,

Box 92-2 Differential Diagnoses of Inhalation Anthrax

Bacterial
- Pneumonic tularemia
- Q fever
- Psittacosis
- Legionnaires' disease
- Community-acquired pneumonia

Fungal
- Histoplasmosis
- Coccidioidomycosis

Viral
- Influenza
- Community-acquired pneumonia
- Influenza-like illnesses (e.g., rhinovirus, adenovirus, and parainfluenza virus infection)

Other
- Malignancy

and hematocrit greater than 45%. In contrast, symptoms more suggestive of an ILI included rhinorrhea or sore throat.

Widening of the mediastinum secondary to mediastinitis is a classic finding in inhalation anthrax. Other thoracic imaging abnormalities seen with inhalation anthrax include pulmonary infiltrates or consolidation and pleural effusion. Diagnostic testing of patients with suspected inhalation anthrax should include the following:

- Blood cultures obtained before antimicrobial therapy
- Pleural fluid, if present, for Gram stain, culture, and PCR
- Cerebrospinal fluid in patients with meningeal signs, for Gram stain, culture, and PCR
- Acute and convalescent serum samples for serologic testing
- Pleural and/or bronchial biopsy specimens for immunohistochemistry, if other test results are negative

Box 92-2 lists the diseases that should be considered in the differential diagnosis of a respiratory syndrome.

Gastrointestinal Anthrax

Information regarding reliability of diagnostic testing is limited for gastrointestinal anthrax. Culture from stool frequently does not yield *B. anthracis*, but Gram stain or culture of oropharyngeal lesions or ascitic fluid may be positive. Blood cultures may also be positive if collected before initiation of antimicrobial therapy. Diagnostic testing of patients with suspected gastrointestinal anthrax should include the following:

- Blood cultures obtained before antimicrobial therapy
- Ascitic fluid for Gram stain, culture, and PCR
- Stool or rectal swab for Gram stain, culture, and PCR
- Oropharyngeal lesion, if present, for Gram stain, culture, and PCR
- Acute and convalescent serum samples for serologic testing

Box 92-3 Differential Diagnoses of Gastrointestinal or Oropharyngeal Anthrax

Gastrointestinal
- Foodborne illness
- Acute appendicitis
- Ruptured viscus
- Diverticulitis
- Dysentery
- Necrotizing enteritis caused by *Clostridium perfringens*

Oropharyngeal
- Vincent's angina
- Ludwig's angina
- Streptococcal pharyngitis
- Parapharyngeal abscess

Other
- Malignancy

Box 92-3 lists the diseases that should be considered in the differential diagnosis of hemorrhagic gastroenteritis or oropharyngeal lesions suspected to be gastrointestinal anthrax.

CLINICAL MANAGEMENT AND TREATMENT

Antimicrobial therapy should be initiated immediately after laboratory or clinical suspicion of anthrax because of the rapid progression of disease. Public health and state health departments should be promptly notified.

Ciprofloxacin, doxycycline, and penicillin G procaine are approved by the Food and Drug Administration (FDA) for the treatment of anthrax, including inhalation anthrax. As inducible β-lactamases may be present, initial use of β-lactam antimicrobial agents is not recommended.

Treatment for uncomplicated, naturally occurring cutaneous anthrax is as follows:

- Ciprofloxacin (500 mg orally twice daily in adults; 10 to 15 mg/kg every 12 hours [not to exceed 1 g/day] in children), *or*
- Doxycycline for 5 to 7 days as follows:
  - Adults: 100 mg orally twice daily
  - Children >8 years old and >45 kg: 100 mg every 12 hours
  - Children >8 years old and ≤45 kg: 2.2 mg/kg every 12 hours
  - Children ≤8 years old: 2.2 mg/kg every 12 hours

With supportive antimicrobial susceptibility profiles, penicillin V (500 mg orally every 6 hours) or amoxicillin (500 mg orally three times daily) may be used to complete treatment. For more severe cutaneous cases with systemic involvement, extensive edema, lesions of the head and neck, or for cutaneous anthrax in children younger than 2 years of age, intravenous ciprofloxacin (400 mg twice daily) or doxycycline (100 mg twice daily) is suggested for treatment. Ciprofloxacin is preferred over doxycycline for serious cases because of the bactericidal effects of the fluoroquinolones. The intravenous doses are the same as oral doses for pediatric patients. With appropriate susceptibility

results, penicillin G (4 to 6 million units four times daily) may be used to complete the 7- to 10-day treatment. For cases of cutaneous anthrax with a risk for potential aerosol exposure, the duration of antimicrobial therapy should be 60 days to provide a full course of postexposure prophylaxis (PEP).

Patients with inhalation anthrax typically seek medical care late in the course of the illness. Therefore first-line antimicrobial treatment should be immediately initiated in patients with suspected anthrax. The failure of single-drug therapy has been reported for the treatment of inhalation anthrax, thus providing rationale for a multidrug approach. Early clinical data for the treatment of inhalation anthrax cases resulting from the 2001 bioterrorism event suggest that intravenous treatment with two or more antimicrobial agents improves survival. The multidrug treatments are ciprofloxacin (400 mg twice a day) plus one or two of the following antimicrobials: doxycycline, rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, meropenem, and clindamycin.

Patients may be switched from intravenous treatment to oral therapy typically after 14 to 21 days or after their condition is stable. A total duration of treatment of 60 days (combination of intravenous and oral therapy) should be applied. Chest tubes or thoracentesis should be used to drain pleural effusions as supportive therapy in all inhalation anthrax cases.

Corticosteroids have also been suggested as adjunctive therapy for some patients with inhalation anthrax because of toxin-related morbidity, including patients with extensive edema, respiratory failure, and meningitis and patients with cutaneous anthrax with extensive edema involving the head and neck.

Anthrax immunoglobulin derived from persons immunized with Anthrax Vaccine Adsorbed (AVA) is available from the CDC, through state and local health departments, under an Investigational New Drug (IND) protocol for the treatment of persons with confirmed cases of life-threatening anthrax. It was used as a part of the successful clinical treatment of an inhalation anthrax case in 2006, but its use in the treatment of a subsequent inhalation anthrax case in 2008 did not prevent a fatal outcome. Clinicians and laboratorians should contact their state and local health departments to request anthrax immunoglobulin from the CDC.

After an exposure to aerosolized *B. anthracis* spores, either bioterrorism-related or naturally occurring, a full-course PEP regimen of 60 days of antimicrobial agent therapy plus three doses of AVA is recommended. Three oral antimicrobial agents have been approved by the FDA and are recommended by the CDC for PEP. The first-line antimicrobial agents for adults and children are as follows:

- Ciprofloxacin (500 mg orally twice daily in adults; 10 to 15 mg/kg every 12 hours [not to exceed 1 g/day] in children). The CDC recommends ciprofloxacin as the first-line drug for PEP in pregnant women and nursing mothers.
- Doxycycline:
  - Adults: 100 mg orally twice daily.
  - Children >8 years old and >45 kg: 100 mg every 12 hours
  - Children >8 years old and ≤45 kg: 2.2 mg/kg every 12 hours
  - Children ≤8 years old: 2.2 mg/kg every 12 hours

The approved second-line antimicrobial agent recommend for PEP is as follows:

- Levofloxacin (500 mg orally once daily in adults; 16 mg/kg/day div q12h, with each dose not to exceed 250 mg, in children ≥6 months of age)

Levofloxacin is considered a second-line antimicrobial agent for PEP when medical issues such as tolerance or resistance may call for its use, as safety data on extended use of levofloxacin in any population for more than 28 days are limited.

Gastrointestinal anthrax manifests rather quickly, after an incubation period of at most 1 week. There are few studied cases of gastrointestinal anthrax; therefore, the treatment regimen is the same as suggested for inhalation anthrax. The duration of treatment should be determined by clinical response to therapy and would not be as prolonged as recommended for inhalation anthrax.

PROGNOSIS

Cutaneous anthrax has had case-fatality rates as high as 20% without appropriate treatment; however, with antimicrobial therapy the case-fatality rate is less than 1%. Gastrointestinal anthrax has an estimated untreated mortality ranging from 25% to 60%; however, with appropriate treatment the mortality is lower (0% to 29%). Inhalation anthrax, if untreated, is usually fatal. Antimicrobial therapy can be successful, especially if initiated early in the course of disease; however, even with early initiation of treatment, five of the 11 patients with inhalation anthrax (45%) associated with the 2001 bioterrorism event in the United States died.

PREVENTION

Prevention of human anthrax is primarily dependent on the control of the disease in animals, especially livestock. Annual immunization of livestock in areas of enzootic anthrax is recommended.

Animal anthrax cases and outbreaks should be reported to agriculture and public health officials. Affected premises or areas should be quarantined and any further slaughter, butchering, and marketing of infected animals or their parts prevented. Antimicrobial treatment of affected animals and immunization of all susceptible livestock on affected and surrounding premises is recommended. Carcasses of animals that die of anthrax, bedding, and other contaminated material should be incinerated completely. If that is not possible, carcasses of infected animals should be deeply buried with a covering of chloride of lime mixed with soil; however, anthrax outbreaks have recurred where carcasses have previously been buried.

For humans, AVA (BioThrax, BioPort, Lansing, Michigan) is the only anthrax vaccine licensed for use in the United States. The vaccine is recommended for persons with an occupational risk, who work in high-risk industries such as those that process imported animal hides, hair, and wool, where industrial hygiene standards and restrictions are insufficient to prevent exposure to anthrax spores; for veterinarians and others who potentially handle infected animals in areas with a high disease incidence; and for laboratory workers who encounter large quantities or

concentrations of *B. anthracis* cultures. Recently the Advisory Committee on Immunization Practices (ACIP) updated the provisional recommendation for the use of anthrax vaccine in persons considered to be at risk for exposure to aerosolized *B. anthracis* spores to include emergency responders, in addition to the previously mentioned recommended populations. Vaccine should be administered in 5 intramuscular injections at 0 and 4 weeks and at 6, 12, and 18 months. To maintain effective immunity, a booster injection is recommended annually.

CONTROL

Because of the resistance of the spore, disinfection of materials contaminated with *B. anthracis* is complicated. A variety of procedures including those using dry heat, steam under pressure, formaldehyde soaking or vapor exposure, ethylene oxide gas exposure, hypochlorite solution soaking, and gamma-irradiation are measures that have been effectively used to decontaminate materials or areas affected by anthrax. The potential benefits associated with the disinfection method should be weighed against the potential risks and the effectiveness of the disinfection method verified by appropriate quality control analysis.

Improvements in industrial hygiene, immunization of at-risk workers, and a decrease in the use of imported, contaminated raw materials resulting from restrictions on the importation of potentially contaminated products of animal origin, have limited industrial anthrax exposure.

Anthrax has plagued humans and animals for centuries. Anthrax persists throughout the world and continues to cause outbreaks, although these outbreaks are now less common in the developed world. As experienced in the 2001 bioterrorist activities in the United States, intentionally caused anthrax remains a great risk.

Appropriate identification methods and treatment regimens must be quick and effective in their approach toward anthrax, because both are essential in improving patient outcomes. Understanding the etiology and epidemiology of anthrax facilitates an appropriate public health response in the treatment of cases, in the control of outbreaks, and in limiting the effects of intentional exposure.

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Tularemia

Jo Hofmann

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ABSTRACT

Tularemia is a zoonotic bacterial infection that occurs throughout the Northern hemisphere; it is caused by several subspecies of the gram-negative coccobacillus *Francisella tularensis*. A wide variety of animals can be infected with *F. tularensis*, and the bacteria can also be carried by insects. Human *F. tularensis* infection is acquired through contact with infected animals, by the bite of an infected insect, or through inhalation or ingestion of the bacteria, which are highly infectious. Thus tularemia is a human disease associated with outdoors activities, especially among hunters and trappers, and may be an occupational disease of landscape workers and gardeners. The severity of tularemia depends on the infecting subspecies of *F. tularensis*, the mode of disease transmission, and the size of the infecting inoculum. The spectrum of human *F. tularensis* ranges from mild, localized infection to life-threatening sepsis. Although *F. tularensis* is an uncommon human illness in the United States, because it is highly infectious, is easily transmissible, and causes severe or fatal illness, it is considered a potential agent of bioterrorism.

GEOGRAPHIC DISTRIBUTION AND MAGNITUDE OF DISEASE BURDEN

Tularemia, also known as *rabbit fever* or *deer fly fever*, is a zoonosis caused by a highly infectious, aerobic, gram-negative coccobacillus, *F. tularensis*. The natural reservoir for *F. tularensis* is small mammals such as rodents or rabbits. The bacterium is found throughout host animals in most of North America and Eurasia. In the United States, tularemia is most commonly caused by two subspecies of *F. tularensis*: *F. tularensis* subsp *tularensis* (type A, which is subdivided into subtypes A1a, A1b and A2), and *Francisella tularensis* subsp *holarctica* (type B). In Europe and Eurasia, *F. tularensis* subsp *holarctica* is the primary cause of tularemia. Human tularemia was first described in the United States in 1910 as "deer fly fever," and the causative agent (at that time known as *Bacterium tularense*) was identified after an outbreak of a plaguelike illness of ground squirrels in Tulare County, California, in 1911. In 1924 a United States Public Health Service physician, Edward Francis, identified *B. tularense* as the cause of human deer fly fever. To honor his contributions to the understanding of this organism, the bacterium was subsequently renamed *Francisella tularensis*.

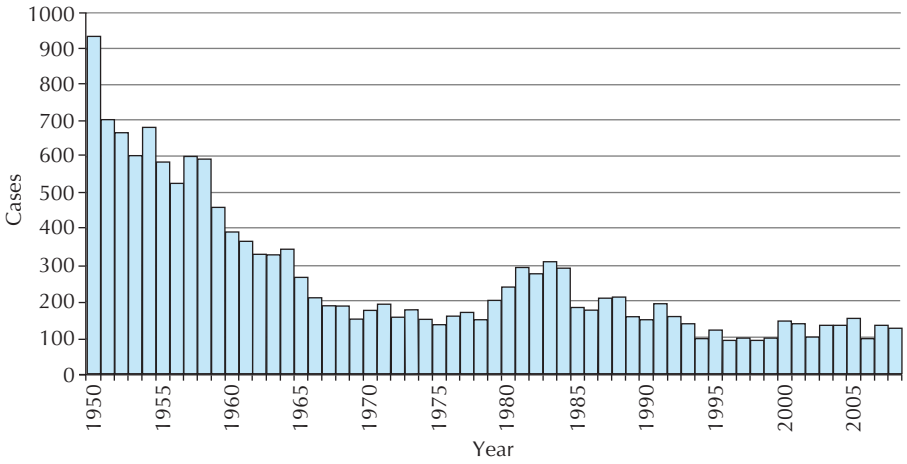
In the United States, human tularemia is rare but has been documented in every state except Hawaii. Tularemia was much more common in the early part of the twentieth century than it is now (Figure 93-1). Since 2000, most cases of tularemia have been reported from rural areas of the United States where infection of host animals is common (or enzootic), such as Arkansas, Kansas, Nebraska, and Missouri. In addition, many cases are reported from Martha's Vineyard, Massachusetts, where hunting clubs imported infected rabbits from enzootic areas in the 1920s and 1930s. From 2000 through 2008, the Centers for Disease Control and Prevention (CDC) received 1133 reports of human tularemia, approximately 126 infections per year (Figure 93-2). Although the global incidence of tularemia has decreased markedly over the past 50 years, periodic outbreaks continue to occur, especially in Northern Europe and Eurasia. These outbreaks have been associated with drinking spring water, hunting, and other outdoor activities, and some have involved hundreds of cases of tularemia. Although rare in humans, tularemia occurs in a wide variety of animals and is maintained in an enzootic cycle with rodents and lagomorphs. Other animals, such as cats and nonhuman primates, may serve as incidental hosts. Outbreaks, or epizootics, of tularemia periodically occur in animal populations and may herald outbreaks of human disease.

RISK FACTORS

The animals most commonly associated with transmission of tularemia to humans in the United States include lagomorphs (rabbits and hares) and rodents (voles, squirrels, muskrats, and beavers). Although animals are the primary reservoir of *F. tularensis*, the infection can also be transmitted by insect bites (especially those of ticks or deer flies) or by contact with bacteria in the environment. *Francisella tularemia tularensis* is a hardy organism that can survive for extended periods in water, mud, and frozen animal carcasses. Tularemia has been reported after skin or mucous membrane contact with contaminated animals or their environment, ingestion of contaminated food or water, and inhalation of aerosolized bacteria (Figure 93-3). Activities associated with risk of tularemia include hunting, trapping, dressing, eating, or handling infected animals; activities that result in exposure to infected insects; farming or gardening with machinery that may aerosolize the carcasses of infected animals; and handling *F. tularensis* in a laboratory without appropriate personal protective equipment. Although inhalational tularemia does occur, the bacteria are not known to spread from person to person.

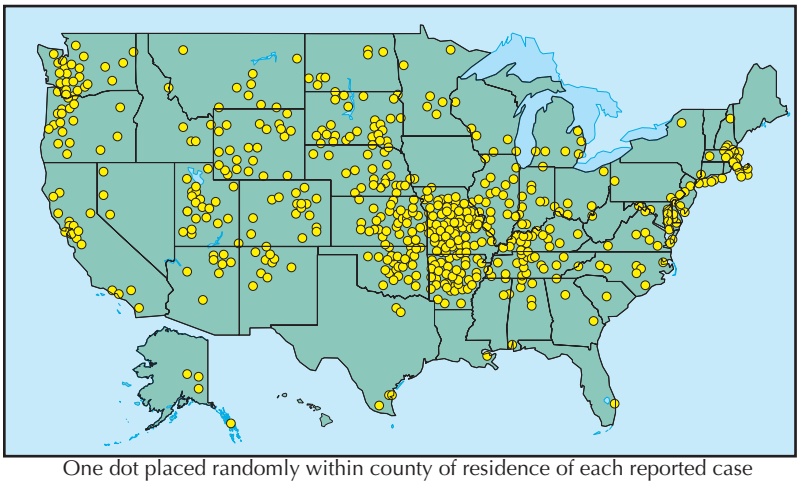
During and after World War II, several countries (including Japan, the former Soviet Union, and the United States) conducted research into the use of *F. tularensis* as a biologic weapon. More recently, most countries have suspended their biologic weapons research and destroyed their weapon stockpiles. However, as a highly infectious bacteria that can be easily mass produced and aerosolized, with the potential to cause severe or fatal illness, *F. tularensis* continues to be designated a Category A Bioterrorism Agent by the CDC.

Recent CDC analyses of laboratory-documented human tularemia reported in the United States from 1964 through



Tularemia was much more common in the early part of the 20th century than it is now.

Figure 93-1 Reported tularemia, United States, 1950 to 2008. *(From Centers for Disease Control and Prevention (CDC):* Tularemia statistics. *Available at: www.cdc.gov/tularemia/Tul_Statistics.html.)*



One dot placed randomly within county of residence of each reported case

Figure 93-2 Reported cases of tularemia by county of residence, United States, 2000 to 2008. *(From Centers for Disease Control and Prevention (CDC):* Tularemia statistics. *Available at: www.cdc.gov/tularemia/Tul_Statistics.html.)*

2004 found that infections tend to be acquired during the warmer months (72% occurred from May through September) and are geographically diverse (type A1 infections cluster toward the eastern United States, type A2 infections occur toward the west, and type B is primarily clustered through the southern and central western areas of the country). Men constitute the majority of infections (74%), and younger age appears to be a risk for infections with type A, compared with type B (median age 38 versus 50 years) (Figure 93-4). Overall, 6% of infections occurred among persons with an immunocompromising condition (e.g., malignancy, organ transplant, or human immunodeficiency virus [HIV] infection). A source of infection was reported for 42% of the cases, and in this subgroup, direct animal contact accounted for about half of all infections (47% of type A and 53% of type B). Among persons with infection associated with animal contact, 53% of type A infections were attributed to lagomorphs and 30% to cats. No persons with type B infection reported lagomorph contact; those infections were linked to either rodents (33%) or cats (22%). Tularemia attributed to insects accounted for 44% of type A infections and 29% of type B infections; among infections resulting from insect bites, tick exposure (87%) was reported more commonly than contact with deer flies. A small proportion of types A (8%) and B (18%) infections were associated with multiple exposures or landscaping activities.

CLINICAL FEATURES

The clinical presentation and severity of tularemia vary according to the infecting type or subtype of *F. tularensis*, the size of the bacterial inoculum, and the initial site of inoculation. The incubation period for tularemia is about 3 to 7 days (range 1 to 14 days). The clinical spectrum of tularemia is quite variable, ranging from localized infection to life-threatening systemic illness; forms include ulceroglandular, glandular, pneumonic, typhoidal, oculoglandular, pharyngeal, and septic syndromes (Figure 93-5). After entry of *F. tularensis* via skin or mucous membranes, the bacteria disseminate to local lymph nodes and subsequently spread via the bloodstream to additional lymph nodes and organs, primarily the spleen, liver, kidney, lungs, and pleura. Regardless of the form of infection, untreated tularemia may become chronic, with fever, malaise, weight loss, and adenopathy lasting months.

Tularemia most commonly manifests as ulceroglandular or glandular disease (about 60% to 80% of infections) that follows entry of the bacteria into disrupted skin from contact with an

Francisella tularensis infects many different animal species; transmission to humans in the United States occurs most commonly from contact with infected rabbits, rodents, or domestic cats.

Human infection can also occur from tick and deer fly bites or through ingestion of contaminated food or water.

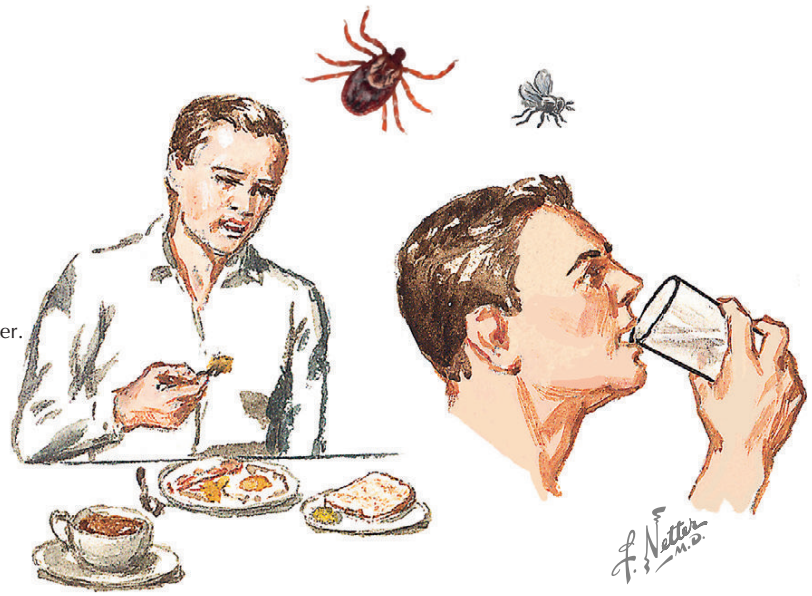
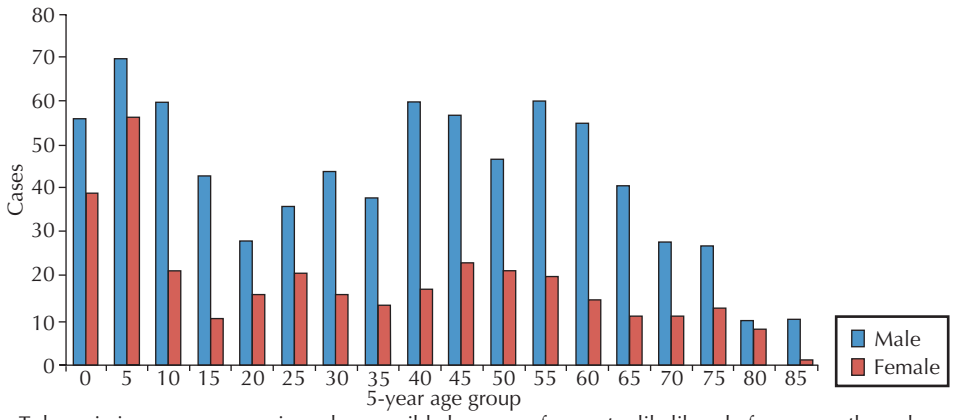


Figure 93-3 Transmission of *Francisella tularensis*.



Tularemia is more common in males, possibly because of a greater likelihood of exposure through hunting and landscaping. Tularemia occurs in persons of all ages, but is most common in children.

Figure 93-4 Reported tularemia by age and gender, United States, 2000 to 2008. *(From Centers for Disease Control and Prevention [CDC]:* Tularemia statistics. *Available at: www.cdc.gov/tularemia/Tul_Statistics.html.)*

infected animal or via the bite of an infected insect. A papule appears at the site of inoculation, and, similar to other presentations of tularemia, the skin lesion is usually accompanied by the abrupt onset of symptoms of a systemic disease: chills, fever, headache, malaise, and myalgias. The skin lesion becomes pustular and tender with local lymphadenopathy, then ulcerates and may develop an eschar; the involved lymph nodes may become fluctuant and suppurate. In glandular tularemia, a less common form, a skin or mucosal lesion is not apparent.

About 15% of infected persons have pneumonic tularemia, which may result from inhalation of bacteria or by hematogenous spread from another site. Typical signs and symptoms

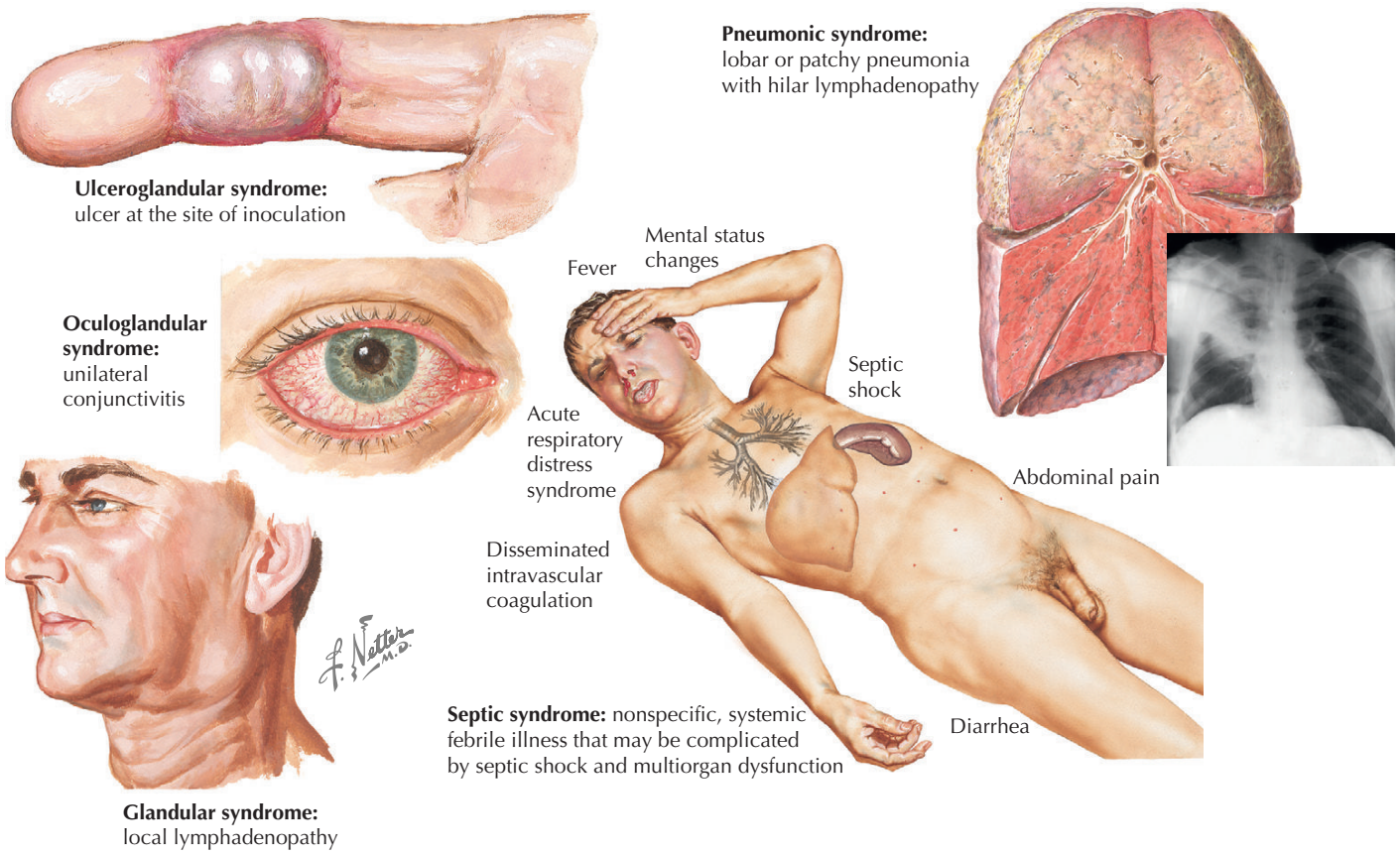


Figure 93-5 Syndromes associated with human tularemia.

include fever and a nonproductive cough with substernal and/or pleuritic chest pain. In early pneumonic tularemia, chest radiographs may show diffuse peribronchial infiltrates that progress to patchy or lobar involvement with pleural effusions and perihilar lymphadenopathy. However, many patients demonstrate systemic findings alone and lack significant pulmonary involvement. In one study in which volunteers were intentionally exposed to aerosolized tularemia, up to 75% had no pulmonary signs or symptoms at the onset of illness. Despite these findings, pneumonic tularemia can rapidly progress to severe, multilobar pneumonia, acute respiratory distress syndrome (ARDS), and death.

Less common presentations of tularemia include typhoidal (a systemic illness that does not involve specific organs or lymph nodes and lacks an obvious site of inoculation), oculoglandular (inoculation of the conjunctiva with mucosal ulceration and local lymphadenopathy), and oropharyngeal (ingestion of bacteria followed by oropharyngeal mucosal ulceration and local lymphadenopathy). Although rare, sepsis is the most serious form of tularemia, a systemic illness that may rapidly progress to shock, multisystem organ failure, and death.

Laboratory findings in tularemia are nonspecific and may include leukocytosis, thrombocytopenia, and hyponatremia, as well as abnormalities associated with multi-organ dysfunction including elevated serum aminotransferases and creatine kinase.

DIAGNOSTIC APPROACH

The nonspecific findings associated with the many forms of tularemia may pose a diagnostic dilemma, especially with typhoidal, pneumonic, or septic disease. Pneumonic tularemia may mimic other causes of atypical pneumonia (e.g., *Mycoplasma*, *Legionella*, or *Chlamydophila* pneumonia, Q fever). Typhoidal tularemia can be indistinguishable from the innumerable causes of prolonged fever without an apparent source (e.g., invasive bacterial, mycobacterial, fungal, and parasitic infections; rheumatologic disorders; malignancies). An atypical presentation of ulceroglandular tularemia may suggest another localized bacterial or herpes virus infection, and glandular disease can be mistaken for a variety of bacterial, mycobacterial, fungal, parasitic, and viral infections that cause chronic fever and lymphadenopathy. Clinical suspicion may be heightened in enzootic areas when a patient has ulceroglandular tularemia, especially in the setting of an epizootic, but most clinicians in the United States lack familiarity with any presentation of tularemia. Factors that may signal an intentional release of *F. tularensis* include clusters of severe, atypical pneumonia or acute febrile illness that rapidly progress if untreated or tularemia that occurs in urban areas or among persons without obvious risk factors.

Preferred specimens for the detection or isolation of *F. tularensis* include biopsy specimens from an ulcer, lymph node, or

other affected tissue; fluid aspirates; or tissue swabs or scrapings. The organism is very rarely isolated from blood. *F. tularensis* requires a cysteine-enriched growth medium, and the bacteria are infrequently identified by Gram stain or isolated from routine cultures of skin or mucosal lesions, blood, sputum, respiratory secretions, or lymph node or pleural aspirates. Although isolation of *F. tularensis* from a clinical specimen is considered the gold standard for a diagnosis of tularemia, clinical laboratories must be alerted that tularemia is suspected so that they can use appropriate growth media and biosafety measures. Antimicrobial susceptibility testing should be performed only at an experienced microbiology laboratory.

Detection of an elevated acute antibody titer against *F. tularensis* provides a presumptive diagnosis of tularemia, whereas a fourfold rise in antibody titers in paired acute and convalescent serum specimens is diagnostic. Convalescent blood specimens should be drawn at least 28 days after the onset of illness. Methods used to detect antibody include enzyme-linked immunosorbent assay (ELISA) and microagglutination and tube agglutination, which detect both immunoglobulin M (IgM) and IgG. However, isolation of the organism or demonstration of a fourfold increase in antibody titers may not be timely enough for clinical or public health management of tularemia. More specialized methods, available at local, state, and federal public health laboratories, include direct fluorescent antibody, polymerase chain reaction assays or immunohistochemical staining of clinical specimens; these methods can provide a rapid, presumptive diagnosis of tularemia, enabling appropriate patient management and public health interventions.

CLINICAL MANAGEMENT AND DRUG TREATMENT

Rapid administration of appropriate antimicrobial therapy is the only treatment for tularemia. No controlled clinical trials have evaluated the duration of therapy required for cure or the efficacy of different antimicrobial regimens. A literature review of case series and reports has suggested that bactericidal aminoglycosides appear to have the highest cure rate and the lowest incidence of relapse, compared with the bacteriostatic agents tetracyclines and chloramphenicol. Ciprofloxacin has also been used in the treatment of tularemia in both adults and children, but experience with this antimicrobial is limited. For years, the drug of choice for tularemia was streptomycin, an aminoglycoside that must be given intramuscularly. However, as of this writing, streptomycin is no longer produced in the United States, and availability of this drug is extremely limited. In the absence of streptomycin, gentamicin is the recommended therapy for tularemia in all adults, including pregnant women (3.0 to 5.0 mg/kg/day, administered intravenously or intramuscularly in a single dose or two or three divided doses for 7 to 14 days), and children (3.0 to 7.5 mg/day administered intravenously or intramuscularly in three divided doses for 7 to 14 days). The dose of aminoglycoside should be adjusted for renal insufficiency. As alternatives to an aminoglycoside, adults and children may be treated with oral doxycycline (doxycycline should not be used in children younger than 8 years of age unless no alternative therapy is available) for 14 days, and adults may be treated with 10 days of doxycycline or ciprofloxacin. Ciprofloxacin has not been approved by the Food and Drug Administration (FDA) for treatment of tularemia in children younger than 18 years of age. More severe tularemia may require a longer course of treatment.

In the event of an intentional release of tularemia, the initial empirical therapy for adults and children would be streptomycin or gentamicin (depending on availability) for 10 days; alternatively, ciprofloxacin (for 10 days), doxycycline, or chloramphenicol (for 14 to 21 days) can be given, with the caveat that chloramphenicol should not be administered to pregnant women.

PROGNOSIS

Even with appropriate and timely administration of antimicrobial therapy, complications of tularemia may occur. Involved lymph nodes may suppurate and require surgical drainage. More severe forms of infection can be complicated by disseminated intravascular coagulation, rhabdomyolysis, and renal and hepatic failure. Before the availability of antimicrobials, fatality rates of 5% to 60% were reported for tularemia, depending on the infecting type and syndrome; however, more recent reviews describe case fatality rates ranging from 4% to 9%. Factors associated with a poor outcome include increasing age, underlying medical conditions, delayed or inappropriate antimicrobial treatment, and typhoidal or pneumonic disease. Although *F. tularensis* type A is classically associated with more severe disease than infections caused by type B, a recent investigation of the molecular diversity of *F. tularensis* using pulsed field gel electrophoresis and multivariate logistic regression analysis found that subtype A1b appears to the most lethal form of tularemia, followed by types B, A1a, and A2, in decreasing order of lethality.

PREVENTION AND CONTROL

Overview

Prevention of tularemia relies on minimizing the potential for contact with *F. tularensis*, especially in enzootic areas. Hunters, trappers, and others in contact with wild animals should wear gloves when handling these animals. Wild-animal meat should always be cooked thoroughly before consumption, and drinking untreated water should be avoided. Anyone engaged in outdoor activities should dress to avoid insect bites (e.g., long sleeves with long pants tucked into socks), use effective insect repellent (e.g., N,N-diethyl-*m*-toluamide [DEET] or picaridin), and perform frequent tick checks if outdoors for prolonged periods of time. When performing landscaping or gardening, consider wearing a dust mask and avoid activities that could aerosolize *F. tularensis*, such as mowing over sick or dead animals.

F. tularensis is one of the most highly infectious microorganisms that laboratory workers may encounter; inoculation with as few as 10 organisms can cause infection. Clinical laboratories should always be alerted before they receive a specimen from a patient suspected to have tularemia. A detailed discussion of laboratory safety is beyond the scope of this chapter; however, whereas most microbiologic procedures involving *F. tularensis* can be performed using biosafety methods common to most clinical laboratories, some procedures require a greater level of biosafety conditions available to few nonresearch

laboratories. Laboratory workers exposed to *F. tularensis* should be monitored for fever and/or provided with chemoprophylaxis for tularemia.

Immunization

Infection with tularemia is thought to confer lifelong immunity, although repeat infections have been reported. A variety of vaccines have been developed to prevent tularemia; however, currently there are no effective human vaccines available for the civilian population in the United States.

Chemoprophylaxis

In the event of an intentional release of *F. tularensis*, chemoprophylaxis may be effective in preventing the development of tularemia if given within the incubation period. The recommended treatment for children and adults (including pregnant women) is oral doxycycline or ciprofloxacin for 14 days. In other high-risk exposure situations (e.g., exposed laboratory workers, animal handlers in contact with animals known to have tularemia), chemoprophylaxis may be indicated. Chemoprophylaxis of persons in contact with someone who has tularemia is not indicated, as *F. tularensis* is not transmitted from person to person.

Infection Control

As noted earlier, tularemia is not transmitted from person to person; therefore in healthcare settings, standard precautions (frequent hand hygiene with soap and water or alcohol-based hand sanitizers; gown and eye protection [i.e., goggles or face shield] during activities that may generate splashes or aerosols of respiratory or other body fluids) alone are recommended for infection control for patients infected with tularemia.

Public Health Measures

The importance of reporting suspected communicable diseases to public health authorities may be overlooked by busy clinicians. Although highly infectious, *F. tularensis* cannot be spread from person to person. However, prompt recognition of clusters of human or animal tularemia may prevent further cases of illness or reveal an intentional release of bacteria. It is important that clinicians report any suspected cases of human tularemia to their local or state health department. Public health personnel can facilitate diagnostic and confirmatory laboratory testing and assist in the identification of potential exposures.

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University of Minnesota Center for Infectious Disease Research and Policy (CIDRAP): Tularemia. Available at: www.cidrap.umn.edu/cidrap/content/bt/tularemia/index.html. *CIDRAP is a collaborative center of the University of Minnesota that focuses on emerging global challenges to public health, including preparedness and response to events such as bioterrorism and pandemic influenza. The site has extensive information about tularemia, including a comprehensive review of the subject that is updated frequently.*

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