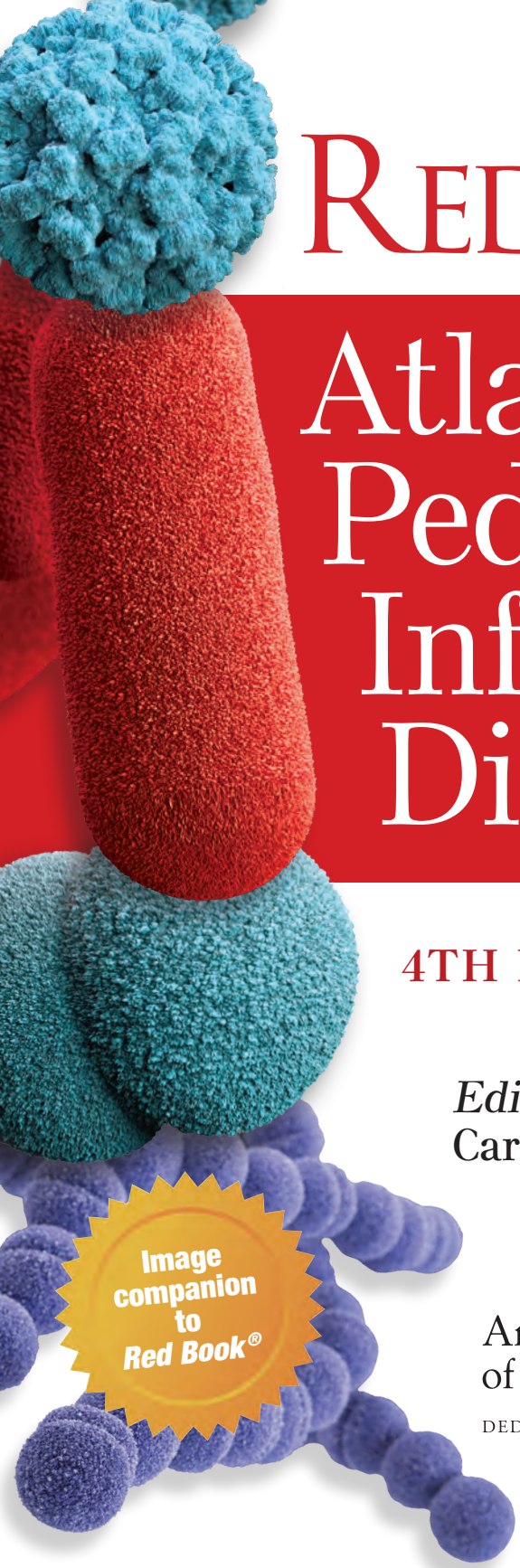

RED BOOK®

Atlas of Pediatric Infectious Diseases

4TH EDITION

Editor
Carol J. Baker, MD, FAAP

American Academy of Pediatrics

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Contents

Preface

The American Academy of Pediatrics (AAP) *Red Book® Atlas of Pediatric Infectious Diseases*, 4th Edition, is a summary of key disease information from the AAP *Red Book®: 2018–2021 Report of the Committee on Infectious Diseases*. It is intended to be a study guide for students, residents, and practicing physicians.

The images of common and unusual features of children with infectious diseases can provide diagnostic clues not found in the print version of *Red Book*. The juxtaposition of these images against text summarizing the clinical manifestations, epidemiology, diagnostic methods, and treatment information will be, I hope, effective as a training tool and a quick reference. The *Red Book Atlas* is not planned to provide detailed information on treatment and management but, rather, a big-picture approach that can be refined, as desired, by reference to authoritative textbooks, original articles, or infectious disease specialists. Complete disease and treatment information from the AAP can be found in the electronic version of the *Red Book* at **https://redbook.solutions.aap.org.**

The *Red Book Atlas* would not exist without the assistance of Heather Babiar, Jason Crase, and Theresa Wiener at the AAP and of those physicians who photographed disease manifestations in their patients and shared these with the AAP. Some diseases have disappeared (ie, smallpox), and others are rare (eg, diphtheria, tetanus, congenital rubella syndrome) because of effective prevention strategies, especially immunization. While photographs cannot replace hands-on familiarity, they helped me to consider the likelihood of alternative diagnoses, and I hope that this will be so for the reader. I also want to thank the many individuals at the Centers for Disease Control and Prevention who generously provided many images of etiologic agents, vectors, and life cycles of parasites and protozoa relevant to some of these infections.

The study of pediatric infectious diseases has been a challenging and ever-changing professional life for me that has brought me enormous joy. To gather data with my ears, eyes, nose, and hands (the growingly obsolete history and physical examination), and to select the least-needed diagnostic tests to solve the mystery for the patient, is still exciting. Putting these pieces together to make a clear picture is akin to solving a crime. On many occasions, just seeing *the* clue (a characteristic rash, an asymmetry, a barely visible scar where a foreign body is hidden unnoticed) has solved the medical puzzle for me, thereby—with proper management—leading to complete recovery of the child. This can bring satisfaction that almost nothing else replaces. It is my hope that readers might catch a bit of this enthusiasm after reading the fourth edition of *Red Book Atlas*.

Carol J. Baker, MD, FAAP
Editor

CHAPTER 1

Actinomycosis

CLINICAL MANIFESTATIONS

Actinomycosis results from pathogen introduction following a breakdown in mucocutaneous protective barriers. Spread within the host is by direct invasion of adjacent tissues, typically forming sinus tracts that cross tissue planes.

There are 3 common anatomic sites of infection. **Cervicofacial** is most common, often occurring after tooth extraction, oral surgery, or other oral/facial trauma or even from carious teeth. Localized pain and induration may progress to cervical abscess and "woody hard" nodular lesions ("lumpy jaw"), which can develop draining sinus tracts, usually at the angle of the jaw or in the submandibular region. **Thoracic** disease most commonly is secondary to aspiration of oropharyngeal secretions but may be an extension of cervicofacial infection. It occurs rarely after esophageal disruption secondary to surgery or nonpenetrating trauma. Thoracic presentation includes pneumonia, which can be complicated by abscesses, empyema, and rarely, pleurodermal sinuses. Focal or multifocal mediastinal and pulmonary masses may be mistaken for tumors. **Abdominal** actinomycosis usually is attributable to penetrating trauma or intestinal perforation. The appendix and cecum are the most common sites; symptoms are similar to appendicitis. Slowly developing masses may simulate abdominal or retroperitoneal neoplasms. Intra-abdominal abscesses and peritoneal-dermal draining sinuses occur eventually. Chronic localized disease often forms draining sinus tracts with purulent discharge. **Other sites** of infection include the liver, pelvis (which, in some cases, has been linked to use of intrauterine devices), heart, testicles, and brain (which usually is associated with a primary pulmonary focus). Noninvasive primary cutaneous actinomycosis has occurred.

ETIOLOGY

A israelii and at least 5 other *Actinomyces* species cause human disease. All are slow-growing, microaerophilic or facultative anaerobic, gram-positive, filamentous branching bacilli. They can be part of normal oral, gastrointestinal tract, or vaginal flora. *Actinomyces* species frequently are copathogens in tissues harboring multiple other anaerobic and/or aerobic species. Isolation of *Aggregatibacter* (*Actinobacillus*) *actinomycetemcomitans*, frequently detected with *Actinomyces* species, may predict the presence of actinomycosis.

EPIDEMIOLOGY

Actinomyces species occur worldwide, being components of endogenous oral and gastrointestinal tract flora. *Actinomyces* species are opportunistic pathogens (reported in patients with human immunodeficiency virus [HIV] and with chronic granulomatous disease), with disease usually following penetrating (including human bite wounds) and nonpenetrating trauma. Infection is uncommon in infants and children, with 80% of cases occurring in adults. The male-to-female ratio in children is 1.5:1. Overt, microbiologically confirmed, monomicrobial disease caused by *Actinomyces* species has become rare in the era of antimicrobial agents.

The incubation period varies from several days to several years.

DIAGNOSTIC TESTS

Only specimens from normally sterile sites should be submitted for culture. Microscopic demonstration of beaded, branched, gram-positive bacilli in purulent material or tissue specimens suggests the diagnosis. Acid-fast testing can distinguish *Actinomyces* species, which are acid-fast negative, from *Nocardia* species, which are variably acid-fast positive staining. Yellow "sulfur granules" visualized microscopically or macroscopically in drainage or loculations of purulent material suggest the diagnosis. A Gram stain of "sulfur granules" discloses a dense aggregate of bacterial filaments mixed with inflammatory debris. *A israelii* forms "spiderlike" microcolonies on culture medium after 48 hours. *Actinomyces* species can be identified in tissue specimens using polymerase chain reaction assay and sequencing of the 16s rRNA.

TREATMENT

Initial therapy should include intravenous penicillin G or ampicillin for 4 to 6 weeks followed by high doses of oral penicillin (up to 2 g/day for adults), usually for a total of 6 to 12 months. Treatment for some cases of cervicofacial disease can be initiated with oral therapy. Amoxicillin, erythromycin, clindamycin, doxycycline, and tetracycline are alternative antimicrobial choices. Amoxicillin/clavulanate, piperacillin/tazobactam, ceftriaxone, clarithromycin, linezolid, and meropenem also show high activity in vitro. All *Actinomyces* species appear to be resistant to ciprofloxacin and metronidazole.

Surgical drainage often is a necessary adjunct to medical management and may allow for a shorter duration of antimicrobial treatment.

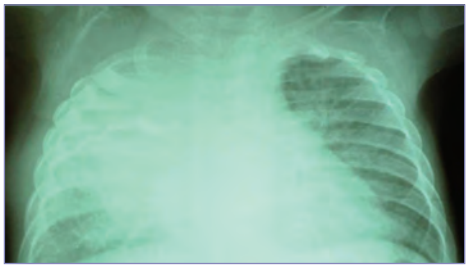


Image 1.1
An 8-month-old boy with pulmonary actinomycosis, an uncommon infection in infancy that may follow aspiration. As in this infant, most cases of actinomycosis are caused by *Actinomyces israelii.*

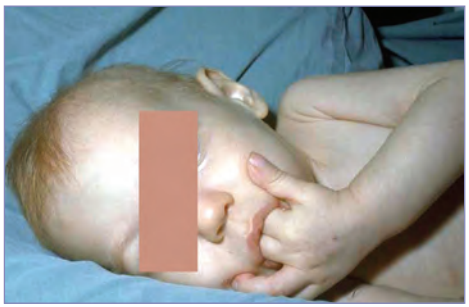


Image 1.3
Clubbing of the thumb and fingers of the 8-month-old boy in Images 1.1 and 1.2 with chronic pulmonary actinomycosis. Blood cultures were repeatedly negative without clinical signs of endocarditis. Courtesy of Edgar O. Ledbetter, MD, FAAP.

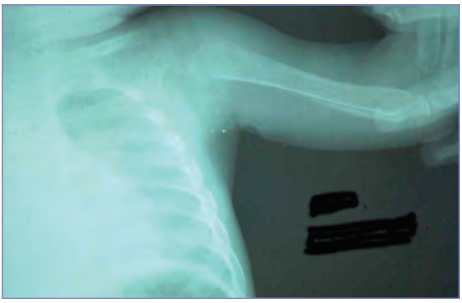


Image 1.2
Periosteal reaction along the left humeral shaft (diaphysis) in the 8-month-old boy in Image 1.1, with pulmonary actinomycosis. The presence of clubbing with this chronic suppurative pulmonary infection and absence of heart disease suggests pulmonary fibrosis contributed to this infant's pulmonary hypertrophic osteoarthropathy. Courtesy of Edgar O. Ledbetter, MD, FAAP.

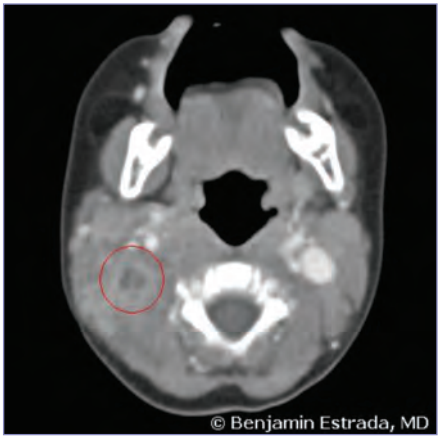


Image 1.4
Actinomyces cervical abscess in a 6-month-old girl. Courtesy of Benjamin Estrada, MD.

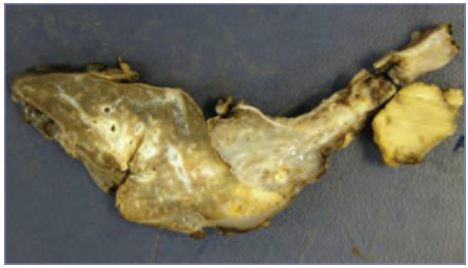


Image 1.5
The resected right lower lobe, diaphragm, and portion of the liver in a 3-year-old previously healthy girl with an unknown source for her pulmonary actinomycosis. Courtesy of Carol J. Baker, MD, FAAP.

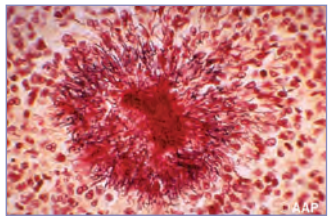


Image 1.7
Tissue showing filamentous branching rods of *Actinomyces israelii* (Brown and Brenn stain). *Actinomyces* species have fastidious growth requirements. Staining of a crushed sulfur granule reveals branching bacilli.

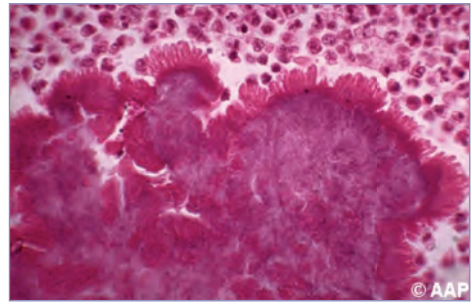


Image 1.6
A sulfur granule from an actinomycotic abscess (hematoxylin-eosin stain). While pathognomonic of actinomycosis, granules are not always present. A Gram stain of sulfur granules shows a dense reticulum of filaments.

CHAPTER 2

Adenovirus Infections

CLINICAL MANIFESTATIONS

Adenovirus infections of the upper respiratory tract are common and often subclinical but may cause common cold symptoms, pharyngitis, tonsillitis, otitis media, and pharyngoconjunctival fever. Life-threatening disseminated infection, lower respiratory infection (eg, severe pneumonia), hepatitis, meningitis, and encephalitis occur occasionally, especially among young infants and immunocompromised people. Adenoviruses occasionally cause a pertussis-like syndrome, croup, bronchiolitis, exudative tonsillitis, and hemorrhagic cystitis. Ocular adenovirus infections may present as follicular conjunctivitis or as epidemic keratoconjunctivitis. Enteric adenoviruses are an important cause of childhood gastroenteritis.

ETIOLOGY

Adenoviruses are double-stranded, nonenveloped DNA viruses of the *Adenoviridae* family and *Mastadenovirus* genus, with more than 50 recognized types and multiple genetic variants divided into 7 species (A–G) that infect humans. Some adenovirus types are associated primarily with respiratory tract disease (types 1–5, 7, 14, and 21), keratoconjunctivitis (types 5, 8, 19, and 37), and gastroenteritis (types 31, 40, and 41).

EPIDEMIOLOGY

Infection in children can occur at any age. Adenoviruses causing respiratory tract infections usually are transmitted by respiratory tract secretions through person-to-person contact, airborne droplets, and fomites. The conjunctiva can provide a portal of entry. Adenoviruses are hardy viruses, can survive on environmental surfaces for long periods, and are not inactivated by many disinfectants. Outbreaks of febrile respiratory tract illness attributable to adenoviruses can be a significant problem in military trainees, although less so since vaccination was reinstituted. Community outbreaks of adenovirus-associated pharyngoconjunctival fever have been attributed to water exposure from contaminated swimming pools and fomites, such as shared towels. Health care-associated transmission of adenoviral respiratory tract, conjunctival, and gastrointestinal tract infections can occur in hospitals, residential institutions, and nursing homes from exposures to infected health care personnel, patients, or contaminated equipment. Adenovirus infections in transplant recipients can occur from donor tissues. Epidemic keratoconjunctivitis commonly occurs by direct contact and has been associated with equipment used during eye examinations. Enteric strains of adenoviruses are transmitted by the fecal-oral route. Adenoviruses do not demonstrate the marked seasonality of other respiratory tract viruses and instead circulate throughout the year. Whether individual adenovirus serotypes demonstrate seasonality is not clear. Enteric disease occurs year-round and primarily affects children younger than 4 years. Adenovirus infections are most communicable during the first few days of an acute illness, but persistent and intermittent shedding for longer periods, even months, is common. In healthy people, infection with one adenovirus type should confer type-specific immunity or at least lessen symptoms associated with reinfection.

The incubation period for respiratory tract infection varies from 2 to 14 days; for gastroenteritis, the incubation period is 3 to 10 days.

DIAGNOSTIC TESTS

Methods for diagnosis of adenovirus infection include molecular detection, isolation in cell culture, and antigen detection. Polymerase chain reaction assays are the preferred diagnostic method for detection of adenoviruses, and these assays now are widely available commercially. However, the persistent and intermittent shedding that commonly follows an acute adenoviral infection can complicate the clinical interpretation of a positive molecular test result. Adenoviruses associated with respiratory tract and ocular disease can be isolated by culture from respiratory specimens (eg, nasopharyngeal swab, oropharyngeal swab, nasal wash, sputum) and eye secretions in standard susceptible cell lines. Rapid antigen-detection techniques, including immunofluorescence and enzyme immunoassay, have been used to detect

virus in respiratory tract secretions, conjunctival swab specimens, and stool, but these methods lack sensitivity.

TREATMENT

Treatment of adenovirus infection is supportive. Randomized clinical trials evaluating specific antiviral therapy have not been performed. However, case reports of the successful use of cidofovir in immunocompromised patients with severe adenoviral disease have been published, albeit without a uniform dose or dosing strategy.

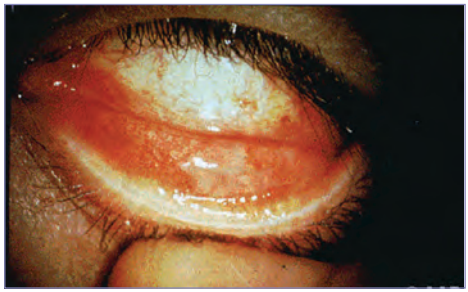


Image 2.1
Acute follicular adenovirus conjunctivitis. Adenoviruses are resistant to alcohol, detergents, and chlorhexidine and may contaminate ophthalmologic solutions and equipment. Instruments can be disinfected by steam autoclaving or immersion in 1% sodium hypochlorite for 10 minutes.

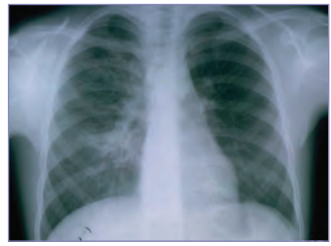


Image 2.2
Adenoviral pneumonia in an 8-year-old girl with diffuse pulmonary infiltrate bilaterally. Most adenoviral infections in the normal host are self-limited and require no specific treatment. Lobar consolidation is unusual.

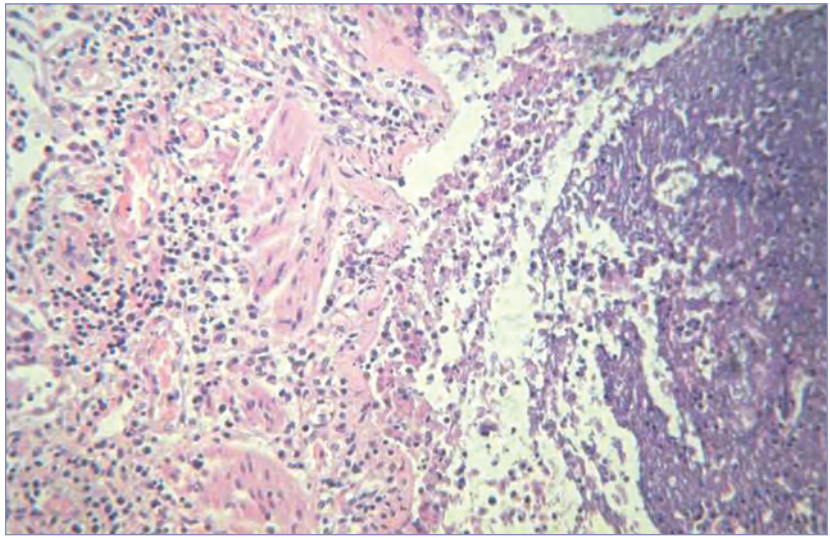


Image 2.3
Histopathology of the lung with bronchiolar occlusion in an immunocompromised child who died with adenoviral pneumonia. Note interstitial mononuclear cell infiltration and hyaline membranes. Adenoviruses types 3 and 7 can cause necrotizing bronchitis and bronchiolitis. Courtesy of Edgar O. Ledbetter, MD, FAAP.

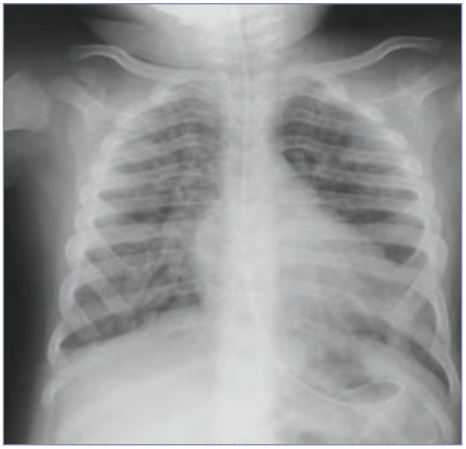


Image 2.4
Adenovirus pneumonia in a 4-year-old boy. Courtesy of Benjamin Estrada, MD.

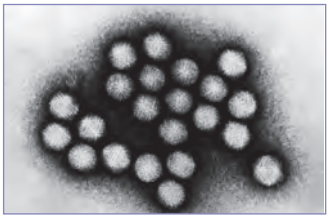


Image 2.6
Transmission electron micrograph of adenovirus. Adenoviruses have a characteristic icosahedral structure. Courtesy of Centers for Disease Control and Prevention.

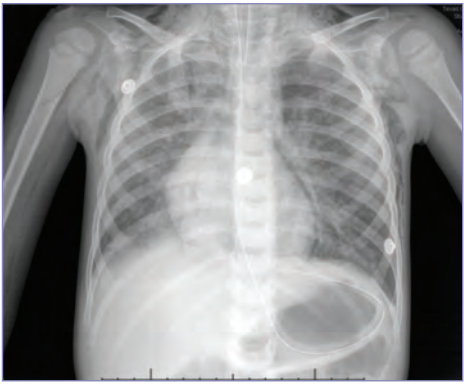


Image 2.5
This previously healthy 3-year-old boy presented with respiratory failure requiring intensive care for adenovirus type 7 pneumonia. He eventually recovered with some mild impairment in pulmonary function studies. Note the pneumomediastinum. Courtesy of Carol J. Baker, MD, FAAP.

CHAPTER 3

Amebiasis

CLINICAL MANIFESTATIONS

Most individuals with *Entamoeba histolytica* have asymptomatic noninvasive intestinal tract infection. When present, symptoms associated with *E histolytica* infection generally include cramps, watery or bloody diarrhea, and weight loss. Occasionally, the parasite may spread to other organs, most commonly the liver (liver abscess), and cause fever and right upper quadrant pain. Disease is more severe in very young people, elderly people, malnourished people, and pregnant women. People with symptomatic intestinal amebiasis generally have a gradual onset of symptoms over 1 to 3 weeks. The mildest form of intestinal tract disease is nondysenteric colitis. Amebic dysentery is the most common clinical manifestation of amebiasis and generally includes diarrhea with either gross or microscopic blood in the stool, lower abdominal pain, and tenesmus. Weight loss is common because of the gradual onset, but fever occurs only in a minority of patients (8%–38%). Symptoms may be chronic, are characterized by periods of diarrhea and intestinal spasms alternating with periods of constipation, and can mimic those of inflammatory bowel disease. Progressive involvement of the colon may produce toxic megacolon, fulminant colitis, ulceration of the colon and perianal area, and rarely, perforation. Colonic progression can occur at multiples sites and has a high fatality rate. Progression can occur in patients inappropriately treated with corticosteroids or antimotility drugs. An ameboma can occur as an annular lesion of the colon and may present as a palpable mass on physical examination. Amebomas can occur in any area of the colon but are most common in the cecum. They may be mistaken for colonic carcinoma. Amebomas usually resolve with antiamebic therapy and do not require surgery.

In a small proportion of patients, extraintestinal disease may occur. The liver is the most common extraintestinal site, and infection can spread from there to the pleural space, lungs, and pericardium. Liver abscess can be acute, with fever, abdominal pain, tachypnea, liver tenderness, and hepatomegaly, or may be chronic, with weight loss, vague abdominal symptoms, and irritability. Rupture of abscesses into the abdomen or chest may lead to death. Evidence of recent intestinal tract infection usually is absent in extraintestinal disease. Infection may spread from the colon to the genitourinary tract and the skin. The organism may spread hematogenously to the brain and other areas of the body.

ETIOLOGY

The genus *Entamoeba* includes 6 species that live in the human intestine. Four of these species are identical morphologically: *E histolytica*, *Entamoeba dispar*, *Entamoeba moshkovskii*, and *Entamoeba bangladeshi*. Not all *Entamoeba* species are virulent. *E dispar* generally is recognized as a commensal, and although *E moshkovskii* generally was believed to be nonpathogenic, it may be associated with diarrhea in infants. *Entamoeba* species are excreted as cysts or trophozoites in stool of infected people.

EPIDEMIOLOGY

E histolytica can be found worldwide but is more prevalent in people of lower socioeconomic status who live in resource-limited countries, where the prevalence of amebic infection may be as high as 50% in some communities. Groups at increased risk of infection in industrialized countries include immigrants from or long-term visitors to areas with endemic infection, institutionalized people, and men who have sex with men. *E histolytica* is transmitted via amebic cysts by the fecal-oral route. Ingested cysts, which are unaffected by gastric acid, undergo excystation in the alkaline small intestine and produce trophozoites that infect the colon. Cysts that develop subsequently are the source of transmission, especially from asymptomatic cyst excreters. Infected patients excrete cysts intermittently, sometimes for years if untreated. Transmission has been associated with contaminated food or water. Fecal-oral transmission can occur in the setting of anal sexual practices or direct rectal inoculation through colonic irrigation devices.

The **incubation period** is variable, ranging from a few days to months or years, but commonly is 2 to 4 weeks.

DIAGNOSTIC TESTS

A definitive diagnosis of intestinal tract infection depends on identifying trophozoites or cysts in stool specimens. Examination of serial specimens may be necessary. Specimens of stool may be examined microscopically by wet mount within 30 minutes of collection or may be fixed in formalin or polyvinyl alcohol (available in kits) for concentration, permanent staining, and subsequent microscopic examination. Microscopy does not differentiate between *E histolytica* and less pathogenic strains, although trophozoites containing ingested red blood cells are more likely to be *E histolytica*. Antigen test kits are available in some clinical laboratories for testing of *E histolytica* directly from stool specimens. The utility of examining biopsy specimens and endoscopy scrapings (not swabs) using similar methods is not well established. Polymerase chain reaction assay and isoenzyme analysis can differentiate *E histolytica* from *E dispar*, *E moshkovskii*, and other *Entamoeba* species; some monoclonal antibody-based antigen detection assays also can differentiate *E histolytica* from *E dispar*.

The indirect hemagglutination (IHA) test has been replaced by commercially available enzyme immunoassay (EIA) kits for routine serodiagnosis of amebiasis. The EIA detects antibody specific for *E histolytica* in approximately 95% or more of patients with extraintestinal amebiasis, 70% of patients with active intestinal tract infection, and 10% of asymptomatic people who are passing cysts of *E histolytica*. Patients may continue to have positive serologic test results even after adequate therapy. Diagnosis of an *E histolytica* liver abscess and other extraintestinal infections is aided by serologic testing, because stool tests and abscess aspirates frequently are not revealing.

Ultrasonography, computed tomography, and magnetic resonance imaging can identify liver abscesses and other extraintestinal sites of infection. Aspirates from a liver abscess usually show neither trophozoites nor leukocytes.

TREATMENT

Treatment should be prioritized for all patients with *E histolytica*, including those who are asymptomatic, given the propensity of this organism to cause invasive infection and to spread among family members. A treatment plan should include antimicrobials to eliminate invading trophozoites as well as organisms carried in the intestinal lumen. Corticosteroids and antimotility drugs administered to people with amebiasis can worsen symptoms and the disease process. In settings where tests to distinguish species are not available, treatment should be administered to symptomatic people on the basis of positive results of microscopic examination. The following regimens are recommended:

- **Asymptomatic cyst excreters (intraluminal infections):** treat with an intraluminal amebicide alone (paromomycin or diiodohydroxyquinoline/iodoquinol, or diloxanide furoate). Metronidazole is not effective against cysts.
- **Patients with invasive colitis manifest as mild to moderate or severe intestinal tract symptoms or extraintestinal disease (including liver abscess):** treat with metronidazole or tinidazole, followed by an intraluminal amebicide or diloxanide furoate or, in the absence of intestinal obstruction, paromomycin. Nitazoxanide may be effective for mild to moderate intestinal amebiasis, although it is not approved by the US Food and Drug Administration for this indication.
- **Percutaneous or surgical aspiration of large liver abscesses occasionally may be required** when response of the abscess to medical therapy is unsatisfactory or there is risk of rupture. In most cases of liver abscess, however, drainage is not required and does not speed recovery.

Follow-up stool examination is recommended after completion of therapy, because no pharmacologic regimen is completely effective in eradicating intestinal tract infection. Household members and other suspected contacts should have adequate stool examinations performed and should be treated if results are positive for *E histolytica*.

E dispar generally is considered to be nonpathogenic and does not necessarily require treatment. The pathogenic significance of finding *E moshkovskii* is unclear; treatment of symptomatic infection is reasonable.

ISOLATION OF THE HOSPITALIZED PATIENT

In addition to standard precautions, contact precautions are recommended for the duration of illness.

CONTROL MEASURES

Careful hand hygiene after defecation, sanitary disposal of fecal material, and treatment of drinking water will control spread of infection. Sexual transmission may be controlled by use of condoms and avoidance of sexual practices that may permit fecal-oral transmission. Because of the risk of shedding infectious cysts, people diagnosed with amebiasis should refrain from using recreational water venues (eg, swimming pools, water parks) until after their course of luminal chemotherapy is completed and any diarrhea they might have been experiencing has resolved.

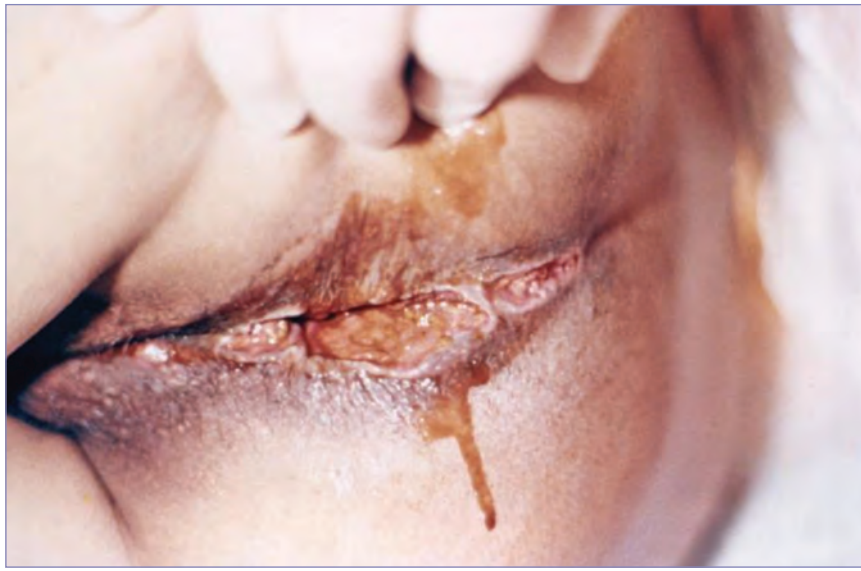


Image 3.1
This patient with amebiasis presented with tissue destruction and granulation of the anoperineal region caused by an *Entamoeba histolytica* infection. Courtesy of Centers for Disease Control and Prevention.

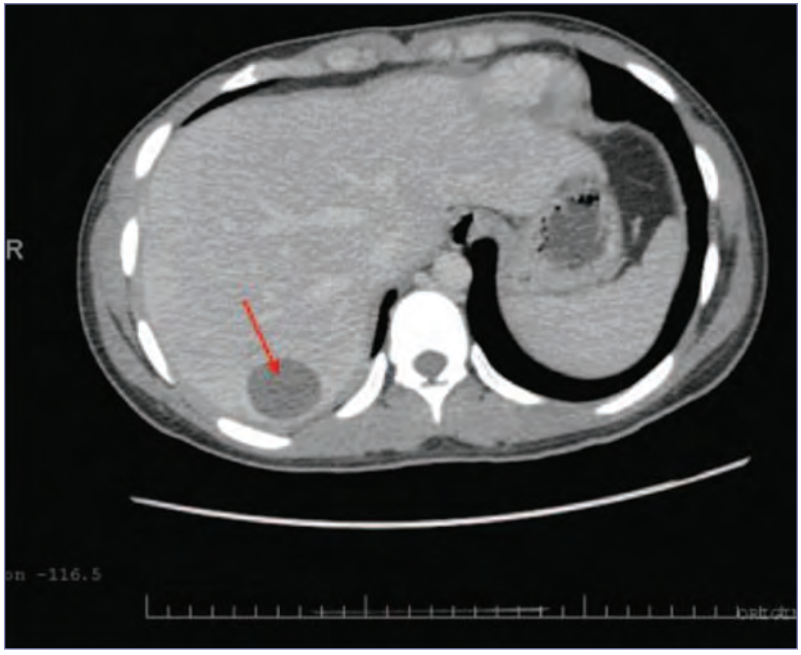


Image 3.2
Computed tomography scan of the abdomen showing a peripherally enhancing low-density lesion in the posterior aspect of the right hepatic lobe. Amebic liver abscess amebiasis, caused by the intestinal protozoal parasite *Entamoeba histolytica,* remains a global health problem, infecting about 50 million people and resulting in 40,000 to 100,000 deaths per year. Prevalence may be as high as 50% in tropical and subtropical countries where overcrowding and poor sanitation are common. In the United States, *E histolytica* infection is seen most commonly in immigrants from developing countries, long-term travelers to endemic areas (most frequently Mexico or Southeast Asia), institutionalized individuals, and men who have sex with men. In 1993, the previously known species *E histolytica* was reclassified into 2 genetically and biochemically distinct but morphologically identical species: the pathogenic *E histolytica* and the nonpathogenic commensal *Entamoeba dispar.* Courtesy of *Pediatrics in Review.*

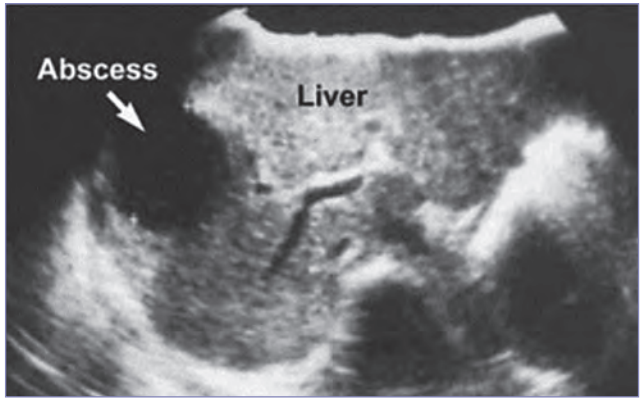


Image 3.3
Abdominal ultrasound showing a liver abscess caused by *Entamoeba histolytica*.

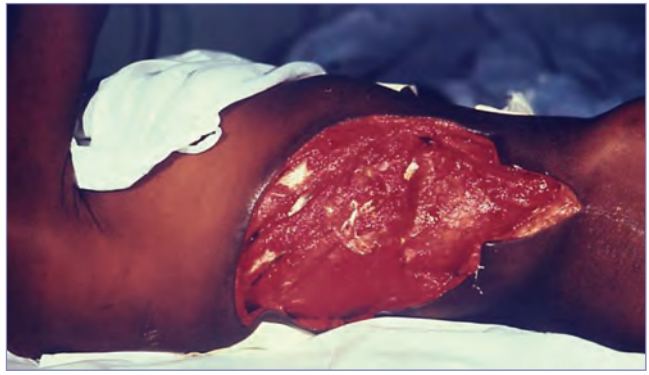


Image 3.4
This patient presented with a case of invasive extraintestinal amebiasis affecting the cutaneous region of the right flank. Courtesy of Centers for Disease Control and Prevention.

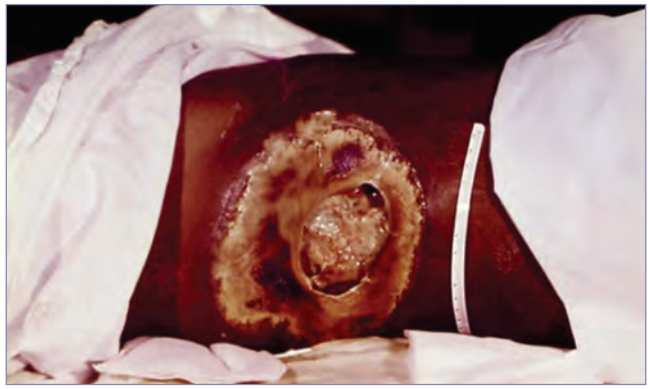


Image 3.5
This patient, also shown in Image 3.4, presented with a case of invasive extraintestinal amebiasis affecting the cutaneous region of the right flank causing severe tissue necrosis. Here we see the site of tissue destruction, pre-debridement. Courtesy of Centers for Disease Control and Prevention/Kerrison Juniper, MD, and George Healy, PhD, DPDx.

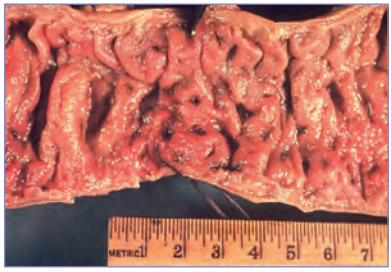


Image 3.6
Gross pathology of intestinal ulcers due to amebiasis. Courtesy of Centers for Disease Control and Prevention.

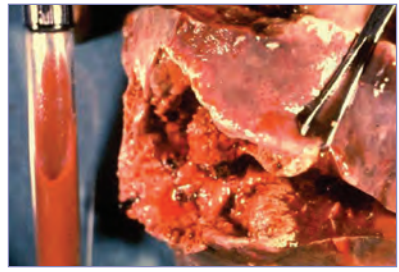


Image 3.7
Gross pathology of amebic (*Entamoeba histolytica*) abscess of liver; tube of "chocolate-like" pus from abscess. Amebic liver abscesses are usually singular and large and in the right lobe of the liver. Bacterial hepatic abscesses are more likely to be multiple. Courtesy of Centers for Disease Control and Prevention.

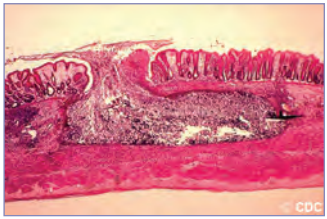


Image 3.8
Histopathologic features of a typical flask-shaped ulcer of intestinal amebiasis in a kitten. Courtesy of Centers for Disease Control and Prevention.

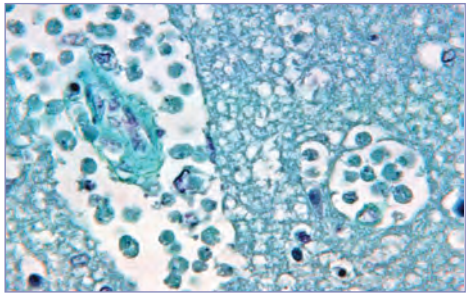


Image 3.9
This micrograph of a brain tissue specimen reveals the presence of *Entamoeba histolytica* amoebae (magnification ×500). In more serious cases of amebiasis, amoebae can cause an infection of tissue outside of the intestinal tract. Courtesy of Centers for Disease Control and Prevention.

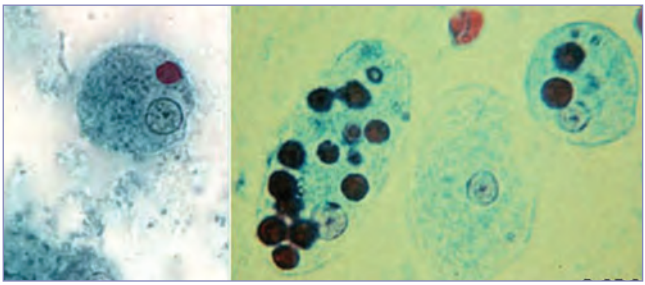


Image 3.10
Trophozoites of *Entamoeba histolytica* with ingested erythrocytes (trichrome stain). The ingested erythrocytes appear as dark inclusions. Erythrophagocytosis is the only characteristic that can be used to differentiate morphologically *E histolytica* from the nonpathogenic *Entamoeba dispar*. In these specimens, the parasite nuclei have the typical small, centrally located karyosome and thin, uniform peripheral chromatin. Courtesy of Centers for Disease Control and Prevention.

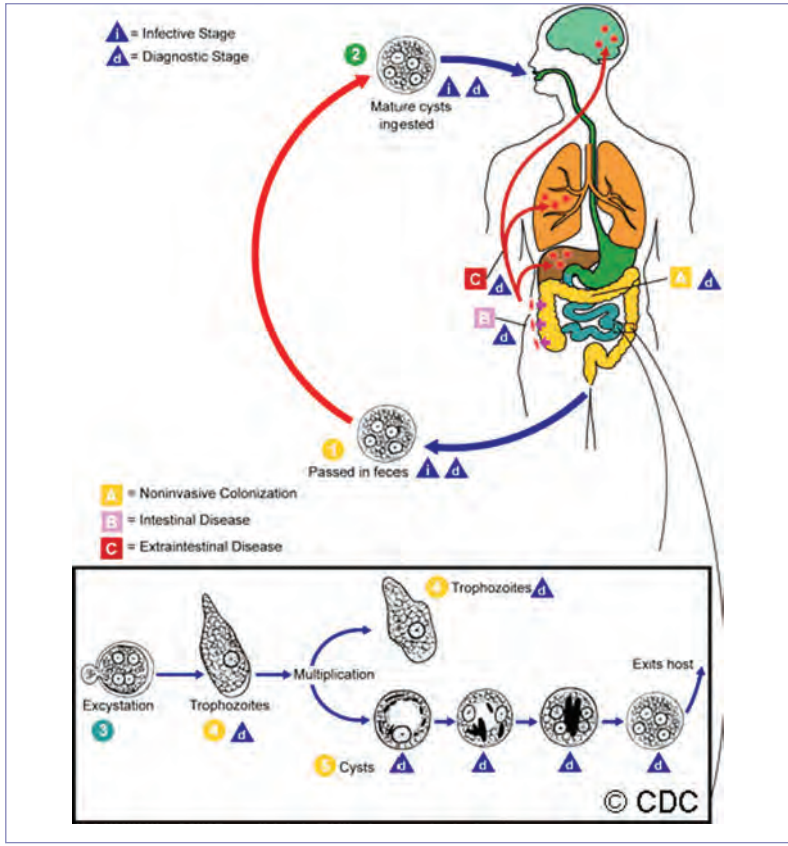


Image 3.11

Cysts are passed in feces (1). Infection by *Entamoeba histolytica* occurs by ingestion of mature cysts (2) in fecally contaminated food, water, or hands. Excystation (3) occurs in the small intestine and trophozoites (4) are released, which migrate to the large intestine. The trophozoites multiply by binary fission and produce cysts (5), which are passed in feces (1). Because of the protection conferred by their walls, the cysts can survive days to weeks in the external environment and are responsible for transmission. (Trophozoites can also be passed in diarrheal stools but are rapidly destroyed once outside the body and, if ingested, would not survive exposure to the gastric environment.) In many cases, trophozoites remain confined to the intestinal lumen (A, noninvasive infection) of individuals who are asymptomatic carriers, passing cysts in their stool. In some patients, trophozoites invade the intestinal mucosa (B, intestinal disease) or, through the bloodstream, extraintestinal sites, such as the liver, brain, and lungs (C, extraintestinal disease), with resultant pathologic manifestations. It has been established that invasive and noninvasive forms represent 2 separate species, *E histolytica* and *Entamoeba dispar,* respectively; however, not all persons infected with *E histolytica* will have invasive disease. These 2 species are morphologically indistinguishable. Transmission can also occur through fecal exposure during sexual contact (in which case not only cysts, but also trophozoites, could prove infective). Courtesy of Centers for Disease Control and Prevention.

CHAPTER 4

Amebic Meningoencephalitis and Keratitis

(*Naegleria fowleri, Acanthamoeba* species, *Sappinia* species, and *Balamuthia mandrillaris*)

CLINICAL MANIFESTATIONS

Naegleria fowleri can cause a rapidly progressive, almost always fatal, primary amebic meningoencephalitis (PAM). Early symptoms include fever, headache, vomiting, and sometimes disturbances of smell and taste. The illness progresses rapidly to signs of meningoencephalitis, including nuchal rigidity, lethargy, confusion, personality changes, and altered level of consciousness. Seizures are common, and death generally occurs within a week of onset of symptoms. No distinct clinical features differentiate this disease from fulminant bacterial meningitis or meningoencephalitis due to other pathogens.

Granulomatous amebic encephalitis (GAE) caused by *Acanthamoeba* species and *Balamuthia mandrillaris* has a more insidious onset and develops as a subacute or chronic disease. In general, GAE progresses more slowly than PAM, leading to death several weeks to months after onset of symptoms. Signs and symptoms may include personality changes, seizures, headaches, ataxia, cranial nerve palsies, hemiparesis, and other focal neurologic deficits. Fever often is low grade and intermittent. The course may resemble that of a bacterial brain abscess or a brain tumor. Chronic granulomatous skin lesions (pustules, nodules, ulcers) may be present without central nervous system (CNS) involvement, particularly in patients with acquired immunodeficiency syndrome, and lesions may be present for months before brain involvement in immunocompetent hosts.

The most common symptoms of amebic keratitis, a vision-threatening infection usually caused by *Acanthamoeba* species, are pain (often out of proportion to clinical signs), photophobia, tearing, and foreign body sensation. Characteristic clinical findings include radial keratoneuritis and stromal ring infiltrate. *Acanthamoeba* keratitis generally follows an indolent course and initially may resemble herpes simplex or bacterial keratitis; delay in diagnosis is associated with worse outcomes.

Sappinia infection is a rare cause of encephalitis, with only 1 case reported.

ETIOLOGY

N fowleri, *Acanthamoeba* species, *Sappinia* species, and *B mandrillaris* are free-living amebae that exist as motile, infectious trophozoites and environmentally hardy cysts.

EPIDEMIOLOGY

N fowleri is found in warm fresh water and moist soil. Most infections with *N fowleri* have been associated with swimming in natural bodies of warm fresh water, such as ponds, lakes, and hot springs, but other sources have included tap water from geothermal sources and contaminated and poorly chlorinated swimming pools. Disease has been reported worldwide but is uncommon. In the United States, infection occurs primarily in the summer and usually affects children and young adults. Disease has followed use of tap water for sinus rinses. The trophozoites of the parasite invade the brain directly from the nose along the olfactory nerves via the cribriform plate. In infections with *N fowleri*, trophozoites, but not cysts, can be visualized in sections of brain or in cerebrospinal fluid (CSF).

The **incubation period** for *N fowleri* infection typically is 3 to 7 days.

Acanthamoeba species are distributed worldwide and are found in soil; dust; cooling towers of electric and nuclear power plants; heating, ventilating, and air conditioning units; fresh and brackish water; whirlpool baths; and physiotherapy pools. The environmental niche of *B mandrillaris* is not delineated clearly, although it has been isolated from soil. CNS infection attributable to *Acanthamoeba* occurs primarily in debilitated and immunocompromised people. However, some patients infected with *B mandrillaris* have had no demonstrable underlying disease or defect. CNS infection by both amebae probably occurs most commonly by inhalation or direct contact with contaminated soil or water. The primary foci of these infections most likely are skin or respiratory tract, followed by hematogenous spread to

the brain. Fatal encephalitis caused by *Balamuthia* species and transmitted by the donated organ has been reported in recipients of organ transplants. *Acanthamoeba* keratitis occurs primarily in people who wear contact lenses, although it also has been associated with corneal trauma. Poor contact lens hygiene and/or disinfection practices as well as swimming with contact lenses are risk factors.

The **incubation periods** for *Acanthamoeba* and *Balamuthia* GAE are unknown but are thought to take several weeks or months. Patients exposed to *Balamuthia* through solid organ transplantation can develop symptoms of *Balamuthia* GAE more quickly—within a few weeks.

DIAGNOSTIC TESTS

In *N fowleri* infection, computed tomography scans of the head without contrast are unremarkable or show only cerebral edema but with contrast might show meningeal enhancement of the basilar cisterns and sulci. These changes, however, are not specific for amebic infection. CSF pressure usually is elevated (300 to >600 mm water), and CSF indices can show a polymorphonuclear pleocytosis, an increased protein concentration, and a normal to very low glucose concentration. *N fowleri* infection can be documented by microscopic demonstration of the motile trophozoites on a wet mount of centrifuged CSF. Smears of CSF should be stained with Giemsa, Trichome, or Wright stains to identify the trophozoites, if present; Gram stain is not useful in diagnosing *N fowleri* CNS infection. Trophozoites can be visualized in sections of the brain. Immunofluorescence and polymerase chain reaction (PCR) assays performed on CSF and biopsy material to identify the organism are available through the Centers for Disease Control and Prevention (CDC).

In infection with *Acanthamoeba* species and *B mandrillaris*, trophozoites and cysts can be visualized in sections of brain, lungs, and skin; in cases of *Acanthamoeba* keratitis, they also can be visualized in corneal scrapings and by confocal microscopy in vivo in the cornea. In GAE infections, CSF indices typically reveal a lymphocytic pleocytosis and an increased protein concentration, with normal or low glucose. Computed tomography and magnetic resonance imaging of the head may show single or multiple space-occupying, ring-enhancing lesions that can mimic brain abscesses, tumors, cerebrovascular accidents, or other diseases. *Acanthamoeba* species, but not *B mandrillaris*, can be cultured by the same method used for *N fowleri*. *B mandrillaris* can be grown using mammalian cell culture. Like *N fowleri*, immunofluorescence and PCR assays can be performed on clinical specimens to identify *Acanthamoeba* species and *Balamuthia* species; these tests are available through the CDC.

TREATMENT

The most up-to-date guidance for treatment of PAM can be found on the CDC website (**www.cdc.gov/naegleria**). Early diagnosis and institution of combination high-dose drug therapy is thought to be important for optimizing outcome. If meningoencephalitis possibly caused by *N fowleri* is suspected, treatment should not be withheld pending confirmation. Although an effective treatment regimen for PAM has not been identified, amphotericin B is the drug of choice in combination with other agents. In vitro testing indicates that *N fowleri* is highly susceptible to amphotericin B. Two survivors recovered after treatment with amphotericin B in combination with an azole drug.

Effective treatment for infections caused by *Acanthamoeba* species and *B mandrillaris* has not been established. Several patients with *Acanthamoeba* GAE and *Acanthamoeba* cutaneous infections without CNS involvement have been treated successfully with a multidrug regimen consisting of various combinations of pentamidine, sulfadiazine, flucytosine, either fluconazole or itraconazole (voriconazole is not active against *Balamuthia* species), trimethoprim-sulfamethoxazole, and topical application of chlorhexidine gluconate and ketoconazole for skin lesions.

Patients with *Acanthamoeba* keratitis should be evaluated by an ophthalmologist. Early diagnosis and therapy are important for a good outcome.

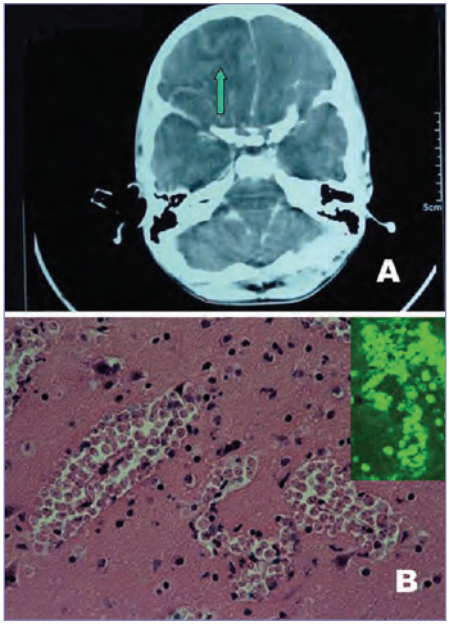


Image 4.1
A, Computed tomographic scan; note the right frontobasal collection (arrow) with a midline shift right to left. B, Brain histology; 3 large clusters of amebic vegetative forms are seen (hematoxylin-eosin stain, magnification ×250). Inset: positive indirect immunofluorescent analysis on tissue section with anti–*Naegleria fowleri* serum. Courtesy of *Emerging Infectious Diseases.*

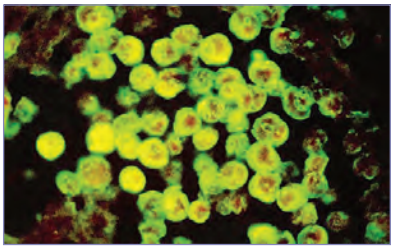


Image 4.3
Histopathologic features of amebic meningoencephalitis due to *Naegleria fowleri* (direct fluorescent antibody stain). Courtesy of Centers for Disease Control and Prevention

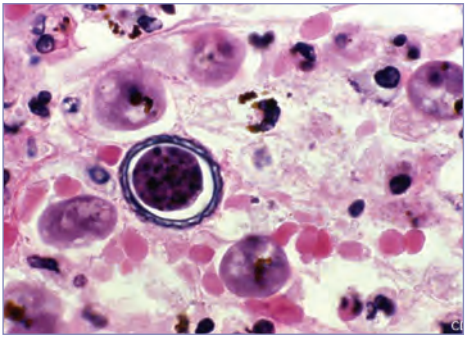


Image 4.2
This photomicrograph of brain tissue reveals free-living amoebas. Courtesy of Centers for Disease Control and Prevention.

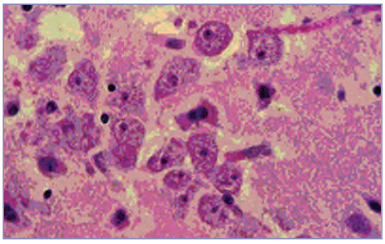


Image 4.4
Balamuthia mandrillaris trophozoites in brain tissue. Courtesy of Centers for Disease Control and Prevention.

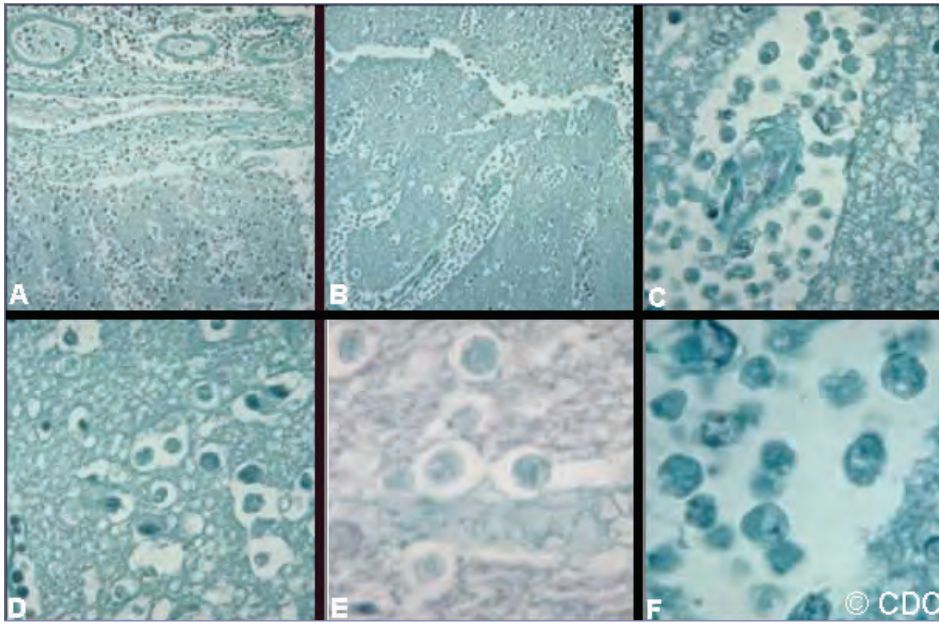


Image 4.5
A–F, *Naegleria fowleri* in brain tissue (trichrome stain). Courtesy of Centers for Disease Control and Prevention.

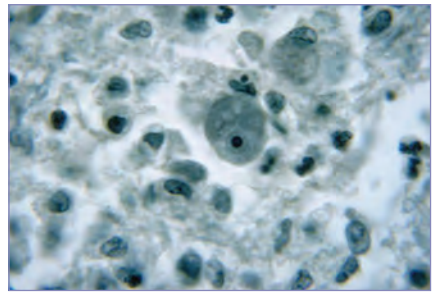


Image 4.6
This photomicrograph of a brain tissue specimen depicts the cytoarchitectural changes associated with a free-living amebic infection, which may have been caused by either *Naegleria fowleri*, or *Acanthamoeba* sp. The organisms were found in the brain of a Japanese prisoner of war in the 1950s, before we knew about the free-living amebas and how they attack the brain. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 5

Anthrax

CLINICAL MANIFESTATIONS

Anthrax resulting from natural infection or secondary to a bioterror event can occur in 4 forms, depending on the route of infection: cutaneous, inhalation, gastrointestinal, or injection.

Cutaneous anthrax accounts for 95% of all human infection and begins as a pruritic papule or vesicle and progresses over 2 to 6 days to an ulcerated lesion with subsequent formation of a central black eschar. The lesion is characteristically painless, with surrounding edema, hyperemia, and painful regional lymphadenopathy. Patients may have associated fever, lymphangitis, and extensive edema.

Inhalation anthrax is a frequently lethal form of the disease and is a medical emergency. The initial presentation is nonspecific and may include fever, sweats, nonproductive cough, chest pain, headache, myalgia, malaise, nausea, and vomiting. Illness progresses to the fulminant phase 2 to 5 days later. In some cases, the illness is biphasic with a period of improvement between prodromal symptoms and overwhelming illness. Fulminant manifestations include hypotension, dyspnea, hypoxia, cyanosis, and shock occurring as a result of hemorrhagic mediastinal lymphadenitis, hemorrhagic pneumonia, hemorrhagic pleural effusions, bacteremia, and toxemia. A widened mediastinum is the classic finding on imaging of the chest. Chest radiography also may show pleural effusions and/or infiltrates, both of which may be hemorrhagic.

Gastrointestinal tract disease can present as one of 2 distinct clinical syndromes—intestinal or oropharyngeal. Patients with the intestinal form have symptoms of nausea, anorexia, vomiting, and fever progressing to severe abdominal pain, massive ascites, hematemesis, and bloody diarrhea related to edema and ulceration of the bowel, primarily in the ileum and cecum. Patients with oropharyngeal anthrax may have dysphagia with posterior oropharyngeal necrotic ulcers, which may be associated with marked, often unilateral neck swelling, regional lymphadenopathy, fever, and sepsis.

Injection anthrax has not been reported to date in children. It occurs primarily among injecting drug users; however, smoking and snorting heroin also have been identified as exposure routes. Systemic illness can result from hematogenous and lymphatic dissemination with any form of anthrax. Most patients with inhalation, gastrointestinal, and injection anthrax have systemic illness. Patients with cutaneous anthrax should be considered to have systemic illness if they have tachycardia, tachypnea, hypotension, hyperthermia, hypothermia, or leukocytosis or have lesions that involve the head, neck, or upper torso or that are large, bullous, multiple, or surrounded by edema. Anthrax meningitis or hemorrhagic meningoencephalitis can occur in any patient with systemic illness and in patients without other apparent clinical presentation. Therefore, lumbar puncture should be performed to rule out meningitis whenever clinically indicated. The case fatality rate for patients with appropriately treated cutaneous anthrax usually is less than 2%. Even with antimicrobial treatment and supportive care, the case fatality rate for inhalation or gastrointestinal tract disease is between 40% and 45% and exceeds 90% for meningitis.

ETIOLOGY

Bacillus anthracis is an aerobic, gram-positive, encapsulated, spore-forming, nonhemolytic, nonmotile rod. *B anthracis* has 3 major virulence factors: an antiphagocytic capsule and 2 exotoxins, called lethal and edema toxins. The toxins are responsible for the substantial morbidity and clinical manifestations of hemorrhage, edema, and necrosis.

EPIDEMIOLOGY

Anthrax is a zoonotic disease most commonly affecting domestic and wild herbivores that occurs in many rural regions of the world. *B anthracis* spores can remain viable in the soil for decades, representing a potential source of infection for livestock or wildlife through ingestion of spore-contaminated vegetation or water. In susceptible hosts, the spores germinate to become viable bacteria. Natural infection of humans occurs through contact with infected animals or contaminated animal products, including carcasses, hides,

hair, wool, meat, and bone meal. Outbreaks of gastrointestinal tract anthrax have occurred after ingestion of undercooked or raw meat from infected animals. Historically, more than 95% of anthrax cases in the United States were cutaneous infections among animal handlers or mill workers. The incidence of naturally occurring human anthrax decreased in the United States from an estimated 130 cases annually in the early 1900s to 0 to 2 cases per year from 1979 through 2013. Recent cases of inhalation, cutaneous, and gastrointestinal tract anthrax have occurred in drum makers working with animal hides contaminated with *B anthracis* spores and in people participating in events where spore-contaminated drums were played. Severe soft tissue infections among heroin users, including cases with disseminated systemic infection, have been reported in Europe.

B anthracis is one of the most likely agents to be used as a biological weapon, because (1) its spores are highly stable; (2) spores can infect via the respiratory route; and (3) the resulting inhalation anthrax has a high mortality rate. In 1979, an accidental release of *B anthracis* spores from a military microbiology facility in the former Soviet Union resulted in at least 68 deaths. In 2001, 22 cases of anthrax (11 inhalation, 11 cutaneous) were identified in the United States after intentional contamination of the mail; 5 (45%) of the inhalation anthrax cases were fatal. In addition to aerosolization, there is a theoretical health risk associated with *B anthracis* spores being introduced into food products or water supplies.

The **incubation period** typically is 1 week or less for cutaneous or gastrointestinal tract anthrax. However, because of spore dormancy and slow clearance of spores from the lungs, the **incubation period** for inhalation anthrax may be prolonged and has been reported to range from 2 to 43 days in humans and up to 2 months in experimental nonhuman primates. Discharge from cutaneous lesions is potentially infectious, but person-to-person transmission rarely has been reported, and other forms of anthrax are not associated with person-to-person transmission. Both inhalation and cutaneous anthrax have occurred in laboratory workers.

DIAGNOSTIC TESTS

Depending on the clinical presentation, Gram stain, culture, and polymerase chain reaction (PCR) testing for *B anthracis* should be performed with the assistance of local health departments on specimens of blood, pleural fluid, cerebrospinal fluid (CSF), tissue biopsy specimens and swabs of vesicular fluid or eschar material from cutaneous or oropharyngeal lesions, rectal swabs, or stool. Acute sera may be tested for lethal factor (one of the 2 exotoxins of anthrax). Whenever possible, specimens for these tests should be obtained before initiating antimicrobial therapy, because previous treatment with antimicrobial agents makes isolation by culture unlikely. Gram-positive bacilli detected on unspun peripheral blood smears or in vesicular fluid or CSF can be an important initial finding. Traditional microbiologic methods can presumptively identify *B anthracis* isolated readily on routine agar media used in clinical laboratories. Definitive identification of suspect *B anthracis* isolates can be performed via the Laboratory Response Network (LRN) in each state, accessed through local health departments. Additional diagnostic tests for anthrax are available through state health departments and the Centers for Disease Control and Prevention (CDC), including bacterial DNA detection in specimens by PCR assay, tissue immunohistochemistry, an enzyme immunoassay that measures immunoglobulin G antibodies against *B anthracis* protective antigen in paired sera, and a MALDI-TOF (matrix-assisted laser desorption/ionization–time-of-flight) mass spectrometry assay measuring lethal factor activity in sera. The sensitivity of DNA and antigen detection methods may decline after antimicrobial treatment has been initiated. A commercially available enzyme-linked immunosorbent assay (QuickELISA Anthrax-PA kit [Immunetics Inc, Boston, MA]) can be used for screening. Clinical evaluation of patients with suspected inhalation anthrax should include a chest radiograph and/or computed tomography scan to evaluate for widened mediastinum, pleural effusion, and/or pulmonary infiltrates. Lumbar punctures should be performed whenever feasible to rule out meningitis and to guide therapy.

TREATMENT

A high index of suspicion and rapid administration of appropriate antimicrobial therapy to people suspected of being infected, along with access to critical care support, are essential for effective treatment of anthrax. No controlled trials in humans have been performed to validate current treatment recommendations for anthrax, and there is limited clinical experience. Case reports suggest that naturally occurring localized or uncomplicated cutaneous disease can be treated effectively with 7 to 10 days of a single oral antimicrobial agent. First-line agents include ciprofloxacin (or an equivalent fluoroquinolone) or doxycycline; clindamycin is an alternative, as are penicillins, if the isolate is known to be penicillin susceptible, which is likely to occur with environmental isolates. For bioterrorism-associated cutaneous disease in adults or children lacking signs and symptoms of systemic illness, either ciprofloxacin or doxycycline are recommended for initial treatment until antimicrobial susceptibility data are available. Doxycycline can be used regardless of patient age. Because of the risk of concomitant inhalational exposure and subsequent spore dormancy in the lungs, the antimicrobial regimen in cases of bioterrorism-associated cutaneous anthrax or that were exposed to other sources of aerosolized spores should be continued for a total of 60 days to provide postexposure prophylaxis in conjunction with administration of vaccine if available.

On the basis of in vitro data and animal studies, ciprofloxacin is recommended as the primary antimicrobial component of an initial multidrug regimen for treatment of all forms of systemic anthrax until results of antimicrobial susceptibility testing are known. Meningeal involvement should be suspected in all cases of inhalation anthrax and other systemic anthrax infections; thus, until meningitis has been excluded, treatment of systemic anthrax should include at least 2 other agents with known central nervous system penetration in conjunction with ciprofloxacin. Meropenem is recommended as the second bactericidal antimicrobial, and if meropenem is not available, doripenem and imipenem/cilastatin are considered alternatives; if the strain is known to be susceptible, penicillin G or ampicillin are equivalent alternatives. Linezolid is recommended as the preferred protein synthesis inhibitor if CNS system involvement is suspected.

Treatment should continue for at least 14 days or longer, depending on patient condition. Intravenous therapy can be changed to oral therapy when progression of symptoms ceases and clinical symptoms are improving. There is the risk of spore dormancy in the lungs in people with bioterrorism-associated cutaneous or systemic anthrax or people who were exposed to other sources of aerosolized spores. In these cases, the antimicrobial regimen should be continued for a total of 60 days to provide PEP, in conjunction with administration of vaccine.

For patients with anthrax and evidence of systemic illness, including fever, shock, and dissemination to other organs, Anthrax Immune Globulin, or obiltoxaximab or raxibacumab, both monoclonal antibodies against *B anthracis*, should be considered in consultation with the CDC. Supportive symptomatic (intensive care) treatment is important.

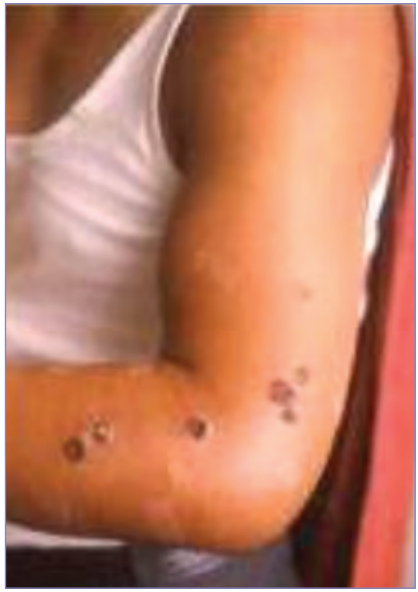


Image 5.1
Cutaneous anthrax. Notice edema and typical lesions. Courtesy of Centers for Disease Control and Prevention.

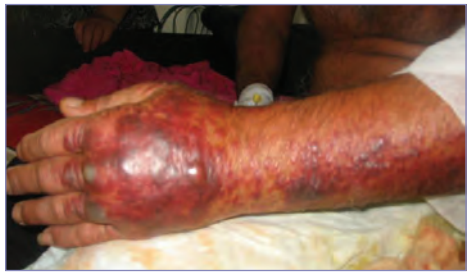


Image 5.3
Generalized cutaneous anthrax infection acquired from an ill cow. The infection began as a papule and was thought to be simple furuncle. Following an attempt at drainage, the infection aggressively spread. Antibiotic therapy was started, and the patient survived. Courtesy of Mariam Svanidze, MD.

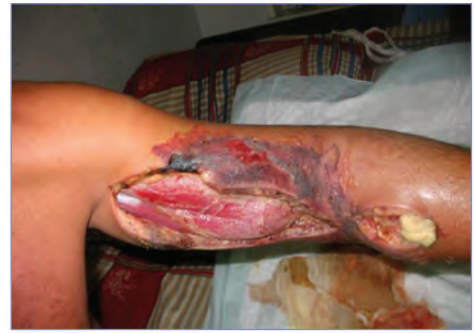


Image 5.2
Generalized cutaneous anthrax infection acquired from an ill cow. The infection began as a papule and was thought to be simple furuncle. Following an attempt at drainage, the infection aggressively spread. Antibiotic therapy was started, and the patient survived. Courtesy of Mariam Svanidze, MD.

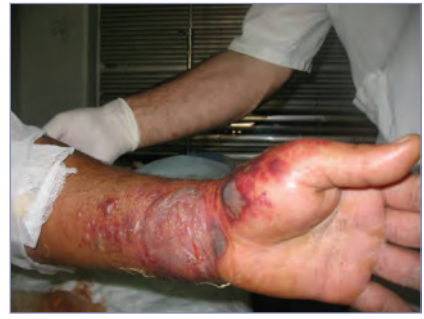


Image 5.4
Generalized cutaneous anthrax infection acquired from an ill cow. The infection began as a papule and was thought to be simple furuncle. Following an attempt at drainage, the infection aggressively spread. Antibiotic therapy was started, and the patient survived. Courtesy of Mariam Svanidze, MD.

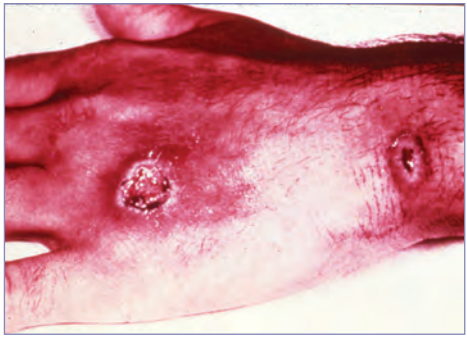


Image 5.5
Anthrax ulcers on hand and wrist of an adult. The cutaneous eschar of anthrax had been misdiagnosed as a brown recluse spider bite. Edema is common and suppuration is absent.

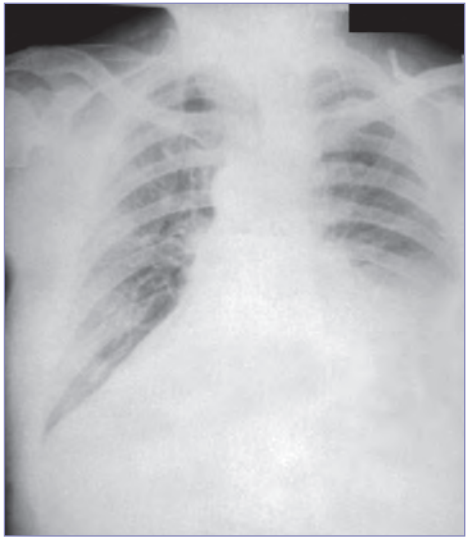


Image 5.7
Posteroanterior chest radiograph taken on the fourth day of illness, which shows a large pleural effusion and marked widening of the mediastinal shadow. Courtesy of Centers for Disease Control and Prevention.

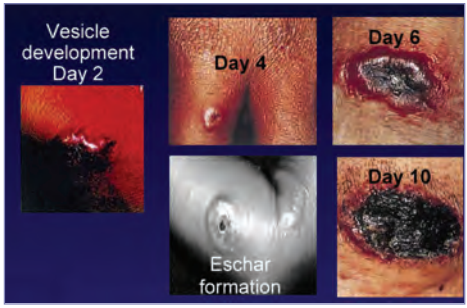


Image 5.6
Cutaneous anthrax. Vesicle development occurs from day 2 through day 10 of progression. Courtesy of Centers for Disease Control and Prevention.

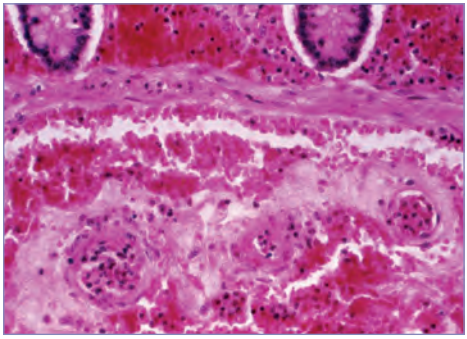


Image 5.8
This micrograph reveals submucosal hemorrhage in the small intestine in a case of fatal human anthrax (hematoxylin-eosin stain, magnification ×240). The first symptoms of gastrointestinal tract anthrax are nausea, loss of appetite, bloody diarrhea, and fever, followed by severe stomach pain. One-fourth to more than half of gastrointestinal anthrax cases lead to death. Note the associated arteriolar degeneration. Courtesy of Centers for Disease Control and Prevention.

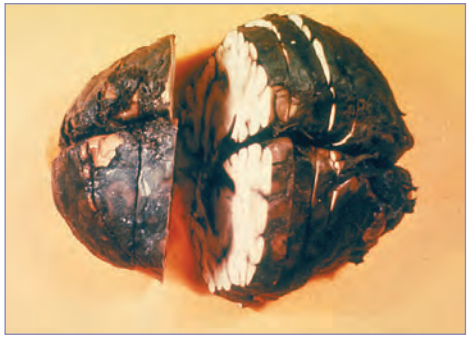


Image 5.9
Gross pathology of fixed, cut brain showing hemorrhagic meningitis secondary to inhalational anthrax. Courtesy of Centers for Disease Control and Prevention.

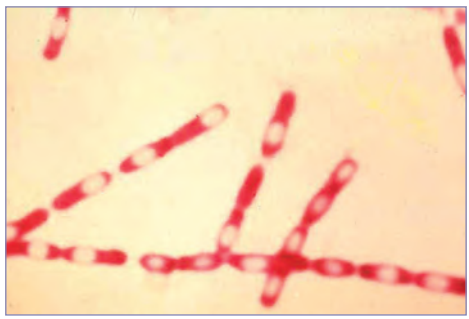


Image 5.11
Sporulation of *Bacillus anthracis*, a gram-positive, nonmotile, encapsulated bacillus.

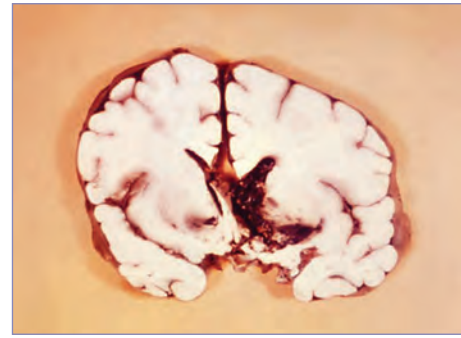


Image 5.10
This is a brain section through the ventricles revealing an interventricular hemorrhage. The 3 virulence factors of *Bacillus anthracis* are edema toxin, lethal toxin, and an antiphagocytic capsular antigen. The toxins are responsible for the primary clinical manifestations of hemorrhage, edema, and necrosis. Courtesy of Centers for Disease Control and Prevention.

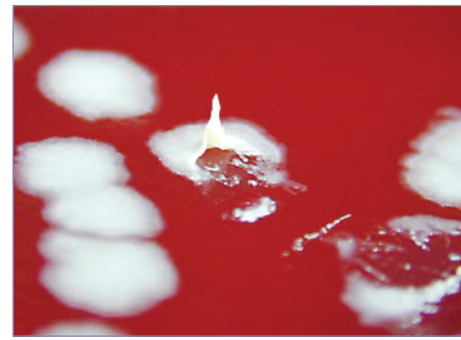
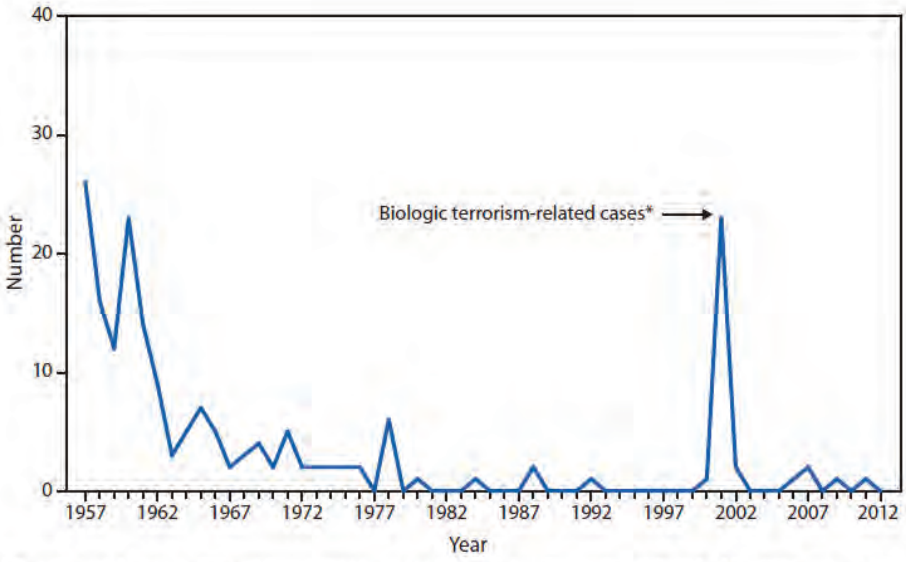


Image 5.12
Bacillus anthracis tenacity positive on sheep blood agar. *B anthracis* colony characteristics: consistency sticky (tenacious). When teased with loop, colony will stand up like beaten egg white. Courtesy of Centers for Disease Control and Prevention.



*Twenty-two bioterrorism-associated cases were reported from Connecticut, Florida, Maryland, New Jersey, Pennsylvania, and Virginia in 2001, and one naturally occurring epizootic-associated case was reported from Texas.

Naturally occurring anthrax epizootics occur annually among U.S. wildlife and livestock populations. In 2012, these were reported in states that routinely experience such outbreaks including Texas, North Dakota, and Nevada; however, livestock outbreaks additionally occurred in 2012 in Mississippi, Oregon, and Colorado, where anthrax outbreaks were not reported in livestock for ≥2 decades. These outbreaks were associated with exposures in persons handling and disposing of affected livestock and collecting diagnostic specimens. Although no human infections resulted, these exposures reflect the importance of timely recognition of anthrax in susceptible animals and the use of appropriate protective measures to prevent human exposures.

Image 5.13
Number of naturally occurring and biological terrorism–related reported cases, by year—United States, 1957 through 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 6

Arboviruses

(Including California serogroup, Colorado tick fever, eastern equine encephalitis, Japanese encephalitis, Powassan, St Louis encephalitis, tickborne encephalitis, Venezuelan equine encephalitis, western equine encephalitis, and yellow fever viruses)

CLINICAL MANIFESTATIONS

More than 100 arthropodborne viruses (arboviruses) are known to cause human disease. Although most infections are subclinical, symptomatic illness usually manifests as 1 of 3 primary clinical syndromes: generalized febrile illness, neuroinvasive disease, or hemorrhagic fever (Table 6.1).

- **Generalized febrile illness.** Most arboviruses are capable of causing a systemic febrile illness that often includes headache, arthralgia, myalgia, and rash. Some viruses can cause more characteristic clinical manifestations, such as focal neurologic defects (see Chapter 163, West Nile Virus), severe polyarthralgia (see Chapter 27, Chikungunya), or jaundice (eg, yellow fever virus). With some arboviruses, fatigue, malaise, and weakness can linger for weeks following the initial infection.
- **Neuroinvasive disease.** Many arboviruses cause neuroinvasive disease, including aseptic meningitis, encephalitis, or acute flaccid myelitis. Illness usually presents with a prodrome similar to the systemic febrile illness followed by neurologic symptoms. The

Table 6.1
Clinical Manifestations for Select Domestic and International Arboviral Diseases

Virus	Systemic Febrile Illness	Neuroinvasive Disease[a]	Hemorrhagic Fever
Domestic			
Chikungunya	Yes[b]	Rare	No
Colorado tick fever	Yes	Rare	No
Dengue	Yes	Rare	Yes
Eastern equine encephalitis	Yes	Yes	No
Jamestown Canyon	Yes	Yes	No
La Crosse	Yes	Yes	No
Powassan	Yes	Yes	No
St Louis encephalitis	Yes	Yes	No
Western equine encephalitis	Yes	Yes	No
West Nile	Yes	Yes	No
Zika	Yes	Yes	No
International			
Japanese encephalitis	Yes	Yes	No
Mayaro	Yes	No	No
Tickborne encephalitis	Yes	Yes	No
Venezuelan equine encephalitis	Yes	Yes	No
Yellow fever	Yes	No	Yes
Toscana virus	Yes	Yes	No

[a] Aseptic meningitis, encephalitis, or acute flaccid myelitis.
[b] Most often characterized by sudden onset of high fever and severe joint pain.

specific symptoms vary by virus but can include vomiting, stiff neck, mental status changes, seizures, or focal neurologic deficits. West Nile virus can cause a syndrome of acute flaccid myelitis, either in conjunction with meningoencephalitis or as an isolated finding. The full range of neurologic manifestations of Zika virus is unclear. The severity and long-term outcome of the illness vary by etiologic agent and the underlying characteristics of the host, such as age, immune status, and preexisting medical condition. The Centers for Disease Control and Prevention has developed a comprehensive website for assessing and managing patients with acute flaccid myelitis as part of its emerging infection surveillance efforts (eg, West Nile virus, enterovirus D68) and in preparation for the final efforts to eradicate polioviruses worldwide (**www.cdc.gov/acute-flaccid-myelitis/hcp/index.html**).

- **Hemorrhagic fever.** Hemorrhagic fevers can be caused by dengue or yellow fever viruses. After several days of nonspecific febrile illness, the patient may develop overt signs of hemorrhage (eg, petechiae, ecchymoses, bleeding from the nose and gums, hematemesis, and melena) and shock (eg, decreased peripheral circulation, azotemia, tachycardia, and hypotension). Hemorrhagic fever and shock caused by yellow fever viruses has a high mortality rate and may be confused with hemorrhagic fevers transmitted by rodents (eg, Argentine hemorrhagic fever, Bolivian hemorrhagic fever, and Lassa fever) or those caused by Ebola or Marburg viruses. Although dengue may be associated with severe hemorrhage, the shock is primarily attributable to a capillary leak syndrome, which, if properly treated with fluids, can result in a high recovery rate.

ETIOLOGY

Arboviruses are RNA viruses that are transmitted to humans primarily through bites of infected arthropods (mosquitoes, ticks, sand flies, and biting midges. The viral families responsible for most arboviral infections in humans are *Flaviviridae* (genus *Flavivirus*), *Togaviridae* (genus *Alphavirus*), and *Bunyaviridae* (genus *Orthobunyavirus* and *Phlebovirus*). *Reoviridae* (genus *Coltivirus*) also are responsible for a smaller number of human arboviral infections (eg, Colorado tick fever) (Table 6.2).

EPIDEMIOLOGY

Most arboviruses maintain cycles of transmission between birds or small mammals and arthropod vectors. Humans and domestic animals usually are infected incidentally as "dead-end" hosts (see Table 6.2). Important exceptions are dengue, yellow fever, chikungunya, and Zika virus, which can be spread from person-to-arthropod-to-person (anthroponotic transmission). For other arboviruses, humans usually do not develop a sustained or high enough level of viremia to infect biting arthropod vectors. Direct person-to-person spread of arboviruses can occur through blood transfusion, organ transplantation, sexual transmission, intrauterine transmission, perinatal transmission, and human milk. Transmission through percutaneous, mucosal, or aerosol exposure to some arboviruses has occurred rarely in laboratory and occupational settings.

In the United States, arboviral infections primarily occur from late spring through early fall, when mosquitoes and ticks are most active. The number of domestic or imported arboviral disease cases reported in the United States varies greatly by specific etiology and year. Underreporting and underdiagnosis of milder disease makes a true determination of the number of cases difficult. Overall, the risk of severe clinical disease for most arboviral infections in the United States is higher among adults than among children. One notable exception is La Crosse virus infection, for which children are at highest risk of severe neurologic disease and possible long-term sequelae. Eastern equine encephalitis virus causes a low incidence of disease but high case fatality rate (40%) across all age groups.

The **incubation periods** for arboviral diseases typically range between 2 and 15 days. Longer incubation periods can occur in immunocompromised people and for tickborne viruses, such as tickborne encephalitis and Powassan viruses.

Table 6.2

Genus, Geographic Location, Vectors, and Average Number of Annual Cases Reported in the United States for Selected Domestic and International Arboviral Diseases

Virus	Predominant Geographic Locations				Number of US Cases/ Year (Range)[a]
	Genus	United States	Non-United States	Vectors	
Domestic					
Chikungunya	*Alphavirus*	Imported, and periodic local transmission	Asia, Africa, Indian Ocean, Western Pacific, Caribbean, South America, North America	Mosquitoes	2006–2013: 28 (5–65) 2014: 2,811 2015: 896
Colorado tick fever	*Coltivirus*	Rocky Mountain states	Western Canada	Ticks	5 (4–14)
Dengue	*Flavivirus*	Puerto Rico, Florida, Texas, and Hawaii	Worldwide in tropical areas	Mosquitoes	725 (254–821)[b]
Eastern equine encephalitis	*Alphavirus*	Eastern and gulf states	Canada, Central and South America	Mosquitoes	7 (4–21)
Jamestown Canyon	*Orthobunyavirus*	Widespread	Canada	Mosquitoes	1 (0–25)
La Crosse	*Orthobunyavirus*	Midwest and Appalachia	Canada	Mosquitoes	78 (50–130)
Powassan	*Flavivirus*	Northeast and Midwest	Canada, Russia	Ticks	7 (0–16)
St Louis encephalitis	*Flavivirus*	Widespread	Canada, Caribbean, Mexico, Central and South America	Mosquitoes	10 (1–49)
Western equine encephalitis	*Alphavirus*	Central and West	Central and South America	Mosquitoes	Less than 1
West Nile	*Flavivirus*	Widespread	Canada, Europe, Africa, Asia, South America	Mosquitoes	2,469 (712–9,862)
Zika	*Flavivirus*	Imported and periodic local transmission	Asia, Africa, Indian Ocean, Western Pacific, Caribbean, South America, North America	Mosquitoes	2010–2014: 11 2015: 54 2016: >2,500[c]

(*continued*)

Table 6.2 (*continued*)

Virus	Predominant Geographic Locations				Number of US Cases/ Year (Range)[a]
	Genus	United States	Non-United States	Vectors	
International					
Japanese encephalitis	*Flavivirus*	Imported only	Asia	Mosquitoes	Less than 1
Mayaro	*Alphavirus*	Imported only	South America	Mosquitoes	Less than 1
Tickborne encephalitis	*Flavivirus*	Imported only	Europe, northern Asia	Ticks	Less than 1
Venezuelan equine encephalitis	*Alphavirus*	Imported only	Mexico, Central and South America	Mosquitoes	Less than 1
Yellow fever	*Flavivirus*	Imported only	South America, Africa	Mosquitoes	Less than 1

[a] Average annual number of domestic and/or imported cases reported from 2003 through 2015, unless otherwise noted.
[b] Data from 2010 through 2015, when dengue was nationally notifiable, includes domestic and imported cases reported to the CDC, excluding local transmission in Puerto Rico and the US Virgin Islands.
[c] Updated information on Zika virus in the Americas can be found at **www.paho.org/hq/index.php?option=com_content&view=article&id=11585&Itemid=41688&lang=en.**

DIAGNOSTIC TESTS

Arboviral infections are confirmed most frequently by detection of virus-specific antibody in serum or cerebrospinal fluid (CSF). Acute-phase serum specimens should be tested for virus-specific immunoglobulin (Ig) M antibody. With clinical and epidemiologic correlation, a positive IgM test result has good diagnostic predictive value, but cross-reaction with related arboviruses from the same viral family can occur (eg, West Nile and St. Louis encephalitis viruses, which both are flaviviruses). For most arboviral infections, IgM is detectable 3 to 8 days after onset of illness and persists for 30 to 90 days, but longer persistence has been documented, especially with West Nile virus. Therefore, a positive serum IgM test result occasionally may reflect a prior infection. Serum collected within 10 days of illness onset may not have detectable IgM, and the test should be repeated on a convalescent sample. IgG antibody generally is detectable in serum shortly after IgM and persists for years. A plaque-reduction neutralization test can be performed to measure virus-specific neutralizing antibodies and to discriminate between cross-reacting antibodies in primary arboviral infections. Either seroconversion or a fourfold or greater increase in virus-specific neutralizing antibodies between acute- and convalescent-phase serum specimens collected 2 to 3 weeks apart may be used to confirm recent infection. In patients who have been immunized against or infected with another arbovirus from the same virus family in the past (ie, secondary infection), cross-reactive antibodies in both the IgM and neutralizing antibody assays may make it difficult to identify which arbovirus is causing the patient's illness. For some arboviral infections (eg, Colorado tick fever), the immune response may be delayed, with IgM antibodies not appearing until 2 to 3 weeks after onset of illness and neutralizing antibodies taking up to a month to develop. Patients with significant immunosuppression (eg, patients who have received a solid organ transplant or recent chemotherapy) may have a delayed or blunted serologic response. Immunization and travel history, date of symptom onset, and information regarding other arboviruses known to circulate in the geographic area that may cross-react in serologic assays should be considered when interpreting results.

Viral culture and nucleic acid amplification tests (NAATs) for RNA can be performed on acute-phase serum, CSF, or tissue specimens. Arboviruses that are more likely to be detected using culture or NAATs early in the illness include Colorado tick fever, dengue, yellow fever, and Zika viruses. For other arboviruses, results of these tests often are negative even early in the clinical course because of the relatively short duration of viremia. Immunohistochemical staining (IHC) can detect specific viral antigen in fixed tissue.

Antibody testing for common domestic arboviral diseases is performed in most state public health laboratories and many commercial laboratories. Confirmatory plaque-reduction neutralization tests, viral culture, NAATs, immunohistochemical staining, and testing for less common domestic and international arboviruses are performed at the Centers for Disease Control and Prevention (CDC; telephone: 970-221-6400) and selected other reference laboratories. Confirmatory testing typically is arranged through local and state health departments.

TREATMENT

The primary treatment for all arboviral disease is supportive. Although various antiviral and immunologic therapies have been evaluated for several arboviral diseases, none have shown clear benefit.

Image 6.1
Digital gangrene in an 8-month-old girl during week 3 of hospitalization. She was admitted to the hospital with fever, multiple seizures, and a widespread rash; chikungunya virus was detected in her plasma. A, Little finger of the left hand; B, index finger of the right hand; C, 4 toes on the right foot. Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases.*

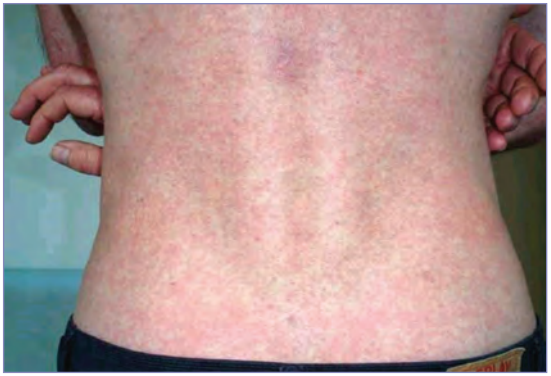


Image 6.2
Cutaneous eruption of chikungunya infection, a generalized exanthema comprising noncoalescent lesions, occurs during the first week of the disease, as seen in this patient with erythematous maculopapular lesions with islands of normal skin. Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases* and Patrick Hochedez.

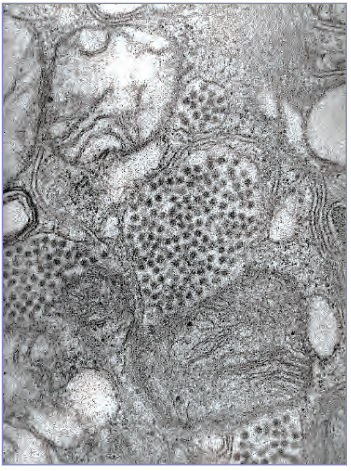


Image 6.3
An electron micrograph of eastern equine encephalomyelitis virus in a mosquito salivary gland; *Alphavirus,* eastern equine encephalomyelitis. Courtesy of Centers for Disease Control and Prevention.

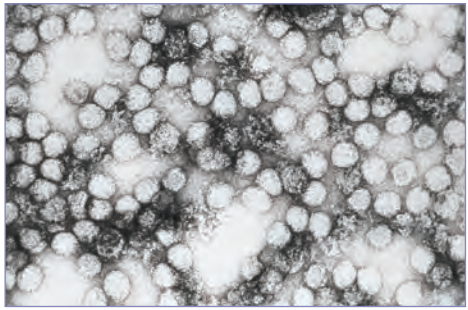


Image 6.4
An electron micrograph of yellow fever virus virions. Virions are spheroidal, uniform in shape, and 40 to 60 nm in diameter. The name "yellow fever" is due to the ensuing jaundice that affects some patients. The vector is the *Aedes aegypti* or *Haemagogus* species mosquito. Courtesy of Centers for Disease Control and Prevention.

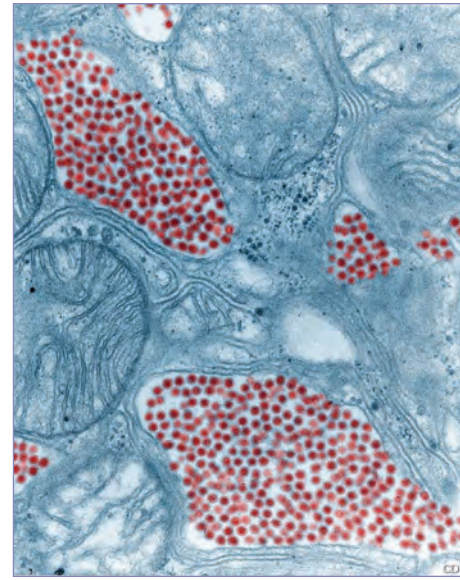


Image 6.5
This colorized transmission electron micrograph depicts a salivary gland that had been extracted from a mosquito, which was infected by the eastern equine encephalitis virus, which has been colorized red (magnification ×83,900). Courtesy of Centers for Disease Control and Prevention/ Fred Murphy, MD, and Sylvia Whitfield.

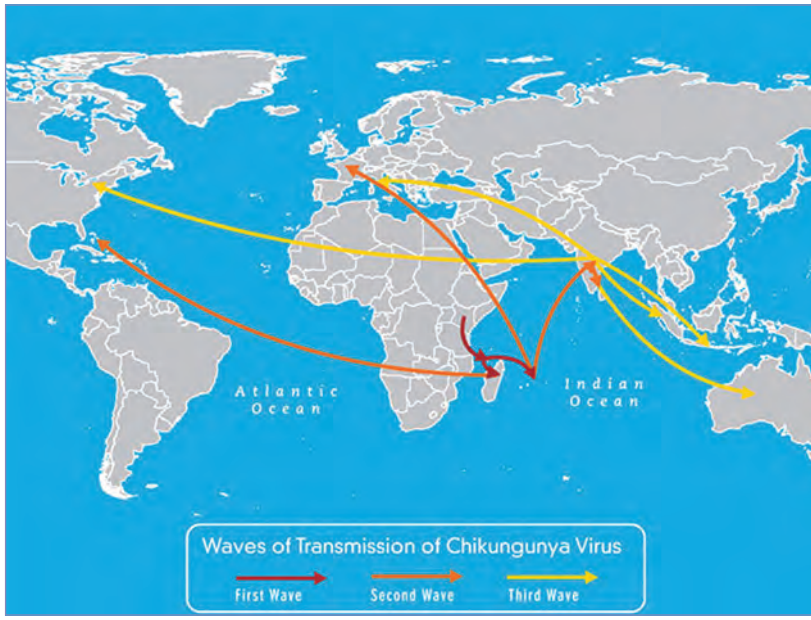


Image 6.6
Global spread of chikungunya virus during 2005 through 2009. Courtesy of *Morbidity and Mortality Weekly Report.*

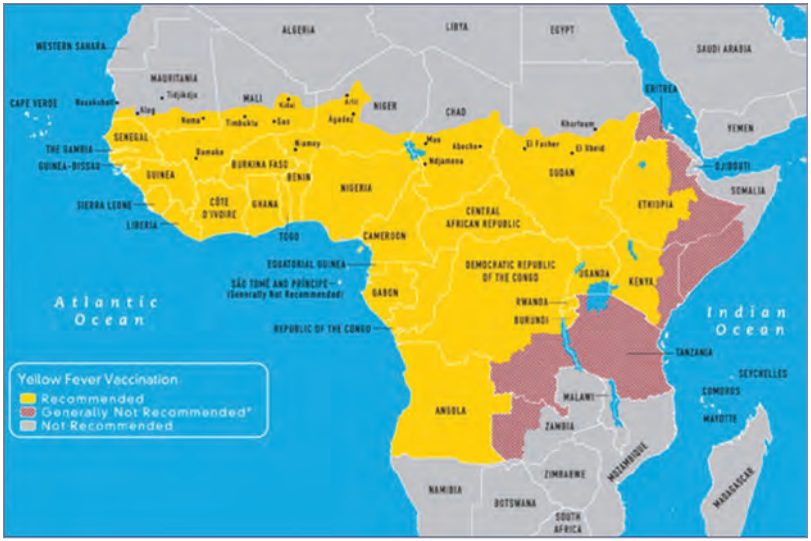


Image 6.7
Yellow fever vaccine recommendations in Africa, 2010. Courtesy of Centers for Disease Control and Prevention.

Image 6.8
Yellow fever vaccine recommendations in the Americas, 2010. Courtesy of Centers for Disease Control and Prevention.

Image 6.9
This horse was displaying symptoms of the arboviral disease Venezuelan equine encephalomyelitis. Etiologic pathogens responsible for equine encephalitic diseases are transmitted to horses by mosquitoes, with reservoirs being various bird species. Courtesy of Centers for Disease Control and Prevention.

Image 6.10
A close-up anterior view of a *Culex tarsalis* mosquito as it was about to begin feeding. The epidemiologic importance of *C tarsalis* lies in its ability to spread western equine encephalomyelitis, St Louis encephalitis, and California encephalitis and is currently the main vector of West Nile virus in the western United States. Courtesy of Centers for Disease Control and Prevention/ James Gathany.

CHAPTER 7

Arcanobacterium haemolyticum Infections

CLINICAL MANIFESTATIONS

Acute pharyngitis attributable to *Arcanobacterium haemolyticum* often is indistinguishable from group A streptococcal pharyngitis. Fever, erythema and exudates, cervical lymphadenopathy, and rash are common, but palatal petechiae and strawberry tongue are absent. A morbilliform or scarlatiniform exanthem is present in half of cases, beginning on extensor surfaces of the distal extremities, spreading centripetally, sparing the face, palms, and soles. Rash typically develops 1 to 4 days after onset of sore throat, although rash preceding pharyngitis can occur. Respiratory tract infections that mimic diphtheria, including membranous pharyngitis, peritonsillar and pharyngeal abscesses, and skin and soft tissue infections, including chronic ulcers, cellulitis, paronychia, and wound infection, have been attributed to *A haemolyticum.* Invasive infections may include peritonsillar abscess, Lemierre syndrome, bacteremia, sepsis, endocarditis, brain abscess, orbital cellulitis, pyogenic arthritis, or rarely, other infections. No nonsuppurative sequelae have been reported.

ETIOLOGY

A haemolyticum is a catalase-negative, weakly acid-fast, facultative, hemolytic, anaerobic, gram-positive to gram-variable, slender, sometimes club-shaped bacillus formerly classified as *Corynebacterium haemolyticum.*

EPIDEMIOLOGY

Humans are the primary reservoir of *A haemolyticum,* and spread is person to person, presumably via droplet respiratory secretions. Severe disease occurs almost exclusively among immunocompromised people. Pharyngitis occurs primarily in adolescents and young adults and only rarely in young children. *A haemolyticum* accounts for approximately 2.5% of pharyngeal infections in 15- to 25-year-olds. Isolation of the bacterium from the nasopharynx of asymptomatic people is rare.

The **incubation period** is unknown.

DIAGNOSTIC TESTS

A haemolyticum grows on blood-enriched agar, but colonies are small, have narrow bands of hemolysis, and may not be visible for 48 to 72 hours. The organism is not detected by rapid antigen tests for group A streptococci. Detection is enhanced by culture on rabbit or human blood agar rather than on sheep blood agar, which yields larger colony size and wider zones of hemolysis. Presence of 5% carbon dioxide enhances growth. *A haemolyticum* is missed in routine throat cultures on sheep blood agar if laboratory personnel are not trained specifically to identify the organism. Pits characteristically form under colonies on blood agar plates. Two biotypes of *A haemolyticum* have been identified: a rough colonial biotype predominates in respiratory tract infections, and a smooth biotype typically in skin and soft-tissue infections.

TREATMENT

Erythromycin and azithromycin are drugs of choice for *A haemolyticum* tonsillopharyngitis, but no prospective trials have been performed. *A haemolyticum* generally is susceptible in vitro to azithromycin, erythromycin, clindamycin, ciprofloxacin, vancomycin, and tetracycline. Treatment failures with penicillin despite predicted susceptibility from in vitro testing have been described, which likely is attributable to the organism's intracellular survival. Resistance to trimethoprim-sulfamethoxazole is common. In rare cases of disseminated infection, susceptibility tests should be performed. Initial empiric combination therapy can be initiated using a parenteral beta lactam agent, with or without a macrolide.

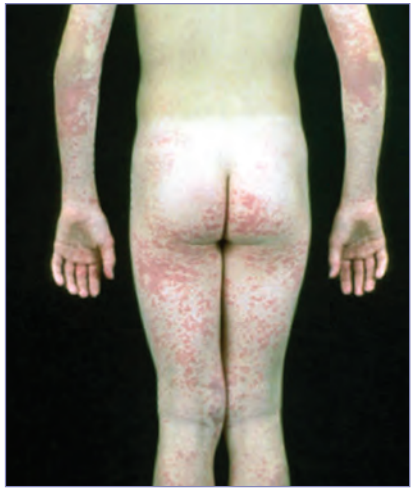


Image 7.1
Arcanobacterium haemolyticum was isolated on pharyngeal culture from this 12-year-old boy with an erythematous rash that was followed by mild desquamation. Copyright Williams/Karofsky.

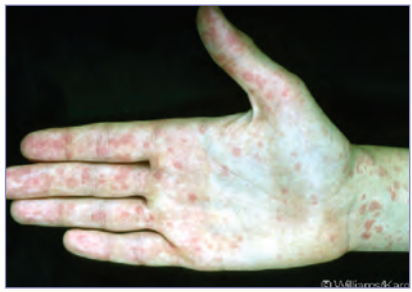


Image 7.3
Note that the palms are affected in this patient, although they are often spared. Copyright Williams/Karofsky.

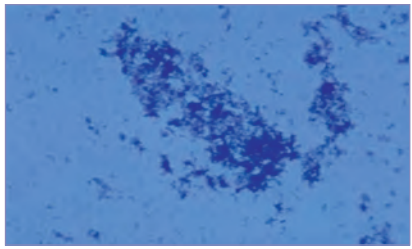


Image 7.5
Arcanobacterium haemolyticum (Gram stain). *A haemolyticum* appears strongly gram-positive in young cultures but becomes more gram-variable after 24 hours of incubation. Copyright Noni MacDonald, MD, FAAP.

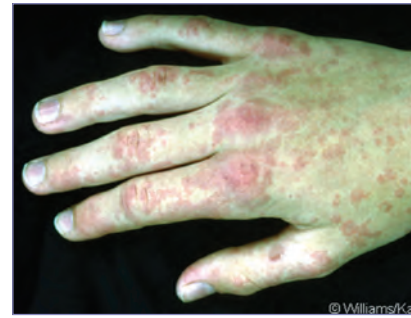


Image 7.2
Arcanobacterium haemolyticum–associated rash on dorsal surface of hand in the 12-year-old boy in Images 7.1, 7.3, and 7.4. Copyright Williams/Karofsky.

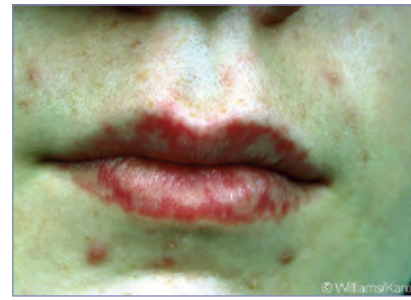


Image 7.4
Although not present in this patient with facial skin lesions associated with *Arcanobacterium haemolyticum* pharyngitis, a pharyngeal membrane similar to that of diphtheria may occur with *A haemolyticum* pharyngeal infection. Copyright Williams/Karofsky.

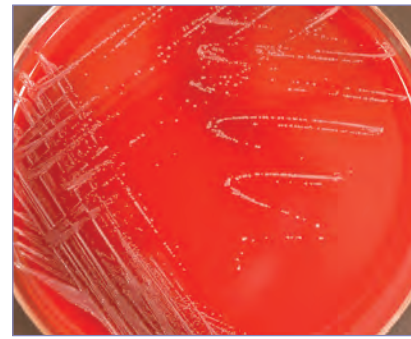


Image 7.6
Arcanobacterium haemolyticum on blood agar. Colonies are small and produce β-hemolysis on blood agar. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 8

Ascaris lumbricoides Infections

CLINICAL MANIFESTATIONS

Most infections with *Ascaris lumbricoides* are asymptomatic, although moderate to heavy infections may lead to nonspecific gastrointestinal tract symptoms, malnutrition, and growth delay. During the larval migratory phase, an acute transient pneumonitis (Löffler syndrome) associated with cough, substernal discomfort, fever, and marked eosinophilia may occur. Acute intestinal obstruction has been associated with heavy infections. Children are prone to this complication because of the small diameter of the intestinal lumen and their propensity to acquire large worm burdens. Worm migration can cause peritonitis secondary to intestinal wall perforation, as well as appendicitis or common bile duct obstruction resulting in biliary colic, cholangitis, or pancreatitis. Adult worms can be stimulated to migrate by stressful conditions (eg, fever, illness, or anesthesia) and by some anthelmintic drugs.

ETIOLOGY

Following ingestion of embryonated eggs, usually from contaminated soil, larvae hatch in the small intestine, penetrate the mucosa, and are transported passively by portal blood to the liver and lungs. After migrating into the airways, larvae ascend through the tracheobronchial tree to the pharynx, are swallowed, and mature into adults in the small intestine. Female worms produce approximately 200,000 eggs per day, which are excreted in stool and must incubate in soil for 2 to 3 weeks to become infectious. Adult worms can live in the lumen of the small intestine for 12 to 18 months. Female worms are longer than male worms and can measure 40 cm in length and 6 mm in diameter.

EPIDEMIOLOGY

A lumbricoides is the most prevalent of all human intestinal nematodes (roundworms), with approximately 1 billion people infected worldwide. Infection with *A lumbricoides* is most common in resource-limited countries, including rural and urban communities characterized by poor sanitation. Direct person-to-person transmission does not occur.

The **incubation period** (interval between ingestion of eggs and development of egg-laying adults) is approximately 9 to 11 weeks.

DIAGNOSTIC TESTS

Ascariasis is diagnosed by examining a fresh preserved stool specimen for eggs using light microscopy. Adult worms also may be passed from the rectum, through the nares, or from the mouth, usually in vomitus. Imaging of the gastrointestinal tract or biliary tree using computed tomography or ultrasonography may detect adult *Ascaris* worms, which can cause filling defects following administration of oral contrast.

TREATMENT

Albendazole (taken with food in a single dose), mebendazole (a single dose or once daily for 3 days), and pyrantel pamoate are first-line agents for treatment of ascariasis. Ivermectin (taken on an empty stomach in a single dose) and nitazoxanide are alternative therapies. Cure rates range from 90% with pyrantel pamoate to 100% with albendazole. Studies in children as young as 1 year suggest that albendazole can be administered safely to this population. Reexamination of stool specimens may be performed 2 to 3 months after therapy and patients who remain infected can be retreated.

Conservative management of small bowel obstruction, including nasogastric suction and intravenous fluids, may alleviate symptoms before administration of anthelmintic therapy. Use of mineral oil or diatrizoate meglumine and diatrizoate sodium solution (Gastrografin), either orally or by nasogastric tube, also may cause relaxation of a bolus of worms. Endoscopic retrograde cholangiopancreatography has been used successfully for extraction of worms from the biliary tree. Surgical intervention (eg, laparotomy) is indicated for intestinal or biliary tract obstruction that does not resolve with conservative therapy or for patients with volvulus or peritonitis secondary to perforation.

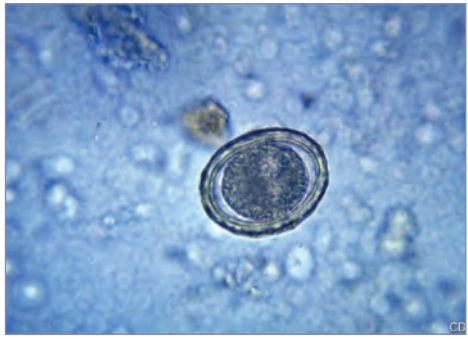


Image 8.1
This micrograph reveals a fertilized egg of the roundworm *Ascaris lumbricoides* (magnification ×400). Fertilized eggs are rounded and have a thick shell, while unfertilized eggs are elongated and larger, thinner shelled, and covered by a more visible mammillated layer, which is sometimes covered by protuberances. Courtesy of Centers for Disease Control and Prevention/Mae Melvin, MD.

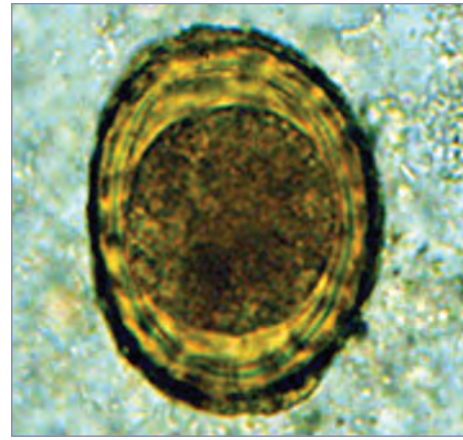


Image 8.2
A fertilized ascaris egg, still at the unicellular stage, which is the usual stage when the eggs are passed in the stool (complete development of the larva requires 18 days under favorable conditions). Courtesy of Centers for Disease Control and Prevention.

Image 8.3
Larva hatching from an ascaris egg. This occurs in the small intestine. Courtesy of Centers for Disease Control and Prevention.

Image 8.4
An adult ascaris. Diagnostic characteristics: tapered ends; length 15 to 35 cm (females tend to be larger). This worm is a female, as evidenced by the size and genital girdle (the dark circular groove at left side of image). Courtesy of Centers for Disease Control and Prevention.

Image 8.5
A mass of large roundworms (*Ascaris lumbricoides*) from a human infestation.

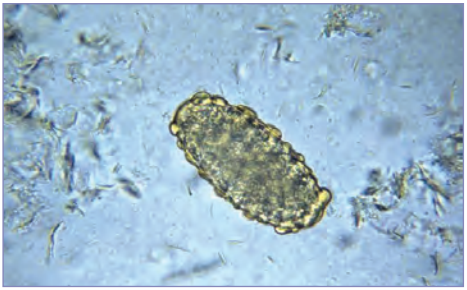


Image 8.6
This micrograph reveals an unfertilized egg of the roundworm *Ascaris lumbricoides* (magnification ×400). Fertilized eggs are rounded and have a thick shell, while unfertilized eggs are elongated and larger, thinner shelled, and covered by a more visible mammillated layer, which is sometimes covered by protuberances, as in this case. Courtesy of Centers for Disease Control and Prevention/Mae Melvin, MD.

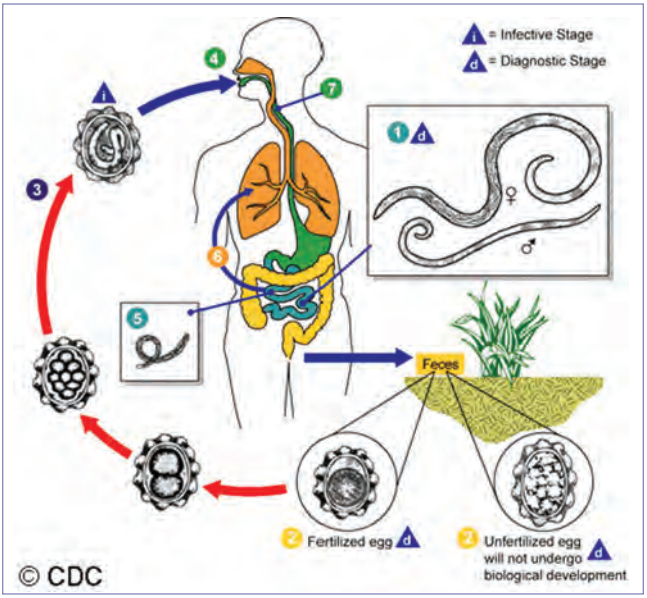


Image 8.7
Adult worms (1) live in the lumen of the small intestine. A female may produce approximately 200,000 eggs per day, which are passed with the feces (2). Unfertilized eggs may be ingested but are not infective. Fertile eggs embryonate and become infective after 18 days to several weeks (3), depending on the environmental conditions (optimum: moist, warm, shaded soil). After infective eggs are swallowed (4), the larvae hatch (5), invade the intestinal mucosa, and are carried via the portal, and then systemic circulation to the lungs (6). The larvae mature further in the lungs (10–14 days), penetrate the alveolar walls, ascend the bronchial tree to the throat, and are swallowed (7). On reaching the small intestine, they develop into adult worms (8). Between 2 and 3 months are required from ingestion of the infective eggs to oviposition by the adult female. Adult worms can live 1 to 2 years. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 9

Aspergillosis

CLINICAL MANIFESTATIONS

Aspergillosis manifests as 5 principal clinical entities: invasive aspergillosis, pulmonary aspergilloma, allergic bronchopulmonary aspergillosis, allergic sinusitis, and chronic aspergillosis. Colonization of the respiratory tract is common. The clinical manifestations and severity depend on the immune status (immunocompromised or atopic) of the host.

- **Invasive aspergillosis** occurs almost exclusively in immunocompromised patients with prolonged neutropenia, graft-versus-host disease, or impaired phagocyte function (eg, chronic granulomatous disease) or those who have received T-lymphocyte immunosuppressive therapy (eg, corticosteroids, calcineurin inhibitors, tumor necrosis factor [TNF]-alpha inhibitors). Children at highest risk include those with new-onset acute myelogenous leukemia, relapse of hematologic malignancy, aplastic anemia, chronic granulomatous disease, and recipients of allogeneic hematopoietic stem cell and certain types (eg, heart, lung) of solid organ transplants. Invasive infection usually involves pulmonary, sinus, cerebral, or cutaneous sites. Rarely, endocarditis, osteomyelitis, meningitis, peritonitis, infection of the eye or orbit, and esophagitis occur. The hallmark of invasive aspergillosis is angioinvasion with resulting thrombosis, dissemination to other organs, and occasionally erosion of the blood vessel wall with catastrophic hemorrhage. Invasive aspergillosis in patients with chronic granulomatous disease is unique in that it is more indolent and displays a general lack of angioinvasion.
- **Pulmonary aspergillomas and otomycosis** are 2 syndromes of nonallergic colonization by *Aspergillus* species in immunocompetent children. Aspergillomas ("fungal balls") grow in preexisting pulmonary cavities or bronchogenic cysts without invading pulmonary tissue; almost all patients have underlying lung disease, such as cystic fibrosis or tuberculosis. Patients with otomycosis have chronic otitis media with colonization of the external auditory canal by a fungal mat that produces a dark discharge.
- **Allergic bronchopulmonary aspergillosis** is a hypersensitivity lung disease that manifests as episodic wheezing, expectoration of brown mucus plugs, low-grade fever, eosinophilia, and transient pulmonary infiltrates. This form of aspergillosis occurs most commonly in immunocompetent children with asthma or cystic fibrosis and can be a trigger for asthmatic flares.
- **Allergic sinusitis** is a far less common allergic response to colonization by *Aspergillus* species than is allergic bronchopulmonary aspergillosis. Allergic sinusitis occurs in children with nasal polyps or previous episodes of sinusitis or in children who have undergone sinus surgery. Allergic sinusitis is characterized by symptoms of chronic sinusitis with dark plugs of nasal discharge and is different from invasive *Aspergillus* sinusitis.
- **Chronic aspergillosis** typically affects patients who are not immunocompromised or are less immunocompromised, although exposure to corticosteroids is common, and patients often have underlying pulmonary conditions. Diagnosis of chronic aspergillosis requires at least 3 months of chronic pulmonary symptoms or chronic illness or progressive radiologic abnormalities along with an elevated *Aspergillus* immunoglobulin (Ig) G concentration or other microbiological evidence. Because of the ubiquitous nature of *Aspergillus* species, a positive sputum culture alone is not diagnostic.

ETIOLOGY

Aspergillus species are ubiquitous molds that grow on decaying vegetation and in soil. *Aspergillus fumigatus* is the most common (>75%) cause of invasive aspergillosis, with *Aspergillus flavus* being the next most common. Several other major species, including *Aspergillus terreus*, *Aspergillus nidulans*, and *Aspergillus niger*, also cause invasive human infections. Of increasing concern are emerging *Aspergillus* species that are resistant to antifungals, such as *Aspergillus calidoustus* (azole resistant).

EPIDEMIOLOGY

The principal route of transmission is inhalation of conidia (spores) originating from multiple environmental sources (eg, plants, vegetables, dust from construction or demolition), soil, and water supplies (eg, shower heads). Incidence of disease in hematopoietic stem cell transplant recipients is highest during periods of neutropenia or during treatment for graft-versus-host disease. In solid organ transplant recipients, the risk is highest approximately 6 months after transplantation or during periods of increased immunosuppression. Disease has followed use of contaminated marijuana in the immunocompromised host. Health care-associated outbreaks of invasive pulmonary aspergillosis in susceptible hosts have occurred in which the probable source of the fungus was a nearby construction site or faulty ventilation system; however, the source of health care-associated aspergillosis frequently is not known. Cutaneous aspergillosis occurs less frequently and usually involves sites of skin injury, such as intravenous catheter sites (including in neonates), sites of traumatic inoculation, and sites associated with occlusive dressings, burns, or surgery. Transmission by direct inoculation of skin abrasions or wounds is less likely. Person-to-person spread does not occur.

The **incubation period** is unknown and may be variable.

DIAGNOSTIC TESTS

Dichotomously branched and septate hyphae, identified by microscopic examination of 10% potassium hydroxide wet preparations or of Gomori methenamine-silver nitrate stain of tissue or bronchoalveolar lavage specimens, are suggestive of the diagnosis. Isolation of *Aspergillus* species or molecular testing with specific reagents is required for definitive diagnosis. The organism usually is not recoverable from blood (except *A terreus*) but is isolated readily from lung, sinus, and skin biopsy specimens when cultured on Sabouraud dextrose agar or brain-heart infusion media (without cycloheximide). *Aspergillus* species can be a laboratory contaminant, but when evaluating results from immunocompromised patients, recovery of this organism frequently indicates infection. Biopsy is required to confirm the diagnosis, and care should be taken to distinguish aspergillosis from mucormycosis, which appears similar by diagnostic imaging studies but is pauci-septate (few septa) and requires a different treatment regimen.

An enzyme immunosorbent assay for detection of galactomannan, a molecule found in the cell wall of *Aspergillus* species, from serum or bronchoalveolar lavage (BAL) fluid is available commercially and has been found to be useful in children and adults. A test result of ≥0.5 from the serum or ≥1.0 from BAL fluid supports a diagnosis of invasive aspergillosis, and monitoring of serum antigen concentrations twice weekly in periods of highest risk (eg, neutropenia and active graft-versus-host disease) may be useful for early detection of invasive aspergillosis in at-risk patients. False-positive test results have been reported and can be related to consumption of food products containing galactomannan (eg, rice and pasta), other invasive fungal infections (eg, *Fusarium*), and colonization of the gut of neonates with *Bifidobacterium* species. Previous cross-reactivity with antimicrobial agents derived from fungi (especially piperacillin-tazobactam) no longer occurs because of manufacturing changes. A negative galactomannan test result does not exclude diagnosis of invasive aspergillosis, and the greatest utility may be in monitoring response to disease rather than in its use as a diagnostic marker. False-negative galactomannan test results consistently occur in patients with chronic granulomatous disease, so the test should not be used in these patients. Galactomannan is not recommended for screening in solid organ transplant recipients because of poor sensitivity.

Limited data suggest that other nonspecific fungal biomarkers, such as 1,3-β-D glucan testing, may be useful in the diagnosis of aspergillosis. *Aspergillus* polymerase chain reaction testing is promising but not yet recommended for routine clinical use. Unlike adults, children frequently do not manifest cavitation or the air crescent or halo signs on chest radiography, and lack of these characteristic signs does not exclude the diagnosis of invasive aspergillosis.

In allergic aspergillosis, diagnosis is suggested by a typical clinical syndrome with elevated total concentrations of IgE (≥1,000 ng/mL) and

Aspergillus-specific serum IgE, eosinophilia, and a positive result from a skin test for *Aspergillus* antigens. In people with cystic fibrosis, the diagnosis is more difficult, because wheezing, eosinophilia, and a positive skin test result not associated with allergic bronchopulmonary aspergillosis often are present.

TREATMENT

Voriconazole is the drug of choice for all clinical forms of invasive aspergillosis, except in neonates, for whom amphotericin B deoxycholate in high doses is recommended. Voriconazole has been shown to be superior to amphotericin B in a large, randomized trial in adults. Immune reconstitution is paramount; decreasing immunosuppression, if possible (specifically corticosteroid dose), is critical to disease control. The diagnostic workup needs to be aggressive to confirm disease, but it should never delay antifungal therapy in the setting of true concern for invasive aspergillosis. Therapy is continued for a minimum of 6 to 12 weeks, but treatment duration should be individualized on the basis of degree and duration of immunosuppression. Monitoring of serum galactomannan concentrations in those with significant elevation at onset may be useful to assess response to therapy concomitant with clinical and radiologic evaluation. Voriconazole is metabolized in a linear fashion in children (nonlinear in adults), so the recommended adult dosing (per kg) is too low for children, especially the youngest children. Children 12 years and older who weigh ≥50 kg should receive the adult dose. Conversion to oral voriconazole requires a dose increase because the bioavailability of oral voriconazole in children is only approximately 50% (versus >90% in adults). Close monitoring of voriconazole serum trough concentrations is critical for both efficacy and safety. Certain *Aspergillus* species (*A calidoustus*) are inherently resistant to azoles, and isolation of azole-resistant *A fumigatus* is increasing.

Alternative therapies include liposomal amphotericin B, isavuconazole, or other lipid formulations of amphotericin B. An echinocandin can be used in settings in which an azole or amphotericin B are contraindicated. In refractory disease, treatment may include posaconazole. The pharmacokinetics and safety of posaconazole have not been evaluated in younger children. Posaconazole absorption is significantly improved with use of the extended-release tablet than the oral suspension. Isavuconazole is an alternative therapy in adults but has not been studied in children. Combination antifungal therapy with voriconazole and an echinocandin may be considered in select patients with documented invasive aspergillosis.

If primary antifungal therapy fails, general strategies for salvage therapy include (a) changing the class of antifungal; (b) tapering or reversal of underlying immunosuppression when feasible; (c) susceptibility testing of any *Aspergillus* isolates recovered; and (d) surgical resection of necrotic lesions in selected cases. In pulmonary disease, surgery is indicated only when a mass is impinging on a great vessel. Surgical excision of a localized cutaneous eschar is usually warranted.

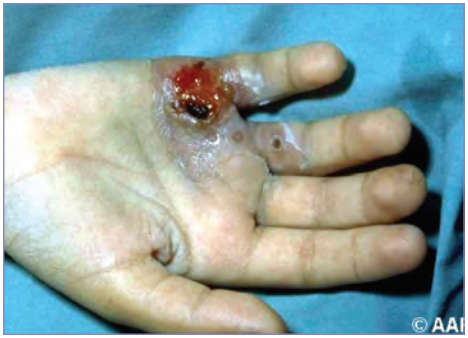


Image 9.1
Aspergilloma of the hand in a 7-year-old boy with chronic granulomatous disease.

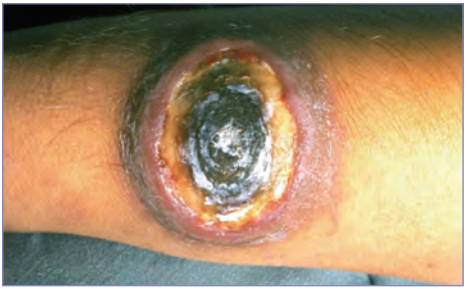


Image 9.2
Aspergilloma at intravenous line site in a 9-year-old boy with acute lymphoblastic leukemia.

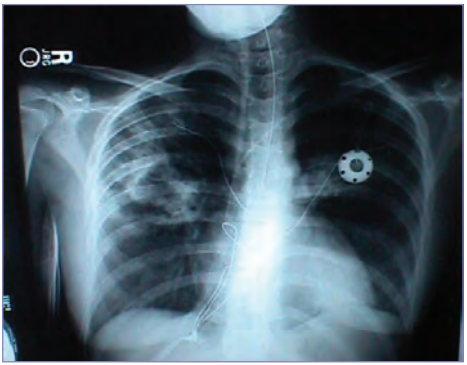


Image 9.3
Aspergillus pneumonia, bilateral, in a 16-year-old boy with acute myelogenous leukemia. Note pulmonary cavitation in the right lung field and perihilar and retrocardiac densities in the left lung field. Copyright Michael Rajnik, MD, FAAP.

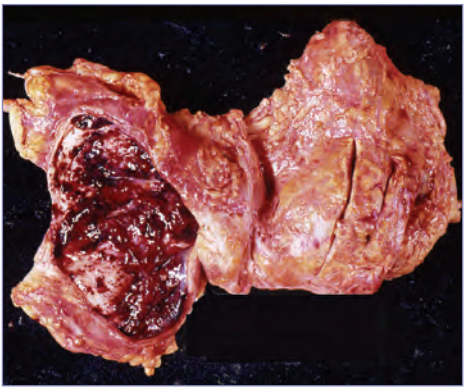


Image 9.4
Pulmonary aspergillosis in a patient with acute lymphatic leukemia. Courtesy of Dimitris P. Agamanolis, MD.

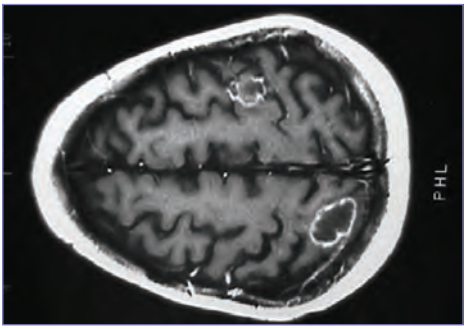


Image 9.5
Aspergillomas in a 10-year-old with Hodgkin-type lymphoma. Courtesy of Benjamin Estrada, MD.

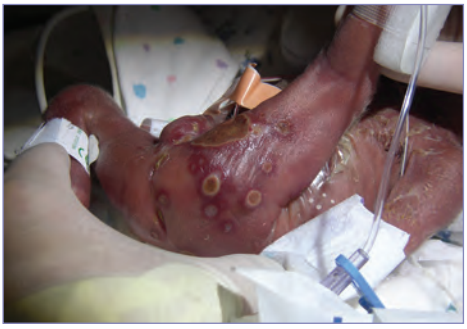


Image 9.6
Cutaneous aspergillosis in a 23-weeks' gestation preterm neonate. Courtesy of David Kaufman, MD.

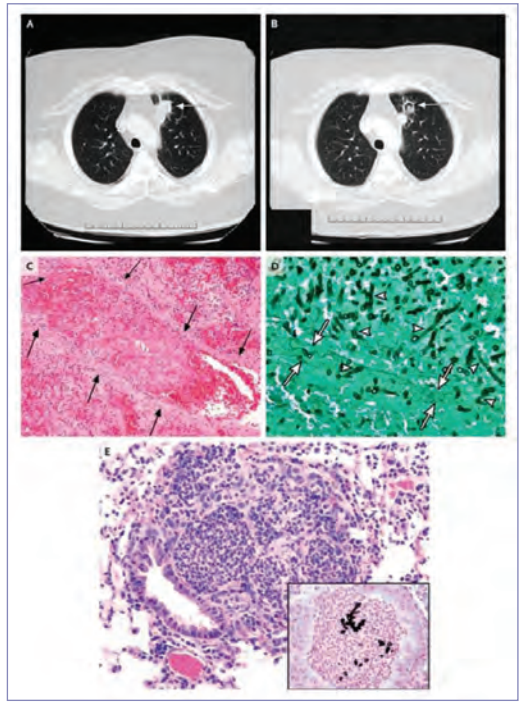


Image 9.7

A, Computed tomographic chest scan of a patient with neutropenia who has invasive aspergillosis (arrow). A positive serum galactomannan test established the diagnosis of probable invasive aspergillosis, which averted the need for an invasive diagnostic procedure. B, Cavitation of the lesion after a successful response to therapy and neutrophil recovery (arrow). C, Vascular invasive aspergillosis can occur in patients with other conditions, such as in this case of fatal aspergillosis in a recipient of an allogeneic hematopoietic stem-cell transplant with severe graft-versus-host disease. A low-power micrograph shows vascular thrombosis (with an arterial vessel outlined by arrows) (hematoxylin-eosin). D, A high-power micrograph shows hyphae (arrowheads) transverse to the blood vessel wall (outlined by arrows) and intravascular invasion (Grocott-Gomori methenamine–silver nitrate stain, with hyphal walls staining dark). The septated hyphae are morphologically consistent with *Aspergillus* species. E, Experimental aspergillosis in a knockout mouse model of chronic granulomatous disease, an inherited disorder of NADPH oxidase. Densely inflammatory pyogranulomatous pneumonia without vascular invasion or tissue infarction is visible (hematoxylin-eosin), with invasive hyphae in the lung as seen with silver staining (inset). Copyright *New England Journal of Medicine*.

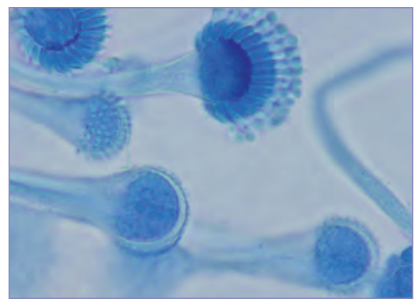


Image 9.8

Aspergillus fumigatus. Courtesy of H. Cody Meissner, MD, FAAP.

CHAPTER 10

Astrovirus Infections

CLINICAL MANIFESTATIONS

Astrovirus illness is characterized by acute diarrhea accompanied by low-grade fever, malaise, and nausea, and less commonly, vomiting and mild dehydration. Illness in an immunocompetent host is self-limited, lasting a median of 5 to 6 days. Asymptomatic infections are common. Recently, astrovirus infections associated with encephalitis and meningitis have been reported, particularly in immunocompromised individuals.

ETIOLOGY

Astroviruses are nonenveloped, single-stranded RNA viruses with a characteristic starlike appearance when visualized by electron microscopy. Four distinct astroviruses have been identified in humans: *Mamastrovirus* (MAstV) 1, MAstV 3, MAstV 8, and MAstV 9. MAstV 1 include the 8 antigenic types of classic human astroviruses, whereas MAstV 3, MAstV 8, and MAstV 9 are novel astroviruses that have been identified in recent years.

EPIDEMIOLOGY

Human astroviruses have a worldwide distribution. Multiple antigenic types cocirculate in the same region. MAstV 1 astroviruses have been detected in as many as 5% to 17% of sporadic cases of nonbacterial gastroenteritis among young children in the community but appear to cause a lower proportion of cases of more severe childhood gastroenteritis requiring hospitalization (2.5% to 9%). MAstV 1 infections occur predominantly in children younger than 4 years and have a seasonal peak during the late winter and spring in the United States. Transmission is via the fecal-oral route through contaminated food or water, person-to-person contact, or contaminated surfaces. Outbreaks tend to occur in closed populations of the young and the elderly, particularly among hospitalized children (health care-associated infections) and children in child care centers. Excretion lasts a median of 5 days after onset of symptoms, but asymptomatic excretion after illness can last for several weeks in healthy children. Persistent excretion may occur in immunocompromised hosts. Astroviruses have been detected sporadically in stool samples, blood, cerebrospinal fluid, and brain tissue of immunocompromised patients with acute encephalitis.

The **incubation period** is 3 to 4 days.

DIAGNOSTIC TESTS

Commercial tests for diagnosis have not been available in the United States until recently, although enzyme immunoassays are available in many other countries. Two multiplex nucleic acid-based assays for the detection of gastrointestinal tract pathogens, one of which includes astrovirus (MAstV 1), are approved by the US Food and Drug Administration (FDA). These multiplex tests are more sensitive and are replacing traditional tests to detect fecal viral pathogens. Interpretation of assay results may be complicated by the frequent detection of viruses in fecal samples from asymptomatic children and the detection of multiple viruses in a single sample. A few research and reference laboratories perform enzyme immunoassay for detection of viral antigen in stool and real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay for detection of viral RNA in stool. Of these tests, RT-PCR assay is the most sensitive.

TREATMENT

No specific antiviral therapy is available. Oral or parenteral fluids and electrolytes are given to prevent and correct dehydration.

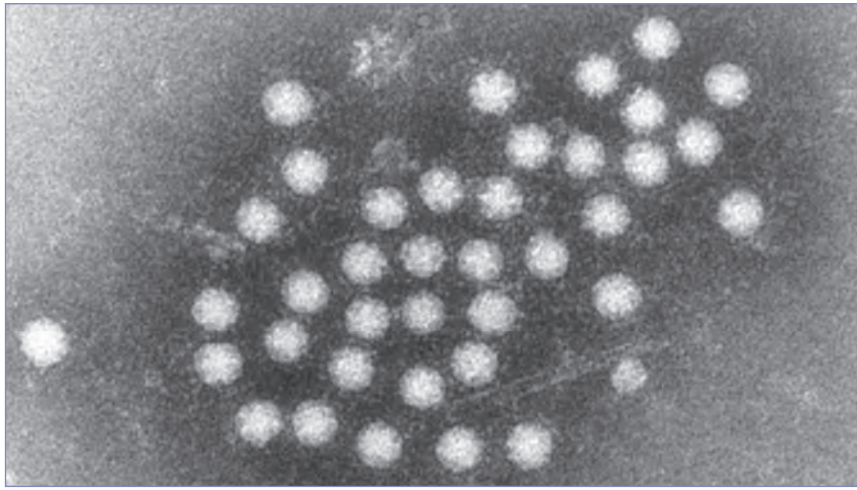


Image 10.1
Electron micrograph of astrovirus obtained from stool of a child with gastroenteritis. Note the characteristic starlike appearance. Courtesy of Centers for Disease Control and Prevention.

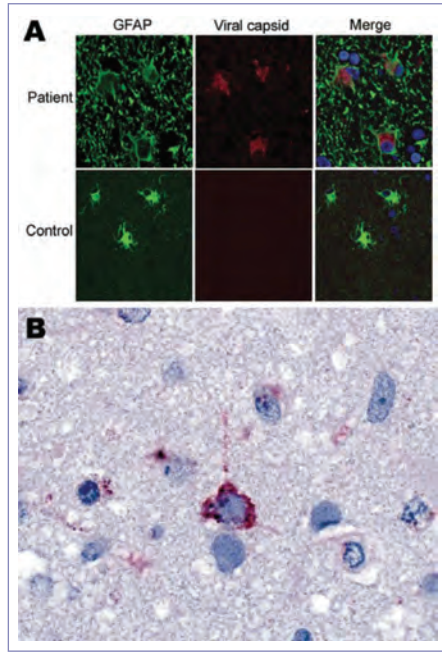


Image 10.2
Astrovirus encephalitis in a boy with X-linked agammaglobulinemia. Encephalitis is a major cause of death worldwide. Although more than 100 pathogens have been identified as causative agents, the pathogen is not determined for up to 75% of cases. This diagnostic failure impedes effective treatment and underscores the need for better tools and new approaches for detecting novel pathogens or determining new manifestations of known pathogens. Although astroviruses are commonly associated with gastroenteritis, they have not been associated with central nervous system disease. Using unbiased pyrosequencing, astrovirus was determined to be the causative agent for encephalitis in a 15-year-old boy with agammaglobulinemia. Courtesy of *Emerging Infectious Diseases.*

CHAPTER 11

Babesiosis

CLINICAL MANIFESTATIONS

Babesia infection often is asymptomatic or associated with mild, nonspecific symptoms. The infection can be severe and life threatening, particularly in people who are asplenic, immunocompromised, or elderly. In general, babesiosis, like malaria, is characterized by the presence of fever and hemolytic anemia; however, some infected people who are immunocompromised or at the extremes of age (eg, preterm infants) are afebrile. Infected people may have a prodromal illness, with gradual onset of symptoms, such as malaise, anorexia, and fatigue, followed by development of fever and other influenza-like symptoms (eg, chills, sweats, myalgia, arthralgia, headache, anorexia, nausea). Less common findings include sore throat, nonproductive cough, abdominal pain, vomiting, weight loss, conjunctival injection, photophobia, emotional lability, and hyperesthesia. Congenital infection with nonspecific manifestations suggestive of sepsis has been reported.

Clinical signs generally are minimal, often consisting only of fever and tachycardia, although hypotension, respiratory distress, mild hepatosplenomegaly, jaundice, and dark urine may be noted. Thrombocytopenia is common; disseminated intravascular coagulation can be a complication of severe babesiosis. If untreated, the infection can last for several weeks or months; even asymptomatic people can have persistent low-level parasitemia, sometimes for longer than 1 year.

ETIOLOGY

Babesia species are intraerythrocytic protozoa. The etiologic agents of babesiosis in the United States include *Babesia microti*, which is the cause of most reported cases, and several other genetically and antigenically distinct organisms, such as *Babesia duncani* (formerly the WA1-type parasite).

EPIDEMIOLOGY

Babesiosis predominantly is a tickborne zoonosis. *Babesia* parasites also can be transmitted via blood transfusion and perinatal routes. In the United States, the primary reservoir host for *B microti* is the white-footed mouse (*Peromyscus leucopus*), and the tick vector is *Ixodes scapularis*, which can transmit other pathogens, such as *Borrelia burgdorferi*, the causative agent of Lyme disease, and *Anaplasma phagocytophilum*, the causative agent of human granulocytic anaplasmosis. The tick bite often is not noticed, in part because the nymphal stage of the tick is about the size of a poppy seed. White-tailed deer (*Odocoileus virginianus*) serve as hosts for blood meals by the tick but are not reservoir hosts of *B microti*. An increase in the deer population in some geographic regions, including in some suburban areas, during the past few decades is thought to be a major factor in the spread of *I scapularis*. The reported vector-borne cases of *B microti* infection have been acquired in the Northeast (particularly, in parts of Connecticut, Massachusetts, New Jersey, New York, and Rhode Island, as well as other states, including Maine and Pennsylvania) and in the upper Midwest (Wisconsin and Minnesota). Occasional human cases of babesiosis caused by other species have been described in various regions of the United States; tick vectors and reservoir hosts for these agents typically have not yet been identified. Whereas most US vector-borne cases of babesiosis occur during late spring, summer, or fall, transfusion-associated cases can occur year-round. There were 1,804 confirmed cases of babesiosis in 2015, with the majority in the New England and 0Mid-Atlantic regions.

The **incubation period** ranges from 1 week to 5 weeks following a tick bite. The median incubation period following a contaminated blood transfusion is 37 days (range, 11 to 176 days) but occasionally is longer.

DIAGNOSTIC TESTS

Acute, symptomatic cases of babesiosis typically are diagnosed by microscopic identification of *Babesia* parasites on Giemsa- or Wright-stained blood smears. If the diagnosis of babesiosis is being considered, manual (nonautomated) review of blood smears for parasites should be requested explicitly. If seen, the tetrad (Maltese-cross) form is pathognomonic. *B microti* and other *Babesia* species can be difficult to distinguish from *Plasmodium*

falciparum; examination of blood smears by a reference laboratory should be considered for confirmation of the diagnosis.

Molecular (eg, polymerase chain reaction [PCR]) and serologic testing are available at some clinical and public health laboratories as well as at the Centers for Disease Control and Prevention. However, PCR assay should be used with caution when monitoring response to therapy, because *B microti* can be detected for weeks and months after parasites no longer are visualized on blood smear.

Antibody detection tests are useful for detecting infected individuals with very low levels of parasitemia (such as asymptomatic blood donors in transfusion-associated cases), for diagnosis after infection is cleared by therapy, and for discrimination between *Plasmodium falciparum* and *Babesia* infection. If indicated, the possibility of concurrent *B burgdorferi* or *Anaplasmataceae* infection should be considered.

TREATMENT

For mild disease in children, atovaquone plus azithromycin orally for 7 to 10 days is the regimen of choice. Recommended therapy for severely ill children and adults is combination therapy using clindamycin plus quinine, intravenously. Exchange transfusions should be considered for patients who are critically ill (eg, with hemodynamic instability, severe hemolysis, or pulmonary, renal, or hepatic compromise), especially, but not necessarily exclusively, in patients with parasitemia levels of approximately 10% or higher.

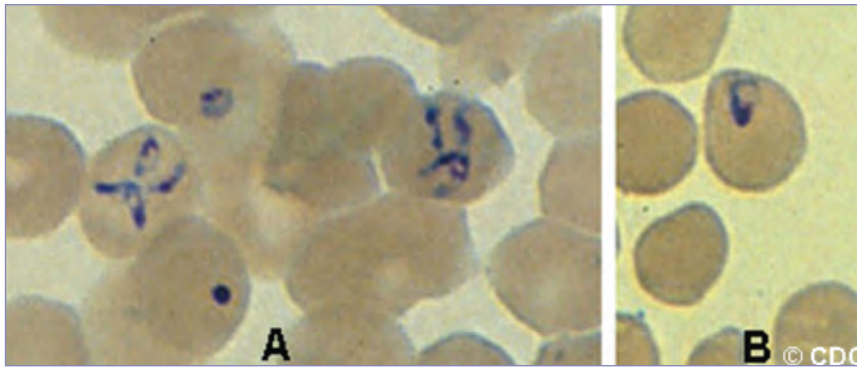


Image 11.1
Infection with *Babesia* in a 6-year-old girl after a splenectomy performed because of hereditary spherocytosis (Giemsa-stained thin smears). A, The tetrad (left side of the image), a dividing form, is pathognomonic for *Babesia*. Note also the variation in size and shape of the ring stage parasites (compare A and B) and the absence of pigment. Courtesy of Centers for Disease Control and Prevention.

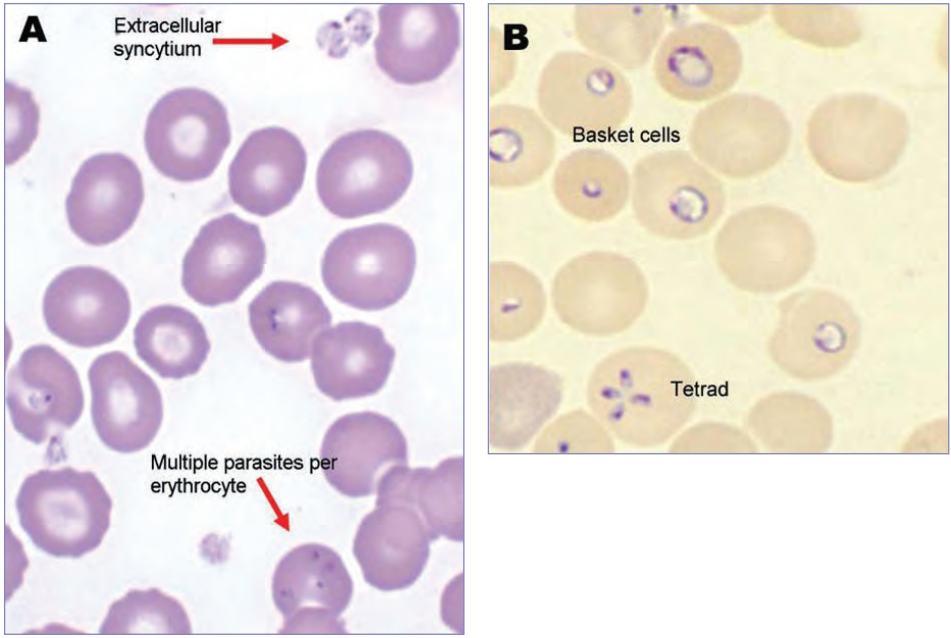


Image 11.2
Giemsa-stained (A) and Wright-stained (B) peripheral blood smear from a newborn with probable *Babesia microti* infection. Parasitemia was estimated in this newborn at approximately 15% based on the number of parasites per 200 leukocytes counted. The smear demonstrated thrombocytopenia and parasites of variable size and morphologic appearance and an absence of pigment (magnification ×1,000). Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases.*

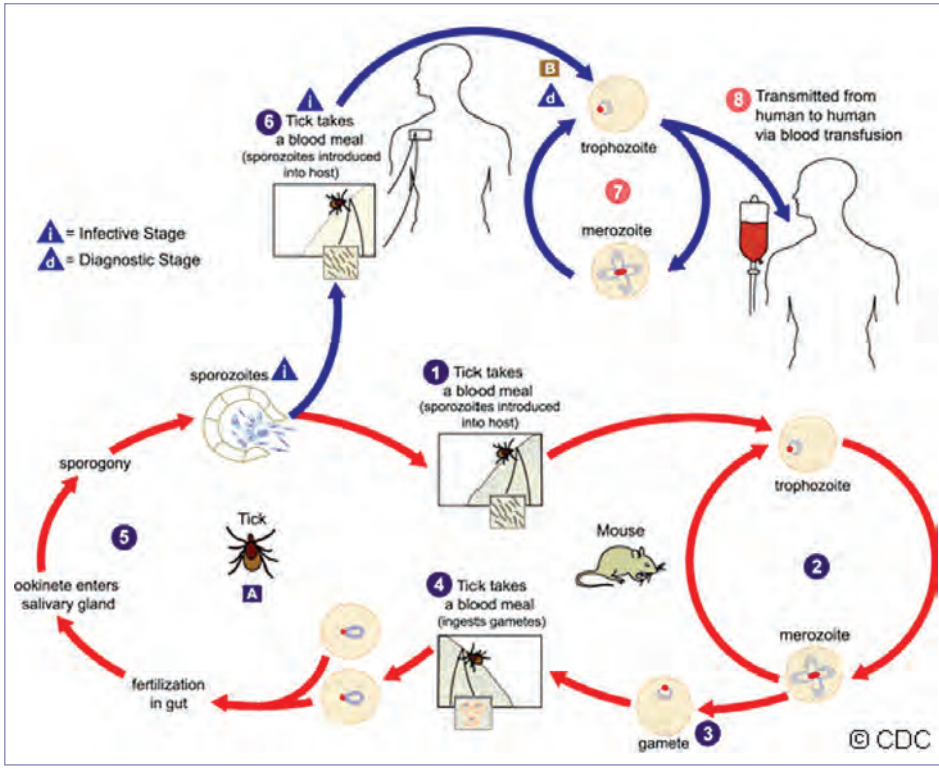


Image 11.3

The *Babesia microti* life cycle involves 2 hosts, which include a rodent, primarily the white-footed mouse (*Peromyscus leucopus*). During a blood meal, a *Babesia*-infected tick introduces sporozoites into the mouse host (1). Sporozoites enter erythrocytes and undergo asexual reproduction (budding) (2). In the blood, some parasites differentiate into male and female gametes, although these cannot be distinguished at the light microscope level (3). The definitive host is a tick, in this case the deer tick (*Ixodes scapularis*). Once ingested by an appropriate tick (4), gametes unite and undergo a sporogonic cycle, resulting in sporozoites (5). Transovarial transmission (also known as vertical, or hereditary, transmission) has been documented for "large" *Babesia* species but not for the "small" *Babesia* species, such as *B microti* (A). Humans enter the cycle when bitten by infected ticks. During a blood meal, a *Babesia*-infected tick introduces sporozoites into the human host (6). Sporozoites enter erythrocytes (B) and undergo asexual replication (budding) (7). Multiplication of the blood stage parasites is responsible for clinical manifestations of the disease. Humans are, for all practical purposes, dead-end hosts, and there is probably little, if any, subsequent transmission that occurs from ticks feeding on infected persons. However, human-to-human transmission is well recognized to occur through blood transfusions (8). Note: Deer are the hosts on which the adult ticks feed and are indirectly part of the *Babesia* cycle, as they influence the tick population. When deer populations increase, tick population also increases, thus heightening the potential for transmission. Courtesy of Centers for Disease Control and Prevention.

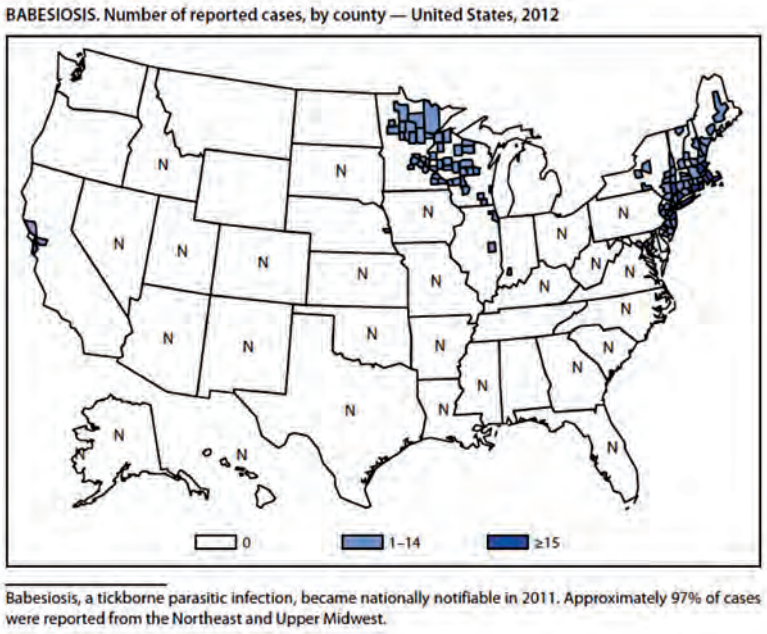


Image 11.4
Number of reported cases, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 12

Bacillus cereus Infections and Intoxications

CLINICAL MANIFESTATIONS

Bacillus cereus is associated primarily with 2 toxin-mediated foodborne illnesses, emetic and diarrheal, but it also can cause invasive extraintestinal infection. The emetic syndrome develops after a short incubation period, similar to staphylococcal foodborne illness. It is characterized by nausea, vomiting, and abdominal cramps, and diarrhea may follow in up to one-third of patients. The diarrheal syndrome has a longer incubation period, is more severe, and resembles *Clostridium perfringens* foodborne illness. It is characterized by moderate to severe abdominal cramps and watery diarrhea, vomiting in approximately 25% of patients, and occasionally low-grade fever. Both illnesses usually are short-lived, but the emetic toxin is occasionally associated with fulminant liver failure.

Invasive extraintestinal infection can be severe and includes wound and soft tissue infections; sepsis and bacteremia, including central line-associated bloodstream infection; endocarditis; osteomyelitis; purulent meningitis and ventricular shunt infection; pneumonia; and ocular infections (ie, endophthalmitis and keratitis). Infection can be acquired through use of contaminated blood products, especially platelets. *B cereus* is a leading cause of bacterial endophthalmitis following penetrating ocular trauma. Endogenous endophthalmitis can result from bacteremic seeding. Other ocular manifestations include an indolent keratitis related to corneal abrasions.

ETIOLOGY

B cereus is an aerobic and facultative anaerobic, spore-forming, gram-positive or gram-variable bacillus.

EPIDEMIOLOGY

B cereus is ubiquitous in the environment because of the high resistance of their endospores to extreme conditions, including heat, cold, desiccation, salinity, and radiation, and commonly is present in small numbers in raw, dried, and processed foods and in the feces of healthy people. The organism is a common cause of foodborne illness in the United States but may be underrecognized, because few people seek care for mild illness and physicians and clinical laboratories do not routinely test for *B cereus*. A wide variety of food vehicles has been implicated.

Spores of *B cereus* are heat resistant and can survive pasteurization, brief cooking, boiling, and high saline concentrations. They germinate to vegetative forms that produce enterotoxins over a wide range of temperatures, both in foods and in the gastrointestinal tract. The diarrheal syndrome is caused by at least 3 distinct toxins that are ingested preformed or are produced after spores germinate in the gastrointestinal tract. The diarrheal toxins are heat labile and can be destroyed by heating. The emetic syndrome occurs after eating contaminated food containing a preformed toxin called cereulide. The emetic syndrome follows ingestion of fried rice made from boiled rice stored at room temperature overnight, but a wide variety of foods, especially starchy foods, have been implicated. Foodborne illness caused by *B cereus* is not transmissible from person to person.

Risk factors for invasive disease attributable to *B cereus* include history of injection drug use, presence of indwelling intravascular catheters or implanted devices, neutropenia or immunosuppression, and preterm birth. *B cereus* endophthalmitis has occurred after penetrating ocular trauma and injection drug use.

The **incubation period** for foodborne illness is 0.5 to 6 hours for the emetic syndrome and 6 to 15 hours for the diarrheal syndrome.

DIAGNOSTIC TESTS

Diagnostic testing is not recommended for sporadic cases. For foodborne outbreaks, isolation of *B cereus* from the stool or vomitus of 2 or more ill people and not from control patients, or isolation of 10^5 colony-forming units/g or greater from epidemiologically implicated food, suggests that *B cereus* is the cause of the outbreak. Because the organism can be recovered from stool specimens from some well people, the presence of *B cereus* in feces or vomitus of ill people is not definitive evidence of infection.

Food samples must be tested for both types of diarrheal enterotoxins, because either alone can cause illness.

TREATMENT

B cereus foodborne illness usually requires only supportive treatment, including rehydration. Antimicrobial therapy is indicated for patients with invasive disease. Prompt removal of any potentially infected foreign bodies, such as central lines or implants, is essential. For intraocular infections, an ophthalmologist should be consulted regarding use of intravitreal vancomycin therapy in addition to systemic therapy. *B cereus* usually is resistant to beta-lactam antibiotics and clindamycin but is susceptible to vancomycin, which is the drug of choice.

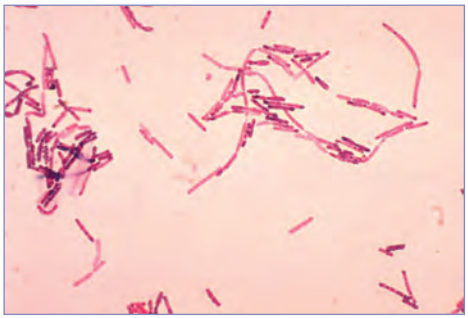


Image 12.1
Bacillus cereus subsp *mycoides* (Gram stain). *B cereus* is a known cause of toxin-induced food poisoning. These organisms may appear gram-variable, as shown here. Courtesy of Centers for Disease Control and Prevention.

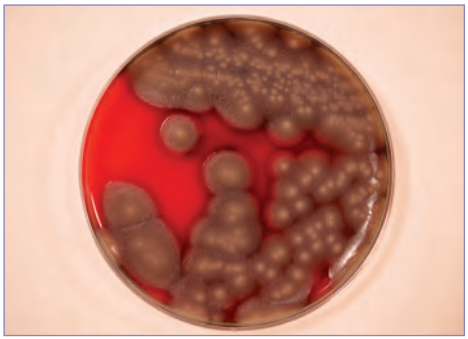


Image 12.3
Bacillus cereus on sheep blood agar. Large, circular, β-hemolytic colonies are noted. The greenish color and ground-glass appearance are typical characteristics of this organism on culture media. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

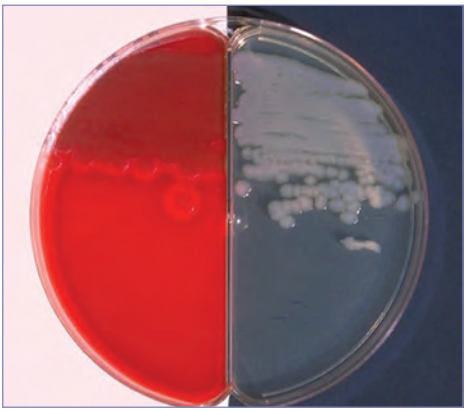


Image 12.2
Blood agar and bicarbonate agar plate cultures of *Bacillus cereus* (negative encapsulation test). Rough colonies of *B cereus* on blood and bicarbonate agars. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 13

Bacterial Vaginosis

CLINICAL MANIFESTATIONS

Bacterial vaginosis (BV) is a polymicrobial clinical syndrome characterized by changes in vaginal flora, with replacement of normally abundant *Lactobacillus* species by high concentrations of anaerobic bacteria. BV is diagnosed primarily in sexually active postpubertal females, but females who have never been sexually active can be affected rarely. BV is asymptomatic in 50% to 75% of females with microbiologic evidence of infection. Symptoms include vaginal discharge and/or vaginal odor. Classic signs, when present, include a thin white or grey, homogenous, adherent vaginal discharge with a fishy odor after intercourse or during menses. Symptoms of vulvovaginal irritation, pruritus, dysuria, or abdominal pain are not associated with BV but are suggestive of mixed vaginitis. In pregnant females, BV has been associated with adverse outcomes, including chorioamnionitis, premature rupture of membranes, preterm delivery, and postpartum endometritis.

Vaginitis and vulvitis in prepubertal girls rarely, if ever, are manifestations of BV. Vaginitis in prepubertal girls frequently is nonspecific, but possible causes include foreign bodies and infections attributable to group A streptococci, *Escherichia coli*, herpes simplex virus, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Trichomonas vaginalis*, or enteric bacteria, including *Shigella* species.

ETIOLOGY

The microbiologic cause of BV has not been delineated fully. Hydrogen peroxide-producing *Lactobacillus* species predominate among vaginal flora and play a protective role. In females with BV, these species largely are replaced by commensal anaerobes. Increased concentrations of *Gardnerella vaginalis*, *Mycoplasma hominis*, *Prevotella* species, *Mobiluncus* species, and *Ureaplasma* species are typical microbiologic findings on vaginal swab specimens.

EPIDEMIOLOGY

BV is the most common cause of vaginal discharge in sexually active adolescent and adult females. Having multiple partners and not using or incorrectly using condoms puts the adolescent population at higher risk. In this population, BV may be the sole cause of the symptoms, or it may accompany other conditions associated with vaginal discharge, such as trichomoniasis or cervicitis secondary to other sexually transmitted infections (STIs). BV occurs more frequently in females with a new sexual partner or a higher number of sexual partners and in those who engage in douching. Although evidence of sexual transmission of BV is inconclusive, BV can influence the acquisition of other STIs, including human immunodeficiency virus (HIV), herpes simplex virus-2, *N gonorrhoeae*, and *C trachomatis*, and increase the risk of infectious complications following gynecologic surgery and pregnancy complications. Because BV is a polymicrobial infection, an **incubation period** has not been defined.

DIAGNOSTIC TESTS

BV most commonly is diagnosed clinically using the Amsel criteria, requiring that 3 or more of the following symptoms or signs are present:

- Homogenous, thin grey or white vaginal discharge that smoothly coats the vaginal walls;
- Vaginal fluid pH greater than 4.5;
- A fishy (amine) odor of vaginal discharge before or after addition of 10% potassium hydroxide (ie, the “whiff test”); or
- Presence of clue cells (squamous vaginal epithelial cells covered with bacteria, which cause a stippled or granular appearance and ragged “moth-eaten” borders) representing at least 20% of the total vaginal epithelial cells seen on microscopic evaluation of vaginal fluid.

An alternative method for diagnosing BV is the Nugent score, which is used widely as the gold standard for making the diagnosis in the research setting. A Gram stain of the vaginal fluid is evaluated, and a numerical score is generated on the basis of the apparent quantity of lactobacilli relative to BV-associated bacteria.

The score is interpreted as normal (0–3), intermediate (4–6), or BV (7–10). Douching, recent intercourse, menstruation, and coexisting infection can alter findings on Gram stain.

The Affirm VPIII (Becton Dickinson, Sparks, MD) is a DNA hybridization probe test that detects *G vaginalis* as well as *Trichomonas vaginalis* and *Candida albicans* and can be used in the evaluation of vaginitis. Clinical Laboratory Improvement Amendments (CLIA)-waived rapid tests for BV that measure the activity of sialidase, an enzyme generated by several BV-associated bacteria, such as OSOM BVBlue Test (Sekisui Diagnostics, Framingham, MA), have acceptable performance criteria compared with the Nugent criteria. Culture for *G vaginalis* is not recommended as a diagnostic tool, because it is not specific. Although a proline aminopeptidase card test is available for the detection of elevated pH and trimethylamine, it has low sensitivity and specificity and, therefore, is not recommended. Papanicolaou (Pap) testing is not recommended for the diagnosis of BV because of its low sensitivity.

Sexually active females with BV should be evaluated for coinfection with other STIs, including syphilis, gonorrhea, chlamydia, trichomoniasis, and HIV infection.

TREATMENT

Symptomatic patients should be treated. The goals of treatment are to relieve the symptoms and signs of infection and potentially to decrease the risk of acquiring other STIs.

Treatment considerations should include patient preference for oral versus intravaginal treatment, possible adverse effects, and the presence of coinfections.

Nonpregnant females may be treated orally with metronidazole or topically with metronidazole gel 0.75% (intravaginally for 5 days), metronidazole gel 1.3% (intravaginally once daily at bedtime for 5 days), or clindamycin cream 2% (intravaginally for 7 days). Alternative regimens include oral tinidazole or clindamycin. There is no evidence that treatment of sexual partners effects treatment response or risk of recurrence. Follow-up is not necessary if symptoms resolve.

Pregnant or breastfeeding females with symptoms of BV should be treated. Topical metronidazole is preferred for treating breastfeeding mothers.

Approximately 30% of appropriately treated females have a recurrence within 3 months. Retreatment with the same regimen or an alternative regimen are both reasonable options for treating persistent or recurrent BV after the first occurrence. For females with multiple recurrences, metronidazole gel 0.75%, twice weekly for 4 to 6 months, has been shown to reduce recurrences, although this benefit might not persist when suppressive therapy is discontinued.

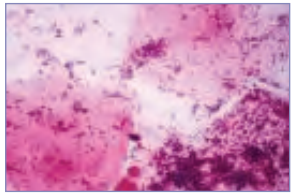


Image 13.1
Mobiluncus species (Gram stain), an anaerobe commonly found in bacterial vaginosis along with other anaerobes, especially *Prevotella* species. Copyright Yamajiku.co.jp.

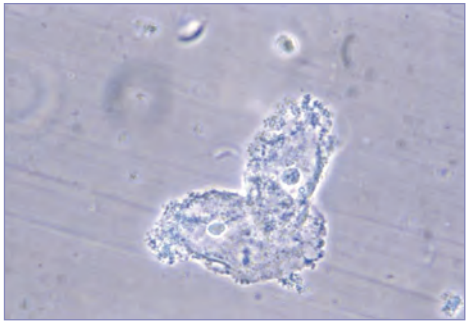


Image 13.3
This photomicrograph reveals bacteria adhering to vaginal epithelial cells known as clue cells. Clue cells are epithelial cells that have had bacteria adhere to their surface, obscuring their borders, and imparting a stippled appearance. The presence of such clue cells is a sign that the patient has bacterial vaginosis. Courtesy of Centers for Disease Control and Prevention.

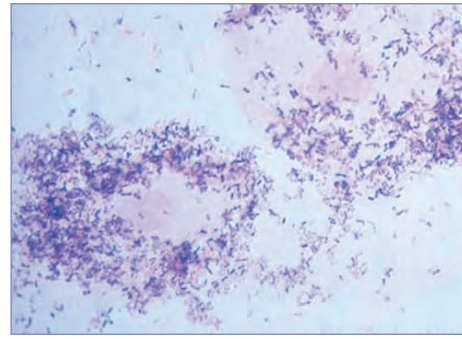


Image 13.2
Clue cells are squamous epithelial cells covered with bacteria found in bacterial vaginosis. Copyright Noni MacDonald, MD.

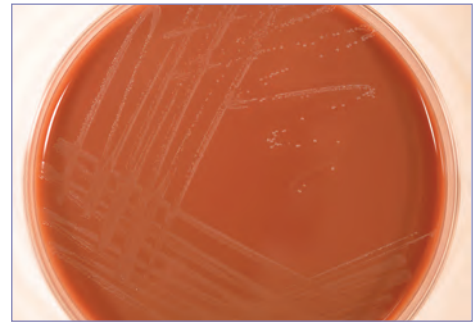


Image 13.4
Gardnerella vaginalis on chocolate agar. Colonies are small, circular, gray, and convex. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 14

Bacteroides, Prevotella, and Other Anaerobic Gram-Negative Bacilli Infections

CLINICAL MANIFESTATIONS

Bacteroides and *Prevotella* and other anaerobic gram-negative bacilli (AGNB) organisms from the oral cavity can cause chronic sinusitis, chronic otitis media, parotitis, dental infection, peritonsillar abscess, cervical adenitis, retropharyngeal space infection, aspiration pneumonia, lung abscess, pleural empyema, or necrotizing pneumonia. Species from the gastrointestinal tract are recovered in patients with peritonitis, intra-abdominal abscess, pelvic inflammatory disease, Bartholin cyst abscess, tubo-ovarian abscess, endometritis, acute and chronic prostatitis, prostatic and scrotal abscesses, scrotal gangrene, postoperative wound infection, and vulvovaginal and perianal infections. Invasion of the bloodstream from the oral cavity or intestinal tract can lead to brain abscess, meningitis, endocarditis, arthritis, or osteomyelitis. Skin and soft tissue infections include bacterial gangrene and necrotizing fasciitis; omphalitis in newborn infants; cellulitis at the site of fetal monitors, human bite wounds, or burns; infections adjacent to the mouth or rectum; and infected decubitus ulcers. Neonatal infections, including conjunctivitis, pneumonia, bacteremia, or meningitis, rarely occur. In most cases in which *Bacteroides*, *Prevotella*, and other AGNB are implicated, the infections are polymicrobial.

ETIOLOGY

Most *Bacteroides*, *Prevotella*, *Porphyromonas*, and *Fusobacterium* organisms associated with human disease are pleomorphic, nonspore–forming, facultatively anaerobic, gram-negative bacilli.

EPIDEMIOLOGY

Bacteroides, *Prevotella*, and other AGNB are part of the normal flora of the mouth, gastrointestinal tract, and female and male genital tracts. Members of the *Bacteroides fragilis* group predominate in the gastrointestinal tract flora; enterotoxigenic *B fragilis* may be a cause of diarrhea. Members of the *Prevotella melaninogenica* (formerly *Bacteroides melaninogenicus*) and *Prevotella oralis* (formerly *Bacteroides oralis*) groups are more common in the oral cavity. These species cause infection as opportunists, usually after an alteration in skin or mucosal membranes in conjunction with other endogenous species. Rates of upper respiratory tract, head, and neck infections associated with AGNB are higher in children. Endogenous infection results from aspiration, bowel perforation, or damage to mucosal surfaces from trauma, surgery, or chemotherapy. Mucosal injury or granulocytopenia predispose to infection. Except in infections resulting from human bites, no evidence of person-to-person transmission exists.

The **incubation period** is variable, usually 1 to 5 days, but depends on the inoculum and the site of involvement.

DIAGNOSTIC TESTS

Anaerobic culture media are necessary for recovery of *Bacteroides*, *Prevotella*, and other AGNB species. Because infections usually are polymicrobial, aerobic and anaerobic cultures should be obtained. A putrid odor, with or without gas in the infected site, suggests anaerobic infection. Use of an anaerobic transport tube or a sealed syringe is recommended for collection of clinical specimens.

TREATMENT

Abscesses should be drained when feasible; abscesses involving the brain, liver, and lungs may resolve with effective antimicrobial therapy. Necrotizing soft tissue lesions should be débrided surgically.

The choice of antimicrobial agent(s) is based on anticipated or known in vitro susceptibility testing and local antimicrobial resistance patterns. *Bacteroides* infections of the mouth and respiratory tract generally are susceptible to penicillin G, ampicillin, and extended-spectrum penicillins, such as piperacillin. However, some species of *Bacteroides* and almost 50% of *Prevotella* species produce beta-lactamase, and penicillin treatment failure has emerged as a consequence, so penicillin is not recommended for empirical coverage or for treatment of severe oropharyngeal or

pleuropulmonary infections or for any abdominopelvic infections. A beta-lactam penicillin active against *Bacteroides* species combined with a beta-lactamase inhibitor (ampicillin-sulbactam, amoxicillin-clavulanate, or piperacillin-tazobactam) can be useful to treat these infections. *Bacteroides* species of the gastrointestinal tract usually are resistant to penicillin G but are susceptible predictably to metronidazole, beta-lactam plus beta-lactamase inhibitors, chloramphenicol, and sometimes clindamycin. More than 80% of isolates are susceptible to cefoxitin, ceftizoxime, linezolid, imipenem, and meropenem. Cefuroxime, cefotaxime, and ceftriaxone are not reliably effective.

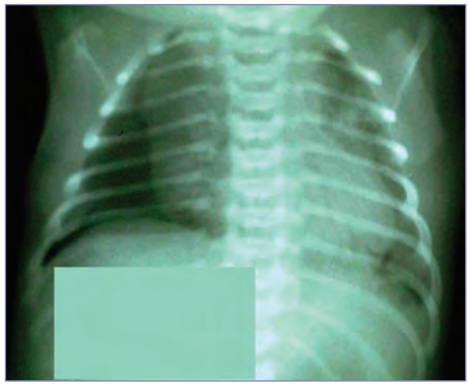


Image 14.1
Bacteroides fragilis pneumonia in a newborn (*B fragilis* isolated from the placenta and blood culture from the newborn). Anaerobic cultures were obtained because of a fecal odor in the amniotic fluid.

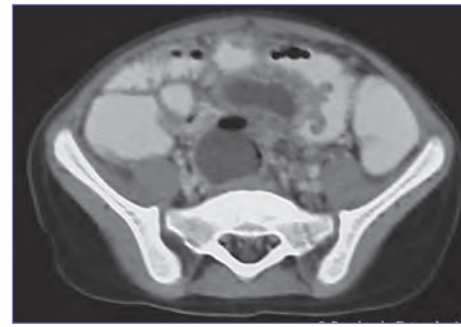


Image 14.2
Bacteroides fragilis abdominal abscess in a 9-year-old boy. Courtesy of Benjamin Estrada, MD.

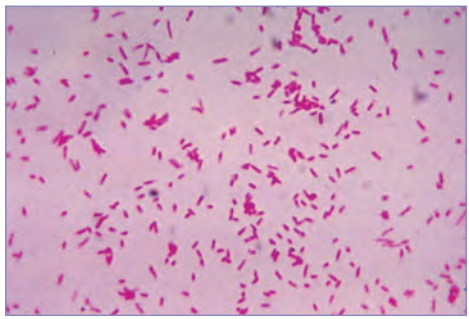


Image 14.3
This photomicrograph shows *Bacteroides fragilis* after being cultured in a thioglycolate medium for 48 hours. *B fragilis* is a gram-negative rod that constitutes 1% to 2% of the normal colonic bacterial microflora in humans. It is associated with extraintestinal infections such as abscesses and soft tissue infections, as well as diarrheal diseases. Courtesy of Centers for Disease Control and Prevention.

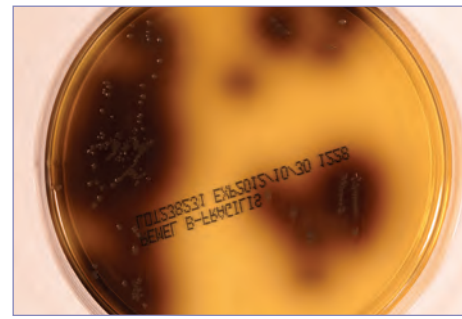


Image 14.4
Bacteroides fragilis on bacteroid bile-esculin agar. This organism is able to grow in 20% bile and also hydrolyzes esculin, causing the browning of the agar. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 15

Balantidium coli Infections

(Balantidiasis)

CLINICAL MANIFESTATIONS

Most human infections are asymptomatic. Acute symptomatic infection is characterized by rapid onset of nausea, vomiting, abdominal discomfort or pain, and bloody or watery mucoid diarrhea. In some patients, the course is chronic with intermittent episodes of diarrhea, anorexia, and weight loss. Rarely, organisms spread to mesenteric nodes, pleura, lung, liver, or genitourinary sites. Inflammation of the gastrointestinal tract and local lymphatic vessels can result in bowel dilation, ulceration, perforation, and secondary bacterial invasion. Colitis produced by *Balantidium coli* often is indistinguishable from colitis produced by *Entamoeba histolytica*. Fulminant disease can occur in malnourished or otherwise debilitated or immunocompromised patients.

ETIOLOGY

B coli, a ciliated protozoan, is the largest pathogenic protozoan known to infect humans.

EPIDEMIOLOGY

Pigs are the primary host reservoir of *B coli*, but other sources of infection have been reported. Infections have been reported in most areas of the world but are rare in industrialized countries. Cysts excreted in feces can be transmitted directly from hand to mouth or indirectly through fecally contaminated water or food. Excysted trophozoites infect the colon. A person is infectious as long as cysts are excreted in stool. Cysts may remain viable in the environment for months.

The **incubation period** is not established but may be several days.

DIAGNOSTIC TESTS

Diagnosis of infection is established by scraping lesions via sigmoidoscopy or colonoscopy, histologic examination of intestinal biopsy specimens, or ova and parasite examination of stool. Diagnosis usually is established by demonstrating trophozoites (or less frequently, cysts) in stool or tissue specimens. Stool examination is less sensitive, and repeated stool examination may be necessary to diagnose infection, because shedding of organisms can be intermittent. Microscopic examination of fresh diarrheal stools must be performed promptly, because trophozoites degenerate rapidly.

TREATMENT

The drug of choice is a tetracycline. Alternative drugs are metronidazole, iodoquinol, and doxycycline. Successful use of nitazoxanide has been reported.

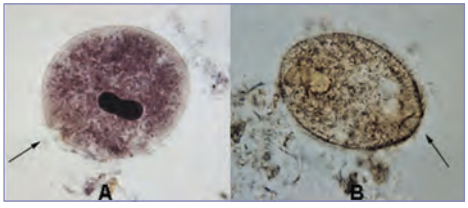


Image 15.1
Balantidium coli trophozoites are characterized by their large size (40–>70 µm); the presence of cilia on the cell surface, which are particularly visible (B); a cytostome (arrows); a bean-shaped macronucleus that is often visible (A); and a smaller, less conspicuous micronucleus. Courtesy of Centers for Disease Control and Prevention.

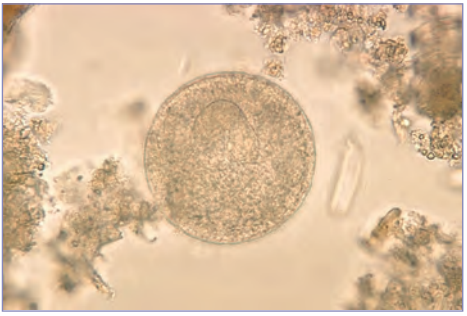


Image 15.2
Balantidium coli cyst in stool preparation. Courtesy of Centers for Disease Control and Prevention.

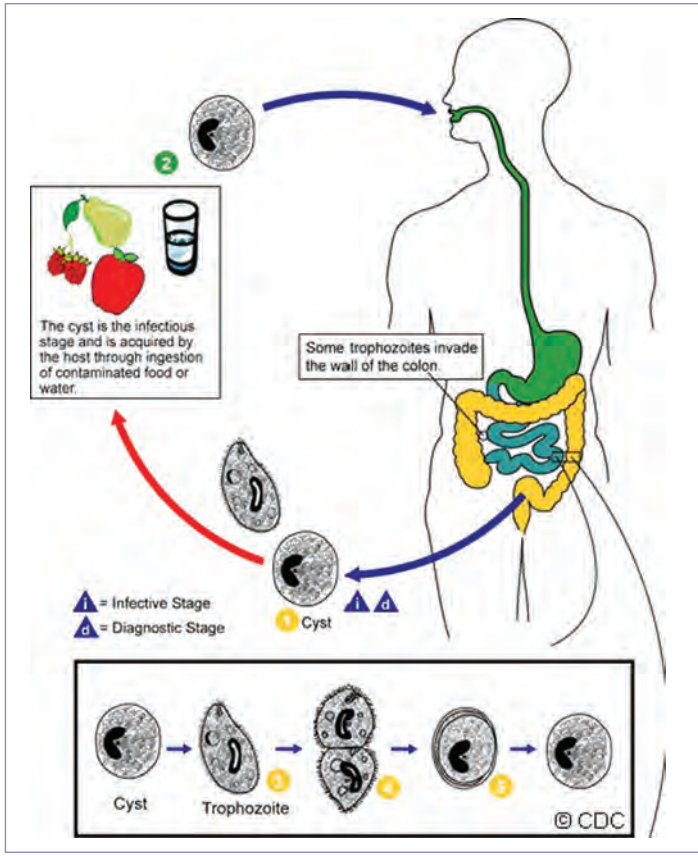


Image 15.3
Cysts are the parasite stage responsible for transmission of balantidiasis (1). The host most often acquires the cyst through ingestion of contaminated food or water (2). Following ingestion, excystation occurs in the small intestine, and the trophozoites colonize the large intestine (3). The trophozoites reside in the lumen of the large intestine of humans and animals, where they replicate by binary fission, during which conjugation may occur (4). Trophozoites undergo encystation to produce infective cysts (5). Some trophozoites invade the wall of the colon and multiply. Some return to the lumen and disintegrate. Mature cysts are passed with feces (1). Courtesy of Centers for Disease Control and Prevention.

CHAPTER 16

Bartonella henselae (Cat-Scratch Disease)

CLINICAL MANIFESTATIONS

The predominant clinical manifestation of *Bartonella henselae* infection (in an immunocompetent person) is regional lymphadenopathy/lymphadenitis (cat-scratch disease [CSD]). Most people with CSD are afebrile or have low-grade fever with mild systemic symptoms, such as malaise, anorexia, fatigue, and headache. Fever and mild systemic symptoms occur in approximately 30% of patients.

A skin papule or pustule often is found at the presumed site of inoculation and usually precedes development of lymphadenopathy by approximately 1 to 2 weeks (range, 5–50 days). Lymphadenopathy involves nodes that drain the site of inoculation, typically axillary, but cervical, submental, epitrochlear, or inguinal nodes can be involved. The skin overlying affected lymph nodes is often tender, warm, erythematous, and indurated, and approximately 10% to 25% of affected nodes suppurate spontaneously. Typically, lymphadenopathy will resolve spontaneously within 2 to 4 months.

Less common manifestations of *B henselae* infection likely reflect bloodborne disseminated disease and include culture-negative endocarditis, encephalopathy, osteolytic lesions, granulomata in the liver and spleen, glomerulonephritis, pneumonia, thrombocytopenic purpura, and erythema nodosum. CSD may present with fevers for 1 to 3 weeks (ie, fever of unknown origin) and may be associated with nonspecific symptoms, such as malaise, abdominal pain, headache, and myalgia.

Ocular manifestations occur in 5% to 10% of patients. The most classic and frequent presentation of ocular *Bartonella* infection is neuroretinitis, characterized by unilateral painless vision impairment, granulomatous optic disc swelling, and macular edema, with lipid exudates (macular star); simultaneous bilateral involvement has been reported but is less common. Inoculation of the periocular tissue can result in Parinaud oculoglandular syndrome, which consists of follicular conjunctivitis and ipsilateral preauricular lymphadenopathy.

Additional rare ocular manifestations include retinochoroiditis, anterior uveitis, vitritis, pars planitis, retinal vasculitis, retinitis, branch retinal arteriolar or venular occlusions, macular hole, or serous retinal detachments (extraordinarily rare).

ETIOLOGY

B henselae, the causative organism of CSD, is a fastidious, slow-growing, gram-negative bacillus that also is the causative agent of bacillary angiomatosis (vascular proliferative lesions of skin and subcutaneous tissue) and bacillary peliosis (reticuloendothelial lesions in visceral organs, primarily the liver). The latter 2 manifestations of infection are reported among immunocompromised patients, primarily those with human immunodeficiency virus infection. Additional species, such as *Bartonella clarridgeiae*, also have been found to cause CSD. *B henselae* is related closely to *Bartonella quintana*, the agent of louse-borne trench fever that caused significant illness and disease among troops during World War I, and also is a causative agent of bacillary angiomatosis. *B quintana* can cause endocarditis.

EPIDEMIOLOGY

B henselae is a common cause of regional lymphadenopathy/lymphadenitis in children. The highest incidence is found in children 5 to 9 years of age; infection occurs more often during the fall and winter. Children 14 years or younger account for 32.5% of all reported cases. Cats are the natural reservoir for *B henselae*, with a seroprevalence of 13% to 90% in domestic and stray cats in the United States. Other animals, including dogs, can be infected and occasionally are associated with human infection. Cat-to-cat transmission occurs via the cat flea (*Ctenocephalides felis*), with feline infection resulting in bacteremia that usually is asymptomatic and lasts weeks to months. Fleas acquire the organism when feeding on a bacteremic cat and then shed infectious organisms in their feces. The bacteria are transmitted to humans by inoculation through a scratch, lick, or bite from a bacteremic cat or by hands contaminated by flea feces touching an open wound or the eye. Most patients have a history of recent contact with apparently healthy cats, typically kittens. Kittens (more

often than cats) and animals from shelters or adopted as strays are more likely to be bacteremic. There is no convincing evidence that ticks are a competent vector for transmission of *Bartonella* organisms to humans. No evidence of person-to-person transmission exists.

The **incubation period** from scratch to appearance of the primary cutaneous lesion is 7 to 12 days; the period from primary cutaneous lesion to the appearance of lymphadenopathy is 5 to 50 days (median, 12 days).

DIAGNOSTIC TESTS

The indirect immunofluorescent antibody (IFA) assay for detection of serum antibodies to antigens of *Bartonella* species is useful for diagnosis of CSD. The IFA test is available at many commercial laboratories and through the Centers for Disease Control and Prevention (CDC), but because of cross-reactivity with other infections, clinical correlation is essential. Enzyme immunoassays for detection of antibodies to *B henselae* have been developed; however, it is not known whether they are more sensitive or specific than the IFA test. Immunoglobulin (Ig) M production is brief and could be missed, yielding low testing sensitivity. Generally speaking, if an IFA IgG titer is <1:64, the patient does not have acute infection. Titers between 1:64 and 1:256 may represent past or acute infection, and follow-up titers in 2 weeks should be considered. An IgG titer of >1:256 is consistent with acute infection. Recent studies report highly specific IgM enzyme-linked immunosorbent assays for *B henselae* using refined N-lauroyl-sarcosine-insoluble proteins.

B henselae is a fastidious organism; recovery by routine culture rarely is successful. Lysis centrifugation tubes or automated blood culture systems can be attempted to grow *Bartonella* species, followed by culture on solid media. Generally, yield on blood culture is poor and delayed.

If tissue (eg, lymph node) specimens are available, bacilli occasionally may be visualized using a silver stain (eg, Warthin-Starry or Steiner stain); however, this test is not specific for *B henselae.* Early histologic changes in lymph node specimens consist of lymphocytic infiltration with epithelioid granuloma formation. Later changes consist of polymorphonuclear leukocyte infiltration with granulomas that become necrotic and resemble granulomas from patients with tularemia, brucellosis, and mycobacterial infections.

TREATMENT

Management of localized uncomplicated CSD primarily is aimed at relief of symptoms, because the disease usually is self-limited, resolving spontaneously in 2 to 4 months. Azithromycin has been shown to have a modest clinical benefit in treating localized CSD (lymphadenopathy/lymphadenitis), with a significantly greater decrease in lymph node volume after 1 month of therapy compared with placebo; however, no other differences in clinical outcome were demonstrated. Painful suppurative nodes can be treated with needle aspiration for relief of symptoms; incision and drainage should be avoided, because this may facilitate fistula formation, and surgical excision generally is unnecessary.

Many experts recommend antimicrobial therapy in acutely or severely ill immunocompetent patients with systemic symptoms, particularly people with retinitis, hepatic or splenic involvement, or painful adenitis. Reports suggest that several oral antimicrobial agents (azithromycin, clarithromycin, ciprofloxacin, doxycycline, trimethoprim-sulfamethoxazole, and rifampin) and parenteral gentamicin are effective. The optimal duration of therapy is not known but may be several months for systemic disease.

Although evidence is lacking, neuroretinitis often is treated with both systemic antimicrobial agents and corticosteroids to decrease the optic disc swelling and promote a more rapid return of vision. Doxycycline plus rifampin is preferred for patients with neuroretinitis.

Antimicrobial therapy is recommended for all immunocompromised people because treatment of bacillary angiomatosis and bacillary peliosis has been shown to be beneficial. Erythromycin or doxycycline is effective for treatment of these conditions; therapy should be administered for several months.

For patients with unusual manifestations of *Bartonella* infection (eg, culture-negative endocarditis, neuroretinitis, disease in

immunocompromised patients), consultation with a pediatric infectious diseases expert is recommended.

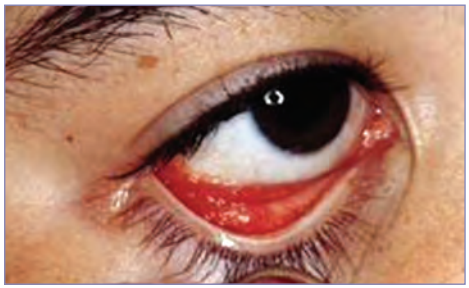


Image 16.1
Clinical manifestations of cat-scratch disease include Parinaud oculoglandular syndrome, which results when inoculation of the eye conjunctiva results in conjunctivitis.

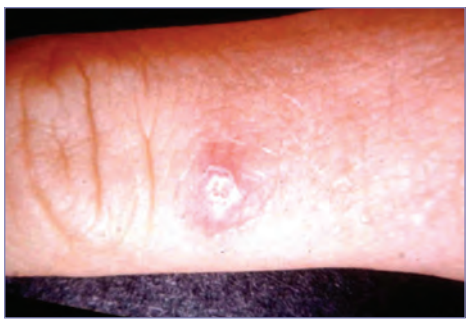


Image 16.3
Cat-scratch granuloma of the finger of a 6-year-old boy. This is a typical inoculation site lesion, which was noted about 10 days before the development of regional lymphadenopathy.

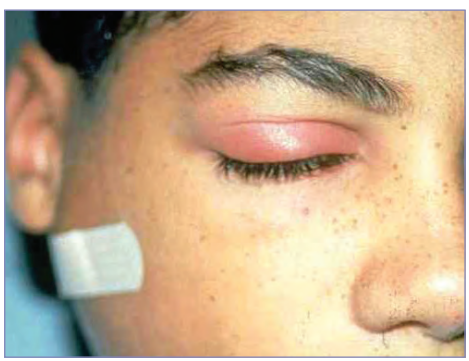


Image 16.5
Parinaud oculoglandular syndrome (inoculation of the conjunctivae with ipsilateral preauricular adenopathy) in a 6-year-old boy.

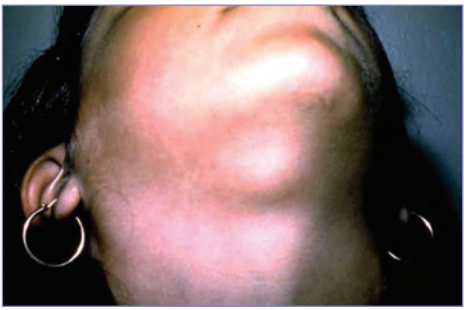


Image 16.2
Submental lymphadenitis due to cat-scratch disease.

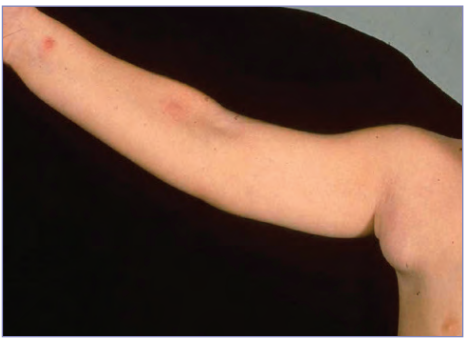


Image 16.4
Cat-scratch granuloma of the wrist with anterior axillary lymphadenitis in a 4-year-old boy. Cat-scratch disease is a common cause of prolonged lymphadenopathy in children.

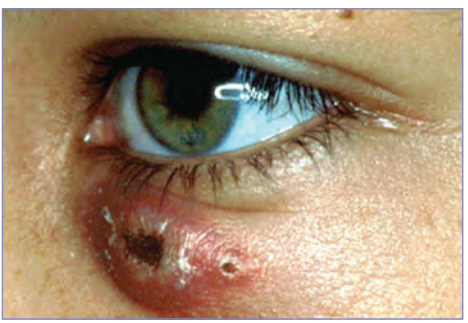


Image 16.6
Papules at inoculation sites on the face of a patient with cat-scratch disease.

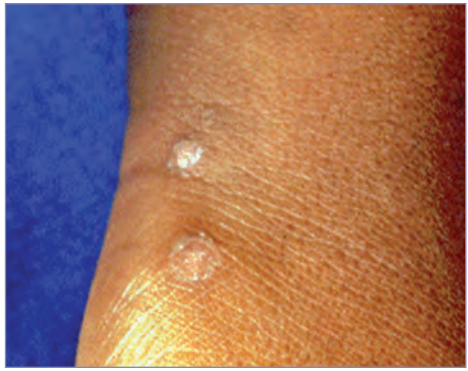


Image 16.7
A papule at each of 2 inoculation sites on the arm of a patient with cat-scratch disease.

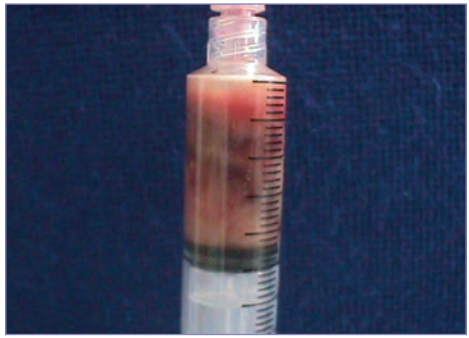


Image 16.9
Sanguinopurulent exudate aspirated from the axillary node of the patient in Image 16.8 with cat-scratch disease. Copyright Michael Rajnik, MD, FAAP.

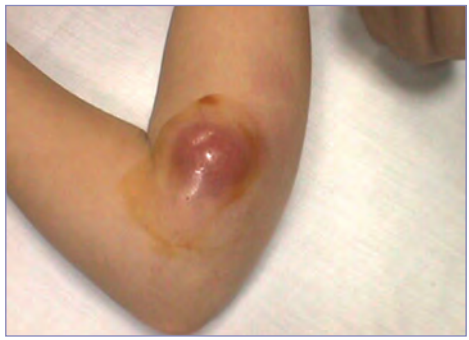


Image 16.11
Epitrochlear suppurative adenitis of cat-scratch disease in the boy in Image 16.10 with a cat-scratch granuloma of the finger. Copyright Michael Rajnik, MD, FAAP.

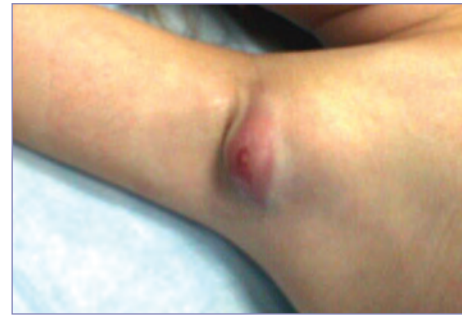


Image 16.8
A 2-year-old with suppurative right axillary lymphadenopathy secondary to cat-scratch disease. Copyright Michael Rajnik, MD, FAAP.

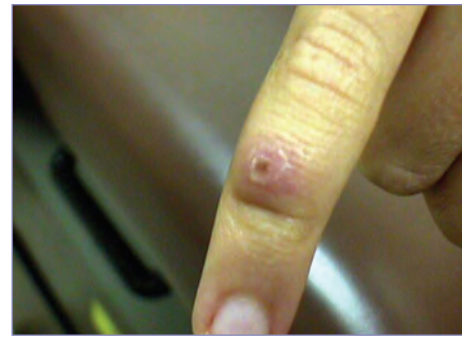


Image 16.10
Cat-scratch disease granuloma of the finger in a 12-year-old boy with epitrochlear node involvement (see Image 16.11). Copyright Michael Rajnik, MD, FAAP.

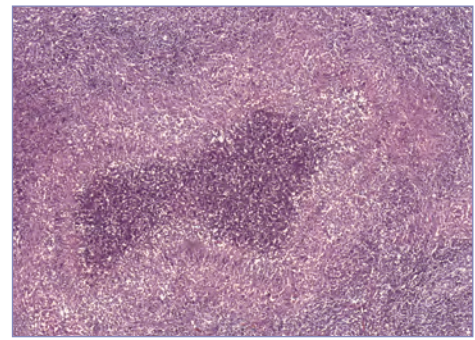


Image 16.12
Stellate microabscess and silver-stained coccobacillary forms of *Bartonella henselae* within the inflammatory infiltrate of the involved lymph node (hematoxylin-eosin stain; original magnification ×12.5). Courtesy of Christopher Paddock, MD.

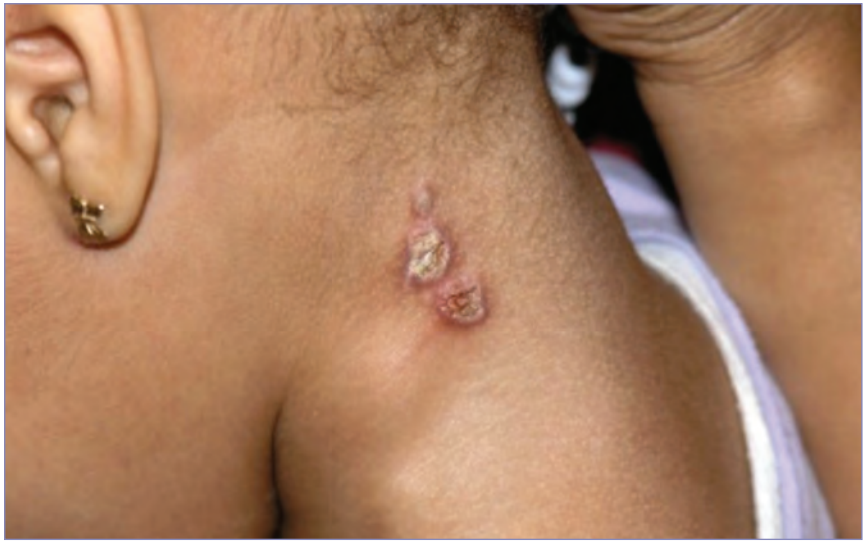


Image 16.13
This 3-year-old was previously scratched on the left side of her neck by a kitten. She developed raised red bumps around the scratch on day 5. This area ulcerated slightly and was slow to heal. No fever was noted, although she was less active for the next several days and complained that her arms and legs were sore. She developed swollen posterior cervical lymph nodes about a week later. Physical examination indicated two 8-mm ulcerations with raised borders and a papule near an enlarged minimally tender posterior cervical node. Serology was positive for *Bartonella henselae*. She improved with time following a course of azithromycin. Courtesy of Will Sorey, MD.

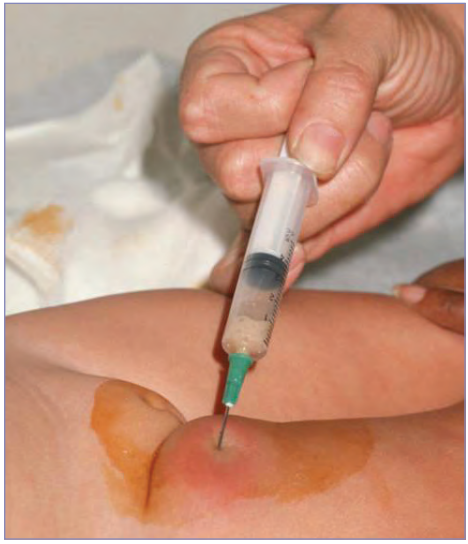


Image 16.14
Needle aspiration of purulent material caused by cat-scratch disease. Courtesy of Ed Fajardo, MD.

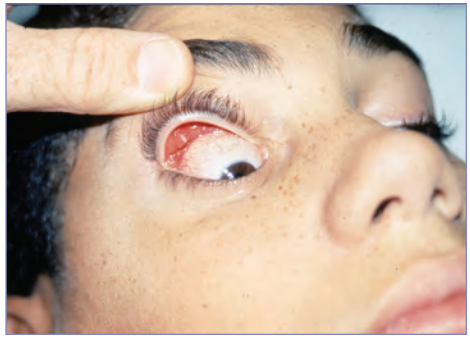


Image 16.15
Parinaud oculoglandular syndrome in cat-scratch disease. Copyright James Brien, DO.

CHAPTER 17

Baylisascaris Infections

CLINICAL MANIFESTATIONS

Infection with *Baylisascaris procyonis,* a raccoon roundworm, can present with nausea and fatigue. It is a rare cause of acute eosinophilic meningoencephalitis. In a young child, acute central nervous system (CNS) disease (eg, altered mental status and seizures) accompanied by peripheral and/or cerebrospinal fluid (CSF) eosinophilia can occur 2 to 4 weeks after infection. Severe neurologic sequelae or death are usual outcomes. *B procyonis* is a rare cause of extraneural disease in older children and adults. Ocular larva migrans can result in diffuse unilateral subacute neuroretinitis; direct visualization of larvae in the retina sometimes is possible. Visceral larval migrans can present with nonspecific signs, such as macular rash, pneumonitis, and hepatomegaly. Similar to visceral larva migrans caused by *Toxocara* species, subclinical or asymptomatic infection is thought to be the most common outcome of infection.

ETIOLOGY

B procyonis is a 10- to 25-cm long roundworm (nematode) with a direct life cycle usually limited to its definitive host, the raccoon. Domestic dogs and some less commonly owned pets, such as kinkajous and ringtails, can serve as definitive hosts and a potential source of human disease.

EPIDEMIOLOGY

B procyonis is distributed focally throughout the United States; in areas where disease is endemic, 22% to 80% of raccoons can harbor the parasite in their intestines. Reports of infections in dogs raise concern that infected dogs may be able to spread the disease. Embryonated eggs containing infective larvae are ingested from the soil by raccoons, rodents, and birds. When infective eggs or an infected host is eaten by a raccoon, the larvae grow to maturity in the small intestine, where adult female worms shed millions of eggs per day. Eggs become infective after 2 to 4 weeks in the environment and may persist long-term in the soil. Cases of raccoon infection have been reported in many parts of the United States. Risk of human infection is greatest in areas where significant raccoon populations live in peridomestic settings. Fewer than 30 cases of *Baylisascaris* CNS disease have been documented in the United States, although cases may be undiagnosed or underreported.

Risk factors for *Baylisascaris* infection include contact with raccoon latrines (communal defecation sites often found at or on the base of trees, raised flat surfaces such as tree stumps, logs, rocks, decks, and rooftops, or unsealed attics or garages), geophagia/pica, age younger than 4 years, and in older children, developmental delay. Most reported cases of CNS disease have been in males.

DIAGNOSTIC TESTS

Baylisascaris infection is confirmed by identification of larvae in biopsy specimens. A presumptive diagnosis can be made on the basis of clinical (meningoencephalitis, diffuse unilateral subacute neuroretinitis, pseudotumor), epidemiologic (raccoon exposure), and laboratory (blood and CSF eosinophilia) findings. Serologic testing (serum, CSF) for patients with clinical symptoms is available at the Centers for Disease Control and Prevention. Neuroimaging results can be normal initially, but as larvae grow and migrate through CNS tissue, focal abnormalities are found in periventricular white matter and elsewhere. In ocular disease, ophthalmologic examination can reveal characteristic chorioretinal lesions or rarely larvae. Because eggs are not shed in human feces, stool examination is not helpful. The disease is not transmitted from person to person.

TREATMENT

On the basis of CNS and CSF penetration and in vitro activity, albendazole, in conjunction with high-dose corticosteroids, has been advocated most widely. Treatment with anthelmintic agents and corticosteroids may not affect clinical outcome once severe CNS disease manifestations are evident. If the infection is suspected, treatment should be initiated while the diagnostic evaluation is being completed. Limited data are available regarding safety and efficacy of alternate anthelmintic therapies in children. Preventive therapy with albendazole should be considered for children with a history of inges-

tion of soil potentially contaminated with raccoon feces; however, no definitive preventive dosing regimen has been established. Larvae localized to the retina may be killed by direct photocoagulation.

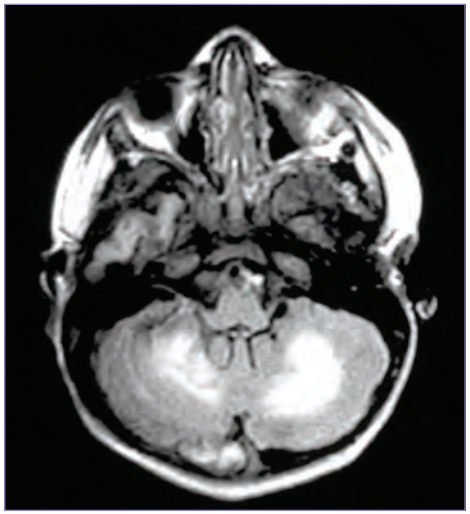


Image 17.1
Neuroimaging of human *Baylisascaris procyonis* neural larval migrans. In acute neural larval migrans, axial flair magnetic resonance image (at the level of the posterior fossa) demonstrates abnormal hyperintense signal of cerebellar white matter.

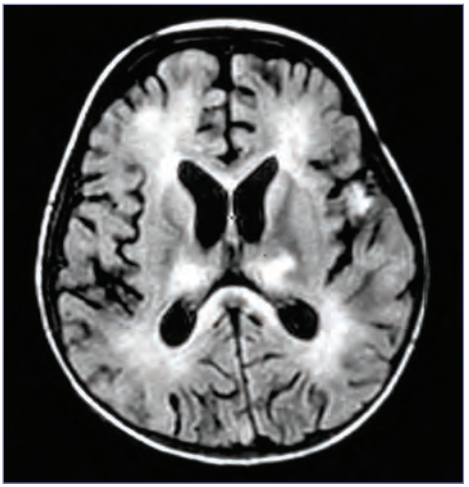


Image 17.2
Neuroimaging of human *Baylisascaris procyonis* neural larval migrans. Axial T2-weighted magnetic resonance image (at the level of the lateral ventricles) demonstrates abnormal patchy hyperintense signal of periventricular white matter and basal ganglia.

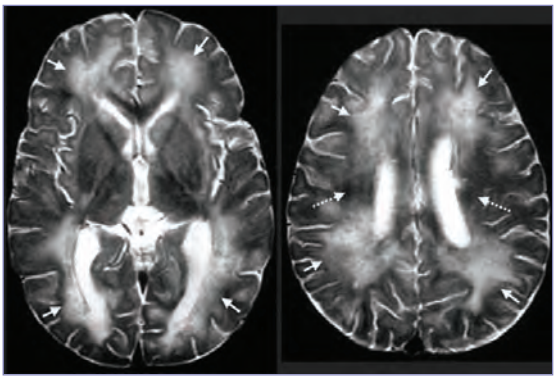


Image 17.3
Biopsy-proven *Baylisascaris procyonis* encephalitis in a 13-month-old boy. Axial T2-weighted magnetic resonance images obtained 12 days after symptom onset show abnormal high signal throughout most of the central white matter (arrows) compared with the dark signal expected at this age (broken arrows). Courtesy of *Emerging Infectious Diseases*.

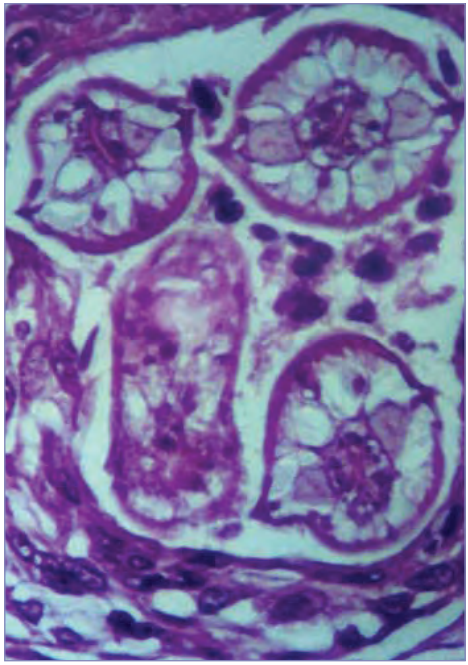


Image 17.4
Cross section of *Baylisascaris procyonis* larva in tissue section of brain, demonstrating characteristic diagnostic features including prominent lateral alae and excretory columns. Courtesy of *Emerging Infectious Diseases.*

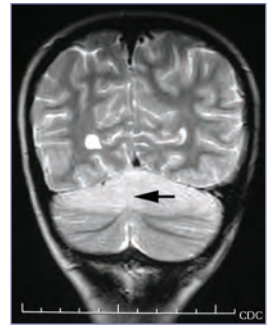


Image 17.5
Coronal T2-weighted magnetic resonance imaging of the brain in a 4-year-old with *Baylisascaris procyonis* eosinophilic meningitis. Arrow shows diffuse edema of the superior cerebellar hemispheres (scale bar increments in centimeters). Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases* and Poulomi J. Pai.

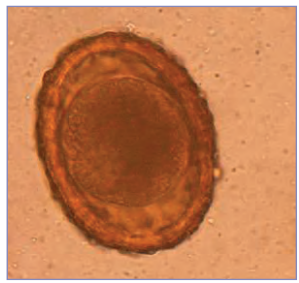


Image 17.6
Unembryonated egg of *Baylisascaris procyonis*. *B procyonis* eggs are 80 to 85 µm by 65 to 70 µm in size, thick-shelled, and usually slightly oval in shape. They have a similar morphology to fertile eggs of *Ascaris lumbricoides*, although eggs of *A lumbricoides* are smaller (55–75 µm × 35–50 µm). The definitive host for *B procyonis* is the raccoon, although dogs may also serve as definitive hosts. As humans do not serve as definitive hosts for *B procyonis*, eggs are not considered a diagnostic finding and are not excreted in human feces. Courtesy of Cheryl Davis, MD, Western Kentucky University.

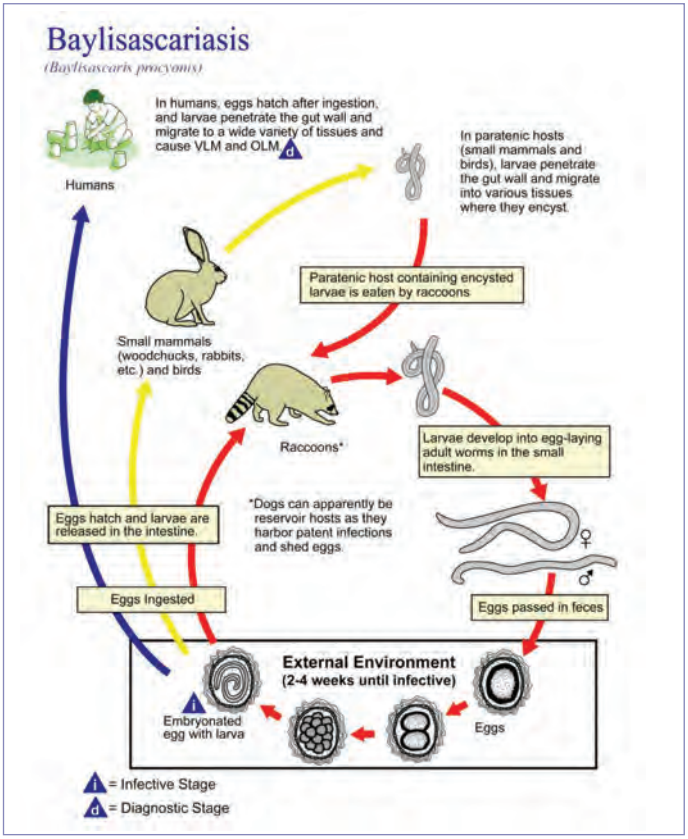


Image 17.7
This illustration depicts the life cycle of *Baylisascaris procyonis*, the causal agent of *Baylisascaris* disease. Courtesy of Centers for Disease Control and Prevention.

Image 17.8
Baylisascaris is raccoon roundworm that may cause ocular and neural larval migrans and encephalitis in humans. Photo used with permission of Michigan DNR Wildlife Disease Lab.

CHAPTER 18

Infections With *Blastocystis hominis* and Other Subtypes

CLINICAL MANIFESTATIONS

The importance of *Blastocystis* species as a cause of gastrointestinal tract disease is controversial. The asymptomatic carrier state is well documented. Clinical symptoms reported include bloating, flatulence, mild to moderate diarrhea without fecal leukocytes or blood, abdominal pain, nausea, and poor growth. Some case series and reports have noted an association between infection with *Blastocystis hominis* and chronic urticaria and irritable bowel syndrome. When *B hominis* is identified in stool from symptomatic patients, other causes of this symptom complex, particularly *Giardia intestinalis* and *Cryptosporidium parvum*, should be investigated before assuming that *B hominis* is the cause of the signs and symptoms.

ETIOLOGY

B hominis previously has been classified as a protozoan, but molecular studies have characterized it as a stramenopile (a eukaryote). Multiple forms have been described: vacuolar, which is observed most commonly in clinical specimens; granular, which is seen rarely in fresh stools; ameboid; and cystic.

EPIDEMIOLOGY

Blastocystis species are recovered from 1% to 20% of stool specimens examined for ova and parasites. Because transmission is believed to be via the fecal-oral route, presence of the organism may be a marker for presence of other pathogens spread by fecal contamination. Transmission from animals occurs.

The **incubation period** has not been established.

DIAGNOSTIC TESTS

Stool specimens should be preserved in polyvinyl alcohol and stained with trichrome or iron-hematoxylin before microscopic examination. Small round cysts, the most common form, are characterized by a large central body (similar to large vacuole) surrounded by multiple nuclei. The parasite may be present in varying numbers, and infections may be reported as light to heavy. The presence of 5 or more organisms per high-power (×400 magnification) field can indicate heavy infection, which to some experts suggests causation when other enteropathogens are absent. Other experts consider the presence of 10 or more organisms per 10 oil immersion fields (×1,000 magnification) to represent heavy infection.

TREATMENT

Indications for treatment are not established. Some experts recommend that treatment should be reserved for patients who have persistent symptoms and in whom no other pathogen or process is found to explain the gastrointestinal tract symptoms. Randomized controlled treatment trials with both nitazoxanide and metronidazole have demonstrated benefit in symptomatic patients. Tinidazole is an alternative that may be tolerated better than metronidazole.

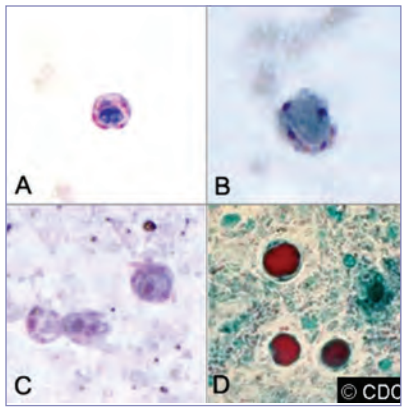


Image 18.1
A–D, *Blastocystis hominis* cystlike forms (trichrome stain). The sizes vary from 4 to 10 µm. The vacuoles stain variably from red to blue. The nuclei in the peripheral cytoplasmic rim are clearly visible, staining purple (B) (4 nuclei). Specimens in A–C contributed by Ray Kaplan, MD, SmithKline Beecham Diagnostic Laboratories, Atlanta, GA. D, Courtesy of Centers for Disease Control and Prevention.

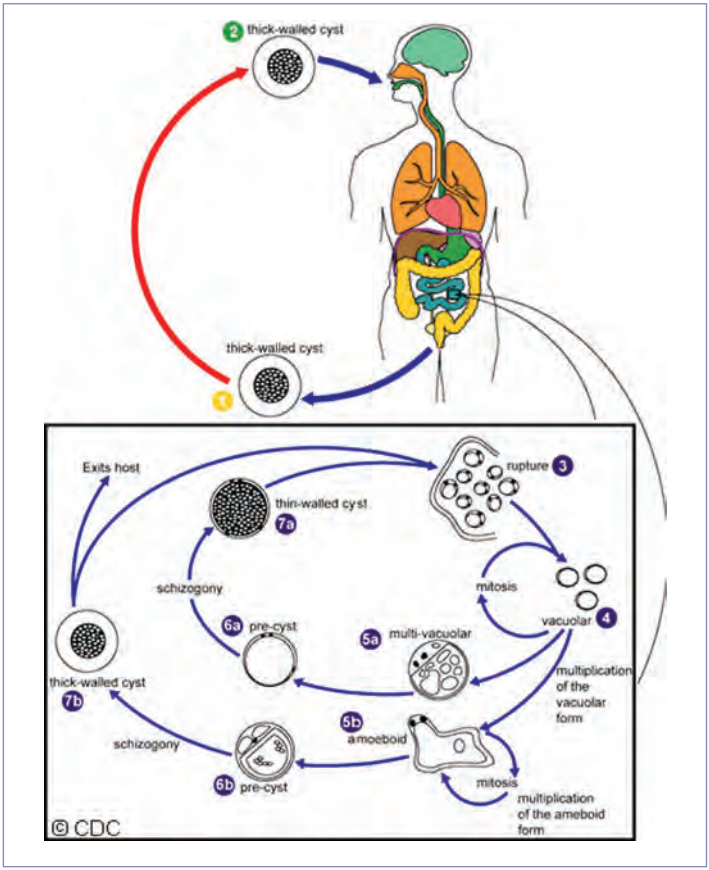


Image 18.2

Knowledge of the life cycle and transmission are still under investigation; therefore, this is a proposed life cycle for *Blastocystis hominis*. The classic form found in human stools is the cyst, which varies tremendously in size from 6 to 40 µm (1). The thick-walled cyst present in the stools (1) is believed to be responsible for external transmission, possibly by the fecal-oral route through ingestion of contaminated water or food (2). The cysts infect epithelial cells of the digestive tract and multiply asexually (3, 4). Vacuolar forms of the parasite give origin to multivacuolar (5a) and ameboid (5b) forms. The multivacuolar form develops into a precyst (6a) that gives origin to a thin-walled cyst (7a) thought to be responsible for autoinfection. The ameboid form gives origin to a precyst (6b), which develops into thick-walled cyst by schizogony (7b). *B hominis* stages were reproduced from Singh M, Suresh K, Ho LC, Ng GC, Yap EH. Elucidation of the life cycle of the intestinal protozoan *Blastocystis hominis*. *Parasitol Res.* 1995;81(5):449. Permission granted by M Singh and Springer-Verlag.

CHAPTER 19

Blastomycosis

CLINICAL MANIFESTATIONS

Infections can be acute, chronic, or fulminant but are asymptomatic in up to 50% of infected people. The most common clinical manifestation of blastomycosis in children is cough (often productive) accompanying pulmonary disease, with fever, chest pain, and nonspecific symptoms such as fatigue and myalgia. Rarely, patients may develop acute respiratory distress syndrome (ARDS). Typical radiographic patterns include consolidation, patchy pneumonitis, a mass-like infiltrate, or nodules. Blastomycosis can be misdiagnosed as bacterial pneumonia, tuberculosis, sarcoidosis, or malignant neoplasm. Disseminated blastomycosis, which can occur in up to 25% of symptomatic cases, most commonly involves the skin, osteoarticular structures, and the genitourinary tract. Cutaneous manifestations can be verrucous, nodular, ulcerative, or pustular. Abscesses usually are subcutaneous but can involve any organ. Erythema nodosum, which is common in patients with histoplasmosis and coccidioidomycosis, is rare in blastomycosis. Central nervous system infection is less common, and intrauterine or congenital infection is rare.

ETIOLOGY

Blastomycosis is caused by *Blastomyces* species (*Blastomyces dermatitidis* and *Blastomyces gilchristii*), thermally dimorphic fungi existing in the yeast form at 37°C (98°F) in infected tissues and in a mycelial form at room temperature and in soil. Conidia, produced from hyphae of the mycelial form, are infectious.

EPIDEMIOLOGY

Infection is acquired through inhalation of conidia from soil. Increased mortality rates for patients with pulmonary blastomycosis have been associated with advanced age, chronic obstructive pulmonary disease, cancer, and African American race. Person-to-person transmission does not occur. In the United States, blastomycosis is endemic in the central states, with most cases occurring in the Ohio and Mississippi river valleys, the southeastern states, and states that border the Great Lakes; however, sporadic cases have occurred outside these areas. Similar to *Histoplasma capsulatum*, *Blastomyces* species can grow in bird and animal excreta. Occupational and recreational activities associated with infection involve disruption of soil and include construction of homes or roads, boating and canoeing, tubing on a river, fishing, exploration of beaver dams and underground forts, and use of a community compost pile.

The **incubation period** ranges from 2 weeks to 3 months.

DIAGNOSTIC TESTS

Definitive diagnosis of blastomycosis is based on microscopic identification of characteristic thick-walled, broad-based, single budding yeast cells either by culture at 37°C or in histopathologic specimens. The organism may be seen in sputum, tracheal aspirates, cerebrospinal fluid, urine, or histopathologic specimens from lesions processed with 10% potassium hydroxide or a silver stain. Children with pneumonia who are unable to produce sputum may require bronchoalveolar lavage or open biopsy to establish the diagnosis. Bronchoalveolar lavage is high yield, even in patients with bone or skin manifestations. Organisms can be cultured on brain-heart infusion media and Sabouraud dextrose agar as a mold. Chemiluminescent DNA probes are available for identification of *B dermatitidis*. Because serologic tests (immunodiffusion and complement fixation) lack adequate sensitivity, effort should be made to obtain appropriate specimens for culture. Sensitivity is low for localized infection and higher in disseminated disease. Negative serum reaction testing during the acute phase may be repeated 3 to 4 weeks later. An enzyme immunoassay that detects *Blastomyces* antigen in urine has replaced classic serologic studies and performs well for the diagnosis of disseminated and pulmonary disease. Antigen testing in urine performs better than antigen testing of serum. Significant cross-reactivity occurs in patients with other endemic mycoses (specifically, *H capsulatum*, *Paracoccidioides brasiliensis*, and *Penicillium marneffei*); clinical and epidemiologic considerations often aid with interpretation.

TREATMENT

Because of the high risk of dissemination, some experts recommend that all cases of blastomycosis in children should be treated. Amphotericin B deoxycholate or an amphotericin B lipid formulation is recommended for initial therapy of severe pulmonary disease for 1 to 2 weeks or until improvement followed by 6 to 12 months of itraconazole therapy. Oral itraconazole is recommended for 6 to 12 months for mild to moderate infection. Some experts suggest 12 months of therapy for patients with osteoarticular disease. For central nervous system infection, a lipid formulation of amphotericin B is recommended for 4 to 6 weeks, followed by fluconazole. Itraconazole is indicated for treatment of non–life-threatening infection outside the central nervous system.

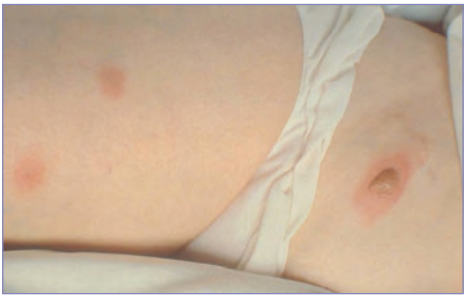


Image 19.1
Nodular skin lesions of blastomycosis, one of which is a bullous lesion on top of a nodule. Aspiration of the bulla revealed yeast forms of *Blastomyces dermatitidis*. Courtesy of Centers for Disease Control and Prevention.

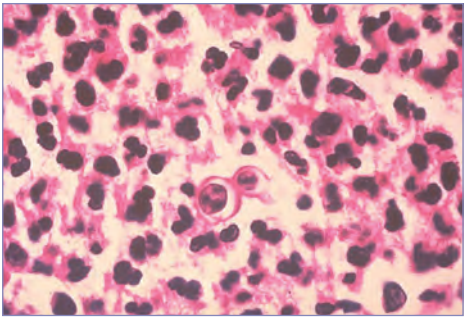


Image 19.3
Histopathology of blastomycosis of skin. Budding cell of *Blastomyces dermatitidis* surrounded by neutrophils. Multiple nuclei are visible. Courtesy of Centers for Disease Control and Prevention.

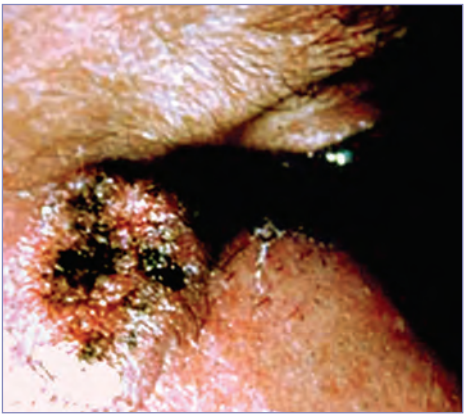


Image 19.2
Cutaneous blastomycosis (face). Cutaneous lesions are nodular, verrucous, or ulcerative, as in this man. Most cutaneous lesions are due to hematogenous spread from a pulmonary infection. Courtesy of Edgar O. Ledbetter, MD, FAAP.

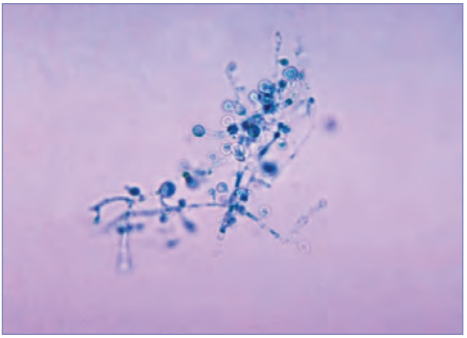


Image 19.4
Photomicrograph of *Blastomyces dermatitidis* using a cotton blue staining technique. Blastomycosis caused by *B dermatitidis* can be asymptomatic or associated with acute, chronic, or fulminant disease. Courtesy of Centers for Disease Control and Prevention.

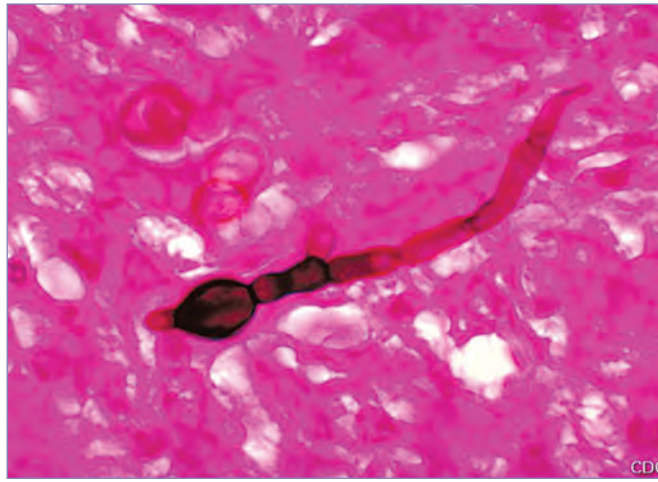


Image 19.5
This micrograph shows histopathologic changes that reveal the presence of the fungal agent *Blastomyces dermatitidis*. Courtesy of Centers for Disease Control and Prevention/ Libero Ajello, MD.

CHAPTER 20

Bocavirus

CLINICAL MANIFESTATIONS

Human bocavirus (HBoV) first was identified in 2005 from a cohort of children with acute respiratory tract symptoms. Cough, rhinorrhea, wheezing, and fever have been attributed to HBoV. HBoV has been identified in 5% to 33% of all children with acute respiratory tract infections in various settings (eg, inpatient facilities, outpatient facilities, child care centers). The role of HBoV as a pathogen in human infection is further confounded by simultaneous detection of other viral pathogens in patients in whom HBoV is identified, with coinfection rates ranging from 20% to as high as 80%. However, some evidence supports the role of HBoV as a pathogen. This include longitudinal cohort studies showing an association of primary infection with symptomatic illness and case-control studies showing associations of illness with monoinfection, high viral load, and detection of mRNA.

Infection with HBoV appears to be ubiquitous, because nearly all children develop serologic evidence of previous HBoV infection by 5 years of age.

ETIOLOGY

HBoV is a nonenveloped, single-stranded DNA virus classified in the family *Parvoviridae*, subfamily *Parvovirinae*, genus *Bocaparvovirus*, on the basis of its genetic similarity to the closely related **bo**vine parvovirus 1 and **ca**nine minute virus, from which the name "**boca**virus" was derived.

EPIDEMIOLOGY

Detection of HBoV has been described only in humans. Transmission is presumed to be from respiratory tract secretions, although fecal-oral transmission may be possible on the basis of the finding of HBoV in stool specimens from children, including symptomatic children with diarrhea.

The frequent codetection of other viral pathogens of the respiratory tract in association with HBoV has led to speculation about the role played by HBoV; it may be a true pathogen or co-pathogen, and emerging evidence seems to support both roles. Codetection of HBoV with other respiratory viruses is more common when HBoV is present at lower viral loads ($\leq 10^4$ copies/mL). Extended and intermittent shedding of HBoV has been reported for up to 12 weeks after initial detection. Because HBoV may be shed for long periods after primary infection and because of the possibility of reactivation during subsequent viral infections and the high rate of detection in healthy people, clinical interpretation of HBoV detection is difficult.

HBoV circulates worldwide and throughout the year. In temperate climates, seasonal clustering in the spring associated with increased transmission of other respiratory tract viruses has been reported.

DIAGNOSTIC TESTS

Commercial molecular diagnostic assays for HBoV are available. HBoV polymerase chain reaction and detection of HBoV-specific antibody also are used by research laboratories to detect the presence of virus and infection, respectively.

TREATMENT

No specific therapy is available.

CHAPTER 21

Borrelia Infections Other Than Lyme Disease

(Relapsing Fever)

CLINICAL MANIFESTATIONS

Two types of relapsing fever occur in humans: tickborne and louse-borne. Both are characterized by sudden onset of high fever, shaking chills, sweats, headache, muscle and joint pain, altered sensorium, nausea, and diarrhea. A fleeting macular rash of the trunk and petechiae of the skin and mucous membranes sometimes occur. Findings and complications can differ between types of relapsing fever and include hepatosplenomegaly, jaundice, thrombocytopenia, iridocyclitis, cough with pleuritic pain, pneumonitis, meningitis, and myocarditis. Mortality rates can exceed 30% in untreated louse-borne relapsing fever (possibly related to comorbidities in refugee-type settings, where this disease typically is found) and 4% to 10% in untreated tickborne relapsing fever. Death occurs predominantly in people with underlying illnesses, infants, and elderly people. Early treatment reduces mortality to less than 5%. Untreated, an initial febrile period of 2 to 7 days terminates spontaneously and is followed by an afebrile period of several days to weeks, then by 1 relapse or more (0–13 for tickborne, 1–5 for louse-borne). Relapses typically become shorter and progressively milder as afebrile periods lengthen. Relapse is associated with expression of new borrelial antigens, and resolution of symptoms is associated with production of antibody specific to those new antigenic determinants. Infection during pregnancy often is severe and can result in spontaneous abortion, preterm birth, stillbirth, or neonatal infection.

ETIOLOGY

Relapsing fever is caused by certain spirochetes of the genus *Borrelia*. Worldwide, at least 14 *Borrelia* species cause tickborne (endemic) relapsing fever, including *Borrelia hermsii*, *Borrelia turicatae*, *Borrelia parkeri*, and *Borrelia miyamotoi* in North America. Louse-borne (epidemic) relapsing fever is cause by *Borrelia recurrentis*.

EPIDEMIOLOGY

Endemic tickborne relapsing fever is distributed widely throughout the world. Most species, including *B hermsii*, *B turicatae*, and *B parkeri*, are transmitted by soft-bodied ticks (*Ornithodoros* species). *B miyamotoi*, which has only recently been recognized as a cause of human illness, is transmitted by hard-bodied ticks (*Ixodes* species). Vector ticks become infected by feeding on rodents or other small mammals and transmit infection via their saliva during subsequent blood meals. Ticks may serve as reservoirs of infection through trans-ovarial and trans-stadial transmission. Because of differences in the distribution, life cycle, and feeding habits of soft- and hard-bodied ticks, the epidemiology of tickborne relapsing fever differs somewhat for infections transmitted by these 2 classes of ticks.

Soft-bodied ticks typically live within rodent nests. They inflict painless bites and feed briefly (15–90 minutes), usually at night, so that people often are unaware of having been bitten. In the United States, vector soft-bodied ticks are found in mountainous areas of the West. Human infection typically results from sleeping in rustic, rodent-infested cabins, although cases have been associated with primary residences and luxurious rental properties. Cases occur sporadically or in small clusters among families or cohabiting groups and may be seen in residents of other states following trips to the Rocky Mountains or Sierra Nevada mountains. *B hermsii* is the most common cause of these infections. *B turicatae* infections occur less frequently; most cases have been reported from Texas and are associated with tick exposures in rodent-infested caves.

The hard-bodied ticks *Ixodes scapularis* and *Ixodes pacificus* transmit *B miyamotoi* in North America. These ticks are better known as vectors of Lyme disease, anaplasmosis, and babesiosis. They are common in areas of the northeastern, Mid-Atlantic, and upper Midwest regions as well as focal areas along the Pacific coast. They live in grassy and wooded areas and must remain attached for approximately 72 hours to obtain a full blood meal. Reported rates of infection with *B miyamotoi* typically

are 1% to 2% across all areas studied. Most human cases in the United States have been reported from the Northeast.

Louse-borne epidemic relapsing fever has been reported in Ethiopia, Eritrea, Somalia, and the Sudan, especially in refugee and displaced populations. Epidemic transmission occurs when body lice (*Pediculus humanus*) become infected by feeding on humans with spirochetemia; infection is transmitted when infected lice are crushed and their body fluids contaminate a bite wound or skin abraded by scratching.

Infected body lice and ticks may remain alive and infectious for several years without feeding. Relapsing fever is not transmitted between individual humans, but perinatal transmission from an infected mother to her infant occurs and can result in preterm birth, stillbirth, and neonatal death.

The **incubation period** is 2 to 18 days, with a mean of 7 days.

DIAGNOSTIC TESTS

Spirochetes can be observed by dark-field microscopy and in Wright-, Giemsa-, or acridine orange-stained preparations of thin or dehemoglobinized thick smears of peripheral blood or in stained buffy-coat preparations. Organisms often can be visualized in blood obtained while the person is febrile, particularly during initial febrile episodes; organisms are less likely to be recovered from subsequent relapses. Spirochetes can be cultured from blood in Barbour-Stoenner-Kelly medium or by intraperitoneal inoculation of immature laboratory mice, although these tests are not widely available. Serum antibodies to *Borrelia* species can be detected by enzyme immunoassay and Western immunoblot analysis at some reference and commercial specialty laboratories; a 4-fold increase in titer is considered confirmatory. These antibody tests are not standardized and are affected by antigenic variations among and within *Borrelia* species and strains. Serologic cross-reactions occur with other spirochetes, including *B burgdorferi*, *Treponema pallidum*, and *Leptospira* species.

TREATMENT

Treatment of tickborne relapsing fever with a 5- to 10-day course of doxycycline produces prompt clearance of spirochetes and remission of symptoms; doxycycline can be used regardless of patient age. For pregnant women, penicillin and erythromycin are the preferred drugs. Penicillin G procaine or intravenous penicillin G is recommended as initial therapy for people who cannot tolerate oral therapy, although low-dose penicillin G has been associated with a higher frequency of relapse. A Jarisch-Herxheimer reaction (an acute febrile reaction accompanied by headache, myalgia, respiratory distress in some cases, and an aggravated clinical picture lasting less than 24 hours) commonly is observed during the first few hours after initiating antimicrobial therapy. Because this reaction sometimes is associated with transient hypotension attributable to decreased effective circulating blood volume (especially in louse-borne relapsing fever), patients should be hospitalized and monitored closely, particularly during the first 4 hours of treatment. However, the Jarisch-Herxheimer reaction in children typically is mild and usually can be managed with antipyretic agents alone.

For louse-borne relapsing fever, single-dose treatment using doxycycline, penicillin, or erythromycin is effective therapy.

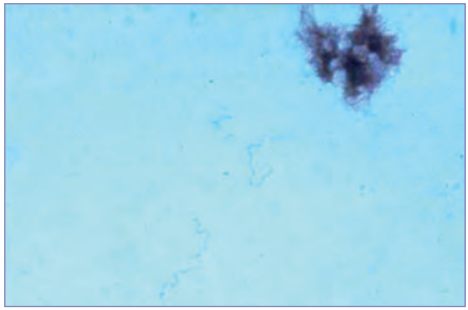


Image 21.1
Borrelia in peripheral blood smear. The spirochetes can be seen with darkfield microscopy and in Wright-, Giemsa-, or acridine orange–stained smears.

Image 21.3
Dorsal view of a female head louse, *Pediculus humanus capitis.* The body louse, *Pediculus humanus humanus,* is the vector of 3 human pathogens: *Rickettsia prowazekii*, the agent of epidemic typhus; *Borrelia recurrentis,* the agent of relapsing fever; and *Bartonella quintana*, the agent of trench fever, bacillary angiomatosis, endocarditis, chronic bacteremia, and chronic lymphadenopathy. Courtesy of Centers for Disease Control and Prevention.

Image 21.2
This image depicts an adult female body louse, *Pediculus humanus*, and 2 larval young. *P humanus* has been shown to serve as a vector for diseases such as typhus, due to *Rickettsia prowazekii*, trench fever caused by *Bartonella* (formerly *Rochalimaea*) *quintana,* and relapsing fever due to *Borrelia recurrentis.* Courtesy of Centers for Disease Control and Prevention.

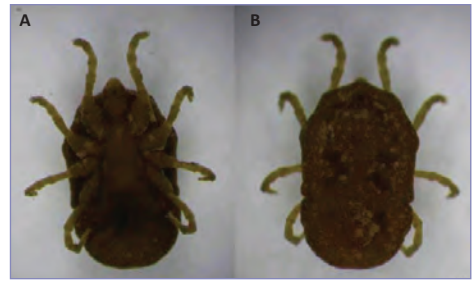


Image 21.4
Ventral (A) and dorsal (B) views of *Ornithodoros tholozani*. Tickborne relapsing fever is transmitted to humans by the *Ornithodoros* species soft ticks and is distributed widely throughout the world. This tick is prevalent in central Asia and the Middle East. Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases* and Marc Victor Assous.

CHAPTER 22

Brucellosis

CLINICAL MANIFESTATIONS

Onset of brucellosis in children can be acute or insidious. Manifestations are nonspecific and include fever, night sweats, weakness, malaise, anorexia, weight loss, arthralgia, myalgia, back pain, abdominal pain, and headache. Physical findings may include lymphadenopathy, hepatosplenomegaly, and arthritis. Abdominal pain and peripheral arthritis are reported more frequently in children than in adults. Neurologic deficits, ocular involvement, epididymo-orchitis, and liver or spleen abscesses are reported. Anemia, leukopenia, thrombocytopenia, or less frequently, pancytopenia are hematologic findings that might suggest the diagnosis. Serious complications include meningitis, endocarditis, and osteomyelitis and, less frequently, pneumonitis and aortic involvement. A detailed history including travel, exposure to animals, and food habits, including ingestion of unpasteurized milk or cheese, and occupational history should be obtained if brucellosis is considered. Chronic disease is less common among children than among adults, although the rate of relapse has been found to be similar. Brucellosis in pregnancy is associated with risk of spontaneous abortion, preterm delivery, miscarriage, and intrauterine infection with fetal death.

ETIOLOGY

Brucella bacteria are small, nonmotile, gram-negative coccobacilli. The species that are known to infect humans are *Brucella abortus*, *Brucella melitensis*, *Brucella suis*, and rarely, *Brucella canis*. Three recently identified species, *Brucella ceti*, *Brucella pinnipedialis*, and *Brucella inopinata*, are potential human pathogens.

EPIDEMIOLOGY

Brucellosis is a zoonotic disease of wild and domestic animals. It is transmissible to humans by direct or indirect exposure to aborted fetuses or tissues or fluids of infected animals. Transmission occurs by inoculation through mucous membranes or cuts and abrasions in the skin, inhalation of contaminated aerosols, or ingestion of undercooked meat or unpasteurized dairy products. People in occupations such as farming, ranching, and veterinary medicine, as well as abattoir workers, meat inspectors, and laboratory personnel, are at increased risk. Clinicians should alert the laboratory if they anticipate *Brucella* might grow from microbiologic specimens so that appropriate laboratory precautions can be taken. In the United States, approximately 100 to 200 cases of brucellosis are reported annually, and 3% to 10% of cases occur in people younger than 19 years. Most pediatric cases reported in the United States result from ingestion of unpasteurized dairy products. Human-to-human transmission is rare, but sexual transmission has been reported, in utero transmission has been reported, and infected mothers can transmit *Brucella* to their infants through breastfeeding.

The **incubation period** varies from less than 1 week to several months, but 3 to 4 weeks after exposure.

DIAGNOSTIC TESTS

A definitive diagnosis is established by recovery of *Brucella* species from blood, bone marrow, or other tissue specimens. A variety of media will support growth of *Brucella* species, but the physician should contact laboratory personnel and ask them to incubate cultures for a minimum of 4 weeks. Newer BACTEC systems have greater reliability and can detect *Brucella* species within 7 days.

In patients with a clinically compatible illness, serologic testing using the serum agglutination test can confirm the diagnosis with a fourfold or greater increase in antibody titers between acute and convalescent serum specimens collected at least 2 weeks apart. The serum agglutination test, the gold standard test for serologic diagnosis, will detect antibodies against *B abortus*, *B suis*, and *B melitensis* but not *B canis*, which requires use of *B canis*-specific antigen. Although a single titer is not diagnostic, most patients with active infection in an area without endemic infection will have a titer of 1:160 or greater within 2 to 4 weeks of clinical disease onset. Lower titers may be found early in the course of infection. Immunoglobulin (Ig) M antibodies are produced within the first week, followed by a gradual increase in IgG synthesis. Low IgM titers may persist for months or years after initial

infection. Increased concentrations of IgG agglutinins are found in acute infection, chronic infection, and relapse. When interpreting serum agglutination test results, the possibility of cross-reactions of *Brucella* antibodies with antibodies against other gram-negative bacteria, such as *Yersinia enterocolitica* serotype 09, *Francisella tularensis*, *Escherichia coli* O116 and O157, *Salmonella urbana*, *Vibrio cholerae*, *Xanthomonas maltophilia*, and *Afipia clevelandensis*, should be considered. Enzyme immunoassay is a sensitive method for determining IgG, IgA, and IgM anti-*Brucella* antibody titers. Until better standardization is established, enzyme immunoassay should be used only for suspected cases with negative serum agglutination test results or for evaluation of patients with suspected chronic brucellosis, reinfection, or complicated cases. Polymerase chain reaction tests that can be performed in blood and body tissue samples have been developed but are not yet available in most clinical laboratories.

TREATMENT

Prolonged antimicrobial therapy is imperative for achieving a cure. Relapses generally are not associated with development of *Brucella* resistance but rather with premature discontinuation of therapy or localized infection. Because monotherapy is associated with a high rate of relapse, combination therapy is recommended as standard treatment. Most combination regimens include oral doxycycline or trimethoprim-sulfamethoxazole plus rifampin.

For treatment of serious infections or complications, including endocarditis, meningitis, spondylitis, and osteomyelitis, a 3-drug regimen should be used, with gentamicin included for the first 7 to 14 days of therapy, in addition to doxycycline (or trimethoprim-sulfamethoxazole, if doxycycline is not used) and rifampin for a minimum of 6 weeks. For life-threatening complications of brucellosis, such as meningitis or endocarditis, the duration of therapy often is extended for 4 to 6 months. Surgical intervention should be considered in patients with complications, such as deep tissue abscesses, endocarditis, mycotic aneurysm, and foreign body infections.

The benefit of corticosteroids for people with neurobrucellosis is unproven.

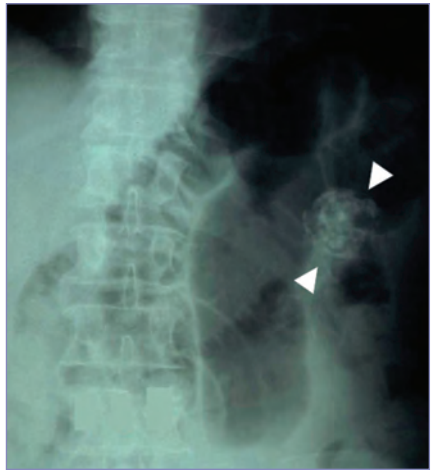


Image 22.1
A calcified *Brucella* granuloma in the spleen of a man with fever of several years' duration. *Brucella* organisms that survive the action of polymorphonuclear leukocytes are ingested by macrophages and become localized in the organs of the reticuloendothelial system.

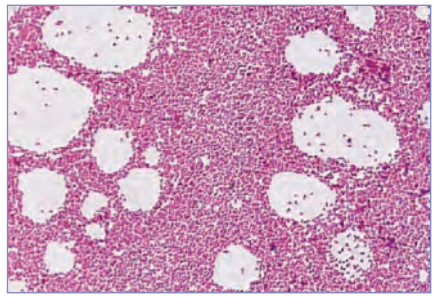


Image 22.2
Brucella species (Gram stain). Typical gram-negative coccobacilli. Courtesy of Robert Jerris, MD.

Image 22.3
Brucella melitensis colonies. *Brucella* species colony characteristics: Fastidious organism and colonies usually are not visible at 24 hours. *Brucella* grows slowly on most standard laboratory media (eg, sheep blood, chocolate, and trypticase soy agars). Pinpoint, smooth, translucent, nonhemolytic colonies are shown at 48 hours of incubation. Courtesy of Centers for Disease Control and Prevention.

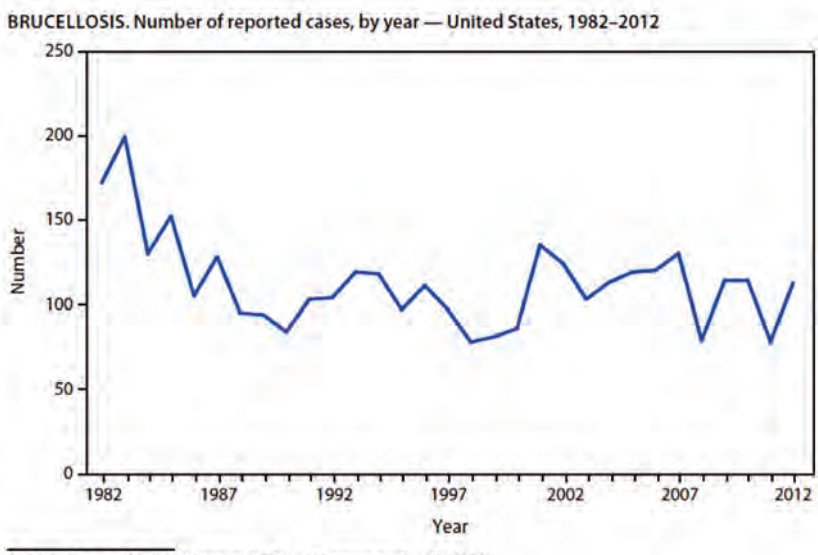


Image 22.4
Brucellosis. Number of reported cases, by year—United States, 1982 through 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

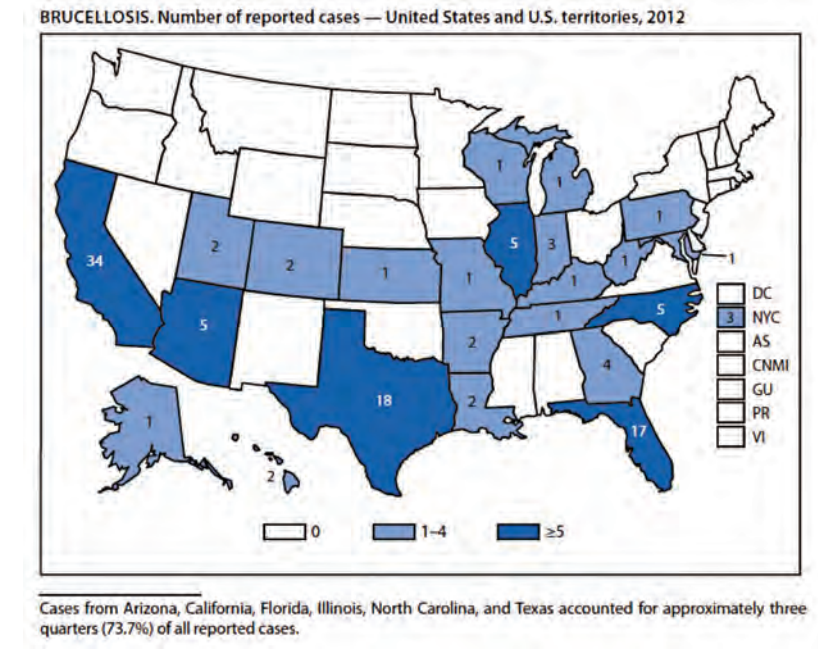


Image 22.5
Brucellosis. Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 23

Burkholderia Infections

CLINICAL MANIFESTATIONS

Species within the *Burkholderia cepacia* complex have been associated with infections in individuals with cystic fibrosis, chronic granulomatous disease, hemoglobinopathies, or malignant neoplasms and in preterm infants. Airway infections in people with cystic fibrosis usually occur late in the course of disease, after respiratory epithelial damage and bronchiectasis have occurred. Patients with cystic fibrosis can become chronically infected with little change in the rate of pulmonary decompensation or can experience an accelerated decline in pulmonary function or an unexpectedly rapid deterioration in clinical status that results in death. In patients with chronic granulomatous disease, pneumonia is the most common manifestation of *B cepacia* complex infection; lymphadenitis also occurs. Disease onset is insidious, with low-grade fever early in the course and systemic effects occurring 3 to 4 weeks later. Pleural effusions are common, and lung abscesses can occur. Health care–associated infections including wound and urinary tract infections and pneumonia have been reported, and clusters of disease have been associated with contaminated pharmaceutical products, including nasal sprays, mouthwash, sublingual probes, prefilled saline flush syringes, and oral docusate sodium.

Burkholderia pseudomallei is the cause of melioidosis. Its geographic range is expanding, and disease now is known to be endemic in Southeast Asia, northern Australia, areas of the Indian Subcontinent, southern China, Hong Kong, Taiwan, several Pacific and Indian Ocean Islands, and some areas of South and Central America. Melioidosis can occur in the United States, usually among travelers returning from areas with endemic disease. Melioidosis can be asymptomatic or can manifest as a localized infection or as fulminant septicemia. Approximately 40% to 60% of adults with melioidosis are bacteremic, but bacteremia is less common in children. Pneumonia is the most commonly reported clinical manifestation of melioidosis in adults. A recent report from Australia found that localized cutaneous disease was the most common presentation in immunocompetent children. Genitourinary infections including prostatic abscesses, septic arthritis and osteomyelitis, and central nervous system involvement, including brain abscesses, also occur. Acute suppurative parotitis is a manifestation that occurs frequently in children in Thailand and Cambodia. Localized infection usually is nonfatal. In severe cutaneous infection, necrotizing fasciitis has been reported. In disseminated infection, hepatic and splenic abscesses can occur, and relapses are common without prolonged therapy.

ETIOLOGY

The *Burkholderia* genus comprises more than 90 species that are nutritionally diverse, oxidase- and catalase-producing, non–lactose-fermenting, gram-negative bacilli. *B cepacia* complex comprises at least 20 species. Additional members of the complex continue to be identified but are rare human pathogens. Other clinically important species of *Burkholderia* include *B pseudomallei*, *Burkholderia gladioli*, and *Burkholderia mallei* (the agent responsible for glanders). *Burkholderia thailandensis* and *Burkholderia oklahomensis* are rare human pathogens.

EPIDEMIOLOGY

Burkholderia species are environmentally derived waterborne and soilborne organisms that can survive for prolonged periods in a moist environment. Depending on the species, transmission may occur from other people (person to person), from contact with contaminated fomites, and from exposure to environmental sources. Epidemiologic studies of recreational camps and social events attended by people with cystic fibrosis from different geographic areas have documented person-to-person spread of *B cepacia* complex. The source of acquisition of *B cepacia* complex by patients with chronic granulomatous disease has not been identified, although environmental sources seem likely. Health care–associated spread of *B cepacia* complex most often is associated with contamination of disinfectant solutions used to clean reusable patient equipment, such as bronchoscopes and pressure transducers, or to disinfect skin. Contaminated medical products, including mouthwash and

inhaled medications, have been identified as a cause of multistate outbreaks of colonization and infection. *B gladioli* has been isolated from sputum of people with cystic fibrosis and may be mistaken for *B cepacia*. *B gladioli* may be associated with transient or more prolonged, chronic infection in patients with cystic fibrosis; poor outcomes have been noted in lung transplant recipients who have *B gladioli* infection.

In areas with highly endemic infection, *B pseudomallei* is acquired early in life, with the highest seroconversion rates between 6 months and 4 years of age. Melioidosis is seasonal, with more than 75% of cases occurring during the rainy season. Disease can be acquired by direct inhalation of aerosolized organisms or dust particles containing organisms, by percutaneous or wound inoculation with contaminated soil or water, or by ingestion of contaminated soil, water, or food. People also can become infected from laboratory exposures when proper techniques and/or proper personal protective equipment guidelines are not followed. Symptomatic infection can occur in children 1 year or younger, with pneumonia and parotitis reported in infants as young as 8 months. Risk factors for melioidosis include frequent contact with soil and water as well as underlying chronic disease, such as diabetes mellitus, renal insufficiency, chronic pulmonary disease, thalassemia, and immunosuppression not related to human immunodeficiency virus (HIV) infection. *B pseudomallei* also has been reported to cause pulmonary infection in people with cystic fibrosis and septicemia in children with chronic granulomatous disease.

The **incubation period** for melioidosis is 1 to 21 days, median 9 days, but can be prolonged.

DIAGNOSTIC TESTS

Culture is the appropriate method to diagnose *B cepacia* complex infection. In cystic fibrosis airway infection, culture of sputum on selective agar is recommended to decrease the potential for overgrowth by mucoid *Pseudomonas aeruginosa.* Confirmation of identification of *B cepacia* complex species by polymerase chain reaction assay (investigational use only) or mass spectroscopy (approved for use) is recommended.

Definitive diagnosis of melioidosis is made by isolation of *B pseudomallei* from blood or other infected sites. The likelihood of successfully isolating the organism is increased by culture of sputum, throat, rectum, and ulcer or skin lesion specimens. A direct polymerase chain reaction assay, available at the Centers for Disease Control and Prevention, is not recommended for routine use. Serologic testing is not adequate for diagnosis in areas with endemic infection because of high background seropositivity. However, a positive result by the indirect hemagglutination assay for a traveler who has returned from an area with endemic infection may support the diagnosis of melioidosis; definitive diagnosis still requires isolation of *B pseudomallei* from an infected site.

TREATMENT

Meropenem is the agent most active against the majority of *B cepacia* complex isolates, although other drugs that may be effective include imipenem, trimethoprim-sulfamethoxazole, ceftazidime, doxycycline, and chloramphenicol. Some experts recommend combinations of antimicrobial agents that provide synergistic activity against *B cepacia* complex in vitro. The majority of *B cepacia* complex isolates are intrinsically resistant to aminoglycosides and polymyxins.

The drugs of choice for initial treatment of melioidosis depend on the type of clinical infection, susceptibility testing, and presence of comorbidities in the patient (eg, diabetes, liver or renal disease, cancer, hemoglobinopathies, cystic fibrosis). Treatment of severe invasive infection should include meropenem or ceftazidime (rare resistance) for a minimum of 10 to 14 days.

Image 23.1
This photograph depicts the colonial morphology displayed by gram-negative *Burkholderia pseudomallei* bacteria, which was grown on a medium of chocolate agar, for a 72-hour period, at a temperature of 37°C (98.6°F). Courtesy of Centers for Disease Control and Prevention.

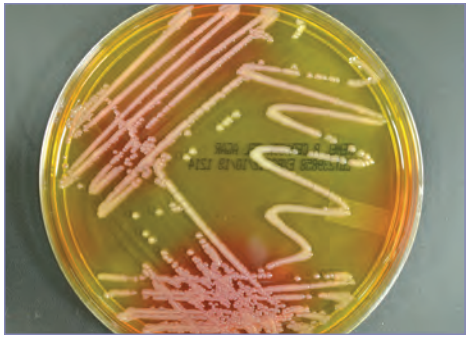


Image 23.2
Burkholderia cepacia on *Burkholderia* selective agar. With vancomycin, gentamicin, and polymyxin B, this agar is used for the isolation of *B cepacia* complex from respiratory secretions of patients with cystic fibrosis. Growth of the organism turns the medium from orange to yellow, and colonies are surrounded by a pink-yellow zone in the medium. Growth may require up to 72 hours of incubation. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

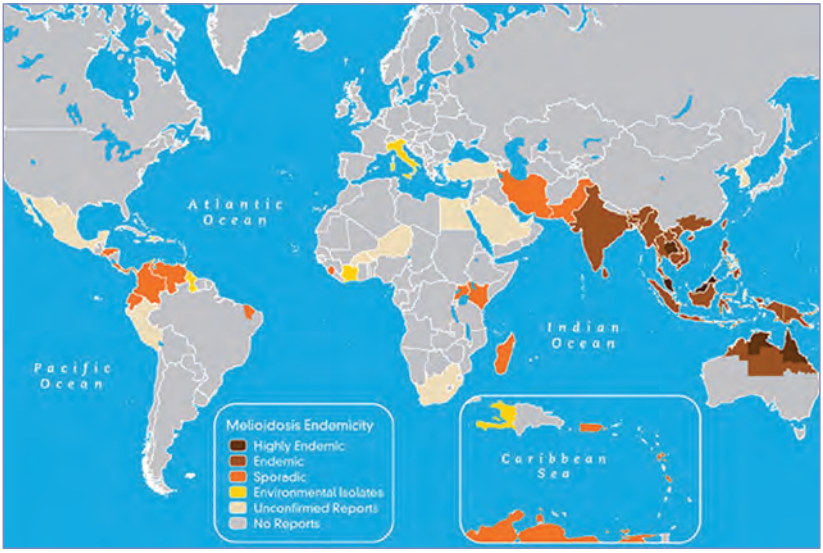


Image 23.3
Endemicity of melioidosis infection. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 24

Campylobacter Infections

CLINICAL MANIFESTATIONS

Predominant symptoms of *Campylobacter* infections include diarrhea, abdominal pain, malaise, and fever. Stools can contain visible or occult blood. In neonates and young infants, bloody diarrhea without fever can be the only manifestation of infection. Pronounced fevers in children can result in febrile seizures that can occur before gastrointestinal tract symptoms. Abdominal pain can mimic that produced by appendicitis or intussusception. Mild infection lasts 1 or 2 days and resembles viral gastroenteritis. Most patients recover in less than 1 week, but 10% to 20% have a relapse or a prolonged or severe illness. Severe or persistent infection can mimic acute inflammatory bowel disease. Bacteremia is uncommon but can occur in elderly patients and in patients with underlying conditions. Immunocompromised hosts can have prolonged, relapsing, or extraintestinal infections, especially with *Campylobacter fetus* and other *Campylobacter* species. Immunoreactive complications, such as Guillain-Barré syndrome (occurring in 1:1,000), Miller Fisher variant of Guillain-Barré syndrome (ophthalmoplegia, areflexia, ataxia), reactive arthritis (with the classic triad, formerly known as Reiter syndrome, consisting of arthritis, urethritis, and bilateral conjunctivitis), myocarditis, pericarditis, and erythema nodosum, can occur during convalescence.

ETIOLOGY

Campylobacter species are motile, comma-shaped, gram-negative bacilli that cause gastroenteritis. There are 25 species within the genus *Campylobacter*, but *Campylobacter jejuni* and *Campylobacter coli* are the species isolated most commonly from patients with diarrhea. *C fetus* predominantly causes systemic illness in neonates and debilitated hosts. Other *Campylobacter* species, including *Campylobacter upsaliensis*, *Campylobacter lari*, and *Campylobacter hyointestinalis*, can cause similar diarrheal or systemic illnesses in children.

EPIDEMIOLOGY

Although incidence decreased in the early 2000s, data from the Foodborne Diseases Active Surveillance Network (**www.cdc.gov/foodnet**) indicate that the 2012 incidence of culture-confirmed cases represented a 14% increase over a 2006–2008 baseline. Disease incidence has remained stable since 2010–2012. The highest rates of infection occur in children younger than 5 years. The majority of *Campylobacter* infections are acquired domestically, but it is also a very common cause of diarrhea in returning international travelers. In susceptible people, as few as 500 *Campylobacter* organisms can cause infection.

The gastrointestinal tracts of domestic and wild birds and animals are reservoirs of the bacteria. *C jejuni* and *C coli* have been isolated from feces of 30% to 100% of healthy chickens, turkeys, and water fowl. Poultry carcasses commonly are contaminated. Many farm animals, pets, and meat sources can harbor the organism and are potential sources of infection. Transmission of *C jejuni* and *C coli* occurs by ingestion of contaminated food or water or by direct contact with fecal material from infected animals or people. Improperly cooked poultry, untreated water, and unpasteurized milk have been the main vehicles of transmission. *Campylobacter* infections usually are sporadic; outbreaks are rare but have occurred among schoolchildren who drank unpasteurized milk, including children who participated in field trips to dairy farms. Person-to-person spread occurs occasionally, particularly among very young children, and risk is greatest during the acute phase of illness. Uncommonly, outbreaks of diarrhea in child care centers have been reported. Person-to-person transmission has occurred in neonates of infected mothers and has resulted in health care-associated outbreaks in nurseries. In perinatal infection, *C jejuni* and *C coli* usually cause neonatal gastroenteritis, whereas *C fetus* often causes neonatal septicemia or meningitis. Enteritis occurs in people of all ages. Excretion of *Campylobacter* organisms typically lasts 2 to 3 weeks without antimicrobial treatment and can be as long as 7 weeks.

The **incubation period** usually is 2 to 5 days but can be longer.

DIAGNOSTIC TESTS

C jejuni and *C coli* can be recovered from feces, and *Campylobacter* species, including *C fetus*, can be recovered from blood. Isolation of *C jejuni* and *C coli* from stool specimens requires selective media, microaerobic conditions, and an incubation temperature of 42°C. Other *Campylobacter* species occasionally are isolated using routine culture methods. Direct-examination, culture-independent methods are available. *C jejuni* and *C coli* can be detected directly (but not differentiated) by commercially available enzyme immunoassays. These immunologic assays provide rapid diagnosis of enteric infection with *C jejuni* and *C coli* but have variable performance. A number of multiplex nucleic acid amplification tests (NAATs) that detect select *Campylobacter* species and other bacterial, viral, or parasitic gastrointestinal pathogens are available, but these assays cannot always distinguish between *Campylobacter* species. Clinical interpretation and experience with these new molecular tests are limited. For serious infection, isolation of the organism is preferred to confirm diagnosis.

TREATMENT

Rehydration is the mainstay of treatment for all children with diarrhea. Azithromycin and erythromycin shorten the duration of illness and excretion of susceptible organisms and prevent relapse when administered early in gastrointestinal tract infection. Treatment with azithromycin or erythromycin for 5 days usually eradicates the organism from stool within 2 or 3 days. A fluoroquinolone, such as ciprofloxacin, may be effective, but resistance to ciprofloxacin is common (34% of *C coli* isolates and 22% of *C jejuni* isolates in the United States in 2013 [**www.cdc.gov/NARMS**]). If antimicrobial therapy is administered for treatment of gastroenteritis, the recommended duration is 3 to 5 days. Antimicrobial agents for bacteremia should be selected on the basis of antimicrobial susceptibility tests. *C fetus* generally is susceptible to aminoglycosides, extended-spectrum cephalosporins, meropenem, imipenem, ampicillin, and erythromycin. Antimotility agents should not be used, because they have been shown to prolong symptoms and may be associated with an increased risk of death.

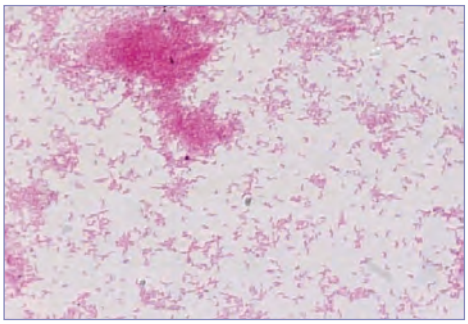


Image 24.1
Campylobacter jejuni (Gram stain) faintly staining short, curved, or spiral-shaped gram-negative rods from a culture of the organism. Courtesy of Robert Jerris, MD.

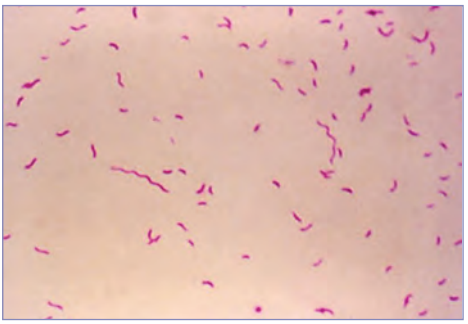


Image 24.2
This image of a Gram-stained specimen shows the spiral rods of *Campylobacter fetus* subsp *fetus* taken from an 18-hour brain-heart infusion with a 7% addition of rabbit blood agar plate culture. Courtesy of Centers for Disease Control and Prevention.

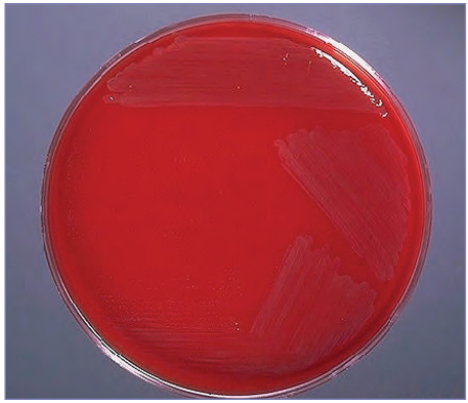


Image 24.3
Blood agar plate culture of *Campylobacter fetus* subsp *intestinalis. C fetus* causes prolonged, relapsing, or extraintestinal illness in immunocompromised hosts. During convalescence, *C fetus* infections have been associated with immunoreactive complications such as Guillain-Barré syndrome, reactive arthritis, and erythema nodosum. Courtesy of Centers for Disease Control and Prevention.

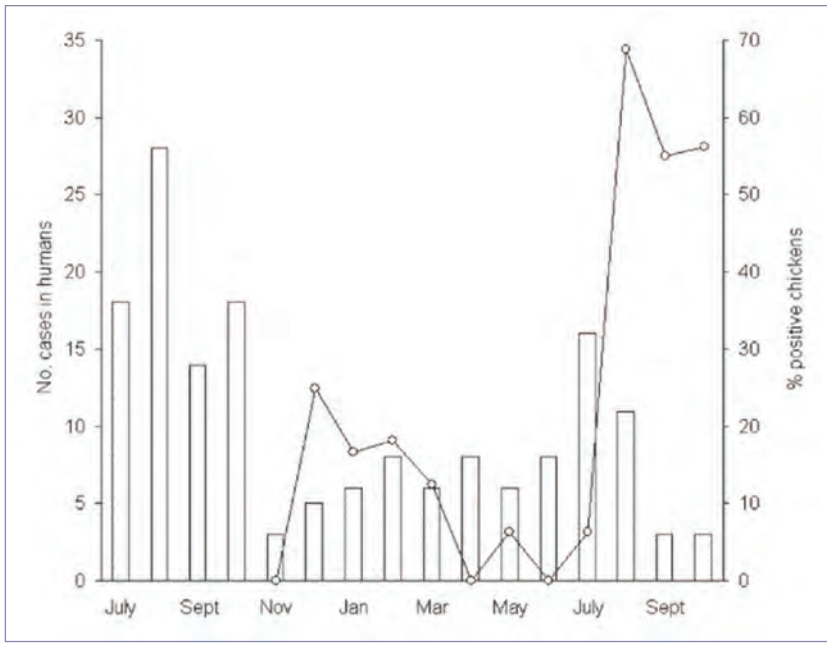


Image 24.4
Monthly distribution of the number of sporadic cases of *Campylobacter* infections in humans from July 2000 to October 2001 (columns) and of the prevalence of *Campylobacter* in whole retail chickens from November 2000 to October 2001 (line graph), Quebec. Courtesy of *Emerging Infectious Diseases*.

CHAPTER 25

Candidiasis

CLINICAL MANIFESTATIONS

Mucocutaneous infection results in oral-pharyngeal (thrush) or vaginal or cervical candidiasis; intertriginous lesions of the gluteal folds, buttocks, neck, groin, and axilla; paronychia; and onychia. Dysfunction of T lymphocytes, other immunologic disorders, and endocrinologic diseases are associated with chronic mucocutaneous candidiasis. Chronic or recurrent oral candidiasis can be the presenting sign of human immunodeficiency virus (HIV) infection or primary immunodeficiency. Esophageal and laryngeal candidiasis can occur in immunocompromised patients. Disseminated candidiasis has a predilection for extremely preterm infants and immunocompromised or debilitated hosts, can involve virtually any organ or anatomic site, and can be rapidly fatal. Candidemia can occur with or without associated end-organ disease in patients with indwelling central vascular catheters, especially in patients receiving prolonged intravenous infusions with parenteral alimentation or lipids. Peritonitis can occur in patients undergoing peritoneal dialysis, especially in patients receiving prolonged broad-spectrum antimicrobial therapy. Candiduria can occur in patients with indwelling urinary catheters, focal renal infection, or disseminated disease.

ETIOLOGY

Candida species are yeasts that reproduce by budding. *Candida albicans* and several other species form long chains of elongated yeast forms called pseudohyphae. *C albicans* causes most infections, but in some regions and patient populations, non-albicans *Candida* species now account for more than half of invasive infections. Other species, including *Candida tropicalis*, *Candida parapsilosis*, *Candida glabrata*, *Candida krusei*, *Candida guilliermondii*, *Candida lusitaniae*, and *Candida dubliniensis*, can cause serious infections, especially in immunocompromised and debilitated hosts. *C parapsilosis* is second only to *C albicans* as a cause of systemic candidiasis. *Candida auris* is a drug-resistant *Candida* species that recently has emerged, virtually always is found in immunocompromised hosts, and often is acquired in health care settings.

EPIDEMIOLOGY

Like other *Candida* species, *C albicans* is present on skin and in the mouth, intestinal tract, and vagina of immunocompetent people. Vulvovaginal candidiasis is associated with pregnancy, and newborn infants can acquire the organism in utero, during passage through the vagina, or postnatally. Mild mucocutaneous infection is common in healthy infants. Person-to-person transmission occurs rarely. Invasive disease typically occurs in those with impaired immunity, with infection usually arising endogenously from colonized sites. Factors such as extreme prematurity, neutropenia, or treatment with corticosteroids or cytotoxic chemotherapy increase the risk of invasive infection. People with diabetes mellitus generally have localized mucocutaneous lesions. People with neutrophil defects, such as chronic granulomatous disease or myeloperoxidase deficiency, are at increased risk. People undergoing intravenous alimentation or receiving broad-spectrum antimicrobial agents, especially extended-spectrum cephalosporins, carbapenems, and vancomycin, or requiring long-term indwelling central venous or peritoneal dialysis catheters have increased susceptibility to infection. Postsurgical patients can be at risk, particularly after cardiothoracic or abdominal procedures.

The **incubation period** is unknown.

DIAGNOSTIC TESTS

The presumptive diagnosis of mucocutaneous candidiasis or thrush usually can be made clinically, but other organisms or trauma can cause clinically similar lesions. Yeast cells and pseudohyphae can be found in *C albicans*-infected tissue and are identifiable by microscopic examination of scrapings prepared with Gram, calcofluor white, or fluorescent antibody stains or in a 10% to 20% potassium hydroxide suspension. Endoscopy is useful for diagnosis of esophagitis. Although ophthalmologic examination can reveal typical retinal lesions attributable to hematogenous dissemination, the yield of routine ophthalmologic evaluation in affected patients is low. Lesions in the brain, kidney, liver, heart, or spleen can be detected

by ultrasonography, computed tomography (CT), or magnetic resonance imaging; however, these lesions typically are not detected by imaging until late in the disease course or after neutropenia has resolved.

A definitive diagnosis of invasive candidiasis requires isolation of the organism from a normally sterile body site (eg, blood, cerebrospinal fluid, bone marrow) or demonstration of organisms in a tissue biopsy specimen. Negative results of culture for *Candida* species do not exclude invasive infection in immunocompromised hosts; in some settings, blood culture is <50% sensitive. Recovery of the organism is expedited using automated blood culture systems or a lysis-centrifugation method. The peptide nucleic acid fluorescent in situ hybridization (PNA FISH) probes cleared by the US Food and Drug Administration (FDA) and multiplex polymerase chain reaction (PCR) assays have been developed for rapid detection of *Candida* species directly from positive blood culture bottles. A new molecular assay (T2Candida [T2 Biosystems, Lexington, MA]) can identify 5 different *Candida* species directly from patient's whole blood in 3 to 5 hours.

Patient serum can be tested using the assay for (1,3)-beta-D-glucan from fungal cell walls, which does not distinguish *Candida* species from other fungi, and there are a significant number of false-positive results.

Testing for azole susceptibility is recommended for all bloodstream and other clinically relevant *Candida* isolates. Testing for echinocandin susceptibility should be considered in patients who have had prior treatment with an echinocandin and among those who have infection with *C glabrata* or *C parapsilosis*.

TREATMENT

Mucous Membrane and Skin Infections

Oral candidiasis in immunocompetent hosts is treated with oral nystatin suspension, clotrimazole troches applied to lesions, or miconazole mucoadhesive buccal tablets. Troches should not be used in infants. Fluconazole may be more effective than oral nystatin or clotrimazole troches and may be considered if other treatments fail. Fluconazole can be beneficial for immunocompromised patients with oropharyngeal candidiasis. For fluconazole-refractory disease, itraconazole, voriconazole, posaconazole, amphotericin B deoxycholate oral suspension, or intravenous echinocandins (caspofungin, micafungin) are alternatives.

Esophagitis caused by *Candida* species generally is treated with oral fluconazole. Intravenous fluconazole, an echinocandin, or amphotericin B should be used for patients who cannot tolerate oral therapy. For disease refractory to fluconazole, itraconazole solution, voriconazole, posaconazole, or an echinocandin is recommended. The recommended duration of therapy is 14 to 21 days. However, the duration of treatment depends on severity of illness and patient factors, such as age and degree of immunocompromise.

Skin infections are treated with topical nystatin, miconazole, clotrimazole, naftifine, ketoconazole, econazole, or ciclopirox. Nystatin usually is effective and is the least expensive of these drugs.

Vulvovaginal candidiasis is treated effectively with many topical formulations, including clotrimazole or miconazole (available over the counter). Such topically applied azole drugs are more effective than nystatin. Oral azole agents also are effective and should be considered for recurrent or refractory cases.

For chronic mucocutaneous candidiasis, fluconazole, itraconazole, and voriconazole are effective drugs. Low-dose amphotericin B administered intravenously is effective in severe cases. Relapses are common with any of these agents once therapy is terminated, and treatment should be viewed as a lifelong process that generally requires intermittent pulses of antifungal agents. Invasive infections in patients with this condition are rare.

For asymptomatic candiduria, elimination of predisposing factors, such as indwelling bladder catheters, is strongly recommended whenever feasible. Antifungal treatment is not recommended unless patients are at high risk of candidemia, such as neutropenic patients, very low birth weight infants (<1,500 g), and patients who will undergo urologic manipulation. For patients with symptomatic *Candida* cystitis, elimination of predisposing factors, such as indwelling bladder catheters, is

strongly recommended, as well as fluconazole for 2 weeks. An alternative is a short course (7 days) of low-dose amphotericin B intravenously. Echinocandins have poor urinary concentration.

Keratomycosis is treated with corneal baths of voriconazole (1%) and always in conjunction with systemic therapy. Vision-threatening infections (near the macula or into the vitreous) require intravitreal injection of antifungal agents, usually amphotericin B deoxycholate or voriconazole, with or without vitrectomy, in addition to systemic antifungal agents.

Invasive Disease

General Recommendations

Most *Candida* species are susceptible to amphotericin B, although *C lusitaniae* and some strains of *C glabrata* and *C krusei* exhibit decreased susceptibility or resistance. *C auris* has been described as often drug resistant, and therapy must be targeted as indicated by susceptibility testing. Among patients with persistent candidemia despite appropriate therapy, investigation for a deep focus of infection should be conducted. Lipid-associated preparations of amphotericin B can be used as an alternative to amphotericin B deoxycholate in non-neonatal patients who experience significant toxicity during therapy.

C krusei is resistant to fluconazole, and more than 50% of *C glabrata* isolates can be resistant. Although voriconazole is effective against *C krusei*, it often is ineffective against *C glabrata*. The echinocandins (caspofungin, micafungin, and anidulafungin) all are active in vitro against most *Candida* species and are appropriate first-line drugs for *Candida* infections in severely ill or neutropenic patients. The echinocandins should be used with caution against *C parapsilosis* infection, because some decreased in vitro susceptibility has been reported.

Removal of infected devices (eg, ventriculostomy drains, shunts, nerve stimulators, prosthetic reconstructive devices) in addition to antifungal treatment is necessary.

Neonatal Candidiasis

Infants are more likely than older children and adults to have meningitis as a manifestation of candidiasis. Although meningitis can occur in association with candidemia, approximately half of infants with *Candida* meningitis do not have a positive blood culture. Central nervous system disease in neonates typically manifests as meningoencephalitis and should be assumed to be present in the infant with candidemia because of the high incidence of this complication. A lumbar puncture, brain imaging, and dilated retinal examination are recommended for all neonates with candidemia. CT or ultrasonography of genitourinary tract, liver, and spleen also should be performed.

Amphotericin B deoxycholate (drug of choice for neonates), fluconazole (for infants who have not received fluconazole prophylaxis), or an echinocandin (generally reserved for salvage therapy) can be used in infants with systemic candidiasis. For initial treatment of meningitis, amphotericin deoxycholate is recommended; after the patient has responded to initial treatment, fluconazole may be used for susceptible isolates. Therapy for candidemia without metastatic disease should continue for 2 weeks. Therapy for central nervous system infection is at least 3 weeks and should be continued until all signs and cerebrospinal fluid and radiological abnormalities, if present, have resolved. Lipid formulations of amphotericin B should be used with caution in infants, particularly in patients with urinary tract involvement. Recent evidence suggests that treatment of infants with lipid formulations of amphotericin may be associated with worse outcomes when compared with amphotericin B deoxycholate.

Older Children and Adolescents

In nonneutropenic and clinically stable children, an echinocandin (caspofungin, micafungin, anidulafungin) is preferred, but fluconazole may be considered in those who are unlikely to have a fluconazole-resistant isolate. Amphotericin B deoxycholate or lipid formulations are alternative therapies. In nonneutropenic patients with candidemia and no metastatic complications, treatment should continue for 2 weeks after

documented clearance of *Candida* organisms from the bloodstream and resolution of clinical manifestations associated with candidemia.

In critically ill neutropenic patients, an echinocandin is recommended because of the fungicidal nature of these agents when compared with fluconazole, which is fungistatic. A lipid formulation of amphotericin B is an effective alternative. In neutropenic patients who are not critically ill, fluconazole is the alternative treatment for patients who have not had recent azole exposure. The duration of treatment for candidemia without metastatic complications is 2 weeks after documented clearance of *Candida* organisms from the bloodstream and resolution of symptoms attributable to candidemia. Avoidance or reduction of systemic immunosuppression is advised when feasible.

For chronic disseminated candidiasis (hepatosplenic infection), initial therapy with lipid formulation amphotericin B or an echinocandin for several weeks is recommended, followed by oral fluconazole. Discontinuation of therapy is recommended once lesions have resolved on repeated imaging.

Management of Indwelling Catheters

Prompt removal of any infected vascular or peritoneal catheters is strongly recommended. For neutropenic children, catheter removal should be considered. The recommendation in this population is weaker, because the source of candidemia in the neutropenic child is more likely to be gastrointestinal, and it is difficult to determine the relative contribution of the catheter. Immediate replacement of a catheter over a wire in the same catheter site is not recommended.

Additional Assessments

In neutropenic patients, ophthalmologic findings of choroidal and vitreal infection are minimal until recovery from neutropenia; thus, dilated fundoscopic examinations should be performed within the first week after recovery from neutropenia. All nonneutropenic patients with candidemia should have a dilated ophthalmologic examination within the first week after diagnosis.

Chemoprophylaxis

Invasive candidiasis in infants is associated with prolonged hospitalization and neurodevelopmental impairment or death in almost 75% of affected infants with extremely low birth weight (less than 1,000 g). The poor outcomes, despite prompt diagnosis and therapy, make prevention of invasive candidiasis in this population desirable. Adherence to optimal infection control practices, including "bundles" for intravascular catheter insertion and maintenance and antimicrobial stewardship, can diminish infection rates and should be optimized before implementation of chemoprophylaxis as standard practice in a neonatal intensive care unit. Fluconazole is the preferred agent for prophylaxis, because it has been shown to be effective and safe. Fluconazole prophylaxis is recommended for extremely low birth weight infants ($<$1,000 g) cared for in neonatal intensive care units with high ($\geq$10%) rates of invasive candidiasis. The recommended regimen for extremely low birth weight infants is to initiate fluconazole treatment intravenously during the first 48 to 72 hours after birth and then to administer it twice a week for up to 6 weeks or until intravenous access no longer is required for care. For infants who tolerate enteral feeds, fluconazole oral absorption is good, even in preterm infants.

Fluconazole prophylaxis can decrease the risk of mucosal (eg, oropharyngeal and esophageal) candidiasis in patients with advanced HIV disease. Adults undergoing allogeneic hematopoietic stem cell transplantation have significantly fewer *Candida* infections when receiving fluconazole, but limited data are available for children. Micafungin has been used for prophylaxis. Among patients without HIV infection receiving prophylaxis with fluconazole, an increased incidence of infections attributable to *C krusei* (which intrinsically is resistant to fluconazole) has been reported. Prophylaxis should be considered for children undergoing allogenic hematopoietic stem cell transplantation and other highly myelosuppressive chemotherapy during the period of neutropenia. Prophylaxis is not recommended routinely for other immunocompromised children, including children with HIV infection.

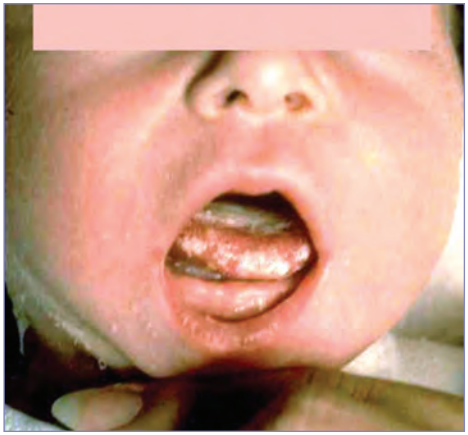


Image 25.1
Candida albicans (thrush) infection in a 1-week-old. Copyright James Brien, DO.

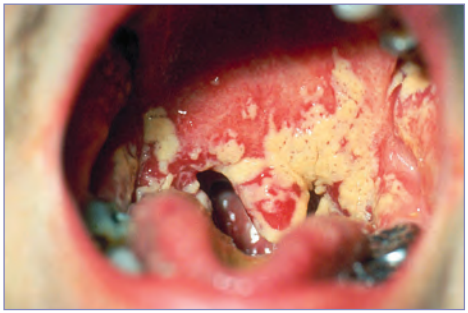


Image 25.3
Oral thrush covering the soft palate and uvula. Courtesy of Centers for Disease Control and Prevention.

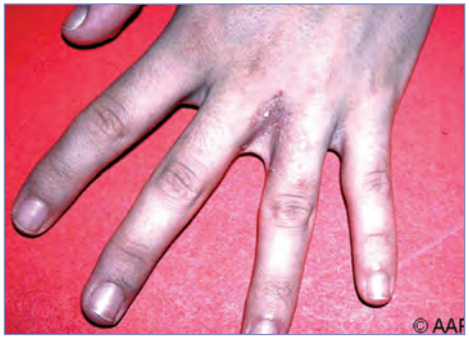


Image 25.5
Intertriginous lesions caused by *Candida albicans*. Copyright James Brien, DO.

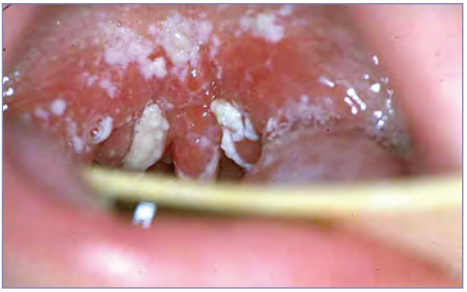


Image 25.2
Candida albicans (thrush) infection of the tonsils and uvula of an otherwise healthy 6-month-old. The white exudate may resemble curds of milk. Copyright Edgar O. Ledbetter, MD, FAAP.

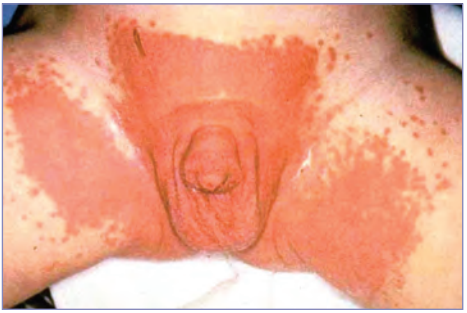


Image 25.4
Candida rash with typical satellite lesions in an infant boy.

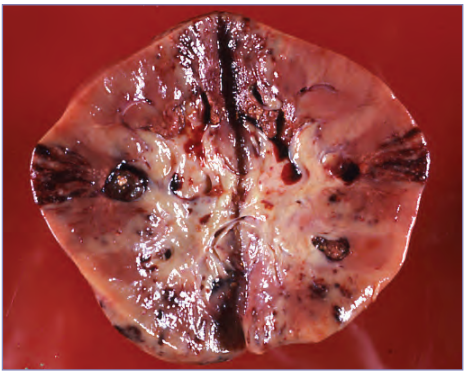


Image 25.6
Disseminated *Candida* infection in a patient with acute lymphocytic leukemia. Hemorrhagic necrotic lesions of the kidney are shown. Courtesy of Dimitris P. Agamanolis, MD.

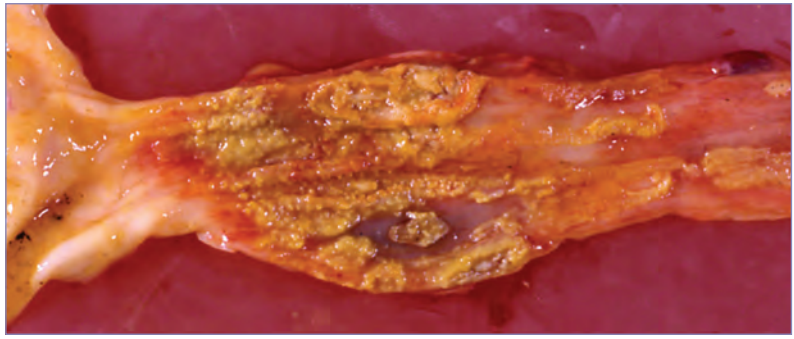


Image 25.7
Candida esophagitis with abscesses and ulceration of the mucosa. Courtesy of Dimitris P. Agamanolis, MD.

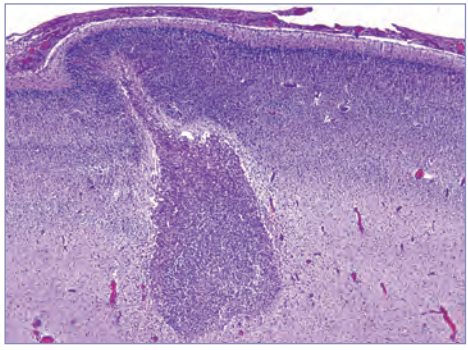


Image 25.8
Disseminated neonatal candidiasis. *Candida* microabscess in the brain. Courtesy of Dimitris P. Agamanolis, MD.

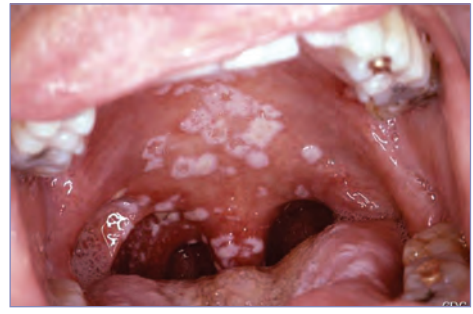


Image 25.9
This patient with HIV/AIDS presented with a secondary oral pseudomembranous candidiasis infection. Courtesy of Centers for Disease Control and Prevention/Sol Silverman Jr, DDS.

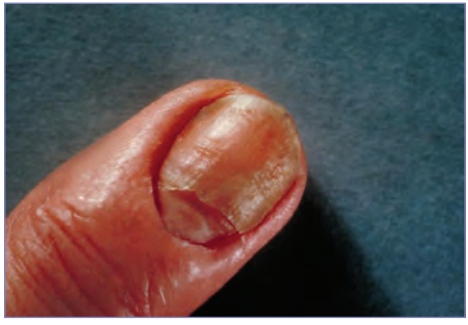


Image 25.10
Candidiasis of the fingernail bed. Courtesy of Centers for Disease Control and Prevention/Sherry Brinkman.

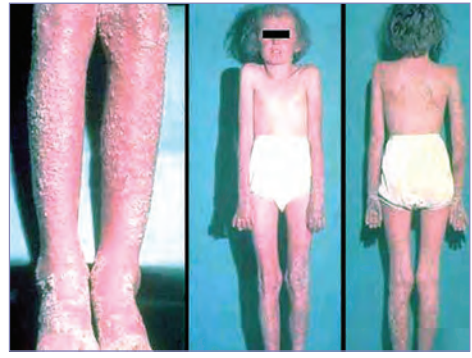


Image 25.11
Chronic mucocutaneous candidiasis in a preadolescent girl with immunodeficiency.

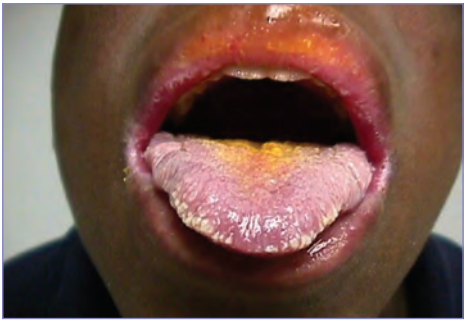


Image 25.12
Candida albicans in a 9-year-old boy with chronic mucocutaneous candidiasis. Courtesy of Benjamin Estrada, MD.

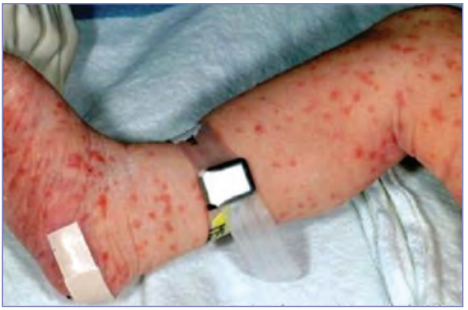


Image 25.13
Congenital candidiasis is characterized by widespread erythematous papules or pustules. Courtesy of Anthony Mancini, MD, FAAP.

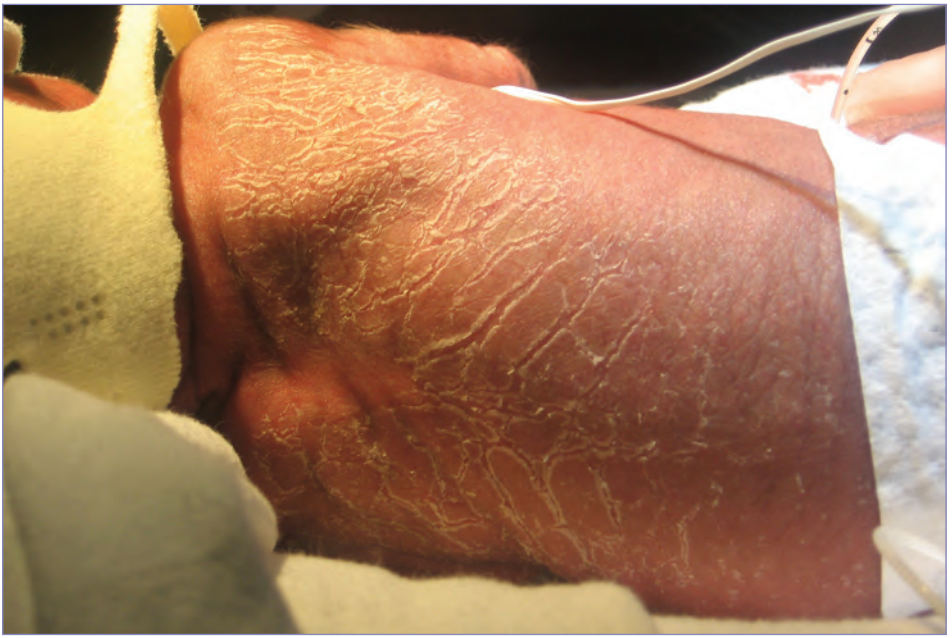


Image 25.14
Extremely low birth weight neonate (<1,000 g) with congenital cutaneous candidiasis of varying presentations (all skin cultures positive for *Candida albicans*). Courtesy of David Kaufman, MD.

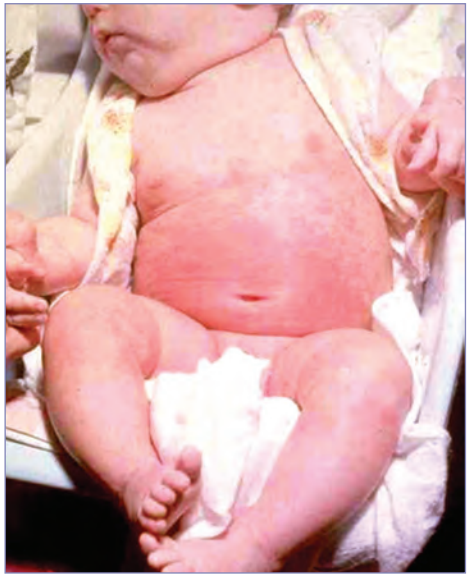


Image 25.15
Cutaneous candidiasis in a 5-week-old.

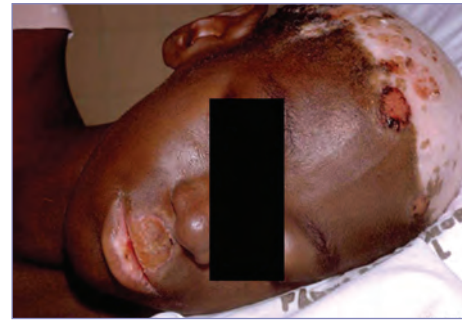


Image 25.16
Chronic mucocutaneous candidiasis in a 15-year-old boy with immunodeficiency. Impaired T cell function predisposes patients to this infection. Copyright David Clark.

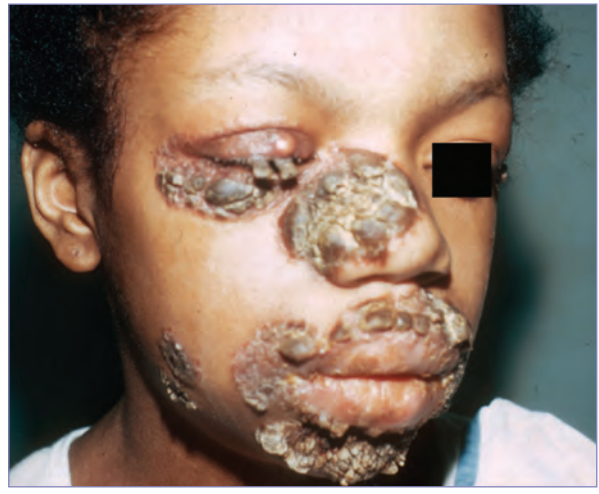


Image 25.17
An immunocompromised 5-year-old boy with multiple *Candida* granulomatous lesions, a rare response to an invasive cutaneous infection. These crusted, verrucous plaques and hornlike projections require systemic candidicidal agents for eradication or palliation. Courtesy of George Nankervis, MD.

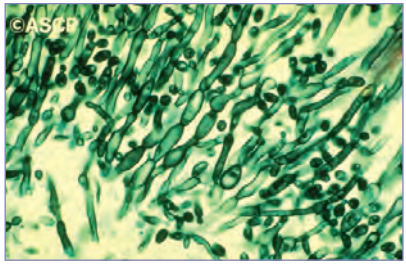


Image 25.18
Histopathologic features of *Candida albicans* infection. Pseudohyphae and true hyphae (methenamine silver stain) found in a tissue biopsy. Copyright American Society for Clinical Pathology.

Image 25.19
Sabhi agar plate culture of the fungus *Candida albicans* grown at 20°C (68°F). Courtesy of Centers for Disease Control and Prevention.

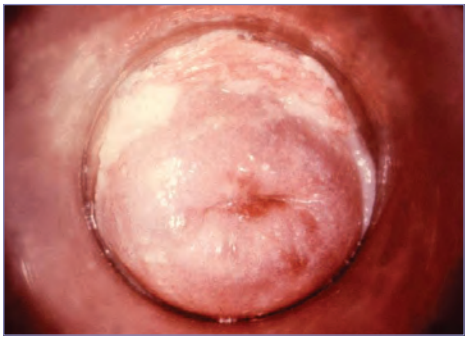


Image 25.20
This girl presented with *Candida* infection of the cervix. *Candida albicans* lives in or on numerous parts of the body as normal flora. However, when an imbalance occurs, such as when antibiotics are administered, *C albicans* can multiply, resulting in a mucosal or skin infection. Courtesy of Centers for Disease Control and Prevention.

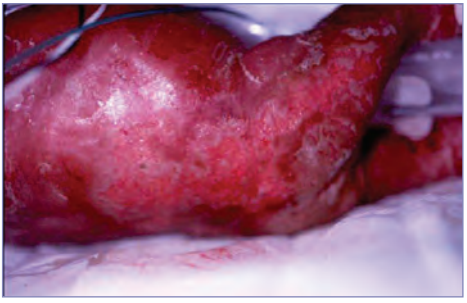


Image 25.21
Photograph of a very low birth weight neonate who developed invasive fungal dermatitis of the back caused by *Candida albicans*. This is an uncommon presentation that is often accompanied by disseminated infection. The diagnosis is established by skin biopsy that reveals invasion of the yeast into the dermis and culture that grows the yeast on routine culture media within 2 to 4 days. Courtesy of Carol J. Baker, MD, FAAP.

CHAPTER 26

Chancroid and Cutaneous Ulcers

CLINICAL MANIFESTATIONS

Chancroid is an acute ulcerative disease of the genitalia that occurs primarily in sexually active adolescents and adults. An ulcer begins as an erythematous papule that becomes pustular and erodes over several days, forming a sharply demarcated, somewhat superficial lesion with a serpiginous border. The base of the ulcer is friable and can be covered with a gray or yellow, purulent exudate. Single or multiple ulcers can be present. Unlike a syphilitic chancre, which is painless and indurated, the chancroid ulcer often is painful and nonindurated and can be associated with a painful, unilateral inguinal suppurative adenitis (bubo). Without treatment, ulcer(s) can spontaneously resolve, cause extensive erosion of the genitalia, or lead to scarring and phimosis, a painful inability to retract the foreskin.

In most males, chancroid manifests as a genital ulcer with or without inguinal tenderness; edema of the prepuce is common. In females, most lesions are at the vaginal introitus, and symptoms include dysuria, dyspareunia, vaginal discharge, pain on defecation, or anal bleeding. Constitutional symptoms are unusual.

In the tropics, cutaneous ulcers in children have long been attributed to *Treponema pallidum* subspecies *pertenue*, or yaws. Recently, the organism that causes chancroid was identified as a major cause of cutaneous ulcers in multiple countries with endemic yaws in equatorial Africa and the South Pacific. The vast majority of these cutaneous ulcers are on the legs. Ulcers attributable to yaws tend to be round and deep with indurated edges, a uniform color, and a granulating ulcer bed; those attributable to *Haemophilus ducreyi* are superficial with ragged edges and tend to be more painful. However, mixed infections are common, and the clinical presentations overlap.

ETIOLOGY

Chancroid and cutaneous ulcers are caused by *H ducreyi*, a gram-negative coccobacillus.

EPIDEMIOLOGY

Chancroid is a sexually transmitted infection associated with poverty, commercial sex work, and illicit drug use. Chancroid is endemic in Africa and the tropics but is rare in the United States, and when it does occur, it usually is associated with sporadic outbreaks. Coinfection with syphilis or herpes simplex virus (HSV) occurs in as many as 17% of patients. Chancroid is a well-established cofactor for transmission of human immunodeficiency virus (HIV). Because sexual contact is the major primary route of transmission, the diagnosis of chancroid ulcers, especially in the genital region or buttocks, in infants and young children is strong evidence of sexual abuse.

Cutaneous ulcers caused by *H ducreyi*, especially on the legs, in children in the tropics are not sexually transmitted and seem to be facilitated by poor hygiene, bed sharing, and close contact between infected individuals. Recent studies suggest that asymptomatic colonization, contaminated bed linens, and flies are environmental sources of *H ducreyi*. In some cases, *T pallidum* subspecies *pertenue* may initiate the ulcers, allowing *H ducreyi* to infect the skin. The acquisition of a leg ulcer attributable to *H ducreyi* in a child who visits a country with endemic infection should not be considered evidence of sexual abuse.

The **incubation period** is 1 to 10 days.

DIAGNOSTIC TESTS

Chancroid usually is diagnosed on the basis of clinical findings (1 or more painful genital ulcers with tender suppurative inguinal adenopathy) and by excluding other genital ulcerative diseases, such as syphilis, HSV infection, or lymphogranuloma venereum. Cutaneous ulcers can be diagnosed on the basis of clinical findings described, but clinical overlap and mixed infections with *H ducreyi* and *T pallidum* subspecies *pertenue* are common. Confirmation is made by isolation of *H ducreyi* from an ulcer or lymph node aspirate, although sensitivity is less than 80%. Because special culture media and conditions are required for isolation, laboratory personnel should be informed of the suspicion of *H ducreyi*. Approximately 30% to 40% of lymph node aspirates grow the organism. Polymerase

chain reaction assays can provide a specific diagnosis but are not available in most clinical laboratories.

TREATMENT

Genital strains of *H ducreyi* have been uniformly susceptible only to third-generation cephalosporins, macrolides, doxycycline, and quinolones. Recommended regimens include azithromycin, ceftriaxone, erythromycin, or ciprofloxacin. Patients with HIV infection may need prolonged therapy. Syndromic management for genital ulcers usually includes treatment for syphilis. Cutaneous ulcers should be treated with single-dose azithromycin for both *T pallidum* subspecies *pertenue* and *H ducreyi*.

Clinical improvement occurs 3 to 7 days after initiation of therapy, and healing is complete in approximately 2 weeks. Adenitis often is slow to resolve and can require needle aspiration or surgical incision. Patients should be reexamined 3 to 7 days after initiating therapy to verify healing. Slow clinical improvement and relapses can occur after therapy, especially in HIV-infected people. Close clinical follow-up is recommended; retreatment with the original regimen usually is effective in patients who experience a relapse.

Patients with chancroid should be evaluated for other sexually transmitted infections, including syphilis, HSV, chlamydia, gonorrhea, and HIV infection, at the time of diagnosis.

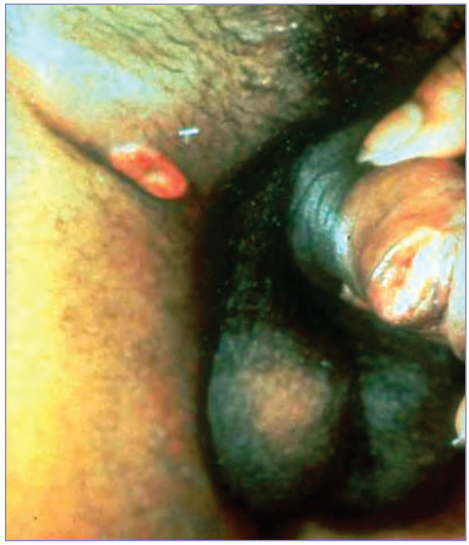


Image 26.1
Penile and inguinal chancroid caused by *Haemophilus ducreyi*, a gram-negative coccobacillus. This sexually transmitted infection is endemic in some areas of the United States and also occurs in discrete outbreaks. Courtesy of Centers for Disease Control and Prevention.

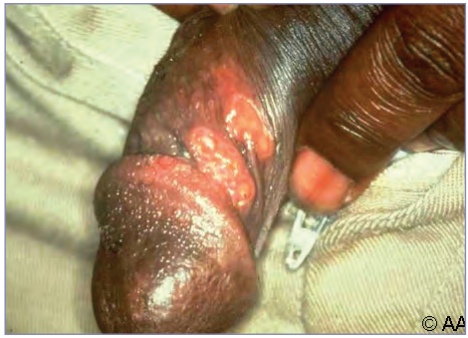


Image 26.2
Haemophilus ducreyi. Chancroid ulcerations of the penis in the same patient as in Image 26.1. Courtesy of Centers for Disease Control and Prevention.

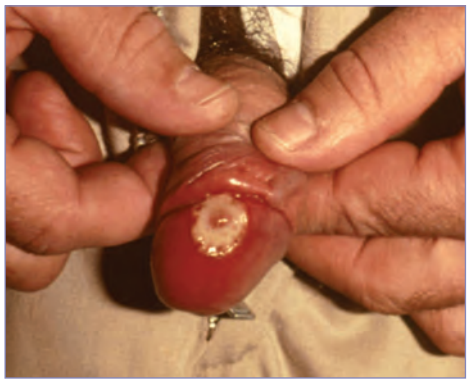


Image 26.4
Chancroid ulcer on the glans penis. Coinfection with syphilis or human herpesvirus occurs in as many as 10% of patients. Courtesy of Hugh Moffet, MD.

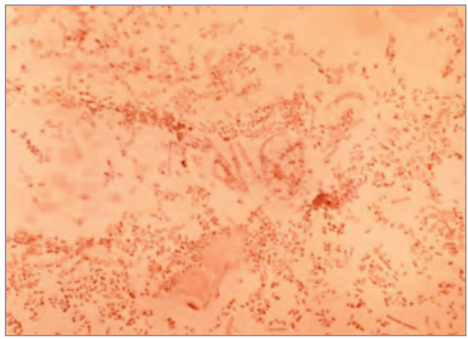


Image 26.6
Haemophilus ducreyi is a gram-negative coccobacillus, as shown in this preparation. Courtesy of Centers for Disease Control and Prevention.

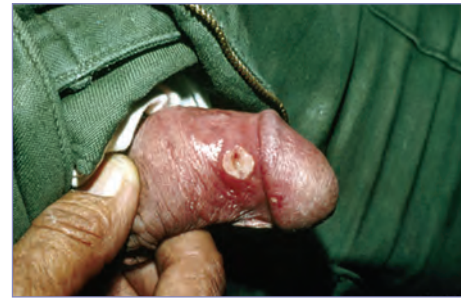


Image 26.3
Ulcerative chancroid lesions with inflammation of the shaft and glans penis caused by *Haemophilus ducreyi*. Chancroid lesions are irregular in shape, painful, and soft (nonindurated) to touch. Courtesy of Hugh Moffet, MD.

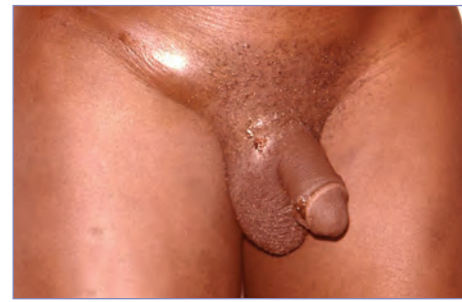


Image 26.5
This adolescent black male presented with a chancroid lesion of the groin and penis affecting the ipsilateral inguinal lymph nodes. First signs of infection typically appear 3 to 5 days after exposure, although symptoms can take up to 2 weeks to appear. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 27

Chikungunya

CLINICAL MANIFESTATIONS

The majority of people (72%–97%) infected with chikungunya virus become symptomatic. The disease most often is characterized by acute onset of high fever (typically >39°C [102°F]) and polyarthralgia. Other symptoms may include headache, myalgia, arthritis, conjunctivitis, nausea, vomiting, or maculopapular rash. Fever typically lasts for several days to a week and can be biphasic. Rash usually occurs after onset of fever and typically involves the trunk and extremities, but the palms, soles, and face may be affected. Joint symptoms often are severe and debilitating, usually are bilateral and symmetrical, and most commonly occur in the hands and feet but can affect more proximal joints. Clinical laboratory findings can include lymphopenia, thrombocytopenia, elevated creatinine, and elevated hepatic transaminases. Acute symptoms typically resolve within 7 to 10 days. Rare complications include uveitis, retinitis, myocarditis, hepatitis, nephritis, bullous skin lesions, hemorrhage, meningoencephalitis, myelitis, Guillain-Barré syndrome, and cranial nerve palsies. In infants, acrocyanosis without hemodynamic instability, symmetrical vesicobullous lesions, and edema of the lower extremities may occur. People at risk for severe disease include neonates exposed perinatally, older adults (eg, ≥65 years), and people with underlying medical conditions (eg, hypertension, diabetes, cardiovascular disease). Some patients may have relapse of rheumatologic symptoms (polyarthralgia, polyarthritis, and tenosynovitis) in the months following acute illness. Studies report variable proportions of patients with persistent joint pains for months to years. Mortality is rare.

ETIOLOGY

Chikungunya virus is a single-stranded RNA virus in the genus *Alphavirus* and *Togaviridae* family.

EPIDEMIOLOGY

Chikungunya virus primarily is transmitted to humans through the bites of infected mosquitoes, predominantly *Aedes aegypti* and *Aedes albopictus.* Humans are the primary host during epidemics. Bloodborne transmission is possible; cases have been documented among laboratory personnel handling infected blood and a health care worker drawing blood from an infected patient. Rare in utero transmission has been documented, mostly during the second trimester. Intrapartum transmission also has been documented when the mother was viremic around the time of delivery.

Prior to 2013, outbreaks of chikungunya infection were reported from countries in Africa, Asia, Europe, and the Indian and Pacific Oceans. In late 2013, chikungunya virus was found for the first time in the Americas on islands in the Caribbean. The virus then spread rapidly throughout the Americas, with local transmission reported from 44 countries and territories and more than 1 million suspected cases reported by the end of 2014. In the United States, widespread outbreaks occurred in Puerto Rico and the US Virgin Islands in 2014. Eleven locally transmitted cases were reported in Florida in 2014 and one locally transmitted case was reported in Texas in 2015.

The **incubation period** typically is between 3 and 7 days (range, 1 to 12 days).

DIAGNOSTIC TESTS

Preliminary diagnosis is based on the patient's clinical features, places and dates of travel, and activities. Laboratory diagnosis generally is accomplished by testing serum to detect virus, viral nucleic acid, or virus-specific immunoglobulin (Ig) M and neutralizing antibodies. During the first week after onset of symptoms, chikungunya virus infection often can be diagnosed by performing reverse transcriptase-polymerase chain reaction (RT-PCR) on serum. Chikungunya virus-specific IgM and neutralizing antibodies normally develop toward the end of the first week of illness. A plaque-reduction neutralization test can be performed to measure virus-specific neutralizing antibodies and to discriminate between cross-reacting antibodies (eg, Mayaro and o'nyong-nyong viruses). IgM antibodies usually persist for 30 to 90 days, but longer persistence has been documented. A positive IgM test result on serum occasionally may reflect a past infection. Immunohistochemical staining can detect specific viral antigen in fixed tissue.

Routine molecular and serologic testing for chikungunya virus is performed at state health departments and the Centers for Disease Control and Prevention (CDC). Plaque-reduction neutralization tests and immunohistochemical staining are performed at CDC and selected other reference laboratories.

TREATMENT

There is no antiviral treatment available for chikungunya. The primary treatment is supportive care and includes rest, fluids, analgesics, and antipyretics. In areas where dengue is endemic, acetaminophen is the preferred treatment for fever and joint pain until a dengue diagnosis is excluded to reduce the risk of hemorrhagic complications. Patients with persistent joint pain may benefit from the use of nonsteroidal anti-inflammatory drugs, corticosteroids, and physiotherapy.

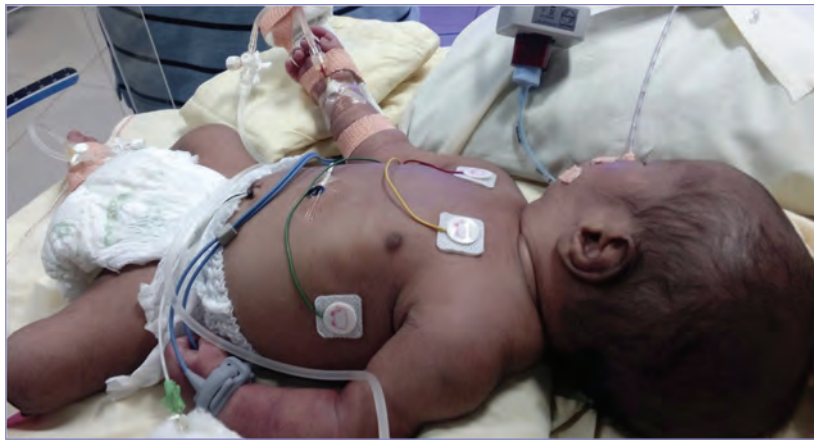


Image 27.1
A newborn with chikungunya. Appearance on day 3 of admission shows hyperpigmentation of the skin. Reprinted with permission from Reddy VS, Jinka DR. A case of neonatal thrombocytopenia and seizures: diagnostic value of hyperpigmentation. *NeoReviews.* 2018;19(8):e502–e506.

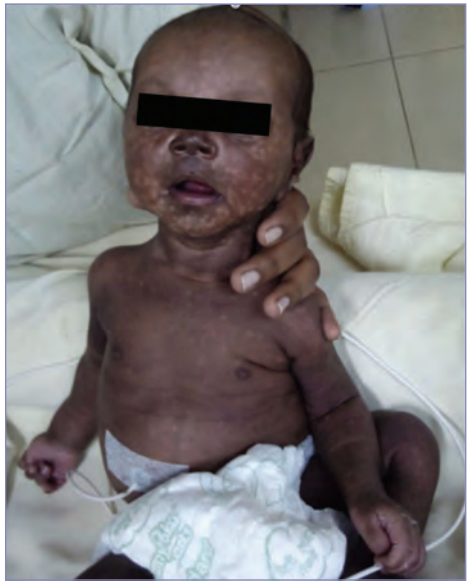


Image 27.2
Generalized hyperpigmentation of chikungunya is shown, with a distinctly prominent pigmentation of the patient's nose. Reprinted with permission from Reddy VS, Jinka DR. A case of neonatal thrombocytopenia and seizures: diagnostic value of hyperpigmentation. *NeoReviews.* 2018;19(8):e502–e506.

CHAPTER 28

Chlamydia pneumoniae

CLINICAL MANIFESTATIONS

Patients may be asymptomatic or mildly to moderately ill with a variety of respiratory tract diseases caused by *Chlamydia pneumoniae*, including pneumonia, acute bronchitis, prolonged cough, and less commonly, pharyngitis, laryngitis, otitis media, and sinusitis. In some patients, a sore throat precedes the onset of cough by a week or more. The clinical course can be biphasic, culminating in atypical pneumonia. *C pneumoniae* can present as severe community-acquired pneumonia in immunocompromised hosts and has been associated with acute exacerbation of respiratory symptoms in patients with asthma, cystic fibrosis, and acute chest syndrome in children with sickle cell disease.

Physical examination may reveal nonexudative pharyngitis, pulmonary rales, and bronchospasm. Chest radiography may reveal a variety of findings ranging from pleural effusion and bilateral infiltrates to a single patchy subsegmental infiltrate. Illness can be prolonged and cough can persist for 2 to 6 weeks or longer.

ETIOLOGY

C pneumoniae is an obligate intracellular bacterium for which entry into mucosal epithelial cells is necessary for intracellular survival and growth. It exists in both an infectious nonreplicating extracellular form called an elementary body and a replicating intracellular form called a reticulate body.

EPIDEMIOLOGY

C pneumoniae infection is presumed to be transmitted from person to person via infected respiratory tract secretions. It is unknown whether there is an animal reservoir. The disease occurs worldwide, but in tropical and less developed regions, disease occurs earlier in life than in industrialized countries in temperate climates. The timing of initial infection peaks between 5 and 15 years of age; however, studies have shown that the prevalence rate of infection in children beyond early infancy is similar to that in adults. In the United States, approximately 50% of adults have *C pneumoniae*-specific serum antibody by 20 years of age, indicating previous infection by the organism. Recurrent infection is common, especially in adults. Clusters of infection have been reported in groups of children and adults. There is no evidence of seasonality.

The mean **incubation period** is 21 days.

DIAGNOSTIC TESTS

Serologic testing has been the primary laboratory means of diagnosis of *C pneumoniae* infection but is problematic. The microimmunofluorescent antibody test is the most sensitive and specific serologic test for acute infection; however, it may be less sensitive in children. A fourfold increase in immunoglobulin (Ig) G titer between acute and convalescent sera or an IgM titer of 1:16 or greater are evidence of acute infection; use of acute and convalescent titers is preferred to a single elevated IgM titer. Use of a single IgG titer in diagnosis of acute infection is not recommended, because during primary infection, IgG antibody may not appear until 6 to 8 weeks after onset of illness during primary infection and increases within 1 to 2 weeks with reinfection. In primary infection, IgM antibody appears approximately 2 to 3 weeks after onset of illness, but caution is advised when interpreting a single IgM antibody titer for diagnosis, because a single result can be either falsely positive because of cross-reactivity with other *Chlamydia* species or falsely negative in cases of reinfection. Early antimicrobial therapy may suppress antibody response. Past exposure is indicated by a stable IgG titer of 1:16 or greater.

C pneumoniae is difficult to culture but can be isolated from swab specimens obtained from the nasopharynx or oropharynx or from sputum, bronchoalveolar lavage, or tissue biopsy specimens. Specimens should be placed into appropriate transport media and stored at 4°C until inoculation into cell culture; specimens that cannot be processed within 24 hours should be frozen and stored at –70°C. A positive culture is confirmed by propagation of the isolate or a positive polymerase chain reaction (PCR) assay result. Nasopharyngeal shedding can occur for months after acute disease, even with treatment.

Because of the difficulty of accurately detecting *C pneumoniae* via culture or serologic testing, several types of PCR assays, including multiplex, hybridization probe methods, and fluorescent probe-based method, have been developed. Sensitivity and specificity of these different PCR techniques remain largely unknown. Multiplex PCR assays have been cleared by the US Food and Drug Administration for the diagnosis of *C pneumoniae* using nasopharyngeal swab samples. The tests appear to have high sensitivity and specificity.

TREATMENT

Most respiratory tract infections thought to be caused by *C pneumoniae* are treated empirically. For suspected *C pneumoniae* infections, treatment with macrolides (eg, azithromycin, erythromycin, or clarithromycin) is recommended. Doxycycline can be used for short durations (ie, 21 days or less) without regard to patient age. Newer fluoroquinolones (levofloxacin and moxifloxacin) are alternative drugs for patients who are unable to tolerate macrolide antibiotic agents.

Duration of therapy typically is 10 to 14 days for erythromycin, clarithromycin, tetracycline, or doxycycline. With azithromycin, the treatment duration typically is 5 days.

CHAPTER 29

Chlamydia psittaci

(Psittacosis, Ornithosis, Parrot Fever)

CLINICAL MANIFESTATIONS

Psittacosis (ornithosis) is an acute respiratory tract infection with systemic symptoms and signs that often include fever, nonproductive cough, dyspnea, headache, myalgia, chills, and malaise. Less common symptoms include pharyngitis, diarrhea, constipation, nausea and vomiting, abdominal pain, arthralgia, rash, and altered mental status. Extensive interstitial pneumonia can occur, with radiographic changes characteristically more severe than would be expected from physical examination findings. Rarely, infection with *Chlamydia psittaci* has been reported to affect organ systems other than the respiratory tract, resulting in conditions including endocarditis, myocarditis, pericarditis, dilated cardiomyopathy, thrombophlebitis, nephritis, hepatitis, cranial nerve palsy (including sensorineural hearing loss), transverse myelitis, meningitis, and encephalitis. Infection in pregnancy may be life-threatening to the mother and cause fetal loss.

ETIOLOGY

C psittaci is an obligate intracellular bacterial pathogen that exists in 2 forms. The extracellular form is called an elementary body (EB) and is infectious. The EB invades the epithelial host cell and transforms to a replicating reticulate body (RB) within a membrane-bound vesicle called an inclusion. Reticulate bodies use host cell nutrients to multiply and later revert to infectious EBs that are released from the host cell to infect neighboring cells.

EPIDEMIOLOGY

Birds are the major reservoir of *C psittaci*. The term **psittacosis** commonly is used, although the term **ornithosis** more accurately describes the potential for nearly all domestic and wild birds to spread this infection, not just psittacine birds (eg, parakeets, parrots, macaws, cockatoos). In the United States, psittacine birds and turkeys have been reported as sources of human disease. Importation and illegal trafficking of exotic birds may be associated with disease in humans, because shipping, crowding, and other stress factors may increase shedding of the organism among birds with latent infection. Infected birds, whether they appear healthy or are obviously ill, may transmit the organism. Infection usually is acquired by direct contact or inhaling aerosolized excrement or respiratory secretions from the eyes or beaks of infected birds. Handling of plumage and mouth-to-beak contact are the modes of exposure described most frequently, although transmission has been reported through exposure to aviaries, bird exhibits, and lawn mowing. Excretion of *C psittaci* from birds may be intermittent or continuous for weeks or months. Pet owners and workers at poultry slaughter plants, poultry farms, and pet shops are at increased risk of infection. Laboratory personnel working with *C psittaci* also are at risk. Psittacosis is worldwide in distribution and tends to occur sporadically in any season.

The **incubation period** usually is 5 to 15 days but may be longer.

DIAGNOSTIC TESTS

The diagnosis of *C psittaci* disease historically has been based on clinical presentation and a positive serologic test result using microimmunofluorescence (MIF) with paired sera. Although the MIF generally is more sensitive and specific than complement fixation (CF) tests, MIF still displays cross-reactivity with other *Chlamydia* species. Because of this, a titer less than 1:128 should be interpreted with caution. Paired acute- and convalescent-phase serum specimens obtained at least 2 to 4 weeks apart should be obtained and performed simultaneously within a single laboratory to ensure consistency of results. Treatment with antimicrobial agents may suppress the antibody response, and in such cases, a third serum sample obtained 4 to 6 weeks after the acute-phase sample may be useful in confirming the diagnosis. Although serologic testing is more commonly used and available than molecular testing, results can often be ambiguous, subjective in their interpretation, and misleading because of the inherent limitations of this approach. Nucleic acid amplification tests (NAATs) have been developed that can distinguish *C psittaci* from other chlamydial species. Real-time PCR assays are now available within specialized laboratories

(**www.cdc.gov/laboratory/specimen-submission/detail.html?CDCTestCode=CDC-10153**). Because the organism is difficult to recover in culture and laboratory-acquired cases have been reported, culture generally is not recommended and should be attempted only by experienced personnel in laboratories in which strict containment measures to prevent spread of the organism are used.

TREATMENT

Doxycycline is the drug of choice and can be used for short durations (ie, 21 days or less) without regard to patient age. Erythromycin and azithromycin are alternative agents and are recommended for pregnant women. Therapy should continue for 10 to 14 days after fever abates. Most *C psittaci* infections are responsive to antimicrobial agents within 1 to 2 days. In patients with severe infection, intravenous doxycycline may be considered.

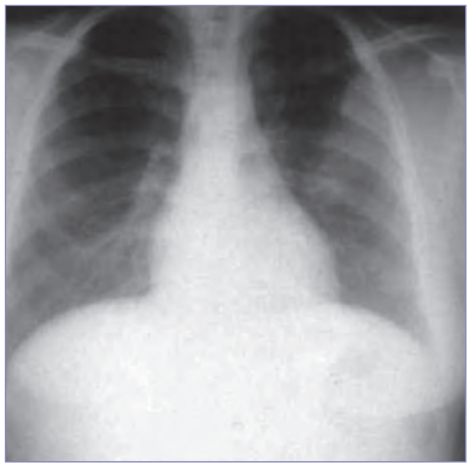


Image 29.1
Chlamydophila psittaci pneumonia in a 16-year-old girl with a cough of 3 weeks' duration. The family had several parrots in the home that were purchased from a roadside stand near the Texas-Mexico border. Interstitial pneumonia, most prominent in the lower lobe of the left lung, is shown. Complement fixation titer for *C psittaci* is 1:128. Copyright David Waagner.

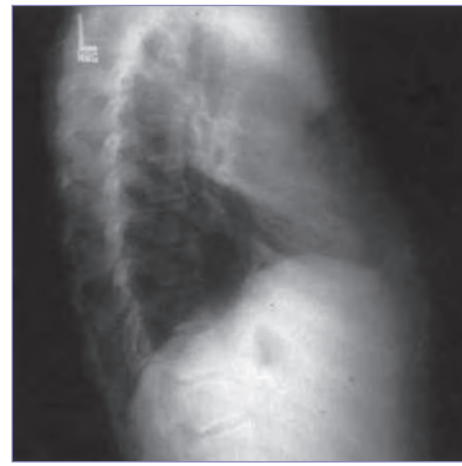


Image 29.2
Lateral chest radiograph of the patient in Image 29.1. Copyright David Waagner.

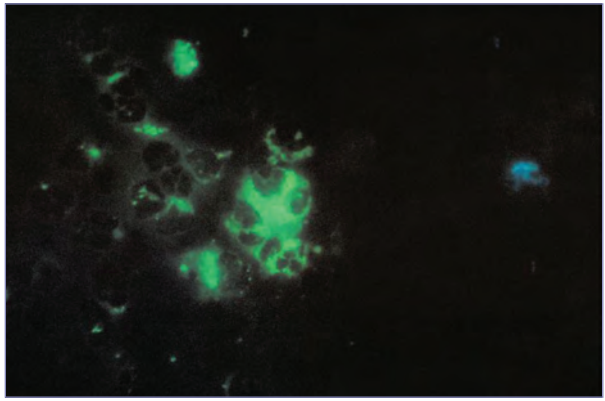


Image 29.3
This direct fluorescent antibody stained mouse brain impression smear reveals the presence of the bacterium *Chlamydophila psittaci.* Psittacosis is acquired by inhaling dried secretions from birds infected with *C psittaci.* Although all birds are susceptible, pet birds and poultry are most frequently involved in transmission to humans. Courtesy of Centers for Disease Control and Prevention/Vester Lewis, MD.

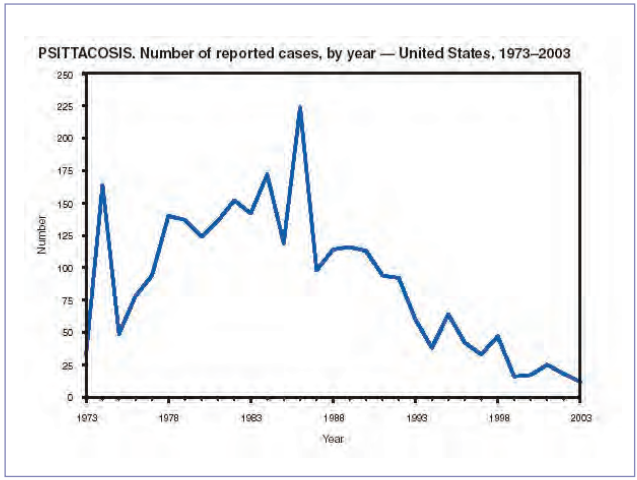


Image 29.4
Number of US cases of psittacosis reported per year, 1973 through 2003. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 30

Chlamydia trachomatis

CLINICAL MANIFESTATIONS

Chlamydia trachomatis is associated with a range of clinical manifestations, including neonatal conjunctivitis, nasopharyngitis, and pneumonia in young infants as well as genital tract infection, lymphogranuloma venereum (LGV), and trachoma in children and adolescents.

- **Neonatal chlamydial conjunctivitis** is characterized by ocular congestion, edema, and discharge developing a few days to several weeks after birth and lasting for 1 to 2 weeks and sometimes longer. In contrast to trachoma, scars and pannus formation are rare.
- **Pneumonia** in young infants usually is an afebrile illness of insidious onset occurring between 2 and 19 weeks after birth. A repetitive staccato cough, tachypnea, and rales in an afebrile 1-month-old infant are characteristic but not always present. Wheezing is uncommon. Hyperinflation usually accompanies infiltrates seen on chest radiographs. Nasal stuffiness and otitis media may occur. Untreated disease can linger or recur. Severe chlamydial pneumonia has occurred in infants and some immunocompromised adults.
- **Genitourinary tract** manifestations, such as vaginitis in prepubertal girls; urethritis, cervicitis, endometritis, salpingitis, proctitis, and perihepatitis (Fitz-Hugh-Curtis syndrome) in postpubertal females; urethritis, epididymitis, and proctitis in males; and reactive arthritis (with the classic triad, formerly known as Reiter syndrome, consisting of arthritis, urethritis, and bilateral conjunctivitis) can occur. Infection can persist for months to years. Reinfection is common. In postpubertal females, chlamydial infection can progress to pelvic inflammatory disease and can result in ectopic pregnancy, infertility, or chronic pelvic pain.
- **LGV** classically is an invasive lymphatic infection with an initial ulcerative lesion on the genitalia accompanied by tender, suppurative inguinal or femoral lymphadenopathy that typically is unilateral. The ulcerative lesion often has resolved by the time the patient seeks care. Proctocolitis may occur in women or men who engage in receptive anal intercourse. Symptoms can resemble those of inflammatory bowel disease, including mucoid or hemorrhagic rectal discharge, constipation, tenesmus, and/or anorectal pain. Stricture or fistula formation can follow severe or inadequately treated infection.
- **Trachoma** is a chronic follicular keratoconjunctivitis with neovascularization of the cornea that results from repeated and chronic infection. Blindness secondary to extensive local scarring and inflammation occurs in 1% to 15% of people with trachoma.

ETIOLOGY

C trachomatis is an obligate intracellular bacterial agent with at least 18 serologic variants (serovars) divided between the following biologic variants (biovars): oculogenital (serovars A–K) and LGV (serovars L1, L2, and L3). Trachoma usually is caused by serovars A through C, and genital and perinatal infections are caused by B and D through K.

EPIDEMIOLOGY

C trachomatis is the most common reportable sexually transmitted infection (STI) in the United States, with high rates among sexually active adolescents and young adult females. A significant proportion of patients are asymptomatic, providing an ongoing reservoir for infection. Prevalence of the organism consistently is highest among adolescent and young adult females. Among sexually active 14- to 24-year-old females participating in the 2007–2012 National Health and Nutrition Examination Survey, the estimated prevalence was 4.7%. Racial disparities are significant. Among sexually active females 14 to 24 years of age, the estimated prevalence among non-Hispanic black females (13.5%) was higher than the estimated prevalence among Mexican American females (4.5%) and non-Hispanic white females (1.8%). Among men who have sex with men (MSM) screened for rectal chlamydial infection, positivity ranges from 11% to 20%. Oculogenital serovars of *C trachomatis* can be transmitted from the genital tract of infected mothers to their infants during birth. Acquisition occurs in

approximately 50% of infants born vaginally to infected mothers and in some infants born by cesarean delivery with membranes intact. The risk of conjunctivitis is 25% to 50%, and the risk of pneumonia is 5% to 30% in infants who contract *C trachomatis.* The nasopharynx is the anatomic site most commonly infected.

Genital tract infection in adolescents and adults is sexually transmitted. The possibility of sexual abuse always should be considered in prepubertal children beyond infancy who have vaginal, urethral, or rectal chlamydial infection. Sexual abuse is not limited to prepubertal children, and chlamydial infections can result from sexual abuse/assault in postpubertal adolescents as well.

Asymptomatic infection of the nasopharynx, conjunctivae, vagina, and rectum can be acquired at birth. Nasopharyngeal cultures have been observed to remain positive for as long as 28 months, and vaginal and rectal cultures have remained positive for more than 1 year from infants with infection acquired at birth. Infection is not known to be communicable among infants and children. The degree of contagiousness of pulmonary disease is unknown but seems to be low.

LGV biovars are worldwide in distribution but particularly are prevalent in tropical and subtropical areas. Although disease occurs rarely in the United States, outbreaks of LGV proctocolitis have been reported among MSM. Infection often is asymptomatic in females. Perinatal transmission is rare. LGV is infectious during active disease. Little is known about the prevalence or duration of asymptomatic carriage.

Although rarely observed in the United States since the 1950s, trachoma is the leading infectious cause of blindness worldwide, causing up to 3% of the world's blindness. Trachoma is transmitted by transfer of ocular discharge and it generally is confined to poor populations in resource-limited nations in Africa, the Middle East, Asia, and Latin America; the Pacific Islands; and remote aboriginal communities in Australia. Predictors of scarring and blindness for trachoma include increasing age and constant, severe trachoma.

The **incubation period** of chlamydial illness is variable, depending on the type of infection, but usually is at least 1 week.

DIAGNOSTIC TESTS

Among **postpubescent individuals,** nucleic acid amplification tests (NAATs) are the most sensitive *C trachomatis* tests and are recommended for laboratory diagnosis. Older, culture-independent methods including DNA probe, direct fluorescent antibody (DFA) assay, or enzyme immunoassay have inferior sensitivity and specificity characteristics and are not recommended for *C trachomatis* testing. NAATs are cleared for testing vaginal (provider or patient collected), endocervical, and male intraurethral swabs; male and female first-catch urine specimens placed in appropriate transport devices are available, as is liquid cytology. Most of these assays are designed to detect *C trachomatis* and *N gonorrhoeae*. Package inserts for individual NAAT products must be reviewed, however, because the particular specimens approved for use with each test may vary. A vaginal swab is the preferred means of screening females and urine is the preferred means for screening males for *C trachomatis* infection by NAAT. Female urine also is an acceptable NAAT specimen but may have slightly reduced performance when compared with cervical or vaginal swab specimens. NAATs have not been FDA-cleared for use with rectal, pharyngeal, or conjunctival swab specimens. The performance of a NAAT on a rectal swab specimen is the preferred approach for testing MSM presenting with proctocolitis. *C trachomatis* testing of pharyngeal specimens from asymptomatic postpubescent individuals generally is not recommended.

Sensitive and specific methods used to diagnose **neonatal chlamydial ophthalmia** include both cell culture-independent methods and nonculture tests (eg, DFA and NAAT). DFA is the only culture-independent method that is FDA approved for the detection of chlamydia from conjunctival swab specimens; NAATs are not FDA cleared for the detection of chlamydia from conjunctival swab specimens.

For diagnosing **infant pneumonia** caused by *C trachomatis*, specimens for chlamydial testing should be collected from the posterior

nasopharynx. Isolation of the organism in cell culture is the definitive standard diagnostic test for chlamydial pneumonia. Culture-independent tests (eg, DFA and NAAT) can be used. DFA is the only culture-independent FDA-approved test for the detection of *C trachomatis* from nasopharyngeal specimens. DFA testing of nasopharyngeal specimens has a lower sensitivity and specificity than culture. Tracheal aspirates and lung biopsy specimens, if collected, should be tested for *C trachomatis* by cell culture.

In the **evaluation of prepubescent children for possible sexual assault,** the CDC recommends culture for *C trachomatis* of a swab specimen collected from the rectum in both boys and girls and from the vagina in girls. A meatal swab specimen should be obtained from boys for chlamydia testing if urethral discharge is present. NAATs are not FDA cleared for this indication. CDC recommends that NAATs can be used for detection of *C trachomatis* either alone or in addition to culture in vaginal specimens or urine from prepubescent girls. Culture remains the method of choice for meatal swab specimens from boys and from non-urogenital sites for both boys and girls. Thus, it is important that clinical laboratories maintain the capability to culture for *C trachomatis* to comply with these recommendations.

Serologic testing has little, if any, value in diagnosing uncomplicated genital *C trachomatis* infection. In **children with pneumonia,** an acute microimmunofluorescent (MIF) serum titer of *C trachomatis*-specific immunoglobulin (Ig) M of 1:32 or greater is diagnostic. Diagnosis of **LGV** can be supported but not confirmed by a positive result (ie, titer >1:64) on a complement-fixation test for *Chlamydia* or a high titer (typically >1:256, but this can vary by laboratory) on a MIF antibody test for *C trachomatis.* However, serologic test interpretation for LGV is not standardized, tests have not been validated for clinical proctitis presentations, and *C trachomatis* serovar-specific serologic tests are not widely available.

Diagnosis of genitourinary tract chlamydial disease in a child should prompt examination for **other STIs,** including syphilis, gonorrhea, trichomoniasis, and human immunodeficiency virus (HIV) infection, and investigation of sexual abuse/assault. In the case of an infant, because cultures can be positive for at least 12 months after infection acquired at birth, evaluation of the mother also is advisable.

Diagnosis of **ocular trachoma** usually is made clinically in countries with endemic infection.

TREATMENT

- **Infants with chlamydial conjunctivitis or pneumonia** are treated with oral erythromycin base or ethylsuccinate for 14 days or with azithromycin for 3 days. Follow-up of infants treated with either drug is recommended to determine whether initial treatment was effective. A diagnosis of *C trachomatis* infection in an infant should prompt treatment of the mother and her sexual partner(s). The need for treatment of infants can be avoided by screening pregnant females to detect and treat *C trachomatis* infection before delivery. Neonates with documented chlamydial infection should be evaluated for possible gonococcal infection but should not be treated with ceftriaxone unless the diagnostic assessment is positive for *N gonorrhoeae.* An association between orally administered erythromycin and azithromycin and infantile hypertrophic pyloric stenosis (IHPS) has been reported in infants younger than 6 weeks. Infants treated with either of these antimicrobial agents should be followed for signs of IHPS. Infants born to mothers known to have untreated chlamydial infection are at high risk of infection, but prophylactic antimicrobial treatment is not indicated.

- For uncomplicated ***C trachomatis*** **anogenital tract infection in adolescents or adults,** oral doxycycline for 7 days or azithromycin in a single oral dose is recommended. Alternatives include oral erythromycin base, erythromycin ethylsuccinate, ofloxacin, or levofloxacin, each for 7 days. Erythromycin may be less efficacious than azithromycin or doxycycline because of gastrointestinal tract adverse effects and frequent dosing. Levofloxacin and ofloxacin are more expensive and offer no advantage in the dosage regimen. **For children who weigh <45 kg,** the recommended regimen is oral erythromycin base or ethylsuccinate for

14 days. Data are limited on the effectiveness and optimal dose of azithromycin for treatment of chlamydial infections in infants and children who weigh <45 kg. **For children who weigh ≥45 kg but who are younger than 8 years,** the recommended regimen is azithromycin orally, in a single dose. **For children 8 years and older,** the recommended regimen is single dose azithromycin or doxycycline for 7 days. **For pregnant females,** the recommended treatment is azithromycin. Amoxicillin or erythromycin base for 7 days are alternative regimens. Doxycycline, ofloxacin, and levofloxacin are contraindicated during pregnancy.

- ***Follow-up Testing.*** Test of cure is not recommended for nonpregnant adult or adolescent patients treated for uncomplicated chlamydial infection unless compliance is in question, symptoms persist, or reinfection is suspected. Reinfection is common after initial infection and treatment, and all infected adolescents and adults should be tested for *C trachomatis* in the next 3 months following initial treatment. If retesting at 3 months is not possible, patients should be retested when they next present for health care in the 12 months after initial treatment.
- For **LGV,** doxycycline for 21 days is the preferred treatment without regard to patient age. Erythromycin for 21 days is an alternative regimen. Azithromycin for 3 weeks probably is effective but has not been as well studied.
- Treatment of **trachoma** is azithromycin, orally, as a single dose as recommended by the World Health Organization for all people diagnosed with trachoma as well as for all of their household contacts.

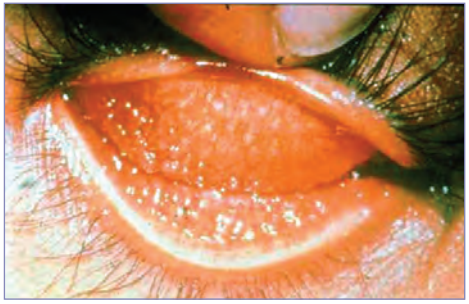


Image 30.1
Conjunctivitis in an infant due to *Chlamydia trachomatis*. The risk of neonatal conjunctivitis is 25% to 50% for infants of mothers who are infected and untreated. Copyright James Brien, DO.

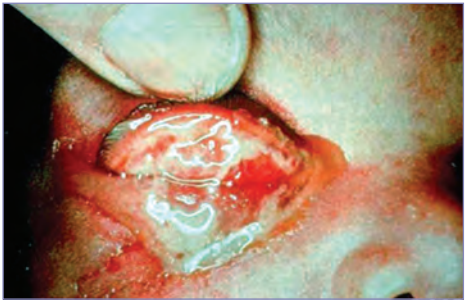


Image 30.2
Conjunctivitis due to *Chlamydia trachomatis*, the most common cause of ophthalmia neonatorum. This is the same infant as in Image 30.1.

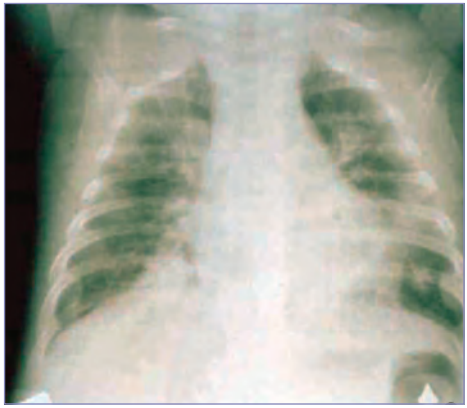


Image 30.3
Chlamydia trachomatis pneumonia, severe and bilateral, in a 5-week-old. Courtesy of Edgar O. Ledbetter, MD, FAAP.

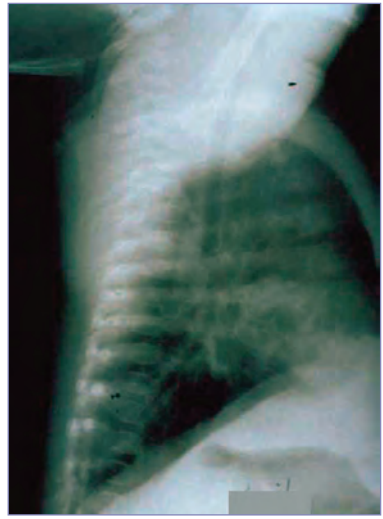


Image 30.4
Left lateral radiograph of the infant in Image 30.3 with *Chlamydia trachomatis* pneumonia. Note the characteristic hyperinflation. Courtesy of Edgar O. Ledbetter, MD, FAAP.

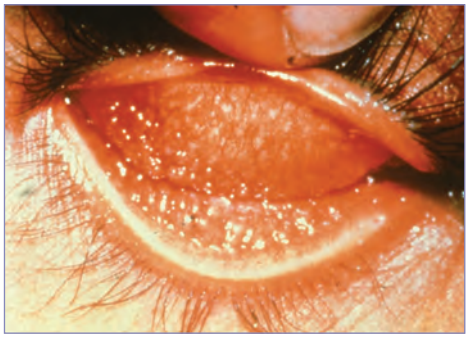


Image 30.5
Chlamydia trachomatis. Copyright James Brien, DO.

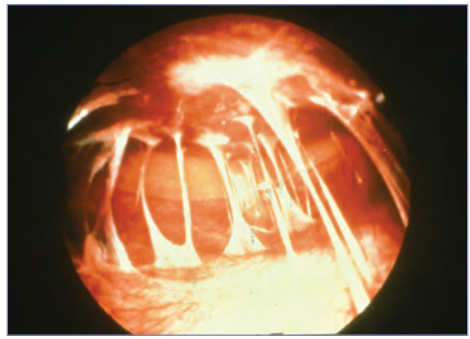


Image 30.6
Chlamydia trachomatis. Copyright James Brien, DO.

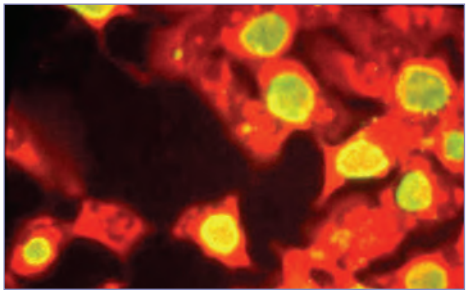


Image 30.7
Infected HeLa cells (fluorescent antibody stain). *Chlamydia trachomatis* is the most common reportable sexually transmitted infection in the United States, with high rates of infection among sexually active adolescents and young adults. Copyright Noni MacDonald, MD.

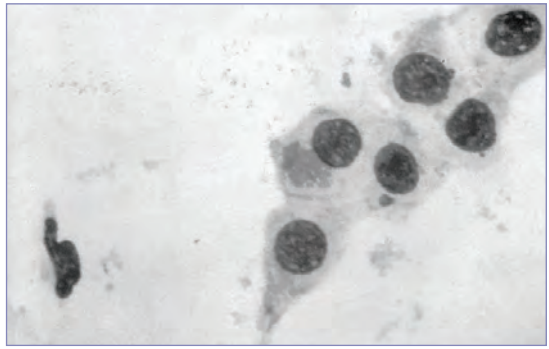


Image 30.8
Photomicrograph of *Chlamydia trachomatis* taken from a urethral scrape (iodine-stained inclusions in McCoy cell line, magnification ×200). Untreated, chlamydia can cause severe, costly reproductive and other health problems, including short- and long-term consequences (eg, pelvic inflammatory disease, infertility, potentially fatal tubal pregnancy).

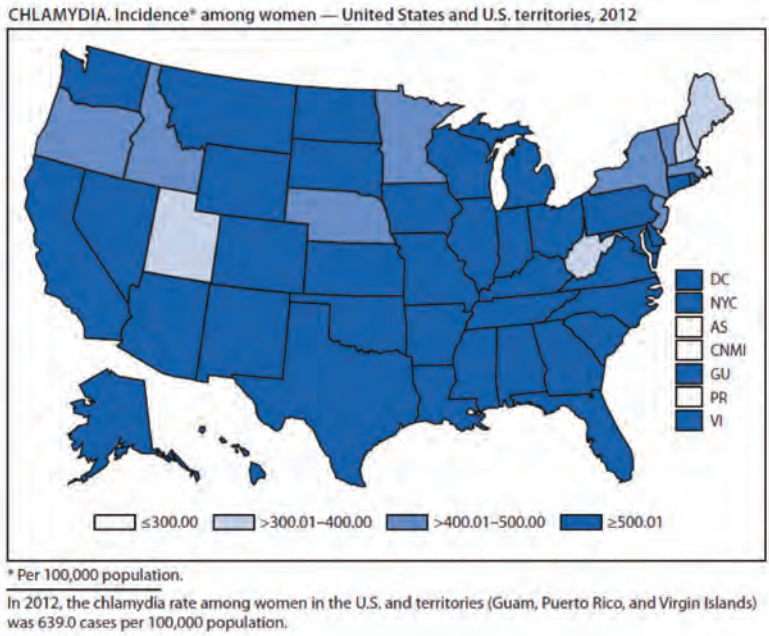


Image 30.9
Chlamydia. Incidence among women—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

CHAPTER 31

Botulism and Infant Botulism

(*Clostridium botulinum*)

CLINICAL MANIFESTATIONS

Botulism is a neuroparalytic disorder characterized by an acute, afebrile, symmetric, descending, flaccid paralysis. Paralysis is caused by blockade of neurotransmitter release at the voluntary motor and autonomic neuromuscular junctions. Four naturally occurring forms of human botulism exist: infant, foodborne, wound, and adult intestinal colonization. Iatrogenic botulism can result from injection of excess therapeutic botulinum toxin, and botulinum neurotoxins are considered a potential agent of bioterrorism. Symptoms of botulism can occur abruptly, within hours of exposure, or evolve gradually over several days and include diplopia, dysphagia, dysphonia, and dysarthria. Cranial nerve palsies are followed by symmetric, descending, flaccid paralysis of somatic musculature in patients who remain fully alert. Infant botulism, which occurs predominantly in infants younger than 6 months (range, 1 day to 12 months), is preceded by or begins with constipation and manifests as decreased movement, loss of facial expression, poor feeding, weak cry, diminished gag reflex, ocular palsies, loss of head control, and progressive descending generalized weakness and hypotonia. Sudden infant death could result from rapidly progressing infant botulism.

ETIOLOGY

Botulism occurs after absorption of botulinum toxin into the circulation from a mucosal or wound surface. Seven antigenic toxin types (A–G) of *Clostridium botulinum* are known. An eighth toxin type (H) has been reported, but its identity as a distinct serotype remains controversial. Non-*botulinum* species of *Clostridium* rarely may produce these neurotoxins and cause disease. The most common botulinum toxin serotypes associated with naturally occurring illness are types A, B, E, and rarely, F. Most cases of infant botulism result from toxin types A and B, but a few cases of types E and F have been caused by *Clostridium butyricum* (type E), *Clostridium botulinum* (type E), and *Clostridium baratii* (type F) (especially in very young infants). *C botulinum* spores are ubiquitous in soils and dust worldwide and have been isolated from the home environment and vacuum cleaner dust of infant botulism cases.

EPIDEMIOLOGY

Infant botulism (annual average, 125 laboratory-confirmed cases in 2011–2015; age range, 1 to 73 weeks; median age, 17.6 weeks) results after ingested spores of *C botulinum* or related neurotoxigenic clostridial species germinate, multiply, and produce botulinum toxin in the large intestine through transient colonization of the intestinal microflora. Cases may occur in breastfed infants at the time of first introduction of nonhuman milk substances; the source of spores usually is not identified. Honey has been identified as an avoidable source of spores. No case of infant botulism has been proven to be attributable to consumption of corn syrup. Rarely, intestinal botulism can occur in older children and adults, usually after intestinal surgery and exposure to antimicrobial agents.

Foodborne botulism (annual average, 15 cases per year in 2011–2014; age range, 8–87 years; median age, 40 years) results when food that carries spores of *C botulinum* is preserved or stored improperly under anaerobic conditions that permit germination, multiplication, and toxin production. Illness follows ingestion of the food containing preformed botulinum toxin. Home processing of foods is the most common cause of foodborne botulism in the United States, followed by rare outbreaks associated with commercially processed foods, restaurant-associated foods, and wine produced in prisons (“pruno” and “hooch”).

Wound botulism (annual average, 13 laboratory-confirmed cases in 2011–2014; age range, 5–66 years; median age, 46 years) results when *C botulinum* contaminates traumatized tissue, germinates, multiplies, and produces toxin. Gross trauma or crush injury can be a predisposing event. During the last decade, self-injection of contaminated black tar heroin has been associated with most cases.

Immunity to botulinum toxin does not develop in botulism. Botulism is not transmitted from person to person.

The usual **incubation period** for foodborne botulism is 12 to 48 hours (range, 6 hours–8 days); for infant botulism, it is estimated at 3 to 30 days from the time of ingestion of spores; and for wound botulism, it is 4 to 14 days from time of injury until onset of symptoms.

DIAGNOSTIC TESTS

A toxin neutralization bioassay in mice is used to detect botulinum toxin in serum, stool, enema fluid, gastric aspirate, or suspect foods. Enriched selective media is required to isolate *C botulinum* from stool and foods. The diagnosis of infant botulism is made by demonstrating botulinum toxin or botulinum toxin-producing organisms in feces or enema fluid or toxin in serum. Wound botulism is confirmed by demonstrating organisms in the wound or tissue or toxin in the serum. To increase the likelihood of diagnosis in foodborne botulism, all suspect foods should be collected, and serum and stool or enema specimens should be obtained from all people with suspected illness. In foodborne cases, serum specimens may be positive for toxin as long as 10 days after illness onset. Although toxin can be demonstrated in serum in some infants with botulism, stool is the best specimen for diagnosis; enema effluent also can be useful. Because results of laboratory bioassay testing may require several days, treatment with antitoxin should be initiated urgently for all forms of botulism on the basis of clinical suspicion. The most prominent electromyographic finding is an incremental increase of evoked muscle potentials at high-frequency nerve stimulation (20–50 Hz), but its absence does not exclude the diagnosis.

TREATMENT

Meticulous Supportive Care

Meticulous supportive care, in particular respiratory and nutritional support, constitutes a fundamental aspect of therapy in all forms of botulism. Recovery from botulism may take weeks to months.

Antitoxin for Infant Botulism

Human-derived antitoxin should be administered immediately. Human Botulism Immune Globulin for intravenous use (BIG-IV; BabyBIG) is licensed by the US Food and Drug Administration (FDA) for treatment of infant botulism caused by *C botulinum* type A or type B. BabyBIG significantly decreases days of mechanical ventilation, days of intensive care unit stay, and total length of hospital stay by almost 1 month and is cost saving. BabyBIG is first-line therapy for naturally occurring infant botulism. Equine-derived heptavalent botulinum antitoxin (BAT) is available through the Centers for Disease Control and Prevention and has been used to treat type F infant botulism patients, where the antitoxin is not contained in BabyBIG.

Antitoxin for Noninfant Forms of Botulism

Immediate administration of antitoxin is the key to successful therapy, because antitoxin treatment ends the toxemia and stops further uptake of toxin. However, because botulinum neurotoxin becomes internalized in the nerve ending, administration of antitoxin does not reverse paralysis. If foodborne botulism is suspected, the state health department should be contacted immediately to discuss and report the case. BAT contains antitoxin against all 7 (A–G) botulinum toxin types and is provided by the CDC.

Antimicrobial Agents

Antimicrobial therapy is not prescribed in infant botulism unless clearly indicated for a concurrent infection. Aminoglycoside agents can potentiate the paralytic effects of the toxin and should be avoided. Given theoretical concerns of toxin release from antibiotic-induced bacterial cell death, providers may consider delaying the use of antibiotics in wound botulism until after antitoxin is administered. The role for antimicrobial therapy in the adult intestinal colonization form of botulism, if any, has not been established.

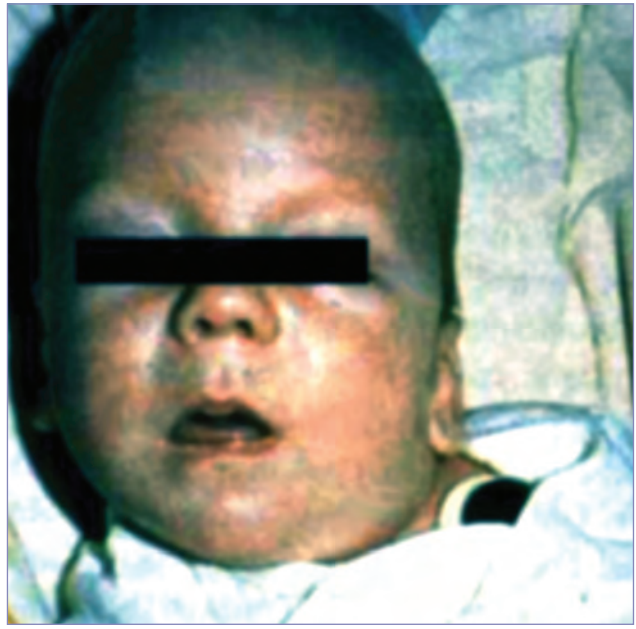


Image 31.1
An infant with mild botulism depicting the loss of facial expression. This infant also had a weak cry, poor feeding, diminished gag reflex, and hypotonia. Infant botulism most often occurs in infants younger than 6 months. Copyright Charles Prober.

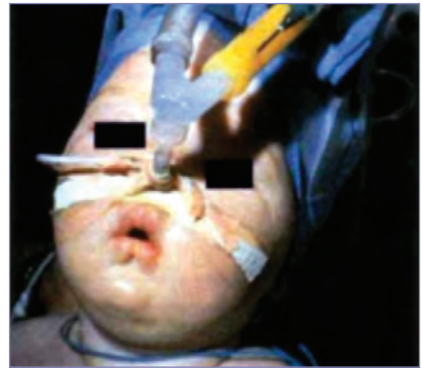


Image 31.2
An infant with severe botulism. This infant required ventilatory support for survival. The source of the toxin producing clostridia was not determined. Copyright Charles Prober.

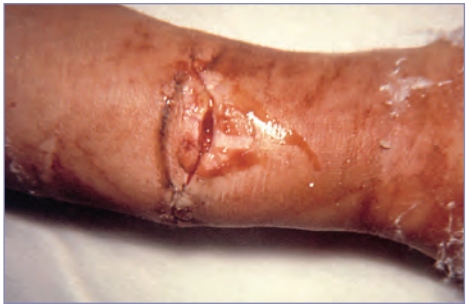


Image 31.3
Wound botulism in the compound fracture of the right arm of a 14-year-old boy. The patient fractured his right ulna and radius and subsequently developed wound botulism. Courtesy of Centers for Disease Control and Prevention.

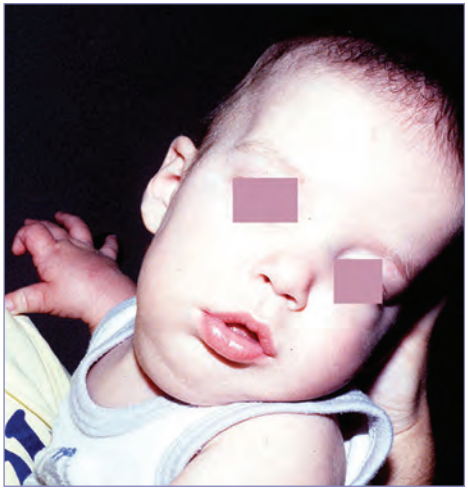


Image 31.5
Infantile botulism in a 4-month-old boy with a 6-day history of progressive weakness, constipation, decreased appetite, and weight loss. The infant had been afebrile, was breastfed, and had not received honey. He was intubated within 24 hours of admission and remained on a ventilator for 26 days. Stool specimens were positive for *Clostridium botulinum* type A. Copyright Larry I. Corman.

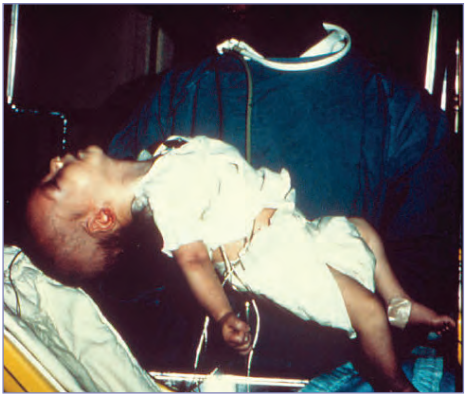


Image 31.4
A 6-week-old with botulism, which is evident as marked loss of muscle tone, especially in the region of the head and neck. Courtesy of Centers for Disease Control and Prevention.

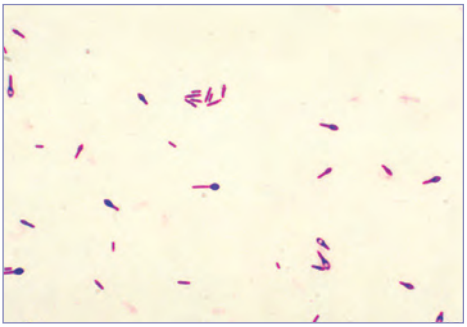


Image 31.6
A photomicrograph of spore forms of *Clostridium botulinum* type A (Gram stain). These *C botulinum* bacteria were cultured in thioglycolate broth for 48 hours at 35°C (95°F). The bacterium *C botulinum* produces a nerve toxin that causes the rare but serious paralytic illness botulism. Courtesy of Centers for Disease Control and Prevention.

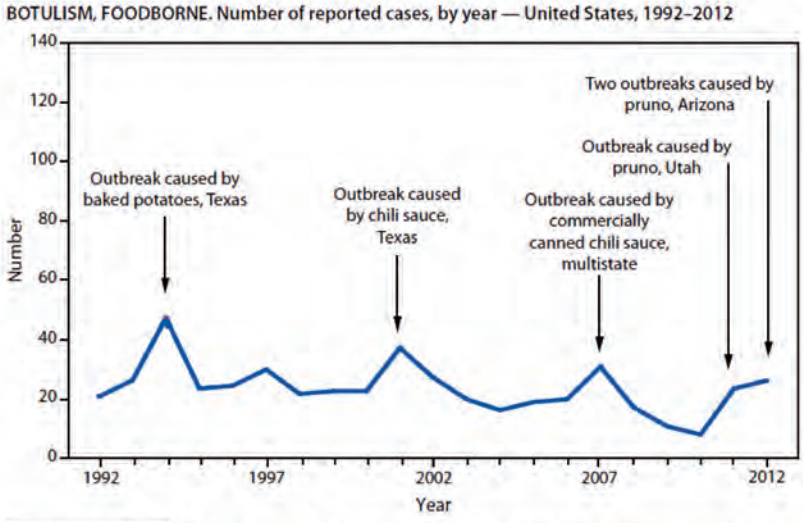


Image 31.7
Botulism, foodborne. Number of reported cases, by year—United States, 1992 through 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

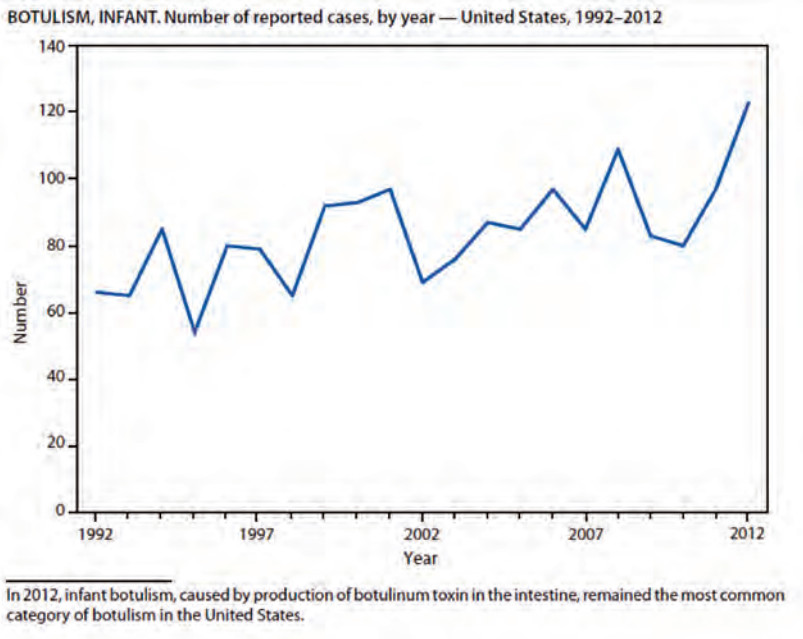


Image 31.8
Botulism, infant. Number of reported cases, by year—United States, 1992 through 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

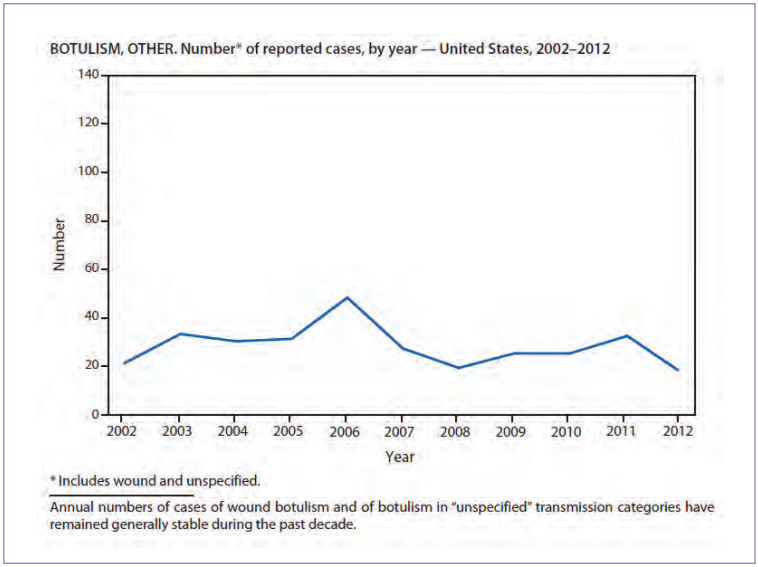


Image 31.9

Botulism, other. Number of reported cases, by year—United States, 2002 through 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

CHAPTER 32

Clostridial Myonecrosis

(Gas Gangrene)

CLINICAL MANIFESTATIONS

Disease onset is heralded by acute and progressive pain at the site of the wound, followed by edema, increasing exquisite tenderness, and exudate. Systemic findings initially include tachycardia disproportionate to the degree of fever, pallor, and diaphoresis. Crepitus is suggestive but not pathognomonic of *Clostridium* infection and is not always present. Tense bullae containing thin, serosanguineous or dark fluid develop in the overlying skin and areas of green-black cutaneous necrosis appear. Fluid in the bullae has a foul odor. Disease can progress rapidly with development of hypotension, renal failure, and alterations in mental status. Diagnosis is based on clinical manifestations, including the characteristic appearance of necrotic muscle at surgery. Untreated gas gangrene can lead to disseminated myonecrosis, suppurative visceral infection, septicemia, and death within hours.

Nontraumatic gas gangrene usually is caused by *Clostridium septicum* and is a complication of bacteremia, which is the result of an occult gastrointestinal mucosal lesion (most commonly colon cancer) or a complication of neutropenic colitis, leukemia, or diabetes mellitus.

ETIOLOGY

Clostridial myonecrosis is caused by *Clostridium* species, most often *Clostridium perfringens.* These organisms are large, gram-positive, spore-forming, anaerobic bacilli with blunt ends. Disease manifestations are caused by potent clostridial exotoxins (eg, *Clostridium sordellii* with medical abortion and *C septicum* with malignancy). Other *Clostridium* species (eg, *Clostridium sordellii, C septicum*, *Clostridium novyi*) also have been associated with myonecrosis. Mixed infection with other gram-positive and gram-negative bacteria is common.

EPIDEMIOLOGY

Clostridial myonecrosis usually results from contamination of deep open wounds. The sources of *Clostridium* species are soil, contaminated foreign bodies, and human and animal feces. Dirty surgical or traumatic wounds, particularly those with retained foreign bodies or significant amounts of devitalized tissue, predispose to disease. Rarely, nontraumatic gas gangrene occurs in immunocompromised people, most frequently in those with underlying malignancy, neutrophil dysfunction, or diseases associated with bowel ischemia.

The **incubation period** from the time of injury is 6 hours to 4 days.

DIAGNOSTIC TESTS

Anaerobic cultures of wound exudate, involved soft tissue and muscle, and blood should be performed. Both matrix-assisted laser desorption/ionization–time-of-flight (MALDI-TOF) devices approved by the US Food and Drug Administration can identify *C perfringens.* Because *Clostridium* species are ubiquitous, their recovery from a wound is not diagnostic unless typical clinical manifestations are present. A Gram-stained smear of wound discharge demonstrating characteristic gram-positive bacilli and few, if any, polymorphonuclear leukocytes suggests clostridial infection. Tissue specimens (not swab specimens) for anaerobic culture must be obtained to confirm the diagnosis. Because some pathogenic *Clostridium* species are exquisitely sensitive to oxygen, care should be taken to optimize anaerobic growth conditions. A radiograph of the affected site may demonstrate gas in the tissue, but this is a nonspecific finding that is not always present. Occasionally, blood cultures are positive and are considered diagnostic.

TREATMENT

Prompt and complete surgical excision of necrotic tissue and removal of foreign material is essential. Repeated surgical débridement may be required to ensure complete removal of all infected tissue. Vacuum-assisted wound closure can be used following multiple débridements. Management of shock, fluid and electrolyte imbalance, hemolytic anemia, and other complications is crucial.

High-dose penicillin G should be administered intravenously. Clindamycin, metronidazole, meropenem, ertapenem, and chloramphenicol

can be considered as alternative drugs for patients with a serious penicillin allergy or for treatment of polymicrobial infections. The combination of penicillin G and clindamycin may be superior to penicillin alone because of the theoretical benefit of clindamycin inhibiting toxin synthesis. Hyperbaric oxygen may be beneficial, but efficacy data from adequately controlled clinical studies are not available.

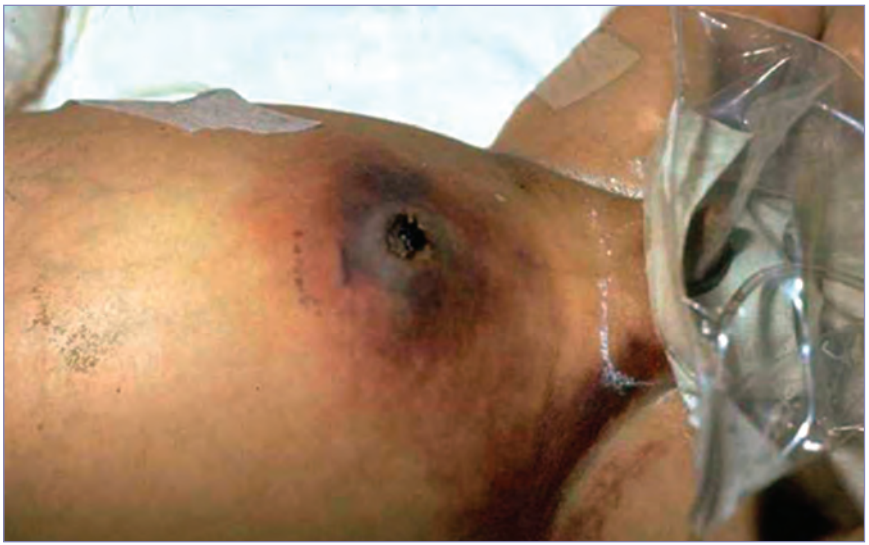


Image 32.1
Clostridial omphalitis in an infant with myonecrosis of the abdominal wall (periumbilical). Early and complete surgical excision of necrotic tissue and careful management of shock, fluid balance, and other complications are crucial for survival.

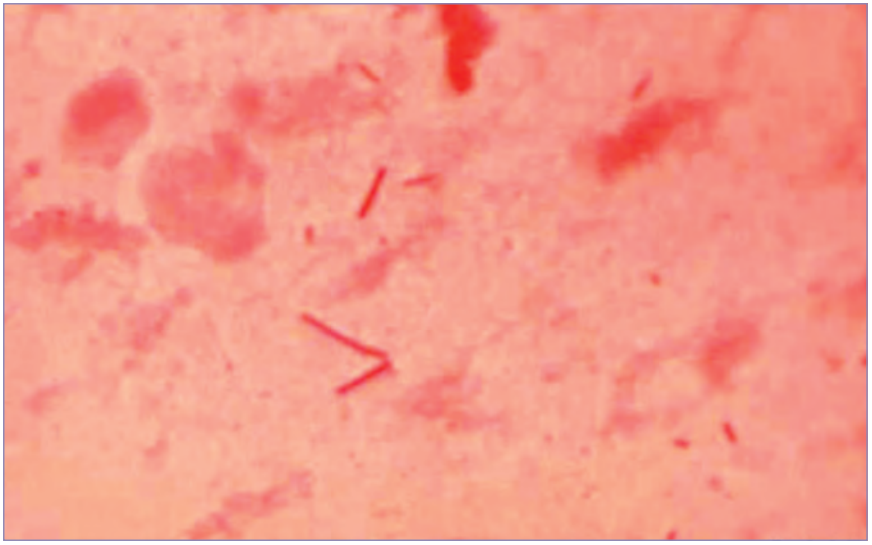


Image 32.2
Gram stain of a tissue aspirate from a patient with clostridial omphalitis showing the characteristic morphology of *Clostridia* bacilli, erroneously stained gram-negative, and sparse polymorphonuclear leukocytes.

CHAPTER 33

Clostridium difficile

CLINICAL MANIFESTATIONS

Clostridium difficile is associated with a spectrum of gastrointestinal illness and with asymptomatic colonization that is common, especially in young infants. Mild to moderate illness is characterized by watery diarrhea, low-grade fever, and mild abdominal pain. Symptoms often begin while the person is hospitalized receiving antimicrobial therapy but can occur up to 10 weeks after therapy cessation. Pseudomembranous colitis is characterized by diarrhea with mucus in feces, abdominal cramps and pain, fever, and systemic toxicity. Toxic megacolon (acute dilatation of the colon) should be considered in children who develop marked abdominal tenderness and distension with minimal diarrhea and may be associated with hemodynamic instability. Other complications of *C difficile* disease include intestinal perforation, hypotension, shock, and death. Complicated infections are less common in children than adults. Severe or fatal disease is more likely to occur in neutropenic children with leukemia, infants with Hirschsprung disease, and patients with inflammatory bowel disease. Clinical illness attributable to *C difficile* is rare in children younger than 12 months. Extraintestinal manifestations of *C difficile* infection can include bacteremia, wound infections, and reactive arthritis.

ETIOLOGY

C difficile is a spore-forming, obligate anaerobic, gram-positive bacillus. Some strains produce exotoxins (toxins A and B), which are responsible for the clinical manifestations of disease when there is overgrowth of *C difficile* in the large intestine.

EPIDEMIOLOGY

C difficile is shed in feces. People can acquire infection from the stool of other colonized or infected people through the fecal-oral route. Any surface (including hands), device, or material that has become contaminated with feces may also transmit *C difficile* spores. Hospitals, nursing homes, and child care facilities are major reservoirs for *C difficile*. Risk factors for acquisition of the bacterium include prolonged hospitalization and exposure to an infected person either in the hospital or the community. Risk factors for *C difficile* disease include antimicrobial therapy, repeated enemas, proton pump inhibitor therapy, prolonged nasogastric tube placement, gastrostomy and tube placement, underlying bowel disease, gastrointestinal tract surgery, renal insufficiency, and immunocompromised state. *C difficile* colitis has been associated with exposure to almost every antimicrobial agent; cephalosporins and fluoroquinolones are considered to be the highest-risk antibiotic agents, particularly for recurrent *C difficile* disease and infections with epidemic strains. The NAP-1 strain is a virulent strain of *C difficile* because of increased toxin production and is associated with an increased risk of severe disease. NAP-1 strains of *C difficile* have emerged as a cause of outbreaks among adults and are reported sporadically in children.

Community-associated *C difficile* disease is occurring with increasing frequency in recent years. Although the rates of both community- and health care-associated *C difficile* disease are increasing in children, recent data suggest the incidence of pediatric community-associated *C difficile* disease may be twice as frequent as health care-associated disease.

Asymptomatic intestinal colonization with *C difficile* (including toxin-producing strains) is common in infants younger than 1 year (up to 50%). Asymptomatic colonization with *C difficile* is common in recently hospitalized patients, with rates upward of 20%.

The **incubation period** is unknown; colitis usually develops 5 to 10 days after initiation of antimicrobial therapy but can occur from 1 day to 10 weeks after therapy cessation.

DIAGNOSTIC TESTS

Endoscopic findings of pseudomembranes (2- to 5-mm, raised yellowish plaques) and hyperemic, friable rectal mucosa suggesting pseudomembranous colitis is highly correlated with *C difficile* disease. More commonly, the diagnosis of *C difficile* disease is based on laboratory methods including the detection of *C difficile* toxin(s) or toxin gene(s) in a diarrheal stool specimen. In general, laboratory tests for *C difficile* should not be ordered on a

patient who is having formed stools unless ileus or toxic megacolon is suspected. There is no agreed upon gold standard test for the diagnosis of *C difficile* disease.

Molecular assays using nucleic acid amplification tests (NAATs) are commonly used testing methods for toxigenic strains of *C difficile* toxins. NAATs detect genes responsible for the production of toxins A and B, rather than free toxins A and B in the stool that are detected by enzyme immunoassay (EIA). EIAs are rapid, performed easily, and highly specific for diagnosis of *C difficile* infection, but their sensitivity is relatively low. The cell culture cytotoxicity assay, which also tests for toxin in stool, is more sensitive than the EIA but is labor intensive and has a long turnaround time, limiting its usefulness in the clinical setting. NAATs combine excellent sensitivity and specificity, and provide results to clinicians in times comparable to EIAs. However, detecting toxin gene(s) in patients who are only colonized by *C difficile* is common and likely contributes to misdiagnosis of *C difficile* infection in children with other causes of diarrhea. Several steps can be taken to reduce the likelihood of misdiagnosis of *C difficile* infection related to use of highly sensitive NAATs. For example, because colonization with *C difficile* in infants is common and symptomatic infection in this age group is not thought to occur, *C difficile* diagnostic testing on samples from children younger than 12 months should be discouraged. Repeat NAAT testing for the same episode of diarrhea is discouraged because it is more likely to represent a false positive test. Furthermore, testing should be avoided or deferred in children with other more likely causes of diarrhea, such as concomitant laxative use and in children with symptoms more consistent of viral or noninfectious etiologies. Finally, because shedding of *C difficile* in the stool can persist for several months after symptoms resolution, tests of cure are impractical and should not be performed.

TREATMENT

A central tenet to control *C difficile* infection is the discontinuation of precipitating antimicrobial therapy; stopping these agents will allow competing gut flora to reemerge. A variety of therapies are available; use of a particular treatment modality is dependent on severity of illness, the number of recurrences of infection, tolerability of adverse effects, and cost. Drugs that decrease intestinal motility should not be administered. Asymptomatic patients should not be treated.

When vancomycin is being used orally, as a cost-saving measure, vancomycin for intravenous use can be administered. Intravenously administered vancomycin is not effective for *C difficile* infection. Fidaxomicin is approved for treatment of *C difficile*-associated diarrhea in adults. Studies have demonstrated equivalent efficacy to oral vancomycin, although subjects with life-threatening and fulminant infection, hypotension, septic shock, peritoneal signs, significant dehydration, or toxic megacolon were excluded. No comparative data of fidaxomicin to metronidazole are available. There are anecdotal reports of fidaxomicin use in children, although it is not approved for use in patients younger than 18 years.

Up to 20% of patients experience a recurrence after discontinuing therapy, but infection usually responds to a second course of the same treatment. Metronidazole should not be used for treatment of a second recurrence or for prolonged therapy, because neurotoxicity is possible. Tapered or pulse regimens of vancomycin may be considered for recurrent disease, often as 3 times a day for several days followed by twice a day for several days. Rifaximin orally for 14 days or nitazoxanide orally for 10 days are alternatives but have not been studied in children.

Fecal transplant (intestinal microbiota transplantation) appears to be effective in adults, but there are limited data in pediatrics. No pediatric data are available evaluating use of human monoclonal antibodies (against toxin A and B). Cholestyramine is not recommended. Other potential adjunctive therapies of unclear efficacy include Immune Globulin therapy and probiotics (particularly *Saccharomyces boulardii* and kefir).

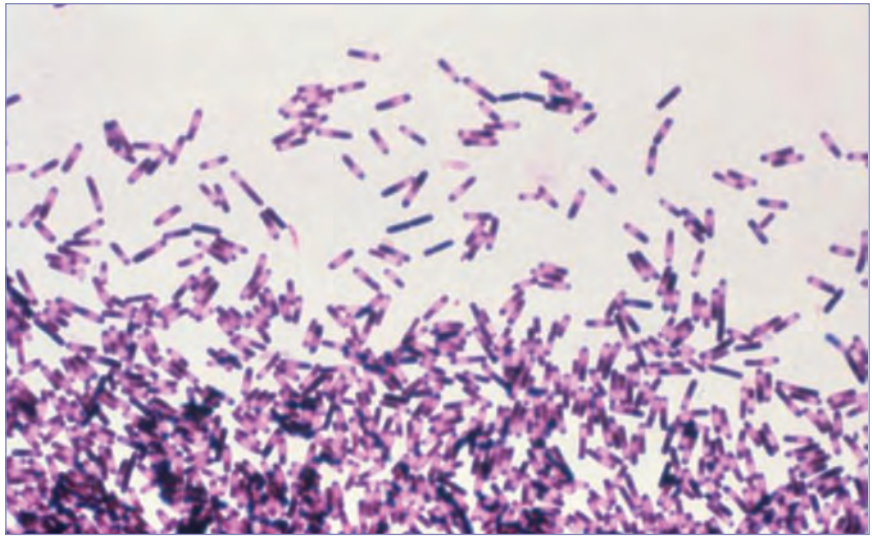


Image 33.1
Clostridium difficile is a gram-positive, spore-forming bacteria that can be part of the normal intestinal flora in as many as 50% of children younger than 2 years. It is a cause of pseudomembranous enterocolitis and antibiotic-associated diarrhea in older children and adults. Courtesy of *AAP News*.

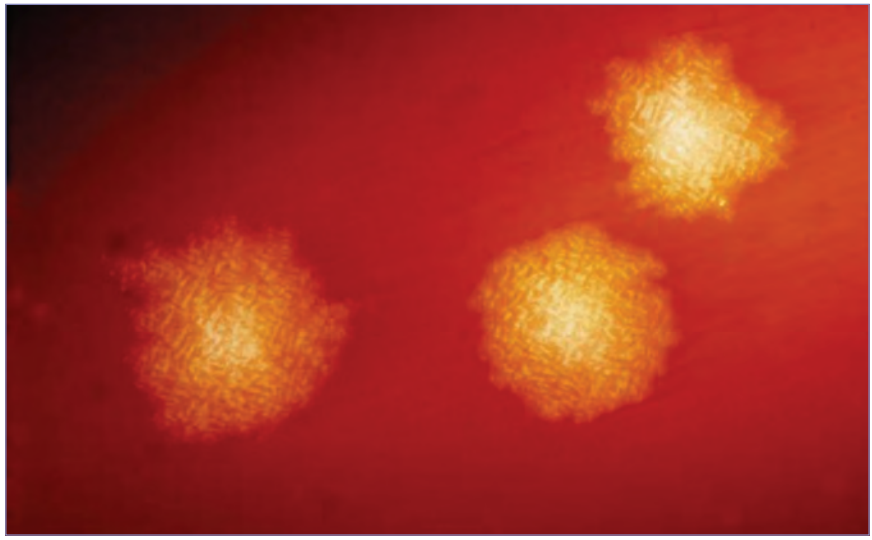


Image 33.2
This photograph depicts *Clostridium difficile* colonies after 48 hours' growth on a blood agar plate (magnification ×4.8). Courtesy of Centers for Disease Control and Prevention.

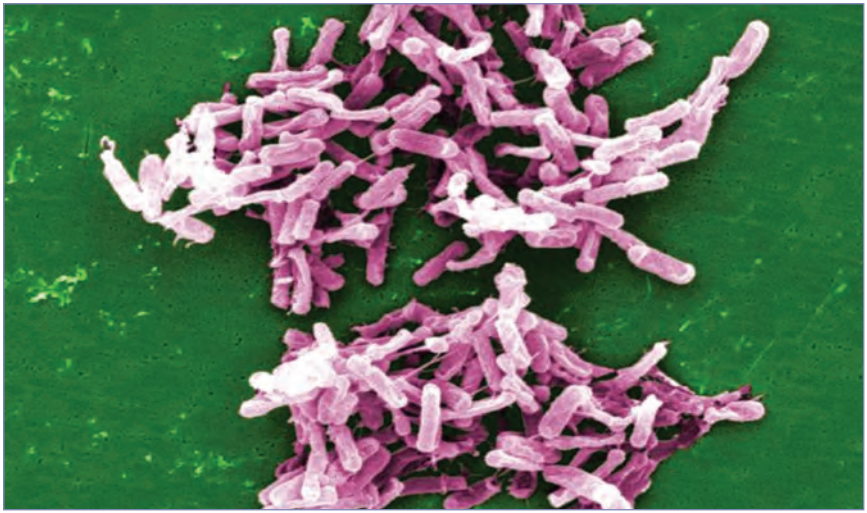


Image 33.3
This micrograph depicts gram-positive *Clostridium difficile* from a stool sample culture obtained using a 0.1-µm filter. People can become infected if they touch items or surfaces that are contaminated with *C difficile* spores and then touch their mouths or mucous membranes. Health care workers can spread the bacteria to other patients or contaminate surfaces through hand contact. Courtesy of Centers for Disease Control and Prevention/ Lois S. Wiggs.

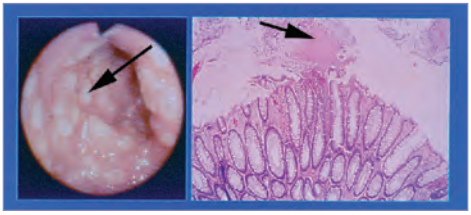


Image 33.4
The right-hand panel shows the typical pseudomembranes of *Clostridium difficile* colitis; the left-hand panel shows the histology, with the pseudomembrane structure at the top middle (arrows). Courtesy of Carol J. Baker, MD, FAAP.

CHAPTER 34

Clostridium perfringens Food Poisoning

CLINICAL MANIFESTATIONS

Clostridium perfringens foodborne illness is characterized by a sudden onset of watery diarrhea and moderate-to-severe crampy, mid-epigastric pain. Symptoms usually resolve within 24 hours. The shorter incubation period, shorter duration of illness, and absence of fever in most patients differentiate *C perfringens* foodborne disease from shigellosis and salmonellosis. *C perfringens* foodborne illness is infrequently associated with vomiting. Diarrheal illness caused by *B cereus* diarrheal enterotoxins can be indistinguishable from that caused by *C perfringens*. Necrotizing colitis and death have been described in patients with disease attributable to type A *C perfringens* who received antidiarrheal medications resulting in constipation. Enteritis necroticans (also known as pigbel) results from hemorrhagic necrosis of the midgut and is a cause of severe illness and death attributable to *C perfringens* food poisoning caused by contamination with *Clostridium* strains carrying a β toxin. Rare cases have been reported in the Highlands of Papua New Guinea and in Thailand; protein malnutrition is an important risk factor. Additionally, enteritis necroticans has been reported in a child with poorly controlled diabetes in the United States who consumed chitterlings (pig intestine).

ETIOLOGY

Typical food poisoning is caused by a heat-labile *C perfringens* enterotoxin, produced during sporulation in the small intestine. *C perfringens* type A, which produces β toxin and enterotoxin, commonly causes foodborne illness. Enteritis necroticans is caused by *C perfringens* type C, which produces a β toxin that causes necrotizing small bowel inflammation.

EPIDEMIOLOGY

C perfringens is a gram-positive, spore-forming bacillus that is ubiquitous in the environment, the intestinal tracts of humans and animals, and commonly present in raw meat and poultry. Spores of *C perfringens* that survive cooking can germinate and multiply rapidly during slow cooling, when stored at temperatures from 20°C to 60°C (68°F–140°F), and during inadequate reheating. At an optimum temperature, *C perfringens* has one of the fastest rates of growth of any bacterium. Illness results from consumption of food containing high numbers of vegetative organisms ($>10^5$ colony forming units/g) that produce enterotoxin in the intestine.

Ingestion of the organism is most commonly associated with foods prepared by restaurants or caterers or in institutional settings (eg, schools and camps) where food is prepared in large quantities, cooled slowly, and stored inappropriately for prolonged periods. Beef, poultry, gravies, and dried or precooked foods are the most commonly implicated sources. Illness is not transmissible from person to person.

The **incubation period** is 6 to 24 hours, usually 8 to 12 hours.

DIAGNOSTIC TESTS

Because the fecal flora of healthy people commonly includes *C perfringens*, counts of *C perfringens* of 10^6 colony forming units (CFU)/g of feces or greater obtained within 48 hours of onset of illness are required to support the diagnosis in ill people. The diagnosis also can be supported by detection of enterotoxin in stool. *C perfringens* can be confirmed as the cause of an outbreak if 106 CFU/g are isolated from stool or enterotoxin is demonstrated in the stool of 2 or more ill people or when the concentration of organisms is at least 105 CFU/g in the implicated food. Although *C perfringens* is an anaerobe, special transport conditions are unnecessary. Stool specimens, rather than rectal swab specimens, should be obtained, transported in ice packs, and tested within 24 hours. For enumeration and enterotoxin testing, obtaining stool specimens in bulk without added transport media is required.

TREATMENT

Oral rehydration or, occasionally, intravenous fluid and electrolyte replacement may be indicated to prevent or treat dehydration. Antimicrobial agents are not indicated.

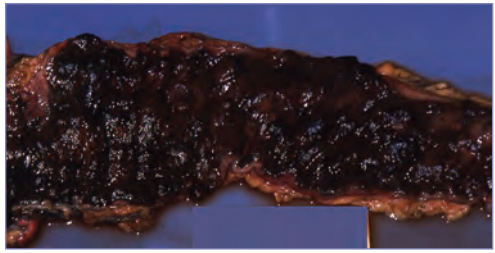


Image 34.1
This slide shows hemorrhagic necrosis of the intestine in a patient with *Clostridium perfringens* sepsis. Courtesy of Dimitris P. Agamanolis, MD.

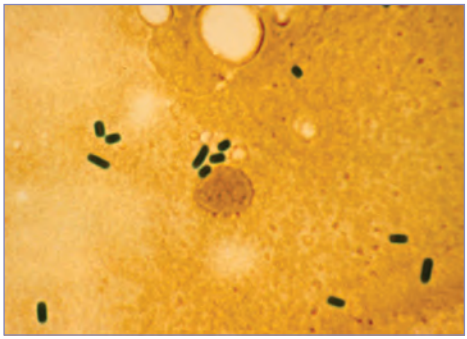


Image 34.2
Clostridium perfringens, an anaerobic, gram-positive, spore-forming bacillus, causes a broad spectrum of pathology, including food poisoning. In Papua New Guinea, *C perfringens* is a cause of severe illness and death called necrotizing enteritis necroticans (locally known as pigbel). Courtesy of Hugh Moffet, MD.

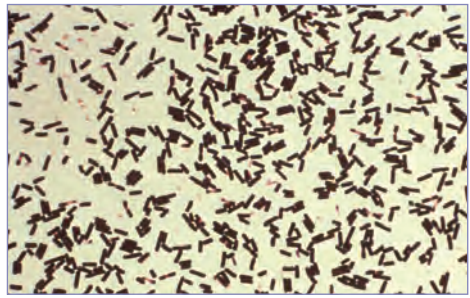


Image 34.3
This photomicrograph reveals numbers of *Clostridium perfringens* bacteria grown in Schaedler broth and subsequently stained using Gram stain (magnification ×1,000). *C perfringens* is a spore-forming, heat-resistant bacterium that can cause foodborne disease. The spores persist in the environment and often contaminate raw food materials. These bacteria are found in mammalian feces and soil. Courtesy of Centers for Disease Control and Prevention/Don Stalons.

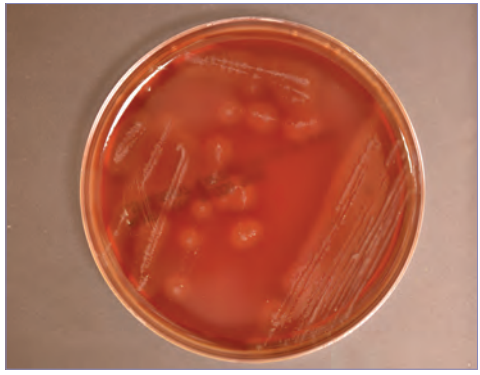


Image 34.4
Clostridium perfringens on phenylethyl alcohol–blood agar. A double zone of hemolysis is often seen surrounding individual colonies. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 35

Coccidioidomycosis

CLINICAL MANIFESTATIONS

Primary pulmonary infection is acquired by inhaling fungal conidia and is asymptomatic or self-limited in 60% to 65% of infected children and adults. Constitutional symptoms, including extreme fatigue and weight loss, are common and can persist for weeks or months. Symptomatic disease can resemble influenza or community-acquired pneumonia, with malaise, fever, cough, myalgia, arthralgia, headache, and chest pain. Pleural effusion, empyema, and mediastinal involvement are more common in children. Acute infection may be associated only with cutaneous abnormalities, such as erythema multiforme, an erythematous maculopapular rash, or erythema nodosum manifesting as bilateral symmetrical violaceous nodules usually overlying the shins. Chronic pulmonary lesions are rare, but approximately 5% of infected people develop asymptomatic pulmonary radiographic residua (eg, cysts, nodules, cavitary lesions, coin lesions).

Nonpulmonary primary infection is rare and usually follows trauma associated with contamination of wounds by arthroconidia. Cutaneous lesions and soft tissue infections often are accompanied by regional lymphadenitis.

Disseminated (extrapulmonary) infection occurs in less than 0.5% of infected people; common sites of dissemination include skin, bones and joints, and the central nervous system (CNS). Meningitis invariably is fatal if untreated. Congenital infection is rare.

ETIOLOGY

Coccidioides species are dimorphic fungi. Molecular studies have divided the genus *Coccidioides* into 2 species: *Coccidioides immitis*, confined mainly to California, and *Coccidioides posadasii*, encompassing the remaining areas of distribution of the fungus within certain deserts of the southwestern United States, northern Mexico, and areas of Central and South America.

EPIDEMIOLOGY

Coccidioides species are found mostly in soil in areas of the southwestern United States with endemic infection, including California, Arizona, New Mexico, west and south Texas, southern Nevada, and Utah; northern Mexico; and throughout certain parts of Central and South America. In areas with endemic coccidioidomycosis, clusters of cases can follow dust-generating events, such as storms, seismic events, archaeologic digging, and recreational and construction activities, including building of solar farms. Most cases occur without a known preceding event. The incidence of reported coccidioidomycosis cases in areas of endemicity (Arizona, California, Nevada, New Mexico, and Utah) has increased substantially over the past decade and a half, rising from 5.3 per 100,000 population in 1998 to 42.6 per 100,000 in 2011. Infection is thought to provide lifelong immunity. Person-to-person transmission of coccidioidomycosis does not occur except in rare instances of cutaneous infection with actively draining lesions, donor-derived transmission via an infected organ, and congenital infection following in utero exposure. People with impairment of T-lymphocyte–mediated immunity caused by a congenital immune defect or HIV infection or those receiving immune modulating medications (eg, tumor necrosis factor [TNF] alpha antagonist) are at major risk for severe primary coccidioidomycosis, disseminated disease, or relapse of past infection. Other people at elevated risk of severe or disseminated disease include people of African or Filipino ancestry, women in the third trimester of pregnancy and those postpartum, and infants.

The **incubation period** typically is 1 to 4 weeks; disseminated infection may develop years after primary infection.

DIAGNOSTIC TESTS

Diagnosis of coccidioidomycosis is best established using serologic, histopathologic, and culture methods. Nucleic acid amplification tests have been developed but are not widely available.

Serologic tests are useful in the diagnosis and management of infection. The immunoglobulin (Ig) M response can be detected by enzyme

immunoassay (EIA) or immunodiffusion methods. In approximately 50% and 90% of primary infections, IgM is detected in the first and third weeks, respectively. IgG response can be detected by immunodiffusion, EIA, or complement fixation (CF) tests. Immunodiffusion is considered more specific, whereas CF is more sensitive. CF antibodies in serum usually are of low titer and are transient if the disease is asymptomatic or mild. Persistent high titers (≥1:16) occur with severe disease and are almost always seen in disseminated infection. Cerebrospinal fluid (CSF) antibodies also are detectable by immunodiffusion or CF testing. Increasing serum and CSF titers indicate progressive disease, and decreasing titers usually suggest improvement. CF titers may not be reliable in immunocompromised patients; low or nondetectable titers in immunocompromised patients should be interpreted with caution.

Spherules are as large as 80 μm in diameter and can be visualized with 100× to 400× magnification in infected body fluid specimens (eg, pleural fluid, bronchoalveolar lavage) and biopsy specimens of skin lesions or organs. For biopsy specimens, use of silver or period-acid Schiff staining is helpful. The presence of a mature spherule with endospores is pathognomonic of infection. Isolation of *Coccidioides* species in culture establishes the diagnosis, even in patients with mild symptoms. Culture of organisms is possible on a variety of artificial media but is hazardous to laboratory personnel, because spherules can convert to arthroconidia-bearing mycelia on culture plates. A DNA probe can identify *Coccidioides* species in cultures.

Although limited in availability, at least one commercial laboratory offers an EIA test for urine, serum, plasma, CSF, or bronchoalveolar lavage fluid for detection of *Coccidioides* antigen. Antigen may be positive in patients with more severe forms of disease (sensitivity 71%). Cross reactions occur in patients with histoplasmosis, blastomycosis, or paracoccidioidomycosis.

TREATMENT

Antifungal therapy for uncomplicated primary infection in people without risk factors for severe disease is controversial. Although most cases will resolve without therapy, some experts believe that treatment may reduce illness duration or risk of severe complications. Most experts recommend treatment of coccidioidomycosis for people at risk of severe disease or people with severe primary infection. Severe primary infection is manifested by complement fixation titers of 1:16 or greater, infiltrates involving more than half of one lung or portions of both lungs, weight loss of greater than 10%, marked chest pain, severe malaise, inability to work or attend school, intense night sweats, or symptoms that persist for more than 2 months. In such cases, fluconazole is recommended for 3 to 6 months. Repeated patient encounters every 1 to 3 months for up to 2 years, either to document radiographic resolution or to identify residual abnormalities or pulmonary or extrapulmonary complications, are recommended. For diffuse pneumonia, defined as bilateral reticulonodular or miliary infiltrates, a preparation of amphotericin B or high-dose fluconazole is recommended. Amphotericin B is used more frequently in the presence of severe hypoxemia or rapid clinical deterioration. The total length of therapy for diffuse pneumonia is 1 year.

Oral fluconazole or itraconazole is the recommended initial therapy for disseminated infection not involving the CNS. Amphotericin B is recommended as alternative therapy if lesions are progressing or are in critical locations, such as the vertebral column, or in fulminant infections, because it is thought to result in more rapid improvement. In patients experiencing failure of conventional amphotericin B deoxycholate therapy or experiencing drug-related toxicities, a lipid formulation of amphotericin B can be substituted.

Consultation with a specialist for treatment of patients with CNS disease caused by *Coccidioides* species is recommended. High-dose oral fluconazole is recommended for treatment of patients with CNS infection. Patients who respond to azole therapy should continue this treatment indefinitely. For CNS infections that are unresponsive to oral azoles or are associated with severe basilar inflammation, intrathecal amphotericin B deoxycholate therapy can be used to augment the azole therapy. A subcutaneous reservoir can facilitate

administration into the cisternal space or lateral ventricle. Hydrocephalus is a common complication of coccidioidal meningitis and nearly always requires a shunt for decompression.

There are reports of success with voriconazole, posaconazole, and isavuconazole in treatment of coccidioidomycosis, but this has not been established in children.

The duration of antifungal therapy is variable and depends on the site(s) of involvement, clinical response, and mycologic and immunologic test results. In general, therapy is continued until clinical and laboratory evidence indicates that active infection has resolved. Treatment for disseminated coccidioidomycosis is at least 6 months but for some patients may be extended to 1 year or longer. However, on discontinuation of therapy, relapses occur in approximately one third of all patients. The role of subsequent suppressive azole therapy is uncertain, except for patients with CNS infection, osteomyelitis, or underlying human immunodeficiency virus (HIV) infection or solid organ transplant recipients. The duration of suppressive therapy may be lifelong for certain high-risk groups. Women should be advised to avoid pregnancy while receiving fluconazole, which is known to be teratogenic.

Surgical débridement or excision of lesions in bone, pericardium, and lung has been advocated for localized, symptomatic, persistent, resistant, or progressive lesions. In some localized infections with sinuses, fistulae, or abscesses, amphotericin B has been instilled locally or used for irrigation of wounds.

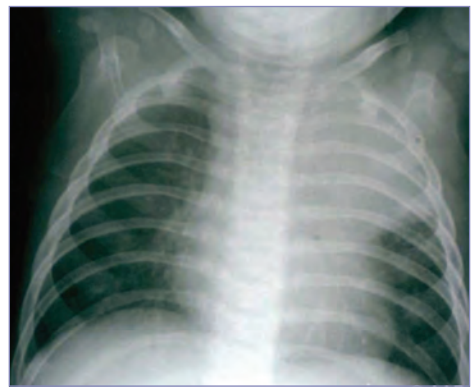


Image 35.1
Pneumonia due to *Coccidioides immitis* in the upper lobe of the left lung of a 5½-month-old. The organism was isolated from gastric aspirate, and complement fixation test result was elevated.

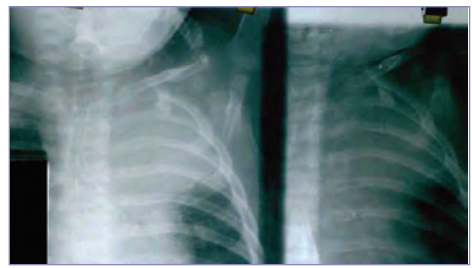


Image 35.2
Coccidioidomycosis of the upper lobe of the left lung of a 1-year-old boy, proven by gastric aspirate culture that tested positive for *Coccidioides immitis*. Courtesy of Edgar O. Ledbetter, MD, FAAP.

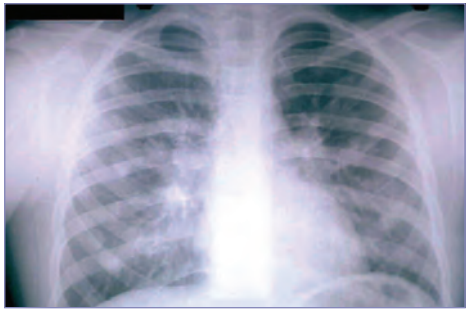


Image 35.3
Primary pulmonary coccidioidomycosis in an 11-year-old boy who recovered spontaneously. The acute disease is usually self-limited in otherwise healthy children. The patient also had erythema nodosum lesions over the tibial area.

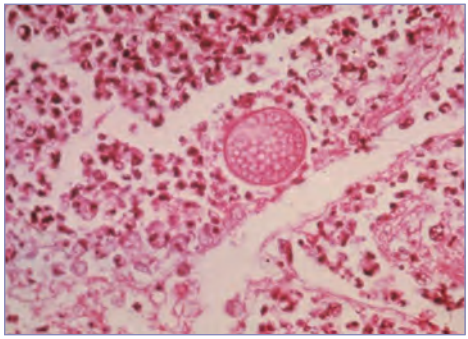


Image 35.5
Histopathology of coccidioidomycosis of lung. Mature spherule with endospores of *Coccidioides immitis* and intense infiltrate of neutrophils (hematoxylin-eosin stain). Courtesy of Centers for Disease Control and Prevention.

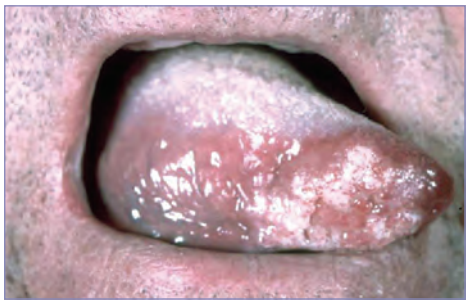


Image 35.7
Coccidioidomycosis of the tongue in an adult male. Courtesy of Edgar O. Ledbetter, MD, FAAP.

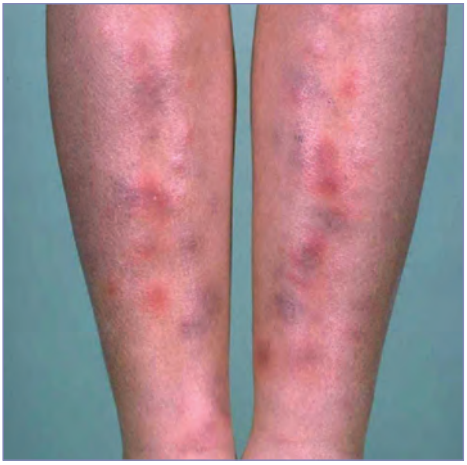


Image 35.4
Erythema nodosum in a preadolescent girl with primary pulmonary coccidioidomycosis.

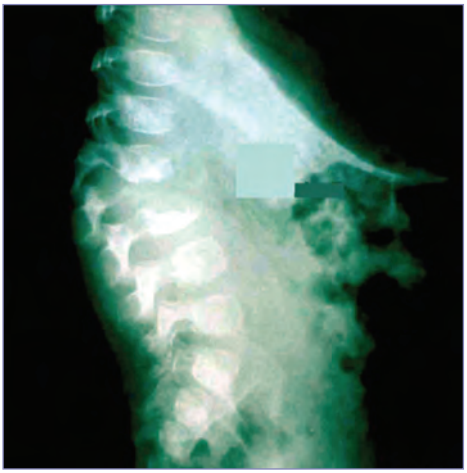


Image 35.6
Spondylitis due to *Coccidioides immitis* in 2-year-old boy with disseminated disease.

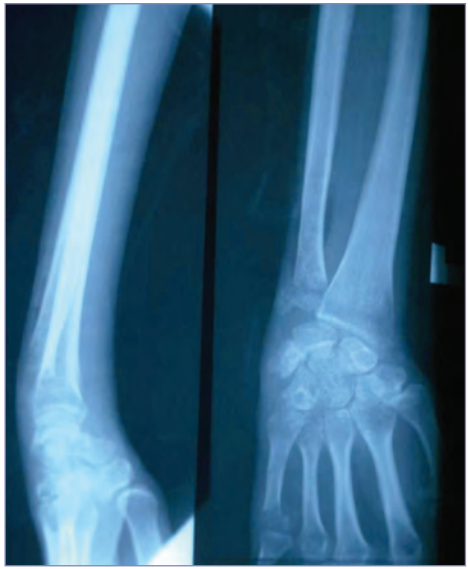


Image 35.8
Disseminated coccidioidomycosis with osteomyelitis of the distal radius and ulna in a preadolescent boy.

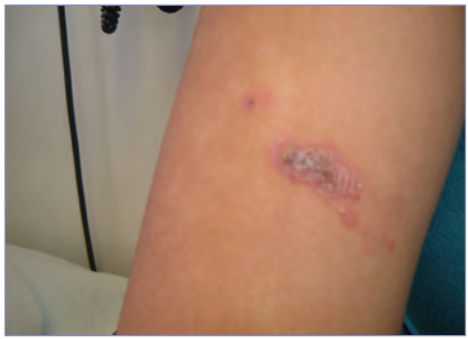


Image 35.10
A 15-year-old girl who originally presented with forehead lesions without other symptoms. At the third visit, she had disseminated coccidioidomycosis disease and had developed extensive cutaneous lesions all over her body with severe nasal involvement. Courtesy of Sabiha Hussain, MD.

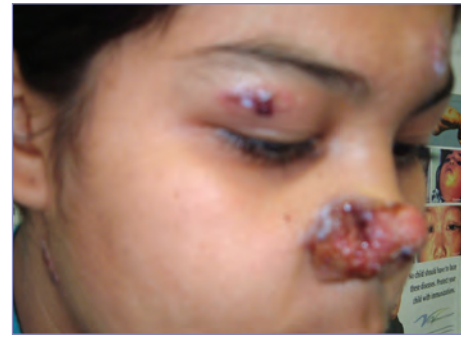


Image 35.9
A 15-year-old girl who originally presented with forehead lesions without other symptoms. At the third visit, she had disseminated coccidioidomycosis disease and had developed extensive cutaneous lesions all over her body with severe nasal involvement. Courtesy of Sabiha Hussain, MD.

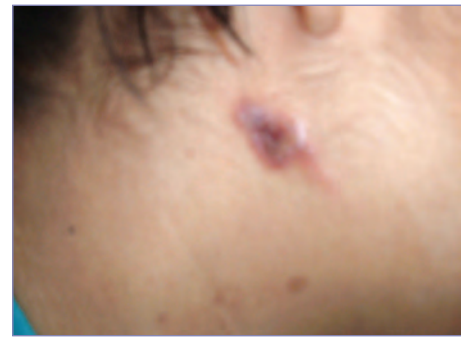


Image 35.11
A 15-year-old girl who originally presented with forehead lesions without other symptoms. At the third visit, she had disseminated coccidioidomycosis disease and had developed extensive cutaneous lesions all over her body with severe nasal involvement. Courtesy of Sabiha Hussain, MD.

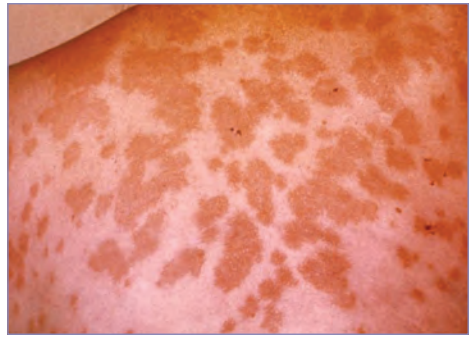


Image 35.12
Erythema nodosum lesions on skin of the back due to hypersensitivity to antigens of *Coccidioides immitis*. Courtesy of Centers for Disease Control and Prevention/Lucille K. Georg, MD.

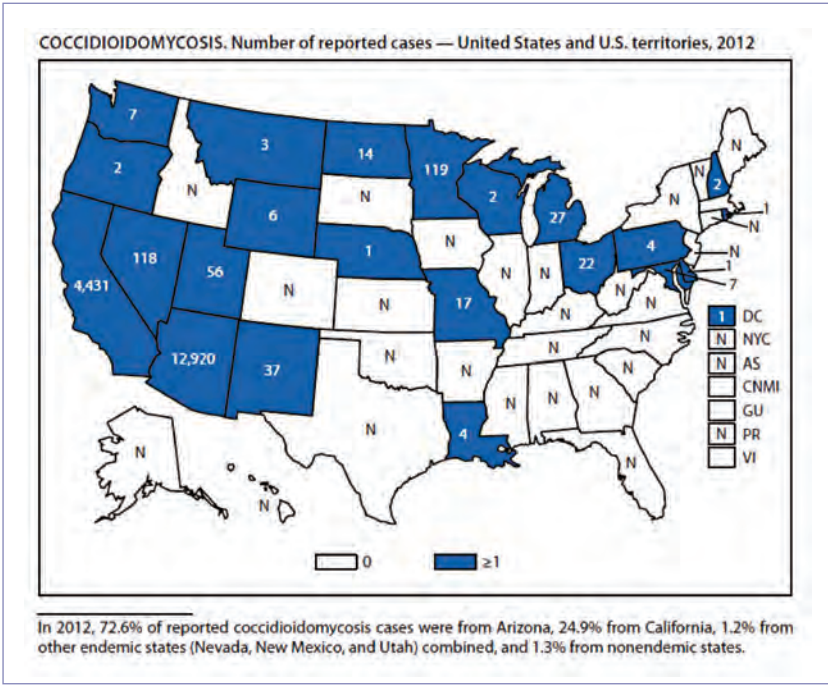


Image 35.13
Coccidioidomycosis. Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

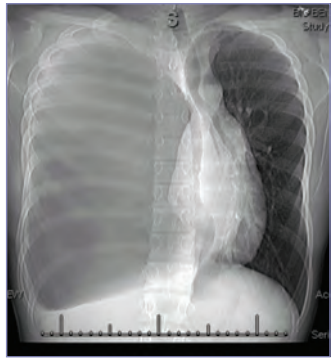


Image 35.14
Chest radiograph of a previously healthy 14-year-old boy who had a several month history of intermittent fever, weight loss, and chest pain and recent onset of exercise intolerance. His pyopneumothorax was caused by *Coccidioides immitis*. He lived in West Texas near the Mexican border. Courtesy of Jeffrey R. Starke, MD.

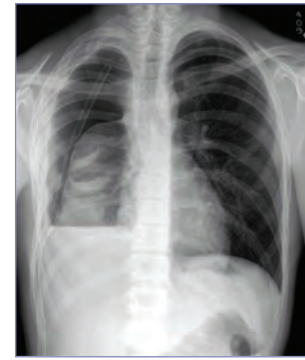


Image 35.15
A chest tube was inserted emergently in the patient in Image 35.14, and his right lung was expanded. Courtesy of Jeffrey R. Starke, MD.

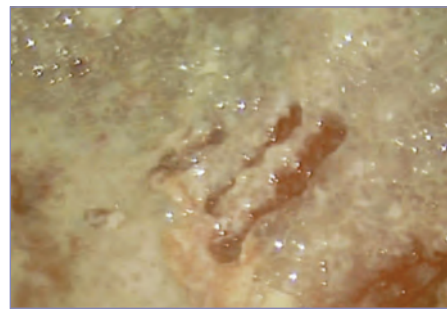


Image 35.16
After 7 days of hospitalization, the patient in Images 35.14 and 35.15 had a video-assisted thoracostomy followed by an open thoracotomy for decortication procedure. This photograph demonstrated the copious fluid and thick fibrinous exudate of a chronic empyema found at surgery. Courtesy of Jeffrey R. Starke, MD.

CHAPTER 36

Coronaviruses, Including SARS and MERS

CLINICAL MANIFESTATIONS

Human coronaviruses (HCoVs) 229E, OC43, NL63, and HKU1 are associated most frequently with an upper respiratory tract infection characterized by rhinorrhea, nasal congestion, sore throat, sneezing, and cough that may be associated with mild fever. Symptoms are self-limited and typically peak on day 3 or 4 of illness. These HCoV infections also may be associated with acute otitis media or asthma exacerbations. Less frequently, they are associated with lower respiratory tract infections, including bronchiolitis, croup, and pneumonia, primarily in infants and immunocompromised children and adults.

SARS-CoV was responsible for the 2002–2003 global outbreak of severe acute respiratory syndrome (SARS), which was associated with more severe symptoms, although a spectrum of disease including asymptomatic infections and mild disease occurred. SARS-CoV disproportionately affected adults, who typically presented with fever, myalgia, headache, malaise, and chills followed by a nonproductive cough and dyspnea generally 5 to 7 days later. Approximately 25% of infected adults developed watery diarrhea. Twenty percent developed respiratory distress requiring intubation and ventilation. The overall mortality rate was approximately 10%, with most deaths occurring in the third week of illness. The case-fatality rate in people older than 60 years approached 50%. Typical laboratory abnormalities include lymphopenia and increased lactate dehydrogenase (LDH) and creatine kinase concentrations. Most had progressive unilateral or bilateral ill-defined airspace infiltrates on chest imaging. Pneumothoraces and other signs of barotrauma were common in critically ill patients receiving mechanical ventilation.

During the 2002–2003 outbreak, SARS-CoV infections in children were less severe than in adults; notably, no infant or child deaths from SARS-CoV infection were documented. Infants and children younger than 12 years who develop SARS typically present with fever, cough, and rhinorrhea. Associated lymphopenia is less severe, and radiographic changes are milder and generally resolve more quickly than in adolescents and adults. Adolescents who develop SARS have clinical courses more closely resembling those of adult disease, presenting with fever, myalgia, headache, and chills. Adolescents also are more likely to develop dyspnea, hypoxemia, and worsening chest radiographic findings. Laboratory abnormalities are comparable to those in adult disease.

MERS-CoV, the HCoV associated with the Middle East respiratory syndrome (MERS), also can cause severe disease. MERS-CoV is associated with a severe respiratory illness similar to that with SARS-CoV, although a spectrum of disease, including asymptomatic infections and mild disease, may occur. The majority of cases have been identified in male adults with comorbidities. Infected children typically present with milder symptoms. Patients initially present with fever, myalgia, and chills followed by a nonproductive cough and dyspnea a few days later. Approximately 25% of patients may experience vomiting, diarrhea, or abdominal pain. Rapid deterioration of oxygenation with progressive unilateral or bilateral airspace infiltrates on chest imaging may follow, requiring mechanical ventilation and often associated with acute renal failure. The case-fatality rate is high, estimated at 36%, but may partially reflect surveillance bias for more severe disease. Laboratory abnormalities may include thrombocytopenia, lymphopenia, and increased LDH, particularly among severely infected individuals.

ETIOLOGY

Coronaviruses are enveloped, nonsegmented, single-stranded, positive-sense RNA viruses named after their corona- or crown-like surface projections observed on electron microscopy that correspond to large surface spike proteins. Coronaviruses are classified in the *Nidovirales* order. Coronaviruses are host specific and can infect humans as well as a variety of different animals, causing diverse clinical syndromes. Four distinct genera have been described: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. HCoVs 229E and NL63 belong to the genus

Alphacoronavirus. HCoVs OC43 and HKU1 belong to lineage A, SARS-CoV belongs to lineage B, and MERS-CoV belongs to lineage C of the genus *Betacoronavirus.*

EPIDEMIOLOGY

Coronaviruses were recognized as animal pathogens in the 1930s. Thirty years later, HCoVs 229E and OC43 were identified as human pathogens, along with other coronavirus strains that were not investigated further and for which little is known regarding their prevalence and associated disease syndromes. In 2003, SARS-CoV was identified as a novel virus responsible for a global outbreak that lasted for 9 months and resulted in 8,096 reported cases and 774 deaths. No SARS-CoV infections have been reported worldwide since early 2004. Data suggest SARS-CoV evolved from a natural reservoir of SARS-CoV-like viruses in horseshoe bats through civet cats or intermediate animal hosts in wet markets of China. Whether or not a large-scale reemergence of SARS will occur is unknown. Finding a novel HCoV sparked a renewed interest in HCoV research, and 2 years later NL63 and HKU1 were identified as newly recognized HCoVs. Investigations have revealed that HCoV NL63 was present in archived human respiratory tract specimens as early as 1981 and HKU1 as early as 1995. In 2012, MERS-CoV was identified as a novel virus responsible for severe respiratory illness, first detected in an individual from the Kingdom of Saudi Arabia and another individual from Qatar. Data suggest MERS-CoV likely evolved from bat CoV, with dromedary camels acting as intermediate hosts.

HCoVs 229E, OC43, NL63, and HKU1 can be found worldwide. They cause most disease in the winter and spring months in temperate climates. Seroprevalence data for these HCoVs suggest that exposure is common in early childhood, with approximately 90% of adults being seropositive for HCoVs 229E, OC43, and NL63 and 60% being seropositive for HCoV HKU1. MERS-CoV cases continue primarily in the Middle East, primarily linked to exposure to camels or close contact with an unrecognized case. Health care-associated transmission has occurred during care of a MERS-CoV-infected patient. In 2015, a large outbreak of MERS-CoV in South Korea, resulting in 186 cases and 36 deaths, was traced back to an individual who returned from travel in the Middle East. Limited other travel-related cases have occurred without comparable secondary transmission.

The modes of transmission for CoVs 229E, OC43, NL63, and HKU1 have not been well studied. However, on the basis of studies of other respiratory tract viruses, it is likely that transmission occurs primarily via a combination of droplet and direct and indirect contact spread. Which of these modes are most important remains to be determined, and the possible role of aerosol spread requires further study. For MERS-CoV, studies suggest that droplet and direct contact spread are likely the most common modes of transmission, although evidence of indirect contact spread and aerosol spread also exist. Fecal droplet and fecal-oral transmission also have been proposed as possible routes of MERS-CoV transmission. There is no evidence of vertical transmission of MERS-CoV. HCoVs 229E and OC43 are most likely to be transmitted during the first few days of illness, when symptoms and respiratory viral loads are at their highest. Further study is needed to confirm that this holds true for HCoVs NL63 and HKU1. SARS-CoV and MERS-CoV are most likely to be transmitted during the second week of illness, when both symptoms and respiratory viral loads peak.

The **incubation period for HCoV-229E** is 2 to 5 days (median 3 days).The **incubation period for SARS-CoV** is estimated to be 2 to 10 days (median, 4 days). The **incubation period for MERS-CoV** is estimated to be 2 to 14 days (median 5 days).

DIAGNOSTIC TESTS

Following the SARS global outbreak, some clinical laboratories started offering comprehensive respiratory molecular diagnostic testing using reverse transcriptase-polymerase chain reaction (RT-PCR) assays, some of which include HCoVs 229E, OC43, NL54, and HKU1 as targets. Public health laboratories offer RT-PCR and antibody testing for MERS-CoV. Diagnostic laboratory and clinical guidance for SARS is available on the Centers for Disease Control and Prevention (CDC) SARS website (**www.cdc.gov/sars/index.html**).

Specimens obtained from the upper and lower respiratory tract are the most appropriate samples for HCoV detection. The yield from lower respiratory tract specimens is higher than that from upper respiratory tract specimens for SARS-CoV and MERS-CoV. Stool and serum samples also frequently test positive using RT-PCR in patients with SARS-CoV and have tested positive in some patients with MERS-CoV and HCoV HKU1. For HCoVs 229E and OC43, specimens are most likely to be positive during the first few days of illness; whether this also is true for HCoVs NL63 and HKU1 requires further study. For SARS-CoV, respiratory and stool specimens may not test positive until the second week of illness when symptoms and viral loads peak; serum samples most likely test positive in the first week of illness. Compared with adults, infants and children with SARS-CoV infections are less likely to have positive test results, consistent with the milder symptoms and presumed corresponding lower viral loads seen in this age group. For both SARS-CoV and MERS-CoV, it is recommended to collect specimens for RT-PCR from the lower respiratory and upper respiratory tract along with serum. A stool sample is recommended for patients with suspected SARS-CoV. Serologic testing is available for SARS-CoV and MERS-CoV at public health laboratories, primarily for research and surveillance purposes.

TREATMENT

Infections attributable to HCoVs generally are treated with supportive care. SARS-CoV and MERS-CoV infections are more serious. Steroids, type 1 interferons, convalescent plasma, ribavirin, and lopinavir/ritonavir all were used clinically to treat patients with SARS, albeit without evidence of efficacy. In vitro data suggest type 1 interferons and lopinavir inhibit MERS-CoV replication. However, treatment efficacy of any antiviral agent for MERS-CoV has yet to be established.

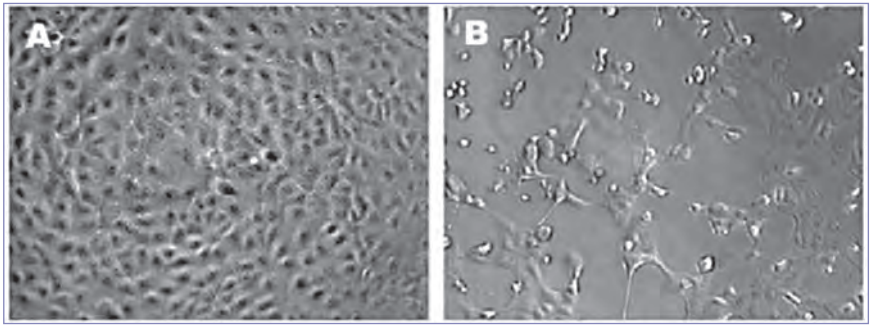


Image 36.1
Microscopic appearance of control (A) and infected (B) Vero E6 cells, demonstrating cytopathic effects. The cytopathic effect of severe acute respiratory syndrome coronavirus on Vero E6 was evident within 24 hours after infection. Courtesy of Centers for Disease Control and Prevention.

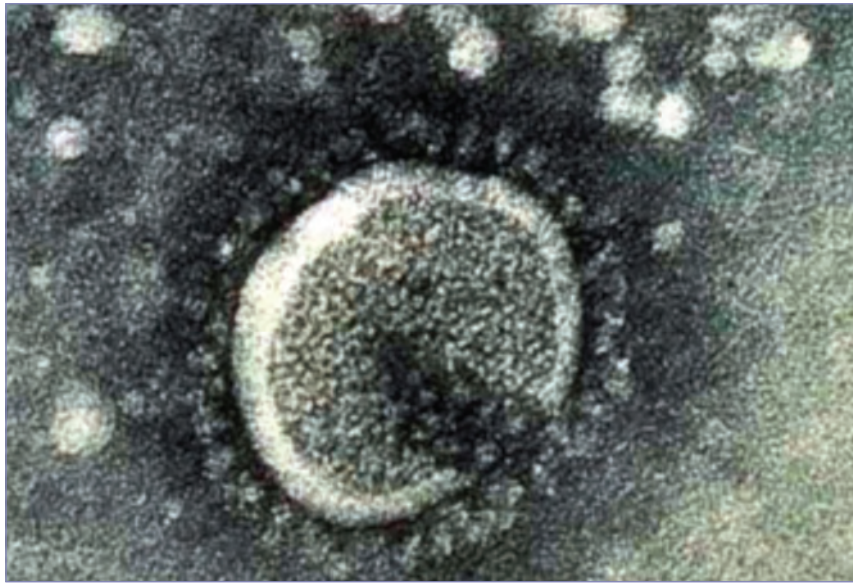


Image 36.2
Electron micrograph of a coronavirus. Pleomorphic virions average 100 nm in diameter and are covered with club-shaped knobs.

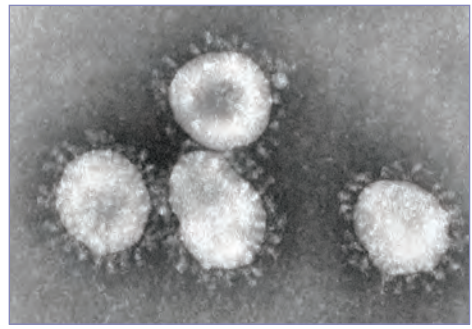


Image 36.3
Coronaviruses are a group of viruses that have a halo or crownlike (corona) appearance when viewed in an electron microscope. Severe acute respiratory syndrome (SARS) coronavirus was the etiologic agent of the 2003 SARS outbreak. Additional specimens are being tested to learn more about this coronavirus and its etiologic link with SARS. Courtesy of Centers for Disease Control and Prevention.

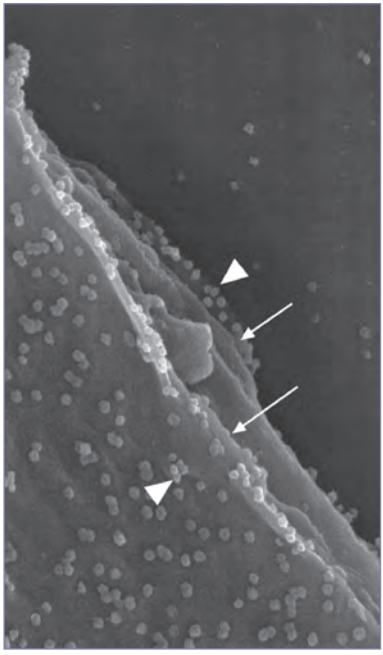


Image 36.4
This scanning electron micrograph (SEM) revealed the thickened, layered edge of severe acute respiratory syndrome–infected Vero E6 culture cells. The thickened edges of the infected cells were ruffled and appeared to comprise layers of folded plasma membranes. Note the layered cell edge (arrows) seen by SEM. Virus particles (arrowheads) are extruded from the layered surfaces. Courtesy of Centers for Disease Control and Prevention.

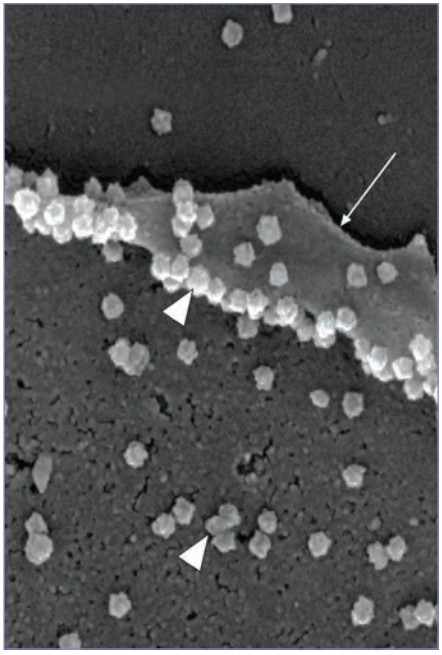


Image 36.5
This scanning electron micrograph (SEM) revealed the thickened, layered edge of severe acute respiratory syndrome–infected Vero E6 culture cells. The thickened edges of the infected cells were ruffled and appeared to comprise layers of folded plasma membranes. Note the layered cell edge (arrow) seen by SEM. Virus particles (arrowheads) are extruded from the layered surfaces. Courtesy of Centers for Disease Control and Prevention.

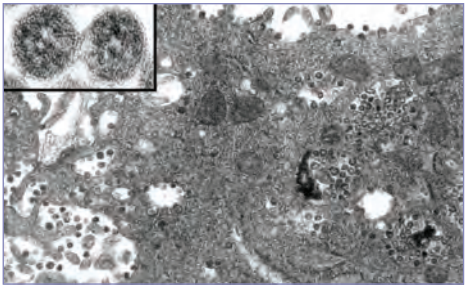


Image 36.6
Note the coronaviruses contained within cytoplasmic membrane-bound vacuoles and cisternae of the rough endoplasmic reticulum. This thin-section electron micrograph of an infected Vero E6 cell reveals coronavirus particles. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 37

Cryptococcus neoformans and *Cryptococcus gattii* Infections

(Cryptococcosis)

CLINICAL MANIFESTATIONS

Primary pulmonary infection is acquired by inhalation of aerosolized *Cryptococcus* fungal elements found in contaminated soil or organic material (eg, trees, rotting wood, and bird guano) and often is asymptomatic or mild. Pulmonary disease, when symptomatic, is characterized by cough, chest pain, and constitutional symptoms. Chest radiographs may reveal solitary or multiple masses; patchy, segmental, or lobar consolidation, which often is multifocal; or nodular or reticulonodular interstitial changes. Pulmonary cryptococcosis may present as acute respiratory distress syndrome (ARDS) and may mimic *Pneumocystis* pneumonia. Hematogenous dissemination to the central nervous system (CNS), bones, skin, and other sites can occur, is uncommon, and almost always occurs in children with defects in T-lymphocyte–mediated immunity (eg, children with leukemia or lymphoma, children taking corticosteroids, children with congenital immunodeficiency or acquired immunodeficiency syndrome [AIDS], or children who have undergone solid organ transplantation). Usually, several sites are infected, but manifestations of involvement at one site predominate. Cryptococcal meningitis, the most common and serious form of cryptococcal disease, often follows an indolent course. Symptoms are characteristic of meningitis, meningoencephalitis, or space-occupying lesions but sometimes manifest only as subtle, nonspecific findings such as fever, headache, or behavioral changes. Cryptococcal fungemia without apparent organ involvement occurs in patients with human immunodeficiency virus (HIV) infection but is rare in children.

ETIOLOGY

Although there are more than 30 species of *Cryptococcus*, only 2 species, *Cryptococcus neoformans* (var *neoformans* and var *grubii*) and *Cryptococcus gattii*, are regarded as human pathogens.

EPIDEMIOLOGY

C neoformans var *neoformans* and *C neoformans* var *grubii* are isolated primarily from soil contaminated with pigeon or other bird droppings and cause most human infections, especially infections in immunocompromised hosts. *C neoformans* infects 5% to 10% of adults with AIDS, but infection is rare in HIV-infected children. *C gattii* (formerly *C neoformans* var *gattii*) is associated with trees and surrounding soil and has emerged as a pathogen producing a respiratory syndrome with or without neurologic findings in individuals from British Columbia, Canada, the Pacific Northwest region of the United States, and occasionally other regions of the United States. A high frequency of disease also has been reported in Aboriginal people in Australia and in the central province of Papua New Guinea. *C gattii* causes disease in immunocompetent and immunocompromised people, and cases have been reported in children. Person-to-person transmission does not occur.

The **incubation period for *C neoformans*** is unknown; dissemination often represents reactivation of latent disease acquired previously. The **incubation period for *C gattii*** is 8 weeks to 13 months.

DIAGNOSTIC TESTS

The cerebrospinal fluid (CSF) profile of cryptococcal meningoencephalitis is characterized by a lack in both cellularity and alterations in biochemical profile, especially in HIV-infected individuals. Laboratory diagnosis of cryptococcal infection is best performed using antigen detection methods or by culture. The latex agglutination test (most commonly used), lateral flow immunoassay, and enzyme immunoassay for detection of cryptococcal capsular polysaccharide antigen (galactoxylomannan) in serum or CSF specimens are excellent rapid diagnostic tests for those with suspected meningitis. India ink stain for screening of CSF in cases of suspected cryptococcal meningitis has significantly lower sensitivity and is not recommended as a stand-alone rapid test. Antigen is detected in CSF or serum specimens from more than 95% of patients with cryptococcal meningitis, but antigen test results can be falsely negative when antigen concentrations are very

high (prozone effect). A lateral flow assay, which shows good agreement with standard antigen testing, has been developed for the diagnosis of cryptococcosis, especially in resource-limited countries.

Definitive diagnosis requires isolation of the organism from body fluid or tissue specimens. Blood should be cultured by lysis-centrifugation. Media containing cycloheximide, which inhibits growth of *C neoformans,* should not be used. Most laboratories confirm the production of urease by *Cryptococcus* species. Differentiation between *C neoformans* and *C gattii* can be made by the use of the selective medium l-canavanine glycine bromothymol blue (CGB) agar. Sabouraud dextrose agar is useful for isolation of *Cryptococcus* organisms from sputum, bronchopulmonary lavage, tissue, or CSF specimens. In refractory or relapse cases, susceptibility testing can be helpful, although antifungal resistance is uncommon. CSF specimens may contain only a few organisms, and a large quantity of CSF may be needed to recover the organism. Polymerase chain reaction assays are investigational. Encapsulated yeast cells can be visualized using India ink or other stains of CSF and bronchoalveolar lavage specimens, but this method has limited sensitivity. Focal pulmonary or skin lesions can be biopsied for fungal staining and culture.

TREATMENT

No trials dedicated to children have been performed for treatment of cryptococcal disease, so optimal dosing and duration is not known. Amphotericin B deoxycholate is indicated as induction therapy for patients with meningeal and other serious cryptococcal infections. Monitoring of blood counts or serum peak flucytosine concentrations (with a target of 40 to 60 μg/mL 2 hours after the dose) is recommended to prevent neutropenia. Patients with meningitis should receive induction combination therapy for at least 2 weeks and until a repeat CSF culture is negative, followed by consolidation therapy with fluconazole for a minimum of 8 weeks. Liposomal amphotericin B or amphotericin B lipid complex can be used in children with renal impairment or those intolerant to amphotericin B deoxycholate. If flucytosine cannot be administered, amphotericin B alone has been successfully used in pediatric cryptococcosis. A lumbar puncture should be performed after 2 weeks of therapy to document microbiologic clearance. The 20% to 40% of patients in whom culture is positive after 2 weeks of therapy will require a more prolonged induction treatment course. For any relapse, induction antifungal therapy should be restarted for 4 to 10 weeks, CSF cultures should be repeated every 2 weeks until sterile, and antifungal susceptibility of the relapse isolate should be determined. Monitoring of serum cryptococcal antigen is not useful to monitor response to therapy in patients with cryptococcal meningitis.

Increased intracranial pressure occurs frequently despite microbiologic response and often is associated with clinical deterioration. Significant elevation of intracranial pressure is a major source of morbidity and should be managed with frequent repeated lumbar punctures or placement of a lumbar drain. Immune reconstitution inflammatory syndrome (IRIS) is described.

Children with HIV infection who have completed initial therapy for cryptococcosis should receive long-term suppressive therapy with fluconazole. Oral itraconazole daily (oral solution preferred over capsule because of better bioavailability and no need to take with food) or amphotericin B deoxycholate, 1 to 3 times weekly, are less effective alternatives. Discontinuing chronic suppressive therapy for cryptococcosis (after 1 year or longer of secondary prophylaxis) can be considered in asymptomatic children 6 years or older who are receiving antiretroviral therapy, have sustained ($\geq$6 months) increases in CD4+ T-lymphocyte counts to $\geq$100 cells/mm^3, and have an undetectable HIV viral load for at least 3 months. Secondary prophylaxis should be reinstituted if the CD4+ T-lymphocyte count decreases to $<$100/mm^3.

Patients with less severe nonmeningeal disease (pulmonary disease) can be treated with fluconazole, but data on use of fluconazole for children with *C neoformans* infection is limited; itraconazole is a potential alternative. Echinocandins are not active against cryptococcal infections and should not be used.

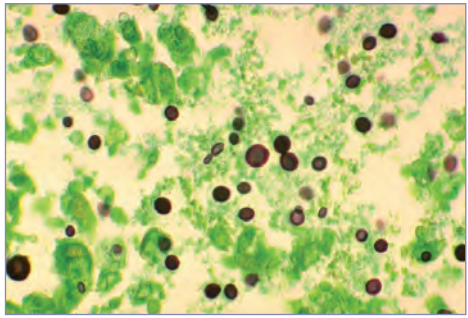


Image 37.1
Cryptococcosis of lung in patient with AIDS (methenamine silver stain). Histopathology of lung shows numerous extracellular yeasts of *Cryptococcus neoformans* within an alveolar space. Yeasts show narrow-base budding and characteristic variation in size. Courtesy of Centers for Disease Control and Prevention.

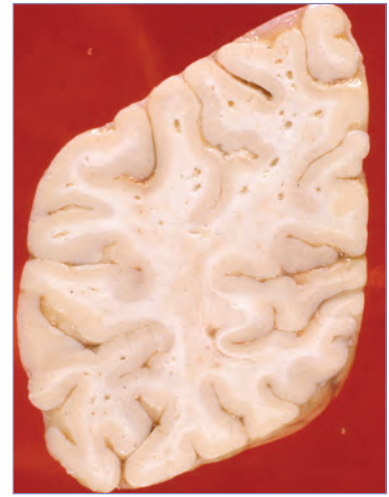


Image 37.2
Cryptococcus meningitis. Cystic lesions resulting from accumulation of organisms in perivascular spaces. Courtesy of Dimitris P. Agamanolis, MD.

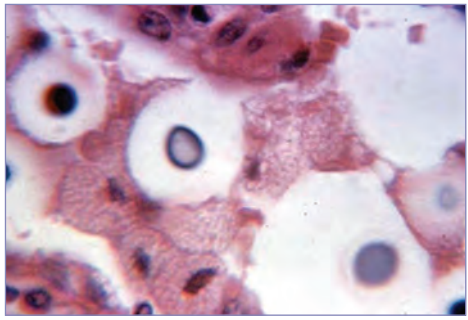


Image 37.3
Cryptococcosis of the liver (original magnification ×810) in an immunodeficient patient with disseminated disease. The mucinous capsules are prominent. Courtesy of Edgar O. Ledbetter, MD, FAAP.

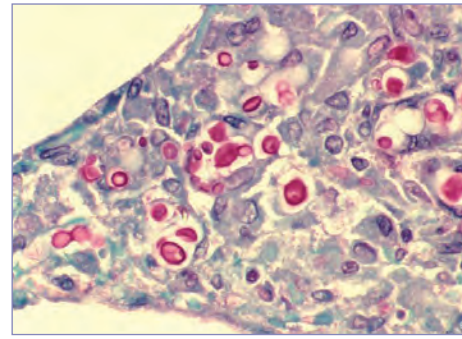


Image 37.4
Cryptococcosis of lung in patient with AIDS (mucicarmine stain). Histopathology of lung shows widened alveolar septum containing a few inflammatory cells and numerous yeasts of *Cryptococcus neoformans*. The inner layer of the yeast capsule stains red. Courtesy of Centers for Disease Control and Prevention/Edwin P. Ewing Jr, MD.

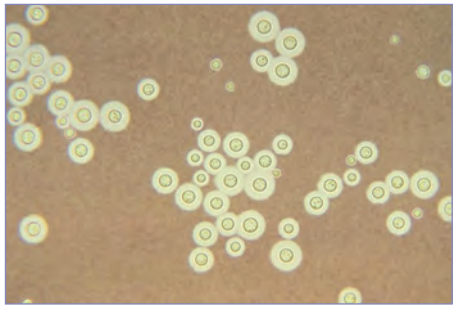


Image 37.5
This photomicrograph depicts *Cryptococcus neoformans* using a light India ink staining preparation. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 38

Cryptosporidiosis

CLINICAL MANIFESTATIONS

Frequent, nonbloody, watery diarrhea is the most common manifestation of cryptosporidiosis, although infection can be asymptomatic. Other symptoms include abdominal cramps, fatigue, fever, vomiting, anorexia, and weight loss. In infected immunocompetent adults and children, diarrheal illness is self-limited, usually resolving within 2 to 3 weeks. Infected immunocompromised hosts, such as children who have received solid organ transplants or who have advanced human immunodeficiency virus (HIV) disease, can experience profuse diarrhea lasting weeks to months; this can lead to malnutrition and wasting. Extraintestinal cryptosporidiosis (eg, disease in the pulmonary or biliary tract or rarely in the pancreas) has been reported in immunocompromised people.

ETIOLOGY

Cryptosporidium species are oocyst-forming coccidian protozoa. Oocysts are excreted in feces of an infected host and are transmitted via the fecal-oral route. *Cryptosporidium hominis* (which predominantly infects people) and *Cryptosporidium parvum* (which infects people, preweaned bovine calves, and other mammals) cause more than 90% of human cryptosporidiosis.

EPIDEMIOLOGY

Extensive waterborne disease outbreaks have been associated with contamination of drinking water and recreational water (eg, swimming pools, lakes, and water playgrounds). Since 2004, the incidence of nationally reported cryptosporidiosis increased 2 to 3 times. In children, the incidence of cryptosporidiosis is greatest during summer and early fall, corresponding to the outdoor swimming season. Cases are most frequently reported in children 1 through 4 years of age, followed by those 5 through 9 years of age.

Because oocysts are extremely chlorine tolerant, multistep treatment processes often are used to remove (eg, filter) and inactivate (eg, ultraviolet treatment) oocysts to protect public drinking water supplies. Typical filtration systems used for swimming pools do not efficiently remove oocysts from contaminated water. As a result, *Cryptosporidium* species have become the leading cause of recreational water–associated illness outbreaks, responsible for 36 (68%) of 53 outbreaks linked to treated aquatic venues (eg, swimming pools) in which an infectious cause was identified.

In addition to waterborne transmission, people can acquire infections from livestock and from animals found in petting zoos, particularly preweaned bovine calves and lambs, or from pets. Foodborne transmission can occur. *Cryptosporidium* organisms have been detected in raw produce and in raw or unpasteurized milk. Person-to-person transmission occurs as well and can cause outbreaks in child care centers, in which up to 70% of attendees reportedly have been infected. *Cryptosporidium* species can cause traveler's diarrhea.

The **incubation period** usually is 2 to 10 days. Recurrence of symptoms has been reported frequently. In immunocompetent people, oocyst shedding usually ceases within 2 weeks after complete symptom resolution. In immunocompromised people, the period of oocyst shedding can continue for months.

DIAGNOSTIC TESTS

Routine laboratory examination of stool for ova and parasites might not include testing for *Cryptosporidium* species, so testing for the organism should be requested specifically. The direct fluorescent antibody (DFA) method for microscopic detection of oocysts in stool, as well as multiwell plate enzyme immunoassays (EIAs) targeting cryptosporidial antigens, are widely available and are recommended for diagnosis of cryptosporidiosis. Some of these assays target both *Cryptosporidium* species and *Giardia lamblia* in a single test format. The detection of oocysts on microscopic examination of stool specimens may be accomplished by direct wet mount if concentration of the oocysts is high. Alternatively, the formalin ethyl acetate stool concentration method can be used followed by staining of the stool specimen with a modified Kinyoun acid-fast stain. Oocysts generally are small (4–6 μm in diameter) and can be missed in a rapid scan of a slide.

Because shedding can be intermittent, at least 3 stool specimens collected on separate days should be examined before considering test results to be negative. Organisms also can be identified in intestinal biopsy tissue or sampling of intestinal fluid. Molecular methods are being used increasingly for detection of cryptosporidiosis, particularly nucleic acid amplification tests (NAATs) that target multiple gastrointestinal tract pathogens in a single assay.

TREATMENT

Generally, immunocompetent people may not need specific therapy. A 3-day course of nitazoxanide oral suspension has been approved by the US Food and Drug Administration (FDA) for treatment of diarrhea associated with cryptosporidiosis in patients 1 year or older. The nitazoxanide dose for healthy children not infected with HIV is age based.Courses of nitazoxanide (generally >14 days) have been recommended in children who are solid organ transplant recipients for the treatment of diarrhea caused by *Cryptosporidium*, although efficacy is questionable. Disease in children with immune dysfunction, especially solid organ transplant recipients or those with HIV infection, can be refractory to therapy.

In HIV-infected patients, improvement in CD4+ T-lymphocyte count associated with antiretroviral therapy can lead to symptom resolution and cessation of oocyst shedding. For this reason, administration of combination antiretroviral therapy (cART) is the primary treatment for cryptosporidiosis in patients with HIV infection. The recommended nitazoxanide dosing duration is 3 to 14 days for HIV-infected children.

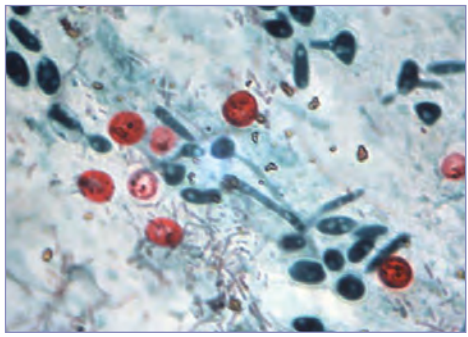


Image 38.1
This micrograph of a direct fecal smear is stained to detect *Cryptosporidium* species, an intracellular protozoan parasite. Using a modified cold Kinyoun acid-fast staining technique and under an oil immersion lens, *Cryptosporidium* species oocysts, which are acid-fast, stain red, and yeast cells, which are not acid-fast, stain green. Courtesy of Centers for Disease Control and Prevention.

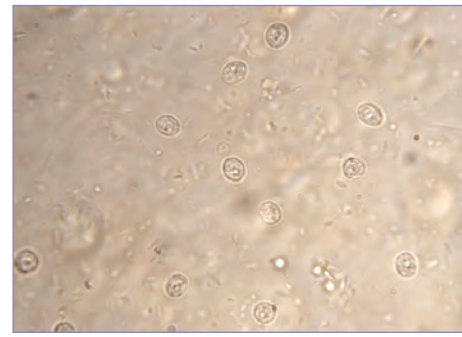


Image 38.2
This micrograph of a stool smear reveals *Cryptosporidium parvum* as the cause of this patient's cryptosporidiosis. *Cryptosporidium* is a microscopic parasite that can live in the intestines of humans and animals. The parasite is protected by an outer shell that allows it to survive outside the body for long periods and makes it resistant to chlorine disinfection. Courtesy of Centers for Disease Control and Prevention.

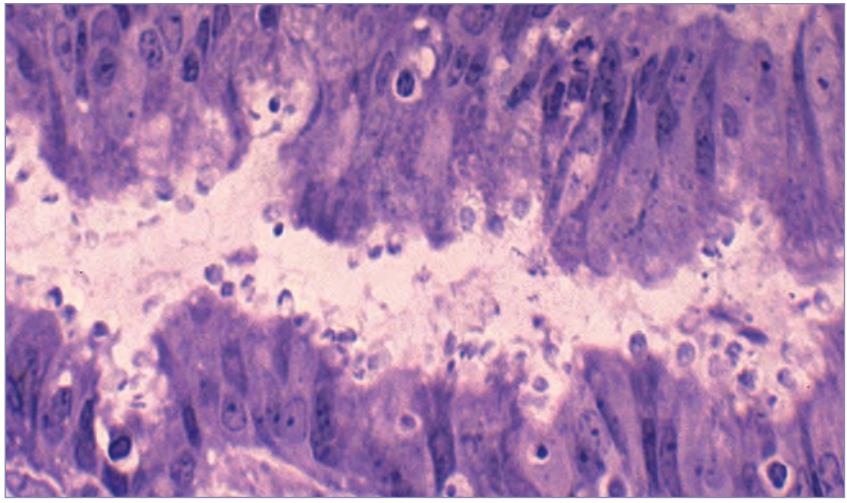


Image 38.3
Histopathology of cryptosporidiosis, intestine. Plastic-embedded, toluidine blue-stained section shows numerous *Cryptosporidium* organisms at luminal surfaces of epithelial cells. Courtesy of Centers for Disease Control and Prevention.

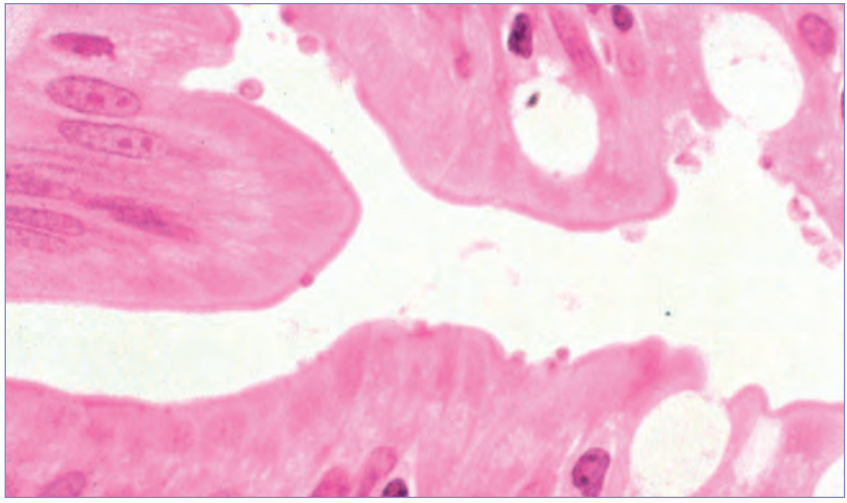


Image 38.4
Cryptosporidium, a spore-forming coccidian protozoan, can be seen on the brush border of intestinal mucosa. *Cryptosporidium* does not invade below the epithelial layer of the mucosa, so fecal leukocytes are absent.

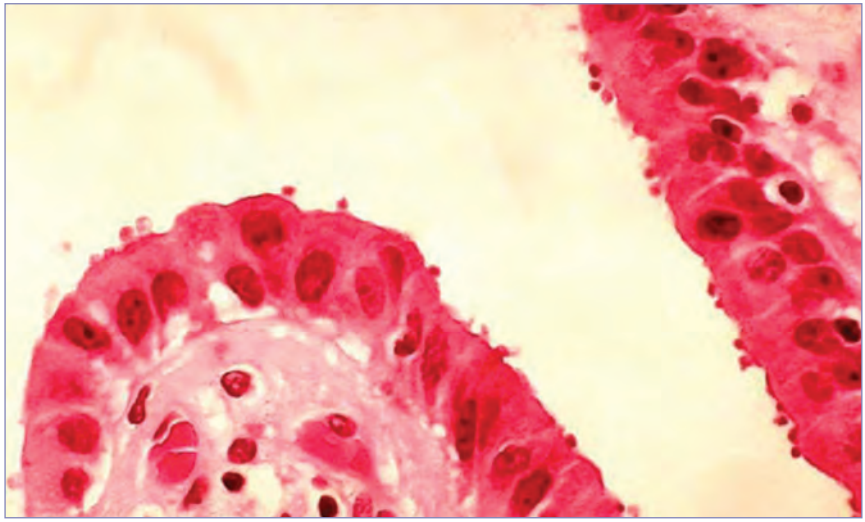


Image 38.5
Cryptosporidiosis of gallbladder in a patient with AIDS. Histopathologic features of gallbladder epithelium include numerous *Cryptosporidium* organisms along luminal surfaces of epithelial cells. Courtesy of Centers for Disease Control and Prevention.

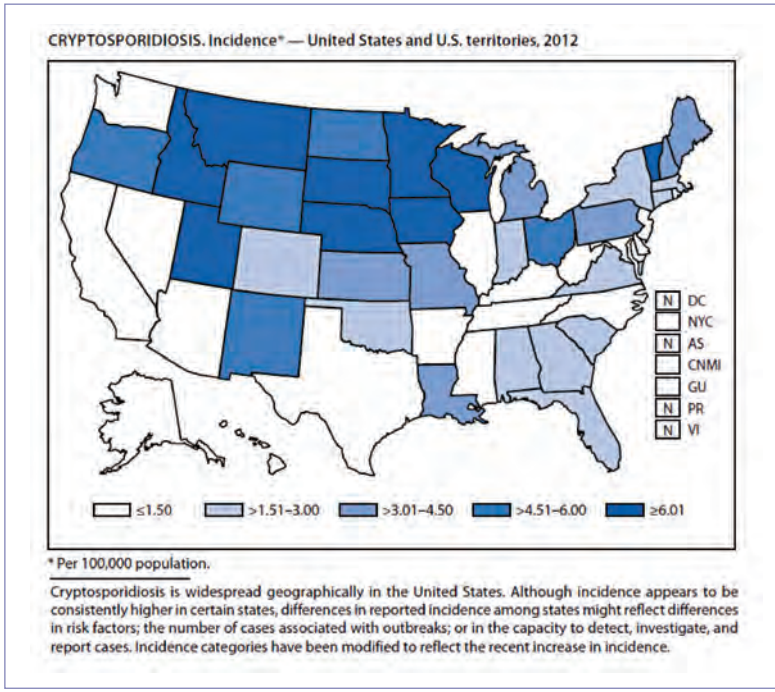


Image 38.6
Incidence—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

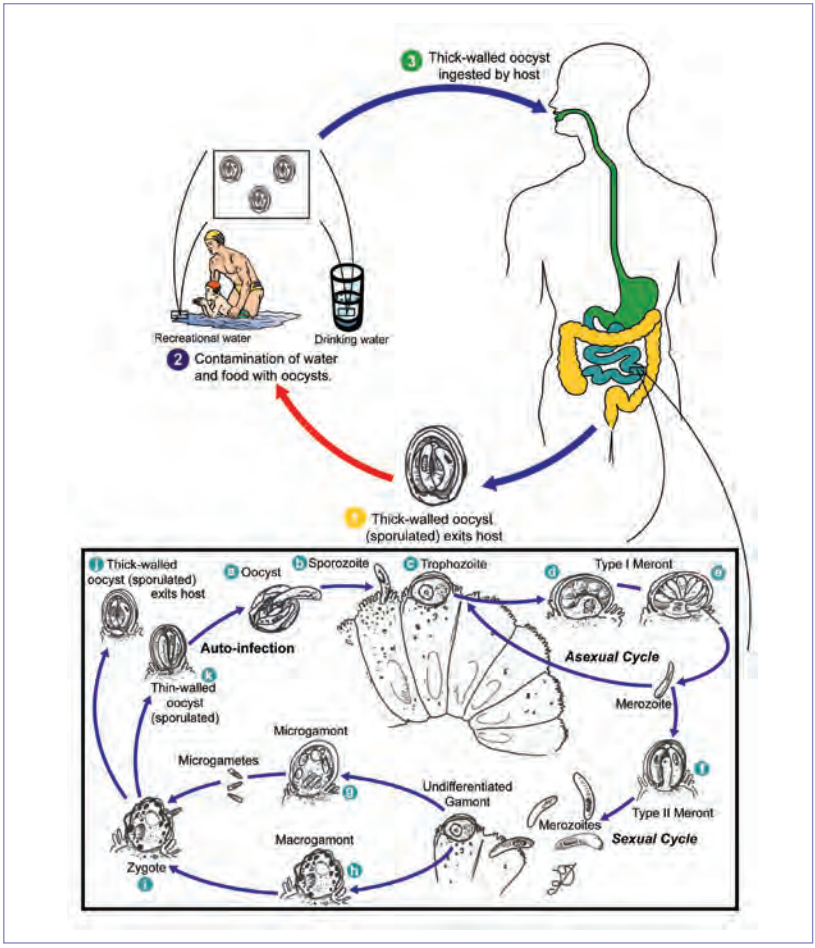


Image 38.7

Life cycle of *Cryptosporidium*. Sporulated oocysts, containing 4 sporozoites, are excreted by the infected host through feces and possibly other routes, such as respiratory secretions (1). Transmission of *Cryptosporidium parvum* occurs mainly through contact with contaminated water (eg, drinking or recreational water). Occasionally, food sources, such as chicken salad, may serve as vehicles for transmission. Many outbreaks in the United States have occurred in water parks, community swimming pools, and child care centers. Zoonotic transmission of *C parvum* occurs through exposure to infected animals or exposure to water contaminated by feces of infected animals (2). Following ingestion (and possibly inhalation) by a suitable host (3), excystation (a) occurs. The sporozoites are released and parasitize epithelial cells (b, c) of the gastrointestinal tract or other tissues. In these cells, the parasites undergo asexual multiplication (schizogony or merogony) (d, e, f) and then sexual multiplication (gametogony), producing microgamonts (male) (g) and macrogamonts (female) (h). On fertilization of the macrogamonts by the microgametes (i), oocysts (j, k) develop that sporulate in the infected host. Two different types of oocysts are produced: the thick-walled, which is commonly excreted from the host (j), and the thin-walled (k), which is primarily involved in autoinfection. Oocysts are infective on excretion, thus permitting direct and immediate fecal-oral transmission. Note that oocysts of *Cyclospora cayetanensis*, another important coccidian parasite, are unsporulated at the time of excretion and do not become infective until sporulation is completed. Refer to the life cycle of *C cayetanensis* for further details. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 39

Cutaneous Larva Migrans

CLINICAL MANIFESTATIONS

Nematode larvae produce pruritic, reddish papules at the site of skin entry. As the larvae migrate through skin, advancing several millimeters to a few centimeters a day, intensely pruritic serpiginous tracks are formed, a condition referred to as creeping eruption. Bullae may develop later as a complication of the larval migration. This condition most often is caused by larvae of the dog and cat hookworm *Ancylostoma braziliense* but can be caused by other nematodes, including *Strongyloides* and human hookworm species. Larval activity can continue for several weeks or months, but the infection is self-limiting. Cutaneous larva migrans is a clinical diagnosis based on advancing serpiginous tracks in the skin with associated intense pruritus. Rarely, in infections with certain species of parasites, larvae may penetrate deeper tissues and cause pneumonitis (Löffler syndrome), which can be severe. Occasionally, the larvae of *Ancylostoma caninum* can reach the intestine and may cause eosinophilic enteritis.

ETIOLOGY

Infective larvae of cat and dog hookworms (ie, *Ancylostoma braziliense* and *Ancylostoma caninum*) are the usual causes. Other skin-penetrating nematodes are occasional causes.

EPIDEMIOLOGY

Cutaneous larva migrans is a disease of children, utility workers, gardeners, sunbathers, and others who come in contact with soil contaminated with cat and dog feces. In the United States, locally acquired cases are mostly in the Southeast, but most identified cases are among travelers, not locally acquired, particularly those who have walked barefoot on beaches.

The **incubation period** typically is short, several days after larval penetration of the skin. In some cases, onset of disease may be delayed for weeks to months.

DIAGNOSTIC TESTS

The diagnosis is made clinically, and biopsies are not indicated. Biopsy specimens typically demonstrate an eosinophilic inflammatory infiltrate, but the migrating parasite is not visualized. Eosinophilia and increased immunoglobulin (Ig) E serum concentrations occur in some cases. Larvae have been detected in sputum and gastric washings in patients with the rare complication of pneumonitis. Enzyme immunoassay or Western blot analysis using antigens of *A caninum* have been developed in research laboratories, but these assays are not available for routine diagnostic use.

TREATMENT

The disease usually is self-limited, with spontaneous cure after several weeks or months. Orally administered ivermectin or albendazole is the recommended therapy. Safety of ivermectin in young infants (<15 kg) and pregnant women remains to be established. Children younger than 2 years or weighing less than 15 kg may be treated with topical preparations.

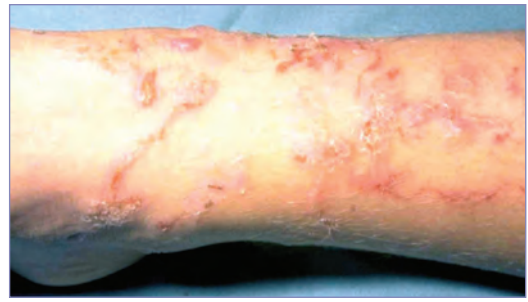


Image 39.1
Cutaneous larva migrans lesions on lower leg (caused by hookworm larvae of *Ancylostoma braziliense* and *Ancylostoma caninum*).

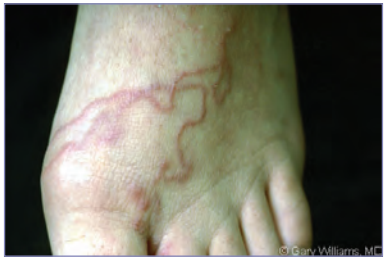


Image 39.2
Cutaneous larva migrans lesions of the foot of a 10-year-old girl. In the United States, this dog and cat hookworm infection is most commonly seen in the Southeast. These raised, serpiginous, pruritic, migrating eruptions may extend rapidly. Copyright Gary Williams, MD.

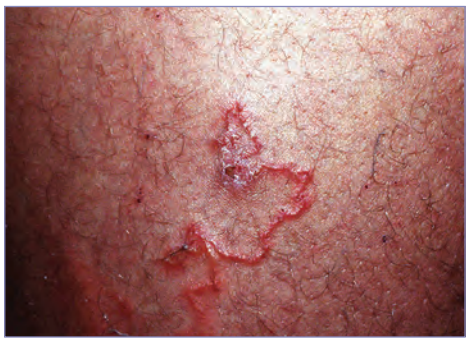


Image 39.4
Adult who noted a migrating skin lesion on left thigh for 2 weeks. Copyright Larry I. Corman.

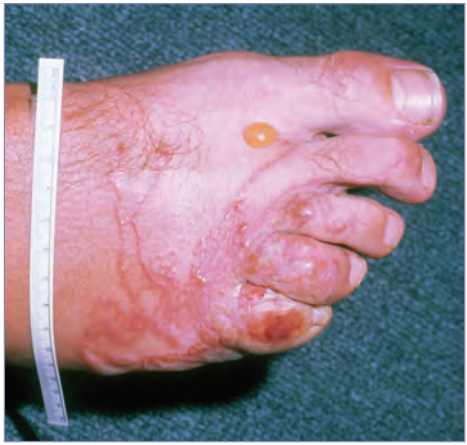


Image 39.3
Cutaneous larva migrans infection of the foot in an adolescent male. Courtesy of George Nankervis, MD.

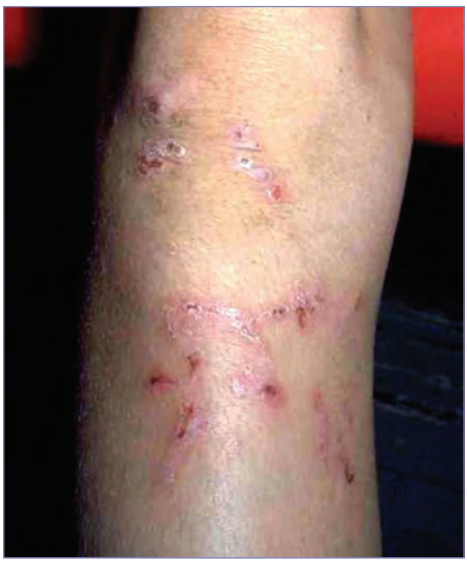


Image 39.5
Cutaneous larva migrans 48 hours after treatment. Orally administered albendazole or ivermectin is the recommended therapy.

CHAPTER 40

Cyclosporiasis

CLINICAL MANIFESTATIONS

Watery diarrhea is the most common symptom of cyclosporiasis and can be profuse and protracted. Anorexia, nausea, vomiting, substantial weight loss, flatulence, abdominal cramping, myalgia, and prolonged fatigue can occur. Low-grade fever occurs in approximately 50% of patients. Biliary tract disease has been reported. Infection usually is self-limited, but untreated people may have remitting, relapsing symptoms for weeks to months. Asymptomatic infection has been documented most commonly in settings where cyclosporiasis is endemic.

ETIOLOGY

Cyclospora cayetanensis is a coccidian protozoan; oocysts (rather than cysts) are passed in stools.

EPIDEMIOLOGY

C cayetanensis is known to be endemic in many resource-limited countries and has been reported as a cause of traveler's diarrhea. Both foodborne and waterborne outbreaks have been reported. Most of the outbreaks in the United States and Canada have been associated with consumption of imported fresh produce (eg, basil, cilantro, raspberries). Humans are the only known hosts for *C cayetanensis.* Direct person-to-person transmission is unlikely, because excreted oocysts take days to weeks under favorable environmental conditions to sporulate and become infective. Oocysts are resistant to most disinfectants used in food and water processing and can remain viable for prolonged periods in cool, moist environments.

The **incubation period** typically is 1 week but ranges from 2 days to 2 or more weeks.

DIAGNOSTIC TESTS

Diagnosis is made by identification of oocysts (8–10 μm in diameter) in stool, intestinal fluid/aspirates, or intestinal biopsy specimens. Oocysts may be shed at low levels, even by people with profuse diarrhea. This constraint underscores the utility of repeated stool examinations, sensitive recovery methods (eg, concentration procedures including formalin-ethyl acetate sedimentation or sucrose centrifugal flotation), and detection methods that highlight the organism. Oocysts are autofluorescent and are variably acid fast after modified acid-fast staining of stool specimens.

TREATMENT

Trimethoprim-sulfamethoxazole, typically for 7 to 10 days, is the drug of choice; immunocompromised patients may need longer courses of therapy. No highly effective alternatives have been identified for people who cannot tolerate trimethoprim-sulfamethoxazole.

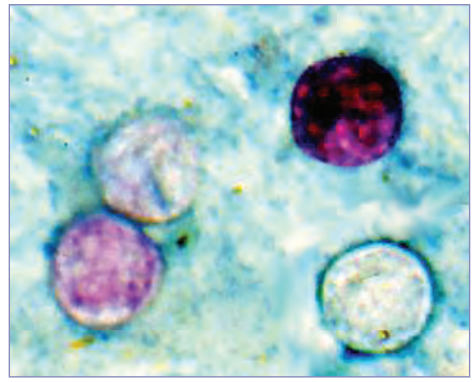


Image 40.1
Four *Cyclospora* oocysts from fresh stool fixed in 10% formalin (acid-fast stain). Compared with wet mount preparations, the oocysts are less perfectly round and have a wrinkled appearance. Most important, the staining is variable among the 4 oocysts. Courtesy of Centers for Disease Control and Prevention.

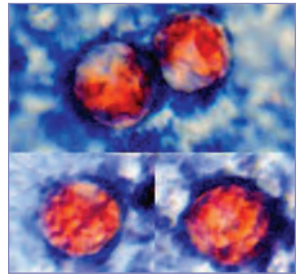


Image 40.2
Four *Cyclospora* oocysts from fresh stool fixed in 10% formalin and stained with safranin, showing the uniform staining of oocysts by this method. Courtesy of Centers for Disease Control and Prevention.

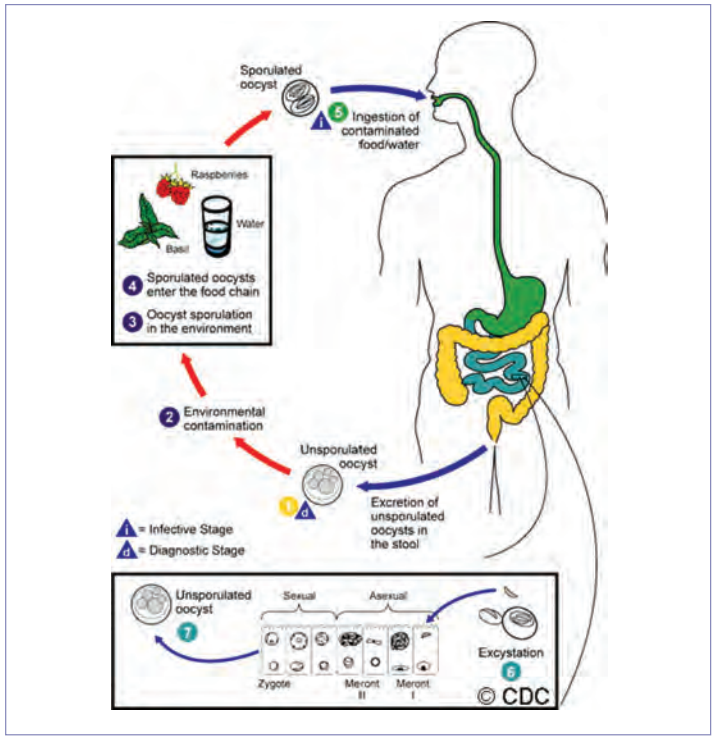


Image 40.3
Cyclospora cayetanensis. When freshly passed in stools, the oocyst is not infective (1) (thus, direct fecal-oral transmission cannot occur; this differentiates *Cyclospora* from another important coccidian parasite, *Cryptosporidium*). In the environment (2), sporulation occurs after days or weeks at temperatures between 22°C and 32°C (71.6°F and 89.6°F), resulting in division of the sporont into 2 sporocysts, each containing 2 elongate sporozoites (3). Fresh produce and water can serve as vehicles for transmission (4) and the sporulated oocysts are ingested (in contaminated food or water) (5). The oocysts excyst in the gastrointestinal tract, freeing the sporozoites which invade the epithelial cells of the small intestine (6). Inside the cells they undergo asexual multiplication and sexual development to mature into oocysts, which will be shed in stools (7). The potential mechanisms of contamination of food and water are still under investigation. Some of elements of this figure were created based on an illustration by Ortega et al. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 41

Cystoisosporiasis

(formerly Isosporiasis)

CLINICAL MANIFESTATIONS

Watery diarrhea is the most common symptom of cystoisosporiasis and can be profuse and protracted, even in immunocompetent people. Manifestations are similar to those caused by other enteric protozoa (eg, *Cryptosporidium* and *Cyclospora* species) and can include abdominal pain, cramping, anorexia, nausea, vomiting, weight loss, and low-grade fever. The proportion of infected people who are asymptomatic is unknown. Severity of infection ranges from self-limiting in immunocompetent hosts to debilitating and life-threatening in immunocompromised patients, particularly people infected with human immunodeficiency virus (HIV). Infections of the biliary tract and reactive arthritis also have been reported. Peripheral eosinophilia may occur.

ETIOLOGY

Cystoisospora belli (formerly *Isospora belli*) is a coccidian protozoan; oocysts (rather than cysts) are passed in stools.

EPIDEMIOLOGY

Infection occurs predominantly in tropical and subtropical regions of the world and can cause traveler's diarrhea. Infection results from ingestion of sporulated oocysts (eg, in contaminated food or water). Humans are the only known host for *C belli* and shed noninfective oocysts in feces. These oocysts must mature (sporulate) outside the host in the environment to become infective. Under favorable conditions, sporulation can be completed in 1 to 2 days and perhaps more quickly in some settings. Oocysts probably are resistant to most disinfectants and can remain viable for prolonged periods in a cool, moist environment.

The **incubation period** is often 1 week (range, several days to 2 or more weeks).

DIAGNOSTIC TESTS

Identification of oocysts in feces or in duodenal aspirates or finding developmental stages of the parasite in biopsy specimens (eg, of the small intestine) is diagnostic. Oocysts in stool are elongate and ellipsoidal (length, 25 to 30 μm). Oocysts can be shed in low numbers, even by people with profuse diarrhea. This constraint underscores the utility of repeated stool examinations, sensitive methods (eg, stool concentration), and methods that highlight the organism (eg, oocysts stain bright red with modified acid-fast techniques and autofluoresce viewed by ultraviolet fluorescence microscopy). The laboratory should be notified when any coccidian parasite is clinically suspected so that special microscopic methods are utilized in addition to traditional ova and parasite examination.

TREATMENT

Trimethoprim-sulfamethoxazole, typically for 7 to 10 days, is the drug of choice. Immunocompromised patients may need higher doses and a longer duration of therapy. Ciprofloxacin is less effective than trimethoprim-sulfamethoxazole. Pyrimethamine (plus leucovorin, to prevent myelosuppression) is an alternative treatment for people who cannot tolerate (or whose infection does not respond to) trimethoprim-sulfamethoxazole. Nitazoxanide has been reported to be effective, but data are limited.

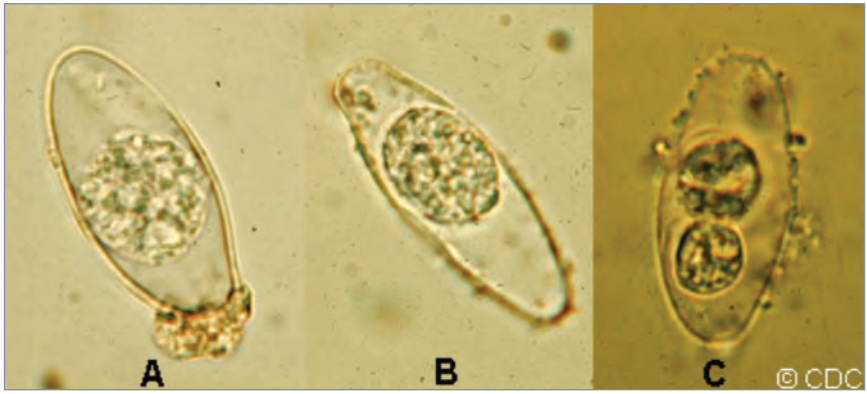


Image 41.1
Oocysts of *Cystoisospora belli* (iodine stain). The oocysts are large (25–30 µm) and have a typical ellipsoidal shape. When excreted, they are immature and contain 1 sporoblast (A, B). The oocyst matures after excretion; the single sporoblast divides into 2 sporoblasts (C), which develop cyst walls, becoming sporocysts, which eventually contain 4 sporozoites each. Courtesy of Centers for Disease Control and Prevention.

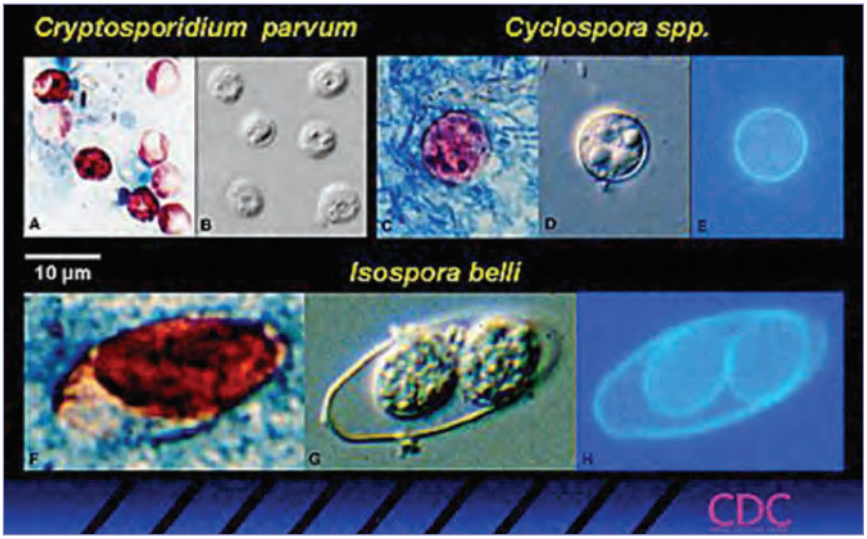


Image 41.2
Oocysts of *Cystoisospora belli* can also be stained with acid-fast stain and visualized by epifluorescence on wet mounts, as illustrated. Three coccidian parasites that most commonly infect humans, seen in acid-fast stained smears (A, C, F), bright-field differential interference contrast (B, D, G), and epifluorescence (E, H, C; *Cryptosporidium parvum* oocysts do not autofluoresce). Courtesy of Centers for Disease Control and Prevention.

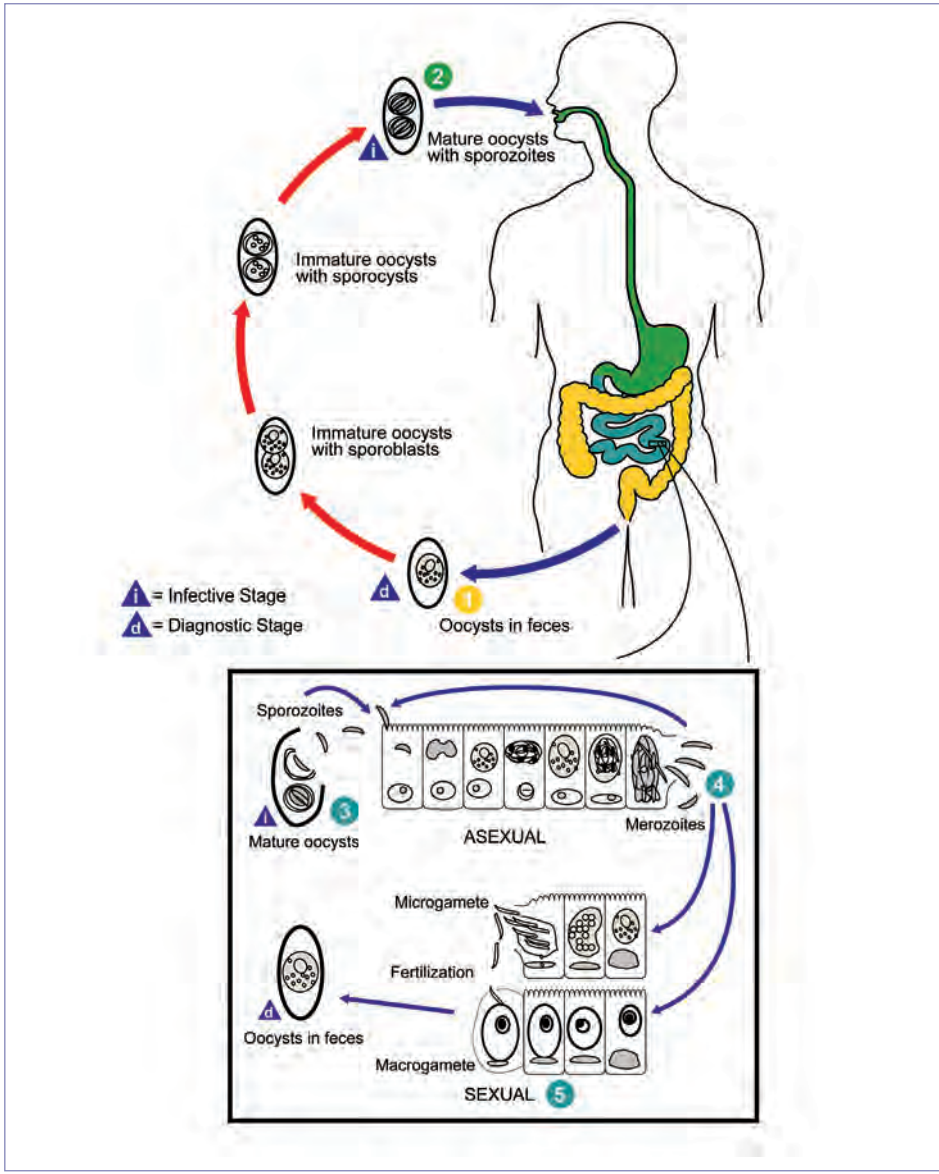


Image 41.3

At the time of excretion, the immature oocyst usually contains 1 sporoblast (more rarely, 2) (1). In further maturation after excretion, the sporoblast divides in 2 (the oocyst now contains 2 sporoblasts); the sporoblasts secrete a cyst wall, thus becoming sporocysts; and the sporocysts divide twice to produce 4 sporozoites each (2). Infection occurs by ingestion of sporocyst-containing oocysts. The sporocysts excyst in the small intestine and release their sporozoites, which invade the epithelial cells and initiate schizogony (3). On rupture of the schizonts, the merozoites are released, invade new epithelial cells, and continue the cycle of asexual multiplication (4). Trophozoites develop into schizonts that contain multiple merozoites. After a minimum of 1 week, the sexual stage begins with the development of male and female gametocytes (5). Fertilization results in the development of oocysts that are excreted in the stool (1). *Cystoisospora belli* infects humans and animals. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 42

Cytomegalovirus Infection

CLINICAL MANIFESTATIONS

Manifestations of acquired human cytomegalovirus (CMV) infection vary with the age and immunocompetence of the host. Asymptomatic infections are the most common, particularly in children. An infectious mononucleosis-like syndrome with prolonged fever and mild hepatitis, occurring in the absence of heterophile antibody production ("monospot negative"), can occur in adolescents and adults. End-organ disease, including pneumonia, colitis, retinitis, meningoencephalitis, or transverse myelitis, or a CMV syndrome characterized by fever, thrombocytopenia, leukopenia, and mild hepatitis can occur in immunocompromised hosts, including people receiving treatment for malignant neoplasms, people infected with human immunodeficiency virus (HIV), and people receiving immunosuppressive therapy for solid organ or hematopoietic stem cell transplantation. Less commonly, patients treated with biologic response modifiers can exhibit CMV end-organ disease, such as retinitis and hepatitis.

Congenital CMV infection has a spectrum of clinical manifestations but usually is not evident at birth (asymptomatic congenital CMV infection). Approximately 10% of infants with congenital CMV infection exhibit clinical findings that are evident at birth (symptomatic congenital CMV disease), with manifestations including jaundice attributable to direct hyperbilirubinemia, petechiae attributable to thrombocytopenia, purpura, hepatosplenomegaly, microcephaly, intracerebral (typically periventricular) calcifications, sensorineural hearing loss, and retinitis; developmental delays are common among affected infants in later infancy and early childhood. Death attributable to congenital CMV is estimated to occur in 3% to 10% of infants with clinically evident disease, or 0.3% to 1.0% of all infants with congenital CMV infection.

Congenital CMV infection is the leading nongenetic cause of sensorineural hearing loss (SNHL) in children in the United States. Approximately 20% of all hearing loss at birth and 25% of all hearing loss at 4 years of age is attributable to congenital CMV infection. SNHL is the most common sequela following congenital CMV infection, with SNHL occurring in up to 50% of children with congenital infections that are clinically evident at birth and up to 15% of those who are healthy appearing at birth. Between 55% and 75% of infants with clinically evident disease and healthy appearing children, respectively, who ultimately develop congenital CMV-associated SNHL will not have hearing loss detectable within the first month of life, illustrating the increased incidence of late-onset SNHL in these populations. For this reason, targeted CMV testing of infants who fail their universal newborn hearing screen will not detect a majority of infants who are at risk of CMV-associated hearing loss. Up to 65% of children with CMV-associated SNHL continue to have further progression of their hearing loss over time. All children with congenital CMV infection should be evaluated at regular intervals for early detection of hearing loss or progression and for implementation of appropriate interventions (eg, hearing aids).

Infection acquired during the intrapartum period from maternal cervical secretions or in the postpartum period from human milk usually is not associated with clinical illness in term infants. In preterm infants, however, postpartum infection resulting from human milk or from transfusion from CMV-seropositive donors has been associated with hepatitis, interstitial pneumonia, hematologic abnormalities including thrombocytopenia and leukopenia, and a viral sepsis syndrome.

ETIOLOGY

Human CMV, also known as human herpesvirus 5, is a member of the herpesvirus family (*Herpesviridae*), the beta-herpesvirus subfamily (*Betaherpesvirinae*), and the *Cytomegalovirus* genus. The viral genome contains double-stranded DNA and is the largest of the human herpesvirus genomes.

EPIDEMIOLOGY

CMV is highly species-specific, and only human CMV has been shown to infect humans and cause disease. The virus is ubiquitous, and CMV strains exhibit extensive genetic diversity. Transmission occurs horizontally (by direct

person-to-person contact with virus-containing secretions), vertically (from mother to infant before, during, or after birth), and via transfusions of blood, platelets, and white blood cells from infected donors. CMV also can be transmitted with organ or hematopoietic stem cell transplantation. Infections have no seasonal predilection. CMV persists after a primary infection, with intermittent virus shedding; symptomatic infection can occur throughout the lifetime of the infected person, particularly under conditions of immunosuppression. Reinfection with other strains of CMV can occur in seropositive hosts, including pregnant women. The seroprevalence of CMV immunoglobulin (Ig) G antibody in a population is determined by many factors, including age, geographic location, race or ethnicity, cultural and socioeconomic status, and child-rearing practices. Studies have shown that in the United States, there appears to be 3 periods in life when there is an increased incidence of CMV acquisition: early childhood, adolescence, and the childbearing years.

Horizontal transmission probably is the result of exposure to saliva, urine, and genital secretions from infected individuals. Spread of CMV in households and child care centers is well documented. Excretion rates from urine or saliva in children 1 to 3 years of age who attend child care centers usually range from 30% to 40% but can be as high as 70%. Children who attend child care frequently excrete large quantities of virus for prolonged periods. Young children can transmit CMV to their parents, including mothers who may be pregnant, and other caregivers, including child care staff. In adolescents and adults, sexual transmission occurs, as evidenced by detection of virus in seminal and cervical fluids. As such, CMV is considered to be a sexually transmitted infection (STI).

CMV-seropositive healthy people have latent CMV in their leukocytes and tissues; hence, blood transfusions and organ transplantation can result in transmission. Severe CMV disease following transfusion or solid organ transplantation is more likely to occur if the recipient is immunosuppressed and CMV seronegative before transplant. In contrast, among nonautologous hematopoietic stem cell transplant recipients, CMV-seropositive recipients who receive transplants from seronegative donors are at greatest risk of disease when exposed to CMV after transplant, perhaps secondary to the failure of transplanted graft to provide immunity to the recipient. Latent CMV may reactivate in immunosuppressed individuals and result in disease if immunosuppression is severe (eg, in patients with acquired immunodeficiency syndrome [AIDS] or solid organ or hematopoietic stem cell transplant recipients).

Vertical transmission of CMV to an infant occurs in one of the following time periods: (1) in utero, by transplacental passage of maternal bloodborne virus; (2) at birth, by passage through an infected maternal genital tract; or (3) postnatally, by ingestion of CMV-positive human milk or by transfusion. Between 0.5% and 1% of all live-born infants are infected in utero and excrete CMV at birth, making this the most common congenital viral infection in the United States. In utero fetal infection can occur in women with no preexisting CMV immunity (maternal primary infection) or in women with preexisting antibody to CMV (maternal nonprimary infection) either by acquisition of a different viral strain during pregnancy or by reactivation of an existing maternal infection. Congenital infection and associated sequelae can occur irrespective of the trimester of pregnancy when the mother is infected, but severe sequelae are associated more commonly with primary maternal infection acquired during the first half of gestation. Damaging fetal infections following nonprimary maternal infection have been reported, and acquisition of a different viral strain during pregnancy in women with preexisting CMV antibody can cause symptomatic congenital infection with sequelae. It is estimated that more than 75% of infants with congenital CMV infection in the United States are born to women with nonprimary infection, and the contribution of nonprimary maternal infection as a cause of damaging congenital CMV infection is believed to be common in populations with higher maternal CMV seroprevalence than the United States. Thus, the definition of protective immunity in congenital CMV infection remains unclear.

Although disease can occur in previously uninfected infants receiving human milk containing CMV from CMV-infected mothers, most infants who acquire CMV from ingestion of human milk do not develop clinical illness or sequelae. Among infants who acquire infection from maternal cervical secretions or human milk, preterm infants born before 32 weeks' gestation and with a birth weight less than 1,500 g are at greater risk of developing CMV disease than are full-term infants.

The **incubation period** for horizontally transmitted CMV infections is highly variable. Infection usually manifests 3 to 12 weeks after blood transfusions and between 1 and 4 months after organ transplantation.

DIAGNOSTIC TESTS

The diagnosis of CMV disease is confounded by the ubiquity of the virus, the high rate of asymptomatic excretion, the frequency of reactivated infections, the development of serum immunoglobulin (Ig) M CMV-specific antibody in some episodes of reactivation, reinfection with different strains of CMV, and concurrent infection with other pathogens.

CMV can be isolated in conventional cell culture from urine, saliva, peripheral blood leukocytes, human milk, semen, cervical secretions, and other tissues and body fluids. Recovery of virus from a target organ provides strong evidence that the disease is caused by CMV infection. Rapid shell vial culture coupled with staining of cells using immunofluorescence antibody techniques for immediate early antigen provides results within 24 to 72 hours.

Viral DNA can be detected by polymerase chain reaction (PCR) and other nucleic acid amplification assay methods in tissues and some fluids, including cerebrospinal fluid (CSF), amniotic fluid, aqueous and vitreous humor fluids, urine, saliva and other respiratory secretions, and peripheral blood. Detection of CMV DNA by PCR in blood does not necessarily indicate acute infection or disease, especially in immunocompetent people. Detection of pp65 antigen (CMV antigenemia assay) in white blood cells or quantification of viral DNA by quantitative PCR assay in whole blood, white blood cells, plasma, or serum (whole blood or plasma is preferred) often is used to detect infection in immunocompromised hosts and for monitoring of CMV disease progression, because these tests can be correlated with active infection in that population. Several antigenemia assays have been cleared by the US Food and Drug Administration (FDA), and at least 2 quantitative PCR assays for detection of CMV have been cleared by the FDA. The same specimen type should always be used when testing any given patient over time.

Various serologic assays, including immunofluorescence assays, latex agglutination assays, and enzyme immunoassays, are available for detecting both IgG and IgM CMV-specific antibodies. Single serum specimens for IgG antibody testing are useful in screening for past infection in individuals at risk for CMV reactivation or for screening potential organ transplant donors and recipients. For diagnosis of suspected recent infection, testing for CMV IgG in paired sera obtained at least 2 weeks apart and testing for IgM in a single serum specimen may be useful.

Amniocentesis has been used in several small series of patients to establish the diagnosis of intrauterine infection. Following delivery, proof of congenital infection requires detection of CMV in urine, saliva, respiratory tract secretions, blood, or CSF obtained within 3 weeks of birth. The analytical sensitivity of CMV DNA detection by PCR assay of dried blood spots is low, limiting use of this type of specimen for widespread screening for congenital CMV infection. A positive PCR assay result from a neonatal dried blood spot confirms congenital infection, but a negative result does not exclude congenital infection. In contrast, PCR assay of liquid and dried saliva specimens from infants has been shown to be >97% sensitive and specific for the identification of infants with congenital CMV infection on newborn screening. Differentiation between intrauterine and perinatal infection is difficult at later than 2 to 4 weeks of age unless clinical manifestations of the former, such as chorioretinitis or intracranial calcifications, are present.

TREATMENT

Intravenous ganciclovir is approved for induction and maintenance treatment of retinitis caused by acquired or recurrent CMV infection

in immunocompromised adult patients, including HIV-infected patients, and for prophylaxis and treatment of CMV disease in adult transplant recipients. Valganciclovir, the oral prodrug of ganciclovir, also is approved for treatment (induction and maintenance) of CMV retinitis in immunocompromised adult patients, including HIV-infected patients, and for prevention of CMV disease in kidney, kidney-pancreas, or heart transplant recipients at high risk of CMV disease. Valganciclovir also is approved for prevention of CMV disease in pediatric kidney transplant patients 4 months and older and for pediatric heart transplant patients 1 month and older. Ganciclovir and valganciclovir are used to treat CMV infections of other sites (esophagus, colon, lungs) and for preemptive treatment of immunosuppressed adults with CMV antigenemia or viremia. Oral valganciclovir is available in both tablet and powder for oral solution formulations.

Neonates with clinically evident congenital CMV disease with or without central nervous system (CNS) involvement have improved audiologic and neurodevelopmental outcomes at 2 years of age when treated with oral for 6 months. Therapy can be accomplished using oral valganciclovir for the entire treatment course, because drug exposure following appropriate dosing of valganciclovir is the same as that achieved with intravenous ganciclovir. If an infant is unable to absorb medications reliably from the gastrointestinal tract (eg, because of necrotizing enterocolitis or other bowel disorders), intravenous ganciclovir can be used initially. Significant neutropenia occurs in one fifth of infants treated with oral valganciclovir and in two thirds of infants treated with parenteral ganciclovir. Absolute neutrophil counts should be performed weekly for 6 weeks, then at 8 weeks, then monthly for the duration of antiviral treatment; serum alanine transaminase concentration should be measured monthly during treatment. Antiviral therapy should be limited to patients with moderate to severe symptomatic congenital CMV disease who are able to start treatment within the first month of life. Infants with clinically silent congenital CMV infection should not receive antiviral treatment.

Preterm infants with perinatally acquired CMV infection can have end-organ disease (eg, pneumonitis, hepatitis, thrombocytopenia). Antiviral treatment has not been studied in this population. In hematopoietic stem cell transplant recipients, the combination of Immune Globulin Intravenous (IGIV) or CMV Immune Globulin Intravenous (CMV-IGIV) and ganciclovir, administered intravenously, has been reported to be synergistic in treatment of CMV pneumonia. Valganciclovir and foscarnet have been approved for treatment and maintenance of CMV retinitis in adults with acquired immunodeficiency syndrome. Foscarnet is more toxic (with high rates of limiting nephrotoxicity) but may be advantageous for some patients with HIV infection, including people with disease caused by ganciclovir-resistant virus or people who are unable to tolerate ganciclovir.

CMV establishes lifelong persistent infection, and as such, it is not eliminated from the body with antiviral treatment of CMV disease. Until immune reconstitution is achieved with antiretroviral therapy, chronic suppressive therapy should be administered to HIV-infected patients with a history of CMV end-organ disease (eg, retinitis, colitis, pneumonitis) to prevent recurrence. All patients who have had anti-CMV maintenance therapy discontinued should continue to undergo regular ophthalmologic monitoring at a minimum of 3- to 6-month intervals for early detection of CMV relapse as well as immune reconstitution uveitis.

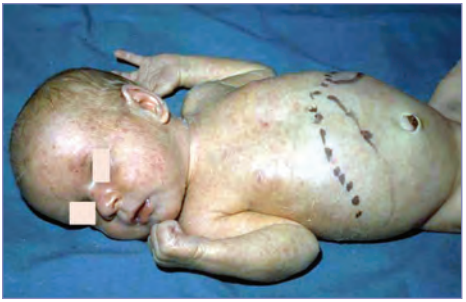


Image 42.1
A 3-week-old with congenital cytomegalovirus infection with purpuric skin lesions and hepatosplenomegaly. Courtesy of Edgar O. Ledbetter, MD, FAAP.

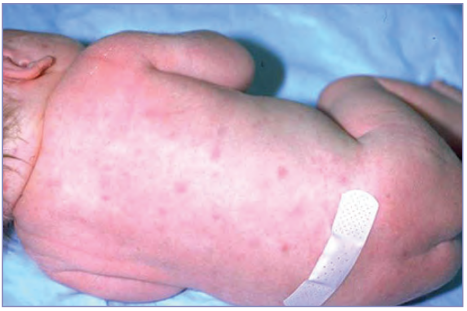


Image 42.2
A newborn with cytomegalovirus infection and hemorrhagic skin lesions on the back.

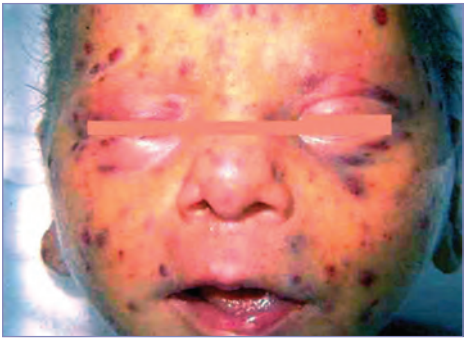


Image 42.3
Cytomegalovirus infection, congenital, with characteristic "blueberry muffin" lesions. Copyright David Clark.

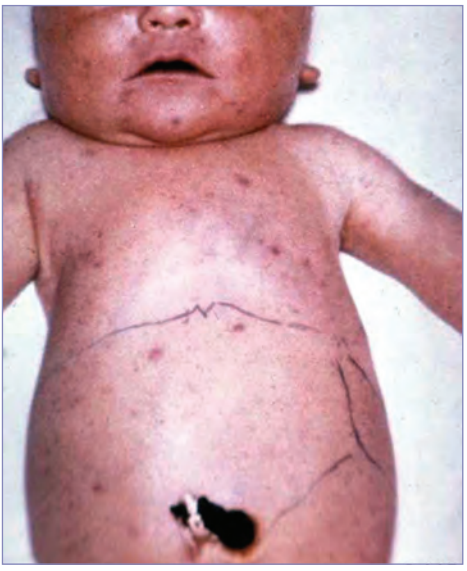


Image 42.4
Infant with lethal congenital cytomegalovirus disease with purpuric skin lesions and striking hepatosplenomegaly. Courtesy of Edgar O. Ledbetter, MD, FAAP.

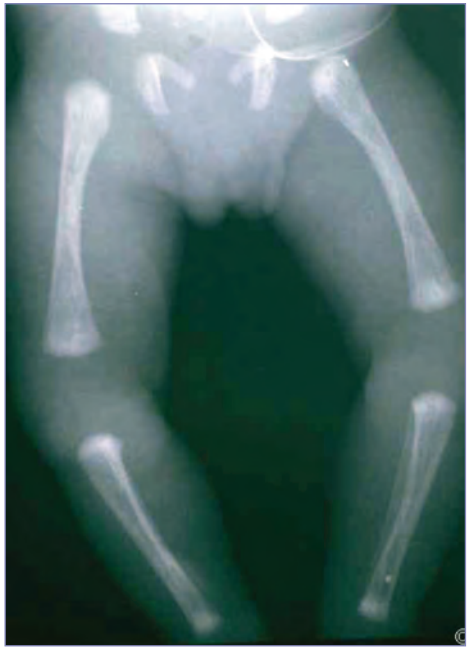


Image 42.5
Infant in Image 42.4 with lethal cytomegalovirus disease with radiographic changes in long bones of osteitis characterized by fine vertical metaphyseal striations. Courtesy of Edgar O. Ledbetter, MD, FAAP.

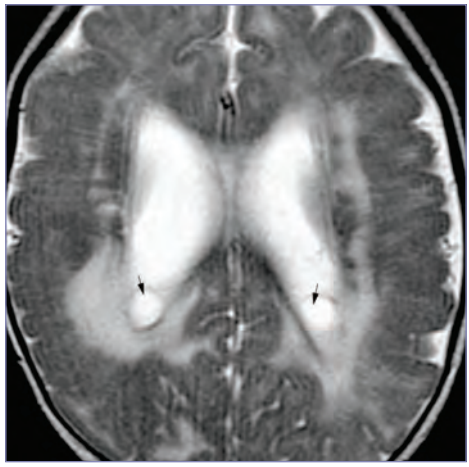


Image 42.8
Axial T2-weighted magnetic resonance image demonstrates periventricular germinolytic cysts (arrows). Also note the periventricular white matter hyperintensities that are representative of demyelination and gliosis.

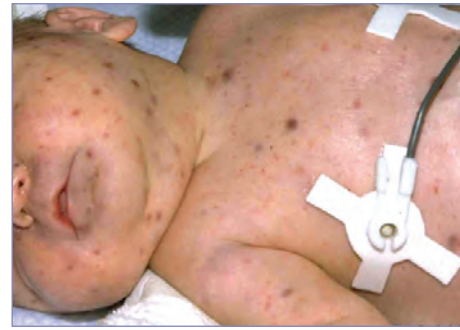


Image 42.6
Neonate with congenital cytomegalovirus infection with purpuric skin lesions.

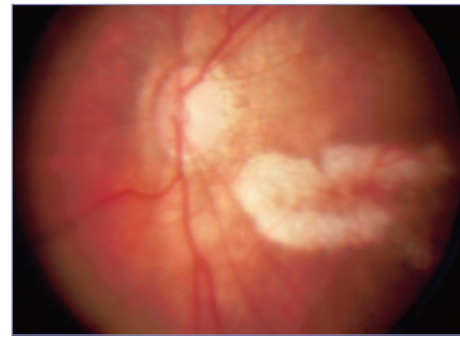


Image 42.7
Characteristic white perivascular infiltrates in the retina of an infant with congenital cytomegalovirus infection. Courtesy of George Nankervis, MD.

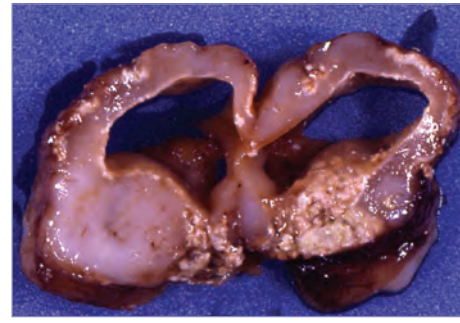


Image 42.9
Congenital cytomegalovirus encephalitis. Microcephaly and cerebral calcification. Courtesy of Dimitris P. Agamanolis, MD.

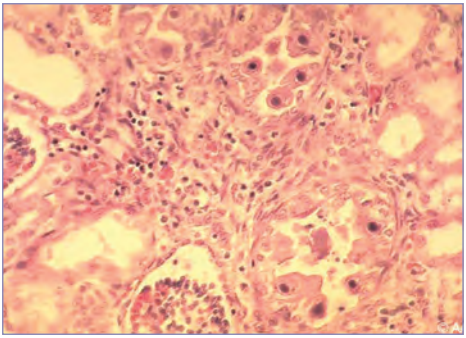


Image 42.10
Cytomegalovirus inclusion cells within renal glomeruli. Courtesy of Edgar O. Ledbetter, MD, FAAP.

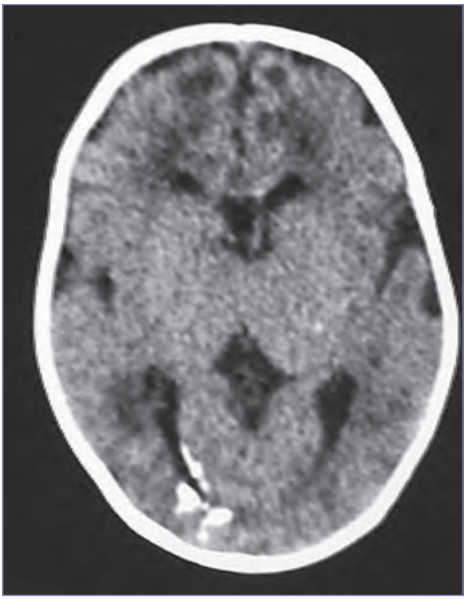


Image 42.12
Cytomegalovirus infection with periventricular calcification. Courtesy of Benjamin Estrada, MD.

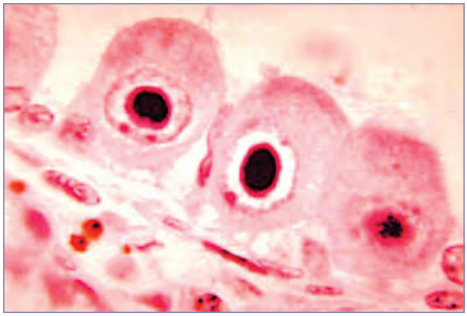


Image 42.11
Histopathologic features of cytomegalovirus infection of the kidney. Intranuclear inclusions are surrounded by a halo and the nuclear membrane, giving an "owl eye" appearance. Courtesy of Centers for Disease Control and Prevention.

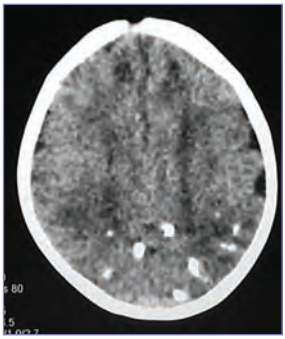


Image 42.13
Cytomegalovirus infection with periventricular calcification. Courtesy of Benjamin Estrada, MD.

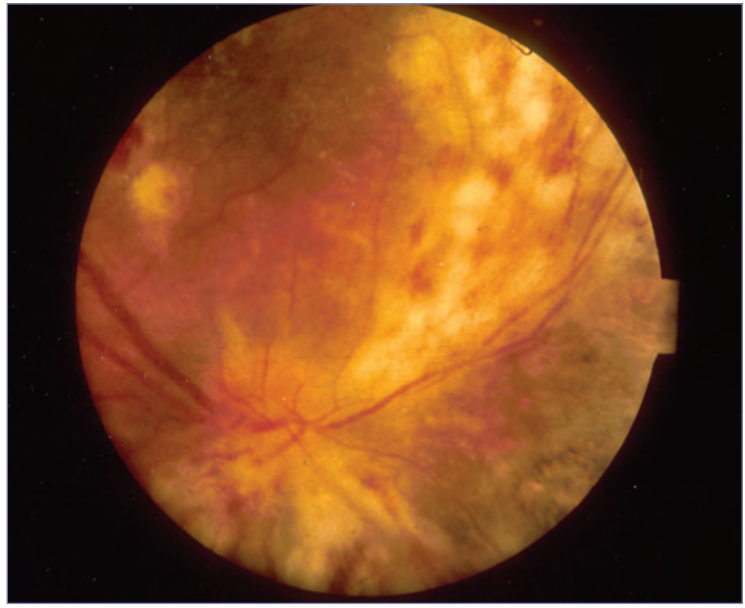


Image 42.14
Widespread "brushfire retinitis" in an infant with congenital cytomegalovirus infection. The perivascular infiltrates and diffuse hemorrhage may result in complete blindness whenever macular involvement occurs. Courtesy of George Nankervis, MD.

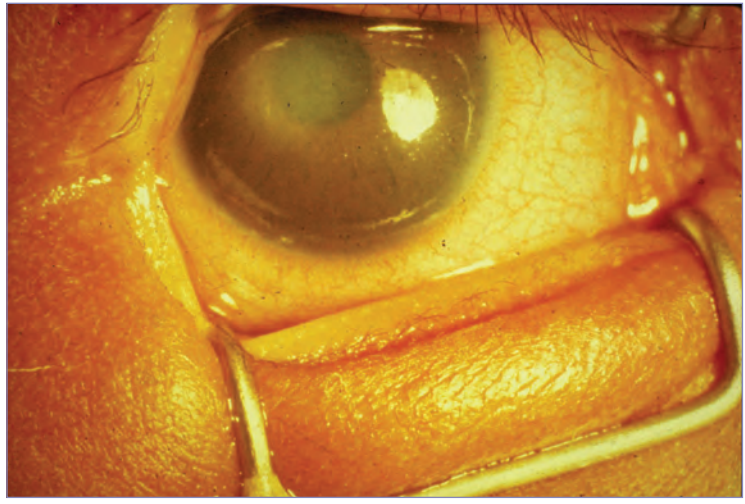


Image 42.15
A neonate with congenital cytomegalovirus infection with Peters anomaly, which was later treated by corneal transplantation. *Peters anomaly* is the term most frequently used when the mesodermal dysgenesis of the anterior ocular segment includes a central stromal opacity with a defect in the posterior stroma and the Descemet membrane. Courtesy of Larry Frenkel, MD.

CHAPTER 43

Dengue

CLINICAL MANIFESTATIONS

Dengue infection may be asymptomatic or, if symptomatic, may have a wide range of clinical presentations. Approximately 5% of patients develop severe dengue (ie, dengue hemorrhagic fever or dengue shock syndrome), a life-threatening disease, which is more common with second or other subsequent infections. Less common clinical syndromes include myocarditis, pancreatitis, hepatitis, and neuroinvasive disease.

Dengue begins abruptly with a nonspecific, acute febrile illness lasting 2 to 7 days (**febrile phase**), often accompanied by muscle, joint, and/or bone pain, headache, retro-orbital pain, facial erythema, injected oropharynx, macular or maculopapular rash, leukopenia, and petechiae or other minor bleeding manifestations. During fever defervescence, usually on days 3 through 7 of illness, an increase in vascular permeability in parallel with increasing hematocrit (hemoconcentration) may occur. The period of clinically significant plasma leakage usually lasts 24 to 48 hours (**critical phase**), followed by a **convalescent phase** with gradual improvement and stabilization of the hemodynamic status. Warning signs of progression to severe dengue occur in the late febrile phase and include persistent vomiting, severe abdominal pain, mucosal bleeding, difficulty breathing, early signs of shock, and a rapid decline in platelet count with an increase in hematocrit. Patients with nonsevere disease begin to improve during the critical phase, but people with clinically significant plasma leakage attributable to increased vascular permeability develop severe disease that may include pleural effusions, ascites, hypovolemic shock, and hemorrhage.

ETIOLOGY

Four related RNA viruses of the genus *Flavivirus* (see Chapter 6, Arboviruses), dengue viruses 1, 2, 3, and 4, cause symptomatic (approximately 25%) and asymptomatic (approximately 75%) infections. Infection with one dengue virus type produces lifelong immunity against that type and a period of cross-protection (often lasting 1 to 3 years) against infection with the other 3 types. After this period of cross-protection, infection with a different strain may predispose to more severe disease. A person has a lifetime risk of up to 4 dengue virus infections.

EPIDEMIOLOGY

Dengue virus primarily is transmitted to humans through the bite of infected *Aedes aegypti* (and less commonly, *Aedes albopictus* or *Aedes polynesiensis*) mosquitoes. Humans are the main amplifying host of dengue virus and the main source of virus for *Aedes* mosquitoes. A sylvatic nonhuman primate dengue virus transmission cycle exists in parts of Africa and Southeast Asia but rarely crosses to humans. Because of the approximately 7 days of viremia, dengue virus can be transmitted following receipt of blood products, donor organs, or tissue; through percutaneous exposure to blood; by exposure in utero or at parturition; and via breastfeeding.

Dengue is a major public health problem in the tropics and subtropics; an estimated 50 to 100 million dengue cases occur annually in more than 100 countries, and 40% of the world's population lives in areas with dengue virus transmission. In the United States, dengue is endemic in Puerto Rico and the Virgin Islands. Periodic outbreaks occur in American Samoa. Millions of US travelers, including children, are at risk, because dengue is the leading cause of febrile illness among travelers returning from the Caribbean, Latin America, and South Asia. Outbreaks with local dengue virus transmission have occurred in Texas, Hawaii, and Florida in the last decade. However, although 16 states have *A aegypti* and 35 states have *A albopictus* mosquitoes, local dengue virus transmission is uncommon because of infrequent contact between people and infected mosquitoes. Dengue occurs in children and adults. It is most likely to cause severe disease in infants, pregnant women, and patients with chronic diseases (eg, asthma, sickle cell anemia, and diabetes mellitus).

The **incubation period** for dengue virus replication in mosquitoes is 8 to 12 days (extrinsic incubation); mosquitoes remain infectious for the remainder of their life cycle. In humans, the

incubation period is 3 to 14 days before symptom onset (intrinsic incubation). Infected people, both symptomatic and asymptomatic, can transmit dengue virus throughout the approximately 7-day viremic period.

DIAGNOSTIC TESTS

Laboratory confirmation of the clinical diagnosis of dengue can be made on a single serum specimen obtained during the febrile phase of the illness by testing for dengue virus either by detection of dengue virus RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) assay or detection of dengue virus nonstructural protein 1 (NS-1) antigen by immunoassay and testing for anti-dengue virus immunoglobulin (Ig) M antibodies by enzyme immunoassay (EIA). Dengue virus is detectable by RT-PCR or NS-1 antigen EIAs from the beginning of the febrile phase until day 7 to 10 after illness onset. Anti-dengue virus IgM antibodies are detectable beginning 3 to 5 days after illness onset but can cross-react with IgM antibodies against Zika virus and other closely related flaviviruses. Other tests, such as IgG anti-dengue virus EIA and hemagglutination inhibition assay, are not as specific for making the diagnosis of dengue. Anti-dengue virus IgG antibody remains elevated for life after dengue virus infection and often is falsely positive in people with previous infection with or immunization against other flaviviruses (eg, West Nile, Japanese encephalitis, yellow fever, or Zika viruses). A 4-fold or greater increase in anti-dengue virus IgG antibody titers between the acute (≤5 days after onset of symptoms) and convalescent (>15 days after onset of symptoms) samples confirms recent infection.

TREATMENT

No specific antiviral therapy exists for dengue. During the febrile phase, patients should stay well hydrated and avoid use of aspirin (acetylsalicylic acid), salicylate-containing drugs, and other nonsteroidal anti-inflammatory drugs (eg, ibuprofen) to minimize the potential for bleeding. Additional supportive care is required if the patient becomes dehydrated or develops warning signs of severe disease at or around the time of fever defervescence.

Early recognition of shock and intensive supportive therapy can reduce risk of death from approximately 10% to less than 1% in severe dengue. During the critical phase, maintenance of fluid volume and hemodynamic status is crucial to management of severe cases. Patients should be monitored for early signs of shock, occult bleeding, and resolution of plasma leak to avoid prolonged shock, end organ damage, and fluid overload.

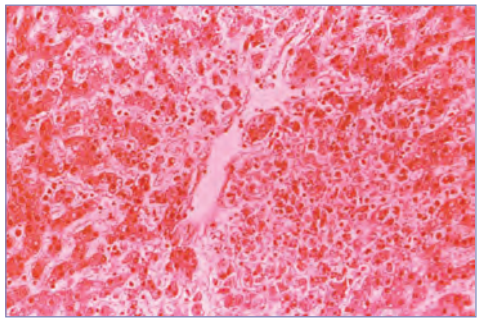


Image 43.1
Cytoarchitectural changes found in a liver tissue specimen extracted from a patient with dengue hemorrhagic fever in Thailand (hematoxylin-eosin stain, magnification ×70). This particular view reveals "mid-lobular necrosis, with accompanying acidophilic degeneration, and moderate hypertrophy of Kupffer cells." Courtesy of Dr Yves Robin and Dr Jean Renaudet, Arbovirus Laboratory at the Pasteur Institute in Dakar, Senegal; World Health Organization.

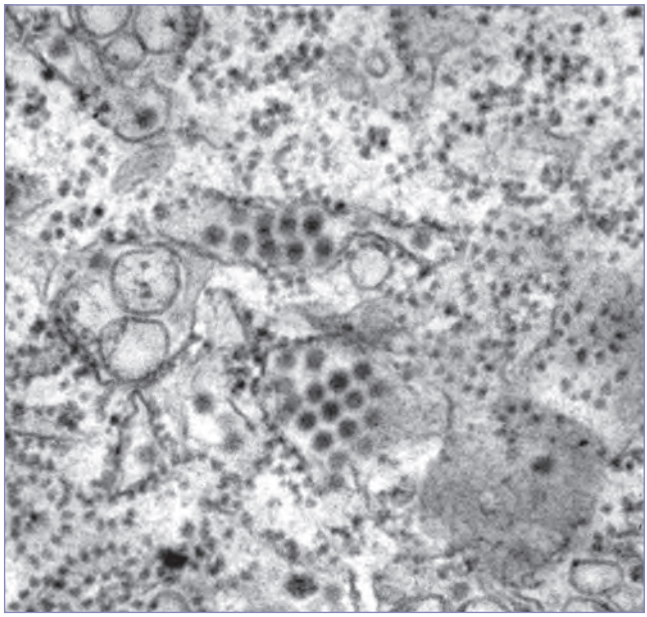


Image 43.2
This transmission electron micrograph depicts a number of round dengue virus particles that were revealed in this tissue specimen. Courtesy of Centers for Disease Control and Prevention.

Image 43.3
Distribution of dengue, western hemisphere. Courtesy of Centers for Disease Control and Prevention.

Image 43.4
Distribution of dengue, eastern hemisphere. Courtesy of Centers for Disease Control and Prevention.

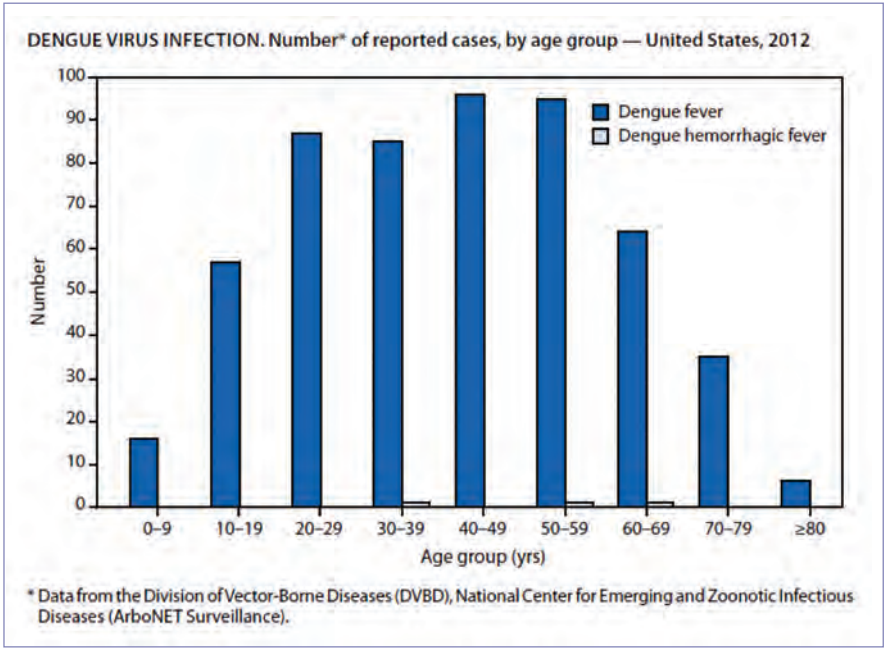


Image 43.5
Dengue virus infection. Number of reported cases, by age group—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

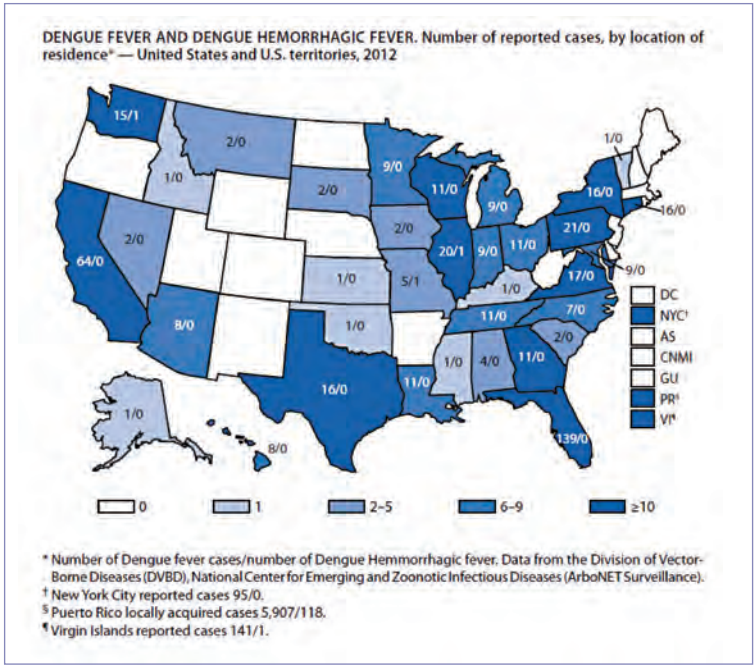


Image 43.6
Dengue and dengue hemorrhagic fever. Number of reported cases, by location of residence—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

CHAPTER 44

Diphtheria

CLINICAL MANIFESTATIONS

Respiratory tract diphtheria usually presents as membranous nasopharyngitis or obstructive laryngotracheitis. Membranous pharyngitis with bloody nasal discharge suggests diphtheria. Local infections are associated with low-grade fever and gradual onset of manifestations over 1 to 2 days. Less commonly, diphtheria presents as cutaneous, vaginal, conjunctival, or otic infection. Cutaneous diphtheria is more common in tropical areas and among urban homeless. Extensive neck swelling with cervical lymphadenitis (bull neck) is a sign of severe disease. Life-threatening complications of respiratory diphtheria include upper airway obstruction caused by membrane formation; myocarditis, with heart block; and cranial and peripheral neuropathies. Palatal palsy, noted by nasal speech, frequently occurs in pharyngeal diphtheria. Case fatality rates are 5% to 10%, sometimes exceeding 20% in older adults.

ETIOLOGY

Diphtheria is caused by toxigenic strains of *Corynebacterium diphtheriae.* Toxigenic strains of *Corynebacterium ulcerans* also have emerged as an important cause of diphtheria-like illness. *C diphtheriae* is an irregularly staining, gram-positive, nonspore-forming, nonmotile, pleomorphic bacillus with 4 biotypes (*mitis*, *intermedius*, *gravis*, and *belfanti*). All biotypes of *C diphtheriae* may be toxigenic or nontoxigenic. Bacteria remain confined to superficial layers of skin or mucosal surfaces, inducing a local inflammatory reaction. Toxigenic strains produce an exotoxin that consists of an enzymatically active A domain and a binding B domain, which promotes the entry of A into the cell. The toxin gene, *tox*, is carried by a family of related corynebacteria phages. The toxin, an ADP-ribosylase toxin, inhibits protein synthesis in all cells, including myocardial, renal, and peripheral nerve cells, resulting in myocarditis, acute tubular necrosis, and delayed peripheral nerve conduction. Nontoxigenic strains of *C diphtheriae* can cause sore throat and, rarely, other invasive infections, including endocarditis and foreign body infections.

EPIDEMIOLOGY

Humans are the sole reservoir of *C diphtheriae.* Infection is spread by respiratory tract droplets and by contact with discharges from skin lesions. In untreated people, organisms can be present in discharges from the nose and throat and from eye and skin lesions 2 to 6 weeks after infection. Patients treated with an appropriate antimicrobial agent usually are not infectious 48 hours after treatment is initiated. Transmission results from intimate contact with patients or carriers. People traveling to areas with endemic diphtheria or people who come into contact with infected travelers from such areas are at increased risk of being infected with the organism; rarely, fomites or milk products can serve as vehicles of transmission. Severe disease occurs more often in people who are unimmunized or inadequately immunized. Fully immunized people may be asymptomatic carriers or have mild sore throat.

From 1980 through 2015, 56 cases of diphtheria were reported in the United States; only 2 cases were reported since 2004. Cases of cutaneous diphtheria still occur in the United States, but only respiratory tract cases are nationally notifiable. The incidence of respiratory diphtheria is greatest during fall and winter, but summer epidemics may occur in warm climates where skin infections are prevalent. Globally, endemic diphtheria occurs in Africa, Latin American, Asia, the Middle East, and parts of Europe where immunization coverage with diphtheria toxoid-containing vaccines is suboptimal. In 2014, 7,321 global cases of diphtheria were reported by the World Health Organization, but it is probable that many more cases went unrecognized.

The **incubation period** usually is 2 to 5 days (range, 1–10 days).

DIAGNOSTIC TESTS

Laboratory personnel should be notified that *C diphtheriae* is suspected. Specimens for culture should be obtained from the nasopharynx and throat or any mucosal or cutaneous lesion. Obtaining multiple samples from respiratory sites increases yield of culture. Material should be obtained for culture from beneath the membrane (if present) or a portion of the membrane. Specimens collected for culture can be

placed in any transport medium (eg, Amies semisolid transport medium) or in a sterile container and transported at 4°C or in silica gel packs. Inoculation on 5% sheep blood agar plus at least 1 selective medium (eg, cystine-tellurite blood agar or modified Tinsdale agar) is required for isolation. All isolates of *C diphtheriae* should be sent through the state health department to the Centers for Disease Control and Prevention (CDC). Nonculture detection methods include matrix-assisted laser desorption/ionization (MALDI-TOF) mass spectroscopy for *C diphtheriae* and *C ulcerans* and polymerase chain reaction-based methods for detection of diphtheria toxin gene in isolates.

TREATMENT

Antitoxin

Because patients with diphtheria can deteriorate rapidly, a single dose of equine antitoxin should be administered on the basis of clinical diagnosis before culture results are available. Antitoxin, its indications for use, suggested dosage, and instructions for administration are available through the CDC. To neutralize toxin as rapidly as possible, intravenous administration of antitoxin is preferred. Before intravenous administration of antitoxin, tests for sensitivity to horse serum should be performed according to instructions provided with the material. Allergic reactions to horse serum varying from anaphylaxis to rash can be expected in 5% to 20% of patients. The dose of antitoxin depends on the site and size of the membrane, duration of illness, and degree of toxic effects; presence of soft, diffuse cervical lymphadenitis suggests moderate to severe toxin absorption. Antitoxin probably is of no value for cutaneous disease, but some experts recommend administration if signs of systemic toxicity are evident.

Antimicrobial Therapy

Erythromycin administered orally or parenterally, aqueous penicillin G administered intravenously, or penicillin G procaine administered intramuscularly, each for 14 days, constitutes acceptable therapy. Antimicrobial therapy is required to stop toxin production, eradicate *C diphtheriae* organism, and prevent transmission but is not a substitute for antitoxin. Elimination of the organisms should be documented 24 hours after completion of treatment by 2 consecutive negative cultures from specimens taken 24 hours apart.

Immunization

Active immunization against diphtheria should be undertaken during convalescence from diphtheria; disease does not necessarily confer immunity.

Cutaneous Diphtheria

Thorough cleansing of the lesion with soap and water and administration of an appropriate antimicrobial agent for 10 days are recommended.

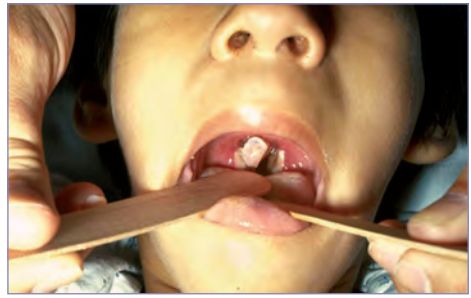


Image 44.1
Pharyngeal diphtheria with membranes covering the tonsils and uvula in a 15-year-old girl. Tonsillar and pharyngeal diphtheria may need to be differentiated from group A streptococcal pharyngitis, infectious mononucleosis, Vincent angina, acute toxoplasmosis, thrush, and leukemia, as well as other, less common entities, including tularemia and acute cytomegalovirus infection.

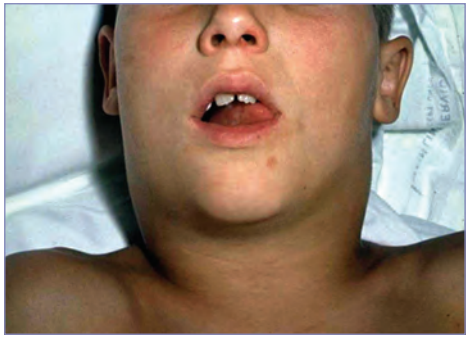


Image 44.2
Bull neck appearance of diphtheritic cervical lymphadenopathy in a 13-year-old boy.

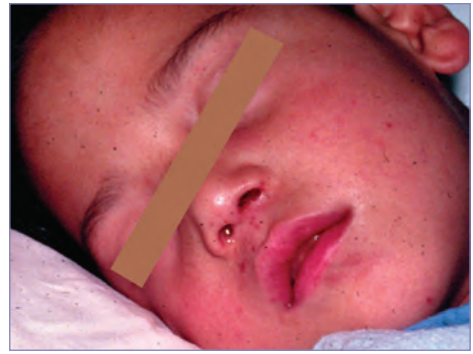


Image 44.3
A 5-year old Latin American boy with nasal diphtheria. Courtesy of Paul Wehrle, MD.

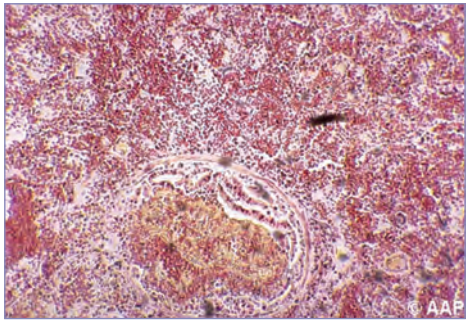


Image 44.4
Diphtheria pneumonia (hemorrhagic) with bronchiolar membranes (hematoxylin-eosin stain). Courtesy of Edgar O. Ledbetter, MD, FAAP.

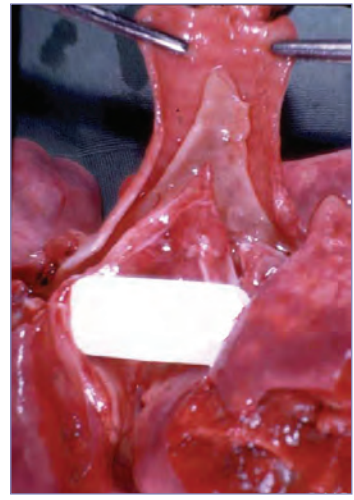


Image 44.5
Diphtheritic tracheobronchial membranes at autopsy of the patient in Image 44.4. Courtesy of Edgar O. Ledbetter, MD, FAAP.

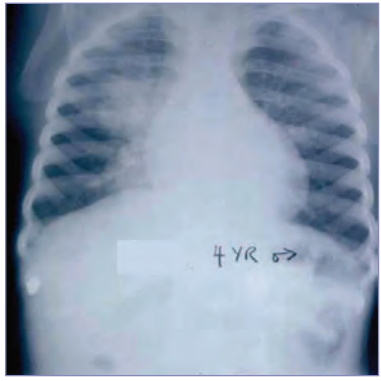


Image 44.6
A 4-year-old boy with fatal sub-laryngeal tracheal diphtheria and hemorrhagic diphtheria pneumonia. Courtesy of Edgar O. Ledbetter, MD, FAAP.

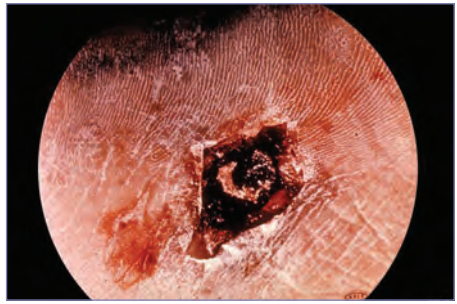


Image 44.7
This is a close-up of a diphtheria skin lesion caused by the organism *Corynebacterium diphtheriae*. Courtesy of Centers for Disease Control and Prevention/Brodsky, MD.

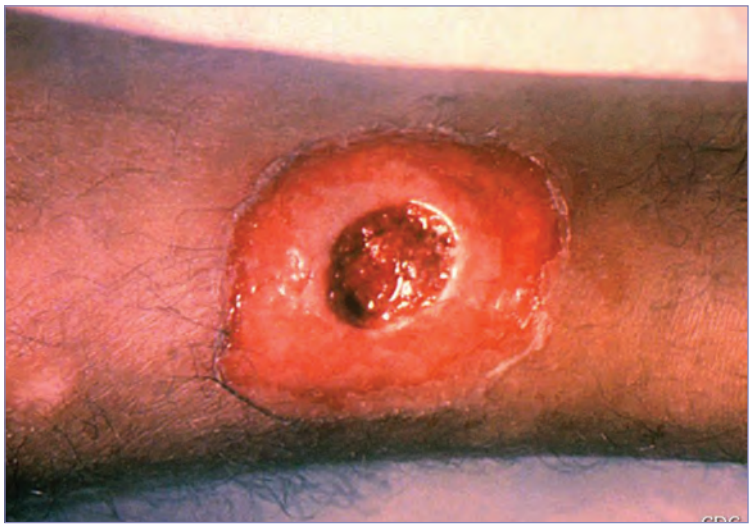


Image 44.8
A diphtheria skin lesion on the leg. *Corynebacterium diphtheriae* can not only affect the respiratory, cardiovascular, renal, and neurologic systems but the cutaneous system as well, where it sometimes manifests as an open, isolated wound. Courtesy of Centers for Disease Control and Prevention.

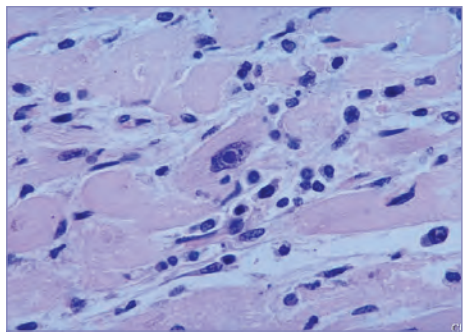


Image 44.9
This micrograph reveals an intranuclear inclusion body in a heart section from a patient with diphtheria-related myocarditis. Courtesy of Centers for Disease Control and Prevention/Martin Hicklin, MD.

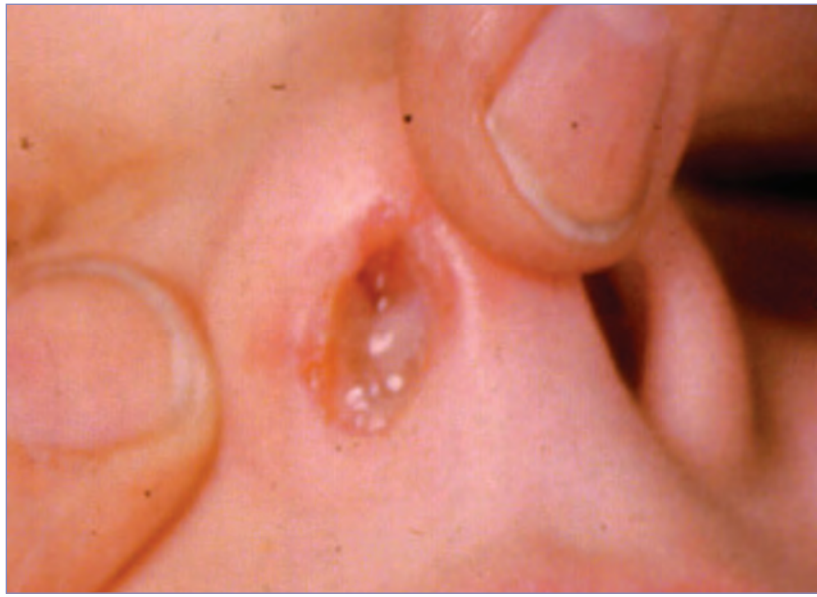


Image 44.10
Nasal membrane of diphtheria in a preschool-aged boy. Courtesy of George Nankervis, MD.

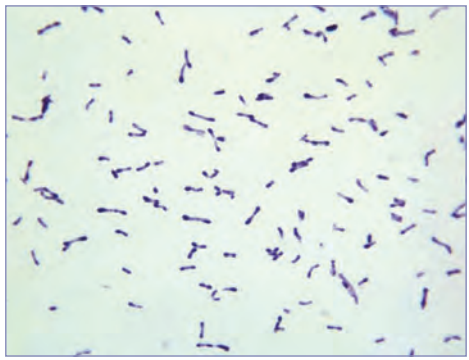


Image 44.11
This photomicrograph depicts numerous gram-positive, rod-shaped *Corynebacterium diphtheriae* bacteria. Courtesy of Centers for Disease Control and Prevention/ Graham Heid.

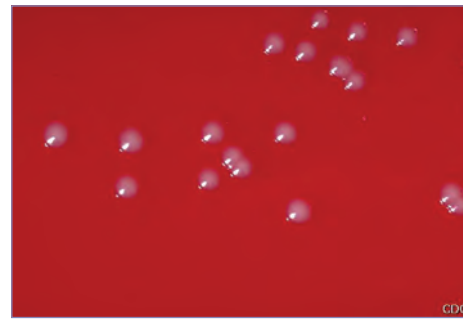


Image 44.12
Blood agar plate culture of *Corynebacterium diphtheriae* mitis. Courtesy of Centers for Disease Control and Prevention/W. A. Clark, MD.

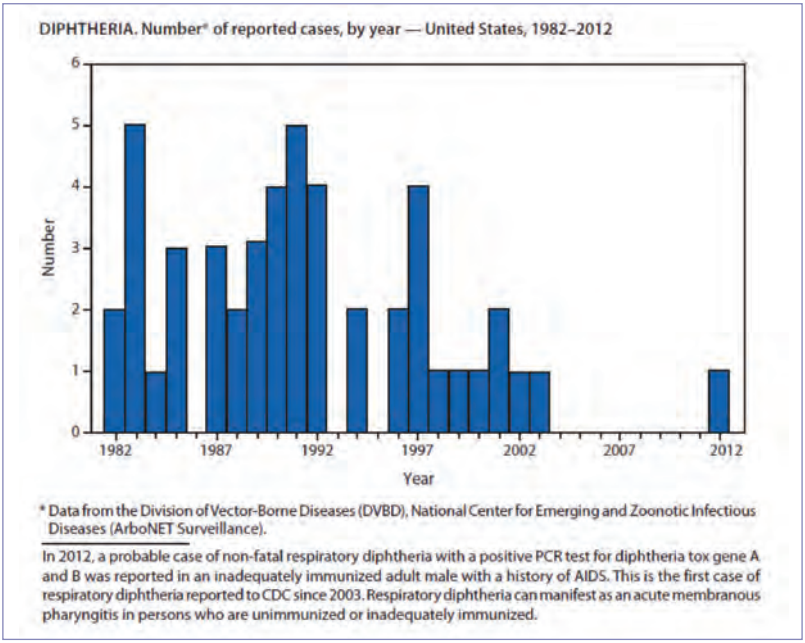


Image 44.13
Number of reported cases, by year—United States, 1982 through 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 44.14
Baby graves dating from the 1890s in a central Mississippi family cemetery. Diphtheria was a common cause of these infant deaths prior to the introduction of a toxoid vaccine around 1921. In the preantibiotic era treatment was limited to comfort care or tracheotomy. Vaccination of children and adults has reduced the number of diphtheria cases in the United States. However, reluctance to immunize children sets the stage for another generation of rows of tiny memories. Courtesy of Will Sorey, MD.

CHAPTER 45

Ehrlichia, Anaplasma, and Related Infections

(Human Ehrlichiosis, Anaplasmosis, and Related Infections Attributable to Bacteria in the Family *Anaplasmataceae*)

CLINICAL MANIFESTATIONS

Infections by members of the bacterial family *Anaplasmataceae* (genera *Anaplasma*, *Ehrlichia*, *Neorickettsia*, and the proposed genus *Candidatus* Neoehrlichia) cause human illness with similar signs, symptoms, and clinical courses. All are acute febrile illnesses with common systemic manifestations including fever, headache, chills, malaise, myalgia, and nausea. More variable symptoms include arthralgia, vomiting, diarrhea, cough, and confusion. Skin rash is reported more often for *Ehrlichia* infections than for *Anaplasma* infections. Rash is seen in up to 60% of *Ehrlichia chaffeensis* cases in children. Neorickettsiosis, most commonly reported in older, immunocompromised adults, is characterized by fever, weakness, anorexia, and lymphadenopathy, which is not common in ehrlichiosis or anaplasmosis. Neoehrlichiosis is characterized by fever, chills, arthralgia, myalgia, and less specific symptoms such as cough, diarrhea, and weight loss. There is a high incidence of vascular events, including thromboembolic complications. Patients may require hospitalization, and more severe manifestations of these diseases can include acute respiratory distress syndrome, encephalopathy, meningitis, disseminated intravascular coagulation, spontaneous hemorrhage, and renal failure.

Significant laboratory findings in *Anaplasma* and *Ehrlichia* infections may include leukopenia with neutropenia (anaplasmosis) or lymphopenia (ehrlichiosis), thrombocytopenia, hyponatremia, and elevated serum hepatic transaminase concentrations. Cerebrospinal fluid abnormalities (eg, pleocytosis with a predominance of lymphocytes and increased total protein concentration) are common. In neoehrlichiosis, leukocytosis and elevated C-reactive protein concentrations can occur, but serum hepatic transaminase concentrations usually are within normal ranges.

Without treatment, symptoms typically last 1 to 2 weeks, but empiric and prompt treatment with doxycycline shortens duration and reduces the risk of serious manifestations and sequelae. Following infection, fatigue can last several weeks; neurologic sequelae have been reported in some children after severe disease and more commonly with *Ehrlichia* infections. Severe disease and fatal outcome are more common in *E chaffeensis* infections (approximately 1%–3% mortality) than with *Anaplasma phagocytophilum* infection (<1% mortality). Secondary or opportunistic infections can occur with severe illness, resulting in a delay in recognition and administration of appropriate antimicrobial treatment. People with underlying immunosuppression are at greater risk of severe disease.

Ehrlichia and *Anaplasma* species do not cause vasculitis or endothelial cell damage characteristic of some other rickettsial diseases. Because of the nonspecific presenting symptoms, Rocky Mountain spotted fever should be considered in the differential diagnosis of tickborne *Anaplasmataceae* infections in the United States. Infections with *Candidatus* Neoehrlichia mikurensis, which has been detected in ticks from several European, Asian, and African countries, have a high incidence of complicating vascular events.

The recently discovered Heartland virus infection also manifests with clinical features similar to ehrlichiosis as well as leukopenia and thrombocytopenia after a tick bite. Heartland virus should be considered in patients without a more likely explanation and who have tested negative for *Ehrlichia* and *Anaplasma* infection or have not responded to doxycycline therapy.

ETIOLOGY

In the United States, human ehrlichiosis and anaplasmosis are caused by at least 4 different species of obligate intracellular bacteria: *E chaffeensis*, *Ehrlichia ewingii*, *Ehrlichia muris eauclairensis*, and *A phagocytophilum* (Table 45.1). However, most US cases are caused by *E chaffeensis* and *A phagocytophilum*. *Ehrlichia* and *Anaplasma* species are gram-negative cocci that measure 0.5 to 1.5 μm

Table 45.1
Human Ehrlichiosis, Anaplasmosis, and Related Infections

Disease	Causal Agent	Major Target Cell	Tick Vector	Geographic Distribution
Ehrlichiosis caused by *Ehrlichia chaffeensis* (also known as human monocytic ehrlichiosis)	*E chaffeensis*	Usually monocytes	Lone star tick (US) (*Amblyomma americanum*)	US: Predominantly southeast, south central, and East Coast states; has been reported outside US
Anaplasmosis (also known as human granulocytic anaplasmosis)	*Anaplasma phagocytophilum*	Usually granulocytes	Blacklegged tick (*Ixodes scapularis*) or Western blacklegged tick (*Ixodes pacificus*) (US)	US: Northeastern and upper Midwestern states and northern California; Europe and Asia
Ehrlichiosis caused by *Ehrlichia ewingii*	*E ewingii*	Usually granulocytes	Lone star tick (US) (*A americanum*)	US: Southeastern, south central, and Midwestern states; Africa, Asia
Ehrlichiosis caused by *Ehrlichia muris eauclairensis*	*E muris eauclairensis*	Unknown, suspected in monocytes	*I scapularis* is identified as a likely vector	US: Minnesota, Wisconsin
Ehrlichiosis caused by *Ehrlichia muris*	*Ehrlichia muris sensu stricto*	Unknown, suspected in monocytes	*Ixodes persulcatus, Ixodes ovatus*	Asia
Ehrlichiosis caused by *Ehrlichia canis*	*E canis*	Monocytes	*Rhipicephalus sanguineus* (suspected)	Venezuela
Thrombocytic anaplasmosis	*Anaplasma platys*	Platelets	*Rhipicephalus sanguineus* (suspected)	Venezuela
Neorickettsiosis, sennetsu fever, glandular fever	*Neorickettsia sennetsu*	Monocytes	Ingestion of infected trematodes residing in fish	Japan, Malaysia, Laos
Neoehrlichiosis	*Candidatus* Neoehrlichia mikurensis	Unknown, demonstrated in endothelium of experimentally infected animals	*Ixodes ricinus, Ixodes persulcatus, Haemaphysalis flava*	Europe and Asia, possibly Africa

in diameter with tropisms for different white blood cell types (monocytes and granulocytes, respectively).

EPIDEMIOLOGY

In the United States, the reported incidences of *E chaffeensis* and *A phagocytophilum* infections during 2008–2012 were 3.2 and 6.3 cases per million population, respectively. Reported incidence of *E ewingii* infections during this interval were 0.04 cases per million population, but the incidence is thought to be underreported.

These diseases are underrecognized; selected active surveillance programs have shown the incidence to be substantially higher in some areas where infection is endemic. Most cases of *E chaffeensis* and *E ewingii* infection are reported from the south central and southeastern United States as well as East Coast states. Ehrlichiosis caused by *E chaffeensis* and *E ewingii* are associated with the bite of the lone star tick (*Amblyomma americanum*) and are reported from states within its geographic range. To date, cases attributable to *E muris eauclairensis* have been reported only from Minnesota and Wisconsin and are thought to be transmitted by the blacklegged tick (*Ixodes scapularis*). Most cases of human anaplasmosis have been reported from the upper Midwest and northeast United States (eg, Wisconsin, Minnesota, Connecticut, and New York) and northern California. In most of the United States, *A phagocytophilum* is transmitted by *Ixodes scapularis*, which also is the vector for Lyme disease (*Borrelia burgdorferi)* and babesiosis (*Babesia microti*). In the western United States, the western blacklegged tick (*Ixodes pacificus*) is the main vector for *A phagocytophilum.* Various mammalian wildlife reservoirs for the agents of human ehrlichiosis and anaplasmosis have been identified, including white-tailed deer and wild rodents. In other parts of the world, other bacterial species of this family are transmitted by the endemic tick vectors for that area. An exception is *N sennetsu*, which is transmitted through ingestion of *Neorickettsia*-infected trematodes residing in fish.

Reported cases of symptomatic ehrlichiosis and anaplasmosis are most frequent in people older than 40 years. However, seroprevalence data indicate that exposure to *E chaffeensis* may be common in children. In the United States, most human infections occur between April and September, with the peak occurrence from May through July. Coinfections of anaplasmosis with other tickborne diseases, including babesiosis and Lyme disease, can cause illness that is more severe or of longer duration than a single infection. Several cases of *Anaplasmataceae* infections have occurred after blood transfusion or solid organ donation from asymptomatic donors.

The **incubation period** usually is 5 to 14 days for *E chaffeensis* and 5 to 21 days for *A phagocytophilum.*

DIAGNOSTIC TESTS

The diagnosis of ehrlichiosis or anaplasmosis must be made on the basis of clinical signs and symptoms and later can be confirmed using specialized laboratory testing. Polymerase chain reaction (PCR) testing on whole blood for the organism is most sensitive for anaplasmosis, ehrlichiosis, and other *Anaplasmataceae* infections during the first week of illness. Sensitivity of PCR decreases rapidly following the administration of doxycycline. Although a positive PCR result is helpful, a negative result does not rule out the diagnosis. Sequence confirmation of the amplified product provides specific identification and often is necessary to identify infection with certain species (eg, *E ewingii* and *E muris eauclairensis* in the United States). In the case of fatal infections, PCR testing can be performed on autopsy specimens, including liver, spleen, and lung. In addition, immunohistochemistry can be used to demonstrate *Ehrlichia* or *Anaplasma* antigen in formalin-fixed, paraffin-embedded tissues.

Occasionally, *Anaplasmataceae* bacteria can be identified in Giemsa or Wright-stained peripheral blood smears or buffy coat leukocyte preparations in the first week of illness by detection of classic microcolonies of *Anaplasma* organisms known as **morulae,** but this is an insensitive method for diagnosis. Culture for isolation is not performed. Serologic testing may be used to demonstrate a fourfold change in IgG-specific antibody titer by

indirect immunofluorescence antibody (IFA) assay between paired acute and convalescent specimens taken 2 to 4 weeks apart. Specific antigens are available for serologic testing of *E chaffeensis* and *A phagocytophilum* infections, although cross-reactivity between species can make interpretation difficult in areas where geographic distributions overlap. Serologic tests are available in reference, commercial, and state public health laboratories, and at the Centers for Disease Control and Prevention (CDC).

TREATMENT

Doxycycline is the drug of choice for treatment of human ehrlichiosis and anaplasmosis and should be used regardless of patient age. Doxycycline also has been shown to be very effective for the other *Anaplasmataceae* infections. Oral dosing is preferred for children who are able tolerate oral medication. Ehrlichiosis and anaplasmosis can be severe or fatal in untreated patients, especially in immunocompromised patients; initiation of therapy early in the course of disease helps minimize complications of illness and should not be delayed awaiting laboratory confirmation. Most patients begin to respond within 48 hours of initiating doxycycline treatment. Treatment with doxycycline should continue for at least 3 days after defervescence; the standard course of treatment is 7 to 14 days. Treatments for neorickettsiosis and neoehrlichiosis are less defined, but similar courses have resulted in good outcomes.

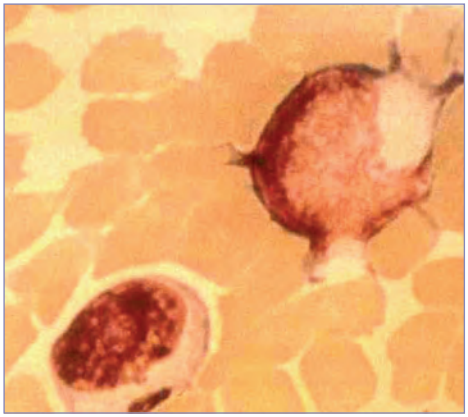


Image 45.1
The intracytoplasmic inclusion, or morula, of human monocytic ehrlichiosis in a cytocentrifuge preparation of cerebrospinal fluid from a patient with central nervous system involvement. Copyright Richard Jacobs, MD.

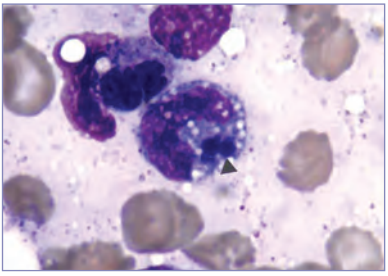


Image 45.2
Bone marrow examination (Wright stain, magnification ×1,000). Intraleukocytic morulae of *Ehrlichia* can be seen (arrow) within monocytoid cells. Courtesy of *Emerging Infectious Diseases.*

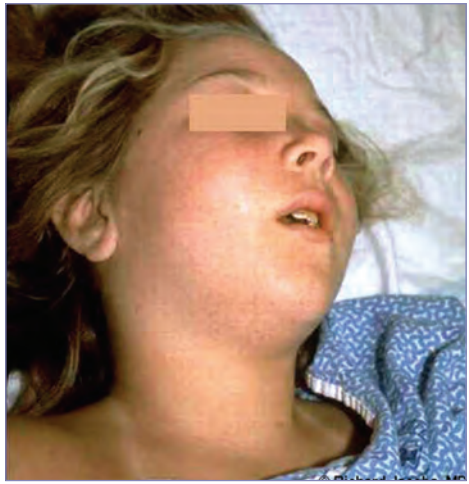


Image 45.3
Human monocytic ehrlichiosis (HME). A semicomatose 16-year-old girl with leukopenia, lymphopenia, thrombocytopenia, and elevated transaminase levels. The HME polymerase chain reaction and serologic test results were positive for HME. Copyright Richard Jacobs, MD.

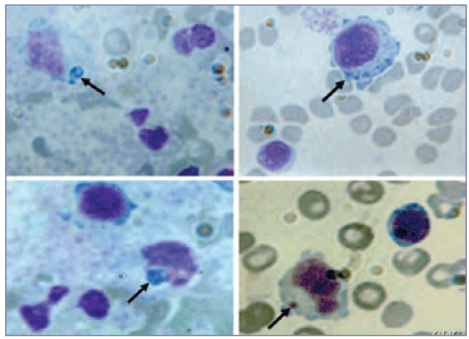


Image 45.6
Peripheral blood smears (buffy coat preparation) showing variable-sized basophilic inclusions (arrows) in mononuclear cells from a 9-year-old boy with human monocytic ehrlichiosis in Carabobo, Venezuela (Dip Quick [Jorgensen Laboratories Inc, Loveland, CO] staining, magnification ×1,000). Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases* and Maria C. Martinez.

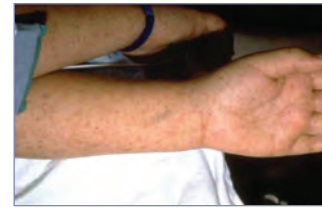


Image 45.4
The petechial and vasculitic rash of human monocytic ehrlichiosis in the patient in Image 45.3. Copyright Richard Jacobs, MD.

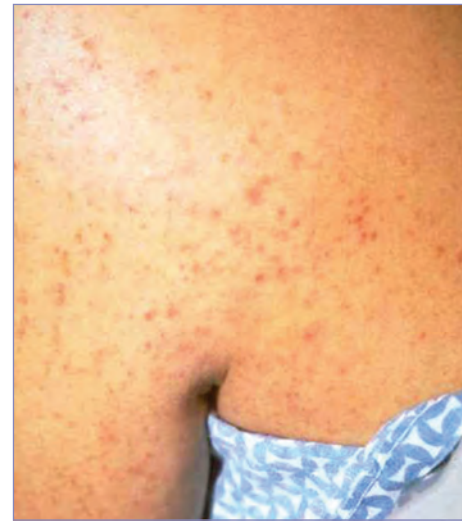


Image 45.5
The same characteristic rash of human monocytic ehrlichiosis in the patient in Images 45.3 and 45.4. The differential diagnosis of this rash includes Rocky Mountain spotted fever, meningococcemia, and Stevens-Johnson syndrome. Other tick-borne diseases, such as Lyme disease, babesiosis, Colorado tick fever, relapsing fever, and tularemia, may need to be considered. Kawasaki disease also has caused some diagnostic confusion. Copyright Richard Jacobs, MD.

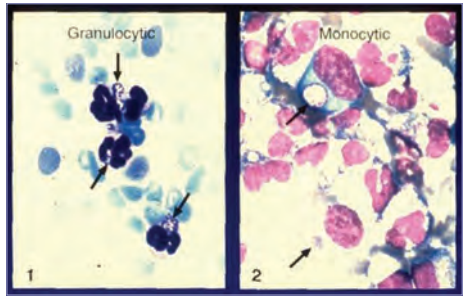


Image 45.7
Etiologic agents of ehrlichiosis. Photomicrographs of human white blood cells infected with the agent of human granulocytic ehrlichiosis (*Anaplasma phagocytophilum* [formerly *Ehrlichia phagocytophila*]) and the agent of human monocytic ehrlichiosis (*Ehrlichia chaffeensis*). Courtesy of Centers for Disease Control and Prevention.

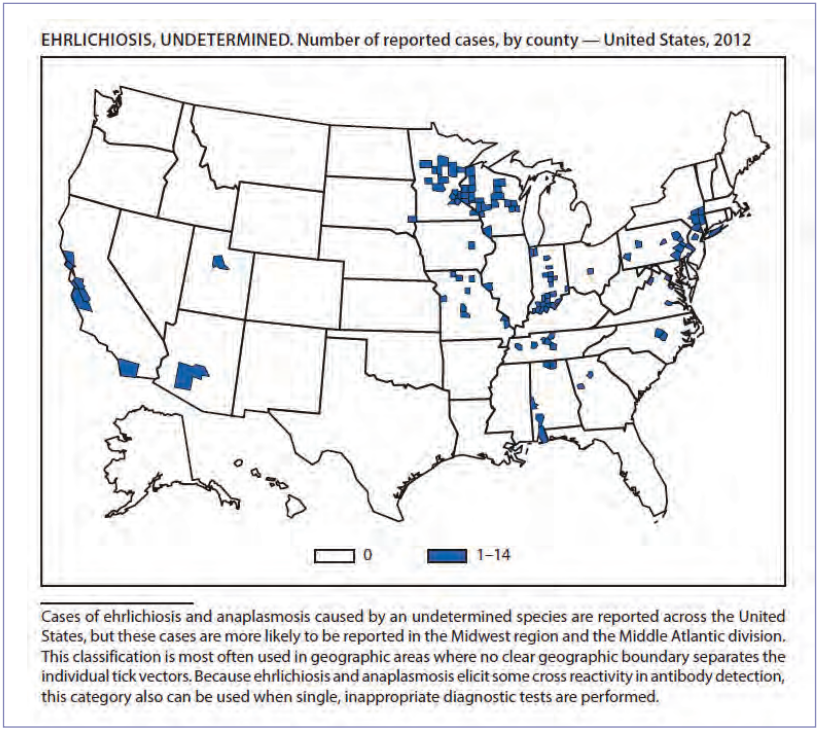


Image 45.8
Granulocytic ehrlichiosis. Number of reported cases, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

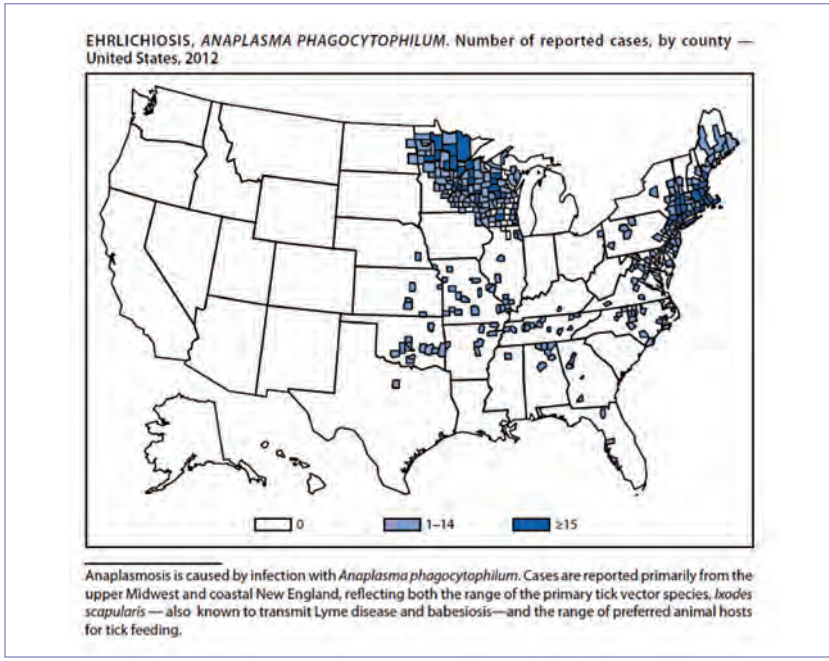


Image 45.9
Ehrlichiosis, *Anaplasma phagocytophilum.* Number of reported cases, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

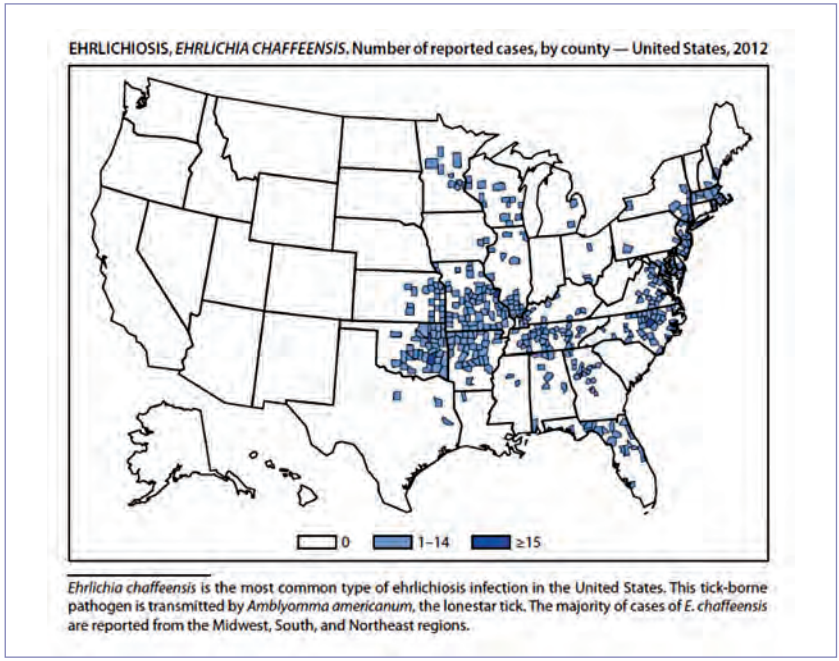


Image 45.10
Ehrlichiosis, *Ehrlichia chaffeensis.* Number of reported cases, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

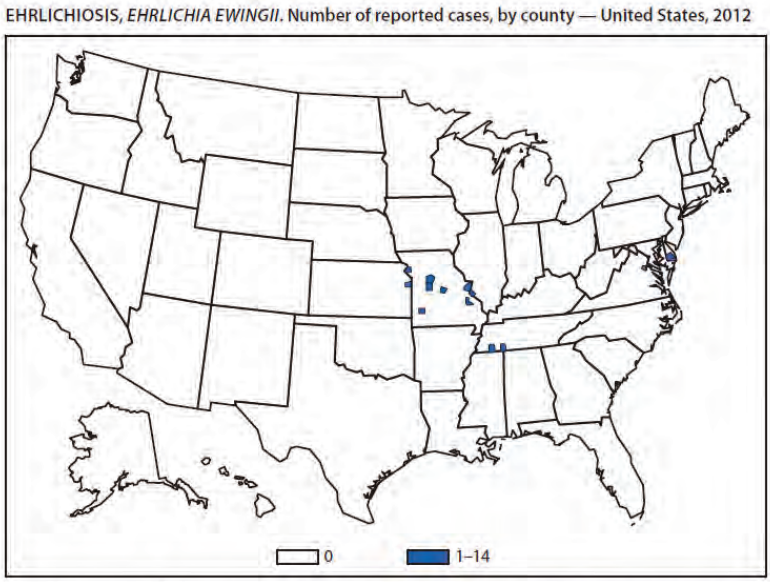


Image 45.11
Ehrlichiosis, *Ehrlichia ewingii.* Number of reported cases, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 45.12
This is a female lone star tick, *Amblyomma americanum*, and is found in the southeastern and mid-Atlantic United States. This tick is a vector of several zoonotic diseases, including human monocytic ehrlichiosis, southern tick-associated rash illness, tularemia, and Rocky Mountain spotted fever. Courtesy of Centers for Disease Control and Prevention.

Image 45.13
Dorsal view of an adult female western black-legged tick, *Ixodes pacificus*, which has been shown to transmit *Borrelia burgdorferi*, the agent of Lyme disease, and *Anaplasma phagocytophilum*, the agent of human granulocytic anaplasmosis (previously known as human granulocytic ehrlichiosis), in the western United States. The small scutum, or tough, chitinous dorsal abdominal plate does not cover its entire abdomen, thereby allowing the abdomen to expand many times when this tick ingests its blood meal (and which identified this specimen as a female). The 4 pairs of jointed legs place these ticks in the phylum *Arthropoda* and the class *Arachnida*. Courtesy of Centers for Disease Control and Prevention/Amanda Loftis, MD; William Nicholson, MD; Will Reeves, MD; and Chris Paddock, MD.

CHAPTER 46

Serious Bacterial Infections Caused by *Enterobacteriaceae*

(With Emphasis on Septicemia and Meningitis in Neonates)

CLINICAL MANIFESTATIONS

Neonatal septicemia or meningitis caused by *Escherichia coli* and other gram-negative bacilli cannot be differentiated clinically from septicemia or meningitis caused by other organisms. The early signs of sepsis can be subtle and similar to signs observed in noninfectious processes. Signs of septicemia include fever, temperature instability, heart rate abnormalities, grunting respirations, apnea, cyanosis, lethargy, irritability, anorexia, vomiting, jaundice, abdominal distention, cellulitis, and diarrhea. Meningitis, especially early in the course, can occur without overt signs suggesting central nervous system involvement. Some gram-negative bacilli, such as *Citrobacter koseri*, *Cronobacter* (formerly *Enterobacter*) *sakazakii*, *Serratia marcescens*, and *Salmonella* species, are associated with brain abscesses in infants with meningitis caused by these organisms.

ETIOLOGY

Enterobacteriaceae are a large family of gram-negative, facultatively anaerobic, rod-shaped bacteria that include *Escherichia* species, *Klebsiella* species, *Enterobacter* species, *Proteus* species, *Providencia* species, and *Serratia* species, among many others. *E coli* strains, often those with the K1 capsular polysaccharide antigen, are the most common cause of septicemia and meningitis in neonates. Other important gram-negative bacilli causing neonatal septicemia include *Klebsiella* species, *Enterobacter* species, *Proteus* species, *Citrobacter* species, *Salmonella* species, *Pseudomonas* species, *Acinetobacter* species, and *Serratia* species. Nonencapsulated strains of *Haemophilus influenzae* and anaerobic gram-negative bacilli are rare causes. *Elizabethkingia meningosepticum* (originally known as *Flavobacterium meningosepticum* after discovery in 1959, then reclassified as *Chryseobacter meningosepticum* before being renamed in 2006) has been associated with outbreaks of neonatal meningitis, with infections in immunocompromised people or with other health care-associated outbreaks related to environmental contamination. *Elizabethkingia anophelis* has been reported as a recent cause of health care-associated infection in adults older than 65 years, with rare cases reported in neonates.

EPIDEMIOLOGY

The source of *E coli* and other gram-negative bacterial pathogens in neonatal infections during the first days of life typically is the maternal genital tract. Reservoirs for gram-negative bacilli can be present within the health care environment. Acquisition of gram-negative organisms can occur through person-to-person transmission from hospital nursery personnel as well as from nursery environmental sites such as sinks, countertops, powdered infant formula, and respiratory therapy equipment, especially among very preterm infants who require prolonged neonatal intensive care management. Predisposing factors in neonatal gram-negative bacterial infections include maternal intrapartum infection, gestation less than 37 weeks, low birth weight, and prolonged rupture of membranes. Metabolic abnormalities (eg, galactosemia), fetal hypoxia, and acidosis have been implicated as predisposing factors. Neonates with defects in the integrity of skin or mucosa (eg, myelomeningocele) or abnormalities of gastrointestinal or genitourinary tracts are at increased risk of gram-negative bacterial infections. In neonatal intensive care units, systems for respiratory and metabolic support, invasive or surgical procedures, indwelling vascular catheters, and frequent use of broad-spectrum antimicrobial agents enable selection and proliferation of strains of gram-negative bacilli that are resistant to multiple antimicrobial agents.

Multiple mechanisms of resistance in gram-negative bacilli can be present simultaneously. Resistance resulting from production of chromosomally encoded or plasmid-derived **AmpC beta-lactamases** or from plasmid-mediated **extended-spectrum beta-lactamases (ESBLs)** occurs primarily in *E coli*, *Klebsiella* species,

and *Enterobacter* species but has been reported in many other gram-negative species. Resistant gram-negative infections have been associated with nursery outbreaks, especially in very low birth weight infants. Additional risk factors associated with neonatal ESBL infection include prolonged mechanical ventilation, extended hospital stay, use of invasive devices, and use of antimicrobial agents. Infants born to mothers colonized with ESBL-producing *E coli* are themselves at an increased risk of acquiring colonization with ESBL-producing *E coli* compared with infants born to mothers without colonization. Organisms that produce ESBLs typically are resistant to penicillins, cephalosporins, and monobactams and can be resistant to aminoglycosides. **Carbapenemase-producing *Enterobacteriaceae* (CPE)** also have emerged, especially *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* species. ESBL- and carbapenemase-producing bacteria often carry additional plasmid-borne genes that encode for high-level resistance to aminoglycosides, fluoroquinolones, and trimethoprim-sulfamethoxazole.

The **incubation period** is variable; time of onset of infection ranges from birth to several weeks after birth or longer in very low birth weight, preterm infants with prolonged hospitalizations.

DIAGNOSTIC TESTS

Diagnosis is established by growth of *E coli* or other gram-negative bacilli from blood, cerebrospinal fluid (CSF), or other usually sterile sites. Isolates may be identified by traditional biochemical tests, by a variety of commercially available biochemical test systems, by mass spectrometry of bacterial cell components, or by molecular methods. Multiplexed molecular tests capable of rapidly identifying a variety of gram-negative rods including *E coli* directly in positive blood culture bottles have been cleared by the US Food and Drug Administration. Special screening and confirmatory laboratory procedures are required to detect some multidrug-resistant gram-negative organisms. Molecular diagnostics are being used increasingly for identification of pathogens; specimens should be saved for resistance testing.

TREATMENT

- Initial empirical treatment for suspected early-onset gram-negative septicemia in neonates should be based on local and regional antimicrobial susceptibility data. The proportion of *E coli* bloodstream infections with onset within 72 hours of life that are resistant to ampicillin is high among very low birth weight infants. These *E coli* infections almost invariably are susceptible to gentamicin, although monotherapy with an aminoglycoside is not recommended.

- Ampicillin and an aminoglycoside may be first-line therapy in areas with low ampicillin resistance. An alternative regimen of ampicillin and an extended-spectrum cephalosporin (such as cefotaxime) can be used, but rapid emergence of cephalosporin-resistant organisms, especially *Enterobacter* species, *Klebsiella* species, and *Serratia* species, and increased risk of colonization or infection with ESBL-producing *Enterobacteriaceae* can occur when cephalosporin use is routine in a neonatal unit. Hence, routine use of an extended-spectrum cephalosporin is not recommended unless gram-negative bacterial meningitis is suspected. If cefotaxime is unavailable or if there is a concern for meningitis caused by a multidrug-resistant gram-negative organism, a carbapenem is the preferred choice for empirical therapy.

- Once the causative agent and its in vitro antimicrobial susceptibility pattern are known, nonmeningeal infections should be treated with ampicillin, an appropriate aminoglycoside, or an extended-spectrum cephalosporin (such as cefotaxime) on the basis of the susceptibility results. Some experts treat nonmeningeal infections caused by *Enterobacter* species, *Serratia* species, or *Pseudomonas* species and some other less commonly occurring gram-negative bacilli with a beta-lactam antimicrobial agent and an aminoglycoside. For ampicillin-susceptible CSF isolates of *E coli*, meningitis can be treated with ampicillin or cefotaxime; meningitis caused by an ampicillin-resistant, cefotaxime-susceptible isolate can be treated with cefotaxime. Combination therapy with

cefotaxime and an aminoglycoside is used for empirical therapy and until CSF is sterile. If cefotaxime is unavailable, a carbapenem should be substituted for empirical therapy for neonates and infants younger than 91 days. Expert advice from an infectious disease specialist is helpful for management of meningitis.

- A carbapenem is the drug of choice for treatment of infections caused by ESBL-producing organisms, especially some *Klebsiella pneumoniae* isolates. Of the aminoglycosides, amikacin retains the most activity against ESBL-producing strains. An aminoglycoside or cefepime can be used if the organism is susceptible, because cefepime does not induce chromosomal AmpC enzymes. *E meningosepticum* intrinsically is resistant to most beta-lactams, including carbapenems, and has variable susceptibility to trimethoprim-sulfamethoxazole and fluoroquinolones; most are susceptible to piperacillin-tazobactam and rifampin. Expert advice from an infectious disease specialist is helpful in management of multidrug-resistant infection (eg, *E meningoseptica*) and ESBL-producing gram-negative infections in neonates.
- The treatment of infections caused by carbapenemase-producing gram-negative organisms is guided by the susceptibility profile and can include an aminoglycoside, especially amikacin; trimethoprim-sulfamethoxazole; or colistin. Isolates often are susceptible to tigecycline, fluoroquinolones, and polymyxin B, for which experience in neonates is limited. Patterns of susceptibility depend on the carbapenemase type. Combination therapy often is used. Expert advice from an infectious disease specialist is helpful in management of carbapenemase-producing gram- negative infections in neonates.
- All neonates with gram-negative meningitis should undergo repeat lumbar puncture to ensure sterility of the CSF after 24 to 48 hours of therapy. If CSF remains culture positive, choice and doses of antimicrobial agents should be reevaluated, and another lumbar puncture should be performed after another 48 to 72 hours.
- Duration of therapy is based on clinical and bacteriologic response of the patient and the site(s) of infection; the usual duration of therapy for uncomplicated bacteremia is 10 to 14 days, and for meningitis, minimum duration is 21 days.
- All infants with gram-negative meningitis should undergo careful follow-up examinations, including testing for hearing loss, neurologic abnormalities, and developmental delay.
- Immune Globulin Intravenous (IGIV) therapy for newborn infants receiving antimicrobial agents for suspected or proven serious infection has been shown to have no effect on outcomes measured and is not recommended.

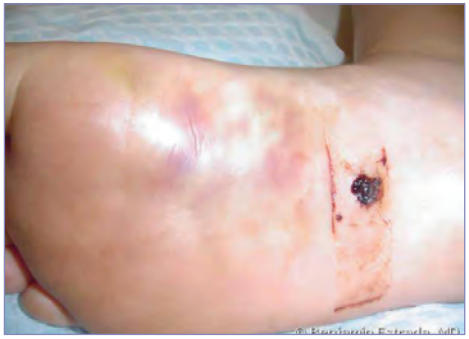


Image 46.1
Aeromonas cellulitis in an 11-year-old boy who previously sustained an injury to the plantar surface of his right foot. Courtesy of Benjamin Estrada, MD.

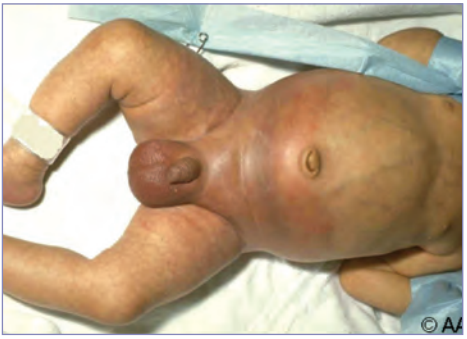


Image 46.2
Icteric preterm neonate with septicemia and perineal and abdominal wall cellulitis due to *Escherichia coli*.

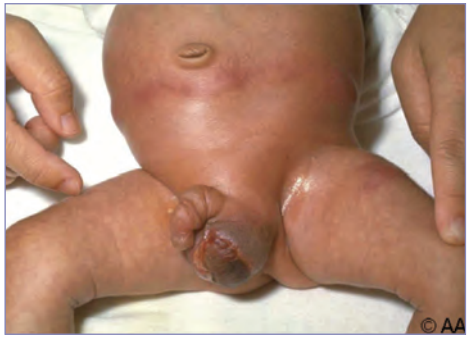


Image 46.3
Neonate in Image 46.2 with *Escherichia coli* septicemia and perineal cellulitis, scrotal necrosis, and abdominal wall abscesses below the navel that required surgical drainage and antibiotics.

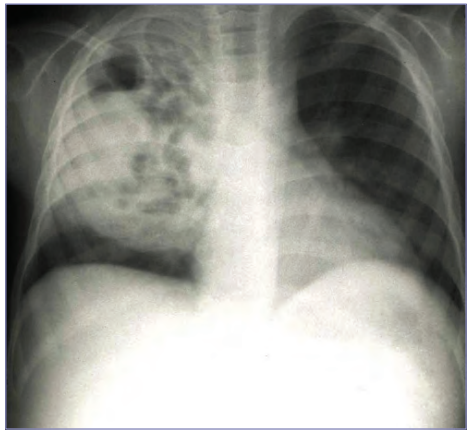


Image 46.5
Pneumonia due to *Klebsiella pneumoniae* with pulmonary necrosis and downward "bulging" of the pleural fissure secondary to accumulation of tenacious secretions.

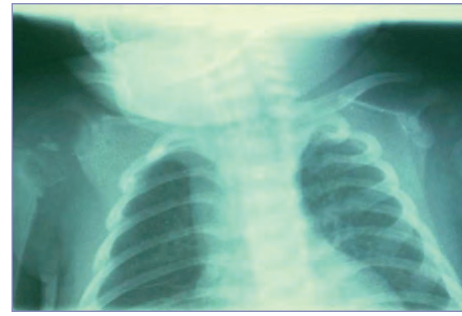


Image 46.4
Infant with osteomyelitis of the proximal right humerus due to *Escherichia coli*.

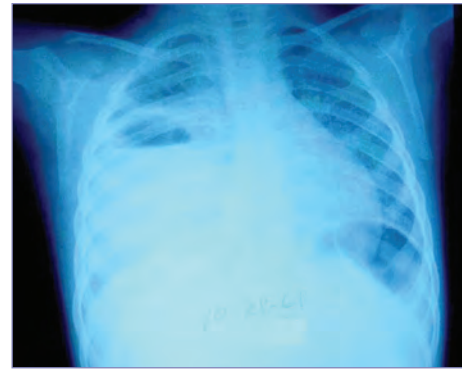


Image 46.6
Lung abscess, anteroposterior view, with air-fluid level. *Klebsiella pneumoniae* was cultured from bronchoscopy secretions. Courtesy of Edgar O. Ledbetter, MD, FAAP.

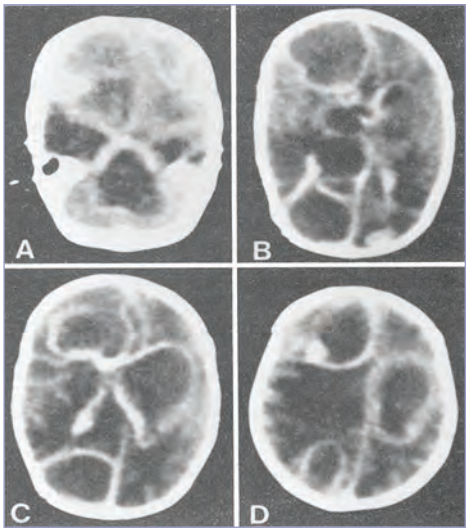


Image 46.7
Computed tomography scan of the head of a neonate 3 weeks after therapy for *Escherichia coli* meningitis demonstrating widespread destruction of cerebral cortex secondary to vascular thrombosis. Neonate was blind, deaf, and globally intellectually disabled and had diabetes insipidus. Courtesy of Carol J. Baker, MD, FAAP.

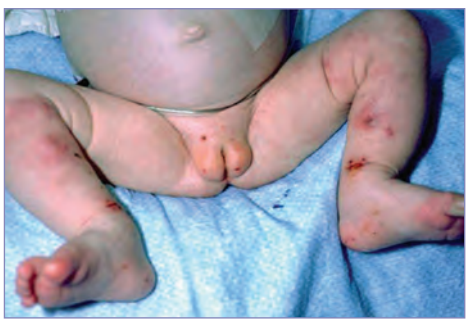


Image 46.9
A 5-week-old girl with *Klebsiella pneumoniae* sepsis and meningitis with bilateral saphenous vein thrombophlebitis (illness began with diarrhea). Copyright Martin G. Myers, MD.

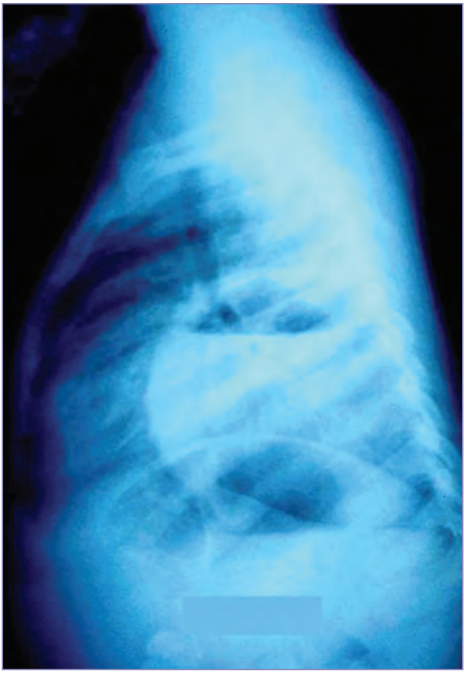


Image 46.8
Lateral view of patient in Image 46.6 with *Klebsiella pneumoniae* pneumonia demonstrating large lung abscess with air-fluid level. Repeated bronchoscopy was necessary for adequate drainage. Courtesy of Edgar O. Ledbetter, MD, FAAP.

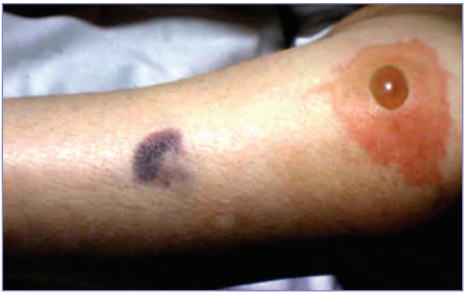


Image 46.10
Skin lesions due to *Pseudomonas aeruginosa* in child with neutropenia and septicemia.

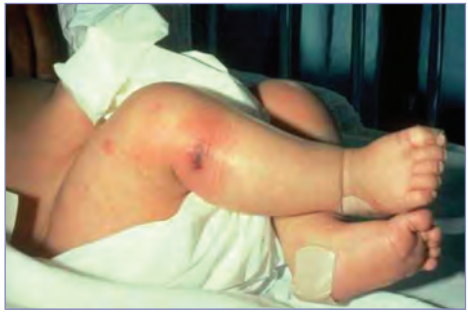


Image 46.11
Sepsis due to *Pseudomonas aeruginosa* with early ecthyma gangrenosum.

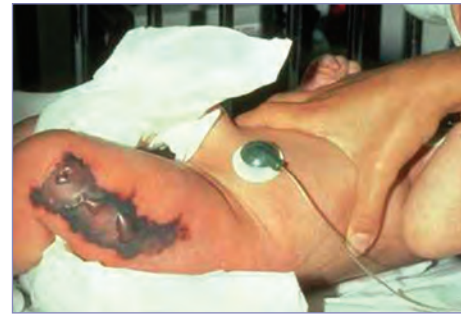


Image 46.12
Sepsis due to *Pseudomonas aeruginosa* with rapidly progressing ecthyma gangrenosum. This is the same patient as in Image 46.11.

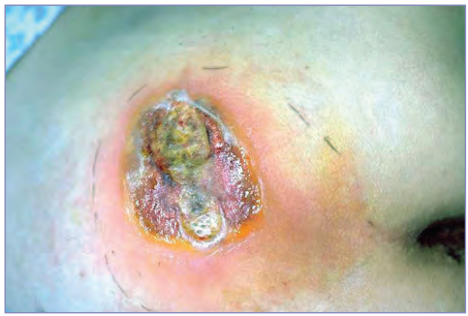


Image 46.13
A preschool-aged boy with acute lymphoblastic leukemia and necrotizing *Pseudomonas* skin lesions called ecthyma gangrenosum. Copyright Martin G. Myers, MD.

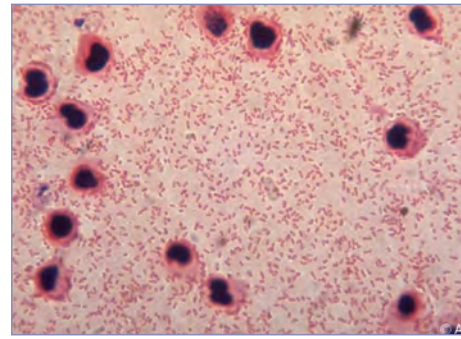


Image 46.14
Gram stain of *Escherichia coli* in the cerebrospinal fluid of a neonate with meningitis.

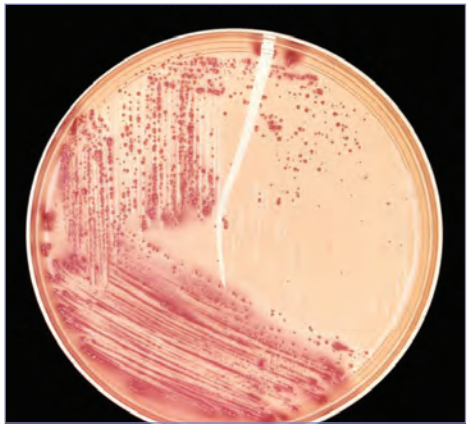


Image 46.15
After 24 hours, this inoculated MacConkey agar culture plate cultivated colonial growth of gram-negative *Escherichia coli* bacteria. Courtesy of Centers for Disease Control and Prevention.

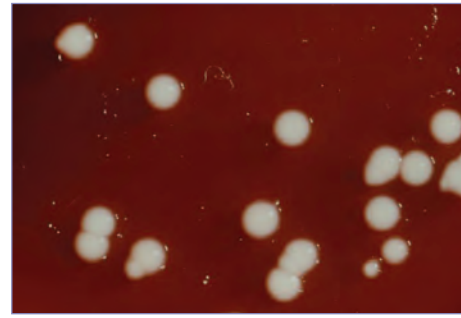


Image 46.16
This blood agar plate grew colonies of gram-negative, small rod-shaped, and facultatively anaerobic *Klebsiella pneumoniae* bacteria. Courtesy of Centers for Disease Control and Prevention.

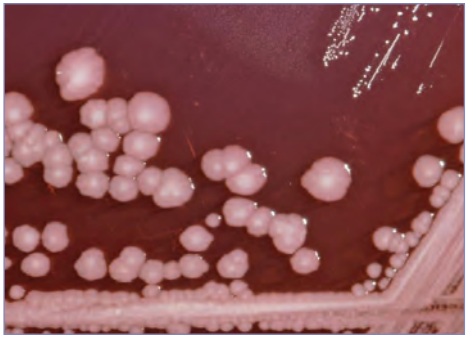


Image 46.17
This photograph depicts the colonies of *Proteus mirabilis* bacteria grown on a xylose-lysine-deoxycholate agar plate. Courtesy of Centers for Disease Control and Prevention.

Image 46.18
Citrobacter freundii on MacConkey agar plate. Colonies appear dark pink on this type of medium, indicating lactose fermentation. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

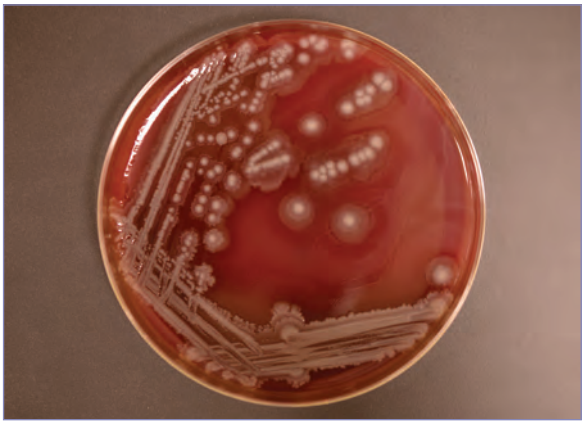


Image 46.19
Proteus vulgaris on blood agar plate. Due to its motility, *Proteus* species will often appear to be swarming on chocolate and blood agar plates, as in this photograph. It may sometimes have the odor of chocolate cake. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 47

Enterovirus (Nonpoliovirus)

(Group A and B Coxsackieviruses, Echoviruses, Numbered Enteroviruses)

CLINICAL MANIFESTATIONS

Nonpolio enteroviruses are responsible for significant and frequent illnesses in infants and children and result in protean clinical manifestations. The most common manifestation is nonspecific febrile illness, which in young infants may lead to evaluation for bacterial sepsis. Other manifestations can include the following: (1) respiratory: coryza, pharyngitis, herpangina, stomatitis, parotitis, croup, bronchiolitis, pneumonia, pleurodynia, and bronchospasm; (2) skin: hand-foot-and-mouth disease, onychomadesis (periodic shedding of nails), and nonspecific exanthems (particularly associated with echoviruses); (3) neurologic: aseptic meningitis, encephalitis, and motor paralysis (acute flaccid myelitis); (4) gastrointestinal/genitourinary: vomiting, diarrhea, abdominal pain, hepatitis, pancreatitis, and orchitis; (5) eye: acute hemorrhagic conjunctivitis and uveitis; (6) heart: myopericarditis; and (7) muscle: pleurodynia and other skeletal myositis. Neonates, especially those who acquire infection in the absence of serotype-specific maternal antibody, are at risk of severe and life-threatening disease, including viral sepsis, meningoencephalitis, myocarditis, hepatitis, coagulopathy, and pneumonitis. Infection with enterovirus 71 is associated with hand-foot-and-mouth disease, herpangina, and in a small proportion of cases, severe neurologic disease, including brainstem encephalomyelitis, paralytic disease, and other neurologic manifestations; secondary pulmonary edema/hemorrhage and cardiopulmonary collapse can occur, resulting in fatalities and sequelae. Other noteworthy but not exclusive serotype associations include coxsackieviruses A6 and A16 with hand-foot-and-mouth disease (including severe hand-foot-and-mouth disease and atypical cutaneous involvement with coxsackievirus A6), coxsackievirus A24 variant and enterovirus 70 with acute hemorrhagic conjunctivitis, and coxsackieviruses B1 through B5 with pleurodynia and myopericarditis.

Enterovirus D68 (EV-D68) is associated with mild to severe respiratory illness in infants, children, and teenagers and was responsible for a large multinational outbreak of respiratory disease in 2014. Disease was characterized by exacerbation of preexisting asthma or new-onset wheezing in children without any history of asthma, often requiring hospitalization and, in some patients, intensive supportive care. Concurrent with this outbreak, cases of a polio-like, acute neurologic syndrome were reported, often with a history of recent respiratory illness, some of which were demonstrated to have been caused by EV-D68. Neurologic illness consisted of acute onset of limb weakness accompanied by cerebrospinal fluid pleocytosis and nonenhancing lesions restricted to the gray matter on magnetic resonance imaging of the spinal cord. EV-D68 was not detectable in cerebrospinal fluid samples, precluding confirmation that it was the cause of neurologic illness, although 2 previously published reports of children with neurologic illnesses confirmed EV-D68 infection by cerebrospinal fluid testing. The full spectrum of disease caused by EV-D68 remains unknown.

Patients with humoral and combined immune deficiencies can develop persistent central nervous system infections, a dermatomyositis-like syndrome, or disseminated infection. Severe neurologic or multisystem disease is reported in hematopoietic stem cell and solid organ transplant recipients, children with malignancies, and patients treated with anti-CD20 monoclonal antibody.

ETIOLOGY

The enteroviruses comprise a genus in the *Picornaviridae* family of RNA viruses. The nonpolio enteroviruses include more than 100 distinct serotypes formerly subclassified as group A coxsackieviruses, group B coxsackieviruses, echoviruses, and newer numbered enteroviruses. A more recent classification system groups these nonpolio enteroviruses into 4 species (Enterovirus [EV] A, B, C, and D) on the basis of genetic similarity, although traditional serotype names are retained for some individual serotypes. Echoviruses 22 and 23 have been reclassified as human parechoviruses 1 and 2, respectively.

EPIDEMIOLOGY

Humans are the only known reservoir for human enteroviruses, although some primates can become infected. Enterovirus infections are common and distributed worldwide; the majority of infections are asymptomatic. Enteroviruses are spread by fecal-oral and respiratory routes, and from mother to infant prenatally, in the peripartum period, and possibly via breastfeeding. EV-D68 is thought to be spread primarily by respiratory transmission. Enteroviruses may survive on environmental surfaces for periods long enough to allow transmission from fomites, and transmission via contaminated water and food can occur. Hospital nursery and other institutional outbreaks may occur. Infection incidence, clinical attack rates, and disease severity typically are greatest in infants and young children, and infections occur more frequently in tropical areas and where poor sanitation, poor hygiene, and high population density are present. Most enterovirus infections in temperate climates occur in the summer and fall (June through October in the northern hemisphere), but seasonal patterns are less evident in the tropics. Epidemics of enterovirus meningitis, enterovirus 71-associated hand-foot-and-mouth disease with neurologic and cardiopulmonary complications (particularly in southern and eastern Asia), and enterovirus 70- and coxsackievirus A24-associated acute hemorrhagic conjunctivitis (characterized by viral shedding in tears and spread by contact; limited to subtropical and tropical regions) occur. Fecal viral shedding of most enteroviruses can persist for several weeks or months after onset of infection, but respiratory tract shedding usually is limited to 1 to 3 weeks or less. Fecal shedding is uncommon with EV-D68. Infection and viral shedding can occur without signs of clinical illness.

The usual **incubation period** for enterovirus infections is 3 to 6 days, except acute hemorrhagic conjunctivitis, where the **incubation period** is 24 to 72 hours.

DIAGNOSTIC TESTS

Enteroviruses generally can be detected by reverse transcriptase-polymerase chain reaction (RT-PCR) assay and culture from a variety of specimens, including stool, rectal swabs, throat swabs, nasopharyngeal aspirates, conjunctival swabs, tracheal aspirates, blood, urine, and tissue biopsy specimens, and from cerebrospinal fluid (CSF) when meningitis is present. RT-PCR assay is more rapid and more sensitive than isolation of enteroviruses in cell culture and can detect all enteroviruses, including serotypes that are difficult to cultivate in viral culture. Patients with enterovirus 71 neurologic disease often have negative results of RT-PCR assay and culture of CSF (even in the presence of CSF pleocytosis) and blood; RT-PCR assay and culture of throat or rectal swab and/or vesicle fluid specimens (in cases of hand-foot-and-mouth disease) more frequently are positive. RT-PCR assays for detection of enterovirus RNA are available at many reference and commercial laboratories for CSF, blood, and other specimens.

EV-D68 is demonstrated primarily in respiratory tract specimens and can be detected with multiplex respiratory RT-PCR assays, but these assays do not distinguish enteroviruses from rhinoviruses. Definitive identification of EV-D68 requires partial genomic sequencing or amplification by an EV-D68-specific RT-PCR assay.

Sensitivity of culture ranges from 0% to 80% depending on serotype and cell lines used. Many group A coxsackieviruses grow poorly or not at all in vitro. Culture usually requires 3 to 8 days to detect growth. Serotyping may be indicated in cases of special clinical interest or for epidemiologic purposes (eg, for investigation of disease clusters or outbreaks). Acute infection with a known enterovirus serotype can be determined at reference laboratories by demonstration of a change in neutralizing or other serotype-specific antibody titer between acute and convalescent serum specimens or by detection of serotype-specific immunoglobulin (Ig) M, but serologic assays are relatively insensitive and lack specificity.

TREATMENT

No specific therapy is available for enteroviruses infections. Immune Globulin Intravenous (IGIV), administered intravenously or via intraventricular administration, may be beneficial for chronic enterovirus meningoencephalitis in immunodeficient patients. IGIV also has been

used for life-threatening neonatal enterovirus infections (maternal convalescent plasma has also been used), severe enterovirus infections in transplant recipients and people with malignancies, suspected viral myocarditis, and enterovirus 71 neurologic disease, but proof of efficacy for these uses is lacking. Interferons occasionally have been used for treatment of enterovirus-associated myocarditis, without definitive proof of efficacy. The antiviral drug pleconaril has activity against enteroviruses (but likely not parechoviruses) but is not available commercially. Pocapavir is another antiviral drug being developed primarily for the treatment of polioviruses, and it has activity against at least some nonpolio enteroviruses.

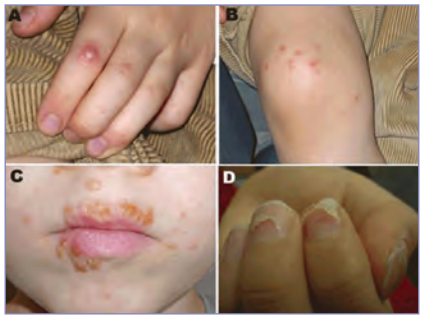


Image 47.1
Vesicular eruptions in hand (A), foot (B), and mouth (C) of a 6-year-old boy with coxsackievirus A6 infection. Several of his fingernails shed (D) 2 months after the pictures were taken. Courtesy of Centers for Disease Control and Prevention/ *Emerging Infectious Diseases.*

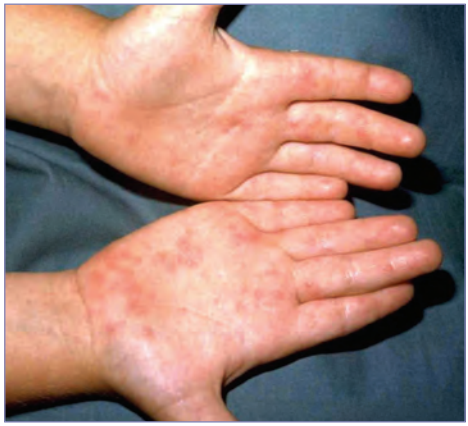


Image 47.3
Enterovirus infection (hand-foot-and-mouth disease) affecting the hands.

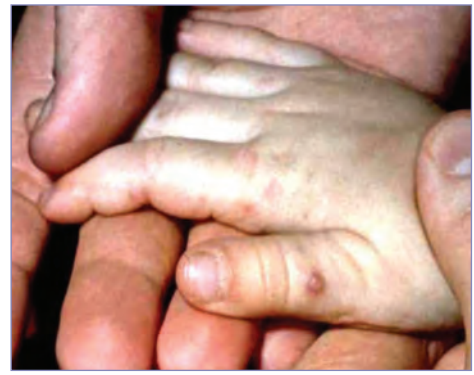


Image 47.2
Enterovirus infection in a preschool-aged girl. Hand-foot-and-mouth disease lesions are caused by coxsackievirus A16 and enterovirus 71.

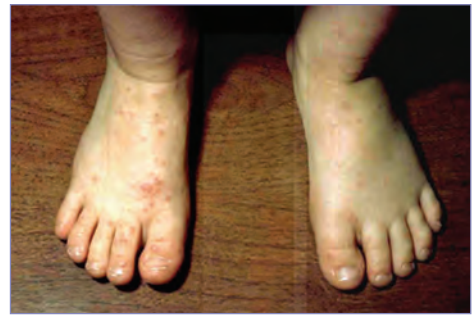


Image 47.4
Enterovirus infection (hand-foot-and-mouth disease) affecting the feet.

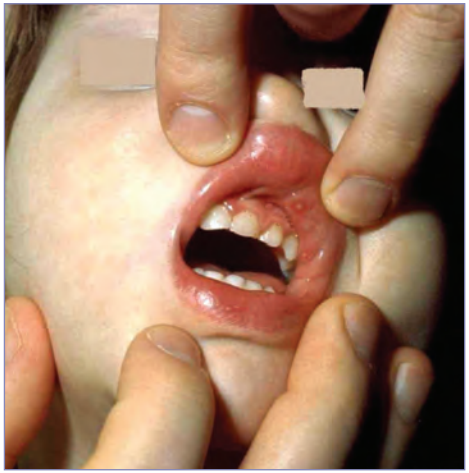


Image 47.5
Enterovirus infection (hand-foot-and-mouth disease) affecting the anterior buccal mucosa. These lesions generally are less painful than herpes simplex lesions.

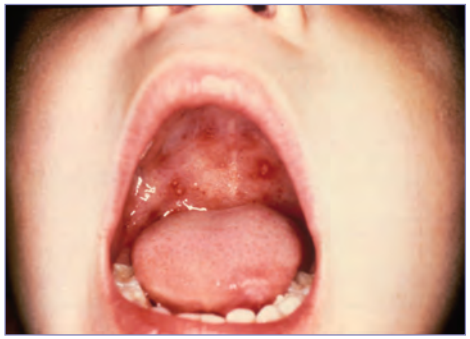


Image 47.7
Characteristic papulovesicular lesions of hand-foot-and-mouth disease in a 2-year-old boy. Courtesy of George Nankervis, MD.

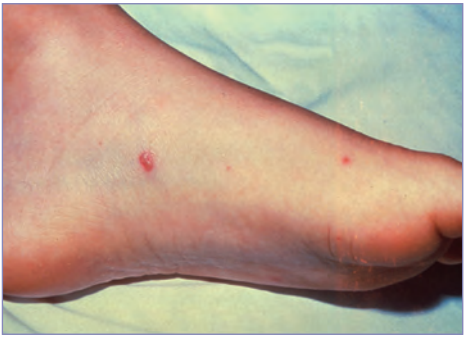


Image 47.6
A papulovesicular lesion on the medial aspect of the foot of a 6-year-old boy with hand-foot-and-mouth disease. Courtesy of George Nankervis, MD.

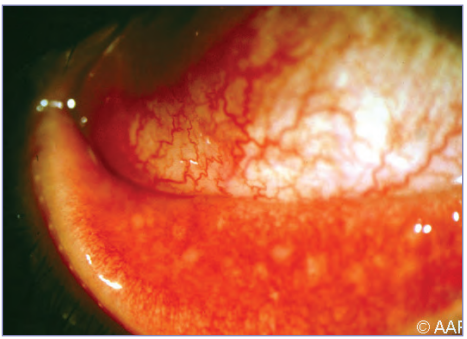


Image 47.8
Enterovirus 71 acute hemorrhagic conjunctivitis, on the second or third day. No neurologic sequelae were present. Copyright Jerri Ann Jenista, MD.

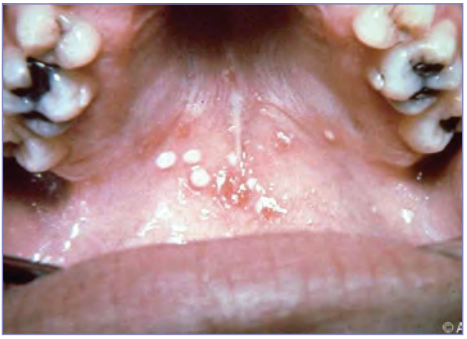


Image 47.9
Herpangina (coxsackievirus) lesions on the posterior palate of a young adult male. Coxsackievirus lesions usually are found in the posterior aspect of the oropharynx and may progress rapidly to painful ulceration.

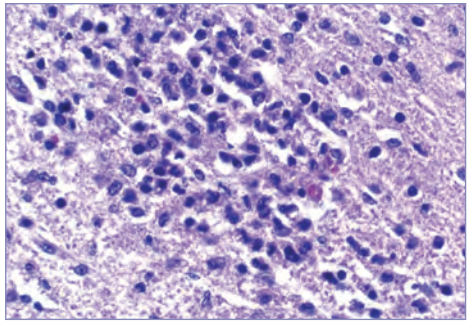


Image 47.10
Enterovirus encephalitis. Microglial nodule. Courtesy of Dimitris P. Agamanolis, MD.

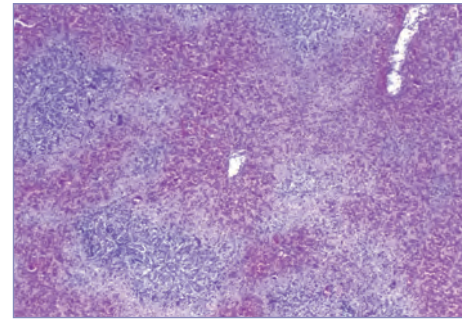


Image 47.11
Extensive hepatic necrosis caused by an enterovirus infection. Courtesy of Dimitris P. Agamanolis, MD.

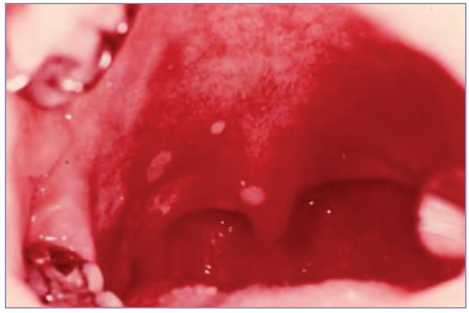


Image 47.12
A 4-year-old girl with pharyngeal inflammation and palatal lesions of hand-foot-and-mouth disease, a coxsackievirus A infection.

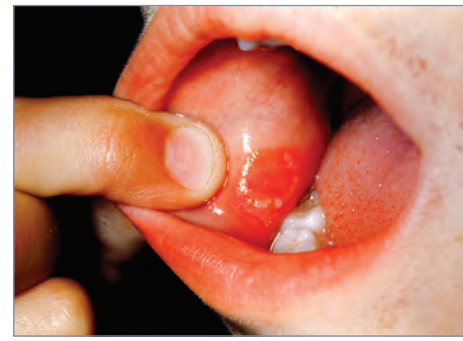


Image 47.13
This 7-year-old girl presented with low-grade fever, malaise, sore throat, and these interesting, slightly raised oral lesions opposite the first molar. She also had approximately 10 maculopapular lesions on each buttock and a few on each foot. She had classic hand-foot-and-mouth disease. Coxsackievirus A16 was grown from throat and rectal swabs. Courtesy of Neal Halsey, MD.

CHAPTER 48

Epstein-Barr Virus Infections

(Infectious Mononucleosis)

CLINICAL MANIFESTATIONS

Infectious mononucleosis is the most common presentation of primary symptomatic Epstein-Barr virus (EBV) infection. It manifests typically as fever, pharyngitis with petechiae, exudative pharyngitis, lymphadenopathy, hepatosplenomegaly, and atypical lymphocytosis. The spectrum of disease is wide, ranging from asymptomatic to fatal infection. Infections commonly are unrecognized in infants and young children. Rash can occur and is more common in patients treated with ampicillin or amoxicillin as well as with other penicillins. Central nervous system (CNS) manifestations include aseptic meningitis, encephalitis, myelitis, optic neuritis, cranial nerve palsies, transverse myelitis, Alice in Wonderland syndrome, and Guillain-Barré syndrome. Hematologic complications include splenic rupture, thrombocytopenia, agranulocytosis, hemolytic anemia, and hemophagocytic lymphohistiocytosis (HLH, or hemophagocytic syndrome). Pneumonia, orchitis, and myocarditis are observed infrequently. Early in the course of primary infection, up to 20% of circulating B lymphocytes are infected with EBV, and EBV-specific cytotoxic/suppressor T lymphocytes account for up to 30% of the CD8+ T lymphocytes in the blood. Replication of EBV in B lymphocytes results in T-lymphocyte proliferation and inhibition of B-lymphocyte proliferation by T-lymphocyte cytotoxic responses. Fatal disseminated infection or B-lymphocyte or T-lymphocyte lymphomas can occur in children with no detectable immunologic abnormality as well as in children with congenital or acquired cellular immune deficiencies.

EBV is associated with several other distinct disorders, including X-linked lymphoproliferative syndrome, post-transplantation lymphoproliferative disorders, Burkitt lymphoma, nasopharyngeal carcinoma, and undifferentiated B- or T-lymphocyte lymphomas and leiomyosarcoma. X-linked lymphoproliferative syndrome occurs in people with an inherited, maternally derived, recessive genetic defect in the SH2DIA gene, which is important in several lymphocyte signaling pathways. The syndrome is characterized by several phenotypic expressions, including occurrence of fatal infectious mononucleosis early in life among boys; nodular B-lymphocyte lymphomas, often with CNS involvement; and profound hypogammaglobinemia. Similarly, "X-linked immunodeficiency with magnesium defect, EBV infection, and neoplasia" (XMEN) disease is characterized by loss-of-function mutations in the gene encoding magnesium transporter 1 (MAGT1), chronic high-level EBV with increased EBV-infected B cells, and heightened susceptibility to EBV-associated lymphomas.

EBV-associated lymphoproliferative disorders result in a number of complex syndromes in patients who are immunocompromised, such as transplant recipients or people infected with human immunodeficiency virus (HIV). The highest incidence of these disorders occurs in liver and heart transplant recipients, in whom the proliferative states range from benign lymph node hypertrophy to monoclonal lymphomas. Other EBV syndromes are of greater importance outside the United States. EBV is present in virtually 100% of endemic Burkitt lymphoma (a B-lymphocyte tumor predominantly found in head and neck lymph nodes primarily in Central Africa) versus 20% in sporadic Burkitt lymphoma (found in abdominal lymphoid tissue predominantly in North America and Europe). EBV is found in nasopharyngeal carcinoma in Southeast Asia and the Inuit populations. EBV also has been associated with Hodgkin disease (B-lymphocyte tumor), non-Hodgkin lymphomas (B and T lymphocyte), gastric carcinoma "lymphoepitheliomas," and a variety of common epithelial malignancies.

Chronic fatigue syndrome is not related to EBV infection; however, fatigue lasting weeks to months can follow approximately 10% of cases of classic infectious mononucleosis.

ETIOLOGY

EBV (also known as human herpesvirus 4) is a gamma herpesvirus of the *Lymphocryptovirus* genus and is the most common cause of infectious mononucleosis (>90% of cases).

EPIDEMIOLOGY

Humans are the only known reservoir of EBV, and approximately 90% of US adults have been infected. Close personal contact usually is required for transmission. The virus is viable in saliva for several hours outside the body, but the role of fomites in transmission is unknown. EBV may be transmitted by blood transfusion or transplantation. Infection commonly is contracted early in life, particularly among members of lower socioeconomic groups, in which intrafamilial spread is common. Endemic infectious mononucleosis is common in group settings of adolescents, such as in educational or military institutions. No seasonal pattern has been documented. Intermittent excretion in saliva is lifelong after infection.

The **incubation period** of infectious mononucleosis is estimated to be 30 to 50 days.

DIAGNOSTIC TESTS

Routine diagnosis depends on serologic testing. Nonspecific tests for heterophile antibody, including the Paul-Bunnell test and slide agglutination reaction test, are available most commonly. The heterophile antibody response primarily is immunoglobulin (Ig) M, which appears during the first 2 weeks of illness and gradually disappears over a 6-month period. The results of heterophile antibody tests often are negative in children younger than 4 years with EBV infection, but heterophile antibody tests identify approximately 85% of cases of classic infectious mononucleosis in older children and adults during the second week of illness. An absolute increase in atypical lymphocytes during the second week of illness with infectious mononucleosis is a characteristic but nonspecific finding. Nevertheless, the finding of greater than 10% atypical lymphocytes together with a positive heterophile antibody test result in the classical illness pattern is considered diagnostic of acute EBV infection.

Multiple specific serologic antibody tests for EBV infection are available in diagnostic virology laboratories (Table 48.1 and Figure 48.1). The most commonly performed test is for antibody against the viral capsid antigen (VCA). Because IgG antibodies against VCA occur in high titer early in infection and persist for life at modest levels, testing of acute and convalescent serum specimens for IgG anti-VCA alone is not useful for establishing the presence of active infection. In contrast, testing for the presence of IgM anti-VCA antibody and the absence (or very low titers) of antibodies to Epstein-Barr nuclear antigen (EBNA) is useful for identifying active and recent infections. Because serum antibody against EBNA is not present until several weeks to months after onset of infection and rises with convalescence, a very elevated anti-EBNA antibody concentration typically excludes active primary infection. Testing for antibodies against early antigen (EA) is not required to assess EBV-associated mononucleosis. However, in selected situations, it may be beneficial. Most clinical laboratories today usually perform enzyme immunoassays for detection of antibodies. Typical patterns of antibody responses to EBV infection are illustrated in Table 48.1 and Figure 48.1.

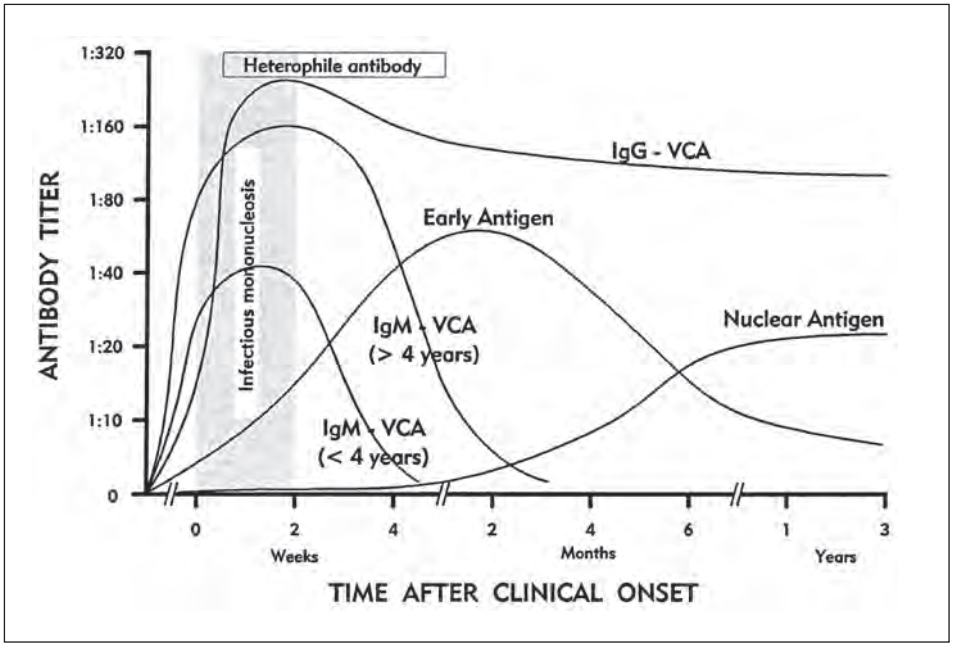
Serologic testing for EBV is useful, particularly for evaluating patients who have heterophile-negative infectious mononucleosis, are younger than 4 years, or in whom the infectious mononucleosis syndrome is not classic. Testing for other agents, especially cytomegalovirus,

Table 48.1
Serum Epstein-Barr Virus (EBV) Antibodies in EBV Infection

Infection	VCA IgG	VCA IgM	EA (D)	EBNA
No previous infection	–	–	–	–
Acute infection	+	+	+/–	–
Recent infection	+	+/–	+/–	+/–
Past infection	+	–	+/–	+

VCA IgG indicates immunoglobulin (Ig) G class antibody to viral capsid antigen; VCA IgM, IgM class antibody to VCA; EA (D), early antigen diffuse staining; and EBNA, EBV nuclear antigen.

Figure 48.1
Schematic representation of the evolution of antibodies to various Epstein-Barr virus antigens in patients with infectious mononucleosis.



Source: *Manual of Clinical Laboratory Immunology.* Washington, DC: American Society for Microbiology; 1997:636. © 1997 American Society for Microbiology. Used with permission. No further reproduction or distribution is permitted without the prior written permission of American Society for Microbiology.

Toxoplasma, human herpesvirus 6, adenovirus, and HIV (in those with HIV risk factors), may be indicated for some patients.

Isolation of EBV from oropharyngeal secretions by culture in cord blood cells is possible, but techniques for performing this procedure usually are not available in routine diagnostic laboratories, and virus isolation does not necessarily indicate acute infection. Polymerase chain reaction (PCR) assay for detection of EBV DNA in serum, plasma, and tissue and reverse transcriptase-PCR assay for detection of EBV RNA in lymphoid cells, tissue, and/or body fluids are available commercially and may be useful in evaluation of immunocompromised patients and in complex clinical situations.

TREATMENT

Patients suspected to have infectious mononucleosis should not receive ampicillin or amoxicillin, which may cause nonallergic morbilliform rashes in a significant proportion of patients with active EBV infection. Although therapy with short-course corticosteroids may have a beneficial effect on some acute symptoms, because of potential adverse effects their use should be considered only for patients with marked tonsillar inflammation with impending airway obstruction, massive splenomegaly, myocarditis, hemolytic anemia, or HLH. Life-threatening HLH has been treated with cytotoxic agents and immunomodulators, including etoposide, cyclosporine, and/or corticosteroids. Decreasing immunosuppressive therapy often is beneficial for patients with EBV-induced post-transplant lymphoproliferative disorders.

Strenuous activity and contact sports should be avoided for 21 days after onset of symptoms of infectious mononucleosis. After 21 days, limited noncontact aerobic activity can be allowed if there are no symptoms and there is no overt splenomegaly. Clearance to participate in contact sports is appropriate after 4 to 6 weeks following the onset of symptoms if the athlete is

asymptomatic and has no overt splenomegaly. Imaging modalities rarely are helpful in decisions about clearance to return to contact sports. Repeat monospot or EBV serologic testing is not useful. It may take 3 to 6 months or longer following mononucleosis for an athlete to return to pre-illness fitness.

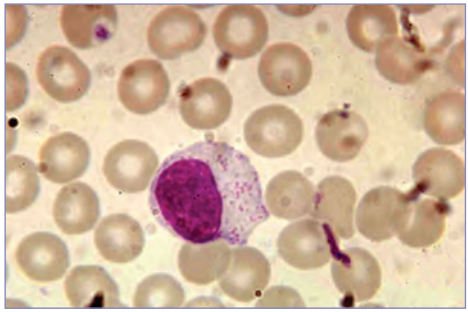


Image 48.1
Atypical lymphocyte in a peripheral blood smear of a patient with infectious mononucleosis. This lymphocyte is larger than normal lymphocytes, with a higher ratio of cytoplasm to nucleus. The cytoplasm is vacuolated and basophilic. This may also be present in cytomegalovirus infections.

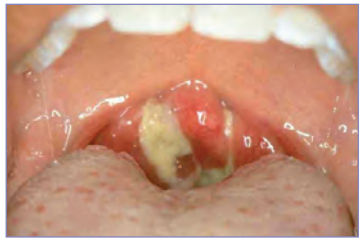


Image 48.3
Epstein-Barr virus disease with pharyngeal and tonsillar exudate. Copyright James Brien, DO.

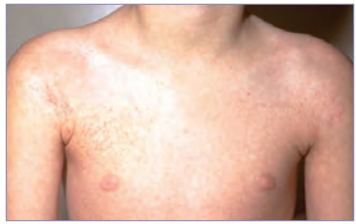


Image 48.5
Rash in a 9-year-old girl with infectious mononucleosis who was prescribed ampicillin.

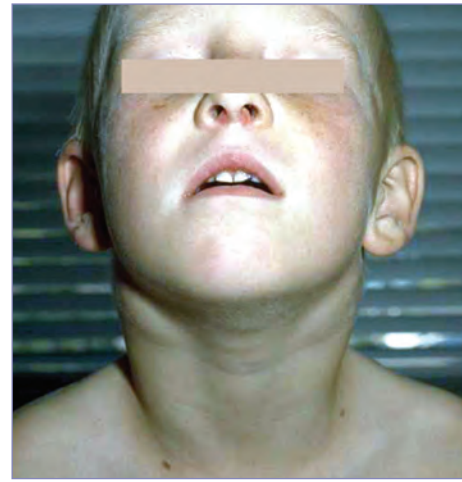


Image 48.2
Bilateral cervical lymphadenopathy in an 8-year-old boy with Epstein-Barr virus disease who remained relatively asymptomatic. Courtesy of Edgar O. Ledbetter, MD, FAAP.

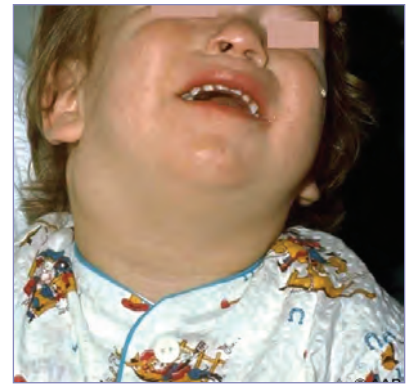


Image 48.4
Cervical lymphadenopathy in a 2-year-old girl with infectious mononucleosis.

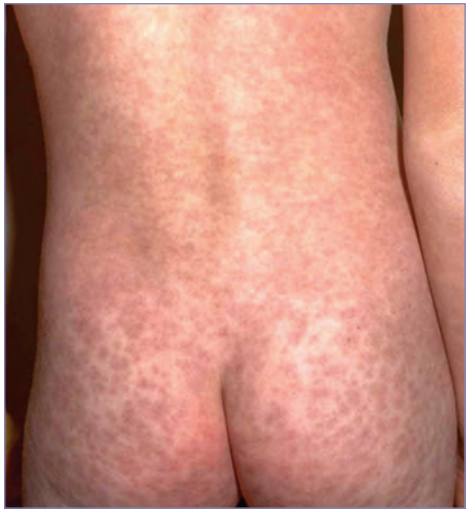


Image 48.6
Rash in the same patient as in Image 48.5 with infectious mononucleosis who was prescribed ampicillin. These morbilliform rashes are considered nonallergic.

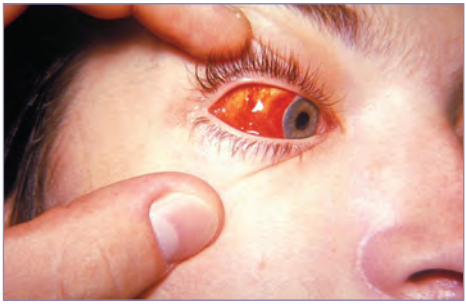


Image 48.8
A conjunctival hemorrhage of the right eye of a patient with infectious mononucleosis. At times, noninfectious conjunctivitis, as well as other corneal abnormalities, may manifest itself due to the body's systemic response to viral infections such as infectious mononucleosis. Courtesy of Centers for Disease Control and Prevention.

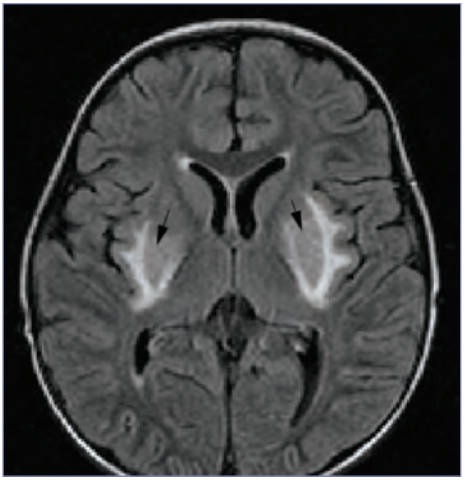


Image 48.7
Epstein-Barr virus encephalitis. Axial fluid attenuated inversion recovery magnetic resonance image shows basal ganglia hyperintensity (arrows).

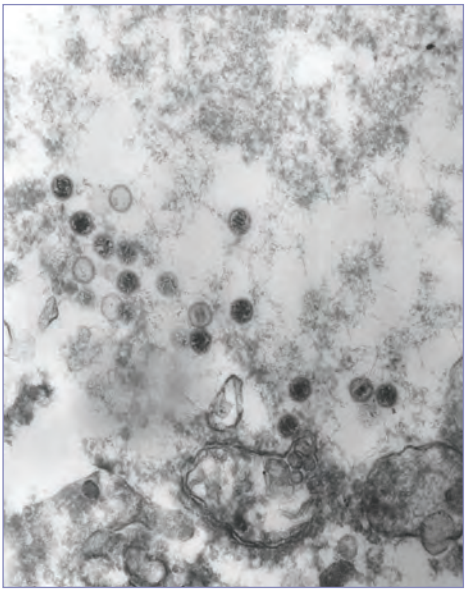


Image 48.9
This negatively stained transmission electron micrograph revealed the presence of numerous Epstein-Barr virus virions, members of the *Herpesviridae* virus family. Epstein-Barr virus is also known as human herpesvirus 4. At the core of its proteinaceous capsid, the Epstein-Barr virus contains a double-stranded DNA linear genome. Courtesy of Centers for Disease Control and Prevention/Fred Murphy, MD.

CHAPTER 49

Escherichia coli Diarrhea

(Including Hemolytic-Uremic Syndrome)

CLINICAL MANIFESTATIONS

At least 5 pathotypes of diarrhea-producing *Escherichia coli* strains have been identified. Clinical features of disease caused by each pathotype are summarized as follows (Table 49.1).

- Shiga toxin-producing *E coli* (STEC) organisms are associated with diarrhea, hemorrhagic colitis, and hemolytic-uremic syndrome (HUS). STEC O157:H7 is the serotype most often implicated in outbreaks and consistently is a virulent STEC serotype, but other serotypes can cause illness. STEC illness typically begins with nonbloody diarrhea. Stools usually become bloody after 2 or 3 days, representing the onset of hemorrhagic colitis. Severe abdominal pain typically is short lived, and low-grade fever is present in approximately one third of cases. Diseases caused by *E coli* O157:H7 and other STEC organisms should be considered in people with presumptive diagnoses of intussusception, appendicitis, inflammatory bowel disease, or ischemic colitis. There are 2 types of Shiga toxin (Stx), Stx1 and Stx2; several variants of each type exist. In general, STEC strains that produce Stx2 are more virulent than strains that only produce Stx1. Diarrhea caused by enteropathogenic *E coli* (EPEC) is watery. Illness occurs almost exclusively in children younger than 2 years and predominantly in resource-limited countries, either sporadically or in epidemics. Although usually mild, diarrhea can result in dehydration and even death, particularly in resource-limited countries. EPEC diarrhea can be persistent and can result in wasting or growth restriction. EPEC infection is uncommon in breastfed infants.
- Diarrhea caused by enterotoxigenic *E coli* (ETEC) is a 1- to 5-day, self-limited illness of moderate severity, typically with watery stools and abdominal cramps. ETEC is

Table 49.1
Classification of *Escherichia coli* Associated With Diarrhea

Pathotype	Epidemiology	Type of Diarrhea	Mechanism of Pathogenesis
Shiga toxin-producing *E coli* (STEC)	Hemorrhagic colitis and hemolytic-uremic syndrome in all ages	Bloody or nonbloody	Shiga toxin production, large bowel adherence, coagulopathy
Enteropathogenic *E coli* (EPEC)	Acute and chronic endemic and epidemic diarrhea in infants in resource-limited countries	Watery	Small bowel adherence and effacement
Enterotoxigenic *E coli* (ETEC)	Infant diarrhea in resource-limited countries and traveler's diarrhea in all ages	Watery	Small bowel adherence, heat stable and/or heat-labile enterotoxin production
Enteroinvasive *E coli* (EIEC)	Diarrhea with fever in all ages	Bloody or nonbloody; dysentery	Mucosal invasion and inflammation of large bowel
Enteroaggregative *E coli* (EAEC)	Acute and chronic diarrhea in all ages	Watery, occasionally bloody	Small and large bowel adherence, enterotoxin and cytotoxin production

common in infants in resource-limited countries and in travelers to those countries. ETEC infection rarely has been diagnosed in the United States, because methods to detect these infections have not been available commercially until recently. However, ETEC infections may be detected more frequently as culture-independent diagnostic tests become more common. Outbreaks and studies with small numbers of patients have demonstrated that ETEC infection occurs in travelers returning from resource-limited countries and occasionally is acquired in the United States.

- Diarrhea caused by enteroinvasive *E coli* (EIEC) is similar clinically to diarrhea caused by *Shigella* species. Although dysentery can occur, diarrhea usually is watery without blood or mucus. Patients often are febrile, and stools can contain leukocytes.
- Enteroaggregative *E coli* (EAEC) organisms cause watery diarrhea and are common in people of all ages in industrialized as well as resource-limited countries. It may present as childhood diarrhea in developing countries, acute diarrhea in travelers, and persistent diarrhea in children or HIV-infected patients. EAEC has been associated with prolonged diarrhea (14 days or longer). Asymptomatic infection can be accompanied by subclinical inflammatory enteritis, which can cause growth disturbance.

Sequelae of STEC Infection

HUS is a serious sequela of STEC enteric infection. *E coli* O157 is the STEC serogroup most commonly associated with HUS, which is defined by the triad of microangiopathic hemolytic anemia, thrombocytopenia, and acute renal dysfunction. HUS occurs in approximately 15% of children younger than 5 years (children 1 through 4 years of age are at higher risk than are infants) with laboratory-confirmed *E coli* O157 infection, as compared with approximately 6% among people of all ages. HUS occurs in approximately 1% of patients of all ages with laboratory-confirmed non-O157:H7 STEC infection.

HUS typically develops 7 days (up to 2 weeks, and rarely 2–3 weeks) after onset of diarrhea. More than 50% of children with HUS require dialysis, and 3% to 5% die. Patients with HUS can develop neurologic complications (eg, seizures, coma, or cerebral vessel thrombosis). Children presenting with an increased white blood cell count ($>20 \times 10^9$/mL) or oliguria or anuria are at higher risk of poor outcome, as are, seemingly paradoxically, children with hematocrit close to normal rather than low. Most patients who survive have a very good prognosis, which can be predicted by normal creatinine clearance and no proteinuria or hypertension 1 year or more after HUS.

ETIOLOGY

The 5 pathotypes of diarrhea-producing *E coli* have been distinguished by genetic, pathogenic, and clinical characteristics. Each pathotype is defined by the presence of virulence-related genes, and each comprises characteristic serotypes, indicated by somatic (O) and flagellar (H) antigens.

EPIDEMIOLOGY

Transmission of most diarrhea-associated *E coli* strains is from food or water contaminated with human or animal feces or from infected symptomatic people. STEC is shed in feces of cattle and, to a lesser extent, sheep, deer, and other ruminants. Human infection is acquired via contaminated food or water or via contact with an infected person, a fomite, or a carrier animal or its environment. Many foods have caused *E coli* O157 outbreaks, including undercooked ground beef, raw leafy vegetables, and unpasteurized milk and juice. Outbreak investigations have implicated petting zoos, drinking water, and ingestion of recreational water. The infectious dose is low; thus, person-to-person transmission is common in households and child care centers. Less is known about the epidemiology of STEC strains other than O157. The non-O157 STEC serogroups most commonly linked to illness in the United States are (in order of incidence) O26, O103, O111, O121, O45, and O145. In fall 2015, a 9-state outbreak of *E coli* O26 infection affecting 55 people was reported from 11 states, and a common-source restaurant food product was implicated, although a specific food was not identified. Whole-genome sequencing performed on 36 isolates showed that all were highly related. No cases of HUS were reported.

A severe outbreak of bloody diarrhea and HUS occurred in Europe in 2011; the outbreak was attributed to an EAEC strain of serotype O104:H4 that had acquired the Shiga toxin 2a-encoding phage. This experience highlights the importance of considering serogroups other than O157 in outbreaks and cases of HUS.

With the exception of EAEC, non-STEC pathotypes most commonly are associated with disease in resource-limited countries, where food and water supplies commonly are contaminated and facilities and supplies for hand hygiene are suboptimal. For young children in resource-limited countries, transmission of ETEC, EPEC, and other diarrheal pathogens via contaminated weaning foods (sometimes by use of untreated drinking water in the foods) is common. ETEC diarrhea occurs in people of all ages but is especially frequent and severe in infants in resource-limited countries. ETEC is a major cause of traveler's diarrhea. EAEC increasingly is reported as a cause of diarrhea in the United States.

The **incubation period** for most *E coli* strains is 10 hours to 6 days; for *E coli* O157:H7, the **incubation period** usually is 3 to 4 days (range, 1–8 days).

DIAGNOSTIC TESTS

Diagnosis of infection caused by diarrhea-associated *E coli* other than STEC is difficult, because tests are not widely available to distinguish these pathotypes from normal *E coli* strains present in stool flora. Culture-independent tests are necessary to detect non-O157:H7 STEC infections. Several US Food and Drug Administration (FDA)-cleared multiplex polymerase chain reaction (PCR) assays can detect a variety of enteric infections, including ETEC and STEC, the latter by detection of the genes encoding Stx1 and Stx2. Several commercially available, sensitive, specific, and rapid immunologic assays for Shiga toxins in stool or broth culture of stool, including enzyme immunoassays (EIA) and immunochromatographic assays, have been approved by the FDA.

Ideally, all stool specimens submitted for routine culture testing from patients with acute community-acquired diarrhea (regardless of patient age, season, or presence or absence of blood in the stool) should be tested for Shiga toxin and cultured simultaneously for *E coli* O157:H7

Rapid and optimal diagnosis facilitates patient management and prompt institution of fluid rehydration to provide nephroprotection. Shiga toxin testing should be performed on growth from broth enrichments or primary isolation media, because this method is more sensitive and specific than direct testing of stool. Most *E coli* O157 isolates can be identified presumptively when grown on sorbitol-containing selective media, because they cannot ferment sorbitol within 24 hours. All presumptive *E coli* O157:H7 isolates and all Shiga toxin-positive stool specimens that did not yield a presumptive *E coli* O157 isolate should be sent to a public health laboratory.

STEC should be sought in stool specimens from all patients diagnosed with postdiarrheal HUS. However, the absence of STEC does not preclude the diagnosis of probable STEC-associated HUS, because HUS typically is diagnosed a week or more after onset of diarrhea, when the organism may not be detectable by conventional bacteriologic methods. When low numbers of organisms are suspected, the selective enrichment of stool samples followed by immunomagnetic separation can markedly enhance the isolation of *E coli* O157 and other STEC for which immunomagnetic reagents are available. The test is available at some state public health laboratories and, through requests to state health departments, at the Centers for Disease Control and Prevention (CDC). Multiplex PCR assays increasingly are available in clinical laboratories and provide sensitive detection of Shiga toxin-encoding genes in fecal samples. Serologic diagnosis using enzyme immunoassay to detect serum antibodies to *E coli* O157 and O111 lipopolysaccharides is available at the CDC for outbreak investigations and for patients with HUS.

TREATMENT

Orally administered electrolyte-containing solutions usually are adequate to prevent or treat dehydration and electrolyte abnormalities. Antimotility agents should not be administered to children with inflammatory or bloody diarrhea. Patients with proven or suspected STEC

infection should be rehydrated fully but prudently as soon as clinically feasible. Many experts advocate intravenous volume expansion during the first 4 days of proven STEC infection to maintain renal perfusion and reduce the risk of HUS. Careful monitoring of patients with hemorrhagic colitis (including complete blood cell count with smear, blood urea nitrogen, and creatinine concentrations) is recommended to detect changes suggestive of HUS. If patients have no laboratory evidence of hemolysis, thrombocytopenia, or nephropathy 3 days after resolution of diarrhea, their risk of developing HUS is low.

In resource-limited countries, nutritional rehabilitation, including supplemental zinc and vitamin A, should be provided as part of case management algorithms for diarrhea where feasible. Feeding, including breastfeeding, should be continued for young children with *E coli* enteric infection. Bismuth subsalicylate has been approved by the FDA for use in children 12 years and older and has been shown to reduce the severity of traveler's diarrhea.

Antimicrobial Therapy

Antimicrobial therapy in patients with STEC infection remains controversial because of its association with an increased risk of developing HUS in some studies. Most experts advise not prescribing antimicrobial therapy for children with *E coli* O157 enteritis or a clinical or epidemiologic picture strongly suggestive of STEC infection.

Empirical self-treatment of diarrhea for travelers to a resource-limited country can slightly reduce duration of diarrhea; however, the prevalence of antimicrobial-resistant enteric pathogens in resource-limited settings is increasing. Azithromycin or a fluoroquinolone have been the most reliable agents for therapy. Rifaximin may be used for people 12 years and older.

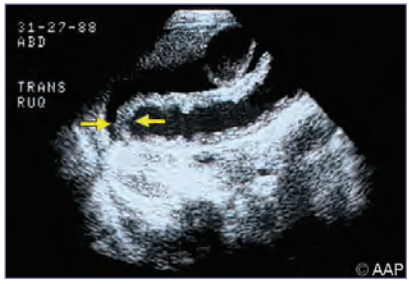


Image 49.1
Ultrasound of a 6-year-old boy with hemorrhagic colitis from *Escherichia coli* O157:H7 who developed hemolytic uremic syndrome. Note the bowel wall edema (arrows).

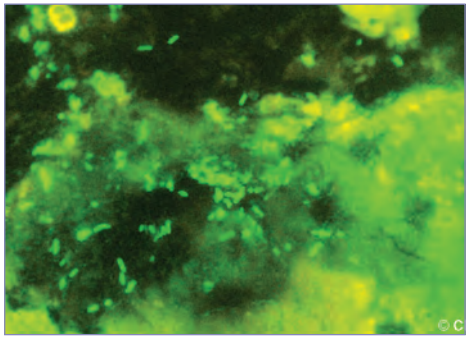


Image 49.2
Escherichia coli in the intestine of an 8-month-old experiencing chronic diarrhea (fluorescent antibody stain). In a small number of individuals (mostly children <5 years and the elderly), *E coli* can cause hemolytic uremic syndrome, in which the red blood cells are destroyed and the kidneys fail. Courtesy of Centers for Disease Control and Prevention.

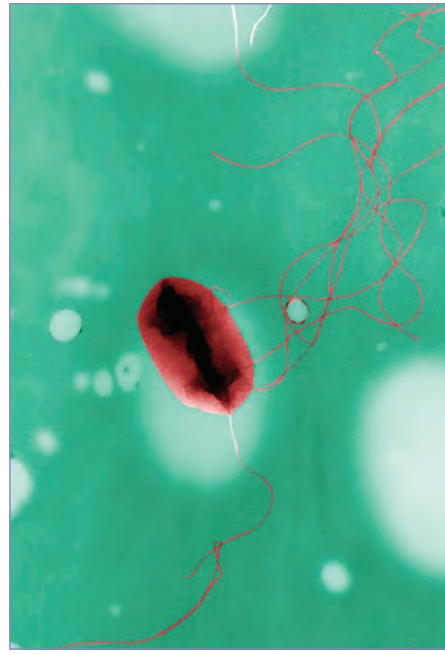


Image 49.3
Transmission electron micrograph of *Escherichia coli* O157:H7. Courtesy of Centers for Disease Control and Prevention/Peggy S. Hayes.

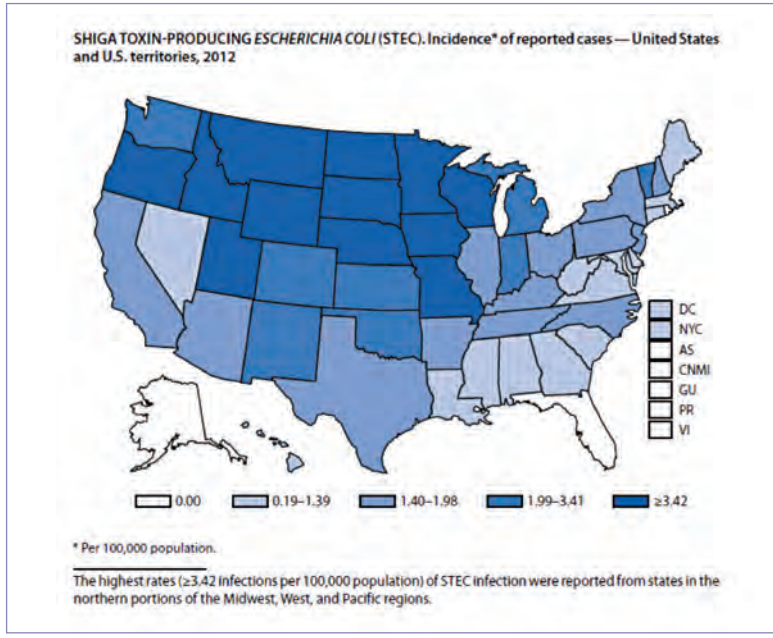


Image 49.4
Shiga toxin-producing *Escherichia coli.* Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

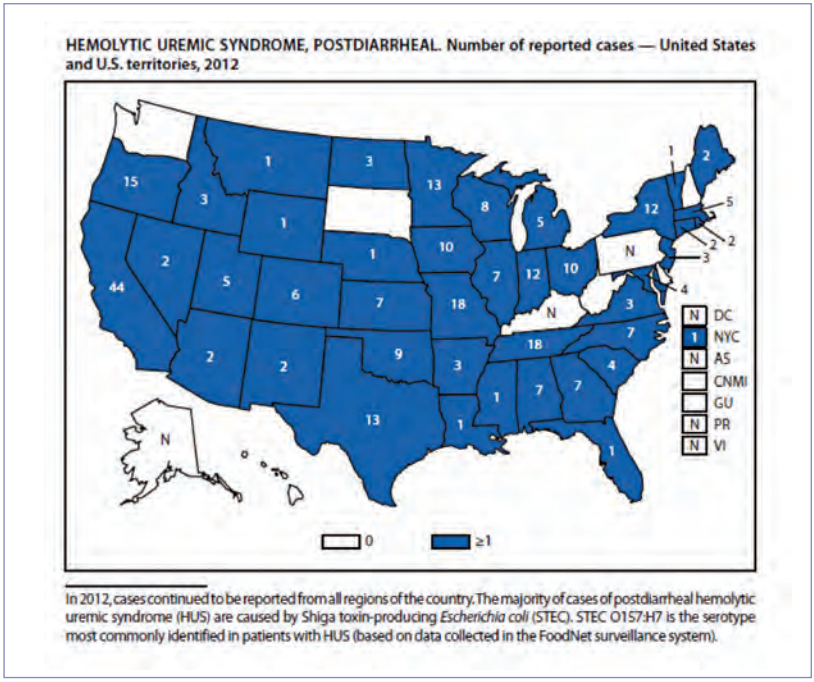


Image 49.5
Hemolytic uremic syndrome, postdiarrheal. Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

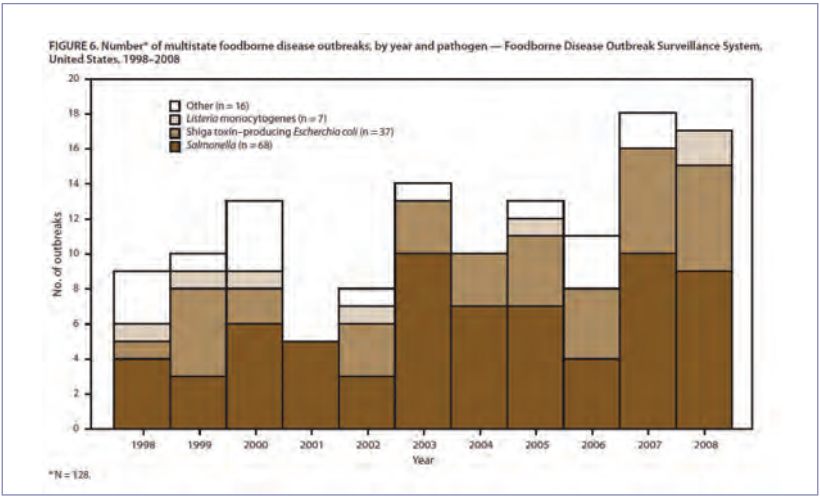


Image 49.6
Number of multistate foodborne disease outbreaks, by year and pathogen—Foodborne Disease Outbreak Surveillance System, United States, 1998–2008. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 50

Other Fungal Diseases

In addition to the mycoses discussed in individual chapters (eg, aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, paracoccidioidomycosis, and sporotrichosis), uncommonly encountered fungi can cause infection in infants and children with immunosuppression or other underlying conditions. These include invasive mold infections, such as mucormycosis, fusariosis, scedosporiosis, and the phaeohyphomycoses (black molds), as well as invasive yeasts such as *Malassezia*, *Trichosporon*, *Rhodotorula*, and many more. Children can acquire infection with these fungi through inhalation via the respiratory tract or through direct inoculation after traumatic disruption of cutaneous barriers. A list of some of these fungi and the pertinent underlying host conditions, reservoirs or routes of entry, clinical manifestations, diagnostic laboratory tests, and treatments can be found in Table 50.1. Taken as a group, few in vitro antifungal susceptibility data are available on which to base treatment recommendations for these uncommon invasive fungal infections, especially in children. Consultation with a pediatric infectious disease specialist experienced in the diagnosis and treatment of invasive fungal infections should be considered when caring for a child infected with one of these mycoses.

Table 50.1
Additional Fungal Diseases

Disease and Agent	Underlying Host Condition(s)	Reservoir(s) or Route(s) of Entry	Common Clinical Manifestations	Diagnostic Laboratory Test(s)	Treatment
Hyalohyphomycosis					
Fusarium species	Granulocytopenia; hematopoietic stem cell transplantation; severe immunocompromise; severe neutropenia and/or T-lymphocyte immunodeficiency	Respiratory tract; sinuses; skin; ingestion	Pulmonary infiltrates; cutaneous lesions (eg, ecthyma); sinusitis; disseminated infection	Culture of blood or tissue specimen, histopathologic examination of tissue	Voriconazole, posaconazole,[a,b] isavuconazole,[a,b] or D-AMB[c]
Pseudallescheria boydii (*Scedosporium apiospermum*) *Scedosporium prolificans*	None or trauma or immunosuppression; cystic fibrosis; chronic granulomatous disease; chronic glucocorticoid use; hematologic malignancy	Environment; respiratory tract; direct inoculation (eg, skin puncture)	Pneumonia; localized pulmonary process or disseminated infection; osteomyelitis or septic arthritis; mycetoma (immunocompetent patients); endocarditis; keratitis and endophthalmitis; brain abscesses; lesions of the skin, soft tissue, or bone	Culture and histopathologic examination of tissue	Voriconazole[d] or isavuconazole[b]
Penicilliosis					
Penicillium (*Talaromyces*) *marneffei*	Human immunodeficiency virus infection and exposure to southeast Asia	Respiratory tract	Pneumonitis; invasive dermatitis; disseminated infection	Culture of blood, bone marrow, or tissue; histopathologic examination of tissue	Amphotericin B drug of choice; alternative, voriconazole[b]

Table 50.1 (*continued*)

Disease and Agent	Underlying Host Condition(s)	Reservoir(s) or Route(s) of Entry	Common Clinical Manifestations	Diagnostic Laboratory Test(s)	Treatment
Phaeohyphomycosis					
Alternaria species	None, trauma, or immunosuppression	Respiratory tract; skin	Sinusitis; cutaneous lesions	Culture and histopathologic examination of tissue	Voriconazole[b] or high-dose D-AMB[c]
Bipolaris species	None, trauma, immunosuppression, or chronic sinusitis	Environment	Sinusitis; cerebral and disseminated infection	Culture and histopathologic examination of tissue	Voriconazole,[b] posaconazole,[b] itraconazole,[e] or D-AMB[c]; surgical excision
Cladophialophora species	None, trauma, or immunosuppression	Environment	Cerebral infection	Culture and histopathologic examination of tissue	Voriconazole,[b] posaconazole,[b] itraconazole,[e] or D-AMB[c]; surgical excision
Curvularia species	Immunosuppression; altered skin integrity; asthma or nasal polyps; chronic sinusitis	Environment	Allergic fungal sinusitis; invasive dermatitis; disseminated infection	Culture and histopathologic examination of tissue	Allergic fungal sinusitis: surgery and corticosteroids Invasive disease: voriconazole,[b] itraconazole,[b,e] or D-AMB[c]
Exophiala species, *Exserohilum* species	None, trauma, or immunosuppression	Environment	Sinusitis; cutaneous lesions; disseminated infection; meningitis associated with contaminated steroid for epidural use	Culture and histopathologic examination of tissue	Voriconazole,[b,f] itraconazole,[b,e] D-AMB, or surgical excision

(*continued*)

Table 50.1 (*continued*)

Disease and Agent	Underlying Host Condition(s)	Reservoir(s) or Route(s) of Entry	Common Clinical Manifestations	Diagnostic Laboratory Test(s)	Treatment
Invasive Yeasts					
Trichosporon species	Immunosuppression; central venous catheter; hematologic malignancy, often with neutropenia; acquired immunodeficiency syndrome; extensive burns; glucocorticoid treatment; heart valve surgery; exposure to tropical environments	Environment; normal flora of gastrointestinal tract	Bloodstream infection; superficial skin lesions endocarditis; peritonitis; pneumonitis; disseminated infection	Blood culture; histopathologic examination of tissue or nodules; urine, sputum and cerebrospinal cultures; bronchoscopy with alveolar lavage cultures	For invasive infections, voriconazole[b,d]; for superficial infections, shaving of the hair and application of a topical azole antifungal to the affected areas
Malassezia species	Immunosuppression; preterm birth; exposure to parenteral nutrition that includes fat emulsions	Skin	Pityriasis versicolor, seborrheic dermatitis, central line-associated bloodstream infection; interstitial pneumonitis; urinary tract infection; meningitis	Culture of blood, catheter tip, or tissue specimen (requires special laboratory handling)	Removal of catheters and temporary cessation of lipid infusion; D-AMB, azole therapy

Table 50.1 (*continued*)

Disease and Agent	Underlying Host Condition(s)	Reservoir(s) or Route(s) of Entry	Common Clinical Manifestations	Diagnostic Laboratory Test(s)	Treatment
Mucormycosis (formerly Zygomycosis)					
Rhizopus; Mucor; *Lichtheimia* (formerly *Absidia*) species; *Rhizomucor* species; *Cunninghamella* species	Immunosuppression; hematologic malignant neoplasm; renal failure; diabetes mellitus; iron overload syndromes	Respiratory tract; skin	Rhinocerebral infection; pulmonary infection; disseminated infection; skin (traumatic wounds) and gastrointestinal tract (less commonly)	Histopathologic examination of tissue and culture	High dose of D-AMB for initial therapy and consider posaconazole[a] for maintenance therapy, with surgical excision and débridement, as feasible; isavuconazole (voriconazole has no activity); echinocandins (eg, caspofungin) may have clinical utility when combined with AMB

D-AMB indicates deoxycholate amphotericin B; if the patient is intolerant of or refractory to D-AMB, liposomal amphotericin B can be substituted.
L-AMB indicates liposomal amphotericin B.
ABLC indicates amphotericin B lipid complex.
[a]Demonstrates activity in vitro, but few clinical data are available for children.
[b]No US Food and Drug Administration indication for this indication.
[c]Consider use of a lipid-based formulation of amphotericin B.
[d]Itraconazole may be the treatment of choice, but data on safety and effectiveness in children are limited.
[e]Itraconazole has been shown to be effective for cutaneous disease in adults, but safety and efficacy have not been established in children younger than 12 years.
[f] Voriconazole demonstrates activity in vitro, but no clinical data are available.

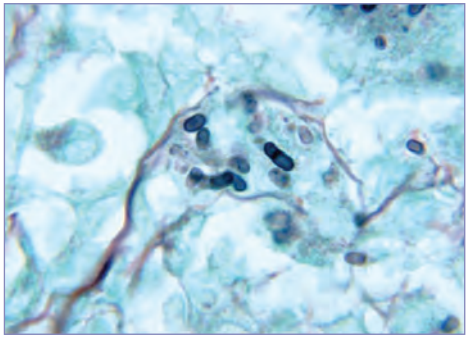


Image 50.1
Note the histopathologic changes seen in a mouse testicle indicating penicilliosis due to *Penicillium marneffei*. Using methenamine silver stain, the histopathologic changes indicative of penicilliosis, due specifically to *P marneffei,* include the presence of globe-shaped yeast cells undergoing multiplication through fission. Courtesy of Centers for Disease Control and Prevention.

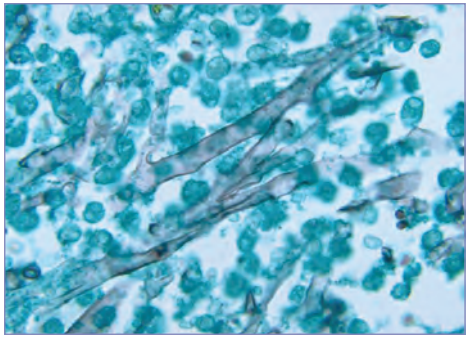


Image 50.2
This slide describes the histopathologic changes seen in a heart valve due to zygomycosis caused by *Rhizomucor pusillus*. Using methenamine silver stain, one can detect the presence of fungal elements associated with zygomycosis, including sparsely septate hyphae, among a mostly acute inflammatory process with some island of chronic granulomatous inflammation. Courtesy of Centers for Disease Control and Prevention.

Image 50.3
This micrograph reveals a conidia-laden conidiophore of the fungus *Bipolaris hawaiiensis*. *Bipolaris* species are known to be one of the causative agents of the fungal illness phaeohyphomycosis, which can be superficially confined to the skin or systemically disseminated and involve the brain, lungs, and bones. Courtesy of Centers for Disease Control and Prevention.

Image 50.4
Note the fine branching tubes of the fungus *Exserohilum rostratum*, which is the cause of phaeohyphomycosis. Phaeohyphomycosis is a fungal infection characterized by superficial and deep tissue involvement caused by dematiaceous, dark-walled fungi that form pigmented hyphae, or fine branching tubes, and yeast-like cells in the infected tissues. Courtesy of Centers for Disease Control and Prevention.

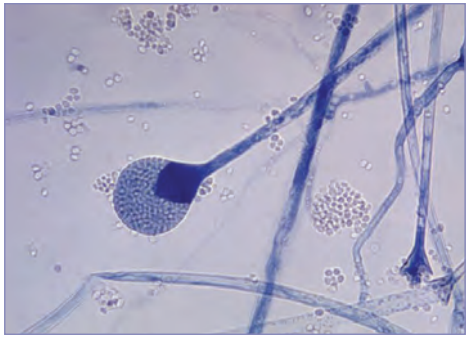


Image 50.5
This photomicrograph reveals a mature sporangium of a *Mucor* species fungus. *Mucor* is a common indoor mold and is among the fungi that cause the group of infections known as zygomycosis. The infection typically involves the rhino-facial-cranial area, lungs, gastrointestinal tract, skin, or, less commonly, other organ systems. Courtesy of Centers for Disease Control and Prevention.

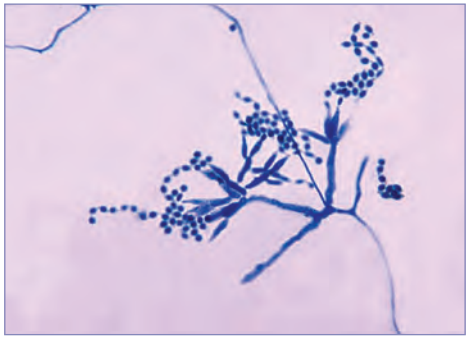


Image 50.7
This micrograph depicts multiple conidia-laden conidiophores and phialides of a *Penicillium marneffei* fungal organism. *Penicillium* species are known to cause penicilliosis, which usually affects immuno-compromised individuals, such as those with AIDS or undergoing chemotherapy. *P marneffei* is normally acquired though inhalation of airborne spores. Courtesy of Centers for Disease Control and Prevention.

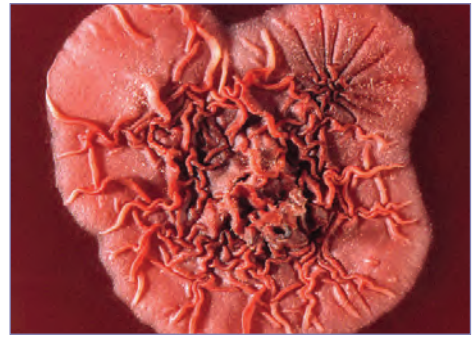


Image 50.6
The surface of a *Penicillium marneffei* colony. *P marneffei* is endemic to Southeast Asia, where it is one of the more common HIV-related opportunistic infections. Courtesy of Centers for Disease Control and Prevention.

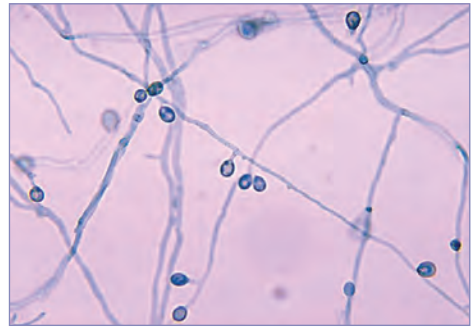


Image 50.8
This micrograph depicts a number of mycelia with attached conidia of the fungal organism *Pseudallescheria boydii*. The opportunistic pathogen *P boydii* is responsible for the infection known as pseudallescheriasis, which normally affects those who are immunocompromised, and is also known to be a cause of white grain mycetoma. Courtesy of Centers for Disease Control and Prevention.

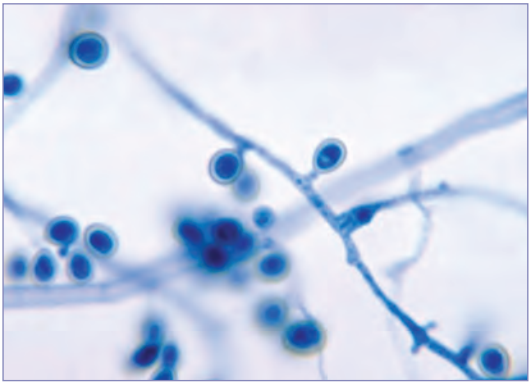


Image 50.9
This photomicrograph reveals the conidiophores with conidia of the fungus *Pseudallescheria boydii* from a slide culture. *P boydii* is pathogenic in humans, especially those who are immunocompromised, causing infections in almost all body regions, and which are classified under the broad heading of pseudallescheriasis. Courtesy of Centers for Disease Control and Prevention.

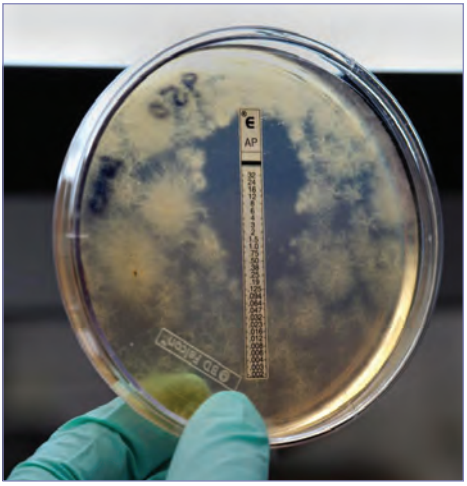


Image 50.10
This culture plate revealed the results of a susceptibility test to the antifungal drug amphotericin B. The drug inhibited growth of the fungal organism *Exserohilum* in the clear area where the amphotericin B had diffused into the medium, while the *Exserohilum* organisms were growing elsewhere on the plate, where the drug had not diffused into the medium.

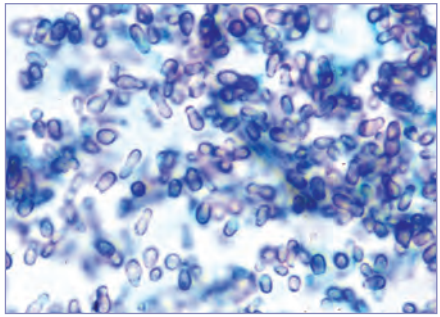


Image 50.11
Malassezia furfur pneumonitis. Organisms seen with a tissue stain for fungi. Courtesy of Dimitris P. Agamanolis, MD.

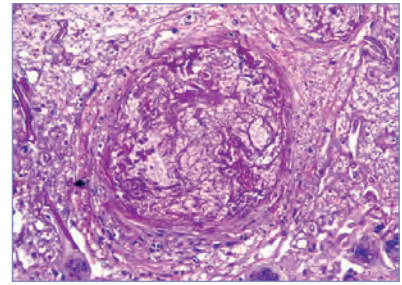


Image 50.12
Cerebral mucormycosis. Fungal organism invaded the vessel wall. The vessel is thrombosed. Courtesy of Dimitris P. Agamanolis, MD.

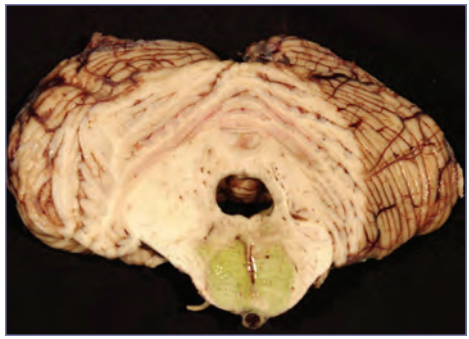


Image 50.13
Cerebral mucormycosis in a patient with acute lymphoblastic leukemia. Occlusion of the basilar artery and infarct of the pons. The patient had jaundice. Courtesy of Dimitris P. Agamanolis, MD.

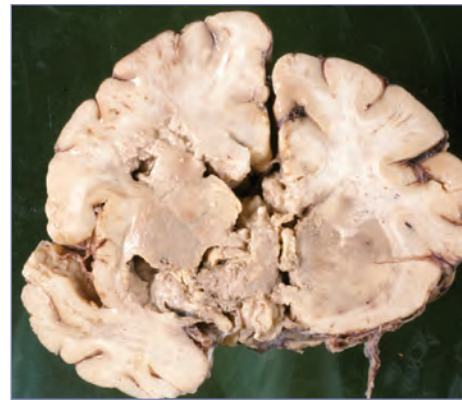


Image 50.14
Extensive cerebral necrosis in a patient with mucormycosis. Courtesy of Dimitris P. Agamanolis, MD.

CHAPTER 51

Fusobacterium Infections

(Including Lemierre Disease)

CLINICAL MANIFESTATIONS

Fusobacterium species, including *Fusobacterium necrophorum* and *Fusobacterium nucleatum*, can be isolated from oropharyngeal specimens in healthy people, are frequent components of human dental plaque, and may lead to periodontal disease. Invasive disease attributable to *Fusobacterium* species has been associated with otitis media, tonsillitis, gingivitis, and oropharyngeal trauma, including dental surgery. *Fusobacterium* species have been associated with acute appendicitis and suppurative portomesenteric vein thrombosis. Ten percent of cases of invasive *Fusobacterium* infections are associated with concomitant Epstein-Barr virus infection. Risk may be increased after use of macrolide-class antibiotic agents.

Otogenic infection is the most frequent primary source in children and can be complicated by meningitis and thrombosis of dural venous sinuses. Invasive infection following tonsillitis was described early in the 20th century and was referred to as postanginal sepsis or Lemierre syndrome. The classic syndrome starts with sore throat symptoms, which may improve or may continue to worsen. Fever and sore throat are followed by severe neck pain (anginal pain) that can be accompanied by unilateral neck swelling, trismus, and dysphagia. Patients with classic Lemierre disease have a sepsis syndrome with multiple organ dysfunction. Metastatic complications from septic embolic phenomena associated with suppurative jugular venous thrombosis (JVT) are common and may manifest as disseminated intravascular coagulation, pleural empyema, pyogenic arthritis, or osteomyelitis. Persistent headache or other neurologic signs may indicate the presence of cerebral venous sinus thrombosis (eg, cavernous sinus thrombosis), meningitis, or brain abscess. *Fusobacterium* species (most commonly *Fusobacterium necrophorum*) is isolated from blood or other normally sterile sites. Lemierre-like syndromes also have been reported following infection with *Arcanobacterium haemolyticum*, *Bacteroides* species, anaerobic *Streptococcus* species, other anaerobic bacteria, and methicillin-susceptible and resistant strains of *Staphylococcus aureus*.

JVT can be completely vaso-occlusive. Surgical débridement of necrotic tissue may be necessary for patients who do not respond to antimicrobial therapy. Some children with JVT associated with Lemierre disease have evidence of thrombophilia at diagnosis. These findings often resolve over several months and can indicate response to the inflammatory, prothrombotic process associated with infection rather than an underlying hypercoagulable state.

ETIOLOGY

Fusobacterium species are anaerobic, non–spore-forming, gram-negative bacilli. Human infection usually results from *F necrophorum* subspecies *funduliforme*, but infections with other species including *F nucleatum*, *F gonidiaformans*, *F naviforme*, *F mortiferum*, and *F varium* have been reported. Infection with *Fusobacterium* species, alone or in combination with other oral anaerobic bacteria, may result in Lemierre disease.

EPIDEMIOLOGY

Fusobacterium species commonly are found in soil and in the respiratory tracts of animals, including cattle, dogs, fowl, goats, sheep, and horses, and can be isolated from the oropharynx of healthy people. *Fusobacterium* infections are most common in adolescents and young adults, but infections, including fatal cases of Lemierre disease, have been reported in infants and young children. Those with sickle cell disease or diabetes mellitus may be at greatest risk for infection.

DIAGNOSTIC TESTS

Fusobacterium species can be isolated using conventional liquid anaerobic blood culture media. However, the organism grows best on semisolid media for fastidious anaerobic organisms or blood agar supplemented with vitamin K, hemin, menadione, and a reducing agent. Colonies generally are cream to yellow colored, smooth, and round and may show a narrow zone of alpha or beta-hemolysis on blood agar, depending on the species of blood used in the medium; however, *F nucleatum* may appear as

bread crumb-like colonies. Many strains fluoresce chartreuse green under ultraviolet light. Most *Fusobacterium* organisms are indole positive. On gram stain, *F nucleatum* usually exhibits spindle-shaped cells with tapered ends, while *F necrophorum* and other species may be highly pleomorphic with swollen areas. The accurate identification of anaerobes to the species level has become important with the increasing incidence of microorganisms that are resistant to multiple drugs. Conventional and commercial culture-based biochemical test systems are reasonably accurate, at least to the genus level.

One should consider Lemierre syndrome in ill-appearing febrile children and especially adolescents having a sore throat and developing exquisite neck pain and swelling over the angle of the jaw. Aerobic and anaerobic blood cultures should be performed to detect invasive *Fusobacterium* species and other possible pathogens. Computed tomography and magnetic resonance imaging are more sensitive than ultrasonography to document thrombosis and thrombophlebitis of the internal jugular vein early in the course of illness and to better identify thrombus extension.

TREATMENT

Fusobacterium species generally are susceptible to metronidazole, clindamycin, chloramphenicol, carbapenems (meropenem or imipenem), cefoxitin, and ceftriaxone.

Antimicrobial resistance has increased in anaerobic bacteria, so susceptibility testing is indicated for all clinically significant anaerobic isolates, including *Fusobacterium* species. Combination therapy with metronidazole or clindamycin, in addition to a beta-lactam agent active against aerobic oral and respiratory tract pathogens (cefotaxime, ceftriaxone, or cefuroxime), is recommended for patients with invasive infection caused by *Fusobacterium* species. Alternatively, some experts use monotherapy with a penicillin-beta-lactamase inhibitor combination (ampicillin-sulbactam or piperacillin-tazobactam) or a carbapenem (meropenem, imipenem, or ertapenem). Up to 50% of *F nucleatum* and 20% of *F necrophorum* isolates produce beta-lactamases, rendering them resistant to penicillin, ampicillin, and some cephalosporins. *Fusobacterium* species intrinsically are resistant to gentamicin, fluoroquinolone agents, and typically, macrolides.

The duration of antimicrobial therapy depends on the anatomic location and severity of infection but usually is several weeks. Surgical intervention involving débridement or incision and drainage of abscesses may be necessary. Anticoagulation therapy has been used in both adults and children with JVT and cavernous sinus thrombosis. In cases with extensive thrombosis, anticoagulation therapy may decrease the risk of clot extension and shorten recovery time.

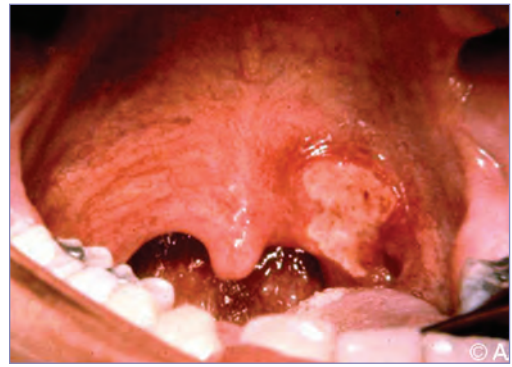


Image 51.1
Vincent stomatitis has been confused with diphtheria, although this infection is usually a mixed infection, including fusiform and spirochetal anaerobic bacteria including *Fusobacterium,* and is associated with severe pain and halitosis. Note ulceration of the soft palate with surrounding erythema. Courtesy of Edgar O. Ledbetter, MD, FAAP.

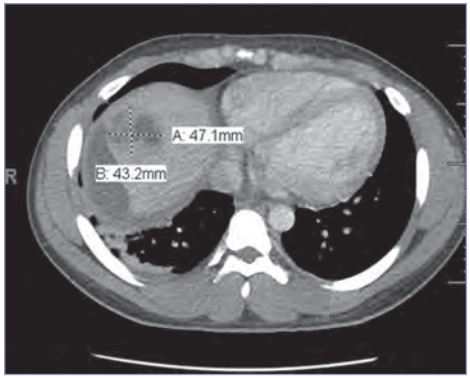


Image 51.2
An abdominal computed tomography scan of a 15-year-old football linebacker who presented with high fever, abdominal pain, and emesis for 5 days showing abscess collections in the liver. Aspiration of 3 discrete abscess areas grew only *Fusobacterium nucleatum*. Courtesy of Carol J. Baker, MD, FAAP.

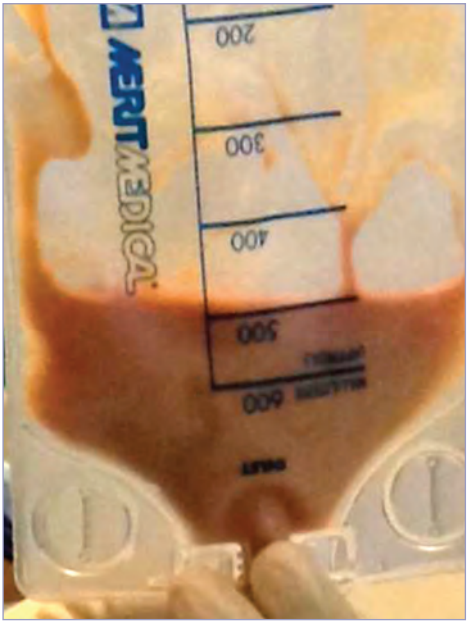


Image 51.3
80 mL of purulent material was aspirated from the liver abscess of the patient in Image 51.2. Courtesy of Carol J. Baker, MD, FAAP.

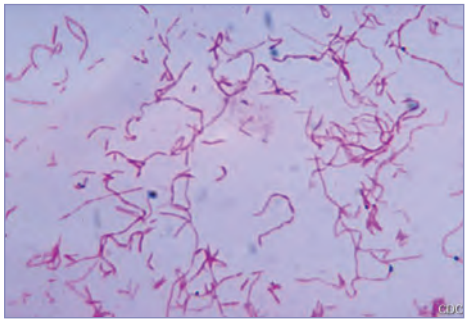


Image 51.4
This photomicrograph shows *Fusobacterium nucleatum* after being cultured in a thioglycolate medium for 48 hours. Courtesy of Centers for Disease Control and Prevention.

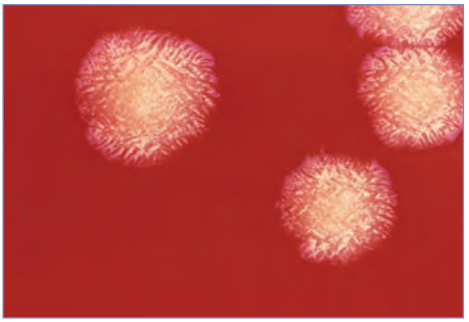


Image 51.5
This photomicrograph shows *Fusobacterium nucleatum* after being cultured on blood agar for 48 hours. Courtesy of Centers for Disease Control and Prevention/V. R. Dowell Jr, MD.

CHAPTER 52

Giardia intestinalis (formerly *Giardia lamblia* and *Giardia duodenalis*) Infections

(Giardiasis)

CLINICAL MANIFESTATIONS

Asymptomatic infection is common, with approximately 50% to 75% of people who acquire infection during outbreaks in child care settings and in the community remaining asymptomatic. Symptomatic infection can manifest with acute infectious diarrhea or, more commonly, chronic diarrhea with failure to thrive or persistent gastrointestinal tract symptoms. Symptoms vary by age, with symptomatic infections more frequent in children than adults. Children can have occasional days of acute watery diarrhea with abdominal cramps, or they may experience a protracted, intermittent, often debilitating disease characterized by passage of foul-smelling stools associated with anorexia, flatulence, malaise, weakness, nausea, vomiting, low-grade fever, and abdominal distention. Humoral immunodeficiencies predispose to chronic symptomatic *Giardia intestinalis* infections. Patients with cystic fibrosis have an increased prevalence of *G intestinalis* infection. Extraintestinal involvement (eg, arthritis, urticaria, retinal changes, and bile or pancreatic ducts) is unusual.

ETIOLOGY

G intestinalis is a flagellate protozoan that exists in trophozoite and cyst forms; the infective form is the cyst. Infection is limited to the small intestine and biliary tract. Giardia cysts are infectious immediately after being excreted in feces and remain viable for 3 months in water at 4°C.

EPIDEMIOLOGY

Giardiasis is the most common intestinal parasitic infection of humans identified in the United States and globally with a worldwide distribution. The highest incidence is reported among children 1 through 9 years of age, adults 45 through 49 years of age, and residents of northern states. Peak onset of illness occurs during early summer through early fall. Humans are the principal reservoir of infection, but *Giardia* organisms can infect dogs, cats, beavers, rodents, sheep, cattle, nonhuman primates, and other animals. *G intestinalis* assemblages are quite species-specific, such that the organisms that affect nonhumans usually are not infectious to humans. People become infected directly from an infected person through ingestion of fecally contaminated water or food, or rarely through animal contact (eg, petting zoo, farm, reptile). Most community-wide epidemics have resulted from a contaminated drinking water supply; outbreaks associated with recreational water also have been reported.

Transmission of *Giardia intestinalis* is common in certain high-risk groups, including (1) children and employees in child care centers; (2) travelers to areas of the world with endemic disease; (3) close contact with infected people; (4) swallowing contaminated drinking water or recreational water; (5) exposure to infected domestic and wild animals (dogs, cats, cattle, deer, and beaver); (6) outdoor activities such as backpacking where unfiltered or untreated water is consumed; and (7) men who have sex with men. Although less common, outbreaks associated with food or food handlers have been reported. Surveys conducted in the United States have identified overall prevalence rates of *Giardia* organisms in stool specimens that range from 5% to 7%, with variations depending on age, geographic location, and seasonality. Duration of cyst excretion is variable but can range from weeks to months. Giardiasis is communicable for as long as the infected person excretes cysts.

The **incubation period** usually is 1 to 3 weeks.

DIAGNOSTIC TESTS

Commercially available, sensitive, and specific enzyme immunoassay (EIA) and direct fluorescence antibody (DFA) assays are the standard tests used for diagnosis of giardiasis in the United States. These antigen-based tests have largely replaced microscopic ova and parasite examination for diagnosis of giardiasis. EIA has a sensitivity of up to 95% and a specificity of 98% to 100% when compared with microscopy. DFA assay has the additional

advantage that organisms are visualized. Both EIA and DFA are available as dual tests for the simultaneous detection of both *Giardia* and *Cryptosporidium* species. Laboratories can reduce reagent and personnel costs by pooling multiple specimens submitted from the same patient before evaluation either by DFA or EIA. In general, it is sufficient to diagnose giardiasis based on a single stool specimen when DFA or EIA is used. This is also true for the more multiplexed nucleic acid amplification tests for detection of *Giardia*, *Cryptosporidium*, and other intestinal pathogens.

There are advantages in use of antigen- or nucleic acid amplification-based tests for giardiasis. When giardiasis is suspected clinically but the organism is not found on repeated stool examination, inspection of duodenal contents obtained by direct aspiration or by using a commercially available string test (Enterotest) may be diagnostic. Rarely, duodenal or intestinal biopsy is required for diagnosis in patients with characteristic clinical symptoms who have negative results of stool examinations and duodenal fluid specimen testing.

TREATMENT

Some infections are self-limited, and treatment is not required. Dehydration and electrolyte abnormalities can occur and should be corrected. Metronidazole, nitazoxanide, and tinidazole are the drugs of choice. Metronidazole (if used for a 5-day course) is the least expensive of these therapies; however, it generally has poor palatability when compounded into a suspension. A 5- to 7-day course of metronidazole has an efficacy of 80% to 100% in pediatric patients. A single dose of tinidazole for children 3 years and older has a median efficacy of 91% and has fewer adverse effects than does metronidazole. A 3-day course of nitazoxanide oral suspension has similar efficacy to metronidazole and has the advantage(s) of treating other intestinal parasites and of being approved for use in children 1 year and older. Paromomycin, a poorly absorbed aminoglycoside that is 50% to 70% effective, is recommended for treatment of symptomatic infection in pregnant women in the second and third trimester.

Symptom recurrence after completing antimicrobial treatment can be attributable to reinfection, post-*Giardia* lactose intolerance (occurs in 20%–40% of patients), immunosuppression, insufficient treatment, or drug resistance. If reinfection is suspected, a second course of the same drug should be effective. Other treatment options include combination of a nitroimidazole plus quinacrine for at least 2 weeks or high-dose courses of the original agent.

Patients who are immunocompromised because of hypogammaglobulinemia or lymphoproliferative disease are at higher risk of giardiasis, and it is more difficult to treat in these patients. Among human immunodeficiency virus (HIV)-infected children and adults without acquired immunodeficiency syndrome (AIDS), effective combination antiretroviral therapy (cART) and antiparasitic therapy are the major initial treatments for these infections. Especially in HIV-infected children, cART should be part of the primary initial treatment for giardiasis. Patients with AIDS often respond to standard therapy; however, in some cases, additional treatment is required. If giardiasis is refractory to standard treatment among HIV-infected patients with AIDS, longer treatment duration, or combination antiparasitic therapy (eg, metronidazole plus one of the following: paromomycin, albendazole, or quinacrine) may be appropriate.

Treatment of asymptomatic carriers is not recommended but could be considered for carriers in households of patients with hypogammaglobulinemia or cystic fibrosis.

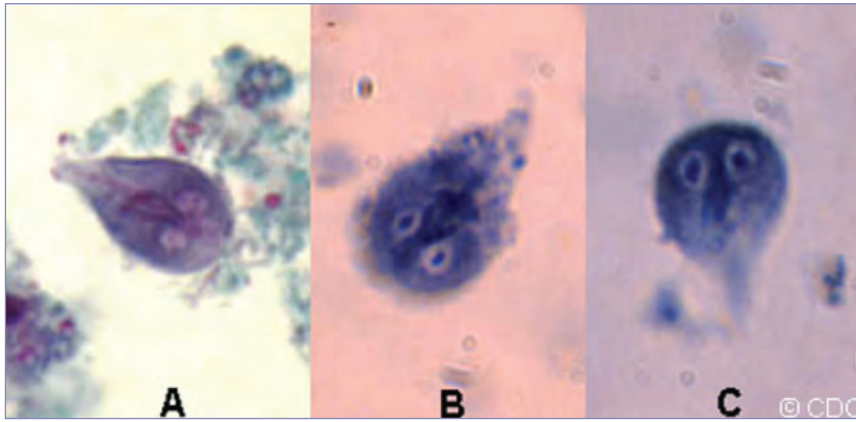


Image 52.1
Three trophozoites of *Giardia intestinalis* (A, trichrome stain; B and C, iron hematoxylin stain). Each cell has 2 nuclei with a large, central karyosome. Cell length is 9 to 21 µm. Trophozoites are usually seen in fresh diarrheal stool or in duodenal mucus. Courtesy of Centers for Disease Control and Prevention.

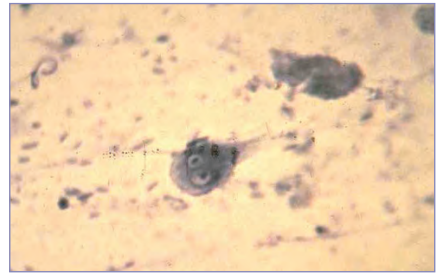


Image 52.2
Giardia intestinalis cyst in a stool preparation. Giardiasis is the most common protozoal infection in the United States. Copyright James Brien, DO.

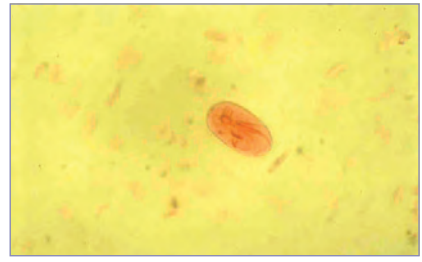


Image 52.3
Giardia intestinalis cyst in a stool preparation. The ingested cyst produces trophozoites in the proximal small intestine. As the trophozoites pass through the intestinal tract, they form cysts that are passed in the stool and are the infective form of *G intestinalis*.

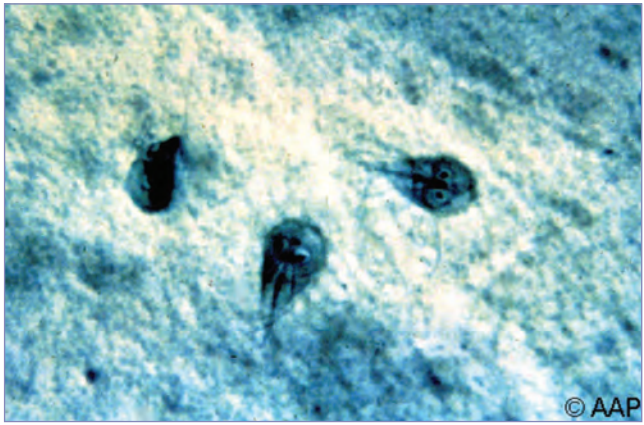


Image 52.4
Giardia intestinalis cysts (trichrome stain). Person-to-person transmission is the most common mode of transmission of giardiasis.

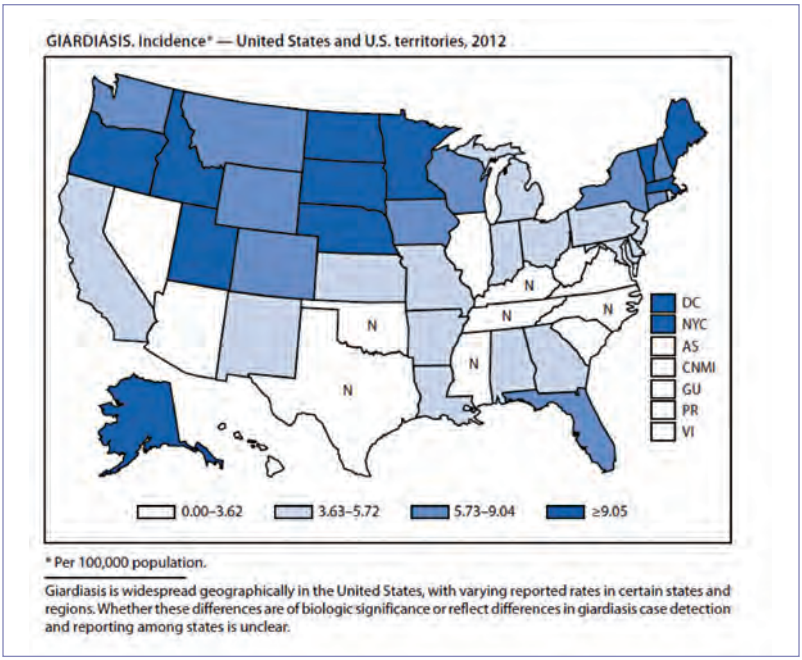


Image 52.5
Giardiasis. Incidence—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

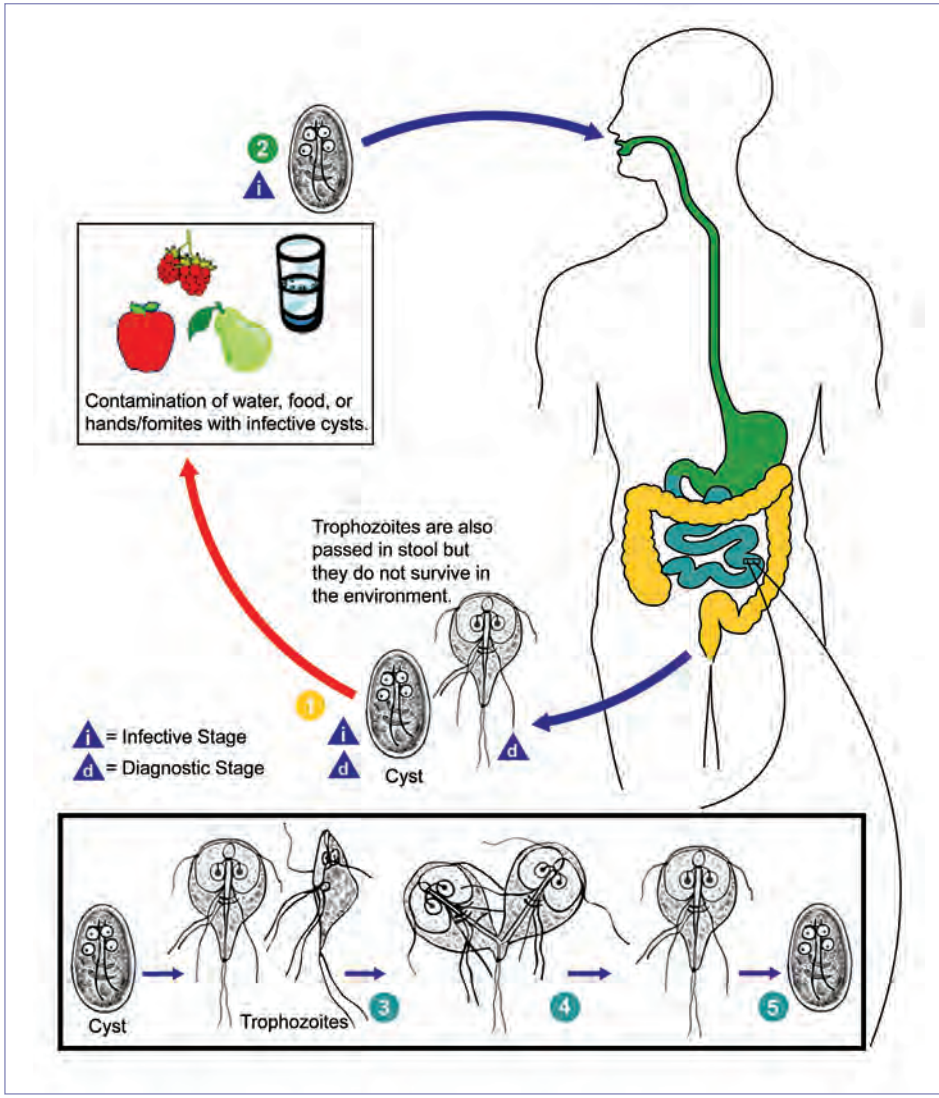


Image 52.6

Cysts are resistant forms and are responsible for transmission of giardiasis. Cysts and trophozoites can be found in the feces (diagnostic stages) (1). The cysts are hardy and can survive several months in cold water. Infection occurs by the ingestion of cysts in contaminated water or food or by the fecal-oral route (hands or fomites) (2). In the small intestine, excystation releases trophozoites (each cyst produces 2 trophozoites) (3). Trophozoites multiply by longitudinal binary fission, remaining in the lumen of the proximal small bowel, where they can be free or attached to the mucosa by a ventral sucking disk (4). Encystation occurs as the parasites transit toward the colon. The cyst is the stage found most commonly in nondiarrheal feces (5). Because the cysts are infectious when passed in the stool or shortly afterward, person-to-person transmission is possible. While animals are infected with *Giardia,* their importance as a reservoir is unclear. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 53

Gonococcal Infections

CLINICAL MANIFESTATIONS

Gonococcal infections in children and adolescents occur in 3 distinct age groups.

- Infection in the **newborn infant** usually involves the eyes. Other possible manifestations of neonatal gonococcal infection include scalp abscess (which can be associated with fetal scalp monitoring) and disseminated disease with bacteremia, arthritis, or meningitis. Vaginitis and urethritis may occur as well.
- In children beyond the newborn period, including **prepubertal children,** gonococcal infection may occur in the genital tract and almost always is transmitted sexually. Vaginitis is the most common manifestation in prepubertal females. Progression to pelvic inflammatory disease (PID) appears to be less common in this age group than in older adolescents. Gonococcal urethritis is possible but uncommon in prepubertal males. Anorectal and tonsillopharyngeal infection can occur in prepubertal children and often is asymptomatic.
- In **sexually active adolescent and young adult females,** gonococcal infection of the genital tract often is asymptomatic. Common clinical syndromes include urethritis, endocervicitis, and salpingitis. In males, infection often is symptomatic, and the primary site is the urethra. Infection of the rectum and pharynx can occur alone or with genitourinary tract infection in either gender. Rectal and pharyngeal infections often are asymptomatic. Extension from primary genital mucosal sites in males can lead to epididymitis and in females can lead to bartholinitis, PID with resultant tubal scarring, and perihepatitis (Fitz-Hugh-Curtis syndrome). Even asymptomatic infection in females can progress to PID with tubal scarring that can result in ectopic pregnancy, infertility, or chronic pelvic pain. Infection involving other mucous membranes can produce conjunctivitis, pharyngitis, or proctitis. Hematogenous spread from mucosal sites can involve skin and joints (arthritis-dermatitis syndrome; disseminated gonococcal infection) and occurs in up to 3% of untreated people with mucosal gonorrhea. Bacteremia can result in a maculopapular rash with necrosis, tenosynovitis, and migratory arthritis. Arthritis may be reactive (sterile) or septic in nature. Meningitis and endocarditis occur rarely.

ETIOLOGY

Neisseria gonorrhoeae is a gram-negative, oxidase-positive diplococcus.

EPIDEMIOLOGY

Gonococcal infections occur only in humans. The source of the organism is exudate and secretions from infected mucosal surfaces; *N gonorrhoeae* is communicable while a person harbors the organism. Transmission results from intimate contact, such as sexual acts, parturition, and very rarely, household exposure in prepubertal children. Sexual abuse should be considered strongly when genital, rectal, or pharyngeal colonization or infection is diagnosed in prepubertal children beyond the newborn period.

N gonorrhoeae infection is the second most commonly reported sexually transmitted infection (STI) in the United States, following *Chlamydia trachomatis* infection. In 2014, a total of 350,062 cases of gonorrhea were reported in the United States, a rate of 111 cases per 100,000 population, and 53% of reported gonorrhea cases were diagnosed among 15- through 24-year-olds. Among males and females, the rate is highest in those 20 through 24 years of age. Racial disparities are remarkable. In 2014, the rate of gonorrhea among black people was 11 times the rate among white people. Rates were 4 times higher among American Indian/Alaska Native people, 3 times higher among Native Hawaiian/Pacific Islander people, and 2 times higher among Hispanic people than among white people. Disparities in gonorrhea rates also are observed by sexual behavior. Surveillance networks that monitor trends in STI prevalence among men who have sex with men (MSM) have found very high proportions of positive gonorrhea pharyngeal, urethral, and rectal test results as well as coinfection with other STIs and human immunodeficiency virus (HIV).

The **incubation period** usually is 2 to 7 days.

Concurrent infection with *C trachomatis* is common. Diagnosis of genitourinary tract gonorrhea infection in a child, adolescent, or young adult should prompt investigation for other STIs, including chlamydia, trichomoniasis, syphilis, and HIV infection.

DIAGNOSTIC TESTS

Microscopic examination of Gram-stained smears of exudate from the conjunctivae, vagina of prepubertal girls, male urethra, skin lesions, synovial fluid, and when clinically warranted, cerebrospinal fluid (CSF) may be useful in the initial evaluation. Identification of gram-negative intracellular diplococci in these smears can be helpful, particularly if the organism is not recovered in culture. However, because of low sensitivity, a negative smear result is not sufficient for excluding infection. Intracellular gram-negative diplococci identified on Gram stain of conjunctival exudate justify presumptive treatment for gonorrhea awaiting culture and antimicrobial susceptibility testing.

N gonorrhoeae can be isolated from normally sterile sites, such as blood, CSF, or synovial fluid, using nonselective chocolate agar with incubation in 5% to 10% carbon dioxide. Selective media that inhibit normal flora and nonpathogenic *Neisseria* organisms are used for cultures from nonsterile sites, such as the cervix, vagina, rectum, urethra, and pharynx. Specimens for *N gonorrhoeae* culture from mucosal sites should be inoculated immediately onto appropriate agar, because the organism is extremely sensitive to drying and temperature changes.

Nucleic acid amplification tests (NAATs) are far superior in overall performance compared with other *N gonorrhoeae* culture and nonculture diagnostic methods for testing genital and nongenital specimens. Most commercially available products now are approved by the US Food and Drug Administration (FDA) for testing male urethral swab specimens, female endocervical or vaginal swab specimens, male or female urine specimens, or liquid cytology specimens. Use of less-invasive specimens, such as urine or vaginal swab specimens, increases feasibility of routine testing of sexually active adolescents by their primary care providers and in other clinical settings. NAATs also permit dual testing of specimens for *C trachomatis* and *N gonorrhoeae.* The vaginal swab specimen, including self-collected specimens, is the preferred means of screening females, and urine is the preferred means of screening males, for *N gonorrhoeae* infection. Female urine remains an acceptable gonorrhea NAAT specimen but may have slightly reduced performance when compared with cervical or vaginal swab specimens.

For identifying *N gonorrhoeae* from nongenital sites, culture is the most widely used test and allows for antimicrobial susceptibility testing to aid in management should infection persist following initial therapy. NAATs are not FDA cleared for *N gonorrhoeae* testing on rectal or pharyngeal swabs but are more sensitive compared with *N gonorrhoeae* culture. Some NAATs have the potential to cross-react with nongonococcal *Neisseria* species that commonly are found in the throat, leading to false-positive test results.

Sexual Abuse

In all prepubertal children beyond the newborn period and in adolescents who have gonococcal infection but report no prior sexual activity, sexual abuse must be considered to have occurred until proven otherwise. Health care providers have a responsibility to report suspected sexual abuse to the state child protective services agency. This mandate does not require that the provider is certain that abuse has occurred but only that there is "reasonable cause to suspect abuse." Cultures should be performed on specimens from the pharynx and anus in boys and girls, the vagina in girls, and the urethra in boys before antimicrobial treatment is administered. Cervical specimens are not recommended for prepubertal girls. For boys with urethral discharge, a meatal discharge specimen is an adequate substitute for an intraurethral swab specimen. All gonococcal isolates from such patients should be retained for additional testing. Nonculture gonococcal tests, including Gram stain, DNA probes, enzyme immunoassays, or NAATs of oropharyngeal, rectal, or genital tract swab specimens in children may have false-positive results. NAATs can be used as alternative to culture

with vaginal swab specimens or urine specimens from prepubertal girls. Culture remains the preferred method for urethral specimens from boys and extragenital specimens (pharynx and rectum) in boys and girls.

Detection of gonorrhea in a child requires an evaluation for other STIs, such as *C trachomatis* infection, syphilis, trichomoniasis, and HIV infection. If the hepatitis B and human papillomavirus vaccine series have not been completed, these immunizations should be offered if appropriate for age.

TREATMENT

The rapid emergence of antimicrobial resistance has led to a limited number of approved therapies for gonococcal infections. Resistance to penicillin and tetracycline is widespread, and as of 2007, the CDC no longer recommends the use of fluoroquinolones for gonorrhea because of the increased prevalence of quinolone-resistant *N gonorrhoeae* in the United States. This leaves the cephalosporins as the only recommended antimicrobial class for the treatment of gonococcal infections. Over the past decade, the minimum inhibitory concentrations (MIC) for cefixime against *N gonorrhoeae* strains circulating in the United States and other countries has increased, suggesting that resistance to this drug is emerging. Treatment failure following the use of cefixime has been described in North America, Europe, and Asia. As of 2012, the CDC no longer recommends the use of cefixime as a first-line treatment for gonococcal infection.

To minimize disease transmission, people treated for gonorrhea should be instructed to abstain from sexual activity for 7 days after treatment and until all sex partners are adequately treated (7 days after receiving treatment and resolution of symptoms, if present). All patients with presumed or proven gonorrhea should be evaluated for concurrent syphilis, HIV, and *C trachomatis* infections.

Uncomplicated Gonococcal Infections of the Cervix, Urethra, and Rectum in Adolescents

Dual therapy using ceftriaxone intramuscularly, once, with azithromycin orally is the recommended treatment for all uncomplicated gonococcal infections. Ceftriaxone and azithromycin should be administered together on the same day under direct observation. Although other parenteral extended-spectrum cephalosporins, such as ceftizoxime, cefoxitin with probenecid, and cefotaxime, may be acceptable, they offer no clear advantage over ceftriaxone in most cases, and their efficacy in the treatment of pharyngeal infections has not been well documented. Oral cefixime, in a single dose, plus azithromycin, orally, should only be considered for treatment of an anogenital infection if parenteral treatment with ceftriaxone is not available.

Pharyngeal Infection

Pharyngeal infection generally is more difficult to cure than anogenital infection. Patients with uncomplicated pharyngeal gonococcal infection should be treated with ceftriaxone intramuscularly and azithromycin orally in a single dose.

Neonatal Disease

Infants with clinical evidence of ophthalmia neonatorum, scalp abscess, or disseminated infections attributable to *N gonorrhoeae* should be hospitalized. Cultures of blood, eye discharge, and other potential sites of infection, such as CSF, should be performed on specimens from infants to confirm the diagnosis and to determine antimicrobial susceptibility. Tests for concomitant infection with *C trachomatis*, congenital syphilis, and HIV infection should be performed; azithromycin should not be administered unless the diagnostic assessment is positive for *C trachomatis.* The mother and her partner(s) need appropriate examination and treatment for *N gonorrhoeae.*

Ophthalmia Neonatorum

Recommended antimicrobial therapy for ophthalmia neonatorum is a single one-time dose of ceftriaxone intravenously or intramuscularly. Ceftriaxone should not be used in neonates (28 days and younger) receiving (or expected to receive) calcium-containing intravenous products. Infants with gonococcal ophthalmia should receive eye irrigations with saline solution immediately and at frequent intervals until discharge is eliminated. Topical antimicrobial treatment is unnecessary when recommended systemic antimicrobial treatment is

administered. Infants with gonococcal ophthalmia should be hospitalized, managed in consultation with an infectious disease specialist, and evaluated for disseminated infection (sepsis, arthritis, meningitis).

Disseminated Neonatal Infections and Scalp Abscesses

Recommended therapy for arthritis, septicemia, or abscess is ceftriaxone intravenously or intramuscularly in a single daily dose for 7 days. Cefotaxime or another advanced generation cephalosporin is recommended for infants with hyperbilirubinemia. If meningitis is documented, treatment should be continued for a total of 10 to 14 days.

Gonococcal Infections in Children Beyond the Neonatal Period and Adolescents

Recommendations for treatment of gonococcal infections, by site of infection, age, and weight, are provided in Table 53.1.

Special Problems in Treatment of Children (Beyond the Neonatal Period) and Adolescents

Providers treating patients with uncomplicated infections of the vagina, endocervix, urethra, or anorectum and a history of severe adverse reactions to cephalosporins (eg, anaphylaxis, ceftriaxone-induced hemolysis, Stevens-Johnson syndrome, toxic epidermal necrolysis) should consult an expert in infectious diseases. In adolescents, dual treatment with a single dose of gemifloxacin plus oral azithromycin or dual treatment with a single dose of intramuscular gentamicin plus oral azithromycin are potential therapeutic options. However, gastrointestinal tract adverse events might limit the use of these regimens. Monotherapy with azithromycin no longer is recommended. In the case of azithromycin allergy, doxycycline for 7 days can be used in place of azithromycin as an alternative second antimicrobial when used in combination with ceftriaxone or cefixime. Children or adolescents with HIV infection should receive the same treatment for gonococcal infection as children without HIV infection.

Acute PID

N gonorrhoeae and *C trachomatis* are implicated in many cases of PID; most cases have a polymicrobial etiology. No reliable clinical criteria distinguish gonococcal from nongonococcal-associated PID. Hence, broad-spectrum treatment regimens are recommended.

Acute Epididymitis

Sexually transmitted organisms, such as *N gonorrhoeae* or *C trachomatis*, can cause acute epididymitis in sexually active adolescents and young adults but rarely, if ever, cause acute epididymitis in prepubertal children. The recommended regimen for sexually transmitted epididymitis is ceftriaxone intramuscularly once plus doxycycline daily for 10 days.

Table 53.1
Uncomplicated Gonococcal Infection: Recommended Treatment of Infants and Children Beyond the Newborn Period[a]

Disease	Prepubertal Children Who Weigh ≤100 lb (≤45 kg)	Disease	Patients Who Weigh >100 lb (>45 kg)
Uncomplicated vulvovaginitis, cervicitis, urethritis, proctitis, or pharyngitis	Ceftriaxone IV or IM, in a single dose	Uncomplicated endocervicitis, urethritis, proctitis, or pharyngitis	Treat with adult regimens. Alternative regimen for patients with severe cephalosporin allergy: consult an expert in infectious diseases.[b]

IV indicates intravenously; IM, intramuscularly.

[a] No data exist regarding the use of dual therapy for treating children with gonococcal infection.

[b] Because data are limited regarding alternative regimens for treating gonorrhea among children who have documented cephalosporin allergy, consultation with an expert in infectious diseases is recommended.

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm* Rep. 2015;64(RR-3):1-137.

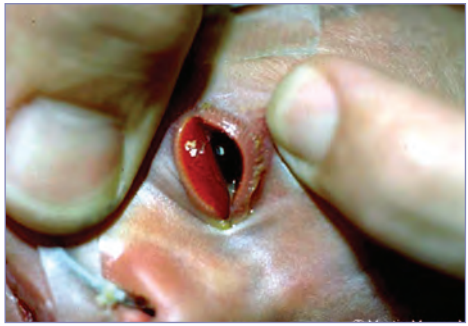


Image 53.1
An infant with gonococcal ophthalmia. In-hospital evaluation and treatment is recommended for infants with gonococcal ophthalmia. Copyright Martin G. Myers, MD.

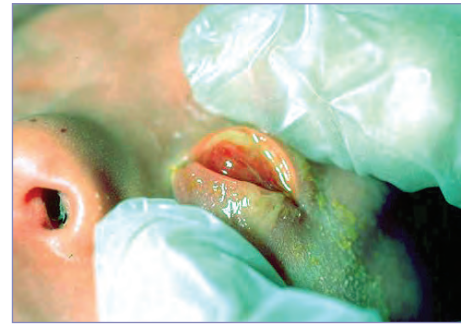


Image 53.2
An 8-day-old with gonococcal ophthalmia. Copyright Martin G. Myers, MD.

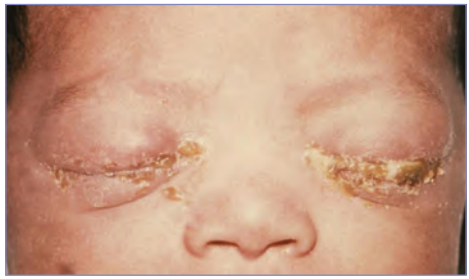


Image 53.3
This newborn has gonococcal ophthalmia neonatorum caused by a maternally transmitted gonococcal infection. Unless preventive measures are taken, it is estimated that gonococcal ophthalmia neonatorum will develop in 28% of neonates born to women with gonorrhea. It affects the corneal epithelium, causing microbial keratitis, ulceration, and perforation. Courtesy of Centers for Disease Control and Prevention.

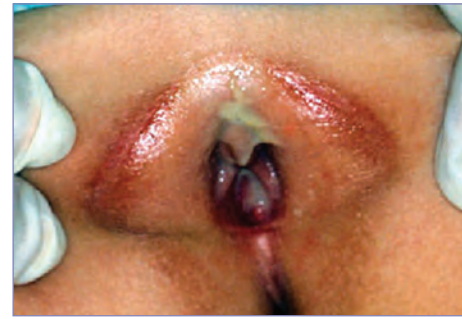


Image 53.4
Profuse, purulent vaginal discharge in an 18-month-old girl who has gonococcal vulvovaginitis. In preadolescent children, this infection is almost always associated with sexual abuse. Identification of the species of cultured gonococci is imperative in suspected cases of sexual abuse.

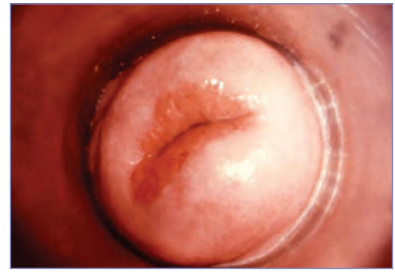


Image 53.5
This colposcopic view of this patient's cervix revealed an eroded ostium due to *Neisseria gonorrhoeae* infection. A chronic *N gonorrhoeae* infection can lead to complications that can be apparent, such as this cervical inflammation, and some can be quite insipid, giving the impression that the infection has subsided while treatment is still needed. Courtesy of Centers for Disease Control and Prevention.

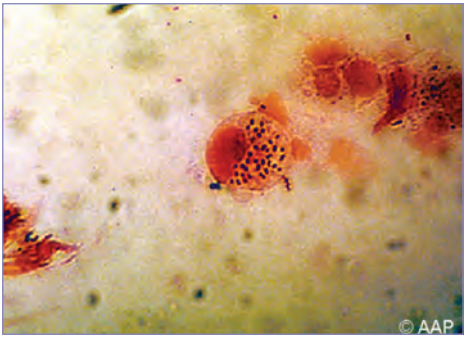


Image 53.6
Gram stain of cervical discharge in an adolescent who has gonococcal cervicitis. Note multiple intracellular diplococci. In children with suspected abuse, it is imperative that the gonococcus be cultured and identified to distinguish pathogens from normal flora.

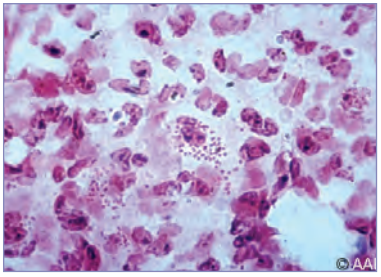


Image 53.8
Intracellular gram-negative diplococci (*Neisseria gonorrhoeae*) isolated on culture of a petechial skin lesion.

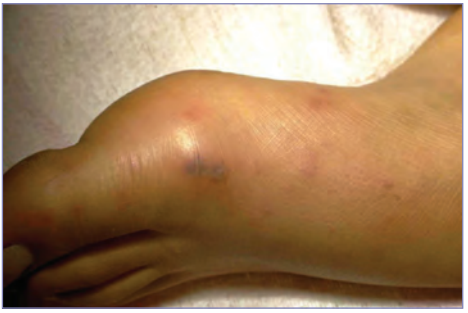


Image 53.7
Gonococcemia with maculopapular and petechial skin lesions, most commonly seen on the hands and feet.

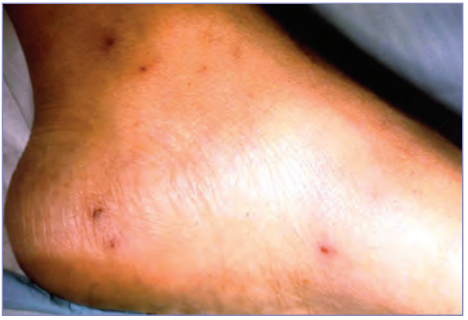


Image 53.9
Adolescent with septic arthritis of left ankle with petechial and necrotic skin lesions on the feet. Blood cultures were positive for *Neisseria gonorrhoeae*.

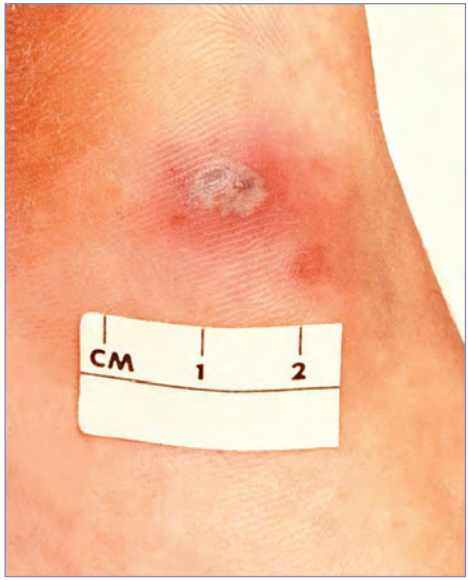


Image 53.10
This patient presented with a cutaneous gonococcal lesion due to a disseminated *Neisseria gonorrhoeae* bacterial infection. Although gonorrhea is a sexually transmitted infection, if a gonococcal infection is allowed to go untreated, *N gonorrhoeae* bacteria can disseminate throughout the body, forming lesions in extragenital locations. Courtesy of Centers for Disease Control and Prevention.

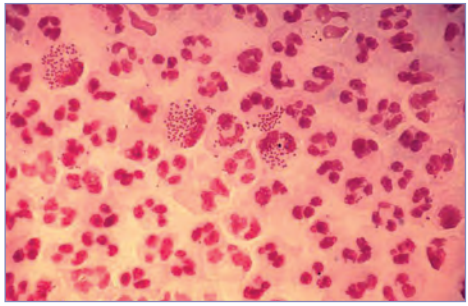


Image 53.12
This photomicrograph reveals the histopathology in an acute case of gonococcal urethritis (Gram stain). This image demonstrates the nonrandom distribution of gonococci among polymorphonuclear neutrophils. Note that there are intracellular and extracellular bacteria in the field of view. Courtesy of Centers for Disease Control and Prevention

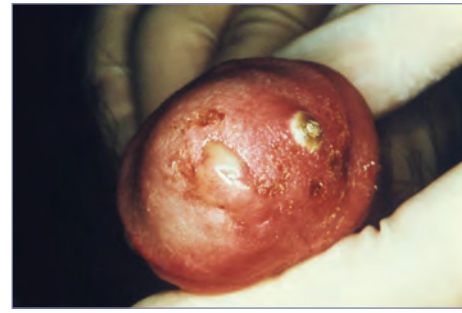


Image 53.11
This male presented with purulent penile discharge due to gonorrhea with an overlying penile pyoderma lesion. Pyoderma involves the formation of a purulent skin lesion, as in this case, located on the glans penis and overlying the sexually transmitted infection gonorrhea. Courtesy of Centers for Disease Control and Prevention.

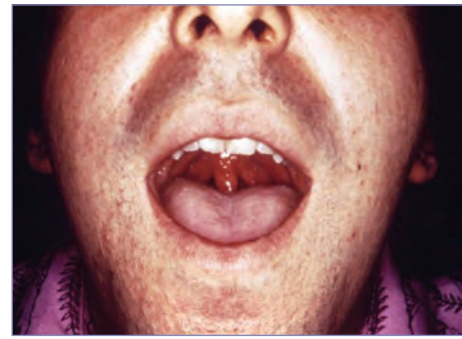


Image 53.13
This patient presented with symptoms later diagnosed as due to gonococcal pharyngitis. Gonococcal pharyngitis is a sexually transmitted infection acquired through oral sex with an infected partner. Most throat infections caused by gonococci have no symptoms, but some with the infection can experience mild to severe sore throat. Courtesy of Centers for Disease Control and Prevention.

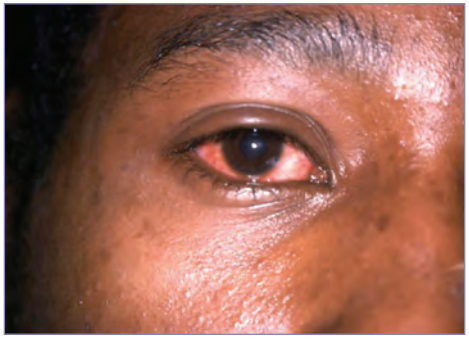


Image 53.14
This patient presented with gonococcal urethritis and gonococcal conjunctivitis of the right eye. If untreated, *Neisseria gonorrhoeae* may spread to the bloodstream and throughout the body. Courtesy of Centers for Disease Control and Prevention/Joe Miller.

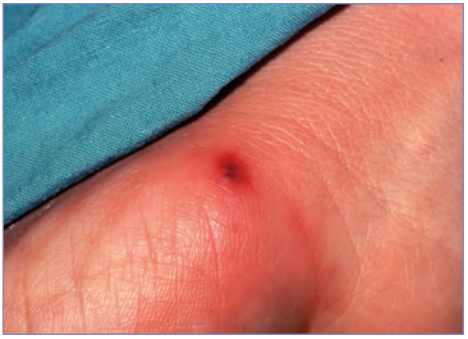


Image 53.15
Disseminated gonococcal infection. Courtesy of Gary Overturf, MD.

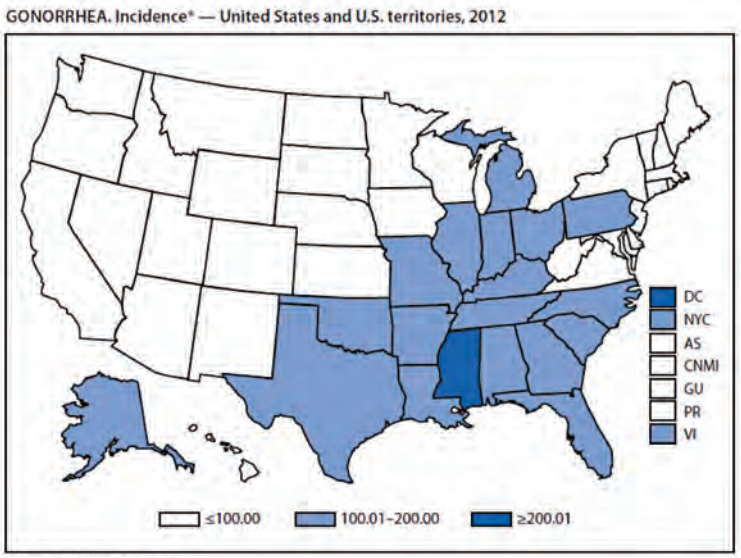


Image 53.16
Gonorrhea. Incidence—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

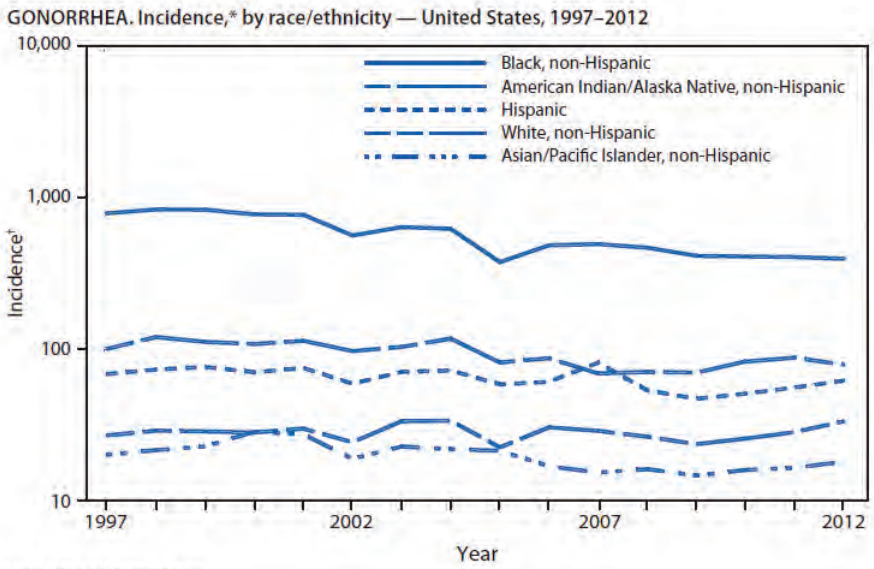


Image 53.17
Gonorrhea. Incidence by race/ethnicity—United States, 1997–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

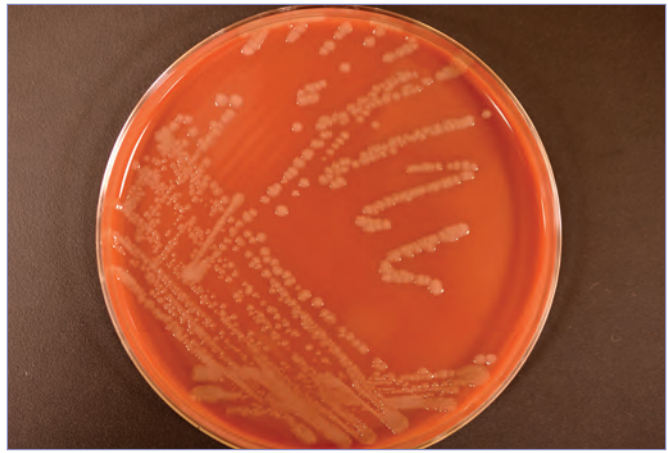


Image 53.18
Neisseria gonorrhoeae on chocolate agar. Colonies appear off-white with no discoloration of the agar. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 54

Granuloma Inguinale

(Donovanosis)

CLINICAL MANIFESTATIONS

Initial lesions of this sexually transmitted infection are single or multiple painless subcutaneous nodules that gradually ulcerate. These nontender, granulomatous ulcers are beefy red and highly vascular and bleed readily on contact. Lesions usually involve the genitalia without regional adenopathy, but anal infections occur in 5% to 10% of patients; lesions at distant sites (eg, face, mouth, or liver) are rare. Subcutaneous extension into the inguinal area results in induration that can mimic inguinal adenopathy (ie, "pseudobubo"). Verrucous, necrotic, and fibrous lesions may occur as well. Fibrosis manifests as sinus tracts, adhesions, and lymphedema, resulting in extreme genital deformity. Urethral obstruction can occur.

ETIOLOGY

The disease, donovanosis, is caused by *Klebsiella granulomatis* (formerly known as *Calymmatobacterium granulomatis*), an intracellular gram-negative bacillus.

EPIDEMIOLOGY

Indigenous granuloma inguinale occurs very rarely in the United States and most industrialized nations. The disease is endemic in some tropical and developing areas, including India, Papua New Guinea, the Caribbean, central Australia, and southern Africa. The incidence of infection seems to correlate with sustained high temperatures and high relative humidity. Infection usually is acquired by sexual intercourse, most commonly with a person with active infection but possibly also from a person with asymptomatic rectal infection. Young children can acquire infection by contact with infected secretions. The period of communicability extends throughout the duration of active lesions or rectal colonization.

The **incubation period** is 8 to 80 days.

DIAGNOSTIC TESTS

The causative organism is difficult to culture, and diagnosis requires microscopic demonstration of dark-staining intracytoplasmic Donovan bodies on Wright or Giemsa staining of a crush preparation from subsurface scrapings of a lesion or tissue. The microorganism also can be detected by histologic examination of biopsy specimens. Lesions should be cultured for *Haemophilus ducreyi* to exclude chancroid. Granuloma inguinale often is misdiagnosed as carcinoma, which can be excluded by histologic examination of tissue or by response of the lesion to antimicrobial agents. Culture of *K granulomatis* is difficult to perform and is not available routinely. Diagnosis by polymerase chain reaction assay and serologic testing is only available in research laboratories.

TREATMENT

The recommended treatment regimen is azithromycin (1 g, orally, once per week, or 500 mg, daily) for at least 3 weeks and until all lesions have completely healed. Alternative therapies include doxycycline, ciprofloxacin, erythromycin base, or trimethoprim-sulfamethoxazole. All treatment regimens should continue for at least 3 weeks and until all lesions have completely healed. Addition of an aminoglycoside, such as gentamicin, to these regimens is an option. Treatment has been shown to halt progression of lesions. Partial healing usually is noted within 7 days of initiation of therapy and typically proceeds inward from the ulcer margins. Prolonged therapy usually is required to permit granulation and re-epithelialization of the ulcers. Relapse can occur, especially if the antimicrobial agent is stopped before the primary lesion has healed completely.

Patients should be evaluated for other sexually transmitted infections, such as gonorrhea, syphilis, chancroid, chlamydia, hepatitis B virus, and human immunodeficiency virus infections. If the hepatitis B and human papillomavirus vaccine series have not been completed, these immunizations should be offered if appropriate for age.

Image 54.1
This patient's penile lesions were due to gram-negative *Klebsiella granulomatis,* formerly known as *Calymmatobacterium granulomatis*. *K granulomatis* cause granuloma inguinale, or donovanosis, a sexually transmitted infection that is a slowly progressive, ulcerative condition of the skin and lymphatics of the genital and perianal area. A definitive diagnosis is achieved when a tissue smear test result is positive for the presence of *K granulomatis* (Donovan bodies). Courtesy of Centers for Disease Control and Prevention.

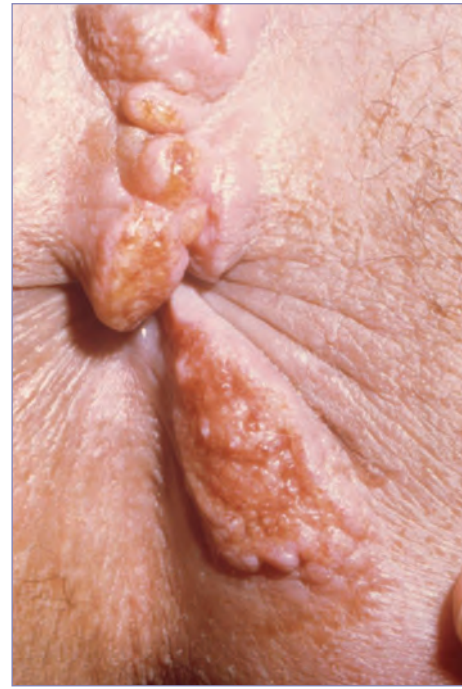


Image 54.2
This 19-year-old girl presented with a perianal granuloma inguinale lesion of about 8 months' duration. A genital ulcerative disease caused by the intracellular gram-negative bacterium *Klebsiella granulomatis,* granuloma inguinale, also known as donovanosis, occurs rarely in the United States. Courtesy of Centers for Disease Control and Prevention.

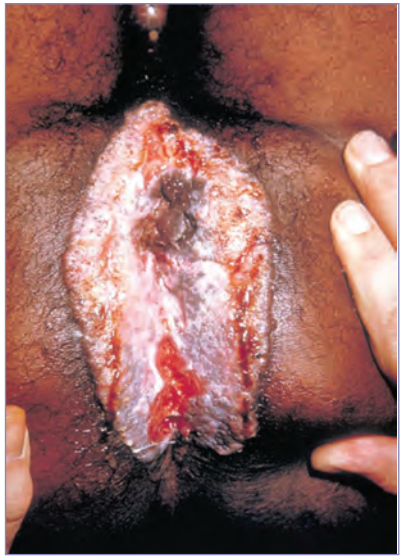


Image 54.3
Granuloma inguinale accompanied by perianal skin ulceration due to the bacterium *Klebsiella granulomatis* (formerly *Calymmatobacterium granulomatis*). The ulcerations are, for the most part, painless and granulomatous in nature (ie, chronic inflammation). Courtesy of Centers for Disease Control and Prevention/Dr Thomas F. Sellers/Emory University.

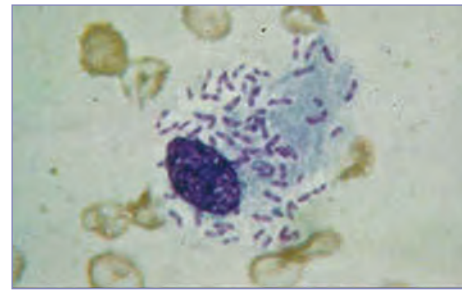


Image 54.4
Giemsa-stained *Klebsiella granulomatis* (Donovan bodies) of granuloma inguinale. Courtesy of Robert Jerris, MD.

CHAPTER 55

Haemophilus influenzae Infections

CLINICAL MANIFESTATIONS

Haemophilus influenzae type b (Hib) causes pneumonia, bacteremia, meningitis, epiglottitis, septic arthritis, cellulitis, otitis media, purulent pericarditis, and less commonly, endocarditis, endophthalmitis, osteomyelitis, peritonitis, and peripheral gangrene. Non-type b encapsulated strains present in a similar manner to type b infections. Nontypable strains more commonly cause infections of the respiratory tract (eg, otitis media, sinusitis, pneumonia, conjunctivitis), but cases of bacteremia, meningitis, and neonatal septicemia occur rarely.

ETIOLOGY

H influenzae is a pleomorphic gram-negative coccobacillus. Encapsulated strains express 1 of 6 antigenically distinct capsular polysaccharides (a through f); nonencapsulated strains lack capsule genes and are designated nontypable.

EPIDEMIOLOGY

The mode of transmission is person to person by inhalation of respiratory tract droplets or by direct contact with respiratory tract secretions. In neonates, infection is acquired intrapartum by aspiration of amniotic fluid or by contact with genital tract secretions containing the organism. Pharyngeal colonization by *H influenzae* is relatively common, especially with nontypable and non-type b capsular type strains. In the pre-Hib vaccine era in the United States and in resource-limited countries where Hib vaccine has not been routinely implemented, the major reservoir of Hib is young infants and toddlers, who carry the organism in the upper respiratory tract.

Before introduction of effective Hib conjugate vaccines, Hib was the most common cause of bacterial meningitis in children in the United States. The peak incidence of invasive Hib infections occurred between 6 and 18 months of age. In contrast, the peak age for Hib epiglottitis was 2 to 4 years of age.

Unimmunized children younger than 5 years are at increased risk of invasive Hib disease. Factors that predispose to invasive disease include sickle cell disease, asplenia, human immunodeficiency virus (HIV) infection, certain immunodeficiency syndromes, and malignant neoplasms. Historically, invasive Hib infection was more common in black, Alaska Native, Apache, and Navajo children; boys; child care attendees; children living in crowded conditions; and children who were not breastfed.

Since introduction of Hib conjugate vaccines in the United States, the incidence of invasive Hib disease has decreased by 99% to fewer than 1 case per 100,000 children younger than 5 years. In 2013, 31 cases of invasive type b disease were reported in children younger than 5 years. In the United States, invasive Hib disease occurs primarily in under-immunized children and among infants too young to have completed the primary immunization series. Hib remains an important pathogen in many resource-limited countries.

The epidemiology of invasive *H influenzae* disease in the United States has shifted in the postvaccination era. Nontypable *H influenzae* now causes the majority of invasive *H influenzae* disease in all age groups. From 2009 through 2014, the annual incidence of invasive nontypable *H influenzae* disease was 1.7/100,000 in children younger than 5 years and 5.0/100,000 in adults 65 years and older. Nontypable *H influenzae* causes approximately 50% of episodes of acute otitis media and sinusitis in children and is a common cause of recurrent otitis media. The rate of nontypable *H influenzae* infections (eg, otitis media and sinusitis) in boys is twice that in girls and peaks in the late fall.

In some North American indigenous populations, *H influenzae* type a (Hia) has emerged as the most common encapsulated serotype causing invasive disease, with a clinical presentation similar to Hib. The 2002–2012 incidence of Hia infection in Alaska Native children younger than 5 years was 18/100,000 (vs 0.5/100,000 in nonnative children). The incidence was highest in southwestern Alaska Native children younger than 5 years (72/100,000). Similarly, Hia has emerged

among northern Canadian indigenous children, who experienced an incidence of 102/100,000/year in children younger than 2 years. There is an ongoing lower level of Hia disease in Navajo children younger than 5 years (20/100,000/year). Invasive disease has also been caused by other encapsulated non-type b strains.

The **incubation period** is unknown.

DIAGNOSTIC TESTS

The diagnosis of invasive disease is established by growth of *H influenzae* from cerebrospinal fluid (CSF), blood, synovial fluid, pleural fluid, or pericardial fluid. Because occult meningitis is well reported in young children with invasive Hib disease, a lumbar puncture should be strongly considered in the presence of invasive disease, even in the absence of central nervous system signs. Gram stain of an infected body fluid specimen can facilitate presumptive diagnosis. Antigen detection methods on CSF, blood, and urine specimens no longer are recommended because they lack sensitivity and specificity. Nucleic acid amplification tests (NAATs) have been developed to detect *H influenzae* directly in clinical specimens, and a multiplexed assay for testing of CSF to detect a variety of agents of encephalitis and meningitis is available. This latter assay detects but does not differentiate among the 6 capsular polysaccharide types. At this time, such NAATs should be used in addition to culture because culture would allow for recovery of an isolate from CSF for serotyping for epidemiologic investigations as well as monitoring anti-microbial susceptibilities.

All *H influenzae* isolates associated with invasive infection should be typed to determine the capsular polysaccharide associated with the isolate. Serotyping by slide agglutination using polyclonal antisera traditionally had been the method of choice for typing. The potential for suboptimal sensitivity and specificity exists with serotyping depending on reagents used and the experience of the technologist. Capsule typing by molecular methods, such as PCR assay of the cap gene locus or outer membrane protein D gene locus, have enhanced sensitivity and specificity and are acceptable methods for capsule typing. If serotyping or typing by molecular methods are not available locally, isolates should be submitted to the state health department or to a reference laboratory for testing.

Otitis media attributable to *H influenzae* is diagnosed by culture of tympanocentesis fluid; organisms isolated from other respiratory tract swab specimens (eg, throat, ear drainage) may not be the same as those from middle-ear culture.

TREATMENT

- Initial therapy for children with *H influenzae* meningitis is cefotaxime or ceftriaxone. If the isolate is susceptible, ampicillin may be substituted. Treatment of other invasive *H influenzae* infections is similar. Therapy is continued for 7 to 10 days by the intravenous route and longer in complicated infections, such as severe meningitis.
- Dexamethasone is beneficial for treatment of infants and children with Hib meningitis to diminish the risk of hearing loss, if administered before or concurrently with the first dose of an antimicrobial agent.
- Epiglottitis is a medical emergency. An airway must be established promptly via controlled intubation.
- Infected pleural or pericardial fluid should be drained.
- For empirical treatment of acute otitis media in children younger than 2 years or in children 2 years or older with severe disease, oral amoxicillin is recommended, unless the child has a prior history of amoxicillin therapy within the past 30 days. For those younger than 2 years, the duration of therapy is 10 days. A 7-day course is considered for children 2 through 5 years of age, and a 5-day course may be used for older children. In the United States, approximately 30% to 40% of *H influenzae* isolates produce beta-lactamase, so amoxicillin may fail, necessitating use of a beta-lactamase–resistant agent, such as amoxicillin-clavulanate; an oral cephalosporin, such as cefdinir; or azithromycin for children with beta-lactam antibiotic allergy.

Image 55.1
A 12-year-old boy with periorbital cellulitis, conjunctivitis, and ethmoid sinusitis caused by *Haemophilus influenzae* type b. Copyright Martin G. Myers, MD.

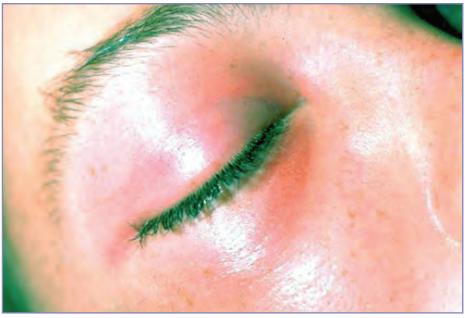


Image 55.2
A 12-year-old boy with periorbital cellulitis and ethmoid sinusitis caused by *Haemophilus influenzae* type b. This is the same patient as in Image 55.1. Copyright Martin G. Myers, MD.

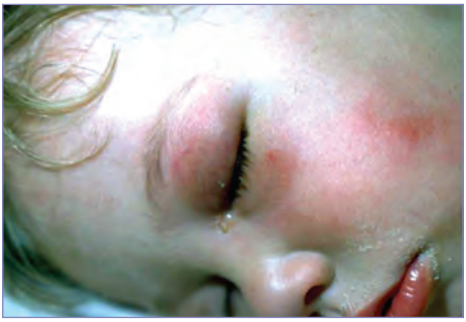


Image 55.3
A 16-month-old girl with periorbital and facial cellulitis caused by *Haemophilus influenzae* type b. The patient had no history of trauma. Copyright Martin G. Myers, MD.

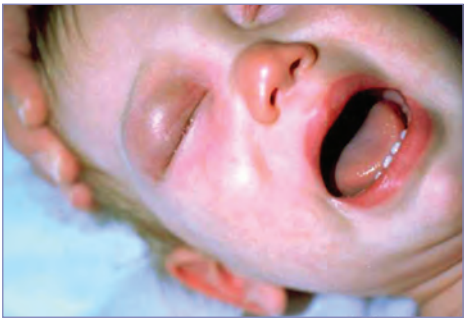


Image 55.4
A 10-month-old boy with periorbital cellulitis due to *Haemophilus influenzae* type b. Copyright Martin G. Myers, MD.

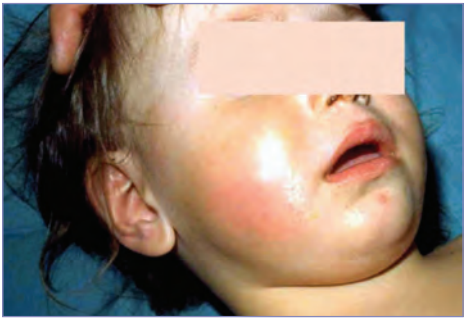


Image 55.5
Haemophilus influenzae type b cellulitis of the face proven by positive subcutaneous aspirate cultures and blood cultures. The cerebrospinal fluid culture was negative. (This is the first of 3 preschool boys from the same child care center who were examined within a period of 72 hours.)

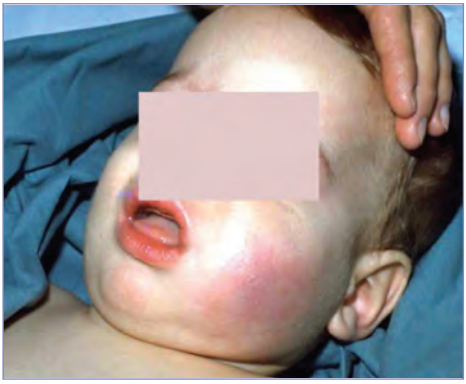


Image 55.6
The second of 3 preschool-aged boys with *Haemophilus influenzae* type b cellulitis of the face proved by positive subcutaneous aspirate cultures and blood cultures.

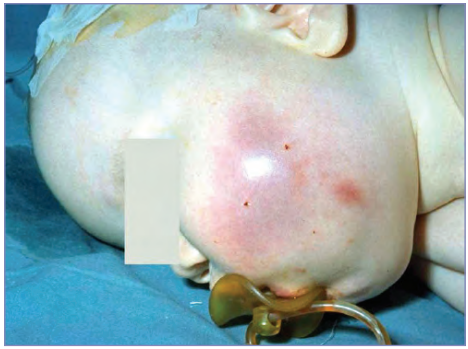


Image 55.7
The third of 3 preschool-aged boys with *Haemophilus influenzae* type b (Hib) cellulitis of the face proved by positive subcutaneous aspirate cultures and blood cultures. The routine administration of the Hib vaccine prevents most of these invasive infections.

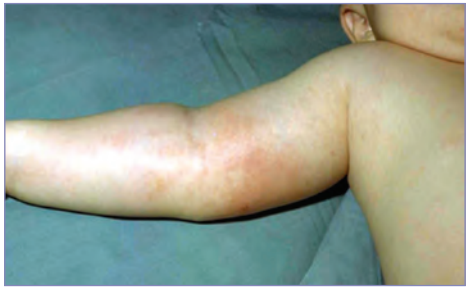


Image 55.9
Haemophilus influenzae type b cellulitis of the arm proved by positive blood culture.

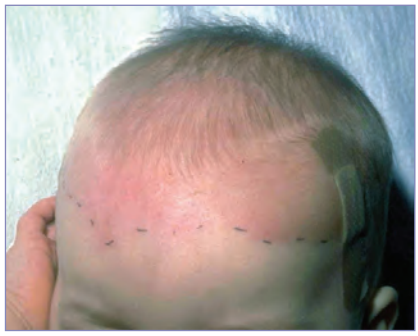


Image 55.11
Haemophilus influenzae type b cellulitis of the forehead proved by positive blood culture. Courtesy of Neal Halsey, MD.

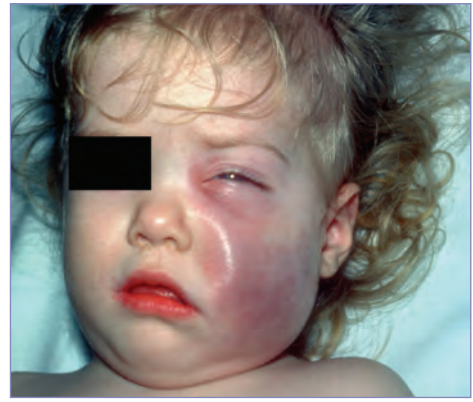


Image 55.8
A classic presentation of *Haemophilus influenzae* type b (Hib) facial cellulitis in a 10-month-old girl. This once-common infection has been nearly eliminated among children who have been immunized with the Hib vaccine. Courtesy of George Nankervis, MD.

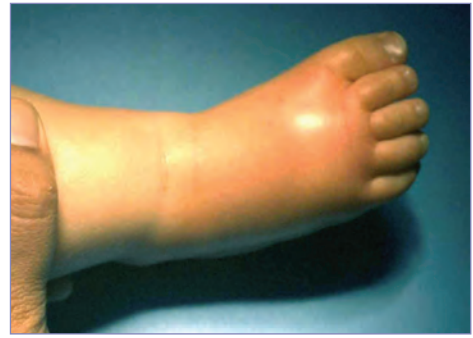


Image 55.10
Haemophilus influenzae type b cellulitis of the foot proved by positive blood culture.

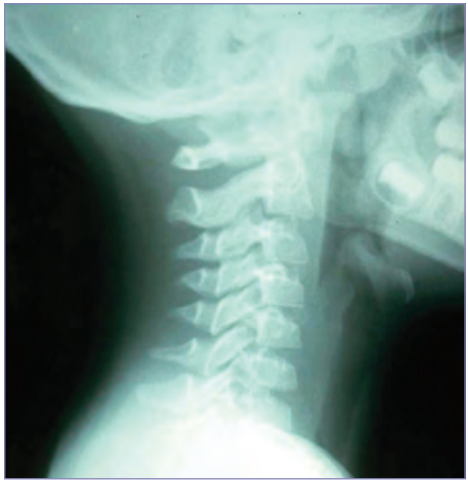


Image 55.12
Acute epiglottitis due to *Haemophilus influenzae* type b proved by blood culture. The swollen inflamed epiglottis looks like the shadow of a thumb on the lateral neck radiograph.

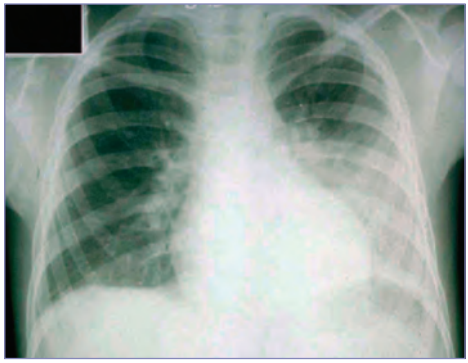


Image 55.14
Haemophilus influenzae type b pneumonia, bilateral, in a patient with acute epiglottitis (proved by blood culture). This is the same patient as in Image 55.13.

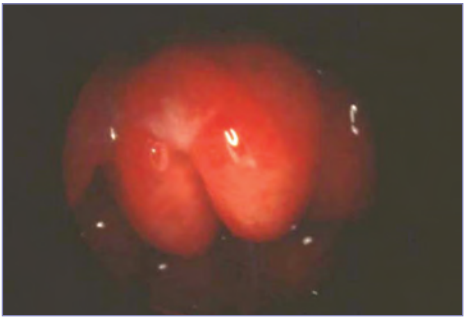


Image 55.13
Acute *Haemophilus influenzae* type b epiglottitis with striking erythema and swelling of the epiglottis. Courtesy of Edgar O. Ledbetter, MD, FAAP.

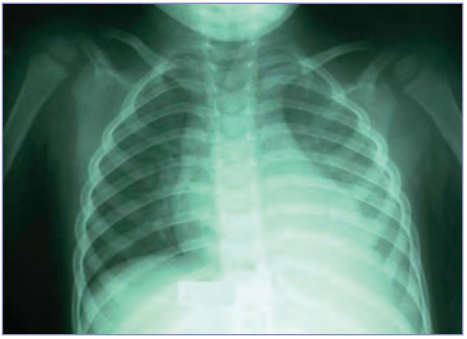


Image 55.15
Haemophilus influenzae type b pneumonia with left pleural effusion. Pleural fluid culture and blood culture were positive for *H influenzae* type b. Courtesy of Edgar O. Ledbetter, MD, FAAP.

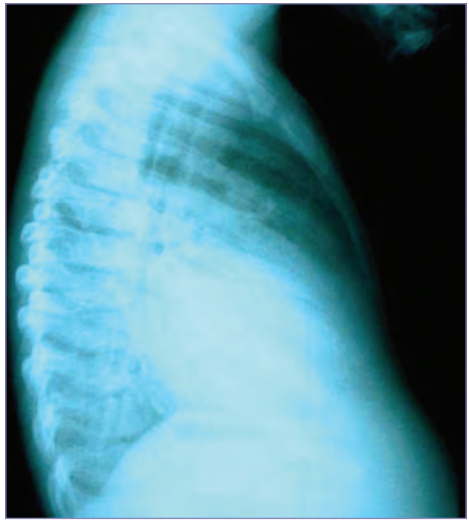


Image 55.16
Lateral radiograph of the patient shown in Image 55.15 with fulminant *Haemophilus influenzae* type b pneumonia. Courtesy of Edgar O. Ledbetter, MD, FAAP.

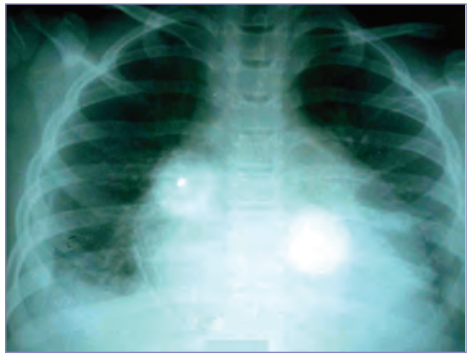


Image 55.18
Haemophilus influenzae type b bilateral pneumonia, empyema, and purulent pericarditis. Pericardiostomy drainage is important in preventing cardiac restriction.

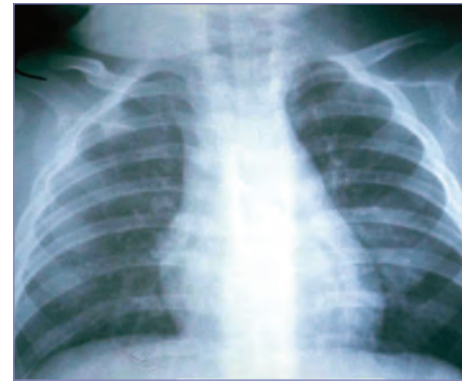


Image 55.17
Retrocardiac *Haemophilus influenzae* type b pneumonia proved by blood culture. Note the air bronchogram.

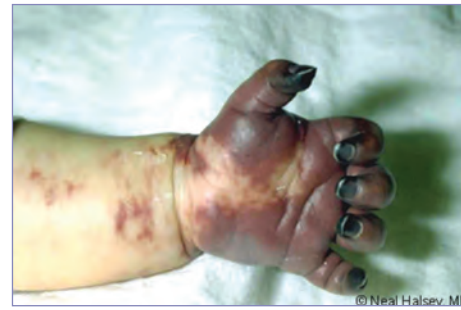


Image 55.19
Haemophilus influenzae type b sepsis with peripheral gangrene. Courtesy of Neal Halsey, MD.

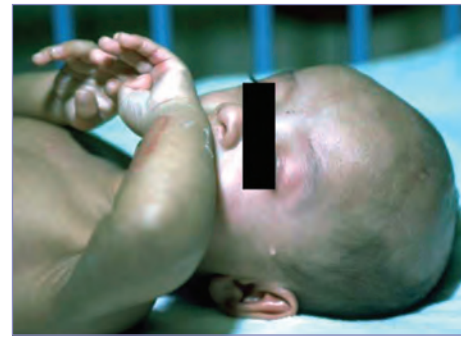


Image 55.20
A 2-year-old boy with *Haemophilus influenzae* type b meningitis and subdural empyema. Note the prominent anterior fontanelle secondary to increased intracranial pressure. Copyright Martin G. Myers, MD.

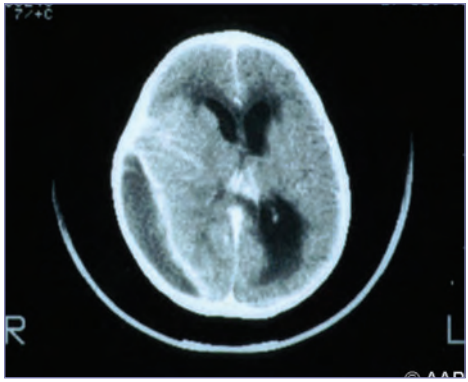


Image 55.21
Magnetic resonance image showing subdural empyema that developed in a patient with *Haemophilus influenzae* type b meningitis.

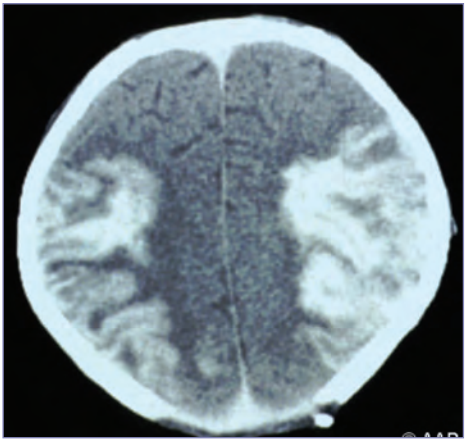


Image 55.23
Magnetic resonance image showing cerebral infarction in a patient who had *Haemophilus influenzae* type b (Hib) meningitis. The routine administration of Hib vaccine has virtually eliminated this type of devastating illness in the United States.

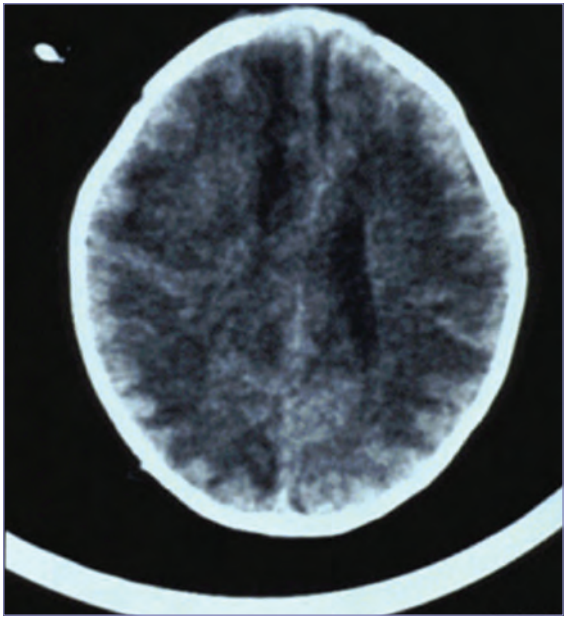


Image 55.22
Magnetic resonance image showing cerebral infarction in a patient with *Haemophilus influenzae* type b meningitis.

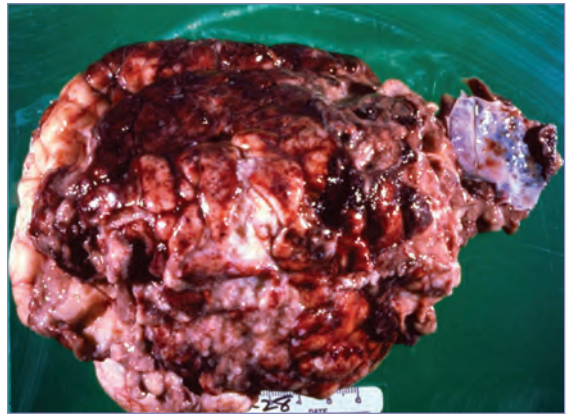


Image 55.24
Haemophilus influenzae meningitis in a 4-month-old who was evaluated in the morning for a well-child visit with normal clinical findings. By afternoon, the child had necrosis of the hands and feet and died 12 hours later. This is the brain of the infant 24 hours after the well-child visit. No immunologic deficit was diagnosed. Copyright Jerri Ann Jenista, MD, MD.

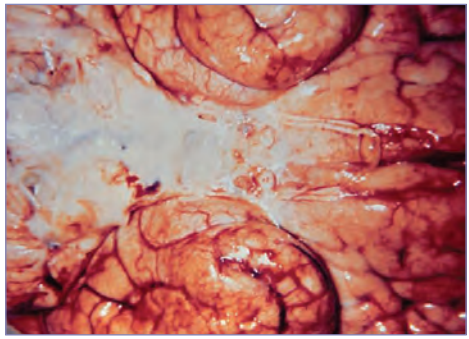


Image 55.25
This is an inferior view of a brain from a child who died from *Haemophilus influenzae* bacteremia and meningitis. Courtesy of Centers for Disease Control and Prevention.

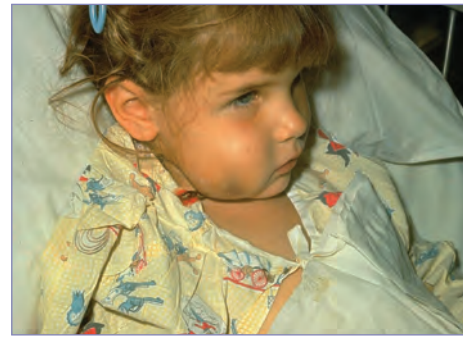


Image 55.26
This girl is hospitalized with *Haemophilus influenzae* type b infection involving deep tissue of the girl's face. *H influenzae* disease can also lead to brain damage, seizures, paralysis, hearing loss, and death. Courtesy of the Immunization Action Coalition.

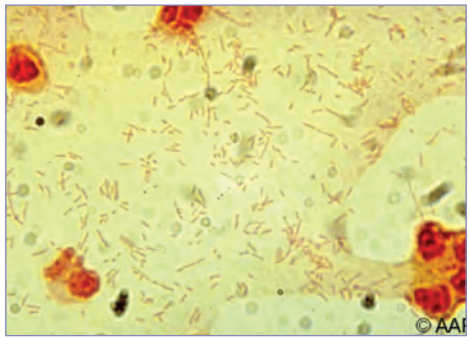


Image 55.27
Gram stain of cerebrospinal fluid (culture positive for *Haemophilus influenzae* type b).

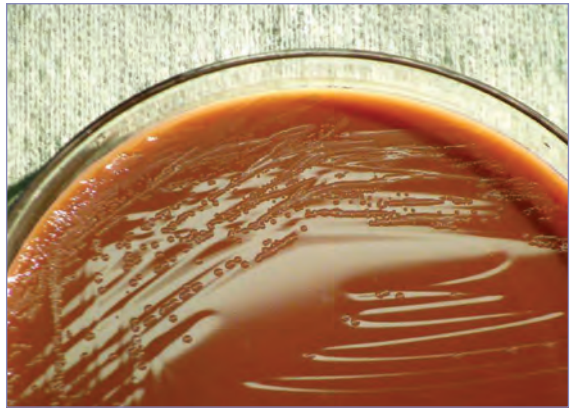


Image 55.28
This photograph depicts the colonial morphology displayed by gram-negative *Haemophilus influenzae* bacteria, which was grown on a medium of chocolate agar for a 24-hour period at a temperature of 37°C (98.6°F). Invasive disease caused by *H influenzae* type b can affect many organ systems. The most common types of invasive disease are pneumonia, occult febrile bacteremia, meningitis, epiglottitis, septic arthritis, cellulitis, otitis media, purulent pericarditis, and other less common infections such as endocarditis and osteomyelitis. Courtesy of Centers for Disease Control and Prevention.

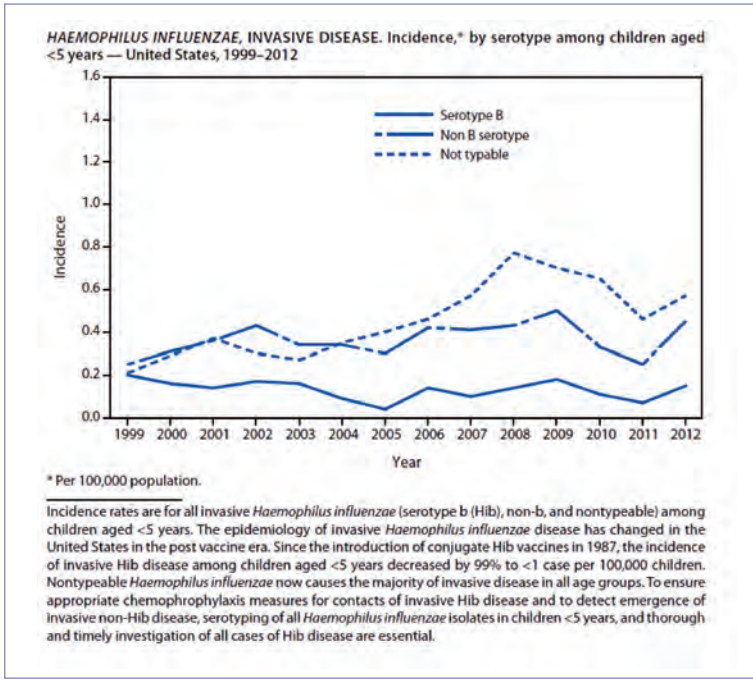


Image 55.29
Haemophilus influenzae, invasive disease. Incidence by serotype among persons younger than 5 years—United States, 1999–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 55.30
Haemophilus influenzae on chocolate agar. This organism thrives on chocolate agar because of the supplication of factors X and V required for its growth. Individual colonies appear gray in color and sometimes mucoid or glistening in quality. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

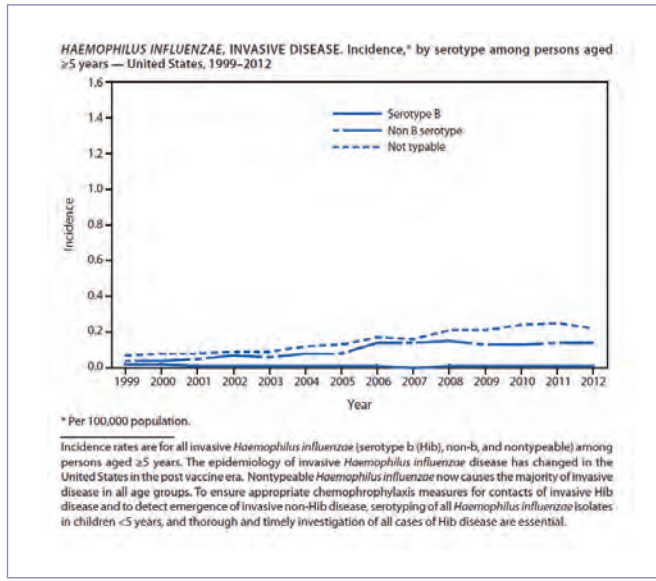


Image 55.31
Haemophilus influenzae, invasive disease. Incidence by serotype among persons 5 years and older—United States, 1999–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 56

Hantavirus Pulmonary Syndrome

CLINICAL MANIFESTATIONS

Hantaviruses cause 2 distinct clinical syndromes: hantavirus pulmonary syndrome (HPS) characterized by noncardiogenic pulmonary edema, which is observed in the Americas; and hemorrhagic fever with renal syndrome (HFRS), which occurs worldwide. The prodromal illness of HPS lasts 3 to 7 days and is characterized by fever, chills, headache, myalgia, nausea, vomiting, diarrhea, dizziness, and sometimes cough. Respiratory tract symptoms or signs usually do not occur during the first 3 to 7 days, but then pulmonary edema and severe hypoxemia appear abruptly and present as cough and dyspnea. The disease then progresses over hours. In severe cases, myocardial dysfunction causes hypotension, which is why the syndrome sometimes is called hantavirus cardiopulmonary syndrome.

Extensive bilateral interstitial and alveolar pulmonary edema with pleural effusions are attributable to diffuse pulmonary capillary leak. Endotracheal intubation and assisted ventilation usually are required for only 2 to 4 days, with resolution heralded by onset of diuresis and rapid clinical improvement.

The severe myocardial depression is different from that of septic shock, with low cardiac indices and stroke volume index, normal pulmonary wedge pressure, and increased systemic vascular resistance. Poor prognostic indicators include persistent hypotension, marked hemoconcentration, a cardiac index of less than 2, and abrupt onset of lactic acidosis with a serum lactate concentration of >4 mmol/L (36 mg/dL).

The mortality rate for patients with HPS is between 30% and 40%; death usually occurs 1 or 2 days after hospitalization. Asymptomatic and milder forms of disease have been reported. Limited information suggests that clinical manifestations and prognosis are similar in adults and children. Serious sequelae are uncommon.

ETIOLOGY

Hantaviruses are RNA viruses of the *Bunyaviridae* family. Sin Nombre virus (SNV) is the major cause of HPS in the western and central regions of the United States. Bayou virus, Black Creek Canal virus, Monongahela virus, and New York virus are responsible for sporadic cases in Louisiana, Texas, Florida, New York, and other areas of the eastern United States. Andes virus, Oran virus, Laguna Negra virus, and Choclo virus are responsible for cases in South and Central America. There are 20 to 40 cases of HPS reported annually in the United States. Cases in children younger than 10 years are exceedingly rare. Children may be less likely to become infected than adults.

EPIDEMIOLOGY

Rodents are the natural hosts for hantaviruses and acquire lifelong, asymptomatic, chronic infection with prolonged viruria and virus in saliva and feces. Humans acquire infection through direct contact with infected rodents, rodent droppings, or rodent nests, or through the inhalation of aerosolized virus particles from rodent urine, droppings, or saliva. Rarely, infection may be acquired from rodent bites or contamination of broken skin with excreta. At-risk activities include handling or trapping rodents, cleaning or entering closed or rarely used rodent-infested structures, cleaning feed storage or animal shelter areas, hand plowing, and living in a home with an increased density of mice. For backpackers or campers, sleeping in a structure also inhabited by rodents has been associated with HPS, with a notable outbreak occurring in 2012 in Yosemite National Park secondary to rodent-infested cabins. Exceptionally heavy rainfall improves rodent food supplies, resulting in an increase in the rodent population with more frequent contact between humans and infected rodents, resulting in more human disease. Most cases occur during the spring and summer, with the geographic location determined by the habitat of the rodent carrier.

SNV is transmitted by the deer mouse, *Peromyscus maniculatus;* Black Creek Canal virus is transmitted by the cotton rat,

Sigmodon hispidus; Bayou virus is transmitted by the rice rat, *Oryzomys palustris;* and New York virus is transmitted by the white-footed mouse, *Peromyscus leucopus.*

DIAGNOSTIC TESTS

HPS should be considered when thrombocytopenia occurs with severe pneumonia clinically resembling acute respiratory distress syndrome in the proper epidemiologic setting. Other characteristic laboratory findings include neutrophilic leukocytosis with immature granulocytes, including more than 10% immunoblasts (basophilic cytoplasm, prominent nucleoli, and an increased nuclear-cytoplasmic ratio) and increased hematocrit.

Molecular detection of virus has been described in peripheral blood mononuclear cells and other clinical specimens from the early phase of the disease but not usually in bronchoalveolar lavage fluids. Viral culture is not useful. Hantavirus-specific immunoglobulin (Ig) M and IgG antibodies often are present at the onset of clinical disease, and serologic testing remains the method of choice for diagnosis. IgG may be negative in rapidly fatal cases.

Immunohistochemical staining of tissues (capillary endothelial cells of the lungs and almost every organ in the body) can establish the diagnosis at autopsy.

TREATMENT

Patients with suspected HPS should be transferred immediately to a tertiary care facility where supportive management of pulmonary edema, severe hypoxemia, and hypotension can occur during the first critical 24 to 48 hours. In severe forms, early mechanical ventilation and inotropic and pressor support are necessary. Extracorporeal membrane oxygenation (ECMO) should be considered when pulmonary wedge pressure and cardiac indices deteriorate and may provide short-term support for the severe capillary leak syndrome in the lungs.

Ribavirin is active in vitro against hantaviruses, including SNV. However, 2 clinical studies of intravenous ribavirin failed to show benefit in treatment of HPS in the cardiopulmonary stage. Cytokine blocking agents for HPS theoretically may have a role, but these agents have not been evaluated in a systematic fashion. Antibacterial agents are unlikely to offer benefit.

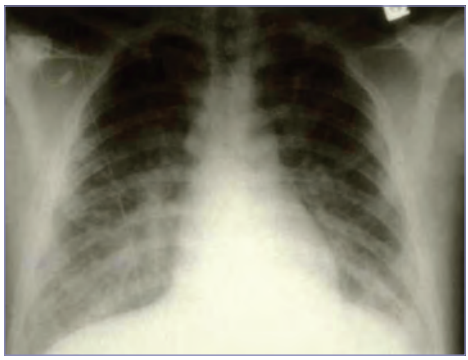


Image 56.1
Hantavirus pulmonary syndrome in a 16-year-old boy with a 36-hour history of fever, myalgia, and shortness of breath. Diffuse interstitial infiltrates with Kerley B lines. Diffuse nodular confluent alveolar opacities with some consolidation consistent with adult respiratory distress syndrome. Hantavirus serology confirmatory by immunoglobulin M at 1:6,400. Patient recovered with supportive care including inhaled nitric oxide. Copyright David Waagner.

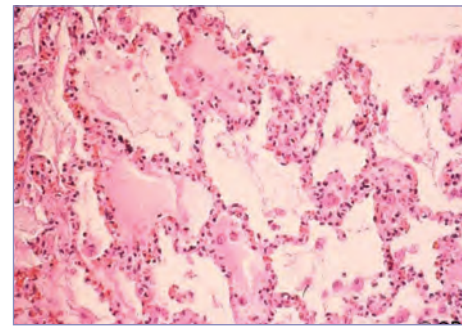


Image 56.2
Histopathologic features of lung in hantavirus pulmonary syndrome include interstitial pneumonitis and intra-alveolar edema. Courtesy of Centers for Disease Control and Prevention.

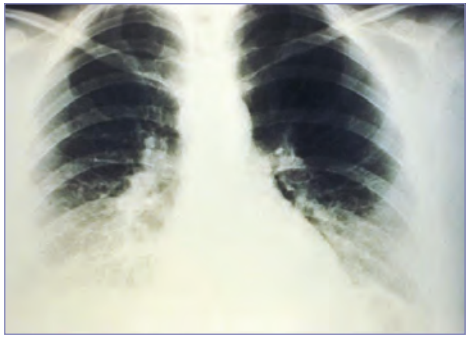


Image 56.3
This anterolateral chest radiograph reveals the early stages of bilateral pulmonary effusion due to hantavirus pulmonary syndrome (HPS). The radiologic evolution of HPS begins with minimal changes of interstitial pulmonary edema and progresses to alveolar edema with severe bilateral involvement. Pleural effusions are common and are often large enough to be evident radiographically. Courtesy of Centers for Disease Control and Prevention.

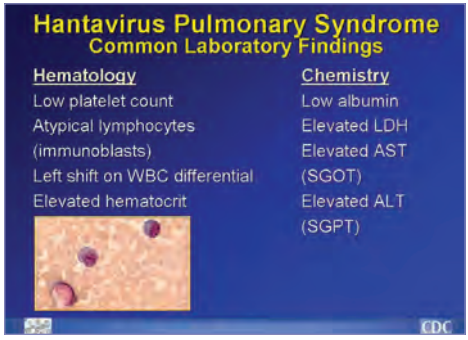


Image 56.5
Common laboratory findings. Notable hematologic findings include low platelet count, immunoblasts, left shift on white blood cell count differential, elevated white blood cell count, and elevated hematocrit. The large atypical lymphocyte shown here is an example of one of the laboratory findings that, when combined with a bandemia and dropping platelet count, are characteristic of hantavirus pulmonary syndrome. Notable blood chemistry findings include low albumin, elevated lactate dehydrogenase, elevated aspartate aminotransferase, and elevated alanine aminotransferase. Courtesy of Centers for Disease Control and Prevention.

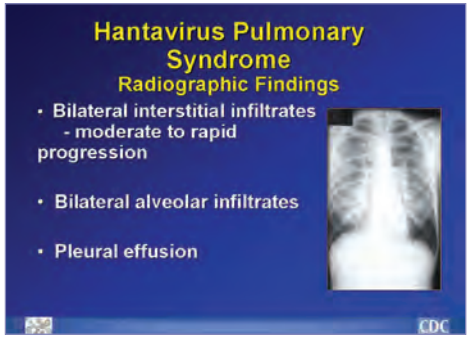


Image 56.4
Radiographic findings of hantavirus pulmonary syndrome. Findings usually include interstitial edema, Kerley B lines, hilar indistinctness, and peribronchial cuffing with normal cardiothoracic ratios. Hantavirus pulmonary syndrome begins with minimal changes of interstitial pulmonary edema and rapidly progressing to alveolar edema with severe bilateral involvement. Pleural effusions are common and are often large enough to be evident radiographically. Courtesy of Centers for Disease Control and Prevention.

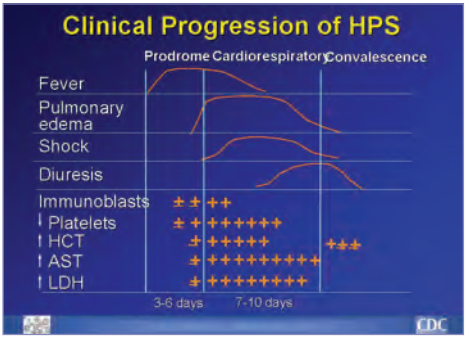


Image 56.6
Clinical course of hantavirus pulmonary syndrome starts with a febrile prodrome that may ultimately lead to hypotension and end-organ failure. The onset of the immune response precedes severe organ failure, which is thought to be immunopathologic in nature. Hypotension does not result in shock until the onset of respiratory failure, but this may reflect the severe physiological effect of lung edema. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 57

Helicobacter pylori Infections

CLINICAL MANIFESTATIONS

Most infections of *Helicobacter pylori* in patients are thought to be asymptomatic. *H pylori* causes chronic active gastritis and may result in duodenal and, to a lesser extent, gastric ulcers. Persistent infection with *H pylori* increases the risk of gastric cancer in adults, but this is an infrequent complication in children. In children, *H pylori* infection can result in gastroduodenal inflammation that can manifest as epigastric pain, nausea, vomiting, hematemesis, and guaiac-positive stools. Symptoms can resolve within a few days or can wax and wane. Nodular gastritis associated with *H pylori* infection commonly occurs in childhood and is regarded as benign with no clinical significance. Extraintestinal conditions in children that have been associated with *H pylori* infection include iron-deficiency anemia, short stature, and chronic immune thrombocytopenia. However, there is no clear association between infection and recurrent abdominal pain in the absence of peptic ulcer disease. *H pylori* infection is not associated with secondary gastritis (eg, autoimmune or associated with nonsteroidal anti-inflammatory agents).

ETIOLOGY

H pylori is a gram-negative, spiral, curved, or U-shaped microaerobic bacillus that has single or multiple flagella at one end. The organism is catalase, oxidase, and urease positive.

EPIDEMIOLOGY

H pylori organisms have been isolated from humans and other primates. An animal reservoir for human transmission has not been demonstrated. Organisms are thought to be transmitted from infected humans by the fecal-oral, gastro-oral, and oral-oral routes.

H pylori is estimated to have infected 70% of people living in resource-limited countries and 30% to 40% of people living in industrialized countries. Infection rates in children are low in resource-rich countries, except in children from lower socioeconomic groups and those living in poor hygienic conditions. Most infections are acquired in the first 5 years of life and can reach prevalence rates of up to 80% in resource-limited countries. Approximately 70% of infected people are asymptomatic; esophagogastroduodenoscopic changes are found in 20% of people, either grossly or with microscopic findings of ulceration; and an estimated 1% have features of neoplasia.

The **incubation period** is unknown.

DIAGNOSTIC TESTS

H pylori infection can be diagnosed by culture of gastric biopsy tissue on nonselective media or selective media at 37°C under microaerobic conditions for 3 to 10 days. Colonies are small, smooth, and translucent. Antimicrobial susceptibility testing of cultured isolates may be necessary to guide therapy in refractory cases. Organisms can be visualized on histologic sections with Warthin-Starry silver, Steiner, Giemsa, or Genta staining. Immunohistological staining with specific *H pylori* antibodies may improve specificity. Because of production of high levels of urease by these organisms, urease testing of a gastric biopsy specimen can give a rapid and specific microbiologic diagnosis.

Noninvasive, commercially available tests include urea breath tests and stool antigen tests; these tests are designed for detection of active infection and have high sensitivity and specificity. Stool antigen tests by enzyme immunoassay monoclonal antibodies are available commercially and can be used for children of any age, especially before and after treatment.

The organism can be detected by polymerase chain reaction (PCR) or fluorescence in situ hybridization (FISH) of gastric biopsy tissue, and PCR also has been applied to detecting the organism in stool specimens.

The European Society for Paediatric Gastroenterology Hepatology and Nutrition and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommend against a "test and treat" strategy for *H pylori* infection in children. Instead, they recommend the following:

- The diagnosis of *H pylori* infection should be based on either (a) histopathology (*H pylori*–positive gastritis) plus at least 1 other positive biopsy-based test, or (b) positive culture.
- When testing for *H pylori*, wait at least 2 weeks after stopping a proton pump inhibitor (PPI) and 4 weeks after stopping antimicrobial agents.
- Testing for *H pylori* should be performed in children with gastric or duodenal ulcers. If *H pylori* infection is identified, then treatment should be advised and eradication should be confirmed.

TREATMENT

Treatment is recommended for infected patients who have peptic ulcer disease, gastric mucosa-associated lymphoid tissue-type lymphoma, or early gastric cancer. Screening for and treatment of infection, if found, may be considered for children who have unexplained and refractory iron-deficiency anemia. For patients with *H pylori* infection in the absence of clinical or endoscopic evidence of peptic ulcer disease, treatment is not recommended unless the patient is within a risk group or region with high incidence of gastric cancer.

The backbone of all recommended therapies includes a PPI and amoxicillin. Additions of metronidazole, clarithromycin, and/or bismuth are based on the patient's previous treatment experience, known susceptibilities to clarithromycin and metronidazole, and the local rates of successful eradication. Reports of increasing prevalence of antibiotic-resistant strains (particularly clarithromycin resistance) as well as increasing failures of triple therapies suggest the need for quadruple therapy regimens and longer durations (14 days) for eradication of *H pylori*. Several treatment regimens have been evaluated for use in adults; the safety and efficacy of these regimens in pediatric patients have not been firmly established. There is no current evidence to support the use of probiotics to reduce medication adverse effects or improve eradication of *H pylori*.

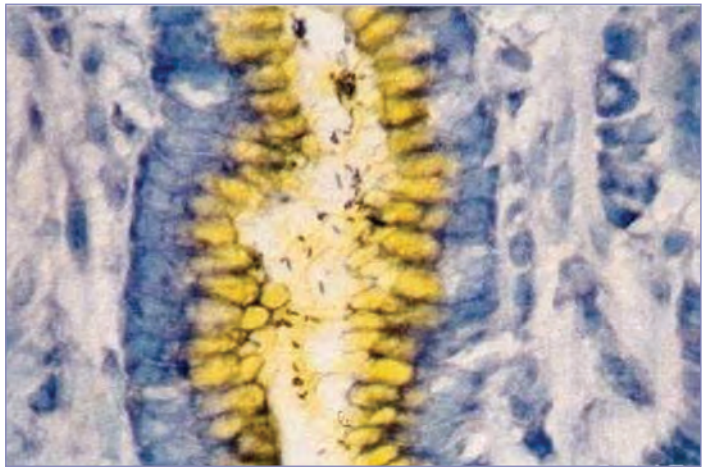


Image 57.1
Histology of the gastric mucosa demonstrates the characteristic curved organisms in the gastric glands. Courtesy of H. Cody Meissner, MD, FAAP.

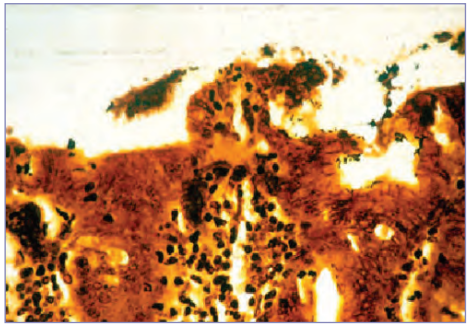


Image 57.2
Gastric mucosal biopsy demonstrating *Helicobacter pylori*. This organism has been isolated from humans and other primates.

Image 57.3
A biopsy of gastric mucosa stained with Warthin-Starry silver stain showing *Helicobacter pylori* organisms. Courtesy of Brian Oliver, MD.

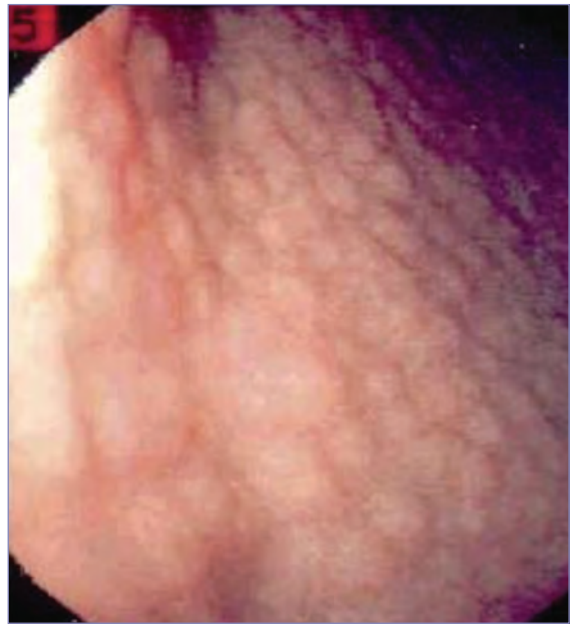


Image 57.4
Helicobacter pylori infection is a known risk factor for gastritis and duodenal ulcers in children and adults. Rarely, and primarily in older adulthood, *H pylori* is also associated with a gastric lymphoma of the mucosal-associated lymphoid tissue. The gold standard for the diagnosis of *H pylori* infection of the stomach is endoscopy with biopsy. Endoscopy may show a nodular gastritis of the antrum. Courtesy of H. Cody Meissner, MD, FAAP.

CHAPTER 58

Hemorrhagic Fevers Caused by Arenaviruses

CLINICAL MANIFESTATIONS

Arenaviruses are responsible for several hemorrhagic fevers (HFs): Old World arenavirus HFs include Lassa fever and Lujo virus infections in western and southern Africa. New World arenavirus HFs include Argentine, Bolivian, Brazilian, Venezuelan, and Chapare virus infection. Lymphocytic choriomeningitis virus (LCMV) is an Old World arenavirus that generally induces less severe disease, although it can cause HFs in immunosuppressed patients. Disease associated with arenaviruses ranges in severity from asymptomatic or mild, acute, febrile infections to severe illnesses in which vascular leak, shock, and multiorgan dysfunction are prominent features. Fever, headache, arthralgia, myalgia, conjunctival suffusion, retroorbital pain, facial flushing, anorexia, vomiting, diarrhea, and abdominal pain are common early symptoms in all infections.

Thrombocytopenia, leukopenia, petechiae, generalized lymphadenopathy, and encephalopathy usually are present in Argentine HF, Bolivian HF, and Venezuelan HF, and exudative pharyngitis often occurs in Lassa fever. Mucosal bleeding generally occurs in severe cases as a consequence of vascular damage, coagulopathy, thrombocytopenia, and platelet dysfunction. However, hemorrhagic manifestations occur in only one third of patients with Lassa fever. Proteinuria is common, but renal failure is unusual. Increased serum concentrations of aspartate transaminase (AST) can portend a severe or possibly fatal outcome of Lassa fever. Shock develops 7 to 9 days after onset of illness in more severely ill patients. Upper and lower respiratory tract symptoms can develop in people with Lassa fever. Encephalopathic signs, such as tremor, alterations in consciousness, and seizures, can occur in South American HFs and in severe cases of Lassa fever. Transitory or permanent deafness is reported in 30% of convalescents of Lassa fever. The mortality rate in South American HFs is 10% to 35% and in Lujo virus infection is 80%. Symptoms resolve 10 to 15 days after disease onset in surviving patients.

ETIOLOGY

Mammalian arenaviruses (mammarenaviruses) are enveloped, bisegmented, single-stranded RNA viruses. The Old World complex of arenaviruses includes Lassa virus, which causes Lassa fever and Lujo virus. The major New World arenavirus HFs occurring in the Western hemisphere are caused by the Tacaribe serocomplex of clade B arenaviruses: Argentine HF caused by Junín virus, Bolivian HF caused by Machupo virus and Chapare virus, Brazilian HF caused by Sabiá virus, and Venezuelan HF caused by Guanarito virus. Clinical disease has not been confirmed in North America. Several other arenaviruses are known only from their rodent reservoirs in the Old and New World.

EPIDEMIOLOGY

Arenaviruses are maintained in nature by association with specific rodent hosts, in which they produce chronic viremia and viruria. The principal routes of infection are inhalation and contact of mucous membranes and skin (eg, through cuts, scratches, or abrasions) with urine and salivary secretions from these persistently infected rodents. Ingestion of food contaminated by rodent excrement also may cause disease transmission. Tacaribe viruses have not been associated with a rodent host; although they have reportedly been isolated in bats, mosquitoes, and ticks, transmission through these vectors has not been definitely confirmed. All arenaviruses are infectious as aerosols, and human-to-human transmission may occur in community or hospital settings following unprotected contact or through droplets. Excretion of arenaviruses in urine and semen for several weeks after infection has been documented. Arenaviruses causing HF should be considered highly hazardous to people working with any of these viruses in the laboratory. Laboratory-acquired infections have been documented with Lassa, Machupo, Junín, and Sabiá viruses. The geographic distribution and habitats of the specific rodents that serve as reservoir hosts largely determine areas with endemic infection and populations at risk. Epidemics of Bolivian HF occurred in small towns between 1962 and 1964; sporadic disease activity in the countryside has continued since then. Venezuelan HF first was identified in 1989 and occurs in rural north-central

Venezuela. Lassa fever is endemic in most of western Africa, where rodent hosts live in proximity with humans, causing thousands of infections annually. Lassa fever has been reported in the United States and Western Europe in people who have traveled to western Africa.

The **incubation periods** are from 6 to 17 days.

DIAGNOSTIC TESTS

Viral nucleic acid can be detected in acute disease by reverse transcriptase-polymerase chain reaction assay. These viruses may be isolated from blood of acutely ill patients as well as from various tissues obtained postmortem, but isolation should be attempted only under Biosafety level-4 (BSL-4) conditions. Virus antigen is detectable by enzyme immunoassay (EIA) in acute specimens and postmortem tissues. Virus-specific immunoglobulin (Ig) M antibodies are present in the serum during acute stages of illness by immunofluorescent antibody or enzyme-linked immunosorbent assays but may be undetectable in rapidly fatal cases. The IgG antibody response is delayed. Diagnosis can be made retrospectively by immunohistochemical staining of formalin-fixed tissues obtained from autopsy.

TREATMENT

Intravenous ribavirin substantially decreases the mortality rate in patients with severe Lassa fever, particularly if they are treated during the first week of illness. For Argentine HF, transfusion of immune plasma in defined doses of neutralizing antibodies is the standard specific treatment; when administered during the first 8 days from onset of symptoms, this reduces mortality to 1% to 2%. Intravenous ribavirin has been used with success to abort a Sabiá laboratory infection and to treat Bolivian HF patients and the only known Lujo virus infection survivor. Ribavirin did not reduce mortality when initiated 8 days or more after onset of Argentine HF symptoms. Whether ribavirin treatment initiated early in the course of the disease has a role in the treatment of Argentine HF remains to be seen. Meticulous fluid balance is an important aspect of supportive care in each of the HFs.

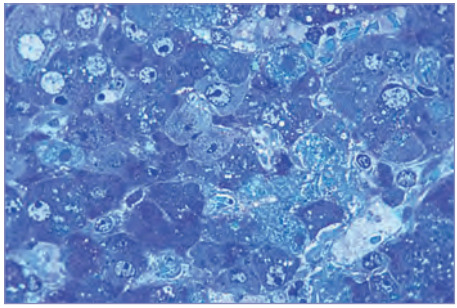


Image 58.1
This photomicrograph shows hepatitis caused by the Lassa virus (toluidine-blue azure II stain). The Lassa virus, which can cause altered liver morphology with hemorrhagic necrosis and inflammation, is a member of the family *Arenaviridae* and is a single-stranded RNA, zoonotic, or animal-borne pathogen. Courtesy of Centers for Disease Control and Prevention.

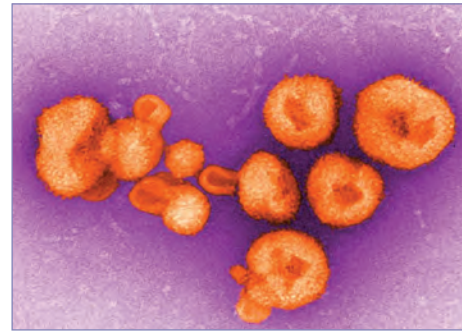


Image 58.2
This transmission electron micrograph depicted virions (viral particles) that are members of the genus *Arenavirus*. Arenaviruses include lymphocytic choriomeningitis virus and the agents of 5 hemorrhagic fevers, including West African Lassa fever virus and Bolivian hemorrhagic fever, also known as Machupo virus. Spread to humans occurs through inhalation of airborne particulates originating from rodent excrement, which can occur during the simple act of sweeping a floor. Courtesy of Centers for Disease Control and Prevention/Charles Humphrey.

CHAPTER 59

Hemorrhagic Fevers Caused by Bunyaviruses

CLINICAL MANIFESTATIONS

Bunyaviruses are vectorborne infections (except for hantavirus) that often result in severe febrile disease with multisystem involvement. Human infection by bunyaviruses may be associated with high rates of morbidity and mortality. In the United States, disease attributable to a bunyavirus most likely is caused by either hantavirus or members of the California serogroup.

Hemorrhagic fever with renal syndrome (HFRS) is a complex, multiphasic disease characterized by vascular instability and varying degrees of renal insufficiency. Fever, flushing, conjunctival injection, headache, blurred vision, abdominal pain, and lumbar pain are followed by hypotension, oliguria, and subsequently, polyuria. Petechiae are frequent, but more serious bleeding manifestations are rare. Shock and acute renal insufficiency may occur. Nephropathia epidemica (attributable to Puumala virus) occurs in Europe and presents as a milder disease with acute influenza-like illness, abdominal pain, and proteinuria. Acute renal dysfunction also occurs, but hypotensive shock and requirement for dialysis are rare. However, more severe forms of HFRS (ie, attributable to Dobrava virus) occur in Europe.

Crimean-Congo hemorrhagic fever (CCHF) is a multisystem disease characterized by hepatitis and profuse bleeding. Fever, headache, and myalgia are followed by signs of a diffuse capillary leak syndrome with facial suffusion, conjunctivitis, icteric hepatitis, proteinuria, and disseminated intravascular coagulation associated with petechiae and purpura on the skin and mucous membranes. A hypotensive crisis often occurs after the appearance of frank hemorrhage from the gastrointestinal tract, nose, mouth, or uterus. Mortality rates range from 20% to 35%.

Rift Valley fever (RVF), in most cases, is a self-limited undifferentiated febrile illness. In 8% to 10% of cases, however, hemorrhagic fever with shock and icteric hepatitis, encephalitis, or retinitis develops.

ETIOLOGY

Bunyaviridae are segmented, single-stranded RNA viruses with different geographic distributions depending on their vector or reservoir. Hemorrhagic fever syndromes are associated with viruses from 3 genera: hantaviruses, nairoviruses (CCHF virus), and phleboviruses (RVF and Heartland virus in the United States, sandfly fever viruses in Europe, and severe fever with thrombocytopenia syndrome [SFTS] virus in China). Old World hantaviruses (Hantaan, Seoul, Dobrava, and Puumala viruses) cause HFRS, and New World hantaviruses (Sin Nombre and related viruses) cause hantavirus pulmonary syndrome.

EPIDEMIOLOGY

The epidemiology of these diseases mainly is a function of the distribution and behavior of their reservoirs and vectors. All genera except hantaviruses are associated with arthropod vectors, and hantavirus infections are associated with airborne exposure to infected wild rodents, primarily via inhalation of virus-contaminated urine, droppings, or nesting materials.

Classic HFRS occurs throughout much of Asia and Eastern and Western Europe, with up to 100,000 cases per year. The most severe form of the disease is caused by the prototype Hantaan and Dobrava viruses in rural Asia and Europe, respectively; Puumala virus is associated with milder disease (nephropathia epidemica) in Western Europe. Seoul virus is distributed worldwide in association with *Rattus* species and can cause a disease of variable severity. Person-to-person transmission never has been reported with HFRS. Fatal outcome is seen in 1% to 15% of cases, depending on the species of virus and the level of care.

CCHF occurs in much of sub-Saharan Africa, the Middle East, areas in West and Central Asia, and the Balkans. CCHF virus is transmitted by hard ticks and occasionally by contact with viremic livestock and wild animals at slaughter. Health care-associated transmission of CCHF is a frequent and serious hazard. Fatal outcome is seen in 9% to 50% of hospitalized patients.

RVF occurs throughout sub-Saharan Africa and has caused large epidemics in Egypt in 1977 and 1993–1995, Mauritania in 1987, Saudi Arabia and Yemen in 2000, Kenya and Tanzania in 1997 and 2006–2007, Madagascar in 1990 and 2008, and South Africa in 2010. The virus is mosquitoborne and is transmitted from domestic livestock to humans. The virus also can be transmitted by aerosol in laboratory conditions and by direct contact with infected aborted tissues or freshly slaughtered infected animal carcasses. Person-to-person transmission has not been reported, but laboratory-acquired cases are well documented. Overall fatal outcome occurs in 1% to 2% of cases but has been reported to be up to 30% in hospitalized patients.

The **incubation periods** for CCHF and RVF range from 2 to 10 days; for HFRS, incubation periods usually are longer (7 to 42 days).

DIAGNOSTIC TESTS

Viral culture of blood and/or tissue, detection of virus antigen by enzyme immunoassay (EIA), acute-phase quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) and serologic testing may facilitate diagnosis. Immunoglobulin (Ig) M antibodies or increasing IgG titers in paired serum specimens, as demonstrated by EIA, are diagnostic; neutralizing antibody tests provide greater virus-strain specificity but rarely are used. Serum IgM and IgG virus-specific antibodies typically develop early in convalescence in CCHF and RVF but can be absent in rapidly fatal causes of CCHF. In HFRS, IgM and IgG antibodies usually are detectable at the time of onset of illness or within 48 hours, when it is too late for virus isolation and qRT-PCR assay. Diagnosis can be made retrospectively by immunohistochemical staining of formalin-fixed tissues.

TREATMENT

Ribavirin, administered intravenously to patients with HFRS within the first 4 days of illness, may be effective in decreasing renal dysfunction, vascular instability, and mortality. However, intravenous ribavirin is not available commercially in the United States. Health care providers who need to obtain intravenous ribavirin should contact the US Food and Drug Administration or the manufacturer. Supportive therapy for HFRS should include treatment of shock, monitoring of fluid balance, dialysis for complications of renal failure, control of hypertension, and early recognition of possible myocardial failure with appropriate therapy.

Oral and intravenous ribavirin, when administered early in the course of CCHF, has been associated with milder disease, although no controlled studies have been performed.

Image 59.1
Isolated male patient diagnosed with Crimean-Congo hemorrhagic fever, a tick-borne hemorrhagic fever with documented person-to-person transmission and a case-fatality rate of approximately 30%. This widespread virus has been found in Africa, Asia, the Middle East, and eastern Europe. Courtesy of Centers for Disease Control and Prevention.

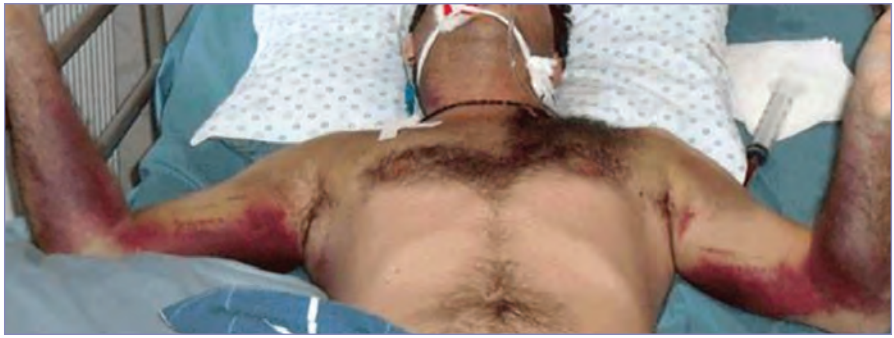


Image 59.2
Intubated patient with Crimean-Congo hemorrhagic fever, Republic of Georgia, 2009, showing massive ecchymoses on the upper extremities that extend to the chest. Courtesy of *Emerging Infectious Diseases*.

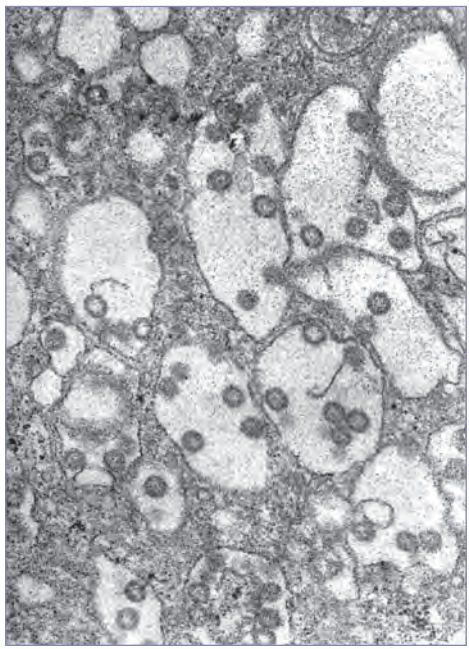


Image 59.3
Electron micrograph of the Rift Valley fever virus, which is a member of the genus *Phlebovirus* in the family *Bunyaviridae*, first reported in livestock in Kenya around 1900. Courtesy of Centers for Disease Control and Prevention.

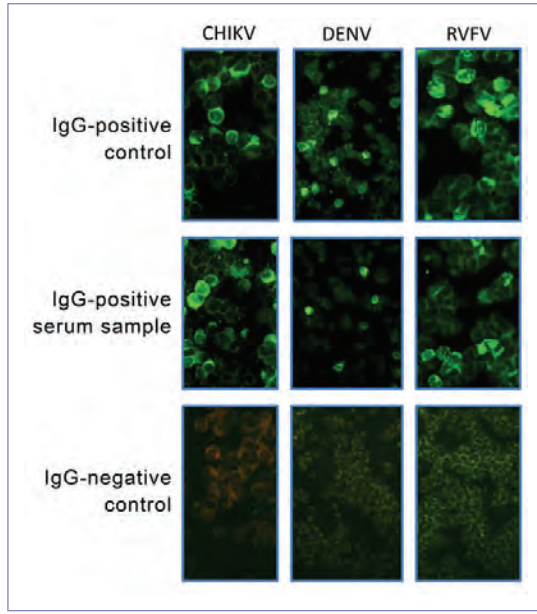


Image 59.4
Images from immunofluorescence assays in Vero E6 cells for immunoglobulin G against chikungunya virus, dengue virus, and Rift Valley fever virus (original magnification ×100 and ×200). Courtesy of *Emerging Infectious Diseases.*

CHAPTER 60

Hemorrhagic Fevers Caused by Filoviruses: Ebola and Marburg

CLINICAL MANIFESTATIONS

Information for Ebola and Marburg virus infections primarily are derived from adult populations. More is known about Ebola virus disease than Marburg virus disease, although the same principles apply generally to the 2 filoviruses known to cause human disease. Asymptomatic cases of human filovirus infections have been reported, and symptomatic disease ranges from mild to severe; case fatality rates for severely affected people range from 25% to 90%. Data from the 2 largest outbreaks have confirmed that the lowest case fatality rates are in adolescents. Disease in children and adults begins with nonspecific signs and symptoms including fever, severe headache, myalgia, fatigue, abdominal pain, and weakness followed several days later by vomiting, diarrhea, and sometimes unexplained bleeding or bruising. Children may have shorter incubation periods than adults. Respiratory symptoms are more common and central nervous system manifestations are less common in children than in adults. A fleeting maculopapular rash on the torso or face after approximately 4 to 5 days of illness may occur. Conjunctival injection or subconjunctival hemorrhage may be present. Leukopenia, frequently with lymphopenia, is followed later by elevated neutrophils, a left shift, and thrombocytopenia. Hepatic dysfunction, with elevations in aspartate transaminase (AST) at markedly higher levels than alanine transaminase (ALT), and metabolic derangements, including hypokalemia, hyponatremia, hypocalcemia, and hypomagnesemia, are common. In the most severe cases, microvascular instability ensues around the end of the first week of disease. Although hemostasis is impaired, hemorrhagic manifestations develop in a minority of patients. In the 2001 Ebola virus outbreak in Uganda and Sudan, all children with laboratory-confirmed Ebola virus disease were febrile and only 16% had hemorrhage. In a study of 122 children from 5 Ebola units during the 2014–2015 outbreak, bleeding was rare at presentation (5%) and manifested subsequently in fewer than 50%. The most common hemorrhagic manifestations consist of bleeding from the gastrointestinal tract, sometimes with oozing from the mucous membranes or venipuncture sites in late stages.

Central nervous system manifestations and renal failure are frequent in end-stage disease. In fatal cases, death typically occurs around 10 to 12 days after symptom onset, usually resulting from viral- or bacterial-induced septic shock and multiorgan system failure. Factors associated with pediatric Ebola deaths in the 2014–2015 outbreak were age <5 years, bleeding at any time during hospitalization, and high viral load. Approximately 30% of pregnant women with Ebola virus disease present with spontaneous abortion and vaginal bleeding. Maternal mortality approaches 90% when infection occurs during the third trimester. New data are emerging that survivors are at risk for reactivation of disease in immune-privileged sites, such as the eye or the central nervous system, because of persistence of Ebola virus. However, disease reactivation currently is thought to be a rare event. Long-term shedding of virus in semen has been implicated in the origin of several clusters of Ebola virus disease in West Africa.

ETIOLOGY

The *Filoviridae* (from the Latin filo meaning thread, referring to their filamentous shape) are single-stranded, negative-sense RNA viruses. Marburg and Ebola viruses are the only known members of the filovirus family. Four of the 5 species in the *Ebolavirus* genus and both of the known species in the *Marburgvirus* genus are associated with human disease. The known human pathogenic filoviruses are endemic only in Africa.

EPIDEMIOLOGY

Fruit bats are believed to be the animal reservoir for filoviruses. Human infection is believed to occur from inadvertent exposure to infected bat excreta or saliva following entry into roosting areas in caves, mines, and forests. Nonhuman primates, especially gorillas and chimpanzees, and other wild animals may become infected from bat contact and serve as intermediate hosts that transmit filoviruses to humans through contact with their blood and

bodily fluids, usually associated with hunting and butchering. For unclear reasons, filovirus outbreaks tend to occur after prolonged dry seasons.

Molecular epidemiologic evidence shows that most outbreaks result from a single point introduction (or very few) into humans from wild animals, followed by human-to-human transmission, almost invariably fueled by health care-associated transmission in areas with inadequate infection-control equipment and resources. Although filoviruses are the most transmissible of all hemorrhagic fever viruses, secondary attack rates in households still generally are only 15% to 20% in African communities and are lower if proper universal and contact precautions are maintained. Human-to-human transmission usually occurs through oral, mucous membrane, or nonintact skin exposure to bodily fluids of a symptomatic person with filovirus disease, most often in the context of providing care to a sick family or community member (community transmission) or patient (health care-associated transmission). Funeral rituals that entail the touching of the corpse also have been implicated. Sexual transmission has been documented. Ebola virus has been detected in human milk. Infection through fomites cannot be excluded. Health care-associated transmission is highly unlikely if rigorous infection-control practices are in place in health care facilities. Filoviruses are not spread through the air, by water, or in general by food. Respiratory spread of virus does not occur.

The degree of viremia correlates with the clinical state. People are most infectious late in the course of severe disease, especially when copious vomiting, diarrhea, and/or bleeding are present. Transmission during the incubation period, when the person is asymptomatic, is not believed to occur. Virus may persist in a few immunologically protected sites for several weeks to months after clinical recovery, including in testicles/semen, human milk, the central nervous system, joints, and the chambers of the eye (resulting in transient uveitis and other ocular problems). Because of the risk of sexual transmission, abstinence or use of condoms is recommended for at least 9 months after recovery and possibly longer.

The 2014–2015 West Africa Ebola outbreak was the largest since the virus was first identified in 1976. Updated information on identification and current management of people traveling from areas of transmission or with contact with a person with Ebola virus infection can be found on the Centers for Disease Control and Prevention (CDC) website (**https://www.cdc.gov/vhf/ebola/index.html**).

DIAGNOSTIC TESTS

The diagnosis of filovirus infection should be considered in a person who develops a fever within 21 days of travel to an area with endemic infection. Because initial clinical manifestations are difficult to distinguish from those of more common febrile diseases, prompt laboratory testing is imperative in a suspected case. Malaria, measles, typhoid fever, Lassa fever, and dengue should be included in the differential diagnosis of a symptomatic person returning from Africa within 21 days and are much more likely than a filovirus to be the cause of fever. Filovirus disease can be diagnosed by testing of blood by reverse transcriptase-polymerase chain reaction (RT-PCR) assay, enzyme-linked immunosorbent assay (ELISA) for viral antigens or immunoglobulin (Ig) M, and virus isolation early in the disease course, with the latter being attempted only under Biosafety level-4 conditions. Viral RNA generally is detectable by RT-PCR assay within 3 to 10 days after the onset of symptoms. IgM and IgG antibodies may be used later in disease course or after recovery. Postmortem diagnosis can be made via immunohistochemical staining of skin or liver or spleen tissue. Testing generally is not performed routinely in clinical laboratories. Local and state public health department officials must be contacted and can facilitate testing at a regional certified laboratory or at the CDC.

TREATMENT

People suspected of having filovirus infection should be placed in isolation immediately, and public health officials should be notified. Management of patients with filovirus disease primarily is supportive, including oral or intravenous fluids with electrolyte repletion, vasopressors, blood products, total parenteral nutrition, and antimalarial and antimicrobial

medications when coinfections are suspected or confirmed. Volume losses can be enormous (10 L/day in adults), and some centers in the United States report better results with repletion using lactated Ringer solution rather than normal saline solution in management of adult patients. When antimicrobial agents are used to treat sepsis, the medications should have coverage for intestinal microbiota based on limited evidence of translocation of gut bacteria into the blood of patients with filovirus disease.

There currently are no specific therapies for filovirus infection. Investigational agents have been evaluated in nonhuman primates, and some candidate agents (eg, monoclonal antibody and convalescent serum products) currently are in clinical development.

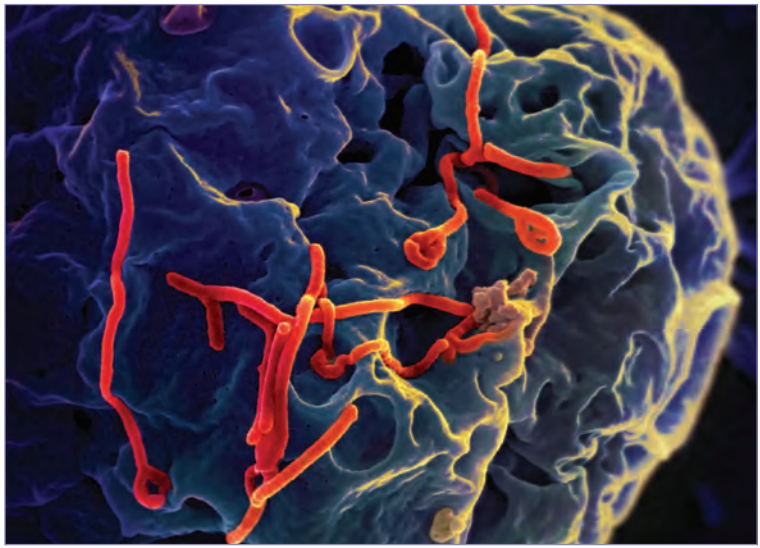


Image 60.1
Under very high magnification, this digitally colorized scanning electron micrograph depicts a number of filamentous Ebola virus particles (red) that had budded from the surface of a Vero cell (blue-gray) of the African green monkey kidney epithelial cell line. Courtesy of National Institute of Allergy and Infectious Diseases.

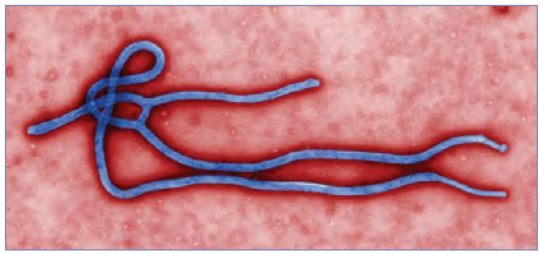


Image 60.2
Created by Centers for Disease Control and Prevention microbiologist Cynthia Goldsmith, this colorized transmission electron micrograph revealed some of the ultrastructural morphology displayed by an Ebola virus virion. Courtesy of Centers for Disease Control and Prevention/Cynthia Goldsmith.

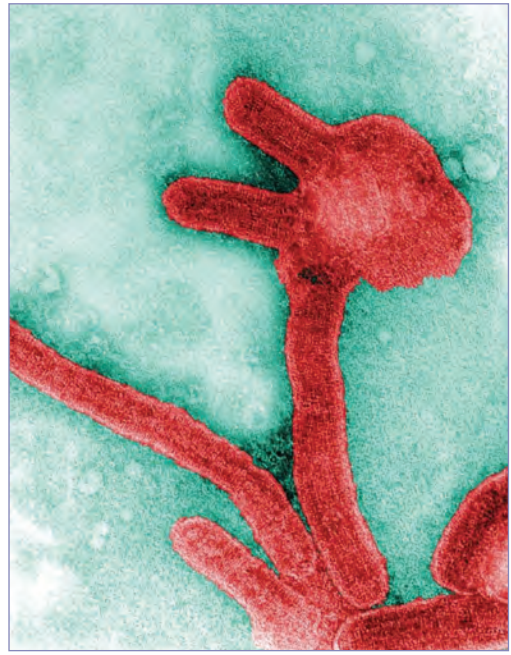


Image 60.3
This colorized negative stained transmission electron micrograph, captured by F.A. Murphy in 1968, depicts a number of Marburg virus virions, which had been grown in an environment of tissue culture cells. Marburg hemorrhagic fever is a rare, severe type of hemorrhagic fever that affects humans and nonhuman primates. Caused by a genetically unique zoonotic (ie, animalborne) RNA virus of the *Filovirus* family, its recognition led to the creation of this virus family. The 4 species of Ebola virus are the only other known members of the *Filovirus* family. After an incubation period of 5 to 10 days, onset of the disease is sudden and is marked by fever, chills, headache, and myalgia. Around the fifth day after the onset of symptoms, a maculopapular rash, most prominent on the trunk (ie, chest, back, stomach), may occur. Nausea, vomiting, chest pain, a sore throat, abdominal pain, and diarrhea may then appear. Symptoms become increasingly severe and may include jaundice, inflammation of the pancreas, severe weight loss, delirium, shock, liver failure, and multiorgan dysfunction. Because many of the signs and symptoms of Marburg hemorrhagic fever are similar to those of other infectious diseases, such as malaria or typhoid fever, diagnosis of the disease can be difficult, especially if only a single case is involved. Courtesy of Centers for Disease Control and Prevention/F.A. Murphy.

Image 60.4
This map illustrates the geographic distribution, as of October 10, 2014, of the West African Ebola outbreak and demarcates some of the salient focal points involved in the epidemiologic investigation of what became an international epidemic, including the location of Ebola treatment units, field laboratories, transit centers, and hospitals. Also indicated were the regions where there were newly active and previously active cases and areas where there were no suspected cases. The 2014 Ebola outbreak is one of the largest Ebola outbreaks in history and the first in West Africa. At the time of this map's creation, countries classified as sustaining "widespread transmission" included Guinea, Liberia, and Sierra Leone. Countries exhibiting "localized transmission" included Nigeria (Port Harcourt and Lagos), Spain (Madrid), and the United States (Dallas, TX). Finally, Senegal exhibited a single case in its capital city of Dakar. Courtesy of World Health Organization.

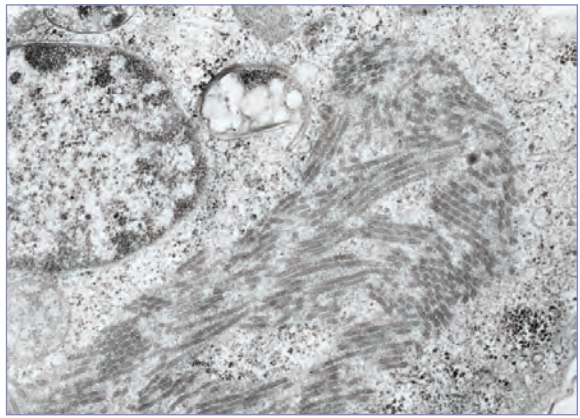


Image 60.5
This electron micrograph shows a thin section containing the Ebola virus, the causative agent for African hemorrhagic fever. The image shows an intracytoplasmic inclusion of Ebola virus nucleocapsids. Courtesy of Centers for Disease Control and Prevention.

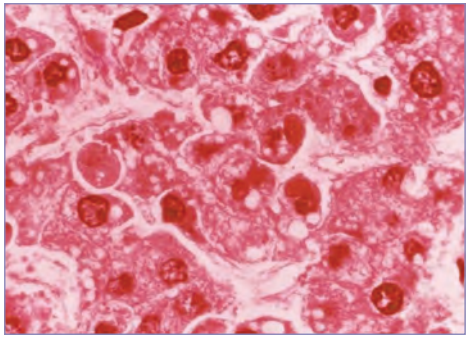


Image 60.6
Under a high magnification of ×400, this hematoxylin-eosin–stained photomicrograph depicts the cytoarchitectural changes found in a liver tissue specimen extracted from a patient with Ebola virus infection in the Democratic Republic of the Congo. This particular view reveals an acidophilic necrosis leading to the formation of a Councilman body and cytoplasmic inclusions. A steatotic (fatty change) vesicle was caught in the process of formation. Courtesy of Centers for Disease Control and Prevention.

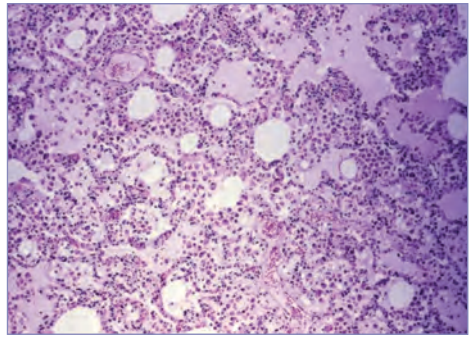


Image 60.7
This photomicrograph revealed the cytoarchitectural histopathologic changes detected in a lung biopsy tissue section from a patient with Marburg virus infection who was treated in Johannesburg, South Africa. Note the necrotic changes indicated by the breakdown of the alveolar walls resulting in pulmonary edema. There is also the presence of numerous alveolar macrophages due to the *Filovirus* infiltrate. Courtesy of Centers for Disease Control and Prevention.

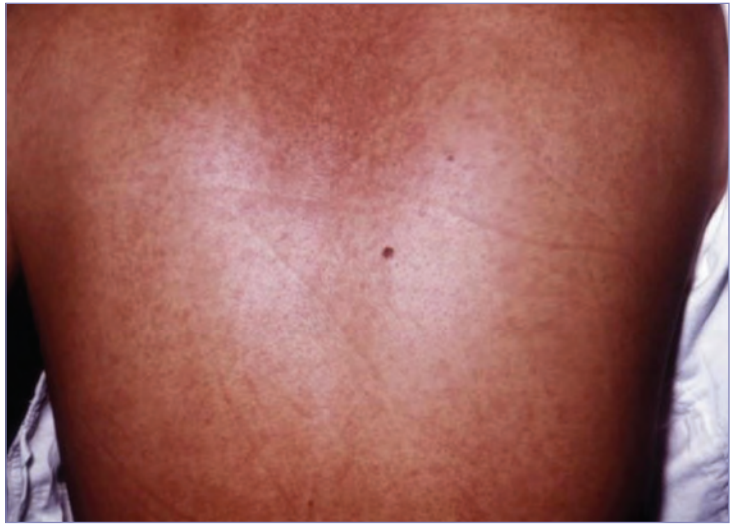


Image 60.8
This patient with Marburg virus infection presented with a measles-like rash located on her back and was hospitalized in Johannesburg, South Africa. This type of maculopapular rash, which can appear on patients with Marburg virus infection around the fifth day after the onset of symptoms, may usually be found on the patient's chest, back, and stomach. This patient's skin blanched under pressure, which is a common characteristic of a Marburg virus rash. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 61

Hepatitis A

CLINICAL MANIFESTATIONS

Hepatitis A characteristically is an acute, self-limited illness associated with fever, malaise, jaundice, anorexia, and nausea. Symptomatic hepatitis A virus (HAV) infection occurs in approximately 30% of infected children younger than 6 years; few of these children will have jaundice. Among older children and adults, infection usually is symptomatic and typically lasts several weeks, with jaundice occurring in 70% or more of cases. Signs and symptoms typically last less than 2 months, although 10% to 15% of symptomatic people have prolonged or relapsing disease lasting as long as 6 months. Fulminant hepatitis is rare but is more common in people with underlying liver disease. Chronic infection does not occur.

ETIOLOGY

HAV is a small, nonenveloped, positive-sense RNA virus with an icosahedral capsid and classified as a member of the family *Picornaviridae*, genus *Hepatovirus*.

EPIDEMIOLOGY

The most common mode of transmission is person to person, resulting from fecal contamination and oral ingestion (ie, the fecal-oral route). In resource-limited countries where infection is endemic, most people are infected during the first decade of life. Rates of HAV decreased drastically in children after universal infant vaccination was recommended. Rates of reported hepatitis A cases in the United States were 0.4/100,000 population in 2015, which has not changed significantly since 2011, when the rate of infections was at a historic low. Vaccine coverage for children 19 to 35 months of age is high. Significant decreases in anti-HAV seroprevalence in older adults (40 years and older) have occurred because of reduced exposure to HAV earlier in life since the introduction of universal infant vaccination, which has resulted in an increasing proportion of adults in the United States being susceptible to hepatitis A. The majority of HAV cases are in adults 20 years and older. The mean age of people hospitalized for HAV infection increased significantly between 2002 and 2011 (mean age, 37.6 years in 2002–2003, compared with 45.5 years in 2010–2011).

Recognized risk factors for HAV infection include close personal contact with a person infected with HAV, international travel, household or personal contact with a newly arriving international adoptee, a recognized foodborne outbreak, men who have sex with men, and use of illegal drugs. Community-wide epidemics have been observed infrequently in recent years; however, outbreaks have been a problem in countries with low incidence of disease after food was imported from countries where HAV is endemic. Waterborne outbreaks are rare and are typically associated with sewage-contaminated or inadequately treated water. Health care-associated outbreaks have occurred through blood transfusions and liver transplantation.

Patients infected with HAV are most infectious during the 1 to 2 weeks before onset of jaundice or elevation of liver enzymes, when concentration of virus in the stool is highest. The risk of transmission subsequently diminishes and is minimal by 1 week after onset of jaundice. However, HAV can be detected in stool for longer periods, especially in neonates and young children.

The **incubation period** is 15 to 50 days, with a mean of 28 days.

DIAGNOSTIC TESTS

Serologic tests for HAV-specific total antibody (ie, immunoglobulin [Ig] G plus IgM), IgG only anti-HAV, and IgM only anti-HAV are available commercially, primarily in enzyme immunoassay format. A single total or IgG anti-HAV test does not have diagnostic value for acute infection. The presence of serum IgM anti-HAV indicates current or recent infection, although false-positive results may occur. IgM anti-HAV generally is included in most acute hepatitis serologic test panels offered by hospital or reference laboratories. IgM anti-HAV is detectable in up to 20% of vaccine recipients when measured 2 weeks after hepatitis A immunization. In most infected people, serum IgM anti-HAV becomes detectable 5 to 10 days before onset of symptoms and declines to undetectable

concentrations within 6 months after infection. People who have positive test results for IgM anti-HAV more than 1 year after infection have been reported. IgG anti-HAV is detectable shortly after appearance of IgM. A positive total anti-HAV (ie, IgM and IgG) test result with a negative IgM anti-HAV test result indicates immunity from past infection or vaccination. Polymerase chain reaction assays for hepatitis A are available and may be considered for detection of very early acute infections and for confirmation of questionable IgM anti-HAV results.

TREATMENT

Supportive.

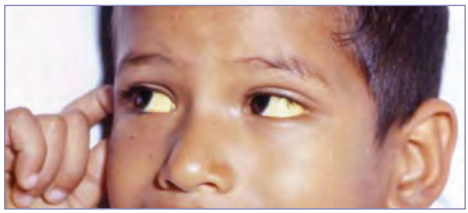


Image 61.1
Acute hepatitis A infection with scleral icterus in a 10-year-old boy. Courtesy of Edgar O. Ledbetter, MD, FAAP.

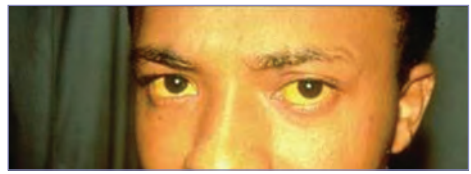


Image 61.2
Hepatitis A infection has caused this man's skin and the whites of his eyes to turn yellow. Other symptoms of hepatitis A can include loss of appetite, abdominal pain, nausea or vomiting, fever, headaches, and dark urine.

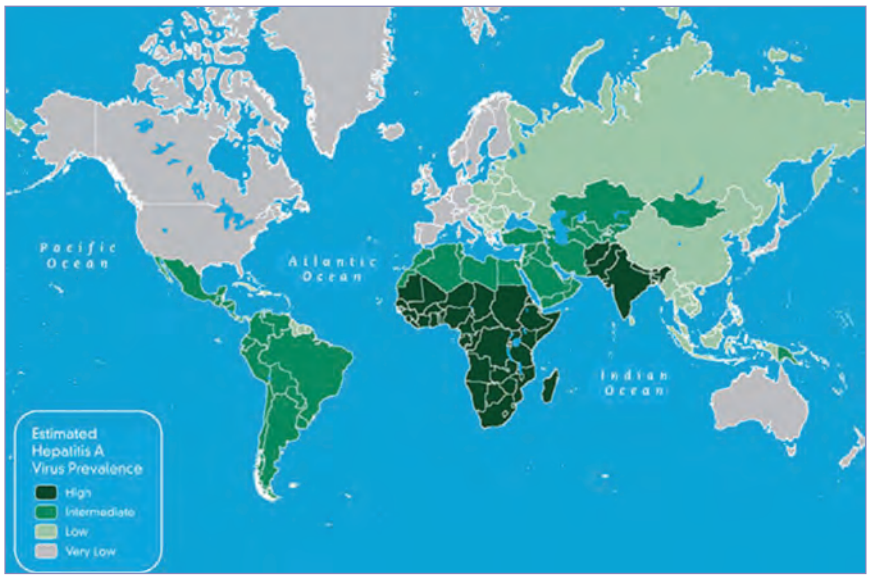


Image 61.3
Estimated prevalence of hepatitis A virus. Courtesy of Centers for Disease Control and Prevention.

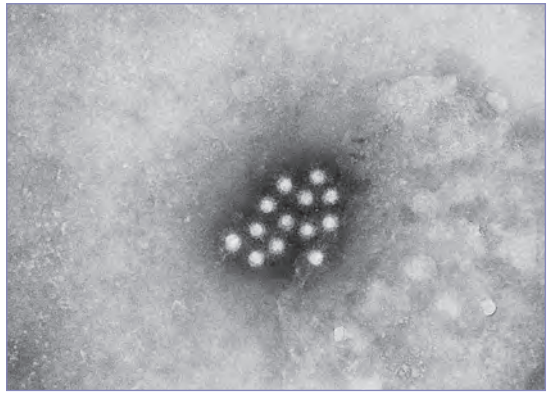


Image 61.4
An electron micrograph of the hepatitis A virus, an RNA virus classified as a member of the picornavirus group. Courtesy of Centers for Disease Control and Prevention.

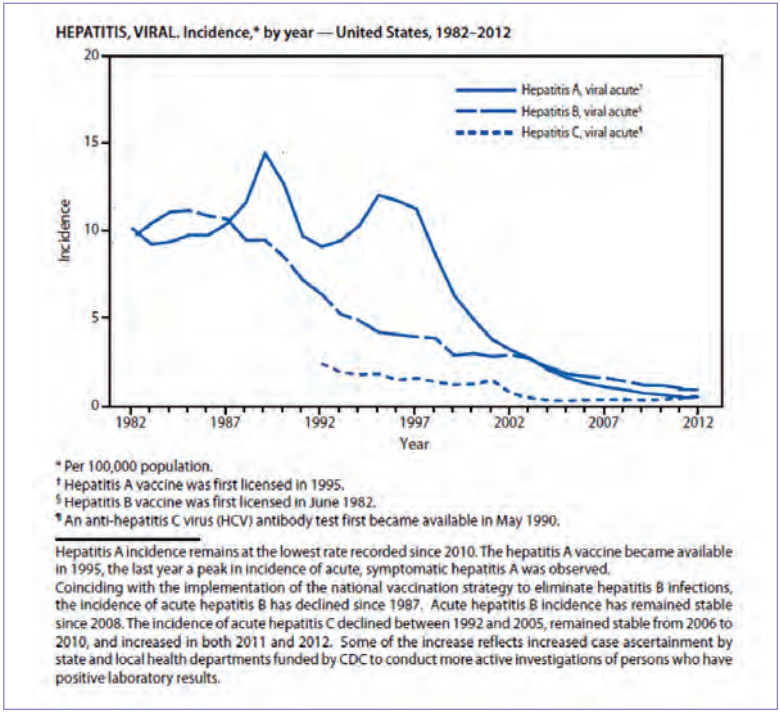


Image 61.5
Hepatitis, viral. Incidence, by year—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

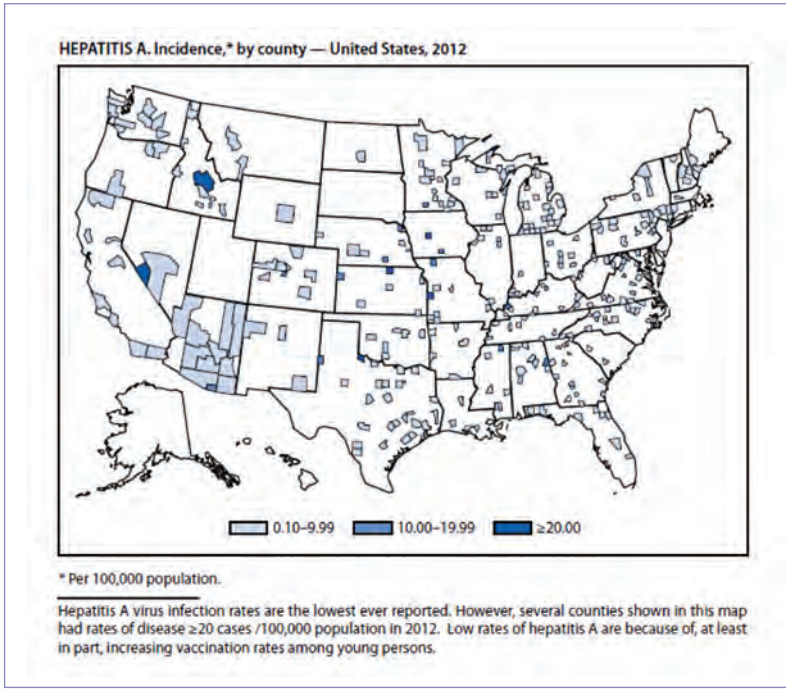


Image 61.6
Hepatitis A. Incidence, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 62

Hepatitis B

CLINICAL MANIFESTATIONS

People acutely infected with hepatitis B virus (HBV) may be asymptomatic or symptomatic. The likelihood of developing symptoms of acute hepatitis is age dependent: less than 1% of infants younger than 1 year, 5% to 15% of children 1 through 5 years of age, and 30% to 50% of people older than 5 years are symptomatic, although few data are available for adults older than 30 years. The spectrum of signs and symptoms is varied and includes subacute illness with nonspecific symptoms (eg, anorexia, nausea, or malaise), clinical hepatitis with jaundice, or fulminant hepatitis. Extrahepatic manifestations, such as arthralgia, arthritis, macular rashes, thrombocytopenia, polyarteritis nodosa, or glomerulonephritis, can occur early and may precede jaundice. Papular acrodermatitis (Gianotti-Crosti syndrome) is an extrahepatic manifestation of infection attributable to several viral infections. However, since the advent of universal HBV immunization in infants, papular acrodermatitis attributable to HBV is rare; it is more commonly caused by Epstein-Barr virus and less commonly by enteroviruses, cytomegalovirus, parvovirus B19, and others. Acute HBV infection cannot be distinguished from other forms of acute viral hepatitis by clinical signs and symptoms or nonspecific laboratory findings.

Chronic HBV infection is defined as persistence in serum for at least 6 months of any one of the following: hepatitis B surface antigen (HBsAg), HBV DNA, or hepatitis B e antigen (HBeAg). Chronic HBV infection is likely in the presence of HBsAg, HBV DNA, or HBeAg in serum from a person who tests negative for antibody of the immunoglobulin (Ig) M subclass to hepatitis B core antigen (IgM anti-HBc).

Age at the time of infection is the primary determinant of risk of progressing to chronic infection. Up to 90% of infants infected perinatally or in the first year of life will develop chronic HBV infection. Between 25% and 50% of children infected between 1 and 5 years of age become chronically infected, whereas 5% to 10% of infected older children and adults develop chronic HBV infection. Patients who become HBV infected while immunosuppressed or with an underlying chronic illness (eg, end-stage renal disease) have an increased risk of developing chronic infection. In the absence of treatment, up to 25% of infants and children who acquire chronic HBV infection will die prematurely from HBV-related hepatocellular carcinoma or cirrhosis.

The clinical course of untreated chronic HBV infection varies according to the population studied, reflecting differences in age at acquisition, rate of loss of HBeAg, and possibly HBV genotype. Most children have asymptomatic infection. Perinatally infected children usually have normal or minimally elevated alanine transaminase (ALT) concentrations and minimal or mild liver histologic abnormalities, with detectable HBeAg and high HBV DNA concentrations (≥20,000 IU/mL) for years to decades after initial infection. Children with chronic HBV may exhibit growth impairment. Chronic HBV infection acquired during later childhood or adolescence usually is accompanied by more active liver disease and increased serum aminotransferase concentrations. Patients with detectable HBeAg (*HBeAg-positive chronic hepatitis B*) usually have high concentrations of HBV DNA and HBsAg in serum and are more likely to transmit infection. Because HBV-associated liver injury is thought to be immune mediated, in people coinfected with human immunodeficiency virus (HIV) and HBV, the return of immune competence with antiretroviral treatment of HIV infection may lead to a reactivation of HBV-related liver inflammation and damage. Over time (years to decades), HBeAg becomes undetectable in many chronically infected people. This transition often is accompanied by development of antibody to HBeAg (anti-HBe) and decreases in serum HBV DNA and serum aminotransferase concentrations and may be preceded by a temporary exacerbation of liver disease. These patients have **inactive chronic infection** but still may have exacerbations of hepatitis. Serologic reversion (reappearance of HBeAg) is more common if loss of HBeAg is not accompanied by development of anti-HBe; reversion with loss of anti-HBe also can occur.

Some patients who lose HBeAg may continue to have ongoing histologic evidence of liver damage and moderate to high concentrations of HBV DNA (*HBeAg-negative chronic hepatitis B*). Patients with histologic evidence of chronic HBV infection, regardless of HBeAg status, remain at higher risk of death attributable to liver failure compared with HBV-infected people with no histologic evidence of liver inflammation and fibrosis.

Resolved hepatitis B is defined as clearance of HBsAg, normalization of serum aminotransferase concentrations, and development of antibody to HBsAg (anti-HBs). Chronically infected adults clear HBsAg and develop anti-HBs at the rate of 1% to 2% annually; during childhood, the annual clearance rate is less than 1%. Reactivation of resolved chronic infection is possible if these patients become immunosuppressed and also is well reported among HBsAg-positive patients receiving anti-tumor necrosis factor agents or disease-modifying antirheumatic drugs (12% of patients).

ETIOLOGY

HBV is a partially double-stranded DNA-containing 42-nm-diameter enveloped virus in the family *Hepadnaviridae*. Important components of the viral particle include an outer lipoprotein envelope containing HBsAg and an inner nucleocapsid consisting of hepatitis B core antigen (HBcAg).

EPIDEMIOLOGY

HBV is transmitted through infected blood or body fluids. Although HBsAg has been detected in multiple body fluids including human milk, saliva, and tears, the most potentially infectious include blood, serum, semen, vaginal secretions, and cerebrospinal, synovial, pleural, pericardial, peritoneal, and amniotic fluids. People with chronic HBV infection are the primary reservoirs for infection. Common modes of transmission include percutaneous and mucosal exposure to infectious body fluids; sharing or using nonsterilized needles, syringes, or glucose monitoring equipment or devices; sexual contact with an infected person; perinatal exposure to an infected mother; and household exposure to a person with chronic HBV infection. The risk of HBV acquisition when a susceptible child bites a child who has chronic HBV infection is unknown. A theoretical risk exists if HBsAg-positive blood enters the oral cavity of the biter, but transmission by this route has not been reported. Transmission by transfusion of contaminated blood or blood products is rare in the United States because of routine screening of blood donors and viral inactivation of certain blood products before administration.

Perinatal transmission of HBV is highly efficient and usually occurs from blood exposures during labor and delivery. In utero transmission accounts for less than 2% of all vertically transmitted HBV infections in most studies. Without postexposure prophylaxis, the risk of an infant acquiring HBV from an infected mother as a result of perinatal exposure is 70% to 90% for infants born to mothers who are HBsAg and HBeAg positive; the risk is 5% to 20% for infants born to HBsAg-positive but HBeAg-negative mothers.

Person-to-person spread of HBV can occur in settings involving interpersonal contact over extended periods, such as in a household with a person with chronic HBV infection. In regions of the world with a high prevalence of chronic HBV infection, transmission between children in household settings may account for a substantial amount of transmission. The precise mechanisms of transmission from child-to-child are unknown; however, frequent interpersonal contact of nonintact skin or mucous membranes with blood-containing secretions, open skin lesions, or blood-containing saliva are potential means of transmission. Transmission from sharing inanimate objects, such as razors or toothbrushes, also may occur. HBV can survive in the environment for 7 or more days but is inactivated by commonly used disinfectants, including household bleach diluted 1:10 with water. HBV is not transmitted by the fecal-oral route.

Transmission among children born in the United States is unusual because of high coverage with hepatitis B (HepB) vaccine administered at birth. Screening mothers during pregnancy for HBV infection allows for additional immunoprophylaxis with Hepatitis B Immune Globulin (HBIG), which, when administered with the hepatitis B vaccine in the immediate newborn period, enhances

prevention of mother-to-infant HBV transmission. The risk of HBV transmission is higher in children who have not completed a vaccine series, children undergoing hemodialysis, institutionalized children with developmental disabilities, and children emigrating from regions and countries with endemic HBV (eg, Southeast Asia, China, Africa). Person-to-person transmission has been reported in child care settings, but risk of transmission in child care facilities in the United States has become negligible as a result of high infant hepatitis B immunization rates.

Acute HBV infection is reported most commonly among adults 30 through 49 years of age in the United States. Since 1990, the incidence of acute HBV infection has decreased in all age categories, with a 98% decline in children younger than 19 years and a 93% decline in young adults 20 through 29 years of age, with most of the decrease among people 20 through 24 years of age. People at high risk for acute hepatitis B virus infection include people who inject drugs, people with multiple sexual partners, men who have sex with men, and those who reported surgery during the 6 weeks to 6 months before onset of symptoms. Others at increased risk include people with occupational exposure to blood or body fluids, staff of institutions and nonresidential child care programs for children with developmental disabilities, patients undergoing hemodialysis, and sexual or household contacts of people with an acute or chronic infection. Approximately 62% of case reports in 2014 with risk exposure or behavior information did not have a readily identifiable risk characteristic. HBV infection in adolescents and adults is associated with other sexually transmitted infections. Investigations have indicated an increased risk of HBV infection among adults with diabetes mellitus. Outbreaks in nonhospital health care settings, including assisted-living facilities and nursing homes, highlight the increased risk among people with diabetes mellitus undergoing assisted blood glucose monitoring.

The prevalence of HBV infection and patterns of transmission vary markedly throughout the world (Table 62.1). Approximately 45% of people worldwide live in regions of high HBV

Table 62.1
Estimated International HBsAg Prevalence[a]

Region	Estimated HBsAg Prevalence[b]
North America	0.1%
Mexico and Central America	0.3%
South America	0.7%
Western Europe	0.7%
Australia and New Zealand	0.9%
Caribbean (except Haiti)	1.0%
Eastern Europe and North Asia	2.8%
South Asia	2.8%
Middle East	3.2%
Haiti	5.6%
East Asia	7.4%
Southeast Asia	9.1%
Africa	9.3%
Pacific Islands	12.0%

HBsAg indicates hepatitis B surface antigen.
[a]Centers for Disease Control and Prevention. 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.* 2006;55(RR-16):1–33.
[b]Level of HBV endemicity defined as high (≥8%), intermediate (2%–7%), and low (<2%).

endemicity, where the prevalence of chronic HBV infection is 8% or greater. Historically in these regions, most new HBV infections occurred as a result of perinatal or early childhood infections. In regions of intermediate HBV endemicity, where the prevalence of HBV infection is 2% to 7%, multiple modes of transmission (ie, perinatal, household, sexual, injection drug use, and health care associated) contribute to the burden of infection. In countries with low endemicity, where chronic HBV infection prevalence is less than 2% and where routine immunization has been adopted, new infections increasingly occur among unimmunized age groups. Many people born in countries with high endemicity live in the United States. Infant immunization programs in some of these countries have, in recent years, greatly reduced the seroprevalence of HBsAg, but many other countries with endemic HBV have yet to implement widespread routine childhood hepatitis B immunization programs.

The **incubation period** for acute HBV infection is 45 to 160 days, with an average of 90 days.

DIAGNOSTIC TESTS

Serologic protein antigen tests are available commercially to detect HBsAg and HBeAg. Serologic antibody assays also are available for detection of anti-HBs, total anti-HBc, IgM anti-HBc, and anti-HBe (Figures 62.1 and 62.2). In addition, nucleic acid amplification testing (NAAT), polymerase chain reaction (PCR) assay, and branched DNA methods as well as hybridization assays are available to detect and quantify HBV DNA in plasma or serum. At least 2 PCR assays for quantitative detection of HBV DNA are used to monitor patients with chronic HBV infection and to evaluate their response to treatment regimens. The assays differ in their limits of detection, dynamic range, and target gene sequences detected. Because of variability in the different assays, it is best to use the same manufacturer's assay performed in the same laboratory to monitor an individual patient's HBV load. Tests to quantify HBsAg and HBeAg currently are being developed but are not yet available commercially.

HBsAg is detectable during acute and chronic infection. If HBV infection is self-limited, HBsAg disappears in most patients within a few weeks to several months after infection, followed by appearance of anti-HBs. The time between disappearance of HBsAg and appearance of anti-HBs is termed the window period of infection. During the window period, the only marker of acute infection is IgM anti-HBc, which is highly specific for establishing the diagnosis of acute infection. However, IgM anti-HBc usually is not present in infants infected perinatally. People with chronic HBV infection have circulating HBsAg and circulating total anti-HBc; in a minority of chronically infected individuals, anti-HBs also is present. Both anti-HBs and total anti-HBc are present in people with resolved infection, whereas anti-HBs alone is present in people immunized with hepatitis B vaccine. The presence of HBeAg in serum correlates with higher concentrations of HBV DNA and greater infectivity. Tests for HBeAg and HBV DNA are useful in selection of candidates to receive antiviral therapy and to monitor response to therapy.

Transient HBsAg antigenemia can occur following receipt of HepB vaccine, with HBsAg being detected as early as 24 hours after and up to 3 weeks following administration of the vaccine.

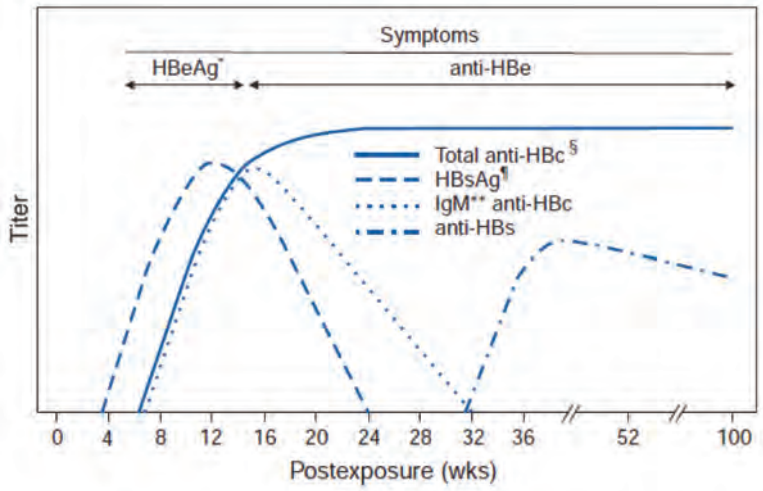
TREATMENT

No specific therapy for uncomplicated acute HBV infection is available, and acute HBV infection usually does not warrant referral to a hepatitis specialist unless there is progression to acute liver failure. In that situation, treatment with a nucleoside or nucleotide analogue is indicated. Acute HBV infection may be difficult to distinguish from reactivation of HBV. If reactivation is a possibility, referral to a hepatitis specialist would be warranted.

Children and adolescents who have chronic HBV infection are at risk of developing serious liver disease, including primary hepatocellular carcinoma (HCC), with advancing age and, therefore, should receive hepatitis A vaccine. Although the peak incidence of primary HCC attributable to HBV infection is in the fifth decade of life, HCC occurs in children as young as 6 years who became infected perinatally or

Figure 62.1

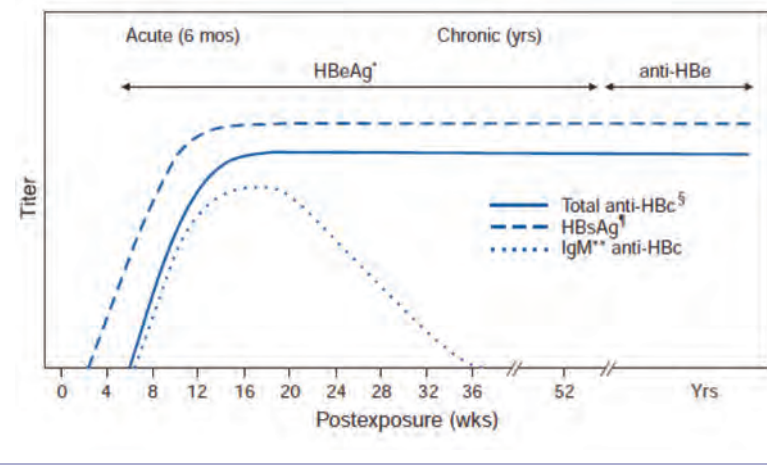
Typical serologic course of acute hepatitis B virus infection with recovery.



* Hepatitis B e antigen.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
**Immunoglobulin M.
From Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.

Figure 62.2

Typical serologic course of acute hepatitis B virus (HBV) infection with progression to chronic HBV infection.



* Hepatitis B e antigen.
§ Antibody to hepatitis B core antigen.
¶ Hepatitis B surface antigen.
**Immunoglobulin M.
From Centers for Disease Control and Prevention. Recommendations for identification and public health management of persons with chronic hepatitis B virus infection. *MMWR Recomm Rep.* 2008;57(RR-8):1-20.

in early childhood. Several algorithms have been published describing the initial evaluation, monitoring, and criteria for treatment. Children with chronic HBV infection should be screened periodically for hepatic complications using serum aminotransferase tests, alpha-fetoprotein concentration, and abdominal ultrasonography. Definitive recommendations on the frequency and indications for specific tests are not yet available because of lack of data on their reliability in predicting sequelae. Patients with serum ALT concentrations persistently exceeding the upper limit of normal and patients with an increased serum alpha-fetoprotein concentration or abnormal findings on abdominal ultrasonography should be referred to a specialist in the management of chronic HBV infection.

The goal of treatment in chronic HBV infection is to prevent progression to cirrhosis, hepatic failure, and HCC. Current indications for treatment of chronic HBV infection include evidence of ongoing HBV viral replication, as indicated by the presence for longer than 6 months of serum HBV DNA greater than 20,000 IU/mL without HBeAg positivity, greater than 2,000 IU/mL with HBeAg positivity, and elevated serum ALT concentrations for longer than 6 months or evidence of chronic hepatitis on liver biopsy. Children without necroinflammatory liver disease and children with immunotolerant chronic HBV infection (ie, normal ALT concentrations despite the presence of HBV DNA) usually do not warrant antiviral therapy. Treatment response is measured by biochemical, virologic, and histologic response. An important consideration in the choice of treatment is to avoid selection of antiviral-resistant mutations.

The FDA has approved 3 nucleoside analogues (entecavir, lamivudine, and telbivudine), 2 nucleotide analogues (tenofovir and adefovir), and 2 interferon-alfa drugs (interferon alfa-2b and pegylated interferon alfa-2a) for treatment of chronic HBV infection in adults. Tenofovir, entecavir, and pegylated interferon alfa-2a are preferred in adults as first-line therapy because of the lower likelihood of developing antiviral resistance mutations over long-term therapy. Of these, FDA licensure in the pediatric population is as follows: interferon alfa-2b, ≥1 year of age; lamivudine and entecavir, ≥2 years of age; adefovir and tenofovir disproxil fumarate, ≥12 years of age; and telbivudine, ≥16 years of age. Pediatric trials of telbivudine, tenofovir, and pegylated interferon currently are underway. Pegylated interferon alfa-2a is not approved for children with chronic HBV but is approved for children ≥5 years of age to treat chronic hepatitis C infection.

The optimal agent(s) and duration of therapy for chronic HBV infection in children remain unclear. There are few large randomized controlled trials of antiviral therapies for chronic hepatitis B in childhood. Studies indicate that approximately 17% to 58% of children with increased serum aminotransferase concentrations who are treated with interferon alfa-2b for 6 months lose HBeAg, compared with approximately 8% to 17% of untreated controls. Response to interferon-alfa is better for children from Western countries (20%–58%) as compared with Asian countries (17%). Children from Asian countries with HBV infection are more likely to have acquired infection perinatally, have a prolonged immune-tolerant phase of infection, and be infected with HBV genotype C. All 3 of these factors are associated with lower response rates to interferon-alfa. Children with chronic HBV infection who were treated with lamivudine had higher rates of virologic response (loss of detectable HBV DNA and loss of HBeAg) after 1 year of treatment than did children who received placebo (23% versus 13%). Resistance to lamivudine can develop during treatment and may occur early. The high rates of lamivudine resistance (~70% after 3 years of therapy) have decreased enthusiasm for the use of this drug. Children coinfected with HIV and HBV should receive the lamivudine dose approved for treatment of HIV. Consultation with health care professionals with expertise in treating chronic hepatitis B in children is recommended.

Image 62.1
This female Cambodian patient presented with a distended abdomen due to a hepatoma resulting from chronic hepatitis B infection. Courtesy of Centers for Disease Control and Prevention.

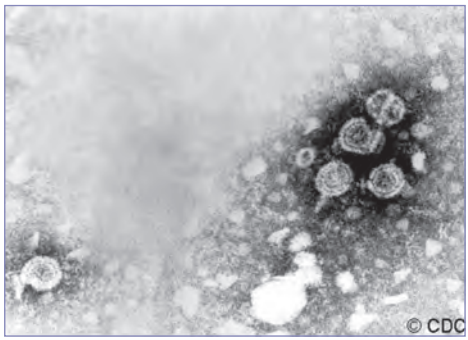


Image 62.3
Transmission electron micrograph of hepatitis B virions, also known as Dane particles. Courtesy of Centers for Disease Control and Prevention.

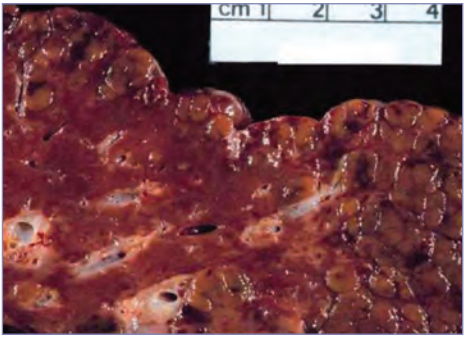


Image 62.2
Section of liver damaged by hepatitis B virus. Note the enlarged cells and blistering of the capsular surface. Courtesy of Immunization Action Coalition.

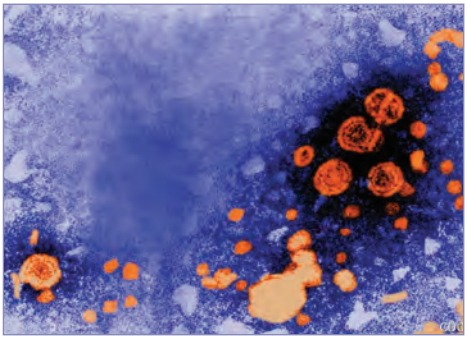


Image 62.4
This transmission electron micrograph revealed the presence of hepatitis B virions. Courtesy of Centers for Disease Control and Prevention/Erskine Palmer, MD.

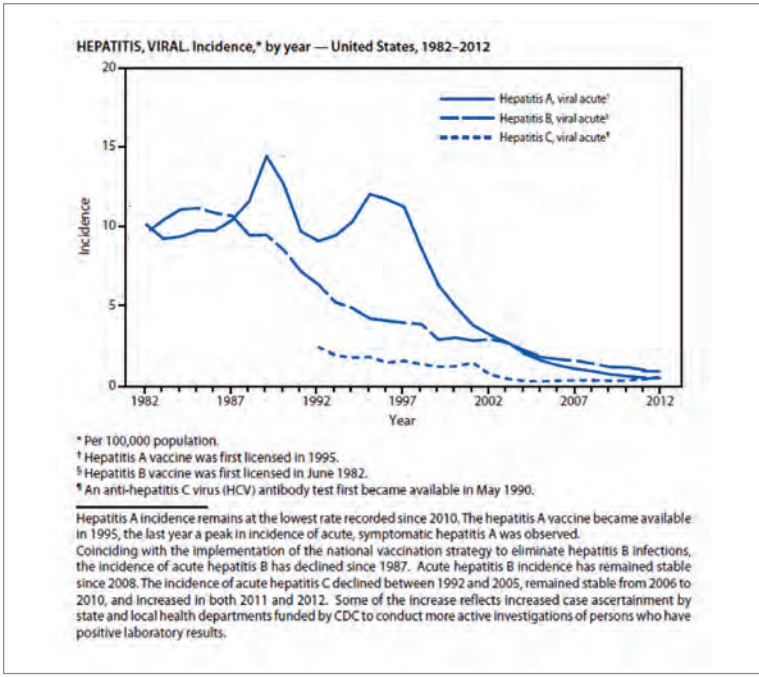


Image 62.5
Hepatitis, viral. Incidence, by year—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

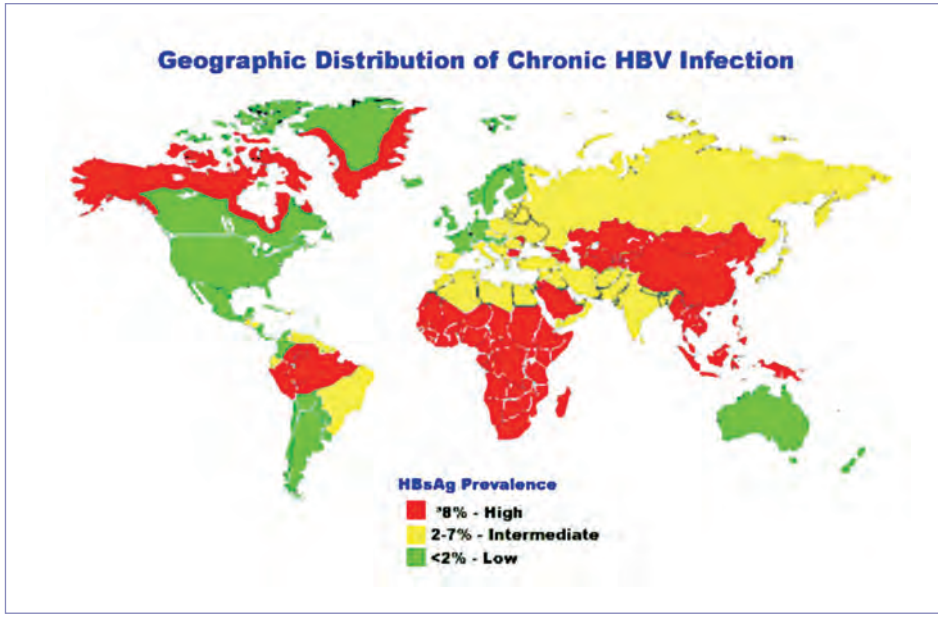


Image 62.6
World map for hepatitis B endemicity. Courtesy of Centers for Disease Control and Prevention.

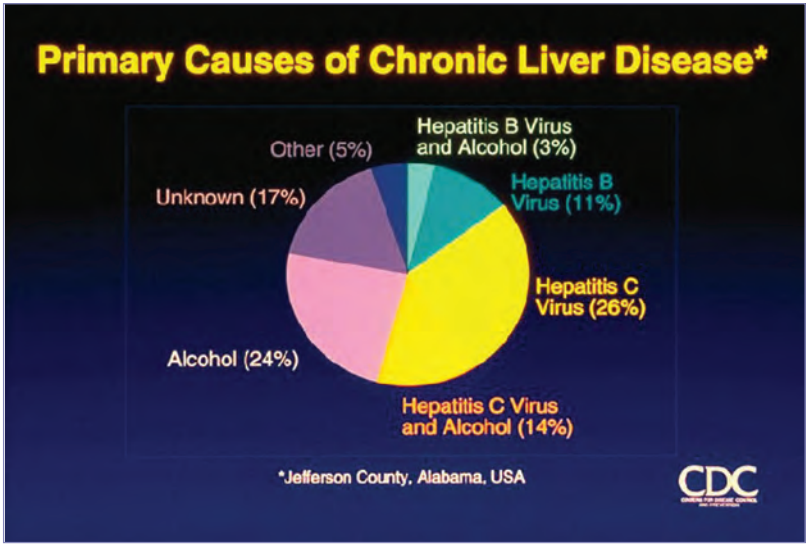


Image 62.7
Pie chart showing causes of chronic liver disease in residents of Jefferson County, AL. Hepatitis B and C viruses contributed to most cases of chronic liver disease in this population. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 63

Hepatitis C

CLINICAL MANIFESTATIONS

Signs and symptoms of hepatitis C virus (HCV) infection are indistinguishable from those of hepatitis A or hepatitis B virus infections. Acute disease tends to be mild and insidious in onset, and most infections are asymptomatic. Jaundice occurs in less than 20% of patients with HCV infection, and abnormalities in serum alanine transaminase concentrations generally are less pronounced than in patients with hepatitis B virus infection. Persistent infection with HCV occurs in up to 80% of infected children, even in the absence of biochemical evidence of liver disease. Most children with chronic infection are asymptomatic. Although chronic HCV infection develops in approximately 75% to 85% of infected adults, limited data indicate that chronic HCV infection and cirrhosis occur less commonly in children, in part because of the usually indolent nature of infection in pediatric patients. Liver failure secondary to HCV infection is one of the leading indications for liver transplantation among adults in the United States.

ETIOLOGY

HCV is a small, single-stranded, positive-sense RNA virus and is a member of the family *Flaviviridae* in the genus *Hepacivirus*. At least 7 HCV genotypes exist with more than 50 subtypes. Distribution of genotypes and subtypes varies by geographic location, with genotype 1a being the most common in the United States.

EPIDEMIOLOGY

The incidence of acute symptomatic HCV infection in the United States was 0.8 per 100,000 in 2015. After asymptomatic infection and underreporting were considered, approximately 30,000 new cases were estimated to have occurred in 2014. For all age groups, the incidence of HCV infection decreased markedly in the United States since the 1990s and reached its lowest incidence in 2006–2010. However, after 2010, there was a 2.6-fold increase in reported cases of acute HCV in the United States by 2014. This increase was mostly seen in white, nonurban young people with a history of using injection drugs and opioid agonists such as oxycodone. A substantial burden of disease still exists in the United States because of the propensity of HCV to establish chronic infection and the high incidence of acute HCV infection through the 1980s. The prevalence of HCV infection in the general population of the United States is estimated at 1.3%, equating to an estimated 3.5 million people in the United States who have chronic HCV infection. Seroprevalence varies among populations according to risk factors. The pediatric prevalence of HCV in 1999–2002 was approximately 0.1%, although the numbers of HCV infections in the younger age groups were too small for reliable estimates. Worldwide, the prevalence of chronic HCV infection is highest in northern Africa, the Middle East, and parts of Asia.

HCV is transmitted primarily through percutaneous (parenteral) exposures to infectious blood that can result from injection drug use, needlestick injuries, and inadequate infection control in health care settings. The most common risk factors for adults to acquire infection are injection drug use or receipt of blood products before 1992. The most common route of infection for children is maternal-fetal transmission. The current risk of HCV infection after blood transfusion in the United States is estimated to be less than 1 per 2 million units transfused because of exclusion of high-risk donors and of HCV-positive units after antibody testing as well as screening of pools of blood units by nucleic acid amplification test (NAAT). All intravenous and intramuscular Immune Globulin products available commercially in the United States undergo an inactivation procedure for HCV or are documented to be HCV RNA negative before release.

Approximately 60% of acute HCV cases reported to public health authorities are in acknowledged injection drug users who have shared needles or injection paraphernalia. For reported chronic HCV cases for which age is known, 63.5% were among people older than 40 years, and almost all infected people are outside the pediatric age range. Data from recent multicenter, population-based cohort studies indicate that approximately one third of young injection drug users 18 to 30 years of age are infected with HCV. People with

sporadic percutaneous exposures, such as health care professionals (approximately 1% of cases), may be infected. Approximately half of the 18,000 people with hemophilia who received transfusions before adoption of heat treatment of clotting factors in 1987 are HCV-seropositive. Also, more recently appreciated has been the number of infections acquired in the health care setting, especially nonhospital clinics where infection control and needle and intravenous hygienic procedures have not been practiced strictly. Prevalence is high among people with frequent but smaller direct percutaneous exposures, such as patients receiving hemodialysis (10%–20%).

Sexual transmission of HCV between monogamous heterosexual partners is extremely rare. HCV virus has been identified in semen. However, studies show that the risk for HCV transmission is greater for parenteral transmission than sexual transmission. The risk for HCV acquisition by sexual transmission is increased with a high number of sexual partners, group sex, and coinfection with human immunodeficiency virus (HIV). Injection drug users may have a greater number of sex partners, so the role of sexual transmission is not fully understood. Sexual transmission of HCV among people coinfected with HIV has been described between HIV-infected men who have sex with men or HIV-infected heterosexual women.

Transmission among family contacts is uncommon but can occur from direct or inapparent percutaneous or mucosal exposure to blood.

Seroprevalence among pregnant women in the United States has been estimated at approximately 1% to 2%. The risk of perinatal transmission averages 5% to 6%, and transmission occurs only from women who are HCV RNA positive at the time of delivery. The exact timing of HCV transmission from mother to infant is not established. Factors that increase perinatal transmission include internal fetal monitoring, vaginal lacerations, and prolonged rupture of membranes (>6 hours). The method of delivery has no effect on perinatal infection risk. Serum antibody to HCV (anti-HCV) and HCV RNA have been detected in colostrum, but the risk of HCV transmission is similar in breastfed and formula-fed infants. Breastfeeding is safe as long as mother's nipples are not cracked or bleeding. When nipples are cracked or bleeding, mothers should stop breastfeeding, pump and discard their milk, and resume breastfeeding when the nipples have healed. Maternal coinfection with (untreated) HIV has been associated with increased risk of perinatal transmission of HCV, with transmission rates between 10% and 20%; transmission depends in part on the concentration of HCV RNA in the mother's blood.

The **incubation period** for HCV infection averages 6 to 7 weeks, range 2 weeks to 6 months. The time from exposure to development of viremia generally is 1 to 2 weeks.

DIAGNOSTIC TESTS

The 2 types of tests available for laboratory diagnosis of HCV infections are immunoglobulin (Ig) G antibody enzyme immunoassays (EIA) or chemiluminescent immunoassays (CIA) for HCV and NAATs to detect HCV RNA. The diagnosis of HCV infection usually is made by serologic testing. Third-generation immunoassays cleared by the US Food and Drug Administration (FDA) are at least 97% sensitive and more than 99% specific. Final results are reported as reactive when at least 2 replicates are positive. Some of the newer assays with high performance allow for reporting of initial possible results without repeat testing. In June 2010, the FDA approved for use in people 15 years and older the OraQuick rapid blood test, which uses a test strip that produces a blue line within 20 minutes if anti-HCV antibodies are present. False-negative results early in the course of acute infection can result from any of the HCV serologic tests because of the prolonged interval between exposure and onset of illness and seroconversion. In a clinical setting where acute HCV infection is considered likely and the initial immunoassay result is negative, repeat testing with a third-generation immunoassay or NAAT should be performed. Within 15 weeks after exposure and within 5 to 6 weeks after onset of hepatitis, 80% of patients will have positive test results for serum anti-HCV antibody. Among infants born to anti-HCV–positive mothers, passively acquired maternal antibody may persist for up to 18 months.

NAATs for qualitative detection of HCV RNA are available commercially and recommended as follow-up for patients with a positive HCV serologic test result. HCV RNA can be detected in serum or plasma within 1 to 2 weeks after exposure to the virus and weeks before onset of liver enzyme abnormalities or appearance of anti-HCV antibody. Assays for detection of HCV RNA are used commonly in clinical practice to: (1) detect HCV infection after needlestick or transfusion and before seroconversion; (2) identify anti-HCV–positive patients with active infection who are viremic; (3) identify infection in infants early in life (ie, perinatal transmission) when maternal antibody interferes with ability to detect antibody produced by the infant; and (4) monitor patients receiving antiviral therapy. However, false-positive and false-negative results of NAATs can occur from improper handling, storage, and contamination of test specimens. Viral RNA may be detected intermittently in acute infection (ie, in the first 6 or 12 months following infection); thus, a single negative assay result is not conclusive if performed during this acute infection period. Highly sensitive quantitative assays for measuring the concentration of HCV RNA have largely replaced qualitative assays. Quantitative RNA and genotyping assays of HCV are useful for determination of drug treatment regimens and duration of treatment. HCV genotyping has become extremely important in determining which direct-acting antiviral agents should be used in individual patients.

Because perinatally HCV-infected infants have a low risk of HCV acquisition, they usually do not exhibit symptoms for years, and there currently are no antiviral therapies available in the first 2 years of life, assessment of HCV infection may rely on serologic testing at 18 months of age.

TREATMENT

Patients with a diagnosis of HCV infection should be referred to a pediatric infectious disease specialist or gastroenterologist for clinical monitoring and consideration of enrollment into clinical trials of direct-acting oral hepatitis C antiviral therapy when available. Traditional interferon and ribavirin-based therapies are expensive, can have significant adverse reactions, and yield variable virologic response rates.

A number of highly effective interferon-free direct-acting antiviral drug regimens have been FDA approved for adults and are the current standard of care therapy for HCV in adults. These drugs are all oral, usually taken once daily, rarely associated with serious adverse effects, and most important, almost always curative (ie, sustained virologic response). Because this is a rapidly changing field, the American Association for the Study of Liver Disease and the Infectious Diseases Society of America are continually updating recommended antiviral drug treatment.

At present, the 3 direct-acting, all-oral combination drug therapy recommended for HCV genotypes 1a and 1b (>75% of all HCV in the United States) and genotype 4 (approximately 2%) include: ledipasvir and sofosbuvir (Harvoni); ombitasvir, dasabuvir, and paritaprevir, with or without ribavirin (Viekira Pak); and grazoprevir and elbasvir (Zepatier). For people with (compensated) cirrhosis or who have failed previous antiviral therapy, treatment duration may vary from 12 to 24 weeks, depending on the treatment regimen used and the patient's previous receipt of HCV antiviral therapy.

Together, these regimens offer hope for cure without significant adverse effects for a large population of adult and, ultimately, pediatric patients with HCV infection. At the current time, several of the all-oral anti-HCV regimens are being evaluated in clinical trials for use in children.

Management of Chronic HCV Infection

All patients with chronic HCV infection should be immunized against hepatitis A and hepatitis B. Among children, progression of liver disease appears to be accelerated when comorbid conditions, including HIV, childhood cancer, iron overload, or thalassemia, are present. Pediatricians should be alert to concomitant infections, alcohol abuse, and concomitant use of prescription and nonprescription drugs, such as acetaminophen, some antiretroviral agents (such as stavudine), and herbal medications, in patients with HCV infection that may worsen liver disease. Children with chronic infection should be followed closely, including sequential monitoring of serum alanine transaminase concentrations, because of the potential for chronic liver disease.

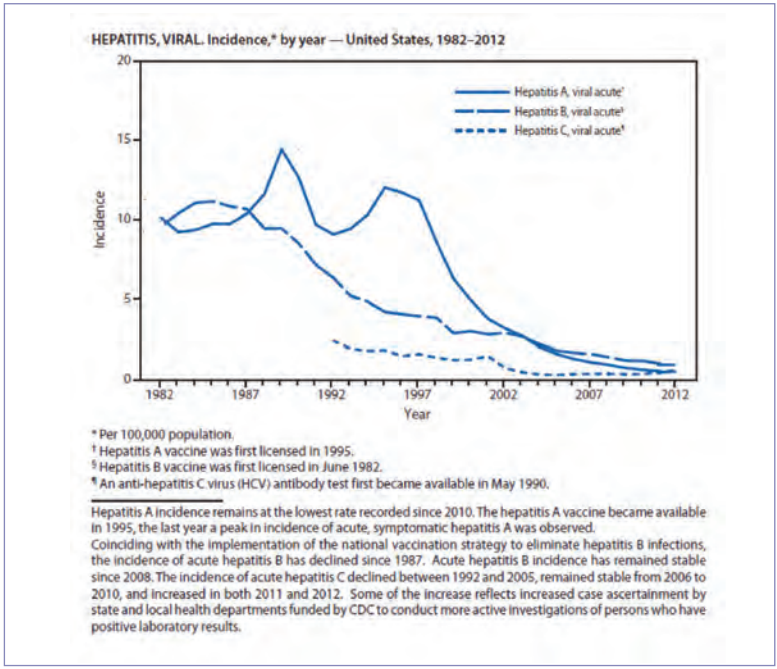


Image 63.1
Hepatitis, viral. Incidence, by year—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report*.

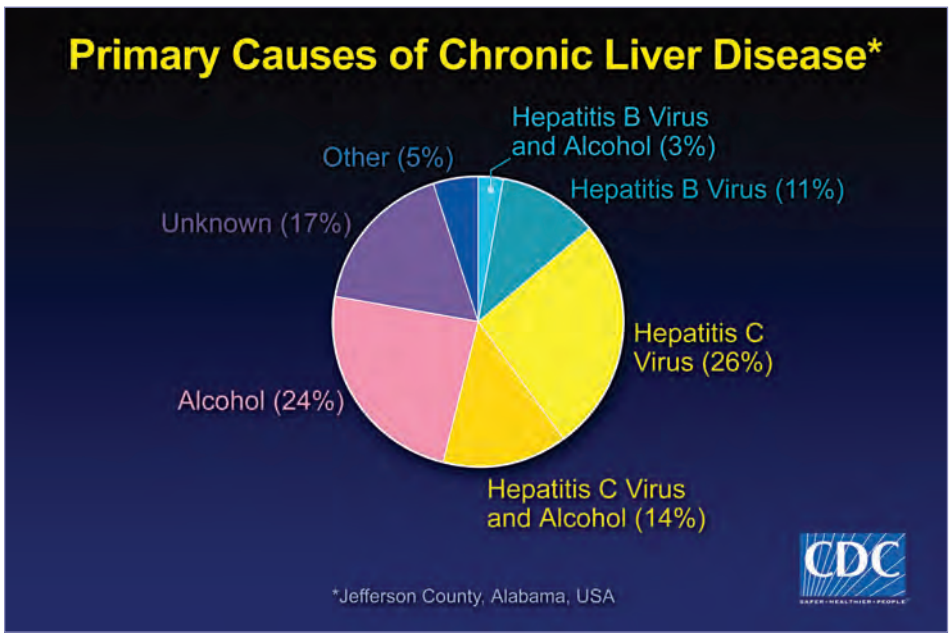


Image 63.2
Pie chart showing causes of chronic liver disease in residents of Jefferson County, AL. Hepatitis B and C viruses contributed to most cases of chronic liver disease in this population. Courtesy of Centers for Disease Control and Prevention.

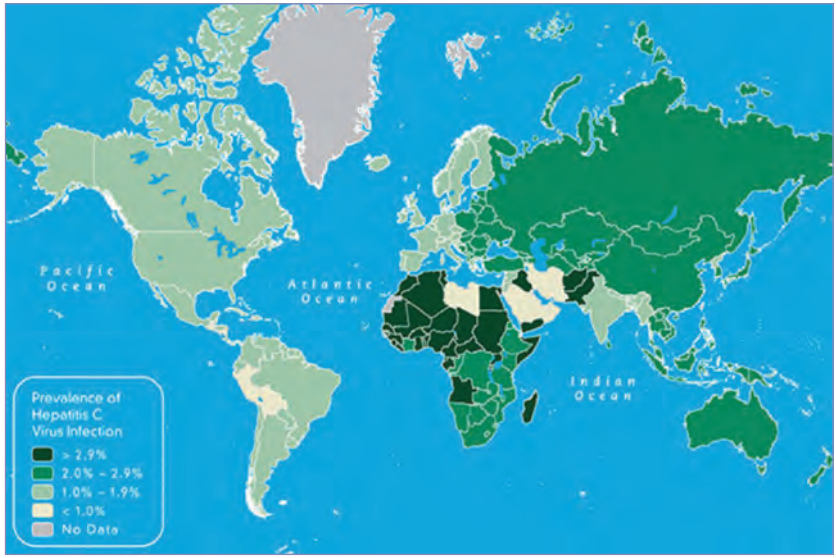


Image 63.3
Prevalence of chronic hepatitis C infection. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 64

Hepatitis D

CLINICAL MANIFESTATIONS

Hepatitis D virus (HDV) causes infection only in people with acute or chronic hepatitis B virus (HBV) infection. HDV requires HBV surface antigen (HBsAg) for replication. The importance of HDV infection lies in its ability to convert an asymptomatic or mild chronic HBV infection into fulminant or more severe or rapidly progressive disease. Acute coinfection with HBV and HDV usually causes an acute illness indistinguishable from acute HBV infection alone, except that the likelihood of fulminant hepatitis can be as high as 5%.

ETIOLOGY

HDV measures 36 to 43 nm in diameter and consists of an RNA genome and a delta protein antigen, both of which are coated with HBsAg.

EPIDEMIOLOGY

HDV infection is present worldwide, in all age groups, and an estimated 15 to 20 million people are infected with the virus, according to surveys performed in the 1980s and 1990s. Over the past 20 years, HDV prevalence has decreased significantly in Western and Southern Europe because of long-standing hepatitis B vaccination programs, although HDV remains a significant health problem in resource-limited countries. At least 8 genotypes of HDV have been described, each with a typical geographic pattern, with genotype 1 being the predominant type in Europe and North America. HDV can cause an infection at the same time as the initial HBV infection (coinfection), or it can infect a person already chronically infected with HBV (superinfection). Acquisition of HDV is by parenteral, percutaneous, or mucous membrane inoculation. HDV can be acquired from blood or blood products, through injection drug use, or by sexual contact, but only if HBV also is present. Transmission from mother to newborn infant is uncommon. Intrafamilial spread can occur among people with chronic HBV infection. High-prevalence areas include parts of Eastern Europe, South America, Africa, Central Asia, and the Middle East. In the United States, HDV infection is found most commonly in people who abuse injection drugs, people with hemophilia, and people who have emigrated from areas with endemic HDV infection.

The **incubation period** for HDV superinfection is approximately 2 to 8 weeks. When HBV and HDV viruses infect simultaneously, the incubation period is similar to that of HBV (45–160 days; mean, 90 days).

DIAGNOSTIC TESTS

People with chronic HBV infection are at risk of HDV coinfection. Accordingly, their care should be supervised by an expert in hepatitis treatment. Consideration should be given to testing for anti-HDV immunoglobulin (Ig) G antibodies using a commercially available test if they have increased transaminase concentrations, particularly if they recently came from a country with high prevalence of HDV. Anti-HDV may not be present until several weeks after onset of illness, and acute and convalescent sera may be required to confirm the diagnosis. In a person with anti-HDV, the absence of IgM hepatitis B core antibody (anti-HBc), which is indicative of chronic HBV infection, suggests that the person has both chronic HBV infection and superinfection with HDV. Presence of anti-HDV IgG antibodies does not prove active infection, and thus, HDV RNA testing should be performed for diagnostic and therapeutic considerations. Patients with circulating HDV RNA should be staged for severity of liver disease, have surveillance for development of hepatocellular carcinoma, and be considered for treatment. Presence of anti-HDV IgM is of lesser utility, because it is present in both acute and chronic HDV infections.

TREATMENT

HDV has proven difficult to treat, and there are no approved therapies for use in children. Data suggest pegylated interferon-alfa may result in up to 40% of patients having a sustained response to treatment. Clinical trials suggest at least a year of therapy may be associated with sustained responses, and longer courses may be warranted if the patient is able to tolerate therapy. Further study of pegylated interferon monotherapy or as combination therapy with a direct-acting antiviral agent needs to be performed before treatment of HDV can be advised

routinely. There are some preliminary data in adult volunteers suggesting that Myrcludex B (MYR GmbH [Burgwedel, Germany]), a lipomyristolated peptide containing 47 amino acids of the pre S1 domain of the HBV large surface protein, given either alone or in combination with pegylated interferon-alfa, significantly inhibits or clears HDV but has no effect on HBsAg.

CHAPTER 65

Hepatitis E

CLINICAL MANIFESTATIONS

Hepatitis E virus (HEV) infection causes an acute illness with symptoms including jaundice, malaise, anorexia, fever, abdominal pain, and arthralgia. Disease is more common among adults than among children and is more severe in pregnant women, in whom mortality rates can reach 10% to 25% during the third trimester. Chronic HEV infection mostly occurs in people with severe immunodeficiency. Approximately 60% of recipients of solid organ transplants fail to clear the virus and develop chronic hepatitis, and 10% will develop cirrhosis.

ETIOLOGY

HEV is a spherical, nonenveloped, positive-sense, single-stranded RNA virus. HEV is classified in the genus *Orthohepevirus* of the family *Hepeviridae*. *Orthohepevirus* A comprises 7 genotypes that infect humans (HEV-1, -2, -3, -4, and -7), pigs (HEV-3 and -4), rabbits (HEV-3), wild boars (HEV-3, -4, -5, and -6), mongooses (HEV-3), deer (HEV-3), yaks (HEV-4), and camels (HEV-7).

EPIDEMIOLOGY

HEV is the most common cause of viral hepatitis in the world. Globally, an estimated 20 million HEV infections occur annually, resulting in 3.4 million cases of acute hepatitis, 70,000 deaths and 3,000 stillbirths. In resource-limited countries, where almost all HEV infections occur, ingestion of fecally contaminated water is the most common route of HEV transmission, and large waterborne outbreaks occur frequently. Sporadic HEV infection has been reported throughout the world and is common in Africa and the Indian subcontinent. Person-to-person transmission appears to be much less efficient than with hepatitis A virus but occurs in sporadic and outbreak settings. Mother-to-infant transmission of HEV, mainly HEV-1, occurs frequently and accounts for a substantial number of fetal loss and perinatal mortality. HEV also is transmitted through blood and blood product transfusion.

Transfusion-transmitted hepatitis E occurs primarily in countries with endemic disease and also is reported in areas without endemic infection. In the United States, serologic studies have demonstrated that approximately 6% of the population has immunoglobulin (Ig) G antibodies against HEV. However, symptomatic HEV infection in the United States is uncommon and generally occurs in people who acquire HEV-1 infection while traveling in countries with endemic HEV. Nonetheless, a number of people without a travel history have been diagnosed with acute hepatitis E, and evidence for the infection should be sought in cases of acute hepatitis with an unknown etiology. Hepatitis E may masquerade as drug-induced liver injury.

The **incubation period** is 2 to 6 weeks.

DIAGNOSTIC TESTS

HEV infection should be considered in any person with symptoms of viral hepatitis who has traveled to or from a region with endemic hepatitis E or from a region where an outbreak has been identified and who tests negative for serologic markers of hepatitis A, B, C, and other hepatotropic viruses. Testing for anti-HEV IgM and IgG is available through some research and commercial reference laboratories. Because anti-HEV assays are not approved by the US Food and Drug Administration and their performance characteristics are not well defined, results should be interpreted with caution, particularly in cases lacking a discrete onset of illness associated with jaundice or with no recent history of travel to a country with endemic HEV transmission. Definitive diagnosis may be made by demonstrating viral RNA in serum or stool samples by means of reverse transcriptase-polymerase chain reaction assay, which is available only in research settings (eg, with prior approval through the Centers for Disease Control and Prevention). Because virus circulates in the body for a relatively short period, the inability to detect HEV in serum or stool does not eliminate the possibility that the person was infected with HEV.

TREATMENT

Supportive care.

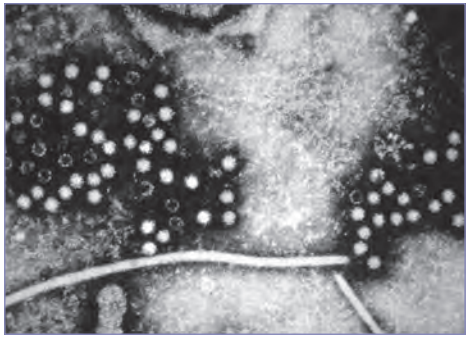


Image 65.1
This electron micrograph depicts hepatitis E viruses. Hepatitis E virus was classified as a member of the *Caliciviridae* family but have been reclassified in the genus *Hepevirus* of the family *Hepeviridae*. There are 4 major recognized genotypes with a single known serotype. Hepatitis E virus, the major etiologic agent of enterically transmitted non-A, non-B hepatitis worldwide, is a spherical, nonenveloped, single-stranded RNA virus that is approximately 32 to 34 nm in diameter. Courtesy of Centers for Disease Control and Prevention.

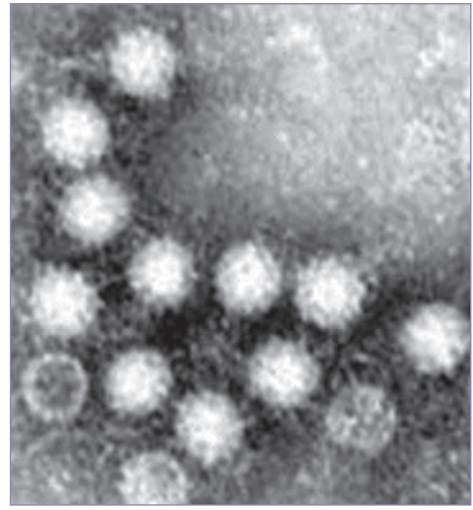


Image 65.2
Electron micrograph of nonhuman primate (marmoset) passaged hepatitis E virus (HEV) (Nepal isolate). Virus is aggregated with convalescent antisera to HEV and negatively stained in phosphotungstic acid. Particle size ranges from 27 to 30 nm. Courtesy of Centers for Disease Control and Prevention.

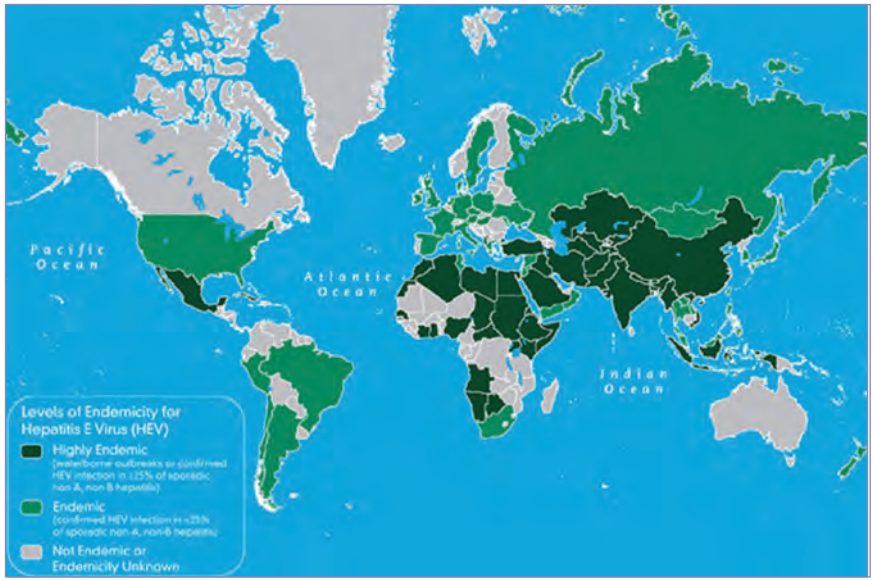


Image 65.3
Distribution of hepatitis E infection, 2010. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 66

Herpes Simplex

CLINICAL MANIFESTATIONS

Neonatal

In newborn infants, herpes simplex virus (HSV) infection can manifest as: (1) disseminated disease involving multiple organs, most prominently liver and lungs, and in 60% to 75% of cases also involving the central nervous system (CNS); (2) localized CNS disease, with or without skin, eye, or mouth involvement (CNS disease); or (3) disease localized to the skin, eyes, and/or mouth (SEM disease). Approximately 25% of cases of neonatal HSV manifest as disseminated disease, 30% manifest as CNS disease, and 45% manifest as SEM disease. In the absence of skin lesions, the diagnosis of neonatal HSV infection is challenging. More than 80% of neonates with SEM disease have skin vesicles; those without vesicles have infection limited to the eyes and/or oral mucosa. Approximately two thirds of neonates with disseminated or CNS disease have skin lesions, but these lesions may not be present at the time of onset of illness. Disseminated infection should be considered in neonates with sepsis syndrome with negative bacteriologic culture results, severe liver dysfunction, consumptive coagulopathy, or suspected viral pneumonia. HSV should be considered as a causative agent in neonates with fever (especially within the first 3 weeks of life), a vesicular rash, or abnormal cerebrospinal fluid (CSF) findings (especially in the presence of seizures or during a time of year when enteroviruses are not circulating in the community). Although asymptomatic HSV infection is common in older children, it rarely, if ever, occurs in neonates.

Neonatal herpetic infections often are severe, with attendant high mortality and morbidity rates, even when antiviral therapy is administered. Mortality rates from neonatal herpes increased between 2004 and 2013, compared with the 20 years prior to that. Recurrent skin lesions are common in surviving infants, occurring in approximately 50% of survivors, often within 1 to 2 weeks of completing the initial treatment course of parenteral acyclovir.

Almost all infected infants develop clinical disease within the first month of life. Infants with disseminated disease and SEM disease have an earlier age of onset, typically presenting between the first and second weeks of life; infants with CNS disease usually present with illness between the second and third weeks of life.

Children Beyond the Neonatal Period and Adolescents

Most primary HSV childhood infections beyond the neonatal period are asymptomatic. Gingivostomatitis, which is the most common clinical manifestation of HSV during childhood, is caused by HSV type 1 (HSV-1) and is characterized by fever, irritability, tender submandibular adenopathy, and an ulcerative enanthem involving the gingiva and mucous membranes of the mouth, often with perioral vesicular lesions.

Genital herpes is characterized by vesicular or ulcerative lesions of the male or female genitalia, perineum, or both. Until recently, genital herpes most often was caused by HSV type 2 (HSV-2), but HSV-1 now accounts for more than half of all cases in the United States. Most cases of primary genital herpes infection in males and females are asymptomatic, so they are not recognized by the infected person or diagnosed by a health care professional.

Eczema herpeticum can develop in patients with atopic dermatitis who are infected with HSV and can be difficult to distinguish from poorly controlled atopic dermatitis. Examination may reveal skin with punched-out erosions, hemorrhagic crusts, and/or vesicular lesions. Pustular lesions attributable to bacterial superinfection also may occur.

In immunocompromised patients, severe local lesions and, less commonly, disseminated HSV infection with generalized vesicular skin lesions and visceral involvement can occur.

After primary infection, HSV persists for life in a latent form. Reactivation of latent virus most commonly is asymptomatic. When symptomatic, recurrent HSV-1 herpes labialis manifests as single or grouped vesicles in the perioral region, usually on the vermilion border of the lips (typically called “cold sores” or “fever

blisters"). Symptomatic recurrent genital herpes manifests as vesicular lesions on the penis, scrotum, vulva, cervix, buttocks, perianal areas, thighs, or back. Among immunocompromised patients, genital HSV-2 recurrences are more frequent and of longer duration. Recurrences may be heralded by a prodrome of burning or itching at the site of an incipient recurrence, identification of which can be useful in instituting early antiviral therapy.

Conjunctivitis and keratitis can result from primary or recurrent HSV infection. Herpetic whitlow consists of single or multiple vesicular lesions on the distal parts of fingers. Wrestlers can develop herpes gladiatorum if they become infected with HSV-1. HSV infection can be a precipitating factor in erythema multiforme, and recurrent erythema multiforme often is caused by symptomatic or asymptomatic HSV recurrences.

HSV encephalitis (HSE) occurs in children beyond the neonatal period, in adolescents, and in adults, and can result from primary or recurrent HSV-1 infection. One fifth of HSE cases occur in the pediatric age group. Symptoms and signs usually include fever, alterations in the state of consciousness, personality changes, seizures, and focal neurologic findings. Encephalitis commonly has an acute onset with a fulminant course, leading to coma and death in untreated patients. Patients who are comatose or semicomatose at initiation of therapy have a poor outcome. HSE usually involves the temporal lobe, and magnetic resonance imaging is the most sensitive imaging modality to detect this. CSF pleocytosis with a predominance of lymphocytes is typical. Historically, erythrocytes in the CSF were considered suggestive of HSE, but with earlier diagnosis (prior to full manifestations of a hemorrhagic encephalitis), this finding is rare today.

HSV infection also can manifest as mild, self-limited aseptic meningitis, usually associated with genital HSV-2 infection. Unusual CNS manifestations of HSV include Bell palsy, atypical pain syndromes, trigeminal neuralgia, ascending myelitis, transverse myelitis, postinfectious encephalomyelitis, and recurrent (Mollaret) meningitis.

ETIOLOGY

HSVs are large, enveloped, double-stranded DNA viruses. They are members of the family *Herpesviridae* and, along with varicella-zoster virus (human herpesvirus 3), are the subfamily *Alphaherpesvirinae*. Two distinct HSV types exist: HSV-1 and HSV-2. Infections with HSV-1 traditionally involve the face and skin above the waist; however, an increasing number of genital herpes cases are attributable to HSV-1. Infections with HSV-2 usually involve the genitalia and skin below the waist in sexually active adolescents and adults. Both HSV-1 and HSV-2 cause herpetic disease in neonates. HSV-1 and HSV-2 establish latency following primary infection, with periodic reactivation to cause recurrent symptomatic disease or asymptomatic viral shedding. Genital HSV-2 infection is more likely to recur than is genital HSV-1 infection.

EPIDEMIOLOGY

HSV infections are ubiquitous and can be transmitted from people who are symptomatic or asymptomatic with primary or recurrent infections.

Neonatal

The incidence of neonatal HSV infection in the United States is estimated to range from 1 in 2,000 to 1 in 3,000 live births. HSV is transmitted to a neonate most often during birth through an infected maternal genital tract but can be caused by an ascending infection through ruptured or apparently intact amniotic membranes. Other less common sources of neonatal infection include postnatal transmission from a parent, sibling, or other caregiver, most often from a nongenital infection (eg, mouth or hands), and intrauterine infection causing congenital malformations.

The risk of transmission to a neonate born to a mother who acquires primary genital HSV infection near the time of delivery is estimated to be 25% to 60%. In contrast, the risk to a neonate born to a mother shedding HSV as a result of reactivation of infection acquired during the first half of pregnancy or earlier is less than 2%. Distinguishing between primary and recurrent HSV infections in women by history or physical examination alone may be impossible,

because primary and recurrent genital infections may be asymptomatic or associated with nonspecific findings (eg, vaginal discharge, genital pain, or shallow ulcers). History of maternal genital HSV infection is not helpful in diagnosing neonatal HSV disease, because more than three quarters of infants who contract HSV infection are born to women with no history or clinical findings suggestive of genital HSV infection during or preceding pregnancy and who, therefore, are unaware of their infection.

Children Beyond the Neonatal Period and Adolescents

Patients with primary gingivostomatitis or genital herpes usually shed virus for at least 1 week and occasionally for several weeks. Patients with symptomatic recurrences shed virus for a shorter period, typically 3 to 4 days. Intermittent asymptomatic reactivation of oral and genital herpes is common and likely occurs throughout the remainder of a person's life. The greatest concentration of virus is shed during symptomatic primary infections and the lowest during asymptomatic reactivation.

Inoculation of abraded skin occurs from direct contact with HSV shed from oral, genital, or other skin sites. This contact can result in herpes gladiatorum among wrestlers, herpes rugbiorum among rugby players, or herpetic whitlow of the fingers in any exposed person.

The **incubation period** for HSV infection occurring beyond the neonatal period ranges from 2 days to 2 weeks.

DIAGNOSTIC TESTS

HSV grows readily in traditional cell culture. Cytopathogenic effects typical of HSV infection usually are observed 1 to 3 days after inoculation. Methods of culture confirmation include fluorescent antibody staining, enzyme immunoassays (EIAs), and monolayer culture with typing. Cultures that remain negative by day 5 likely typically remain negative. A spin amplification culture method involving centrifugation of the specimen onto glass coverslips in small vials (shell vial technique) followed by fluorescent antibody staining of the coverslips and fluorescent microscopy may be used to reduce time to detection to 24 to 48 hours. An alternative, commercially available rapid culture technique known as ELVIS (enzyme-linked, virus-inducible system) uses genetically engineered cells to allow for HSV gene expression and detection of infected cells by light microscopy. Sensitivity of culture is highly dependent on proper specimen collection, quality of reagents, and expertise of testing personnel, in addition to the stage of lesion development, with crusted lesions being less likely to be culture positive.

Polymerase chain reaction (PCR) assay usually can detect HSV DNA in CSF from neonates with CNS infection (neonatal HSV CNS disease) and from older children and adults with HSE and is the diagnostic method of choice for CNS HSV involvement. PCR assay of CSF can yield negative results in cases of HSE, especially early in the disease course. In difficult cases in which repeated CSF PCR assay results are negative, histologic examination and viral culture of a brain tissue biopsy specimen is the most definitive method of confirming the diagnosis of HSE. There currently are 2 PCR for the detection of HSV in CSF: a singleplex assay and a multiplex assay that is capable of detection HSV and several other bacterial and viral agents of meningitis and encephalitis. There are limited clinical data on the efficacy of these assays, and results should be interpreted cautiously. Detection of intrathecal antibody against HSV also can assist in the diagnosis. Viral cultures of CSF usually are negative.

For diagnosis of neonatal HSV infection, all of the following specimens should be obtained for each patient: (1) swab specimens from the mouth, nasopharynx, conjunctivae, and anus ("surface specimens") for HSV culture (if available) or PCR assay; (2) specimens of skin vesicles for HSV culture (if available) or PCR assay; (3) CSF for HSV PCR assay; (4) blood for HSV PCR assay; and (5) blood for measuring alanine transaminase (ALT). Positive cultures obtained from any of the surface sites more than 12 to 24 hours after birth indicate viral replication and are suggestive of infant infection rather than merely contamination after intrapartum exposure. As with any PCR assay, false-negative and false-positive results can occur. Any of the 3 manifestations of neonatal HSV disease (disseminated, CNS, SEM) can have associated

viremia, so a positive whole blood PCR assay for HSV should not be used to determine extent of disease and duration of treatment; likewise, no data exist to support use of serial blood PCR assays to monitor response to therapy. Rapid diagnostic techniques are available, such as direct fluorescent antibody staining of vesicle scrapings or EIA detection of HSV antigens. These techniques are as specific but slightly less sensitive than culture. Radiographs and clinical manifestations can suggest HSV pneumonitis, and elevated transaminase values can suggest HSV hepatitis. Histologic examination of lesions for presence of multinucleated giant cells and eosinophilic intranuclear inclusions typical of HSV (eg, with Tzanck test) should *not* be performed because of low sensitivity.

HSV PCR assay and cell culture are the preferred tests for detecting HSV in genital lesions. The sensitivity of viral culture is low, especially for recurrent lesions, and declines rapidly as lesions begin to heal. PCR assays for HSV DNA are more sensitive and increasingly are used in many settings. There are currently several PCR assays for the detection of HSV in skin, oral, and genital lesions in adults. Failure to detect HSV in genital lesions by culture or PCR assay does not exclude HSV infection because viral shedding is intermittent.

Both type-specific and type-common antibodies to HSV develop during the first several weeks after infection and persist indefinitely. Approximately 20% of HSV-2 first episode patients seroconvert by 10 days, and the median time to seroconversion is 21 days with a type-specific enzyme-linked immunosorbent assay (ELISA); more than 95% of people seroconvert by 12 weeks following infection. Although type-specific HSV-2 antibody usually indicates previous anogenital infection, the presence of HSV-1 antibody reliably does not distinguish anogenital from orolabial infection because a substantial proportion of initial genital infections and virtually all initial orolabial infections are caused by HSV-1. Type-specific serologic tests can be useful in confirming a clinical diagnosis of genital herpes caused by HSV-2. Additionally, these serologic tests can be used to evaluate individuals with recurrent or atypical genital tract symptoms with negative HSV culture or PCR evaluations and to manage sexual partners of people with genital herpes. Serologic testing is not useful in neonates.

Both laboratory-based assays and point-of-care tests that provide results for HSV-2 antibodies from capillary blood or serum are available. The sensitivities of these glycoprotein G type-specific tests for the detection of HSV-2 antibody vary from 80% to 98%. The most commonly used test, HerpeSelect 2 ELISA IgG (Focus Diagnostics, Cypress, CA), might be falsely positive at low index values. Such low values should be confirmed with another test, such as Biokit or the Western blot; the HerpeSelect 2 Immunoblot IgG should not be used for confirmation, because it uses the same antigen as the HerpeSelect 2 ELISA IgG. Repeat testing is indicated if recent acquisition of genital herpes is suspected. The HerpeSelect 1 ELISA IgG kit is insensitive. IgM testing for HSV-1 or HSV-2 is not useful, because IgM tests are not type-specific and might be positive during recurrent genital or oral episodes of herpes.

TREATMENT

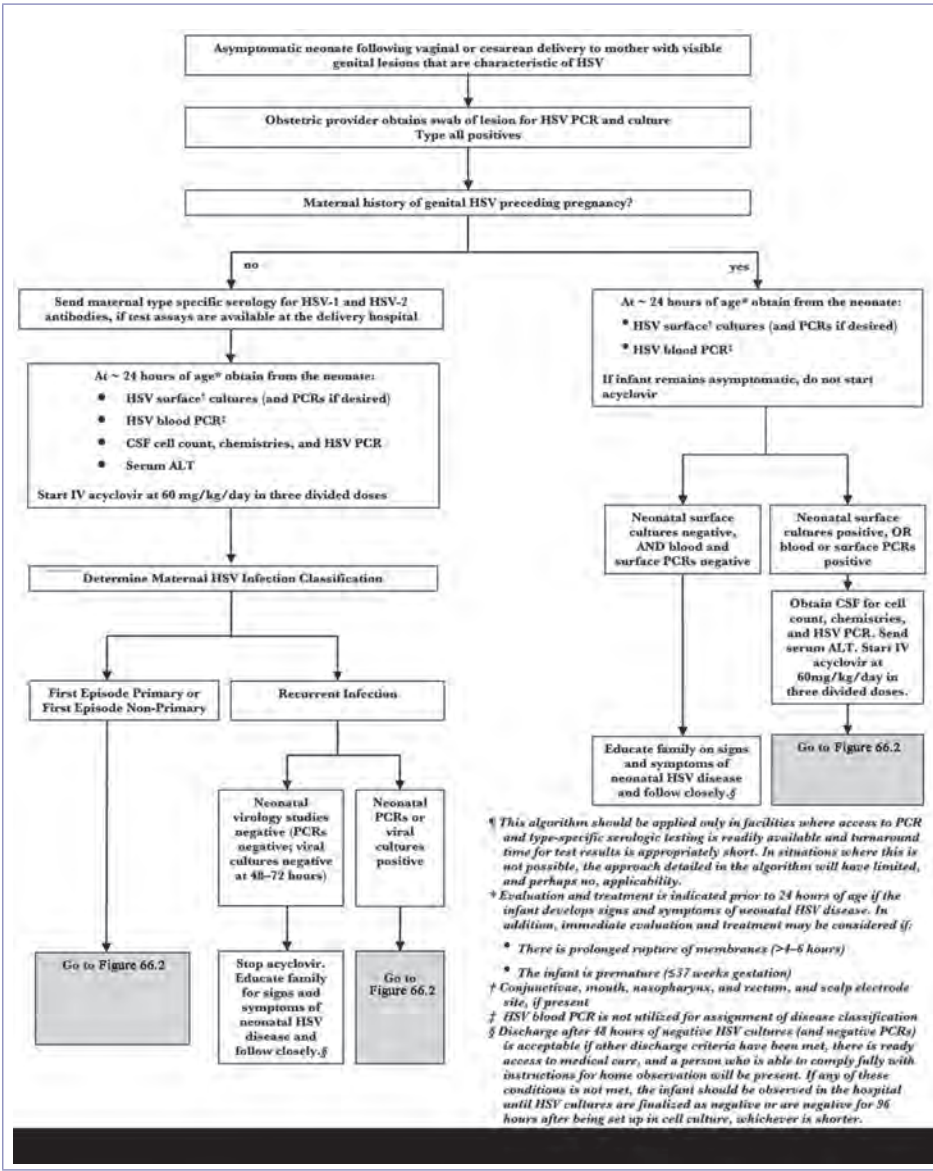
Acyclovir administered intravenously is the drug of choice for treating serious HSV infections. Valacyclovir is an L-valyl ester of acyclovir that is metabolized to acyclovir after oral administration, resulting in higher serum concentrations than those achieved with oral acyclovir and similar serum concentrations as those achieved with intravenous administration of acyclovir. Famciclovir is converted rapidly to penciclovir after oral administration. Valacyclovir can be given to pediatric patients 12 years and older for the treatment of cold sores (herpes labialis).

Neonatal

Parenteral acyclovir is the treatment for neonatal HSV infections (Figures 66.1 and 66.2). Acyclovir is administered intravenously for 14 days in SEM disease and for a minimum of 21 days in CNS disease or disseminated disease. All infants with neonatal HSV disease, regardless of disease classification, should have an ophthalmologic examination and neuroimaging to establish baseline brain anatomy; magnetic resonance imaging is the most sensitive imaging modality but may require

Figure 66.1

Algorithm for the evaluation of asymptomatic neonates after vaginal or cesarean delivery to women with active genital herpes lesions.

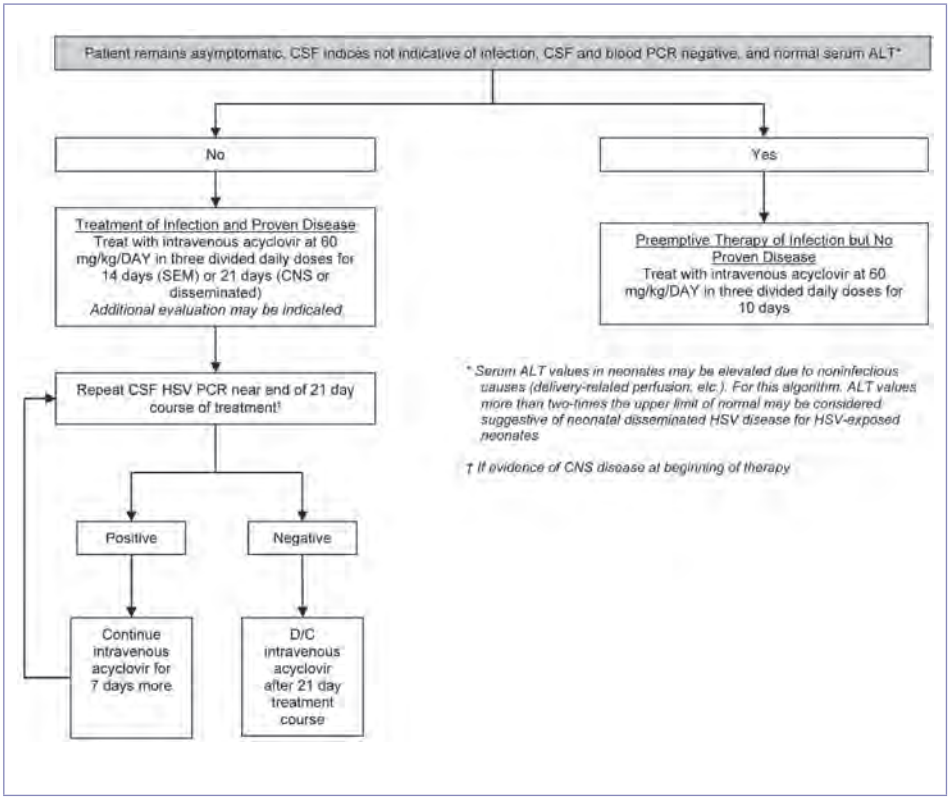


Reproduced from Kimberlin DW, Baley J; American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics*. 2013;131(2):e635–e646.

sedation, so computed tomography or ultrasonography of the head are acceptable alternatives. All infants with CNS involvement should have a repeat lumbar puncture performed near the end of therapy to document that the CSF is negative for HSV by PCR assay; in the unlikely event that the PCR result remains positive near the end of a 21-day treatment course, intravenous acyclovir should be administered for another week, with repeat CSF PCR assay

Figure 66.2

Algorithm for the treatment of asymptomatic neonates after vaginal or cesarean delivery to women with active genital herpes lesions.



Reproduced from Kimberlin DW, Baley J; American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Guidance on management of asymptomatic neonates born to women with active genital herpes lesions. *Pediatrics.* 2013;131(2):e635–e646.

performed near the end of the extended treatment period. Parenteral antiviral therapy should not be stopped until the CSF PCR result for HSV DNA is negative. Consultation with a pediatric infectious diseases specialist is warranted in these cases.

Infants surviving neonatal HSV infections of any classification (disseminated, CNS, or SEM) should receive oral acyclovir suppression for 6 months after the completion of parenteral therapy; the dose should be adjusted monthly to account for growth. Absolute neutrophil counts should be assessed at 2 and 4 weeks after initiating suppressive acyclovir therapy and then monthly during the treatment period. Valacyclovir should not be used routinely for antiviral suppression in infants for neonatal HSV.

Infants with ocular involvement attributable to HSV infection should receive a topical ophthalmic drug as well as parenteral antiviral therapy. An ophthalmologist should be involved in the management and treatment of acute neonatal ocular HSV disease.

Genital Infection

Primary

Oral acyclovir therapy for 7–10 days shortens the duration of illness and viral shedding. Valacyclovir and famciclovir do not seem to be more effective than acyclovir but offer the advantage of less frequent dosing. Intravenous acyclovir is indicated for patients with a severe or complicated primary infection that requires hospitalization for 2–7 days or until clinical

improvement is observed, followed by oral antiviral therapy to complete the treatment course. Treatment of primary herpetic lesions does not affect the subsequent frequency or severity of recurrences.

Recurrent

Antiviral therapy for recurrent genital herpes can be administered either episodically to ameliorate or shorten the duration of lesions or continuously as suppressive therapy to decrease the frequency of recurrences. Many patients benefit from antiviral therapy, and treatment options should be discussed with patients with recurrent disease. Suppressive therapy has the additional advantage of decreasing the risk of genital HSV-2 transmission to susceptible partners. Acyclovir and valacyclovir have been approved for suppression of genital herpes in immunocompetent adults. Either may be administered orally to pregnant women with first-episode genital herpes or severe recurrent herpes, and acyclovir should be administered intravenously to pregnant women with severe HSV infection.

Mucocutaneous

Immunocompromised Hosts

Intravenous acyclovir is effective for treatment of mucocutaneous HSV infections. Acyclovir-resistant strains of HSV have been isolated from immunocompromised people receiving prolonged treatment with acyclovir. Foscarnet is the drug of choice for acyclovir-resistant HSV isolates.

Immunocompetent Hosts

Limited data are available on effects of acyclovir on the course of primary or recurrent nongenital mucocutaneous HSV infections in immunocompetent hosts. Therapeutic benefit has been noted in a limited number of children with primary gingivostomatitis treated with oral acyclovir. A small therapeutic benefit of oral acyclovir therapy for 5 to 7 days has been demonstrated among adults with recurrent herpes labialis. Topical acyclovir is ineffective.

In a controlled study of a small number of adults with recurrent herpes labialis (6 or more episodes per year), suppressive acyclovir twice a day was effective for decreasing the frequency of recurrent episodes. Although no studies of suppressive therapy have been performed in children, those with frequent recurrences may benefit from daily oral acyclovir therapy, with reevaluation being performed after 6 months to 1 year of continuous therapy.

Other HSV Infections

Central Nervous System

Patients with HSE should be treated for 21 days with intravenous acyclovir. For people with Bell palsy, the combination of acyclovir and prednisone may be considered.

Ocular

Treatment of eye lesions should be undertaken in consultation with an ophthalmologist. Several topical drugs have proven efficacy for superficial keratitis. Topical corticosteroids administered without concomitant antiviral therapy are contraindicated in suspected HSV conjunctivitis. For children with recurrent ocular lesions, oral suppressive therapy with acyclovir may be of benefit and may be indicated for months or even years.

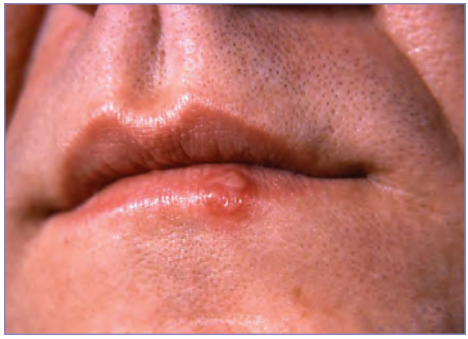


Image 66.1
This is a close-up of a herpes simplex lesion on the lower lip on the second day after onset. Also known as a cold sore, this lesion is caused by the contagious herpes simplex virus type 1 and should not be confused with a canker sore, which is not contagious. Courtesy of Centers for Disease Control and Prevention.

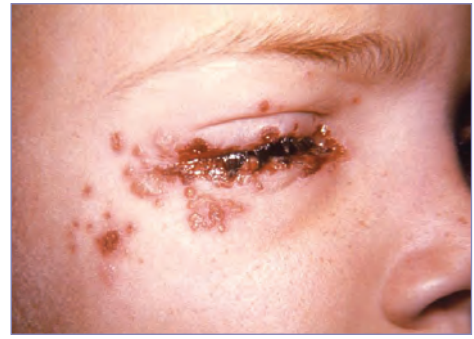


Image 66.2
This 7-year-old with a history of recurrent herpes labialis presented with periocular herpes simplex. Courtesy of Centers for Disease Control and Prevention.

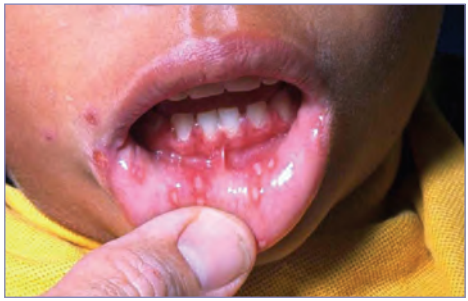


Image 66.3
Herpes simplex stomatitis, primary infection of the anterior oral mucous membranes. Tongue lesions also are common with primary herpes simplex virus infections.

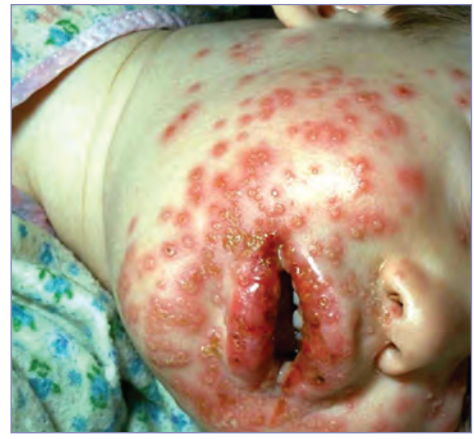


Image 66.4
Herpes simplex stomatitis, primary infection with extension to the face.

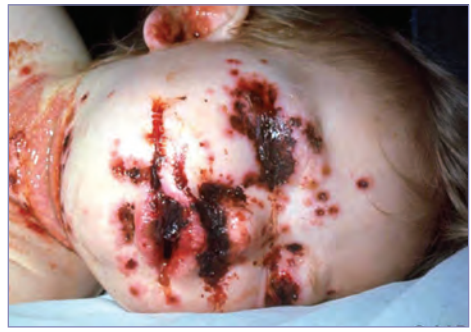


Image 66.5
Herpes simplex infection in a child with eczema with Kaposi varicelliform eruption and Stevens-Johnson syndrome.

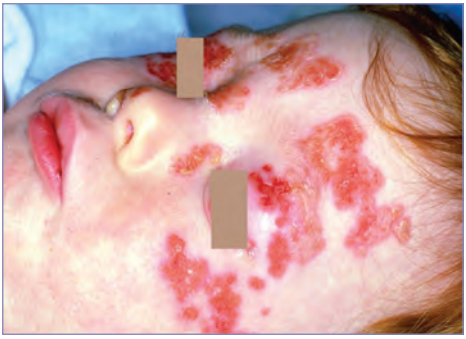


Image 66.6
Eczema herpeticum on the face of a boy with eczema and primary herpetic gingivostomatitis, day 3 to 4 of the onset. The herpetic lesions spread over a period of 2 to 3 days to extensive covering of the skin, and systemic therapy with acyclovir was provided. The patient recovered after a prolonged hospital stay for secondary nosocomial bacterial infections. Copyright Jerri Ann Jenista, MD.

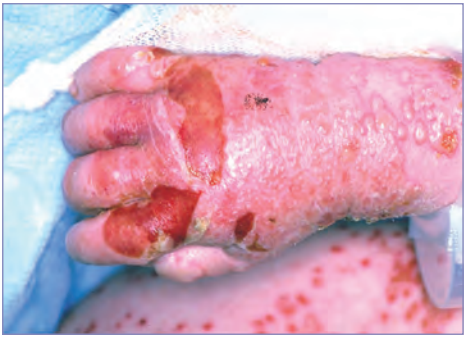


Image 66.8
Hand of the patient in Images 66.6 and 66.7 with eczema and primary herpetic gingivostomatitis that spread over 2 to 3 days to extensively cover the skin. Copyright Jerri Ann Jenista, MD.

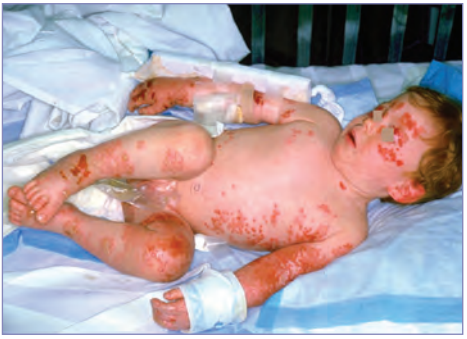


Image 66.7
Patient in Image 66.6 with generalized eczema and primary herpetic gingivostomatitis with extensive eczema herpeticum. Copyright Jerri Ann Jenista, MD.

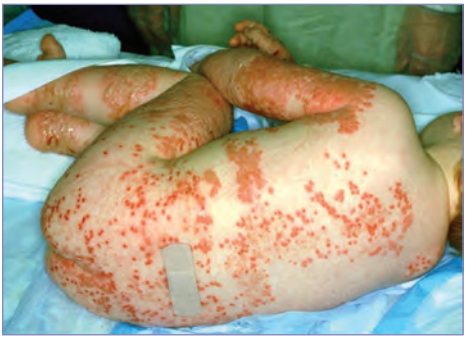


Image 66.9
The patient shown in Images 66.6, 66.7, and 66.8 with extensive eczema herpeticum and primary herpetic gingivostomatitis. Copyright Jerri Ann Jenista, MD.

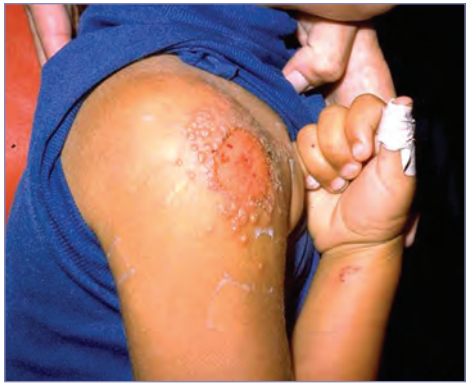


Image 66.10
Herpes simplex virus infection at a diphtheria, tetanus, and pertussis vaccine injection site reflecting self-inoculation. Courtesy of Edgar O. Ledbetter, MD, FAAP.

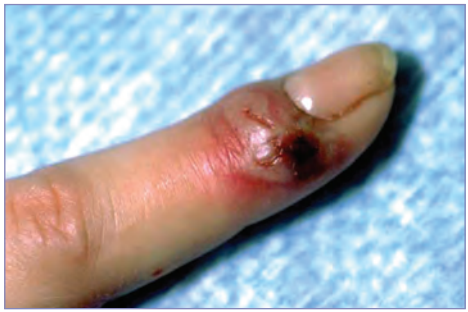


Image 66.12
An adolescent girl with herpetic whitlow secondary to orolabial lesions with self-inoculation. Copyright Martin G. Myers, MD.

Image 66.14
Neonatal herpes simplex infection with disseminated vesicular lesions.

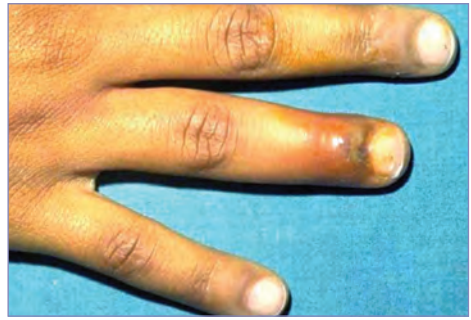


Image 66.11
Herpetic whitlow in a 10-year-old boy with recurrent herpes simplex infection.

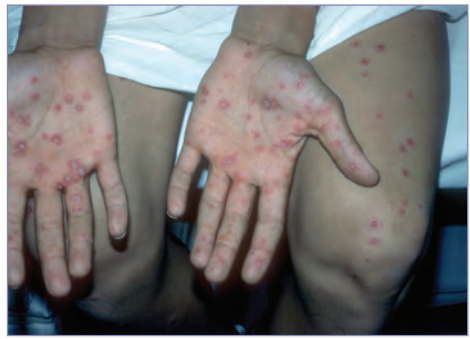


Image 66.13
Disseminated herpes simplex infection in a 17-year-old boy with Hodgkin disease. Courtesy of George Nankervis, MD.

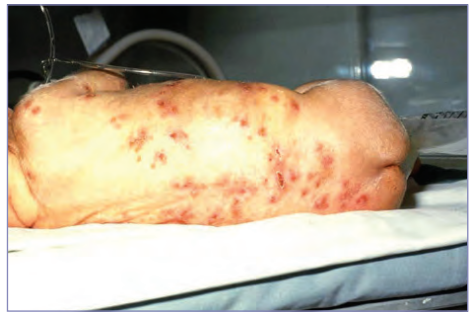


Image 66.15
Neonatal herpes simplex infection. This is the same patient as in Image 66.14.

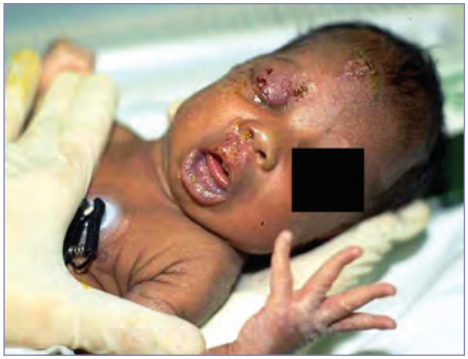


Image 66.16
Neonatal herpes skin lesions of the face. A preterm 14-day-old developed vesicular lesions over the right eye and face on days 11 to 14 after birth. Herpes simplex virus type 2 was recovered from viral culture of the vesicular fluid. Keratoconjunctivitis was diagnosed by ophthalmology and the neonate was treated with topical antiviral eye drops in addition to intravenous acyclovir. The neonate was born via a spontaneous vaginal delivery with a vertex presentation. Membranes had ruptured 8 hours prior to delivery. There was no history of genital herpes or fever blisters in either parent. The lesions were concentrated on the face and head, the presenting body parts in delivery. Copyright Barbara Jantausch, MD, FAAP.

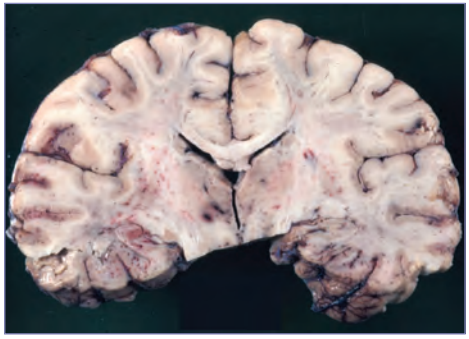


Image 66.19
Postneonatal herpes simplex encephalitis. Hemorrhagic necrosis of the temporal lobes. Courtesy of Dimitris P. Agamanolis, MD.

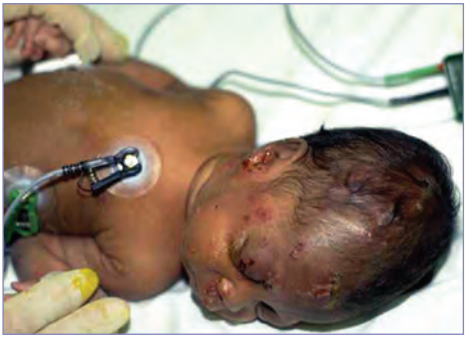


Image 66.17
Neonatal herpes skin lesions of the head and face. This is the same patient as shown in Image 66.16. Copyright Barbara Jantausch, MD, FAAP.

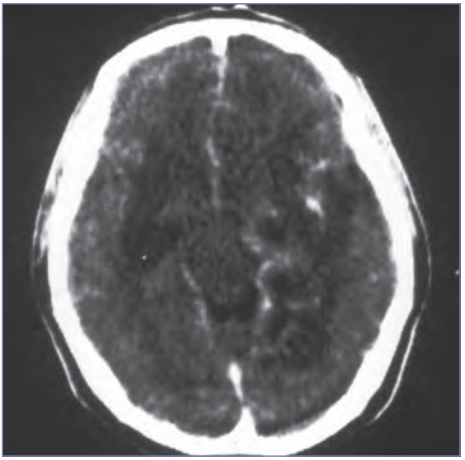


Image 66.18
Computed tomography scan of a patient with herpes simplex encephalitis with temporal lobe changes.

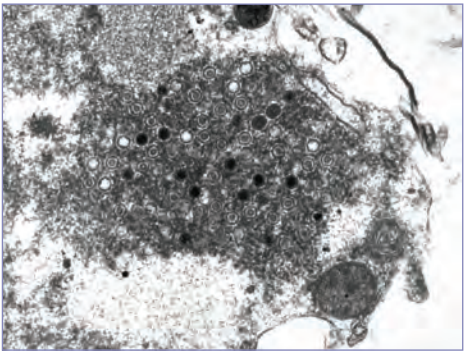


Image 66.20
Herpes simplex encephalitis. Viral particles in an intranuclear inclusion. Courtesy of Dimitris P. Agamanolis, MD.

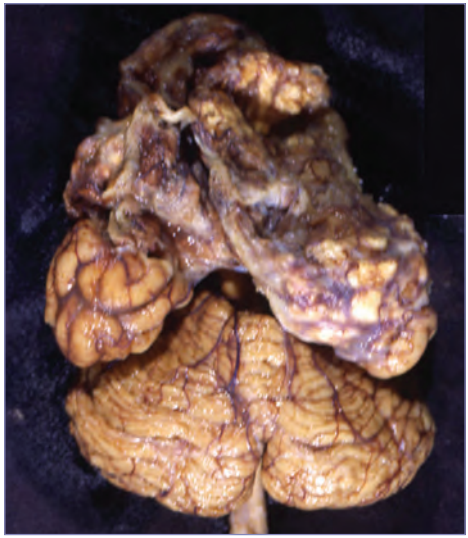


Image 66.21
Burned out neonatal herpes simplex virus encephalitis. Severe atrophy and distortion of the cerebral hemispheres. Courtesy of Dimitris P. Agamanolis, MD.

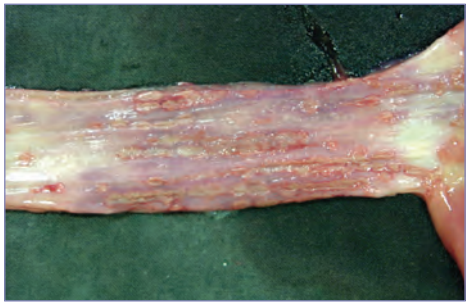


Image 66.23
Herpes simplex esophagitis. Courtesy of Dimitris P. Agamanolis, MD.

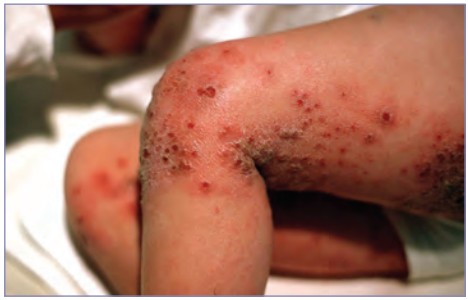


Image 66.25
Herpes simplex infection in a 4-year-old boy with eczema (Kaposi varicelliform eruption). Courtesy of Ed Fajardo, MD.

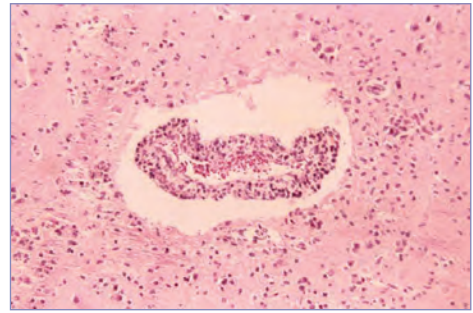


Image 66.22
Histopathologic changes seen in brain tissue due to herpes simplex encephalitis (hematoxylin-eosin stain, magnification ×125). Herpes simplex encephalitis is characterized by headaches, fever, and altered mental state due to inflammation of the brain. Herpes simplex virus, the cause of herpes simplex encephalitis, is one of the main causes of non-epidemic, sporadic encephalitis. Courtesy of Centers for Disease Control and Prevention.

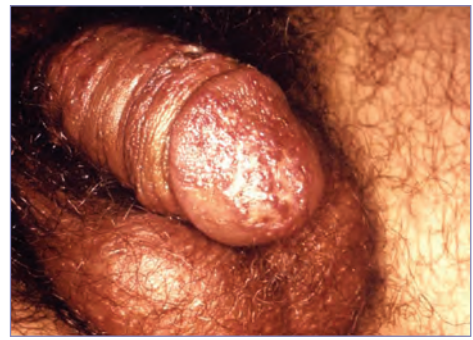


Image 66.24
This male presented with primary vesiculopapular herpes genitalis lesions on his glans penis and penile shaft. When signs of herpes genitalis do occur, they typically appear as one or more blisters on or around the genitals or rectum. The blisters break, leaving tender ulcers (sores) that may take 2 to 4 weeks to heal the first time they occur. Courtesy of Centers for Disease Control and Prevention.

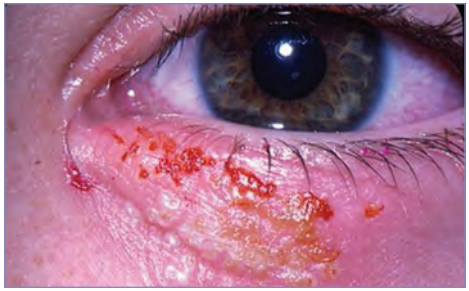


Image 66.26
A 15-year-old white girl with recurrent facial and ocular herpes simplex infection. Courtesy of Larry Frenkel, MD.

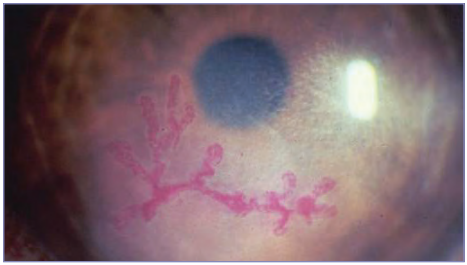


Image 66.27
A 15-year-old girl with recurrent facial and ocular herpes simplex infection. This is the same patient as Image 66.26. Courtesy of Larry Frenkel, MD.

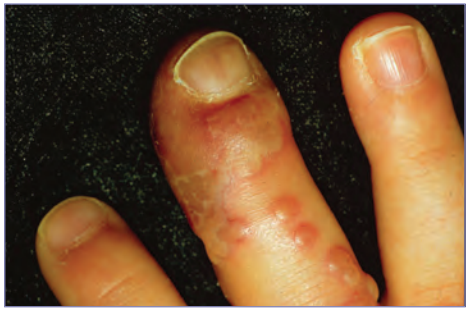


Image 66.28
A 2-year-old boy with herpes simplex infection of the index finger. Courtesy of Larry Frenkel, MD.

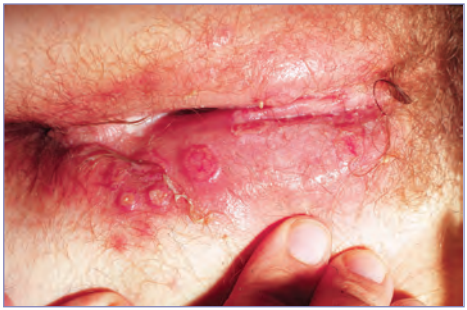


Image 66.29
A 15-year-old girl with primary herpes simplex infection of the genital area. Courtesy of Larry Frenkel, MD.

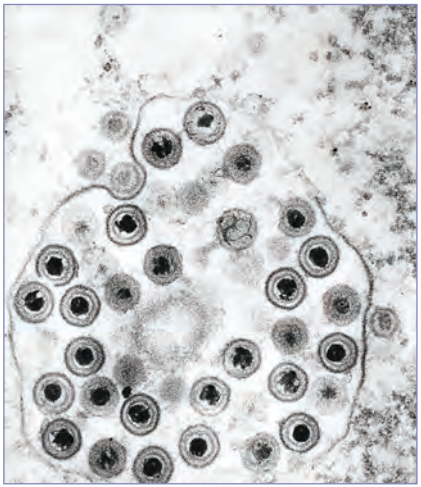


Image 66.30
This negatively stained transmission electron micrograph reveals the presence of numerous herpesvirus virions, members of the *Herpesviridae* virus family. Courtesy of Centers for Disease Control and Prevention.

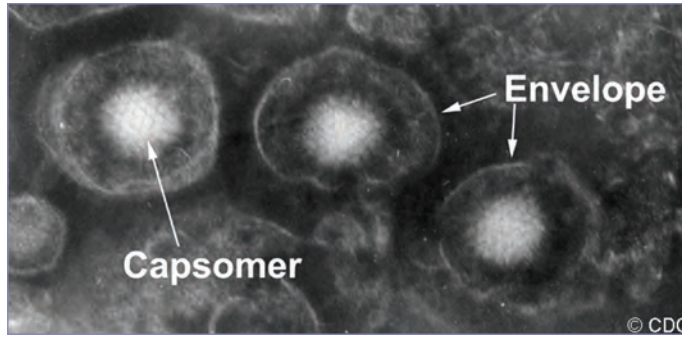


Image 66.31
Electron micrograph image of herpesvirus (negative stain). A viral envelope surrounds the nucleocapsid, which measures approximately 100 nm and is composed of an icosahedron formed by hollow capsomers. Courtesy of Centers for Disease Control and Prevention.

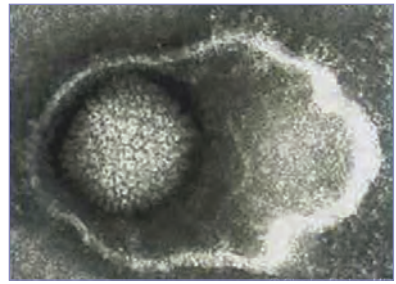


Image 66.32
Herpesvirus, electron micrograph. Copyright Charles Prober.

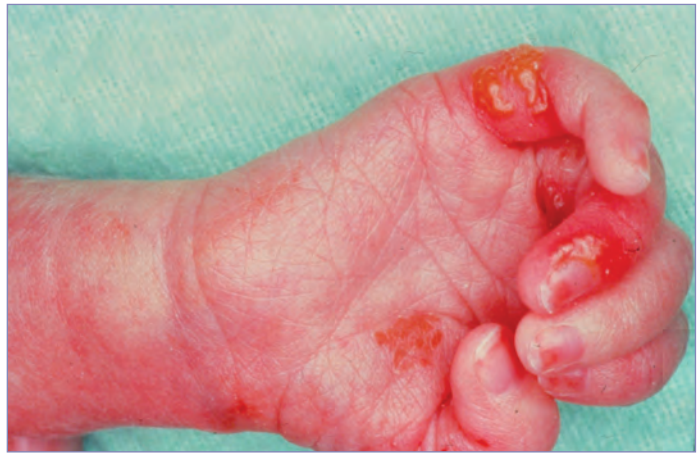


Image 66.33
A term 3-week-old who presented with fever and poor feeding. A blood culture grew group B *Streptococcus*. On day 2 of antibiotic therapy, these vesicular lesions on the hand were noted and lesion fluid grew herpes simplex virus type 2. Courtesy of Carol J. Baker, MD.

CHAPTER 67

Histoplasmosis

CLINICAL MANIFESTATIONS

Histoplasma capsulatum causes symptoms in fewer than 5% of infected people. Clinical manifestations are classified according to site (pulmonary or disseminated), duration (acute, subacute, or chronic), and pattern (primary or reactivation) of infection. Most symptomatic patients have acute pulmonary histoplasmosis, a brief, self-limited illness characterized by fever, chills, nonproductive cough, and malaise. Radiographic findings may consist of hilar or mediastinal adenopathy, or diffuse interstitial or reticulonodular pulmonary infiltrates. Most patients recover without treatment 2 to 3 weeks after onset of symptoms. Exposure to a large inoculum of conidia can cause severe pulmonary infection associated with high fevers, hypoxemia, diffuse reticulonodular infiltrates, and acute respiratory distress syndrome (ARDS). Mediastinal involvement, a rare complication of pulmonary histoplasmosis, includes mediastinal lymphadenitis, which can cause airway encroachment in young children. Erythema nodosum can occur in adolescents and adults. Primary cutaneous infections after trauma are rare. Chronic cavitary pulmonary histoplasmosis is extremely rare in children.

Progressive disseminated histoplasmosis (PDH) may occur in otherwise healthy infants and children younger than 2 years, or in older children with primary or acquired cellular immune dysfunction. It can be a rapidly progressive illness following acute infection, or it can be a more chronic, slowly progressive disease. Early manifestations of PDH in children include prolonged fever, failure to thrive, and hepatosplenomegaly; if untreated, malnutrition, diffuse adenopathy, pneumonitis, mucosal ulceration, pancytopenia, disseminated intravascular coagulopathy, and gastrointestinal tract bleeding can ensue. PDH in adults occurs most often in people with underlying immune deficiency (eg, HIV, solid organ transplant, hematologic malignancy, and biologic response modifiers including tumor necrosis factor antagonists). Central nervous system involvement occurs in 5% to 25% of patients with chronic progressive disease. Chronic PDH generally occurs in adults with immune suppression and is characterized by prolonged fever, night sweats, weight loss, and fatigue; signs include hepatosplenomegaly, mucosal ulcerations, adrenal insufficiency, and pancytopenia. Clinicians should be alert to the risk of disseminated histoplasmosis in patients receiving tumor necrosis factor-alpha antagonists and disease-modifying antirheumatic drugs and biologics.

ETIOLOGY

Histoplasma strains, which may be classified into at least 7 distinct clades, are thermally dimorphic, endemic fungi that grow in the environment as a spore-bearing mold but convert to the yeast phase at 37°C.

EPIDEMIOLOGY

H capsulatum is encountered in most parts of the world (including Africa, the Americas, Asia, and Europe) and is highly endemic in the central and eastern United States, particularly the Mississippi, Ohio, and Missouri River valleys. *H capsulatum* var *duboisii* is found only in central and western Africa. Infection is acquired following inhalation of conidia that are aerosolized by disturbance of soil, especially when contaminated with bat guano or bird (especially chicken) droppings. The inoculum size, strain virulence, and immune status of the host affect the severity of the ensuing illness. Infections occur sporadically. In regions with endemic disease, recreational and occupational activities, such as playing in hollow trees, caving, mud runs, construction, excavation, demolition, farming, and cleaning of contaminated buildings, have been associated with outbreaks. Person-to-person transmission does not occur except via transplantation of infected organs. Prior infection confers partial immunity; reinfection can occur but requires a larger inoculum.

The **incubation period** is variable but usually is 1 to 3 weeks.

DIAGNOSTIC TESTS

Detection of *H capsulatum* polysaccharide antigen in serum, urine, bronchoalveolar lavage fluid, or cerebrospinal fluid using a quantitative enzyme immunoassay is the preferred method of testing. Urine antigen detection is

substantially more sensitive than serum antigen detection. Antigen detection is most sensitive for severe, acute pulmonary infections and for progressive disseminated infections. Results often are transiently positive early in the course of acute, self-limited pulmonary infections. A negative test result does not exclude infection. If the result initially is positive, antigen testing also is useful for monitoring treatment response and in identifying relapse or reinfection. Cross-reactions may occur in patients with blastomycosis, coccidioidomycosis, paracoccidioidomycosis, sporotrichosis, and penicilliosis; clinical and epidemiologic distinctions aid in differentiating these entities.

Serologic testing is available and is most useful in patients with subacute or chronic pulmonary disease. Complement fixation, immunodiffusion, and latex agglutination tests are available. A fourfold increase in either yeast-phase or mycelial-phase complement fixation titers or a single titer of ≥1:32 in either test is strong presumptive evidence of active or recent infection in patients exposed to or residing within regions of endemicity. Cross-reacting antibodies can result most commonly from *Blastomyces dermatitidis* and *Coccidioides* species but also rarely with *Aspergillus* and *Cryptococcus* infections. The immunodiffusion test is a qualitative method that is more specific, but slightly less sensitive, than the complement fixation test. It detects the H and M glycoproteins of *H capsulatum* found in histoplasmin. The immunodiffusion assay is approximately 80% sensitive but is more specific than the complement fixation assay. It commonly is used in conjunction with the complement fixation test. A latex agglutination test is commercially available for the detection of immunoglobulin (Ig) M antibodies to histoplasmin. It is used primarily for the diagnosis of acute histoplasmosis.

Culture is the definitive method of diagnosis. *H capsulatum* organisms from bone marrow, blood, sputum, and tissue specimens grow in the mycelia (mold) phase on standard mycologic media in 1 to 6 weeks. The yeast phase of the organism can be recovered on primary culture using enriched media such as brain-heart infusion agar with blood (BHIB) incubated at 35°C to 37°C. The lysis-centrifugation method is preferred for blood cultures. A DNA probe for *H capsulatum* permits rapid identification of mycelial-phase cultured isolates. Care should be taken in working with the organism in the laboratory, because mold-phase growth may release large numbers of infectious microconidia into the air.

Demonstration of typical intracellular yeast forms by examination with Wright or Giemsa stains of blood, bone marrow, or bronchoalveolar lavage specimens or with Gomori methenamine silver or other stains of tissue strongly supports the diagnosis of histoplasmosis when clinical, epidemiologic, and other laboratory studies are compatible.

TREATMENT

Immunocompetent children with uncomplicated or mild-to-moderate acute pulmonary histoplasmosis may not require therapy, because infection usually is self-limited. However, if the patient does not improve within 4 weeks, itraconazole should be administered for 6 to 12 weeks.

In contrast, treatment is imperative for all forms of disseminated histoplasmosis, which can be either an acute (rapid onset and progression, usually in an immunocompromised patient) or chronic illness (slower evolution, usually in an immunocompetent patient). For severe acute pulmonary or disseminated infections, treatment with a lipid formulation of amphotericin B is recommended. After clinical improvement occurs in 1 to 2 weeks, itraconazole is recommended for an additional 12 weeks. Itraconazole is preferred over other azoles by most experts; when used in adults, itraconazole is more effective, has fewer adverse effects, and is less likely to induce resistance than is fluconazole. Serum trough concentrations of itraconazole should be checked after 1 to 2 weeks of therapy to ensure adequate drug exposure.

All patients with chronic pulmonary histoplasmosis (eg, progressive cavitation of the lungs) should be treated. Mild to moderate cases should be treated with itraconazole for 1 to 2 years. Severe cases should be treated initially with a lipid formulation amphotericin B followed by itraconazole for the same duration.

Mediastinal and inflammatory manifestations of infection generally do not need to be treated with antifungal agents. However, mediastinal adenitis that causes obstruction of a bronchus, the esophagus, or another mediastinal structure may improve with a brief course of corticosteroids. In these instances, itraconazole should be used concurrently and continued for 6 to 12 weeks. Dense fibrosis of mediastinal structures without an associated granulomatous inflammatory component does not respond to antifungal therapy, and surgical intervention may be necessary for severe cases.

For treatment of moderately severe to severe progressive disseminated histoplasmosis (PDH) in an infant or child, a lipid formulation of amphotericin B is the drug of choice and usually is given for a minimum of 2 weeks.

When the child has demonstrated substantial clinical improvement and a decline in the serum concentration of *Histoplasma* antigen, oral itraconazole is administered for 12 weeks. Prolonged therapy for up to 12 months may be required for patients with severe disease, primary immunodeficiency syndromes, acquired immunodeficiency that cannot be reversed, or patients who experience relapse despite appropriate therapy. For those with mild to moderate PDH, itraconazole for 12 months is recommended. After completion of treatment for PDH, urine antigen concentrations should be monitored for 6 months. Stable, low, and decreasing concentrations that are unaccompanied by signs of active infection may not necessarily require prolongation or resumption of treatment.

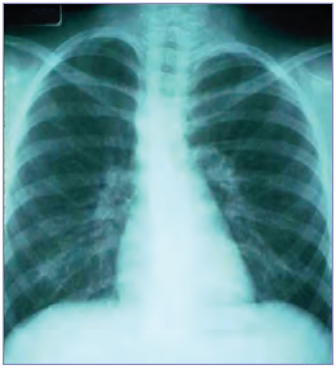


Image 67.1
Acute, primary histoplasmosis in a 13-year-old girl. Progressive disseminated histoplasmosis is unusual in otherwise healthy children.

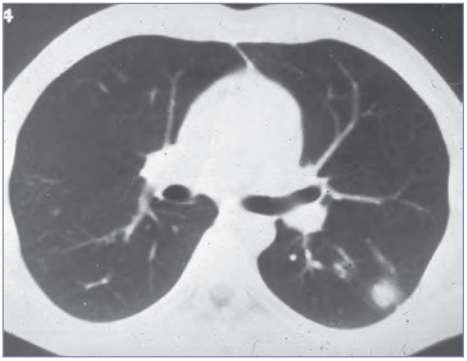


Image 67.2
Computed tomography scan showing single pulmonary nodule of histoplasmosis. Courtesy of Centers for Disease Control and Prevention.

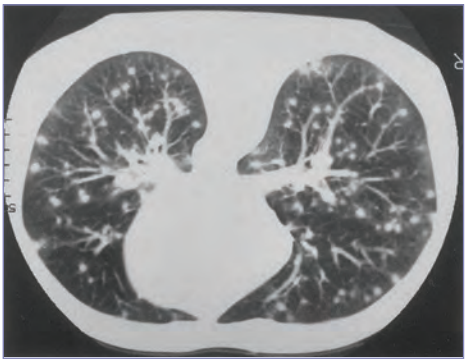


Image 67.3
Computed tomography scan of lungs showing classic snowstorm appearance of acute histoplasmosis. Courtesy of Centers for Disease Control and Prevention.

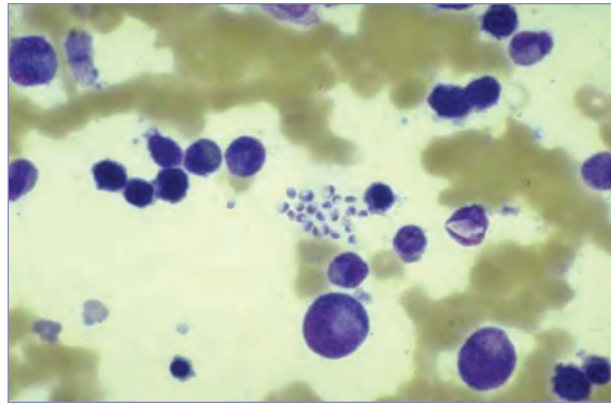


Image 67.4
Histoplasma capsulatum in peripheral blood smear. Copyright Martha Lepow.

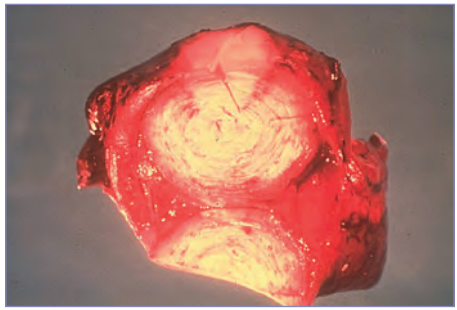


Image 67.5
Gross pathology specimen of lung showing cut surface of fibrocaseous nodule due to *Histoplasma capsulatum*. Courtesy of Centers for Disease Control and Prevention.

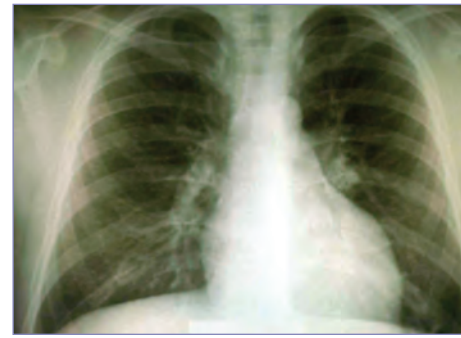


Image 67.6
A preadolescent with calcified left hilar lymph nodes bilaterally secondary to histoplasmosis.

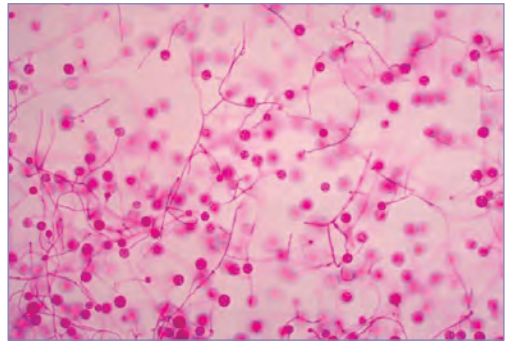


Image 67.7
This photomicrograph shows the smooth macroconidia of the Jamaican isolate of *Histoplasma capsulatum*. *H capsulatum* is a dimorphic fungus (ie, morphologically grows in 2 different forms). It takes a mycelial form when grown at a lower temperature (ie, 25°C [77°F] creating macroconidia, and a yeast form at 35°C [95°F] on enriched media). Courtesy of Centers for Disease Control and Prevention.

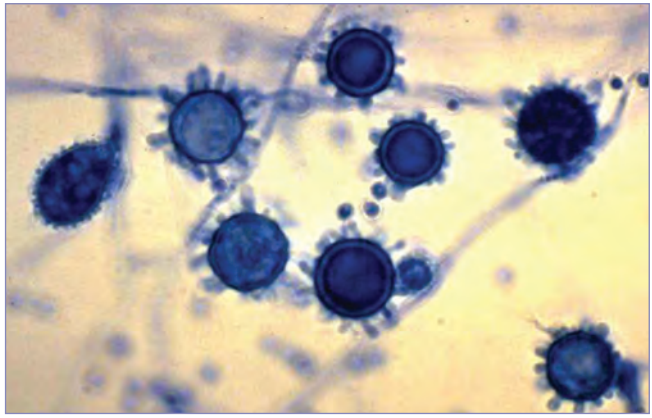


Image 67.8
Asexual spores (conidia). Tuberculate macroconidia of *Histoplasma capsulatum* (toluidine blue stain). Microconidia are also present. Courtesy of Centers for Disease Control and Prevention.

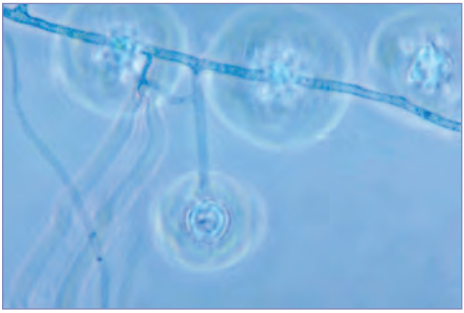


Image 67.9
This photomicrograph reveals a conidiophore of the fungus *Histoplasma capsulatum*. *H capsulatum* grows in soil and material contaminated with bat or bird droppings. Spores become airborne when contaminated soil is disturbed. Breathing the spores causes pulmonary histoplasmosis. Courtesy of Centers for Disease Control and Prevention.

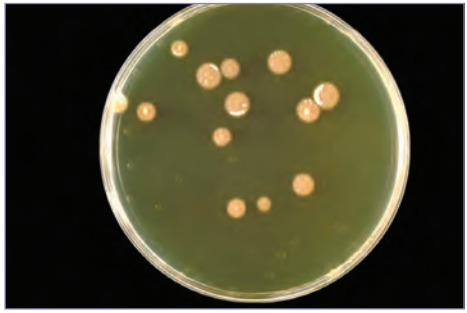


Image 67.10
Pictured is a Sabhi agar plate culture of the fungus *Histoplasma capsulatum* grown at 20°C (68°F). Positive histoplasmin skin test results occur in as many as 80% of the people living in areas where *H capsulatum* is common, such as the eastern and central United States. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 68

Hookworm Infections

(*Ancylostoma duodenale* and *Necator americanus*)

CLINICAL MANIFESTATIONS

Patients with hookworm infection often are asymptomatic; however, chronic hookworm infection is a common cause of moderate and severe hypochromic, microcytic anemia in people living in resource-limited tropical countries, and heavy infection can cause hypoproteinemia with edema. Chronic hookworm infection in children may lead to physical growth delay, deficits in cognition, and developmental delay. After contact with contaminated soil, initial skin penetration of larvae, often involving the feet, can cause a stinging or burning sensation followed by pruritus and a papulovesicular rash ("ground itch") that may persist for 1 to 2 weeks. Pneumonitis associated with migrating larvae (Löffler-like syndrome) is uncommon and usually mild, except in heavy infestations. Colicky abdominal pain, nausea, diarrhea, and marked eosinophilia can develop 4 to 6 weeks after exposure. Blood loss secondary to hookworm infection develops 10 to 12 weeks after initial infection, and symptoms related to serious iron-deficiency anemia can develop in long-standing moderate or heavy hookworm infections. Pharyngeal itching, hoarseness, nausea, and vomiting can develop shortly after oral ingestion of infectious *Ancylostoma duodenale* larvae.

ETIOLOGY

Necator americanus is the major cause of hookworm infection worldwide, although *A duodenale* also is an important hookworm in some regions. Mixed infections can occur. Other species of hookworm also can infect humans (eg, *Ancylostoma ceylanicum*). Each of these roundworms (nematodes) has a similar life cycle, with the exception of *A ceylanicum*, a zoonotic parasite. Other animal hookworm species cause cutaneous larva migrans when filariform larvae penetrate the skin and migrate in the upper dermis, causing an intensely pruritic track.

EPIDEMIOLOGY

Humans are the only reservoir for *A duodenale* and *N americanus.* Dogs, cats, and hamsters can harbor *A ceylanicum.* Hookworms are prominent in rural, tropical, and subtropical areas where soil contamination with human feces is common. *N americanus* is predominant in the Western hemisphere, sub-Saharan Africa, Southeast Asia, and a number of Pacific islands. *A duodenale* is the predominant species in the Mediterranean region, northern Asia, and selected foci of South America. *A ceylanicum* is found in Asia, Australia, some Pacific islands, South Africa, and Madagascar. Larvae and eggs survive in loose, sandy, moist, shady, well-aerated, warm soil (optimal temperature 23°C–33°C [73°F–91°F]). Hookworm eggs from stool hatch in soil in 1 to 2 days as rhabditiform larvae. These larvae develop into infective filariform larvae in soil within 5 to 7 days and can survive for 3 to 4 weeks. Percutaneous infection occurs after exposure to infectious larvae. *A duodenale* transmission can occur by oral ingestion and possibly through human milk. Untreated infected patients can harbor worms for 5 years or longer.

INCUBATION PERIOD

The time from exposure to development of noncutaneous symptoms is 4 to 12 weeks.

DIAGNOSTIC TESTS

Microscopic demonstration of hookworm eggs in feces is diagnostic. Adult worms or larvae rarely are seen. Approximately 5 to 8 weeks are required after infection for eggs to appear in feces. A direct stool smear with saline solution or potassium iodide saturated with iodine is adequate for diagnosis of heavy hookworm infection; light infections require concentration techniques. Quantification techniques (eg, Kato-Katz, Beaver direct smear, or Stoll egg-counting techniques) to determine the clinical significance of infection and the response to treatment may be available from state or reference laboratories. Cutaneous larva migrans is diagnosed clinically.

TREATMENT

Albendazole, mebendazole, and pyrantel pamoate all are effective treatments. Albendazole must be taken with food; a fatty meal increases oral bioavailability. Pyrantel pamoate suspension can be mixed with milk or fruit juice. Although data suggest that these drugs are safe in children younger than 2 years, the risks and benefits of therapy should be considered before administration. In 1-year-old children, the World Health Organization recommends reducing the albendazole dose to half of that given to older children and adults. Reexamination of stool specimens 2 weeks after therapy to determine whether worms have been eliminated is helpful for assessing response to therapy. Retreatment is indicated for persistent infection. Nutritional supplementation, including iron, is important when moderate or severe anemia is present.

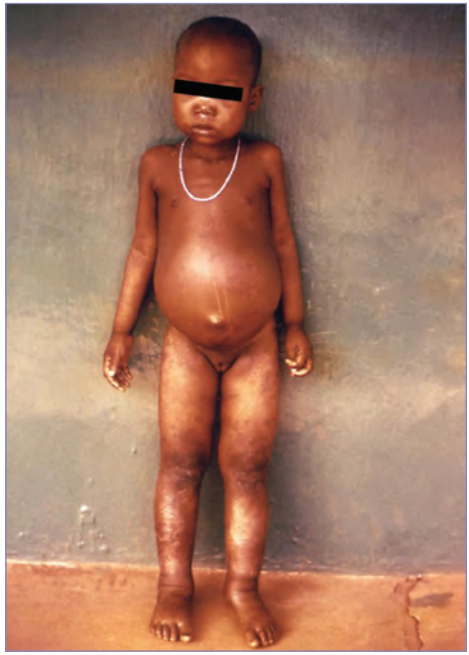


Image 68.1
This child with hookworm shows visible signs of edema and was diagnosed with anemia as well. Courtesy of Centers for Disease Control and Prevention.

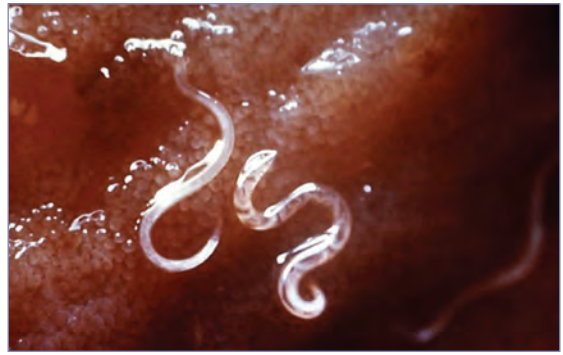


Image 68.2
This enlargement shows hookworms, *Ancylostoma caninum*, attached to the intestinal mucosa. Barely visible larvae penetrate the skin (often through bare feet), are carried to the lungs, go through the respiratory tract to the mouth, are swallowed, and eventually reach the small intestine. This journey takes about a week. Courtesy of Centers for Disease Control and Prevention.

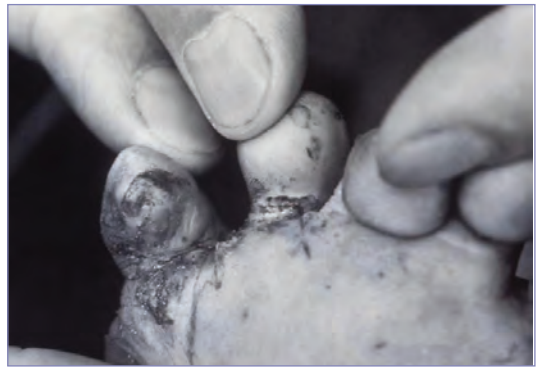


Image 68.3
This patient presented with a hookworm infection involving the toes of the right foot, which is also known as ground itch. Usually the first sign of infection is itching and a rash at the site where skin touched contaminated soil or sand, which occurs when the larvae penetrate the skin, followed by anemia, abdominal pain, diarrhea, loss of appetite, and weight loss. Courtesy of Centers for Disease Control and Prevention.

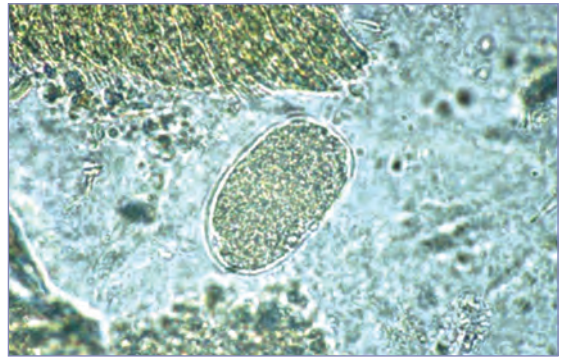


Image 68.4
Hookworm (*Necator americanus*) ova in stool preparation.

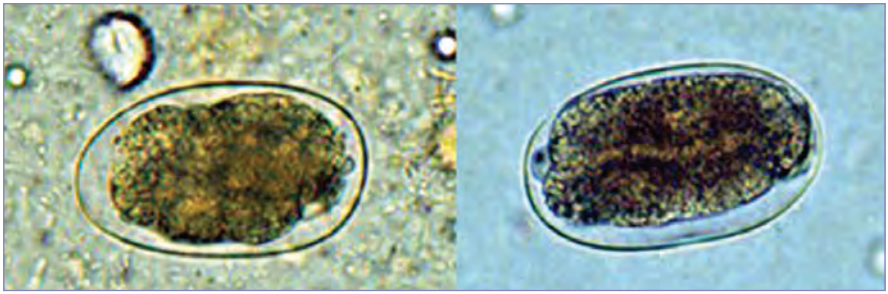


Image 68.5
Hookworm eggs examined on wet mount (eggs of *Ancylostoma duodenale* and *Necator americanus* cannot be distinguished morphologically). Diagnostic characteristics: 57 to 76 µm by 35 to 47 µm, oval or ellipsoidal, thin shell. The embryo (right) has begun cellular division and is at an early developmental stage (gastrula). Courtesy of Centers for Disease Control and Prevention.

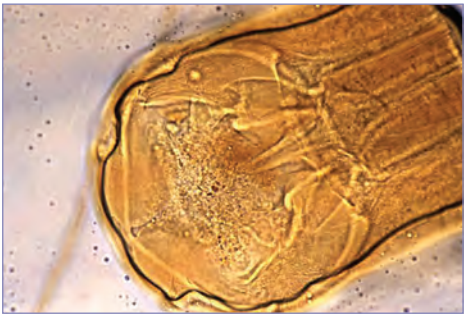


Image 68.6
This micrograph reveals the head of the hookworm *Necator americanus* and its mouth's cutting plates (magnification ×400). The hookworm uses these sharp cutting teeth to grasp firmly to the intestinal wall and, while remaining fastened in place, ingests the host's blood, obtaining its nutrients in this fashion. Courtesy of Centers for Disease Control and Prevention.

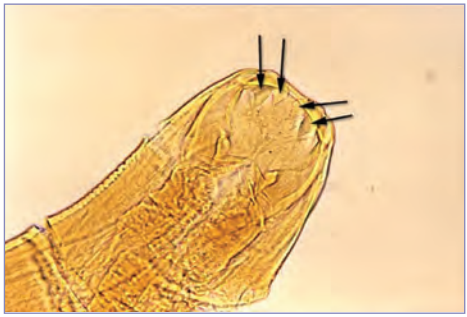


Image 68.7
This unstained micrograph reveals the *Ancylostoma duodenale* hookworm's mouth parts (magnification ×125). Courtesy of Centers for Disease Control and Prevention.

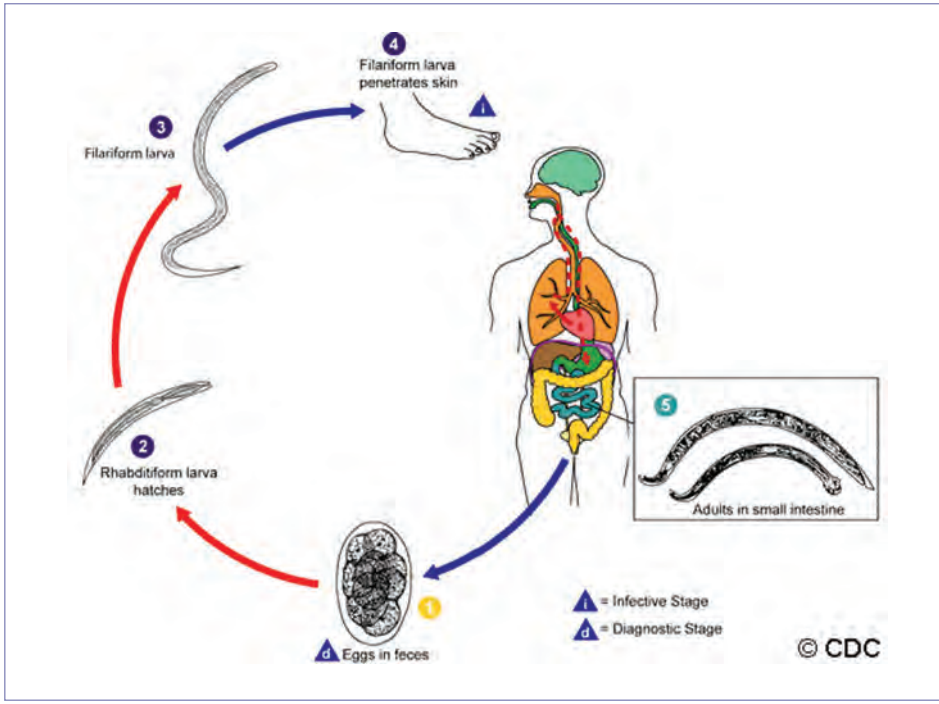


Image 68.8

Eggs are passed in the stool (1) and, under favorable conditions (moisture, warmth, shade), larvae hatch in 1 to 2 days. The released rhabditiform larvae grow in the feces and/or the soil (2), and, after 5 to 10 days (and 2 molts), they become filariform (third-stage) larvae that are infective (3). These infective larvae can survive 3 to 4 weeks in favorable environmental conditions. On contact with the human host, the larvae penetrate the skin and are carried through the veins to the heart and then to the lungs. They penetrate into the pulmonary alveoli, ascend the bronchial tree to the pharynx, and are swallowed (4). The larvae reach the small intestine, where they reside and mature into adults. Adult worms live in the lumen of the small intestine, where they attach to the intestinal wall with resultant blood loss by the host (5). Most adult worms are eliminated in 1 to 2 years, but longevity records can reach several years. Some *Ancylostoma duodenale* larvae, following penetration of the host skin, can become dormant (in the intestine or muscle). In addition, infection by *A duodenale* may also occur by the oral and transmammary route. *Necator americanus*, however, requires a transpulmonary migration phase. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 69

Human Herpesvirus 6 (Including Roseola) and 7

CLINICAL MANIFESTATIONS

Clinical manifestations of primary infection with human herpesvirus 6B (HHV-6B) include roseola (exanthem subitum) in approximately 20% of infected children, as well as a nonspecific febrile illness without rash or localizing signs. Acute HHV-6B infection may be accompanied by cervical and characteristic postoccipital lymphadenopathy, gastrointestinal tract or respiratory tract signs, and inflamed tympanic membranes. Fever often is high (temperature >39.5°C [103.0°F]) and persists for 3 to 7 days. Approximately 20% of all emergency department visits for febrile children 6 through 12 months of age are attributable to HHV-6B. Roseola is distinguished by an erythematous maculopapular rash that appears once fever resolves and can last hours to days. Febrile seizures, sometimes leading to status epilepticus, are the most common complication and reason for hospitalization among children with primary HHV-6B infection. Approximately 10% to 15% of children with primary HHV-6B infection develop febrile seizures, predominantly between the ages of 6 and 18 months. Other reported neurologic manifestations include a bulging fontanelle and encephalopathy or encephalitis, more commonly noted in Japan than in the United States or Europe. Hepatitis has been reported as a rare manifestation of primary HHV-6B infection. Approximately 5% of mononucleosis syndrome cases are attributable to HHV-6B. Congenital infection with HHV-6B and HHV-6A, which occurs in approximately 1% of newborn infants, has not been linked to any clinical disease. Similarly, infection with HHV-6A has not been associated with any recognized disease.

The clinical manifestations occurring with human herpesvirus 7 (HHV-7) infection are less clear than with HHV-6B. Most primary infections with HHV-7 presumably are asymptomatic or mild and not distinctive. Some initial infections can present as typical roseola and may account for second or recurrent cases of roseola. Febrile illnesses associated with seizures also have been documented to occur during primary HHV-7 infection. Some investigators suggest that the association of HHV-7 with these clinical manifestations results from the ability of HHV-7 to reactivate latent HHV-6.

Following infection, HHV-6B, HHV-6A, and HHV-7 remain in a latent state and may reactivate. The clinical circumstances and manifestations of reactivation in healthy people are unclear. Illness associated with HHV-6B reactivation has been described primarily among recipients of solid organ and hematopoietic stem cell transplants. Clinical findings associated with HHV-6B reactivation in solid organ and hematopoietic stem cell transplants include fever, rash, hepatitis, bone marrow suppression, graft rejection, pneumonia, and encephalitis. The best characterized of these is post-transplantation acute limbic encephalitis, a specific syndrome associated with HHV-6B reactivation in the central nervous system characterized by anterograde amnesia, seizures, insomnia, confusion, and the syndrome of inappropriate antidiuretic hormone secretion. Patients undergoing cord blood transplantation are at an increased risk of developing post-transplantation acute limbic encephalitis, with significant morbidity and mortality attributed to this complication. Other clinical findings associated with HHV-6B reactivation in transplant patients are fever, rash, hepatitis, bone marrow suppression, graft rejection, pneumonia, and delirium. A few cases of central nervous system symptoms have been reported in association with HHV-7 reactivation in immunocompromised hosts, but clinical findings generally have been reported much less frequently with HHV-7 than with HHV-6B reactivation.

ETIOLOGY

HHV-6B, HHV-6A, and HHV-7 are lymphotropic viruses that are closely related members of the *Herpesviridae* family, subfamily *Betaherpesvirinae.* As betaherpesviruses, HHV-6B, HHV-6A, and HHV-7 are most closely related to cytomegalovirus. As with all human herpesviruses, they establish lifelong latency after initial acquisition. In 2012, HHV-6A and HHV-6B were recognized as distinct species rather than as variants of the same species. Essentially all postnatally acquired primary infections are caused by HHV-6B.

EPIDEMIOLOGY

HHV-6B and HHV-7 cause ubiquitous infections in children worldwide. Humans are the only known natural host. Nearly all children acquire HHV-6B infection within the first 2 years of life, probably resulting from asymptomatic shedding of infectious virus in secretions of a healthy family member or other close contact. During the acute phase of primary infection, HHV-6B and HHV-7 can be isolated from peripheral blood mononuclear cells and HHV-7 from saliva of some children. Viral DNA subsequently may be detected throughout life by polymerase chain reaction (PCR) assay in multiple body sites. Virus-specific maternal antibody, which is present uniformly in the sera of infants at birth, provides transient partial protection. The infection rate increases rapidly in early infancy, peaking between 6 and 24 months of age. Essentially all children are seropositive for HHV-6B before 4 years of age. Infections occur throughout the year. Occasional outbreaks of roseola have been reported.

Congenital infection occurs in approximately 1% of newborn infants, as determined by the presence of HHV-6A or HHV-6B DNA in cord blood. Most congenital infections appear to result from the germline passage of maternal or paternal chromosomally integrated HHV-6 (ciHHV-6), a unique mechanism of transmission of human viral congenital infection. Transplacental HHV-6 infection also may occur from reinfection or reactivation of maternal HHV-6 infection or from reactivated maternal ciHHV-6. HHV-6 has not been identified in human milk. Congenital infection typically is without clinical signs of illness, and the implications of ciHHV-6 are not fully known.

HHV-7 infection usually occurs later in childhood than HHV-6B infection. By adulthood, the seroprevalence of HHV-7 is approximately 85%. Infectious HHV-7 is present in more than 75% of saliva specimens obtained from healthy adults. Acquisition of virus via infected respiratory tract secretions of healthy contacts is the probable mode of transmission of HHV-7 to young children. HHV-7 has been detected in human milk, peripheral blood mononuclear cells, cervical secretions, and other body sites. Congenital HHV-7 infection has not been demonstrated by the examination of large numbers of cord blood samples for HHV-7 DNA.

The mean **incubation period** for HHV-6B is 9 to 10 days. For HHV-7, this is unknown.

DIAGNOSTIC TESTS

Multiple assays for detection of HHV-6 and HHV-7 have been developed, but because laboratory diagnosis of HHV-6 or HHV-7 usually does not influence clinical management (infections among the severely immunocompromised may be an exception), these tests have limited use in clinical practice.

Reference laboratories offer diagnostic testing for HHV-6B, HHV-6A, and HHV-7 infections by detection of viral DNA in blood, cerebrospinal fluid (CSF), other body fluids, or tissue specimens. However, detection of HHV-6A, HHV-6B, or HHV-7 DNA by PCR assay might not differentiate between new infection, persistence of virus from past infection, or chromosomal integration of HHV-6. At least one multiplexed PCR diagnostic panel designed to detect agents of meningitis and encephalitis in CSF contains HHV-6 as one of its target pathogens; however, given the likelihood of ciHHV-6 (1%), which would give a positive CSF PCR result if cells are present, a positive test result should be interpreted with caution. DNA detection of HHV-6B or HHV-7 by PCR assay in conjunction with seroconversion or, in an infant with maternal antibodies, a fourfold titer increase confirms primary infection.

Serologic tests include immunofluorescent antibody assay, neutralization, immunoblot, and enzyme immunoassay (EIA). A fourfold increase in serum antibody concentration alone does not necessarily indicate new infection, because an increase in titer may occur with reactivation and in association with other infections, especially other beta-herpesvirus infections. However, documented seroconversion is considered evidence of recent primary infection, and serologic tests may be useful for epidemiologic studies. Detection of specific immunoglobulin (Ig) M antibody is not reliable for diagnosing new infection, because IgM antibodies to HHV-6 and HHV-7 are not always detectable in children with primary infection.

These antibody assays do not differentiate HHV-6A from HHV-6B infections. In addition, the diagnosis of primary HHV-7 infection in children with previous HHV-6B infection is confounded by concurrent increase in HHV-6 antibody titer from antigenic cross-reactivity or from reactivation of HHV-6B by a new HHV-7 infection

TREATMENT

Supportive. The use of ganciclovir (and, therefore, valganciclovir) or foscarnet may be beneficial for immunocompromised patients with HHV-6 disease and is recommended for treatment of encephalitis in hematopoietic stem cell transplant patients. Antiviral resistance may occur.

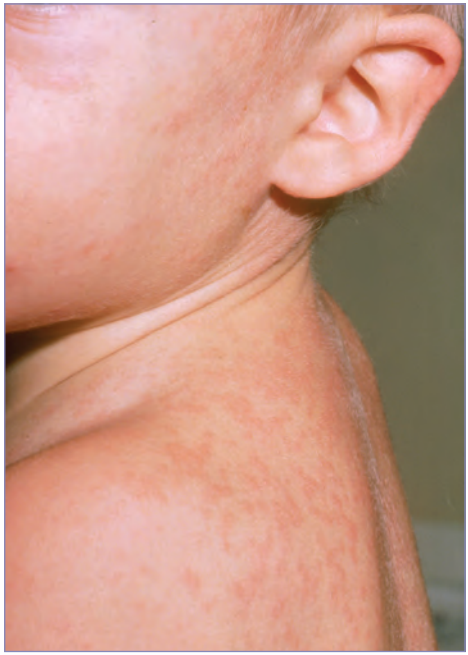


Image 69.1
A 13-month-old boy developed high fever that persisted for 4 days without recognized cause. The child appeared relatively well, and the fever subsided to be followed by a maculopapular rash that began on the trunk and spread to involve the face and extremities. The course was typical for roseola infantum. Courtesy of George Nankervis, MD.

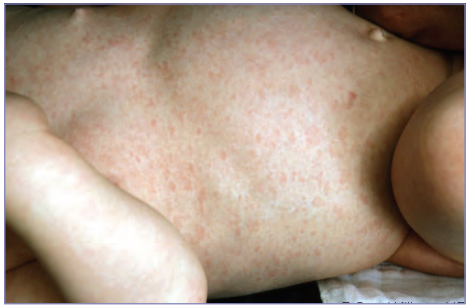


Image 69.2
Roseola rash in a 10-month-old. Seizures are not uncommon during the febrile phase of primary infections. Copyright Gary Williams, MD.

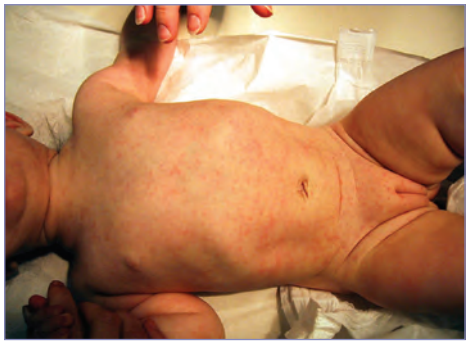


Image 69.3
An 8-month-old with a temperature between 38.3°C and 39.4°C (101°F and 103°F) for 3 consecutive days. The child appeared well, with no additional symptoms aside from mild irritability and decreased appetite. After cessation of the fever, the patient developed a maculopapular rash heavy on the trunk, but, aside from this, the patient still appeared well. The rash resolved in the next 48 hours. The clinical course and rash are compatible with roseola. Copyright Stan Block, MD, FAAP.

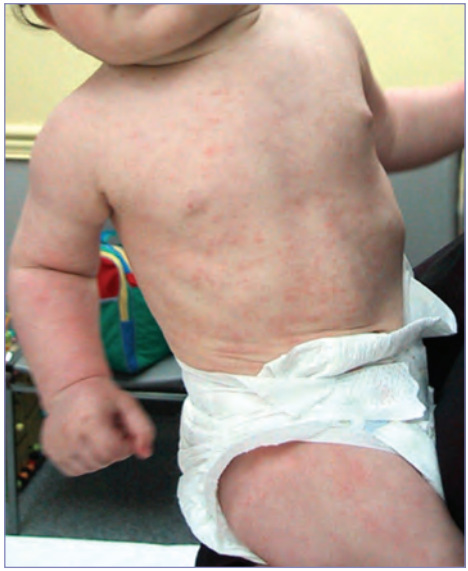


Image 69.4
Clinical course and rash compatible with roseola. This is the same patient as in Image 69.3. Copyright Stan Block, MD, FAAP.

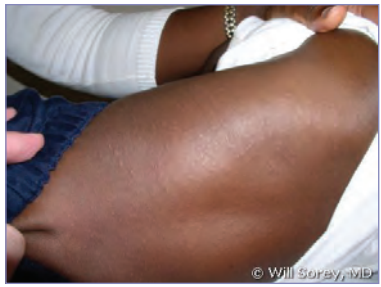


Image 69.6
A 3-year-old with 2 days of bounding fever to 39.4°C (103°F). Although the child was febrile, he had still been active between fever spikes. He had a brief tonic-clonic seizure but was not started on anticonvulsants because of his well appearance at the emergency department. He was diagnosed with a febrile seizure. The fever resolved, but the child was restricted from child care because of a fine rash all over. He was asymptomatic at the time his rash developed and was diagnosed with roseola. Despite reassurance, school admission was refused until the rash faded. Courtesy of Will Sorey, MD.

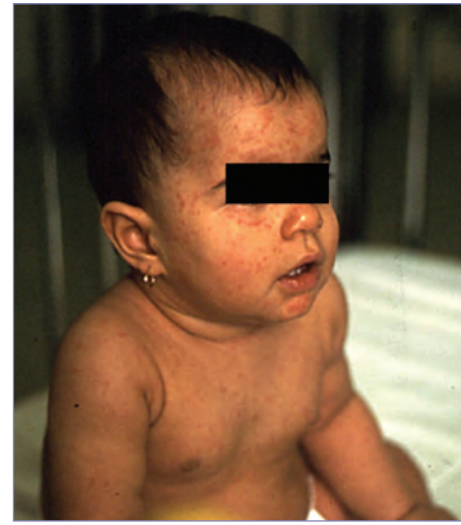


Image 69.5
A female toddler with the exanthem of roseola following several days of high fever. Courtesy of Larry Frenkel, MD.

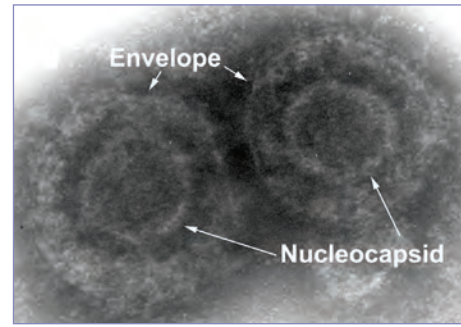


Image 69.7
Thin-section electron micrograph image of human herpesvirus 7, which, like human herpesvirus 6, can cause roseola. Virions consist of a darkly staining core within the capsid that is surrounded by a proteinaceous tegument layer and enclosed within the viral envelope. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 70

Human Herpesvirus 8

CLINICAL MANIFESTATIONS

Human herpesvirus (HHV-8) is the etiologic agent associated with Kaposi sarcoma (KS), primary effusion lymphoma, multicentric Castleman disease (MCD), and "the Kaposi sarcoma herpesvirus-associated inflammatory cytokine syndrome (KICS)." MCD results in a proliferation of immune cells (both B and T lymphocytes) with multiorgan dysfunction that is associated with a hyperactive immune response resulting in excessive release of proinflammatory cytokines. HHV-8 also is one of the triggers of hemophagocytic lymphohistiocytosis (HLH). In regions with endemic HHV-8, a nonspecific primary infection syndrome in immunocompetent children consists of fever and a maculopapular rash, often accompanied by upper respiratory tract signs. Primary infection among immunocompromised people and men who have sex with men tends to have more severe manifestations, including pancytopenia, fever, rash, lymphadenopathy, splenomegaly, diarrhea, arthralgia, disseminated disease, and/or KS. In parts of Africa, among children with and without HIV infection, KS is a frequent, aggressive malignancy. In the United States, KS is rare in children and occurs primarily in adults with poorly controlled HIV infection. Among organ transplant recipients and other immunosuppressed patients, KS is an important cause of cancer-related deaths. Primary effusion lymphoma is rare among children. MCD has been described in immunosuppressed and immunocompetent children, but the proportion of cases attributable to infection with HHV-8 is unknown.

ETIOLOGY

HHV-8 is a member of the family *Herpesviridae*, the *Gammaherpesvirinae* subfamily, and the *Rhadinovirus* genus, and is related closely to Epstein-Barr virus and to herpesvirus saimiri of monkeys.

EPIDEMIOLOGY

In areas of Africa, the Amazon basin, the Mediterranean, and the Middle East with endemic HHV-8, seroprevalence ranges from approximately 30% to 80%. Low rates of seroprevalence, generally less than 5%, have been reported in the United States, Northern and Central Europe, and most areas of Asia. Higher rates, however, occur in specific geographic regions, among adolescents and adults with or at high risk of acquiring HIV infection, injection drug users, and children adopted from some Eastern European countries.

Acquisition of HHV-8 in areas with endemic infection frequently occurs before puberty, likely by oral inoculation of saliva of close contacts, especially mothers and siblings. Virus is shed frequently in saliva of infected people and becomes latent for life in peripheral blood mononuclear cells, primarily CD19+ B lymphocytes, and lymphoid tissue. In areas where infection is not endemic, sexual transmission appears to be the major route of infection, especially among men who have sex with men. Studies from areas with endemic infection have suggested transmission may occur by blood transfusion, but in the United States, evidence for this is lacking. Transplantation of infected donor organs has been documented to result in HHV-8 infection in the recipient. HHV-8 DNA has been detected in blood drawn at birth from infants born to HHV-8 seropositive mothers, but vertical transmission seems to be rare. Viral DNA has been detected in human milk, but transmission via human milk is yet to be proven.

The **incubation period** of HHV-8 is unknown.

DIAGNOSTIC TESTS

Nucleic acid amplification testing and serologic assays for HHV-8 are available. Polymerase chain reaction (PCR) tests may be used on peripheral blood, fluid from body cavity effusions, and tissue biopsy specimens of patients with HHV-8–associated disease, such as KS. Detection of HHV-8 in peripheral blood specimens by PCR assay has been used to support the diagnosis of KS and to identify exacerbations of HHV-8-associated diseases, primarily MCD and KICS (especially at high copy number in these 2 diseases). However, HHV-8 DNA detection in the peripheral blood also occurs in asymptomatically infected people.

Currently available serologic assays measuring antibodies to HHV-8 include immunofluorescence antibody (IFA) assay, enzyme

immunoassays (EIAs), and Western blot assays using recombinant HHV-8 proteins. These serologic assays detect both latent and lytic infection, but each has challenges with accuracy or convenience, with resulting limitations on their use in the diagnosis and management of acute clinical disease.

TREATMENT

No antiviral treatment is approved for HHV-8 disease. Several antiviral agents have in vitro activity against HHV-8. Case reports document an effect of ganciclovir, ganciclovir combined with zidovudine, cidofovir, and foscarnet. HHV-8 associated malignancies can be treated with radiation and cancer chemotherapies.

CHAPTER 71

Human Immunodeficiency Virus Infection

CLINICAL MANIFESTATIONS

Human immunodeficiency virus (HIV) infection results in a wide array of clinical manifestations. HIV type 1 (HIV-1) is much more common in the United States than HIV type 2 (HIV-2). Unless otherwise specified, this chapter addresses HIV-1 infection. Acquired immunodeficiency syndrome (AIDS) is the name given to an advanced stage of HIV infection based on specific criteria for children, adolescents, and adults established by the Centers for Disease Control and Prevention (CDC).

Acute retroviral syndrome develops in 50% to 90% of adolescents and adults within the first few weeks after they become infected with HIV. Acute retroviral syndrome is characterized by nonspecific mononucleosis-like symptoms, including fever, malaise, lymphadenopathy, and skin rash.

With timely diagnosis of HIV infection in pregnant women, infants, and children and appropriate treatment, clinical manifestations of HIV infection, including the occurrence of AIDS-defining illnesses, now are rare among children in the United States and other industrialized countries. Early clinical manifestations of untreated pediatric HIV infection include unexplained fevers, generalized lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, persistent or recurrent oral and diaper candidiasis, recurrent diarrhea, parotitis, hepatitis, central nervous system (CNS) disease (eg, encephalopathy, hyperreflexia, hypertonia, floppiness, developmental delay), lymphoid interstitial pneumonia, recurrent invasive bacterial infections, and other opportunistic infections (OIs) (eg, viral, parasitic, and fungal).

In the era of combination antiretroviral therapy (cART), there has been a substantial decrease in frequency of all OIs. The frequency of different OIs in the pre-cART era varied by age, pathogen, previous infection history, and immunologic status. In the pre-cART era, the most common OIs observed among children in the United States were infections caused by invasive encapsulated bacteria, *Pneumocystis jiroveci* (previously called *Pneumocystis carinii* pneumonia, hence the still-used acronym PCP), varicella-zoster virus, cytomegalovirus, herpes simplex virus, *Mycobacterium avium* complex, and *Candida* species. Less commonly observed opportunistic pathogens included Epstein-Barr virus (EBV), *Mycobacterium tuberculosis*, *Cryptosporidium* species, *Cystoisospora* (formerly *Isospora*) species, other enteric pathogens, *Aspergillus* species, and *Toxoplasma gondii*.

Immune reconstitution inflammatory syndrome (IRIS) is a paradoxical clinical deterioration often seen in severely immunosuppressed individuals that occurs shortly after the initiation of cART. Local and/or systemic symptoms develop secondary to an inflammatory response as cell-mediated immunity is restored. Underlying infection with mycobacteria (including *Mycobacterium tuberculosis*), herpesviruses, and fungi (including *Cryptococcal* species) predispose to IRIS.

Malignant neoplasms in children with HIV infection are relatively uncommon, but leiomyosarcomas and non-Hodgkin B-cell lymphomas of the Burkitt type (including some that occur in the CNS) occur more commonly in children with HIV infection than in immunocompetent children. Kaposi sarcoma, caused by human herpesvirus 8, is rare in children in the United States but has been documented in HIV-infected children who have emigrated from sub-Saharan African countries. The incidence of malignant neoplasms in HIV-infected children has decreased during the cART era.

The incidence of HIV encephalopathy is high among untreated HIV-infected infants and young children. In the United States, pediatric HIV encephalopathy has decreased substantially in the cART era, although other neurologic signs and symptoms have been appreciated, such as myelopathy or peripheral neuropathies, sometimes associated with antiretroviral therapy.

Without cART, the prognosis for survival is poor for untreated infants who acquired HIV infection through mother-to-child transmission (MTCT) and who have high viral loads (ie, >100,000 copies/mL) and severe suppression of CD4+ T-lymphocyte counts

Table 71.1
HIV Infection Stage, Based on Age-Specific CD4+ T-Lymphocyte Count or CD4+ T-Lymphocyte Percentage of Total Lymphocytes[a,b]

	Age on Date of CD4+ T-Lymphocyte Test					
	<1 y		1 Through 5 y		6 y Through Adult	
Stage[a]	Cells/μL	%	Cells/μL	%	Cells/μL	%
1	≥1,500	≥34	≥1,000	≥30	≥500	≥26
2	750–1,499	26–33	500–999	22–29	200–499	14–25
3	<750	<26	<500	<22	<200	<14

[a]The stage is based primarily on the CD4+ T-lymphocyte count; the CD4+ T-lymphocyte count takes precedence over the CD4+ T-lymphocyte percentage, and the percentage is considered only if the count is missing. If a Stage 3-defining opportunistic illness has been diagnosed, then the stage is 3 regardless of CD4+ T-lymphocyte test results.
[b]Source: Centers for Disease Control and Prevention. Revised surveillance case definition for HIV infection—United States, 2014. *MMWR Recomm Rep.* 2014;63(RR-3):1–10.

(Table 71.1). In these children, AIDS-defining conditions developing during the first 6 months of life, including PCP, progressive neurologic disease, and severe wasting, are predictors of a poor outcome.

ETIOLOGY

HIV-1 and HIV-2 are cytopathic lentiviruses (genus *Lentivirus*) belonging to the family *Retroviridae* and are related closely to the simian immunodeficiency viruses, which infect a variety of nonhuman primate species in sub-Saharan Africa. Retroviruses are characterized by the presence of a viral reverse transcriptase (RT) enzyme that converts the single-stranded viral RNA genome into a double-stranded DNA copy. The double-stranded genome copy, termed the provirus, integrates into the host cell genome in a reaction catalyzed by the viral integrase enzyme.

Three distinct genetic groups of HIV exist worldwide: M (major), O (outlier), and N (new). Group M viruses are the most prevalent worldwide and comprise 8 genetic subtypes, or clades, known as A through K, each of which has a distinct geographic distribution.

HIV-2, the second AIDS-causing virus, is found predominantly in West Africa. The prevalence of HIV-2 in the United States is extremely low. HIV-2 is thought to have a milder disease course with a longer time to development of AIDS than HIV-1. Accurate diagnosis of HIV-2 is important clinically, because HIV-2 is resistant to nonnucleoside reverse transcriptase inhibitors (NNRTIs) and at least 1 fusion inhibitor (enfuvirtide). CDC guidelines state that HIV-2 serologic testing should be performed in patients who: (1) are from countries of high prevalence, mainly in Western Africa; (2) share needles or have sex partners known to be infected with HIV-2 or from areas with endemic infection; (3) received transfusions or nonsterile medical care in areas with endemic infection; or (4) are children of women with risk factors for HIV-2 infection.

EPIDEMIOLOGY

Humans are the only known reservoir for HIV-1 and HIV-2. Latent virus persists in peripheral blood mononuclear cells and in cells of the brain, bone marrow, and genital tract even when plasma viral load is undetectable. Only blood, semen, cervicovaginal secretions, and human milk have been implicated epidemiologically in transmission of infection.

Established modes of HIV transmission include: (1) sexual contact (vaginal, anal, or orogenital); (2) percutaneous blood exposure (from contaminated needles or other sharp instruments); (3) mucous membrane exposure to contaminated blood or other body fluids; (4) MTCT in utero, around the time of labor and delivery (perinatally), and postnatally through breastfeeding; and (5) transfusion with contaminated blood products. Cases of probable HIV transmission from HIV-infected caregivers to children through feeding blood-tinged premasticated food have been reported in the United States. Because of highly effective

screening assays and protocols, transfusion of blood, blood components, and clotting factors has virtually been eliminated as a cause of HIV transmission in the United States since 1985. Transmission of HIV has not been associated with normal activities in households, schools, or child care settings but has been documented after contact of nonintact skin with blood-containing body fluids.

Since the mid-1990s, the number of reported pediatric AIDS cases has decreased significantly, primarily because of prevention of MTCT of HIV. This decrease in rate of MTCT of HIV in the United States was attributable to the development and implementation of antenatal HIV testing programs and other interventions to prevent transmission: antiretroviral (ARV) prophylaxis during the antepartum, intrapartum, and postnatal periods; cesarean delivery before labor and before rupture of membranes; and complete avoidance of breastfeeding. Currently in the United States, most HIV-infected pregnant women receive 3-drug cART regimens for treatment of their own HIV infection and for prevention of MTCT of HIV.

In the absence of breastfeeding, the risk of HIV infection for an infant born to an untreated HIV-infected mother in the United States is approximately 25%, with most transmission occurring around the intrapartum period. Maternal viral load is a critical determinant affecting the likelihood of MTCT of HIV, although transmission has been observed across the entire range of maternal viral loads. The risk of MTCT increases with each hour increase in the duration of ruptured membranes, which should be considered when evaluating the need for obstetric interventions. Cesarean delivery performed before onset of labor and before rupture of membranes has been shown to reduce MTCT. Current US guidelines recommend cesarean delivery before labor and before rupture of membranes at 38 completed weeks of gestation for HIV-infected women with a viral load >1,000 copies/mL (irrespective of use of ARVs during pregnancy) and for women with unknown viral load near the time of delivery. Cesarean delivery before labor and before rupture of membranes is not routinely recommended for women with undetectable viral loads.

Postnatal transmission via breastfeeding is the most common mode of MTCT of HIV in resource-limited settings, where safe alternatives to human milk may not be readily available. HIV genomes have been detected in cell-associated and cell-free fractions of human milk, even in women receiving cART who have low HIV viral loads, and MTCT of HIV has been reported in a small percentage of these women. Therefore, replacement (formula) feeding continues to be recommended for US mothers receiving cART, because safe alternatives to human milk are readily available. In resource-limited settings, women whose HIV infection status is unknown are encouraged to breastfeed their infants exclusively for the first 6 months of life, because the morbidity associated with formula feeding is unacceptably high. In addition, these women should be offered HIV testing. The World Health Organization recommended in 2010 that HIV-infected mothers exclusively breastfeed their infants for the first 6 months of life if safe alternatives to human milk are not available. The introduction of complementary foods should occur after 6 months of life, and breastfeeding should continue through 12 months of life. Breastfeeding should be replaced only when a nutritionally adequate and safe diet can be maintained without human milk. In areas where ARVs are available, infants should receive daily nevirapine prophylaxis until 1 week after human milk consumption stops, and their mothers should receive ARV (consisting of an effective cART regimen) indefinitely. For infants known to be HIV infected, mothers are encouraged to breastfeed exclusively for the first 6 months of life, and after the introduction of complementary foods, breastfeeding should continue up to 2 years of age, as per recommendations for the general population.

Although the rate of acquisition of HIV infection among infants has decreased significantly in the United States, the rate of new HIV infections during adolescence and young adulthood continues to increase. HIV infection in adolescents occurs disproportionately among youth of minority race or ethnicity. Transmission of HIV to adolescents is attributable primarily to sexual

exposure and secondarily to injection drug use. In 2014, it was estimated that, for the 13- to 24-year age group, males accounted for the clear majority of those in whom HIV infection was diagnosed. Young men who have sex with men (MSM) are at particularly high risk of acquiring HIV infection, and the rates of HIV infection in this demographic group continue to increase. In the United States in 2014, for the 13- to 24-year age group, an estimated 95% of new HIV infection diagnoses among males were attributed to male-to-male sexual contact, accounting for 83% of all HIV diagnoses in this age group. In contrast, in the same year, 91% of diagnoses of HIV infection in women 13 to 24 years of age were attributed to heterosexual contact. In 2010, there were an estimated 40,144 adolescents and young adults 13 to 24 years of age living with a diagnosis of HIV infection in the United States and 6 dependent areas (American Samoa, Guam, the Northern Mariana Islands, Puerto Rico, the Republic of Palau, and the US Virgin Islands). Of these, 61% were black, 20% were Hispanic, and 14% were non-Hispanic white. Rates of HIV infection among adolescents are particularly high in the southeastern and northeastern United States. Most HIV-infected adolescents and young adults are asymptomatic and, without testing, remain unaware of their infection. In 2014, youth 13 to 24 years of age represented an estimated 22% of new HIV infections annually, and of these, almost half (44%) were unaware that they were infected.

INCUBATION PERIOD

The usual age of onset of symptoms is approximately age 12 to 18 months for untreated infants and children in the United States who acquire HIV infection through MTCT. However, some HIV-infected children become ill in the first few months of life, whereas others remain relatively asymptomatic for more than 5 years and, rarely, until early adolescence. Without therapy, a bimodal distribution of symptomatic infection has been described: 15% to 20% of untreated HIV-infected children die before 4 years of age, with a median age at death of 11 months (rapid progressors), and 80% to 85% of untreated HIV-infected children have delayed onset of milder symptoms and survive beyond 5 years of age (slower progressors).

Acute retroviral syndrome occurring in adolescents and adults following HIV acquisition occurs 7 to 14 days following viral acquisition and lasts for 5 to 7 days. Only a minority of patients are ill enough to seek medical care.

DIAGNOSTIC TESTS

Serologic Assays

Immunoassays are used widely as the initial test for serum HIV antibody or for p24 antigen and HIV antibody (Table 71.2). Serologic assays for the diagnosis of HIV include

- Antigen/antibody combination immunoassays (fourth-generation tests) that detect HIV-1/HIV-2 antibodies as well as HIV-1 p24 antigen: recommended for initial testing;
- HIV-1/HIV-2 immunoassays (third-generation antibody tests): alternative for initial testing;
- HIV-1/HIV-2 antibody differentiation immunoassay that differentiates HIV-1 antibodies from HIV-2 antibodies (Multispot HIV-1/HIV-2 test): recommended for supplemental confirmatory testing;
- HIV-1 Western blot and HIV-1 indirect immunofluorescent antibody assays (first-generation tests): alternative for supplemental confirmatory testing;
- HIV-1 and HIV-2 antibodies (separate results for each) as well as p24 antigen (fifth-generation test): initial HIV screening, but not as a confirmatory test.
- These tests are highly sensitive and specific. Repeated immunoassay testing in duplicate of initially reactive specimens is common practice and is followed by additional testing to establish the diagnosis of HIV. HIV antibody tests can be performed on samples of serum/plasma, whole blood, or oral fluid; antigen/antibody tests can be performed only on serum or plasma. Both laboratory and single-use device (point-of-care) rapid tests can deliver expedited test results. Rapid point-of-care tests have been approved for use in the United States; these tests are used widely throughout the world, particularly to screen mothers with unknown serostatus in maternity settings. As with laboratory immunoassays, additional testing is required after a reactive rapid test. Results from rapid tests

are available from 1 to 20 minutes; in contrast, immunoassay results and follow-up testing might take 2 days or longer.

The 2014 CDC HIV laboratory testing algorithm recommends an initial HIV-1/HIV-2 antigen/antibody combination assay (fourth-generation assay) followed by an HIV-1/HIV-2 antibody differentiation assay. If acute HIV infection or end-stage AIDS is suspected, virologic testing may be indicated because of false-negative antibody assay results in these populations.

Nucleic Acid Amplification Assays

Plasma HIV DNA or RNA assays have been used to diagnose HIV infection. Currently, there is one HIV-1 qualitative RNA assay (APTIMA HIV-1 RNA Qualitative assay [Hologic Inc, Marlborough, MA]). The DNA polymerase chain reaction (PCR) assays can detect 1 to 10 DNA copies of proviral DNA in peripheral blood mononuclear cells and are used qualitatively to diagnose HIV infection. In addition, RNA PCR quantitative (viral load) assays provide results that serve as a predictor of disease progression and are useful in monitoring changes in viral load during treatment with cART.

Antigen Detection

Detection of the p24 antigen (including immune complex-dissociated) is less sensitive than the HIV proviral DNA PCR assay or culture. False-positive test results occur in samples obtained from infants younger than 1 month. This test generally should not be used, although newer assays have been reported to have sensitivities similar to HIV proviral DNA PCR assays.

HIV-2 Detection

Most HIV immunoassays detect but do not differentiate between HIV-1 and HIV-2 antibodies. An HIV-1 Western blot performed as a supplemental confirmatory test following a positive immunoassay result might report a negative or indeterminate result or, in >60% of cases, misclassify the HIV-2 virus as HIV-1 (eg, detection of only p24 and gp160 bands). Therefore, HIV-1/HIV-2 antibody differentiation assays should be used in lieu of the Western blot to identify antibodies and distinguish HIV-1 from HIV-2. Nucleic acid amplification tests for detection and quantitation of viral load are specific to HIV-1 and do not detect HIV-2. No nucleic acid amplification tests are approved by the FDA for HIV-2 viral load.

Diagnosis of Perinatally and Postnatally Acquired Infection

Because children born to HIV-infected mothers acquire passive maternal antibodies, antibody assays are not informative for the diagnosis of infection in children younger than 24 months unless assay results are negative. Therefore, laboratory diagnosis of HIV infection during the first 24 months of life is based on detection of the virus or viral nucleic acid (see Table 71.1). In children 24 months and older, HIV antibody assays can be used for diagnosis. Historically, 18 months was considered the age at which a positive antibody assay could accurately distinguish between presence of maternal and infant antibodies. However, using medical record data for a cohort of HIV-uninfected infants born from 2000 to 2007, it was demonstrated that clearance of maternal HIV antibodies occurred later than previously reported. Despite a median age of seroreversion of 13.9 months, 14% of infants remained seropositive after 18 months, 4.3% remained seropositive after 21 months, and 1.2% remained seropositive after 24 months.

In the United States, the preferred test for diagnosis of HIV infection in children younger than 24 months is the HIV DNA PCR assay. The sensitivity of the test performed at birth is 55% but increases to more than 90% by 2 to 4 weeks of age and to 100% at 3 months of age. A positive result from a specimen obtained within 48 hours of life suggests in utero transmission. A single HIV DNA PCR assay has a sensitivity of 95% and a specificity of 100% for samples collected from infected children 1 to 36 months of age. Results of DNA PCR assay, which detects cell-associated integrated HIV DNA, remain positive even among individuals with undetectable plasma viral loads.

Plasma HIV quantitative RNA assays also can be used to diagnose infection in HIV-exposed infants, with comparable sensitivity and specificity to DNA PCR regardless of the receipt of infant zidovudine prophylaxis. However, low levels of plasma viral load may result in

false-negative RNA PCR assay results. In many cases, an HIV RNA assay is used as a supplemental test for an infant with positive DNA PCR assay results, providing both confirmation and an initial viral load measurement.

Plasma viral loads among untreated infants who acquire HIV infection through MTCT increase rapidly to very high levels (typically from several hundred thousand to more than 1 million copies/mL) after birth, decreasing only slowly to a "set point" by approximately 2 years of age. This contrasts with infection in adults, in whom the viral load generally does not reach the high levels that are seen in newly infected infants and for whom the "set point" occurs approximately 6 months after acquisition of infection. An HIV RNA assay result with only a low-level viral copy number in an HIV-exposed infant may indicate a false-positive result, reinforcing the importance of repeating any positive assay result to confirm the diagnosis of HIV infection in infancy. Like HIV DNA PCR assays, the sensitivity of HIV RNA assays for diagnosing infections in the first week of life is low (25%–40%), because transmission usually occurs around the time of delivery.

In HIV-exposed infants, diagnostic testing with HIV DNA or RNA assays is recommended at 14 to 21 days of age and, if results are negative, again at 1 to 2 months of age and at 4 to 6 months of age. An infant is considered infected if 2 samples from 2 different time points test positive by DNA or RNA PCR assay. If testing is performed shortly after birth, umbilical cord blood should not be used because of possible contamination with maternal blood. HIV-infected infants should be transitioned from neonatal ARV prophylaxis to cART treatment.

In nonbreastfed HIV-exposed children younger than 18 months with negative HIV virologic test results, *presumptive* exclusion of HIV infection is based on

- Two negative HIV DNA or RNA virologic test results, from separate specimens, both of which were obtained at 2 weeks of age or older and one of which was obtained at 4 weeks of age or older; **OR**
- One negative HIV DNA or RNA virologic test result from a specimen obtained at 8 weeks of age or older; **OR**
- One negative HIV antibody test result obtained at 6 months of age or older;

  AND
- No other laboratory or clinical evidence of HIV infection (ie, no subsequent positive results from virologic tests if tests were performed and no AIDS-defining condition).

In nonbreastfed HIV-exposed children younger than 12 months with negative HIV virologic test results, *definitive* exclusion of HIV is based on

- At least 2 negative HIV DNA or RNA virologic test results, from separate specimens, both of which were obtained at 1 month of age or older and one of which was obtained at 4 months of age or older; **OR**
- At least 2 negative HIV antibody test results from separate specimens obtained at 6 months of age or older;

  AND
- No other laboratory or clinical evidence of HIV infection (ie, no subsequent positive results from virologic tests if tests were performed and no AIDS-defining condition).

In HIV-exposed children with 2 negative HIV DNA PCR test results, many clinicians will confirm the absence of antibody (ie, loss of passively acquired maternal antibody) to HIV on testing at 18 through 24 months of age ("seroreversion"). In addition, some clinicians have a slightly more stringent requirement that the 2 separate antibody-negative blood samples obtained after 6 months of age be drawn at least 1 month apart for a child to be considered HIV-uninfected.

Adolescents and HIV Testing

Routine screening should be offered to all adolescents at least once by 16 through 18 years of age in health care settings. Use of any licensed HIV antibody test is appropriate. For any positive test result, referral to an HIV specialist is appropriate to confirm diagnosis and initiate management. Adolescents with behaviors that

increase risk of HIV acquisition (eg, multiple sex partners, illicit drug use) should be tested at least annually. HIV testing is recommended and should be routine for all patients in sexually transmitted infection (STI) clinics and those seeking treatment for STIs in other clinical settings.

Suspicion of acute retroviral syndrome should prompt urgent assessment with an antigen/antibody immunoassay or HIV RNA in conjunction with an antibody test. If the immunoassay is negative or indeterminate, then testing for HIV RNA should follow. Clinicians should not assume that a laboratory report of a negative HIV antibody test result indicates that the necessary RNA screening for acute HIV infection has been conducted.

Consent for Diagnostic Testing

The CDC recommends that diagnostic HIV testing and opt-out HIV screening be part of routine clinical care in all health care settings for patients 13 through 64 years of age. Patients or people responsible for the patient's care should be notified verbally that testing is planned, advised of the indication for testing and the implications of positive and negative test results, and offered an opportunity to ask questions and to decline testing. With such notification, the patient's general consent for medical care is considered sufficient for diagnostic HIV testing. Laws concerning consent and confidentiality for HIV care differ among states. Public health statutes and legal precedents allow for evaluation and treatment of minors for sexually transmitted infections without parental knowledge or consent, but not every state has explicitly defined HIV infection as a condition for which testing or treatment may proceed without parental consent.

TREATMENT

Antiretroviral Therapy

Because HIV treatment options and recommendations change with time and vary with occurrence of ARV drug resistance and the adverse event profile, consultation with an expert in pediatric HIV infection is recommended in the care of HIV-infected infants, children, and adolescents. Whenever possible, enrollment of HIV-infected infants, children, and adolescents in clinical trials should be encouraged.

cART is indicated for HIV-infected pediatric patients and should be provided as soon as possible after diagnosis of HIV infection is established. The principal objectives of therapy are to provide maximum suppression of viral replication, to restore and preserve immune function, to reduce HIV-associated morbidity and mortality, to minimize drug toxicity, to maintain normal growth and development, and to improve quality of life. Data from both observational studies and clinical trials indicate that very early initiation of therapy, regardless of presence or absence of HIV-related symptoms or immunosuppression, reduces morbidity and mortality compared with starting treatment when clinically symptomatic or immune suppressed. Effective administration of early therapy will maintain the viral load at low or undetectable concentrations and will reduce viral mutation and evolution.

Initiation of treatment of adolescents generally follows guidelines for adults, and initiation of treatment is recommended strongly for all HIV-infected adolescents or adults regardless of CD4+ T-lymphocyte count if medication readiness is apparent. Dosages of ARVs can be prescribed according to age, weight, and body surface area or sexual maturity rating (previously Tanner stage). Adolescents in early puberty (sexual maturity ratings I and II) should be prescribed doses based on pediatric schedules, and adolescents in late puberty (sexual maturity rating III, IV, and V) should be prescribed doses based on adult schedules. In general, cART with at least 3 active drugs is recommended for all HIV-infected individuals requiring ARV therapy. ARV resistance testing (viral genotyping) is recommended before starting treatment. Suppression of virus to undetectable levels is the desired goal. A change in ARV therapy should be considered if there is evidence of disease progression (virologic, immunologic, or clinical), toxicity of or intolerance to drugs, development of drug resistance, or availability of data suggesting the possibility of a superior regimen.

Immunologic Classification for Opportunistic Infection and Vaccination Decision Making

For purposes of surveillance of pediatric HIV infection, the CDC uses a case definition that incorporates an immunologic classification system (Table 71.1) which emphasizes the importance of the CD4+ T-lymphocyte count and percentage as critical determinants of prognosis. Data regarding plasma HIV-1 RNA concentration (viral load) are not included in this classification. The immune status of an HIV-infected child no longer is used to determine when to start ARV therapy, because all children are started on antiretroviral therapy at the time of diagnosis. Immune status still is used for initiation and discontinuation of prophylaxis for opportunistic infections and for determining whether it is safe to administer a live vaccine. Because the specific CD4+ T-lymphocyte count may vary for different opportunistic infections or live vaccines, recommendations for prophylaxis of opportunistic infections or safety of live vaccines can be found in the specific chapter for the opportunistic infection or live vaccine.

Opportunistic Infections

Early diagnosis, prophylaxis, and aggressive treatment of OIs prolong survival. This is particularly true for PCP, which accounts for approximately one third of pediatric AIDS diagnoses overall and may occur early in the first year of life. Prophylaxis is not recommended for HIV-exposed infants who meet the criteria for presumptive or definitive absence of HIV infection. Thus, for infants with negative HIV diagnostic test results up through 4 weeks of age (eg, no positive test results or clinical symptoms), PCP prophylaxis would not need to be initiated. Because mortality rates are high, PCP chemoprophylaxis should be given to all HIV-exposed infants with indeterminate HIV infection status starting at 4 to 6 weeks of age but can be stopped if the child subsequently meets criteria for presumptive or definitive absence of HIV infection. All infants with HIV infection should receive PCP prophylaxis through 1 year of age regardless of immune status. The need for PCP prophylaxis for HIV-infected children 1 year and older is

Table 71.2
Laboratory Diagnosis of HIV Infection[a]

Test	Comment
HIV DNA PCR	Preferred test to diagnose HIV infection in infants and children younger than 18 months; highly sensitive and specific by 2 weeks of age and available; performed on peripheral blood mononuclear cells.
HIV p24 Ag	Less sensitive, false-positive results during first month of life, variable results; not recommended.
ICD p24 Ag	Negative test result does not rule out infection; not recommended.
HIV culture	Expensive, not readily available, requires up to 4 weeks for results; not recommended.
HIV RNA PCR	Preferred test to identify HIV-1 infections. Similar sensitivity and specificity to HIV DNA PCR in infants and children younger than 18 months, but DNA PCR is generally preferred because of greater clinical experience with that assay.
HIV indicates human immunodeficiency virus; PCR, polymerase chain reaction; Ag, antigen; ICD, immune complex dissociated.	

[a] Read JS; American Academy of Pediatrics Committee on Pediatric AIDS. Diagnosis of HIV-1 infection in children younger than 18 months in the United States. *Pediatrics.* 2007;120(6):e1547–e1562 (Reaffirmed February 2015). http://pediatrics.aappublications.org/cgi/content/full/120/6/e1547. Accessed February 6, 2019.

determined by the degree of immunosuppression from CD4+ T-lymphocyte percentage and count.

Guidelines for prevention and treatment of OIs in children and adolescents and adults provide indications for administration of drugs for infection with *Mycobacterium avium* complex, cytomegalovirus, *T gondii*, and other organisms.

Immunization Recommendations

All recommended childhood immunizations should be administered to HIV-exposed infants. If HIV infection is confirmed, guidelines for the HIV-infected child should be followed. Children and adolescents with HIV infection should be immunized as soon as is age appropriate with all inactivated vaccines. Inactivated influenza vaccine (IIV) should be administered annually according to the most current recommendations. The 2-dose series of human papillomavirus vaccine; tetanus toxoid, reduced diphtheria toxoid, and acellular pertussis (Tdap) vaccine; and meningococcal conjugate vaccine all are indicated in HIV-infected adolescents.

The live-virus measles-mumps-rubella (MMR) vaccine and monovalent varicella vaccine can be administered to asymptomatic HIV-infected children and adolescents without severe immunosuppression (that is, can be administered to children 1 through 13 years of age with a CD4+ T-lymphocyte percentage ≥15% and to adolescents ≥14 years with a CD4+ T-lymphocyte count ≥200 lymphocytes/mm^3). Severely immunocompromised HIV-infected infants, children, adolescents, and young adults (eg, children 1 through 13 years of age with a CD4+ T-lymphocyte percentage <15% and adolescents ≥14 years with a CD4+ T-lymphocyte count <200 lymphocytes/mm^3) should not receive measles virus-containing vaccine, because vaccine-related pneumonia has been reported. The quadrivalent measles-mumps-rubella-varicella (MMRV) vaccine should not be administered to any HIV-infected infant, regardless of degree of immunosuppression, because of lack of safety data in this population.

Rotavirus vaccine should be administered to HIV-exposed and HIV-infected infants irrespective of CD4+ T-lymphocyte percentage or count.

All HIV-infected children should receive a dose of 23-valent polysaccharide pneumococcal vaccine after 24 months of age, with a minimal interval of 8 weeks since the last pneumococcal conjugate vaccine. HIV-infected children who are 5 years and older and have not received Hib vaccine should receive 1 dose of Hib vaccine. Infants and children with HIV infection 2 months of age or older should receive an age-appropriate series of the meningococcal ACWY conjugate vaccine (MenACWY). The recommendations for children 2 months through 2 years of age and people 25 years or older are based on expert opinion, because the vaccine was not studied in HIV-infected people in these age groups. The same vaccine product should be used for all doses. However, if the product used for previous doses is unknown or unavailable, the vaccination series may be completed with any age- and formulation-appropriate meningococcal ACWY conjugate vaccine. Although no data on interchangeability of meningococcal conjugate vaccines in HIV-infected people are available, limited data from a postlicensure study in healthy adolescents suggests safety and immunogenicity of MenACWY-CRM are not adversely affected by prior immunization with MenACWY-D. For HIV-infected infants aged 2 through 23 months, only MenACWY-CRM (Menveo) can be used, because interference with immune response to pneumococcal conjugate vaccine occurs with MenACWY-D (Menactra).

Children Who Are HIV Uninfected Residing in the Household of an HIV-Infected Person

Members of households in which an adult or child has HIV infection can receive MMR vaccine, because these vaccine viruses are not transmitted person-to-person. To decrease the risk of transmission of influenza to patients with symptomatic HIV infection, all household members 6 months or older should receive yearly influenza immunization. Immunization with varicella vaccine of siblings and susceptible adult caregivers of patients with HIV infection is encouraged to prevent acquisition of wild-type varicella-zoster virus infection, which can cause severe disease in immunocompromised hosts. Transmission of varicella vaccine virus from an immunocompetent host to a household contact is very uncommon.

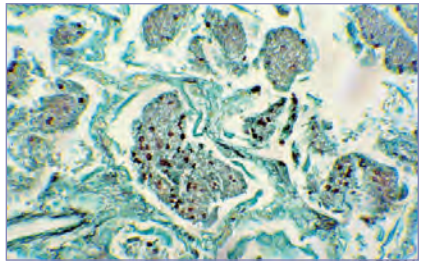


Image 71.1
Pneumocystis jiroveci (formerly *P carinii*) pneumonia lung biopsy specimen from a child with HIV infection and pneumonia. Numerous dark-staining cysts of *P jiroveci* (Gomori-methenamine silver stain). Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

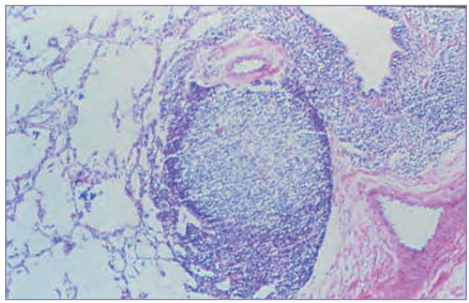


Image 71.3
Biopsy specimen showing a nodular aggregate of mononuclear cells in the lung of a child with HIV infection and lymphoid interstitial pneumonitis/pulmonary lymphoid hyperplasia. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

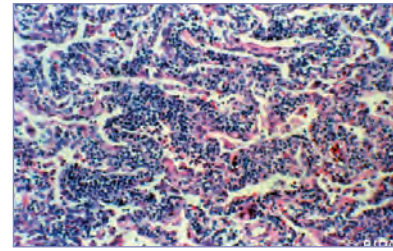


Image 71.2
Lung biopsy specimen showing mononuclear interstitial infiltration in a child with HIV infection and lymphoid interstitial pneumonitis/pulmonary lymphoid hyperplasia (LIP/PLH). The pathogenesis of LIP/PLH is poorly understood, but Epstein-Barr virus has been implicated as a cofactor in its development. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

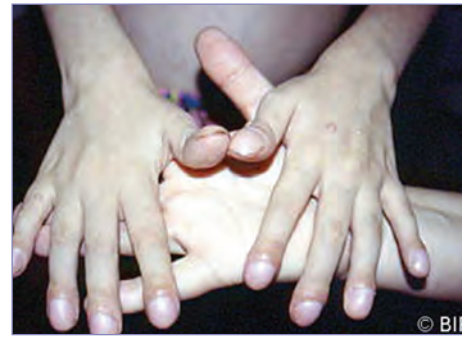


Image 71.4
Digital clubbing in a child with HIV infection and lymphoid interstitial pneumonitis/pulmonary lymphoid hyperplasia (LIP/PLH). Marked lymphadenopathy, hepatosplenomegaly, and salivary gland enlargement also are observed in many children with LIP/PLH. The clinical course of LIP/PLH is variable. Exacerbation of respiratory distress and hypoxemia can occur in association with intercurrent viral respiratory illnesses. Spontaneous clinical remission sometimes is observed. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

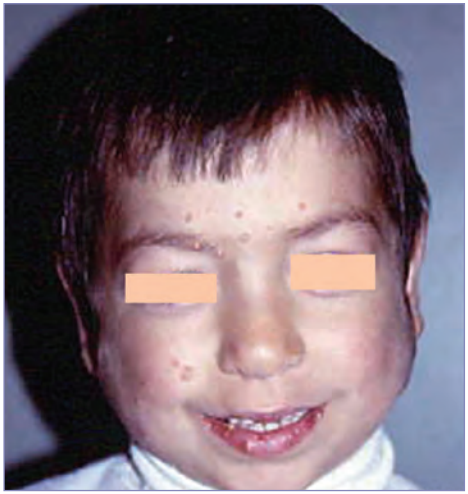


Image 71.5
Bilateral parotid gland enlargement in an HIV-infected male child with lymphoid interstitial pneumonitis/pulmonary lymphoid hyperplasia. Note the presence of multiple lesions of molluscum contagiosum, which are commonly seen in patients with HIV, particularly those with a low CD4 lymphocyte count. (See also Molluscum Contagiosum.) Copyright Baylor International Pediatric AIDS Initiative/ Mark Kline, MD, FAAP.

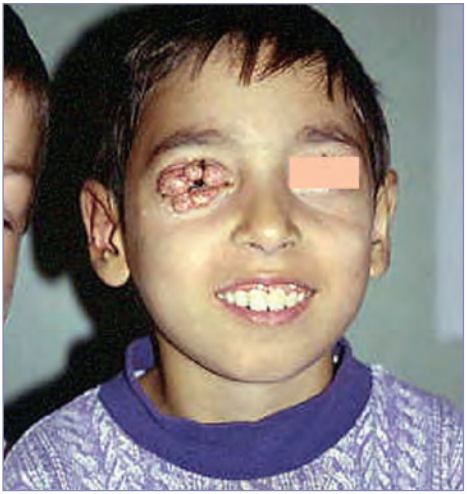


Image 71.6
Severe molluscum contagiosum in a boy with HIV infection. Some HIV-infected children develop molluscum contagiosum lesions that are unusually large or widespread. They are often seated more deeply in the epidermis. (See also Molluscum Contagiosum.) Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

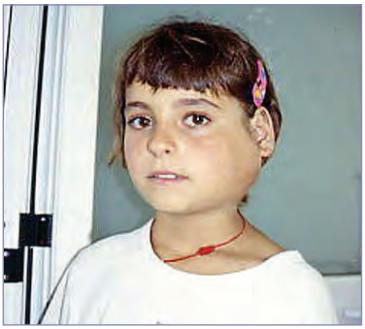


Image 71.7
Suppurative parotitis in a girl with HIV infection. Note the marked swelling and redness overlying the left parotid gland. On palpation of the gland, pus could be seen exuding from the Stensen duct. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

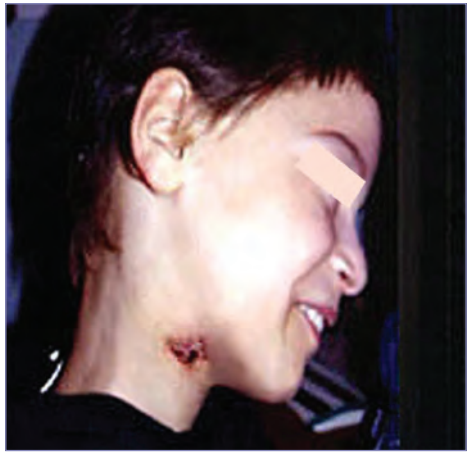


Image 71.8
An 8-year-old boy with HIV and tuberculous lymphadenitis (scrofula). Copious amounts of pus spontaneously drained from this lesion. In an immunocompromised child, other causes of lymphadenitis include infections with gram-positive bacteria, atypical mycobacterium, and *Bartonella henselae* (cat-scratch disease); malignant neoplasms such as lymphoma; masses such as branchial cleft cysts or cystic hygromas masquerading as lymph nodes; and adenitis due to HIV itself. (See also Nontuberculous Mycobacteria.) Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

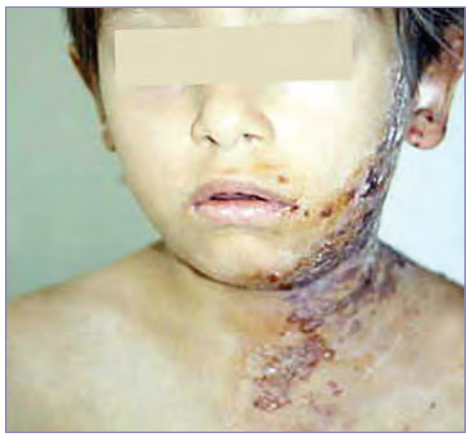


Image 71.10
Herpes zoster (shingles) in a boy with HIV infection. Such cases can be complicated by chronicity or dissemination. (See also Varicella-Zoster Virus Infections.) Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

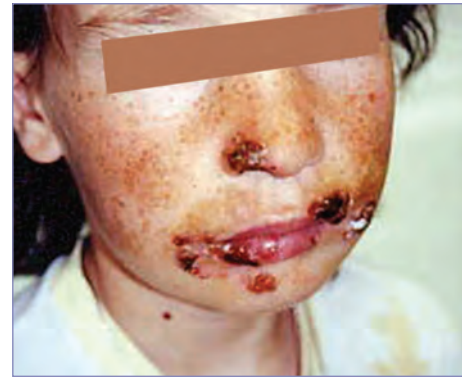


Image 71.9
Herpes simplex infection in a girl with HIV infection. Chronic or progressive herpetic skin lesions are observed occasionally in HIV-infected children, although, unlike varicella-zoster virus infections in these patients, herpes simplex infections much less commonly cause disseminated disease. (See also Herpes Simplex.) Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

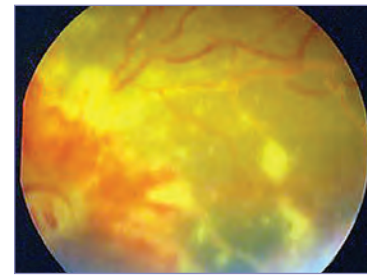


Image 71.11
Funduscopic examination of a 16-year-old girl with HIV infection and cytomegalovirus retinitis. There are extensive areas of hemorrhage, with white retinal exudates. Children with cytomegalovirus retinitis usually present with painless visual impairment. (See also Cytomegalovirus Infection.) Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

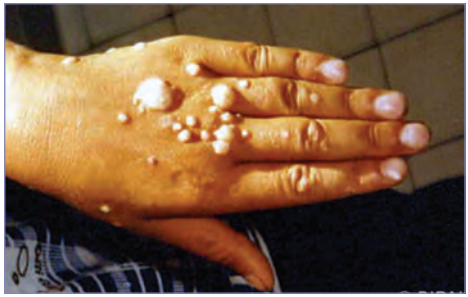


Image 71.12
Severe cutaneous warts (human papillomavirus infection) in a boy with HIV infection. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

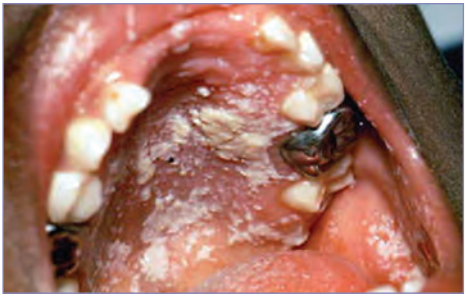


Image 71.13
Pseudomembranous candidiasis in a person with HIV infection. (See also Candidiasis.) Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP

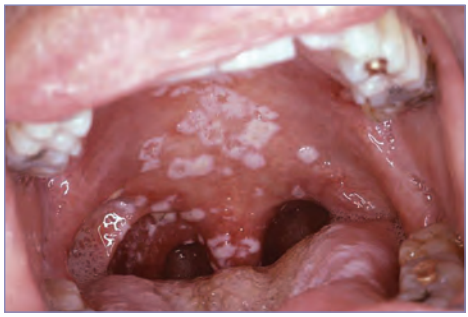


Image 71.14
This patient with HIV/AIDS presented with a secondary oral pseudomembranous candidiasis infection. The immune system suffers when HIV therapy undergoes a dramatic reduction in its effectiveness, resulting in the greater possibility of secondary infections, as in this patient. This infection responded to fluconazole, 100 mg daily, for 1 week. Courtesy of Centers for Disease Control and Prevention.

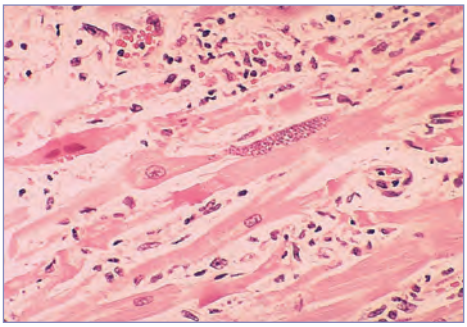


Image 71.15
Histopathology of toxoplasmosis of heart in fatal case of AIDS. Courtesy of Centers for Disease Control and Prevention.

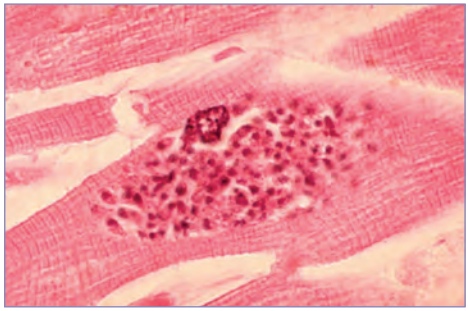


Image 71.16
Toxoplasmosis of the heart in a patient with AIDS. Courtesy of Centers for Disease Control and Prevention.

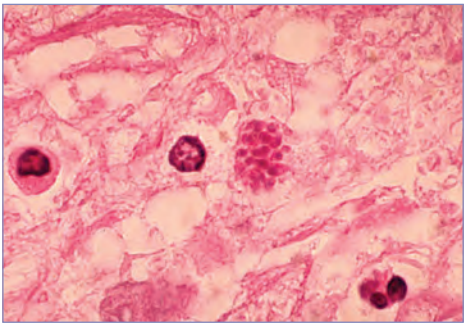


Image 71.17
Histopathology of toxoplasmosis of the brain in fatal case of AIDS. Courtesy of Centers for Disease Control and Prevention.

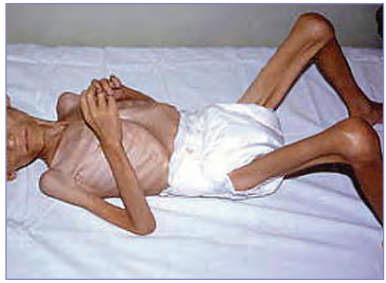


Image 71.18
Severe wasting in a patient with HIV infection. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

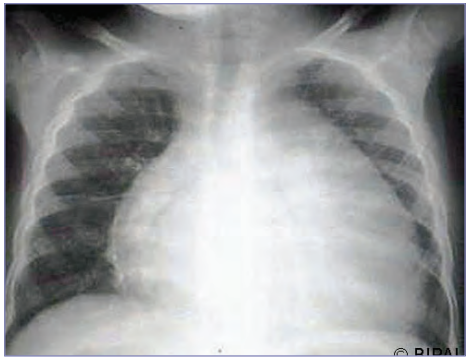


Image 71.20
Chest radiograph showing cardiomegaly in a 5-year-old girl with HIV infection, cardiomyopathy, and congestive heart failure. Many children with HIV infection with congestive heart failure respond well to medical management. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

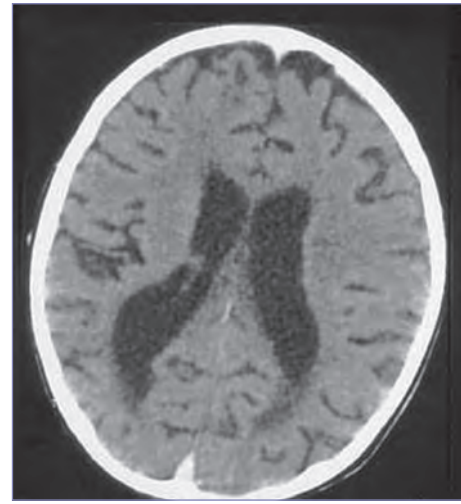


Image 71.19
Computed tomography scan of the brain of an 8-year-old boy with HIV infection and generalized brain atrophy. Cerebral atrophy is observed commonly among children with HIV-associated encephalopathy, but it also may be observed among children who are normal neurologically and developmentally. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

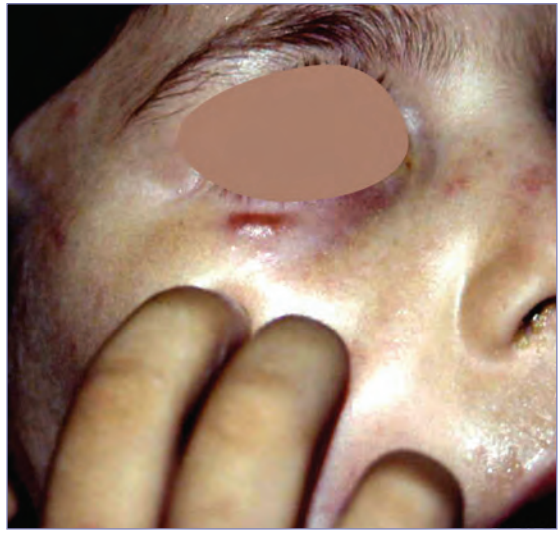


Image 71.21
A 7-year-old girl with HIV infection and a Kaposi sarcoma lesion. This tumor is rarely diagnosed among US children, with the occasional exceptions of children of Haitian descent with vertical HIV infection or older adolescents. Kaposi sarcoma is observed more commonly among HIV-infected children in some other geographic locales, including parts of Africa (eg, Zambia, Uganda) and Romania. Kaposi sarcoma has been linked to infection with a novel herpesvirus, now known as human herpesvirus 8 or Kaposi sarcoma–associated virus. Copyright Baylor International Pediatric AIDS Initiative/Mark Kline, MD, FAAP.

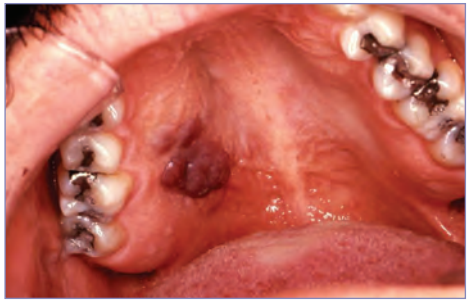


Image 71.22
This patient with HIV infection presented with intraoral Kaposi sarcoma of the hard palate secondary to his AIDS infection. Approximately 7.5% to 10% of patients with AIDS display signs of oral Kaposi sarcoma, which can range in appearance from small asymptomatic growths that are flat purple-red in color to larger nodular growths. Courtesy of Centers for Disease Control and Prevention.

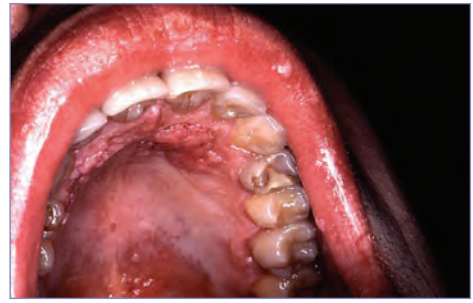


Image 71.23
This HIV-positive patient was exhibiting signs of a secondary condyloma acuminata infection (ie, venereal warts). This intraoral eruption of condyloma acuminata, or venereal warts, was caused by human papillomavirus (HPV). Although oral HPV is a rare occurrence, HIV reduces the body's immune response and, therefore, such secondary infections can manifest themselves. Courtesy of Centers for Disease Control and Prevention.

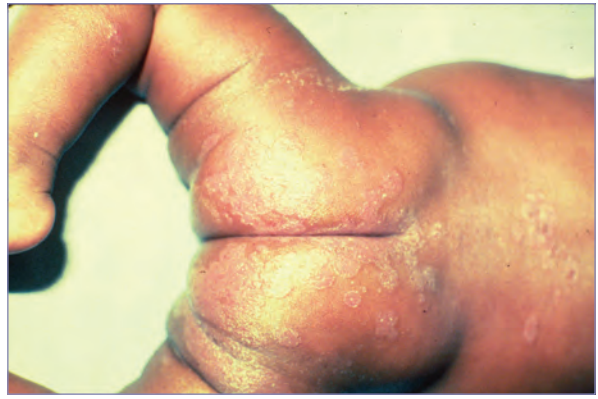


Image 71.24
A 12-month-old boy with HIV infection with a chronic *Trichophyton* infection (tinea corporis) mostly marked over the buttocks and lower extremities. Courtesy of Larry Frenkel, MD.

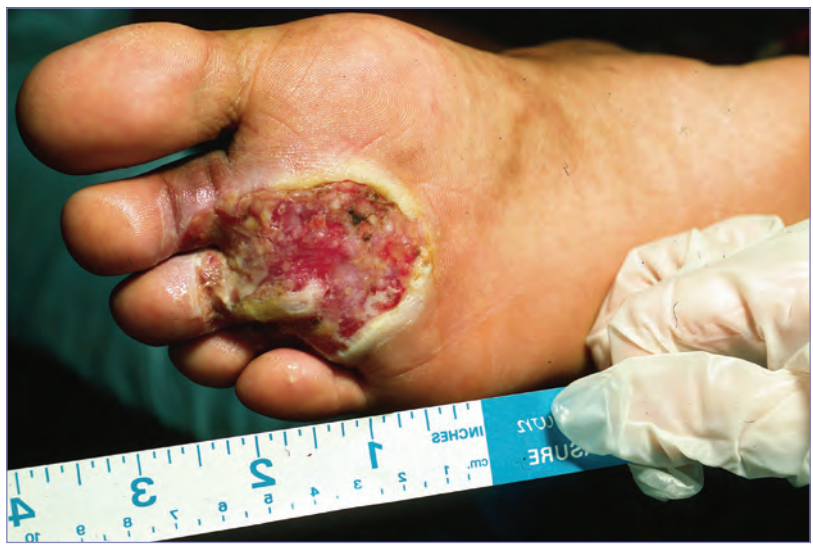


Image 71.25
A 17-year-old boy with HIV infection with an ulcerative lesion on the plantar surface of the left foot of several months' duration. A viral culture result was positive for human herpesvirus, which led to the diagnosis of HIV. Courtesy of Larry Frenkel, MD.

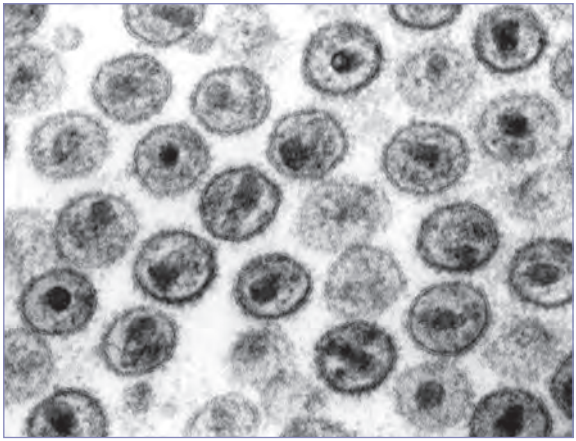


Image 71.26
HIV type 1 transmission electron micrograph. Cone-shaped cores are sectioned in various orientations. Viral genomic RNA is located in the electron-dense wide end of core. Courtesy of Centers for Disease Control and Prevention.

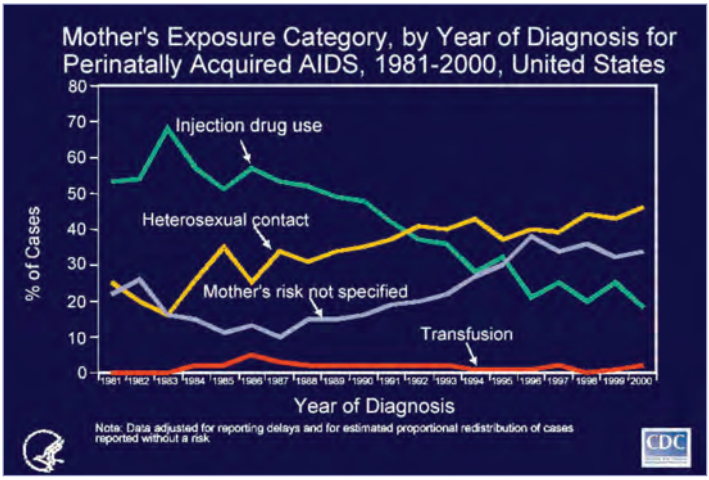


Image 71.27
Mothers' exposure category, by year of diagnosis, for AIDS acquired via perinatal infection, 1981–2000, United States. Changes have occurred in the distribution of exposure categories for the mothers of children who were infected perinatally and in whom AIDS developed. In the 1980s, most of the women who transmitted HIV vertically were exposed to HIV through injection drug use, and a smaller proportion through heterosexual contact. In the 1990s, a smaller proportion of women who transmitted HIV vertically were exposed to HIV through injection drug use and a larger proportion through heterosexual contact. Courtesy of Centers for Disease Control and Prevention.

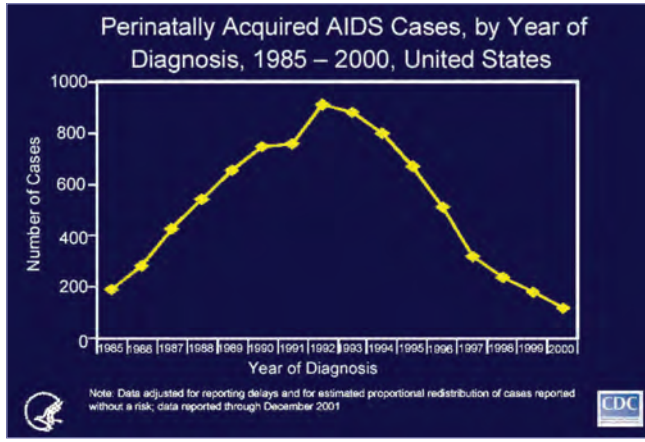


Image 71.28

Cases of AIDS acquired via perinatal infection, by year of diagnosis, 1985–2000, United States. The estimated number of AIDS infections diagnosed among persons perinatally exposed to HIV peaked in 1992 and has decreased in recent years. The decline of these cases is likely associated with the implementation of US Public Health Service guidelines for the universal counseling and voluntary HIV testing of pregnant women and the use of antiretroviral therapy for pregnant women and newborn infants (*MMWR Recomm Rep.* 2002;51[RR-18]:1–38). Other contributing factors are the effective treatment of HIV infections that slow progression of AIDS and the use of prophylaxis to prevent opportunistic AIDS infections among children. Courtesy of Centers for Disease Control and Prevention.

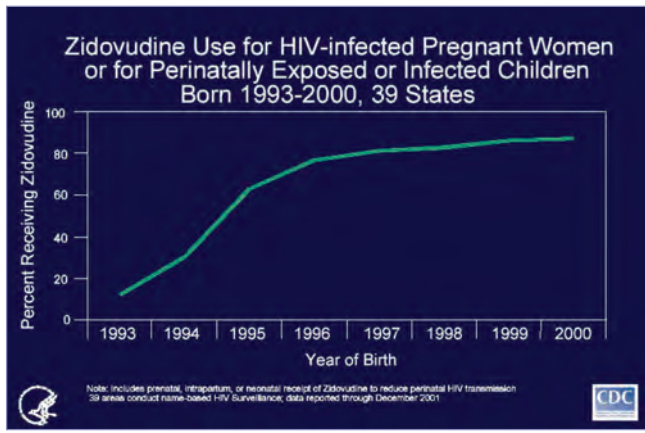


Image 71.29

Zidovudine (ZDV) use for pregnant women with HIV infection or for children who were born from 1993 to 2000 and perinatally exposed or infected, 39 states. In April 1994, the US Public Health Service released guidelines for the use of ZDV to reduce perinatal HIV transmission; in 1995, recommendations for HIV counseling and voluntary testing for pregnant women were published; and in 2002, recommendations on the use of antiretroviral drugs in pregnant women with HIV infection were updated. Since then, the proportion of children who were perinatally exposed to or infected with HIV who received ZDV has increased markedly. This increase in ZDV use, including receipt by the mother during the prenatal or intrapartum period and receipt by the neonate, has been accompanied by a decrease in the number of children perinatally infected with HIV and is responsible for the dramatic decline in cases of AIDS acquired perinatally. The data presented here are from the 30 states with name-based HIV infection surveillance and may not represent all states in the United States. Courtesy of Centers for Disease Control and Prevention.

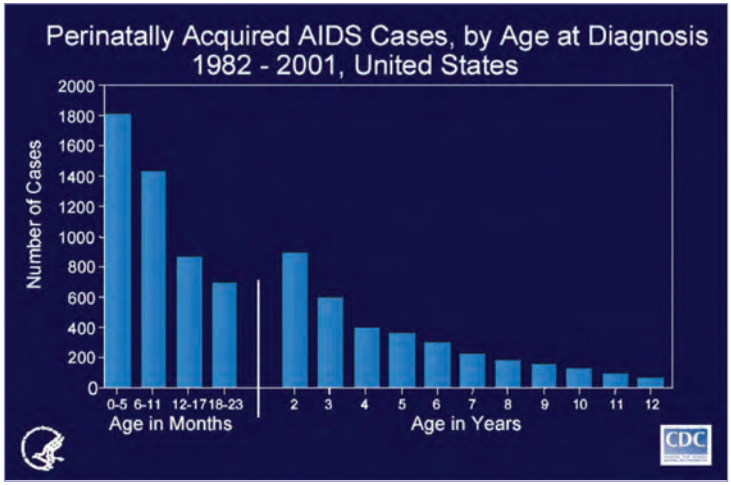


Image 71.30
Perinatally acquired AIDS cases, by age at diagnosis, 1982–2001, United States. Perinatally acquired AIDS was diagnosed for nearly 40% of infected infants within the first year after birth and for 22% within the first 6 months. This distribution could change if more childbearing women with HIV infection become aware of their HIV status and seek medical care early in their infants' lives, when treatment could possibly prevent the progression from HIV infection to AIDS in their children. Courtesy of Centers for Disease Control and Prevention.

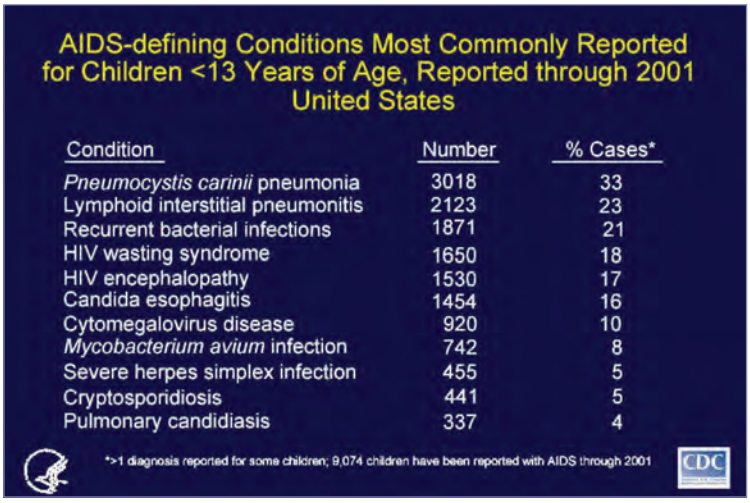


Image 71.31
AIDS-defining conditions most commonly reported for children younger than 13 years, reporting through 2001, United States. Certain clinical conditions are used to define AIDS among persons infected with HIV. The most commonly reported conditions for children are listed on this image. From the beginning of the epidemic through 2001, 33% of children with AIDS had a diagnosis of *Pneumocystis jiroveci* (formerly *P carinii*) pneumonia; another 23% a diagnosis of lymphoid interstitial pneumonitis; and 21% had recurrent bacterial infections. Courtesy of Centers for Disease Control and Prevention.

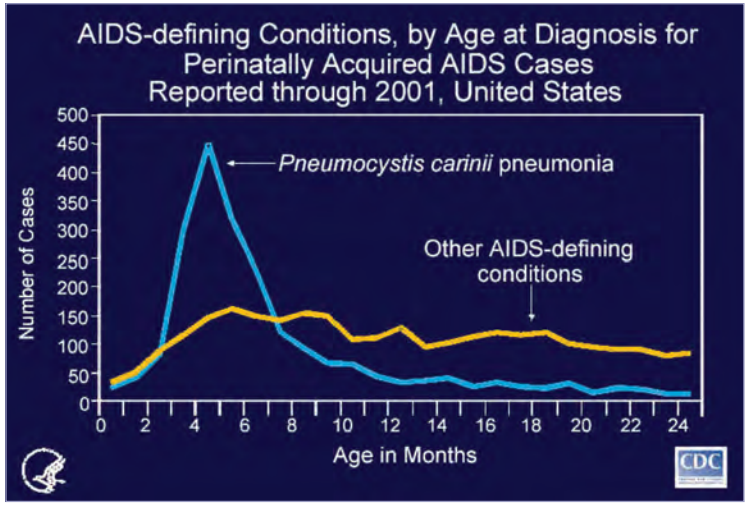


Image 71.32

AIDS-defining conditions, by age at diagnosis for perinatally acquired AIDS, reported through 2001, United States. The incidence of *Pneumocystis jiroveci* (formerly *P carinii*) pneumonia (PCP) in children with perinatally acquired AIDS peaks at 3 to 6 months of age. The age at diagnosis for the other AIDS-defining conditions is much more evenly distributed during the first 2 years after birth. Because PCP occurs early, prophylaxis is recommended for all children exposed perinatally to HIV, beginning at 6 weeks of age. The occurrence of PCP in children may indicate missed opportunities for testing pregnant women, the use of zidovudine or other antiretroviral therapies to prevent transmission, or therapy (including PCP prophylaxis) for HIV-exposed children. The Centers for Disease Control and Prevention has a high-priority initiative to reduce HIV transmission from mothers to children by promoting voluntary maternal testing prenatally (intrapartum if women do not receive prenatal care) and zidovudine therapy. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 72

Influenza

CLINICAL MANIFESTATIONS

Influenza typically begins with sudden onset of fever, often accompanied by chills or rigors, headache, malaise, diffuse myalgia, and nonproductive cough. Subsequently, respiratory tract signs and symptoms, including sore throat, nasal congestion, rhinitis, and cough, become more prominent. Conjunctival injection, abdominal pain, nausea, vomiting, and diarrhea less commonly are associated with influenza illness. In some children, influenza can appear as an upper respiratory tract illness or as a febrile illness with few respiratory tract symptoms. When influenza viruses are circulating in a community, the diagnosis of influenza should be considered in all children and adults (including health care personnel) with acute onset of respiratory symptoms, regardless of degree of symptoms, whether or not there is fever, and regardless of influenza vaccination status. Influenza is an important cause of otitis media. Acute myositis secondary to influenza can present with calf tenderness and refusal to walk. In infants, influenza can produce a nonspecific sepsis-like illness picture, and in infants and young children, influenza occasionally causes croup, pertussis-like illness, bronchiolitis, or pneumonia.

Although the large majority of children with influenza recover fully after 3 to 7 days, previously healthy children can have severe symptoms and complications. Neurologic complications associated with influenza range from febrile seizures to severe encephalopathy and encephalitis with status epilepticus, resulting in neurologic sequelae or death. Reye syndrome, which now is a very rare condition, has been associated with influenza infection and the use of aspirin therapy during the illness. Children with influenza or suspected influenza should not be given aspirin, and children with diseases that necessitate long-term aspirin therapy or salicylate-containing medication, including juvenile idiopathic arthritis or Kawasaki disease, should be recognized as being at increased risk for complications from influenza. Death from influenza-associated myocarditis has been reported. Invasive secondary infections or coinfections with group A streptococcus, *Staphylococcus aureus* (including methicillin-resistant *S aureus* [MRSA]), *Streptococcus pneumoniae*, or other bacterial pathogens can result in severe disease and death.

ETIOLOGY

Influenza viruses are orthomyxoviruses of 3 genera or types (A, B, and C). Epidemic disease is caused by influenza virus types A and B, and both influenza A and B virus antigens are included in influenza vaccines. Type C influenza viruses cause sporadic mild influenza-like illness in children, and type C antigens are not included in influenza vaccines. Influenza A viruses are subclassified into subtypes by 2 surface antigens, hemagglutinin (HA) and neuraminidase (NA). Examples of these virus subtypes include H1N1 and H3N2 influenza A viruses. Specific antibodies to these various antigens, especially to hemagglutinin, are important determinants of immunity.

A minor antigenic variation within the same influenza A or B subtypes is termed *antigenic drift*. Antigenic drift occurs continuously and results in new strains of influenza A and B viruses, leading to seasonal epidemics. On the basis of ongoing global surveillance data, there have been only 5 times since 1986 that the vaccine strains in the influenza vaccine have not changed from the previous season.

Antigenic shifts, on the other hand, are major changes in influenza A viruses that result in new subtypes that contain a new HA alone or with a new NA. Antigenic shift occurs only with influenza A viruses and can lead to a pandemic if the new strain can infect humans and be transmitted efficiently from person to person in a sustained manner in the setting of little or no preexisting immunity. The virus type or subtype may have an effect on the number of hospitalizations and deaths that season. For example, seasons with influenza A (H3N2) as the predominant circulating strain have had 2.7 times higher average mortality rates than non–H3N2-predominant seasons. The 2009 influenza A (H1N1) pandemic combined both exceptional pediatric virulence and lack of immunity, which resulted in nearly 4 times as many pediatric deaths as usually recorded. Antigenic shift has produced 4 influenza

pandemics in the 20th and 21st centuries. The 2009 pandemic was associated with 2 waves of substantial activity in the United States, which occurred in the spring and fall of 2009, extending well into winter 2010. During this time, more than 99% of virus isolates characterized were the 2009 pandemic influenza A (H1N1) virus. As with previous antigenic shifts, the 2009 pandemic influenza A (H1N1) viral strain subsequently has replaced the previously circulating seasonal influenza A (H1N1) strain in the ensuing influenza seasons.

Humans of all ages occasionally are infected with influenza A viruses of swine or avian origin. Human infections with swine influenza viruses have manifested as typical influenza-like illness, and confirmation of infection caused by an influenza virus of swine origin has been discovered retrospectively during routine surveillance typing of human influenza isolates. Human infections with avian influenza viruses are uncommon but may result in a spectrum of disease from mild respiratory symptoms and conjunctivitis to severe lower respiratory tract disease, acute respiratory distress syndrome (ARDS), and death. Most notable among avian influenza viruses are A (H5N1) and A (H7N9), both of which have been associated with severe disease and high case-fatality rates. Influenza A (H5N1) viruses emerged as human infections in 1997 and have since caused human disease in Asia, Africa, Europe, and the Middle East, areas where these viruses are present in domestic or wild birds. Influenza A (H7N9) infections were first detected in 2013 and have been associated with sporadic disease in China. As of 2017, Asian H7N9 is ranked as the influenza virus with the highest potential pandemic risk. No efficient or sustained human-to-human transmission has been detected, but when human infections occur, they are associated with severe illness and high mortality. Infection with a novel influenza A virus is a nationally notifiable disease and should be reported to the Centers for Disease Control and Prevention (CDC) through state health departments.

EPIDEMIOLOGY

Influenza is spread person to person, primarily through large-particle respiratory droplet transmission (eg, coughing or sneezing near a susceptible person), which requires close contact between the person who is the source and person who is the recipient, because droplets generally only travel short distances. Another indirect mode of transmission comes from hand transfer of influenza virus from droplet-contaminated surfaces to mucosal surfaces of the face (autoinoculation). Airborne transmission via small-particle aerosols in the vicinity of the infectious individual also may occur. Each year from 2010 through 2016, seasonal influenza epidemics were associated with an estimated 4.3 to 16.7 million medical visits, 140,000 to 710,000 hospitalizations, and 12,000 to 56,000 respiratory and circulatory deaths annually in the United States.

During community outbreaks of influenza, the highest incidence occurs among school-aged children. Secondary spread to adults and other children within a family is common. Incidence and disease severity depend in part on immunity developed as a result of previous experience (by natural disease) or recent influenza immunization with the circulating strain or a related strain. Influenza A and B viruses circulate worldwide, but the prevalence of each type and subtype can vary among communities and within a single community over the course of an influenza season. In temperate climates, seasonal epidemics usually occur during winter months. Peak influenza activity in the United States can occur anytime from November to May but most commonly occurs between January and March. Community outbreaks can last 4 to 8 weeks or longer. Circulation of 2 or 3 influenza virus strains in a community may be associated with a prolonged influenza season of 3 months or more and may produce bimodal peaks in activity. Influenza is highly contagious, especially among semienclosed institutionalized populations; other ongoing closed-group gatherings, such as schools and preschool/child care classrooms; or travelers who have returned from areas where influenza viruses may be circulating, including

participants in organized tour groups, international mass gatherings, summer camps, or cruise or military ship passengers. Patients may be infectious 24 hours before onset of symptoms. Viral shedding in nasal secretions usually peaks during the first 3 days of illness and ceases within 7 days but can be prolonged in young children and immunodeficient patients for 10 days or even longer. Viral shedding is correlated directly with degree of fever.

Incidence of influenza in healthy children generally is 10% to 40% each year, but illness rates as low as 3% also have been reported, depending on the circulating strain. Tens of thousands of children visit medical clinics and emergency departments because of influenza illness each season. Influenza and its complications have been reported to result in a 10% to 30% increase in the number of courses of antimicrobial agents prescribed to children during the influenza season. Although bacterial coinfections with a variety of pathogens have been reported, medical care encounters for children with influenza are an important cause of inappropriate antimicrobial use.

Hospitalization rates among children younger than 2 years are similar to hospitalization rates among people 65 years and older. Rates vary among studies (190–480 per 100,000 population) because of differences in methodology and severity of influenza seasons. It is clear, however, that children younger than 24 months consistently are at a substantially higher risk of hospitalization than older children. Antecedent influenza infection sometimes is associated with development of pneumococcal or staphylococcal pneumonia in children. Methicillin-resistant staphylococcal community-acquired pneumonia, with a rapid clinical progression and a high fatality rate, has been reported in previously healthy children and adults with concomitant influenza infection. In the 2016–2017 influenza season, more than 40% of all children hospitalized with influenza had no known underlying conditions. Rates of hospitalization and morbidity attributable to complications, such as bronchitis and pneumonia, are greater in children with high-risk conditions, including pulmonary diseases such as asthma, metabolic diseases such as diabetes mellitus, hemoglobinopathies such as sickle cell disease, hemodynamically significant cardiac disease, immunosuppression, and neurologic and neurodevelopmental disorders.

Fatal outcomes, including sudden death, have been reported in both chronically ill and previously healthy children. Since 2004, the number of influenza-related deaths among children reported annually in nonpandemic seasons has ranged from 46 (2005–2006 season) to 171 (2012–2013 season); during the 2009–2010 season, the number of pediatric deaths recorded in the United States was 288. During the entire influenza A (H1N1) pandemic period lasting from April 2009 to August 2010, a total of 344 laboratory-confirmed, influenza-associated pediatric deaths were reported. Both influenza A and B viruses have been associated with deaths in children, most of which occurred in children younger than 5 years. Almost half of children who die do not have a high-risk condition as defined by the Advisory Committee on Immunization Practices (ACIP). All influenza-associated pediatric deaths are nationally notifiable and should be reported to the CDC through state health departments.

The **incubation period** usually is 1 to 4 days, with a mean of 2 days.

Influenza Pandemics

Influenza pandemics can lead to substantially increased morbidity and mortality rates compared with seasonal influenza. During the 20th century, there were 3 influenza pandemics, in 1918 (H1N1), 1957 (H2N2), and 1968 (H3N2). The pandemic in 1918 killed at least 20 million people in the United States and perhaps as many as 50 million people worldwide. The 2009 influenza A (H1N1) pandemic was the first in the 21st century, lasting from April 2009 to August 2010; there were 18,449 deaths among laboratory-confirmed influenza cases, although this is believed to represent only a fraction of the true number of deaths. On the basis of a modeling study from the CDC, it is estimated that the 2009 influenza A (H1N1) pandemic was associated with between 151,700 and 575,400 deaths worldwide. Public health authorities have developed plans for pandemic preparedness and response to a pandemic in the United States. Pediatric health care professionals should be familiar with national, state,

and institutional pandemic plans, including recommendations for vaccine and antiviral drug use, health care surge capacity, and personal protective strategies that can be communicated to patients and families. Up-to-date information on pandemic influenza can be found at **www.pandemicflu.gov**.

DIAGNOSTIC TESTS

Influenza testing should be performed when the results are anticipated to influence clinical management (eg, to inform the decision to initiate antiviral therapy or pursue other diagnostic testing, to prescribe antibiotic agents, or to implement infection prevention and control measures). The decision to test is related to the level of suspicion for influenza, local influenza activity, and the sensitivity and specificity of commercially available influenza tests (Table 72.1), including rapid influenza molecular assays, reverse transcriptase-polymerase chain reaction (RT-PCR) assays, multiplex RT-PCR assays, immunofluorescence assays (direct fluorescent antibody [DFA] or indirect fluorescent antibody [IFA] staining), and rapid influenza diagnostic tests (RIDTs). Choice of influenza test depends on the clinical setting.

To diagnose influenza in the outpatient setting, upper respiratory tract (ie, nasopharyngeal or nasal) swab specimens should be collected as soon after illness onset as possible, preferably within 4 days of onset. The optimal respiratory tract swab specimen to collect depends on which influenza test is being used. Nasopharyngeal swab specimens have the highest yield of upper respiratory tract specimens for detection of influenza viruses. Midturbinate nasal swab specimens are acceptable. Testing with combined nasal and throat swab specimens may increase the detection of influenza viruses over single specimens from either site (particularly over throat swab specimens), depending on the test used, and is an option if nasopharyngeal swab specimens are not available. Using flocked swabs likely improves influenza virus detection over nonflocked swabs.

For inpatients without severe lower respiratory tract disease, nasopharyngeal, nasal, or combined nasal-throat swab specimens should be collected. For patients with respiratory failure receiving mechanical ventilation, including patients with negative influenza testing results on upper respiratory tract specimens, endotracheal aspirate or bronchoalveolar lavage (BAL) fluid specimens should be obtained. Nonrespiratory specimens such as blood, plasma, serum, cerebrospinal fluid, urine, and stool should not be collected or tested for seasonal influenza viruses. Specimens should be obtained, if possible, during the first 4 days of illness, because the quantity of virus shed decreases rapidly as illness progresses beyond that point.

Results of influenza testing should be properly interpreted in the context of clinical findings and local community influenza activity. Molecular tests have the best performance characteristics. RIDTs are significantly less sensitive than other methods and, therefore, produce more false-negative results. Some rapid diagnostic antigen tests cannot distinguish between influenza subtypes, a feature that can be critical during seasons with strains that differ in antiviral susceptibility and/or relative virulence (see Table 72.1). Careful clinical judgment must be exercised, because the prevalence of circulating influenza viruses influences the positive and negative predictive values of these influenza screening tests. False-positive results are more likely to occur during periods of low influenza activity; false-negative results are more likely to occur during periods of peak influenza activity. Decisions regarding treatment and infection control can be made on the basis of positive rapid diagnostic test results. Positive results are helpful, because they may reduce additional testing to identify the cause of the child's influenza-like illness. Treatment should not be withheld in high-risk patients awaiting test results. Information about influenza surveillance is available through the CDC Voice Information System (influenza update, 888-232-3228) or through **https://www.cdc.gov/flu/index.htm**.

TREATMENT

In the United States, 2 classes of antiviral medications currently are approved for treatment or prophylaxis of influenza infections: neuraminidase inhibitors (oral oseltamivir, inhaled zanamivir, and intravenous peramivir) and adamantanes (amantadine and rimantadine). Guidance for use of these

Table 72.1
Summary of Influenza Diagnostic Tests

Influenza Diagnostic Test	Method	Availability	Typical Processing Time	Sensitivity	Distinguishes Influenza A Virus Subtypes
Rapid influenza diagnostic tests	Antigen detection	Wide	<15 min	10%–70%	No
Rapid influenza molecular assays	RNA detection	Wide	<20 min	86%–100%	No
Nucleic acid amplification tests (including RT-PCR)	RNA detection	Limited	1–8 h	86%–100%	Yes
Direct and indirect immunofluorescence assays	Antigen detection	Wide	1–4 h	70%–100%	No
Rapid cell culture (shell vials and cell mixtures)	Virus isolation	Limited	1–3 d	100%	Yes
Viral cell culture	Virus isolation	Limited	3–10 d	100%	Yes

RT-PCR indicates reverse transcriptase-polymerase chain reaction.

antiviral agents is summarized in Table 72.2. Oseltamivir remains the antiviral drug of choice. Zanamivir is an acceptable alternative but is more difficult to administer, especially in young children. Peramivir was approved in 2017 for use in children 2 years and older. Intravenous formulations are especially important for children who cannot absorb orally administered oseltamivir or cannot tolerate inhaled zanamivir. The US Food and Drug Administration (FDA) has approved oseltamivir for children as young as 2 weeks of age. Given preliminary pharmacokinetic data and limited safety data, oseltamivir can be used to treat influenza in both term and preterm infants from birth, because benefits of therapy are likely to outweigh possible risks of treatment.

Widespread resistance to adamantanes has been documented among H3N2 and H1N1 influenza viruses since 2005 (influenza B viruses intrinsically are not susceptible to adamantanes). Since January 2006, neuraminidase inhibitors have been the only influenza antiviral drugs recommended for use in influenza infections. Resistance to oseltamivir has been documented to be approximately 1% at most for any of the tested influenza viral samples during the past few years.

Treatment for influenza virus infection should be offered as early as possible, without waiting for confirmatory influenza testing, to any hospitalized child presumed clinically to have influenza disease or with serious, complicated, or progressive illness attributable to influenza, irrespective of influenza vaccination status or whether illness began greater than 48 hours before admission. Treatment also should be offered to influenza-infected children at high risk of complications from influenza, regardless of severity of illness. Treatment may be considered for any otherwise healthy child clinically presumed to have influenza disease. The greatest effect on outcome will occur if treatment can be initiated within 48 hours of illness onset, but treatment still should be considered if it is later in the course of progressive, symptomatic illness. Children with severe influenza should be evaluated carefully for possible coinfection with bacterial pathogens that might require antimicrobial therapy.

The duration of treatment for the neuraminidase inhibitors oseltamivir and zanamivir is 5 days, and treatment with intravenous peramivir is 1 dose administered over 15 to 30 minutes.

Control of fever with acetaminophen or another appropriate nonsalicylate-containing antipyretic agent may be important in some children, because fever and other symptoms of influenza could exacerbate underlying chronic conditions.

Table 72.2
Antiviral Drugs for Influenza[a]

Drug (Trade Name)	Virus	Administration	Treatment Indications	Chemoprophylaxis Indications	Adverse Effects
Oseltamivir (Tamiflu)	A and B	Oral	Birth or older[b]	3 mo or older	Nausea, vomiting
Zanamivir (Relenza)	A and B	Inhalation	7 y or older	5 y or older	Bronchospasm
Peramivir (Rapivab)	A and B[c]	Intravenous	2 y or older	N/A	Diarrhea; some reports of skin reactions
Amantadine[d] (Symmetrel)	A	Oral	1 y or older	1 y or older	Central nervous system, anxiety, gastrointestinal
Rimantadine[d] (Flumadine)	A	Oral	13 y or older	1 y or older	Central nervous system, anxiety, gastrointestinal

[a]For current recommendations about treatment and chemoprophylaxis of influenza, including specific dosing information, see **www.cdc.gov/flu/professionals/antivirals/index.htm** or **www.aapredbook.org/flu.**

[b]Approved by the FDA for children as young as 2 wk of age. Given preliminary pharmacokinetic data and limited safety data, the AAP believes that oseltamivir can be used to treat influenza in both term and preterm infants from birth because benefits of therapy are likely to outweigh possible risks of treatment.

[c]Peramivir efficacy is based on clinical trials in which the predominant influenza virus type was influenza A; a limited number of subjects infected with influenza B virus were enrolled.

[d]High levels of resistance to amantadine and rimantadine persist, and these drugs should not be used unless resistance patterns change significantly. Antiviral susceptibilities of viral strains are reported weekly at **www.cdc.gov/flu/weekly/fluactivitysurv.htm.**

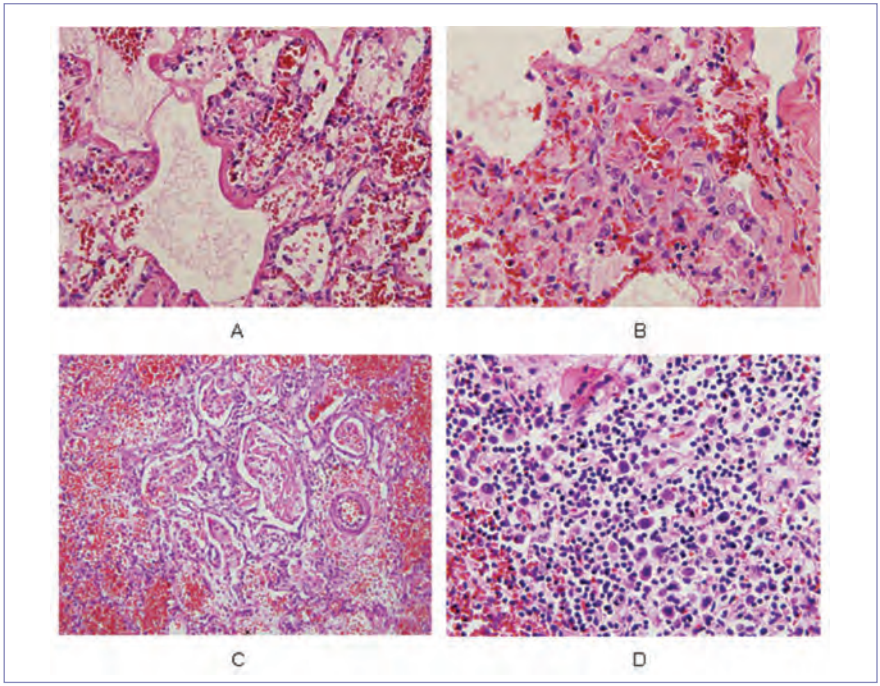


Image 72.1
Pathologic findings from a patient with confirmed influenza A (H5N1) infection (hematoxylin-eosin stain, magnification ×40). A, Hyaline membrane formation lining the alveolar spaces of the lung and vascular congestion with a few infiltrating lymphocytes in the interstitial areas. Reactive fibroblasts are also present. B, An area of lung with proliferating reactive fibroblasts within the interstitial areas. Few lymphocytes are seen, and no viral intranuclear inclusions are visible. C, Fibrinous exudates filling the alveolar spaces, with organizing formation and few hyaline membranes. The surrounding alveolar spaces contain hemorrhage. D, A section of spleen showing numerous atypical lymphoid cells scattered around the white pulp. No viral intranuclear inclusions are seen. Courtesy of Centers for Disease Control and Prevention.

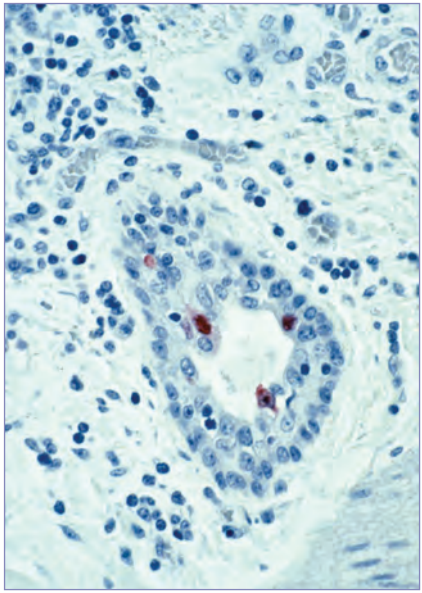


Image 72.2
Influenza viral antigens in bronchial epithelial lining cells as seen by immunohistochemistry. Courtesy of Centers for Disease Control and Prevention.

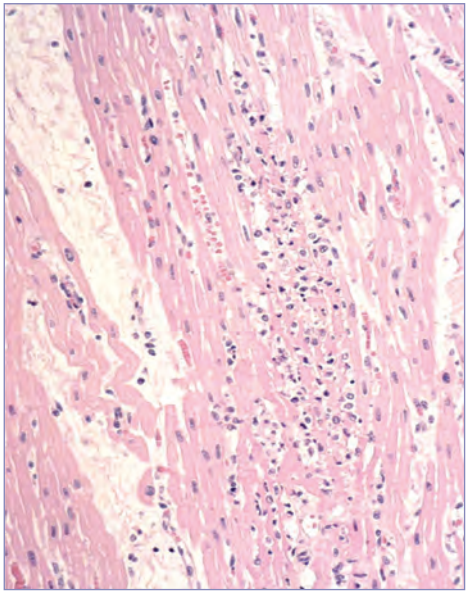


Image 72.3
Focal myocarditis seen in a patient with influenza B infection. Note myocardial necrosis associated with areas of mostly mononuclear inflammation. Courtesy of Centers for Disease Control and Prevention.

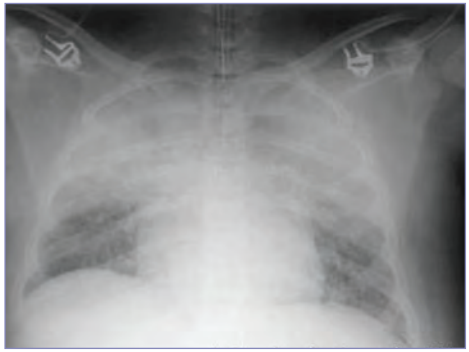


Image 72.4
Influenza pneumonia in a 12-year-old boy with respiratory failure. Courtesy of Benjamin Estrada, MD.

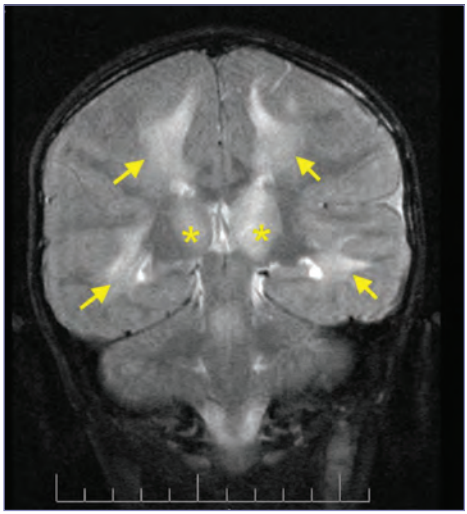


Image 72.5
Coronal T2-weighted magnetic resonance image of a 5-year-old with influenza-associated encephalopathy demonstrating bilateral confluent signal hyperintensity in the white matter (arrows) and thalami (asterisks). Courtesy of James Sejvar, MD.

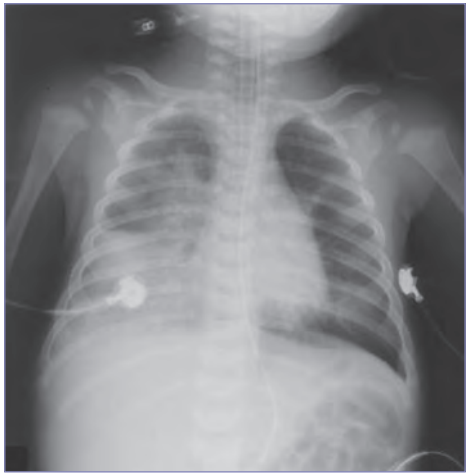


Image 72.6
Influenza A with *Staphylococcus aureus* pneumonia with empyema in a preschool-aged child. Courtesy of Benjamin Estrada, MD.

Image 72.8
Emergency hospital during 1918 influenza epidemic, Camp Funston, KS. Source: National Museum of Health and Medicine, Armed Forces Institute of Pathology, Washington, DC, Image NCP 1603. Courtesy of Immunization Action Coalition.

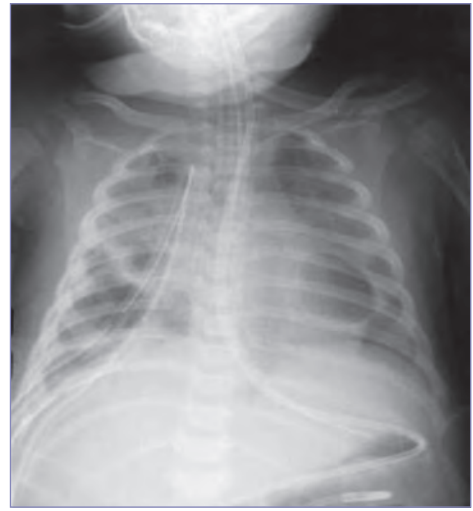


Image 72.7
Influenza A with *Staphylococcus aureus* superinfection in a 6-year-old. Note the presence of bilateral pneumatoceles. Courtesy of Benjamin Estrada, MD.

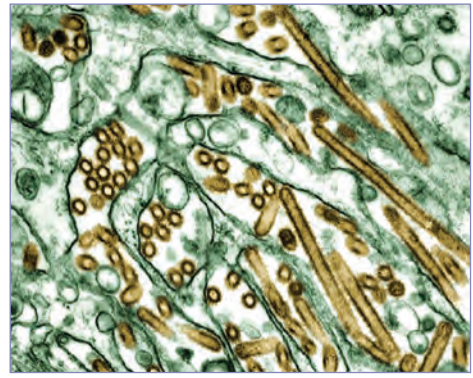


Image 72.9
Colorized transmission electron micrograph of avian influenza A (H5N1) viruses (seen in gold) grown in Madin-Darby canine kidney epithelial cells (seen in green). Avian influenza A viruses do not usually infect humans; however, several instances of human infections and outbreaks have been reported since 1997. When such infections occur, public health authorities monitor these situations closely. Courtesy of Centers for Disease Control and Prevention.

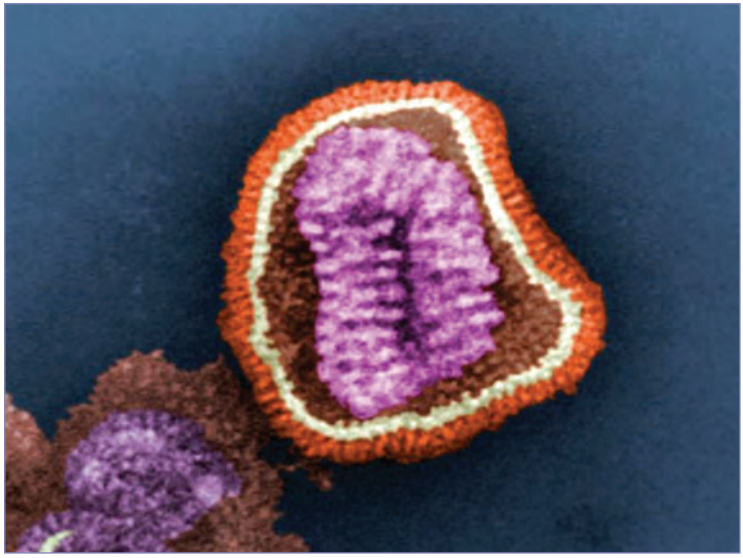


Image 72.10
This negative-stained transmission electron micrograph depicts the ultrastructural details of an influenza virus particle, or virion. Courtesy of Centers for Disease Control and Prevention/Erskine L. Palmer, MD/M. L. Martin, MD.

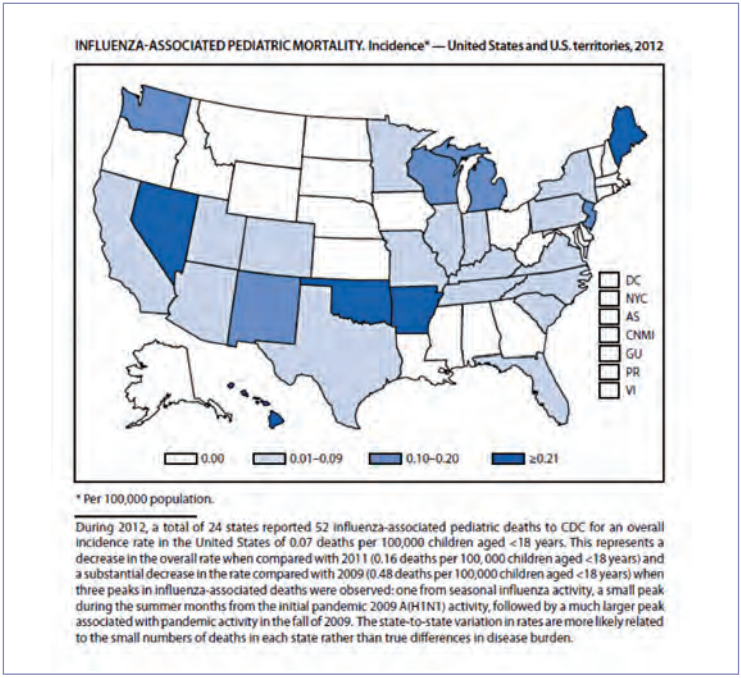


Image 72.11
Influenza-associated pediatric mortality. Incidence—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

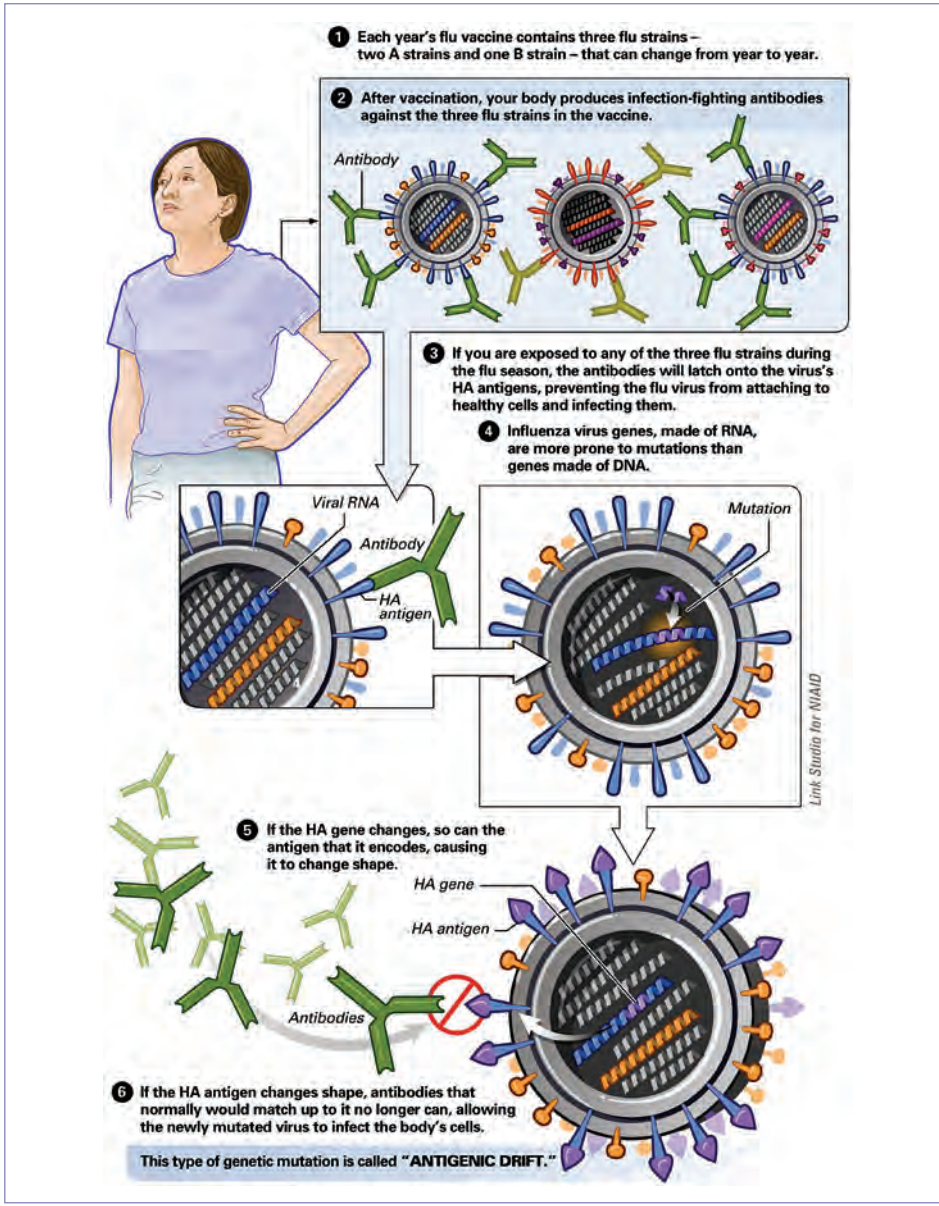


Image 72.12

Antigenic drift. Each year's flu vaccine contains 3 flu strains—2 A strains and 1 B strain—that can change from year to year. After vaccination, your body produces infection-fighting antibodies against the 3 flu strains in the vaccine. If a vaccinated individual is exposed to any of the 3 flu strains during the flu season, the antibodies will latch onto the virus hemagglutinin (HA) antigens, preventing the flu virus from attaching to healthy cells and infecting them. Influenza virus genes, made of RNA, are more prone to mutations than genes made of DNA. If the HA gene changes, so can the antigen that it encodes, causing it to change shape. If the HA antigen changes shape, antibodies that normally would match up to it no longer can, allowing the newly mutated virus to infect the body's cells. This type of genetic mutation is called *antigenic drift.* Courtesy of National Institute of Allergy and Infectious Diseases.

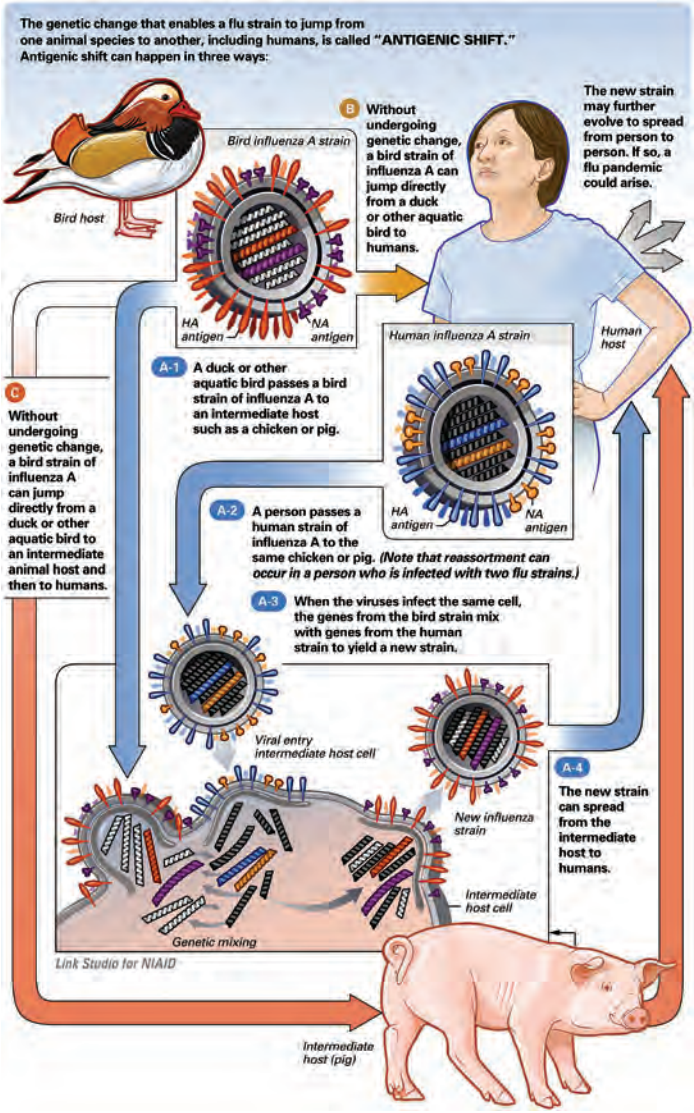


Image 72.13

Antigenic shift. The genetic change that enables a flu strain to jump from one animal species to another, including humans, is called *antigenic shift.* Antigenic shift can happen in 3 ways. Antigenic shift 1: A duck or other aquatic bird passes a bird strain of influenza A to an intermediate host, such as a chicken or pig. A person passes a human strain of influenza A to the same chicken or pig. When the viruses infect the same cell, genes from the bird strain mix with genes from the human strain to yield a new strain. The new strain can spread from the intermediate host to humans. Antigenic shift 2: Without undergoing genetic change, a bird strain of influenza A can jump directly from a duck or other aquatic bird to humans. Antigenic shift 3: Without undergoing genetic change, a bird strain of influenza A can jump directly from a duck or other aquatic bird to an intermediate animal host and then to humans. The new strain may further evolve to spread from person to person. If so, a flu pandemic could arise. Courtesy of National Institute of Allergy and Infectious Diseases.

CHAPTER 73

Kawasaki Disease

CLINICAL MANIFESTATIONS

Kawasaki disease is a self-limited vasculitis of medium-sized arteries. The diagnosis is made in patients with fever plus the following clinical criteria:

1. Bilateral injection of the bulbar conjunctivae with limbic sparing and without exudate;
2. Erythematous mouth and pharynx, strawberry tongue, and red, cracked lips;
3. A polymorphous, generalized, erythematous rash, often with accentuation in the groin, which can be morbilliform, maculopapular, scarlatiniform, or erythema multiforme-like;
4. Changes in the peripheral extremities consisting of erythema of the palms and soles and firm, sometimes painful, induration of the hands and feet, often with periungual desquamation within 2 to 3 weeks after fever onset;
5. Acute, nonsuppurative, usually unilateral, anterior cervical lymphadenopathy with at least 1 node ≥1.5 cm in diameter.

The diagnosis of classic (or complete) Kawasaki disease is based on the presence of ≥5 days of fever and ≥4 of the 5 principal features described. If all 5 principal clinical criteria, particularly when erythema and swelling of the hands and feet are present and without an alternative explanation, the diagnosis may be made after only 4 days of fever. Individual clinical manifestations may appear and self-resolve rather than all being present simultaneously. It is important to question about previous presence of relevant manifestations when a patient seeks medical attention for persistent fever.

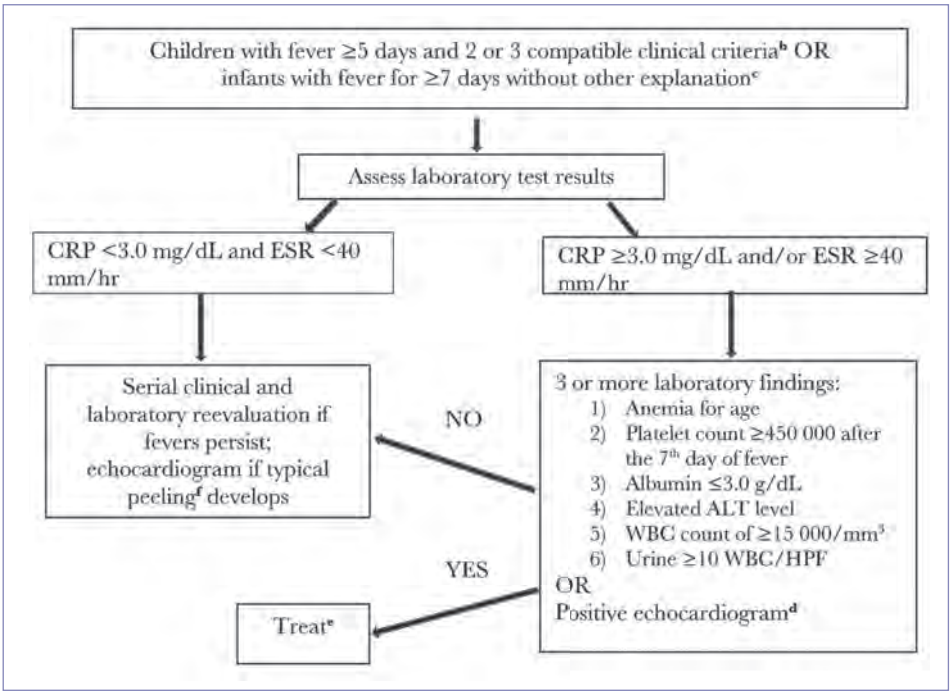
The correct diagnosis sometimes is delayed in patients who seek medical attention because of fever and unilateral neck swelling, which mistakenly is thought to be attributable to bacterial lymph node or para- or retropharyngeal infection. A distinguishing clinical and imaging feature in these cases is that suppuration is unlikely in Kawasaki disease. Concurrent viral upper respiratory infection sometimes is present in a patient with Kawasaki disease and, even if confirmed by virus detection, should not delay treatment of Kawasaki disease. An exception is the patient with fever, exudative conjunctivitis, and exudative pharyngitis in whom adenovirus is detected. In such cases, Kawasaki disease is considered extremely unlikely.

The following mucocutaneous or laboratory findings should prompt a search for an alternative diagnosis to Kawasaki disease: bullous, vesicular, or petechial rash; oral ulcers; pharyngeal or conjunctival exudates; generalized lymphadenopathy or splenomegaly; or leukopenia or relative lymphocyte predominance.

The diagnosis of incomplete Kawasaki disease should be considered in children with unexplained fever for ≥5 days plus fewer than 4 of the principal clinical criteria. Supportive laboratory data also are sought when considering the diagnosis of incomplete Kawasaki disease. In 2017, the American Heart Association (AHA) published updated guidelines for the diagnosis, treatment, and long-term management of Kawasaki disease. The algorithm for diagnosis and treatment of suspected incomplete Kawasaki disease is reproduced in Figure 73.1. A high index of suspicion for Kawasaki disease should be maintained for infants, particularly those younger than 6 months, because compared with older children, infants have heightened risk of incomplete manifestations, delayed diagnosis, and development of coronary artery aneurysms. Kawasaki disease should be considered in infants younger than 6 months with prolonged unexplained fever, with or without aseptic meningitis, with evidence of systemic inflammation, even with fewer than 2 of the characteristic features of Kawasaki disease; in infants with a shock-like syndrome in whom an inciting infection is not confirmed; and in infants as well as older children when presumed cervical lymphadenitis or para- or retropharyngeal nonsuppurative infection fails to respond to appropriate antibiotic therapy.

If coronary artery aneurysm or ectasia is evident (z score ≥2.5) in any patient evaluated for fever, a presumptive diagnosis of Kawasaki disease should be made. A normal early echocardiographic study is typical and does not exclude the diagnosis but may be useful in evaluation of patients with suspected incomplete

Figure 73.1
Evaluation of suspected incomplete Kawasaki disease.[a]



CRP indicates C-reactive protein; ESR, erythrocyte sedimentation rate; ALT, alanine transaminase; WBC, white blood cell; HPF, high-powered field.
[a]In the absence of a "gold standard" for diagnosis, this algorithm cannot be evidence based but rather represents the informed opinion of the expert committee. Consultation with an expert should be sought anytime assistance is needed.
[b]See text for clinical findings of Kawasaki disease.
[c]Infants ≤6 months of age are the most likely to develop prolonged fever without other clinical criteria for Kawasaki disease; these infants are at particularly high risk of developing coronary artery abnormalities.
[d]Echocardiography is considered positive for purposes of this algorithm if any of 3 conditions are met: z score of left anterior descending coronary artery or right coronary artery ≥2.5; coronary artery aneurysm is observed; or ≥3 other suggestive features exist, including decreased left ventricular function, mitral regurgitation, pericardial effusion, or z scores in left anterior descending coronary artery or right coronary artery of 2 to 2.5.
[e]Treatment should be given within 10 days of fever onset. See text for indications for treatment after the tenth day of fever.
[f]Typical peeling begins under the nail beds of fingers and toes.

Kawasaki disease. In one study, 80% of patients with Kawasaki disease who ultimately developed coronary artery disease had abnormalities (z score ≥2.5) on an echocardiogram obtained during the first 10 days of illness.

Other clinical features of Kawasaki disease include irritability, abdominal pain, diarrhea, and vomiting. Other examination and laboratory findings include urethritis with sterile pyuria (70% of cases), mild anterior uveitis (80%), mild elevation of serum hepatic transaminase concentrations (50%), arthralgia or arthritis (10%–20%), meningismus with cerebrospinal fluid pleocytosis (40%), hydrops of the gallbladder (<10%), pericardial effusion of at least 1 mm (<5%), myocarditis manifesting as congestive heart failure (<5%), and cranial nerve palsy (<1%). Persistent resting tachycardia and a hyperdynamic precordium are common findings, and an S3 gallop can be present. Fine desquamation in the groin area can occur in the acute phase of disease. Inflammation or ulceration may be observed at the inoculation scar of previous bacille Calmette-Guérin immunization. Rarely, Kawasaki disease can present with acute shock; these children often have significant thrombocytopenia attributable to consumption coagulopathy, which also causes a low erythrocyte sedimentation rate (ESR). Group A streptococcal or *Staphylococcus aureus* toxic shock syndrome should be excluded in such cases.

The average duration of fever in untreated Kawasaki disease is 10 days; however, fever can last 2 weeks or longer. After fever resolves, patients can remain anorectic or irritable with decreased energy for 2 to 3 weeks. During this phase, branny desquamation of fingers, toes, hands, and feet and fine desquamation of other areas may occur. Transverse lines across the nails (Beau lines) sometimes are noted month(s) later. Recurrent disease develops in approximately 1% to 2% of patients in the United States a median of 1.5 years after the index episode. The recurrence rate is 3.5% in Asian and Pacific Islander people.

Coronary artery abnormalities are serious sequelae of Kawasaki disease, occurring in 20% to 25% of untreated children. Increased risk of developing coronary artery abnormalities is associated with male sex; age <12 months or >8 years; fever for more than 10 days; white blood cell count >15,000/mm^3; high relative neutrophil (>80%) and band count; low hemoglobin concentration (<10 g/dL); hypoalbuminemia, hyponatremia, or thrombocytopenia; and fever persisting or recurring >36 hours after completion of Immune Globulin Intravenous (IGIV) administration. Aneurysms of the coronary arteries most typically occur between 1 and 4 weeks after onset of illness; onset later than 6 weeks is rare. Giant coronary artery aneurysms (internal diameter ≥8 mm) are highly predictive of long-term complications. Aneurysms occurring in other medium-sized arteries (eg, iliac, femoral, renal, and axillary vessels) are uncommon and generally do not occur in the absence of significant coronary abnormalities. In addition to coronary artery disease, carditis can involve the pericardium, myocardium, or endocardium, and mitral or aortic regurgitation or both can develop. Carditis generally resolves when fever resolves.

In children with only mild coronary artery dilation, coronary artery dimensions often return to baseline within 6 to 8 weeks after onset of disease. Approximately 50% of coronary aneurysms (but only a small proportion of giant aneurysms) regress by echocardiography to normal luminal size within 1 to 2 years, although this process can result in luminal stenosis or a poorly compliant, fibrotic vessel wall or both.

The current case-fatality rate for Kawasaki disease in the United States and Japan is less than 0.2%. The principal cause of death is myocardial infarction resulting from coronary artery occlusion attributable to thrombosis or progressive stenosis. The relative risk of mortality is highest within 6 weeks of onset of acute symptoms, but myocardial infarction and sudden death can occur months to years after the acute episode. There is no current evidence that the vasculitis of Kawasaki disease predisposes to premature atherosclerotic coronary artery disease.

ETIOLOGY

The etiology is unknown. Epidemiologic and clinical features suggest an infectious or an environmental cause or trigger in genetically susceptible individuals.

EPIDEMIOLOGY

Peak age of occurrence in the United States is between 18 and 24 months. Fifty percent of patients are younger than 2 years, and 80% are younger than 5 years; cases are uncommon in children older than 8 years, but rare cases have occurred even in adults. The prevalence of coronary artery abnormalities is higher if treatment (IGIV) is delayed beyond the 10th day of illness. The male-to-female ratio is approximately 1.5:1. In the United States, 4,000 to 5,500 cases are estimated to occur each year; the incidence is highest in children of Asian ancestry. Kawasaki disease first was described in Japan, where a pattern of endemic occurrence with superimposed epidemic outbreaks was recognized. More cases, including clusters, occur during winter and spring. No evidence indicates person-to-person or common-source spread, although the incidence is tenfold higher in siblings of children with the disease than in the general population.

The **incubation period** is unknown.

DIAGNOSTIC TESTS

No specific diagnostic test is available. The diagnosis is established by fulfillment of the clinical criteria after consideration of other possible illnesses, such as staphylococcal or streptococcal toxin-mediated disease; drug reactions (eg, Stevens-Johnson syndrome); measles, adenovirus, Epstein-Barr virus,

parvovirus B19, or enterovirus infections; rickettsial exanthems; leptospirosis; systemic-onset juvenile idiopathic arthritis; and reactive arthritis. The identification of a respiratory virus by molecular testing does not exclude the diagnosis of Kawasaki disease in infants and children who otherwise have met diagnostic criteria. A markedly increased ESR or serum C-reactive protein (CRP) concentration during the first 2 weeks of illness and an increased platelet count (>450,000/mm^3) on days 10 to 21 of illness are almost universal laboratory features. ESR and platelet count usually are normal within 6 to 8 weeks; CRP concentration returns to normal much sooner.

TREATMENT

Management during the acute phase is directed at decreasing inflammation of the myocardium and coronary artery wall and providing supportive care. Therapy should be initiated as soon as the diagnosis is established or strongly suspected. Once the acute phase has subsided, therapy is directed at prevention of coronary artery thrombosis.

Primary Treatment

Immune Globulin Intravenous (IGIV)

A single dose of IGIV, 2 g/kg, administered over 10 to 12 hours, results in more rapid resolution of fever and other clinical and laboratory indicators of acute inflammation and has been proven to reduce the risk of coronary artery aneurysms from 17% to 4% in children with a normal first echocardiogram. IGIV plus aspirin is the treatment of choice and should be initiated as soon as possible in all patients when criteria of classic or incomplete Kawasaki disease are met and alternative diagnoses are unlikely, whether or not coronary artery abnormalities are detected. Despite prompt treatment with IGIV and aspirin, approximately 2% to 4% of patients develop coronary artery aneurysms even when treatment is initiated before the onset of coronary artery abnormalities.

Efficacy of therapy initiated later than the 10th day of illness or after detection of aneurysms has not been evaluated fully. However, therapy with IGIV and aspirin should be provided for patients in whom the diagnosis is made more than 10 days after the onset of fever (ie, the diagnosis was not made earlier) who have manifestations of continuing inflammation (ie, elevated ESR or CRP ≥3.0 mg/dL) plus either fever or coronary artery luminal dimension z score >2.5.

IGIV infusion reactions (fever, chills, hypotension) are not uncommon. A sometimes severe Coombs-positive hemolytic anemia can complicate IGIV therapy, especially in individuals with AB blood type, and usually occurs within 5 to 10 days of infusion. Aseptic meningitis can result from IGIV therapy and resolves quickly without neurologic sequelae. IGIV infusion results in elevation of the ESR; therefore, ESR is not a useful test to monitor disease activity after infusion; CRP is not affected by IGIV administration and can be used.

Aspirin

Aspirin is used for its anti-inflammatory (high-dose) and antithrombotic (low-dose) activity, although aspirin alone does not decrease the risk of coronary artery abnormalities. Aspirin is given in doses of 80 to 100 mg/kg per day in 4 divided doses when the diagnosis is made and concurrently with IGIV administration. Children with acute Kawasaki disease have decreased aspirin absorption and increased clearance and rarely achieve therapeutic serum concentrations. It generally is not necessary to monitor salicylate concentrations. High-dose aspirin therapy usually is given until the patient has been afebrile for 48 to 72 hours. Low-dose aspirin (3 to 5 mg/kg/day, in a single daily dose) then is given until a follow-up echocardiogram at 6 to 8 weeks after onset of illness is normal or is continued indefinitely for children in whom coronary artery abnormalities are present. In general, ibuprofen should be avoided in children with coronary aneurysms taking aspirin.

The child and all household contacts older than 6 months should receive influenza vaccine according to seasonal recommendations. The inactivated injectable influenza vaccine (not live attenuated vaccine) should be used in the child receiving aspirin.

Management of IGIV Resistance and Retreatment

Approximately 30% of patients who receive IGIV have fever within the first 36 hours after completing the IG infusion, which is not an indication of therapeutic failure. However, 10% to 20% of treated patients have recrudescent or persistent fever beyond 36 hours after completion of their IGIV infusion and are termed IGIV-resistant. In these situations, the diagnosis of Kawasaki disease should be reevaluated. If Kawasaki disease still is most likely, retreatment with IGIV usually is given and high-dose aspirin is continued.

Cardiac Care

Echocardiography should be performed at the time of suspected diagnosis and repeated at 2 weeks and 6 to 8 weeks after diagnosis.

Children at higher risk—for example, children with persistent or recrudescent fever after initial IGIV or with baseline coronary artery abnormalities—may require more frequent echocardiograms to guide the need for additional therapies. Children should be assessed during this time for arrhythmias, congestive heart failure, and valvular regurgitation. The care of patients with significant cardiac abnormalities should involve a pediatric cardiologist experienced in management of patients with Kawasaki disease.

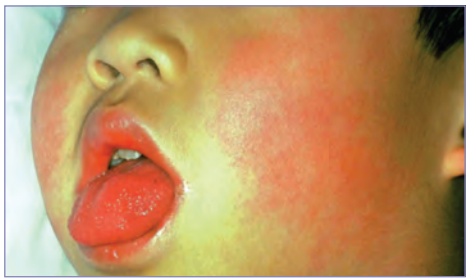


Image 73.1
A child with Kawasaki disease with striking facial rash and erythema of the oral mucous membrane.

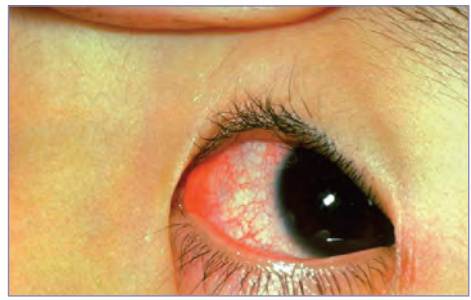


Image 73.2
A child with Kawasaki disease with conjunctivitis. Note the absence of conjunctival discharge.

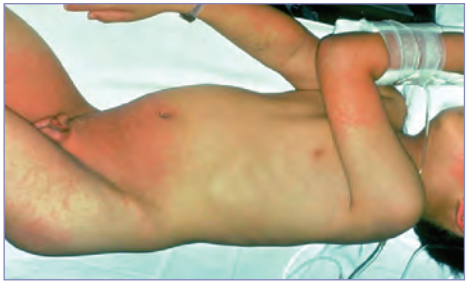


Image 73.3
Characteristic distribution of erythroderma of Kawasaki disease. The rash is accentuated in the perineal area in approximately two-thirds of patients.

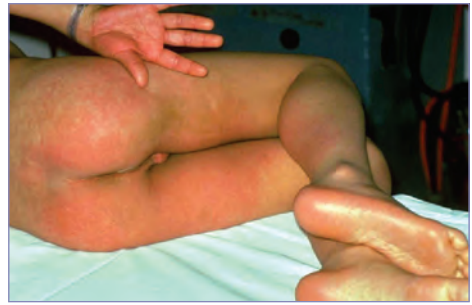


Image 73.4
Generalized erythema and early perianal and palmar desquamation. This is the same patient as in Image 73.3.

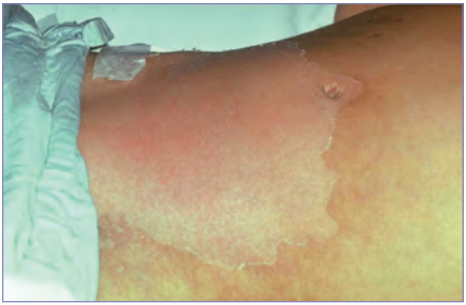


Image 73.5
Characteristic desquamation of the skin over the abdomen in a patient with Kawasaki disease. This is the same patient as in Images 73.3 and 73.4.

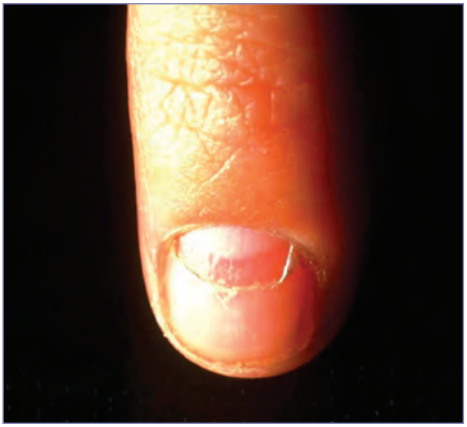


Image 73.6
Periungual desquamation of a patient with Kawasaki disease. This is the same patient as in Images 73.3, 73.4, and 73.5.

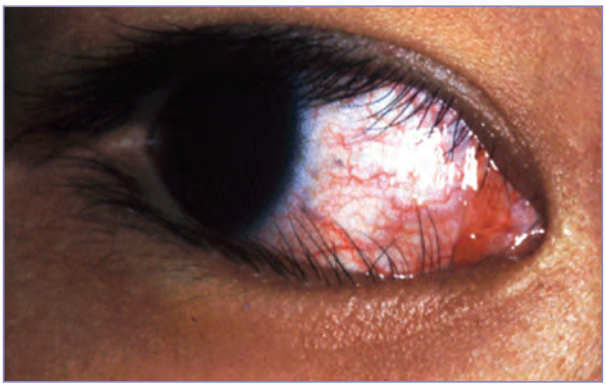


Image 73.7
Bulbar conjunctivitis in a patient is generally absent.

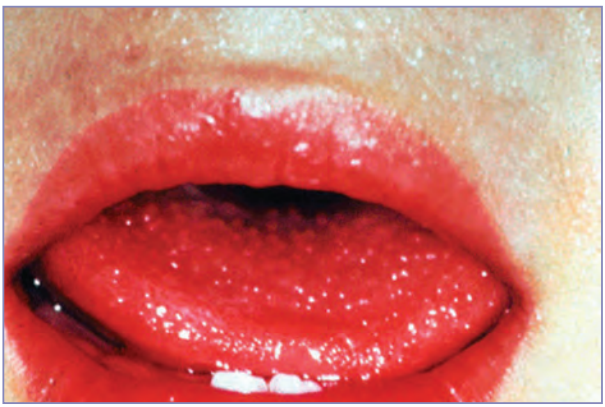


Image 73.8
Erythematous lips and injection of the oropharyngeal membranes in a patient with Kawasaki disease. Scarlet fever, toxic shock syndrome, staphylococcal scalded skin syndrome, and measles may be confused with this disease.

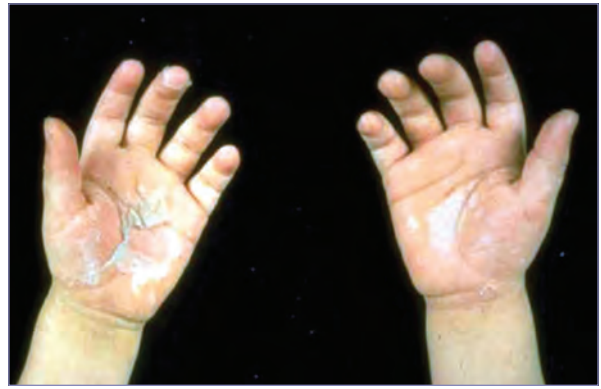


Image 73.9
A child with the characteristic desquamation of the hands in a later stage of Kawasaki disease. Copyright Charles Prober.

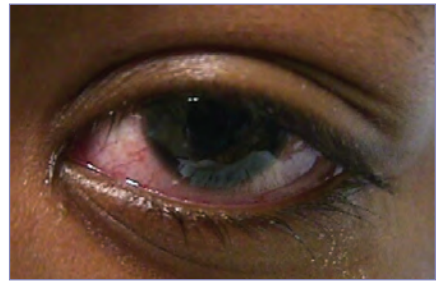


Image 73.10
Bulbar conjunctivitis in a 3-year-old boy with Kawasaki disease. Courtesy of Benjamin Estrada, MD.

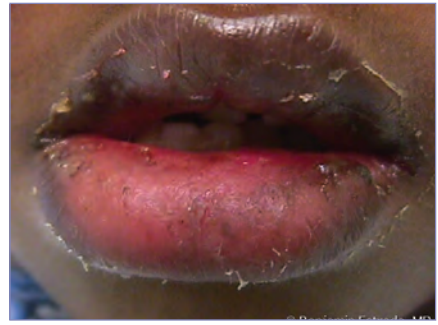


Image 73.11
Mucositis in a 3-year-old boy with Kawasaki disease. Courtesy of Benjamin Estrada, MD.

CHAPTER 74

Kingella kingae Infections

CLINICAL MANIFESTATIONS

The most common infections attributable to *Kingella kingae* are pyogenic arthritis, osteomyelitis, and bacteremia. Other infections caused by *K kingae* include diskitis, endocarditis (*K kingae* belongs to the HACEK group of organisms), meningitis, and pneumonia. The majority of *K kingae* infections affect children younger than 3 years.

K kingae is a primary cause of skeletal infections in the first 3 years of life. *K kingae* pyogenic arthritis generally is monoarticular and most commonly involves the knee, hip, or ankle. *K kingae* osteomyelitis most often involves the femur or tibia and has an unusual predilection for small bones, including the small bones of the foot. The clinical manifestations of *K kingae* pyogenic arthritis and osteomyelitis are similar to manifestations of skeletal infection attributable to other bacterial pathogens in immunocompetent children, although a subacute course may be more common.

K kingae bacteremia can occur in previously healthy young children and in children with preexisting chronic medical problems. Children with *K kingae* bacteremia present with fever and frequently have concurrent symptoms of respiratory or gastrointestinal tract disease.

ETIOLOGY

K kingae is a gram-negative organism that belongs to the *Neisseriaceae* family. It is a fastidious, facultative anaerobic, β-hemolytic, small bacillus that appears as pairs or short chains with tapered ends and that often resists decolorization, sometimes resulting in misidentification as a gram-positive organism.

EPIDEMIOLOGY

The usual habitat of *K kingae* is the human posterior pharynx. The organism colonizes young children more frequently than older children or adults and can be transmitted among children in child care centers, occasionally causing clusters of cases. Infection may be associated with preceding or concomitant stomatitis or upper respiratory tract infection.

The **incubation period** relative to acquisition of colonization is not well defined but presumably is variable.

DIAGNOSTIC TESTS

K kingae can be isolated from blood, synovial fluid, bone, cerebrospinal fluid, respiratory tract secretions, and other sites of infection. Organisms grow best in aerobic conditions with enhanced carbon dioxide. In patients with *K kingae* pyogenic arthritis or osteomyelitis, blood cultures often are negative. Synovial fluid and bone aspirates from patients with suspected *K kingae* infection should be inoculated to both solid media and a blood culture system and held for 5 to 7 days to maximize recovery. When available, conventional and real-time polymerase chain reaction (PCR) methods markedly improve detection of *K kingae*, which should be suspected in young children with culture-negative skeletal infections. Such tests are available only in specialty laboratories.

TREATMENT

Because some β-lactam antibiotic resistance is seen among isolates in the United States, ampicillin-sulbactam or a first-, second-, or third-generation cephalosporin is recommended for children with osteoarticular infections suspected to be attributable to *K kingae*.

K kingae usually is highly susceptible to penicillins and first-, second-, and third-generation cephalosporins. However, TEM-1 β-lactamase production has been reported in occasional isolates in parts of the United States and other countries, resulting in low-level resistance to penicillin and ampicillin. The TEM-1 β-lactamase lacks activity against second- and third-generation cephalosporins. Nearly all isolates are susceptible to aminoglycosides, macrolides, trimethoprim-sulfamethoxazole, tetracyclines, and fluoroquinolones. Between 40% and 100% of isolates are resistant to clindamycin.

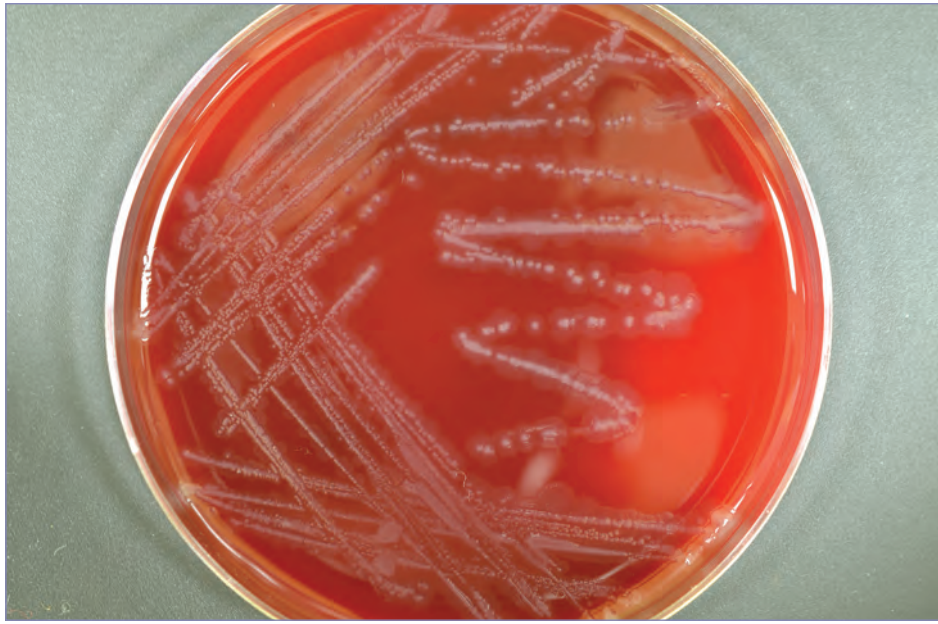


Image 74.1
Kingella kingae on blood agar. Smooth, gray colonies may pit the agar and are surrounded by a small but distinct zone of β-hemolysis on blood agar. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

Image 74.2
Kingella kingae on chocolate agar. Colonies appear after 2 to 4 days of incubation on blood and chocolate agar. This species demonstrates β-hemolysis on blood agar. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 75

Legionella pneumophila Infections

CLINICAL MANIFESTATIONS

Legionellosis is associated primarily with 2 clinically and epidemiologically distinct illnesses: legionnaires' disease and Pontiac fever. **Legionnaires' disease** varies in severity from mild to severe pneumonia characterized by fever, cough with or without chest pain, and progressive respiratory distress. Legionnaires' disease can be associated with chills and rigors, headache, myalgia, and gastrointestinal tract, central nervous system, and renal manifestations. Respiratory failure and death can occur. **Pontiac fever** is a milder febrile illness without pneumonia that is characterized by an abrupt onset of a self-limited, influenza-like illness (fever, myalgia, headache, weakness) resulting from host inflammation to the bacterium. Cervical lymphadenitis caused by *Legionella* species has been reported and may produce a syndrome clinically similar to nontuberculous mycobacterial infection.

ETIOLOGY

Legionella species are fastidious, small, aerobic bacilli that stain gram negative after recovery on buffered charcoal yeast extract (BCYE) media. They constitute a single genus in the family *Legionellaceae.* At least 20 of the more than 60 species have been implicated in human disease, but the most common species causing infections in the United States is *Legionella pneumophila*, with most isolates belonging to serogroup 1. Multiplication of *Legionella* organisms in water sources occurs optimally in temperatures between 25°C (77°F) and 42°C (108°F), although *Legionella* organisms have been recovered from water outside this temperature range.

EPIDEMIOLOGY

Legionnaires' disease is acquired through inhalation and microaspiration of aerosolized water contaminated with *Legionella* species. Only one case of possible person-to-person transmission has been reported. Most cases are sporadic and can be associated with travel or a stay in a health care facility; sporadic cases may be connected with unrecognized outbreaks or clusters. Outbreaks commonly are associated with buildings or structures that have complex water systems, like hotels and resorts, long-term care facilities, hospitals, and cruise ships. The most likely sources of infection include contaminated water aerosolized from showerheads, hot tubs, decorative fountains, and cooling towers (parts of centralized air-conditioning systems for large buildings). Health care-associated infections occur and often are related to contamination of the hot water supply. In patients who develop pneumonia during or after their hospitalization, legionnaires' disease should be considered in the differential diagnosis. Legionnaires' disease occurs most commonly in individuals who are elderly, are immunocompromised, have underlying lung or heart disease, are of male gender, are current or former cigarette smokers, exhibit end-stage renal failure, or have systemic malignancy. Infection in children is rare, with ≤1% cases of pneumonia caused by *Legionella* and may be asymptomatic or mild and unrecognized. Severe disease has occurred in children with malignancy, severe combined immunodeficiency, chronic granulomatous disease, organ transplantation, end-stage renal disease, and underlying pulmonary disease and those treated with systemic corticosteroids or other immunosuppression. Health care-associated cases and outbreaks of infection in newborn infants have been associated with a contaminated water source and may result in severe illness.

The **incubation period** for legionnaires' disease (pneumonia) is 2 to 10 days (up to 19 days); for Pontiac fever, the **incubation period** is 1 to 2 days (short as 4 hours).

DIAGNOSTIC TESTS

When a patient is suspected of having legionnaires' disease, testing should include both culture of a lower respiratory tract swab specimen and urine antigen testing. Recovery of *Legionella* from respiratory tract secretions, lung tissue, pleural fluid, or other normally sterile fluid specimens by using supplemented BCYE media provides definitive evidence of infection, but the sensitivity of culture is laboratory dependent. Detection of *Legionella* lipopolysaccharide antigen in urine by

commercially available immunoassays is highly specific. Such tests are sensitive for *L pneumophila* serogroup 1 but much less sensitive in patients infected with other *L pneumophila* serogroups or other *Legionella* species. Urinary antigen test sensitivity is also dependent on the assay method used and on the severity of disease. Genus-specific polymerase chain reaction (PCR)-based assays have been developed that detect *Legionella* DNA in respiratory secretions as well as in blood and urine of some patients with pneumonia. There is a single PCR assay available for detection of *Legionella* serotypes 1 through 14 in sputum.

For serologic diagnosis, a fourfold increase in antibody titer, as measured by indirect immunofluorescent antibody (IFA), confirms a recent infection. This serologic result is not useful for treatment decisions, however, because convalescent titers take 3 to 4 weeks to increase (and the increase may be delayed for 8 to 12 weeks). Antibodies to several gram-negative organisms, including *Pseudomonas* species, *Bacteroides fragilis*, and *Campylobacter jejuni*, can cause false-positive IFA test results.

TREATMENT

Patients with legionnaires' disease should receive antimicrobial agents. In immunocompetent patients, either intravenously administered azithromycin or levofloxacin (or another fluoroquinolone) is the drug of choice. Once the patient is improved clinically, oral therapy can be substituted. Levofloxacin (or another fluoroquinolone) is the drug of choice for immunocompromised children and adults and those with severe disease. Doxycycline and trimethoprim-sulfamethoxazole are alternative drugs. Duration of therapy is 5 to 10 days for azithromycin and 14 to 21 days for other drugs, with the longer courses of therapy for patients who are immunocompromised or who have severe disease.

Antimicrobial treatment for patients with Pontiac fever is not recommended.

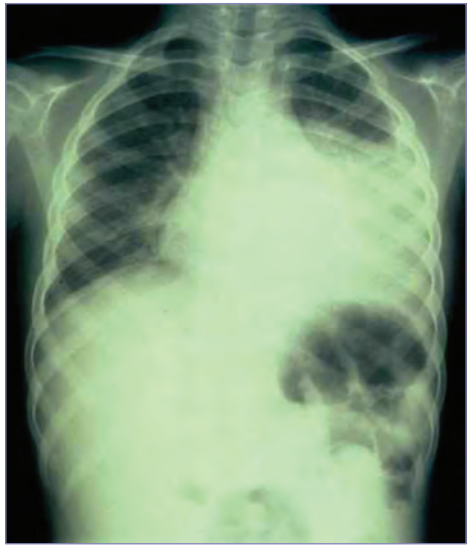


Image 75.1
An adult with pneumonia due to *Legionella pneumophila*. *Legionella* infections are rare in otherwise healthy children. Although nosocomial infections and hospital outbreaks are reported, this infection is not transmitted from person to person.

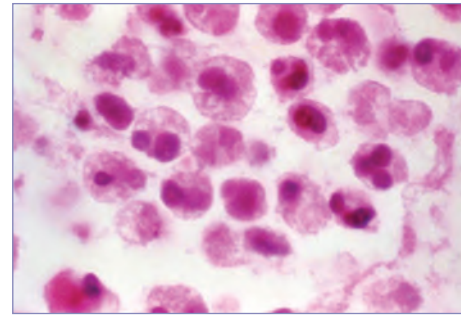


Image 75.2
This hematoxylin-eosin–stained micrograph of lung tissue biopsied from a patient with legionnaires' diseases revealed the presence of an intra-alveolar exudate consisting of macrophages and polymorphonuclear leucocytes. The *Legionella pneumophila* bacteria are not stained in this preparation (magnification ×500). Courtesy of Centers for Disease Control and Prevention.

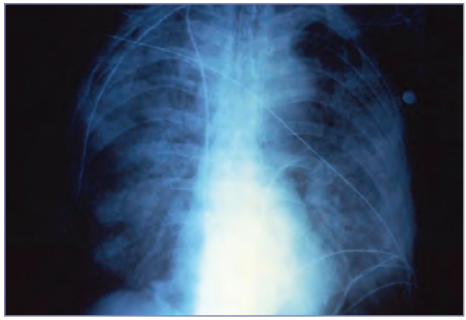


Image 75.3
This anteroposterior radiograph revealed bilateral pulmonary infiltrates in a patient with legionnaires' disease. Legionnaires' disease is an acute and sometimes fatal respiratory illness caused by *Legionella pneumophila* bacteria, whereby headache, high fever, cough, and flu-like symptoms accompany the condition. Courtesy of Centers for Disease Control and Prevention.

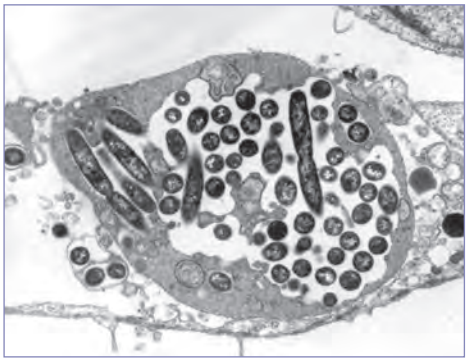


Image 75.5
Legionella pneumophila multiplying inside a cultured human lung fibroblast. Courtesy of Centers for Disease Control and Prevention.

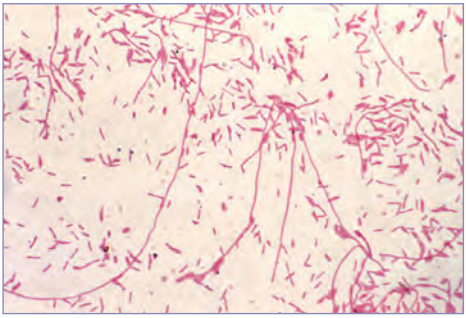


Image 75.4
This Gram-stained micrograph reveals chains and solitary gram-negative *Legionella pneumophila* bacteria found within a sample taken from a victim of the 1976 legionnaires' disease outbreak in Philadelphia, PA. Legionnaires' disease is the more severe form of legionellosis and is characterized by pneumonia, commencing 2 to 10 days after exposure. Pontiac fever is an acute-onset, flu-like, non-pneumonic illness, occurring within 1 to 2 days of exposure. Courtesy of Centers for Disease Control and Prevention.

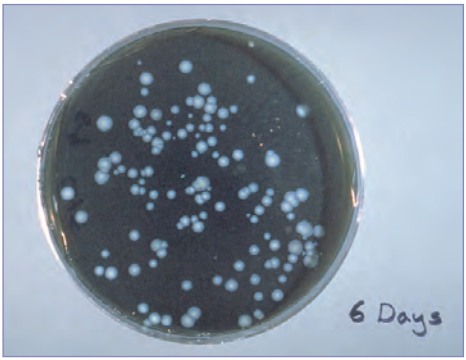


Image 75.6
Charcoal-yeast extract agar plate culture of *Legionella pneumophila*. Courtesy of Centers for Disease Control and Prevention.

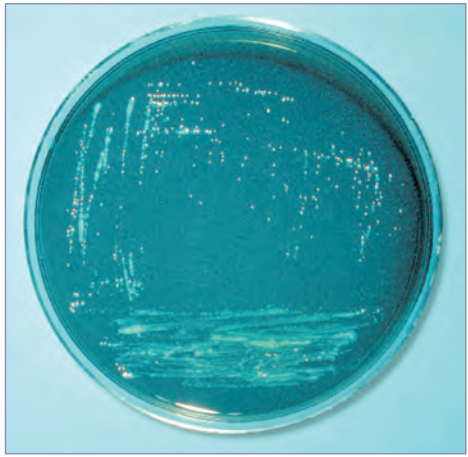


Image 75.7
Charcoal-yeast extract agar plate culture of *Legionella pneumophila*. Courtesy of Centers for Disease Control and Prevention.

Image 75.8
This photograph shows numbers of *Legionella* species colonies, which had been cultivated on an agar-cultured plate and illuminated using UV light. At least 46 *Legionella* species and 70 serogroups have been identified. *Legionella pneumophila*, a ubiquitous aquatic bacterial organism that thrives in warm environments, primarily at temperatures ranging from 32°C to 45°C (89.6°F–113.0°F), causes more than 90% of cases of legionnaires' disease in the United States. Courtesy of Centers for Disease Control and Prevention.

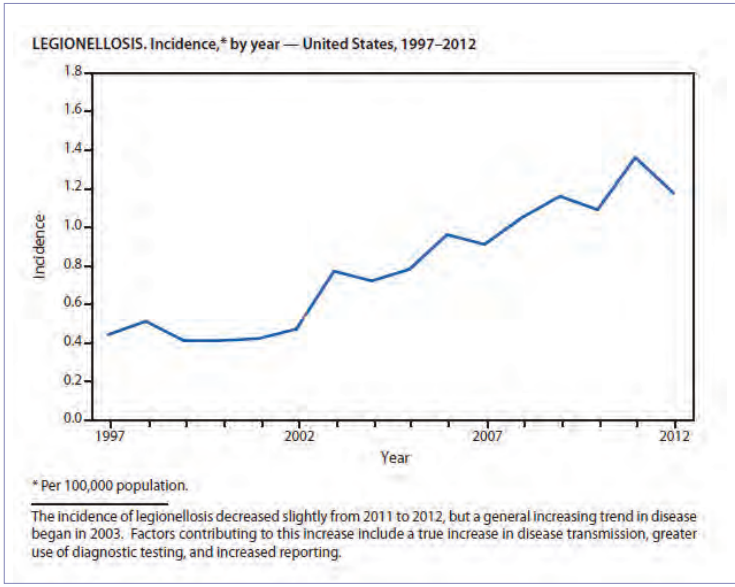


Image 75.9
Legionellosis. Incidence, by year—United States, 1997–2012. Courtesy of *Morbidity and Mortality Weekly Report*.

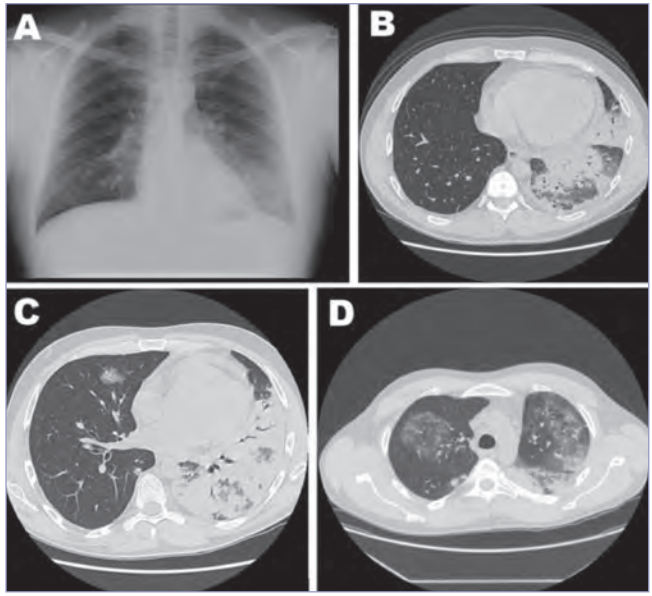


Image 75.10
Imaging studies of a 42-year-old man with severe pneumonia caused by *Legionella pneumophila* serogroup 11, showing lobar consolidation of the left lower lung lobe, with an air-bronchogram within the homogeneous airspace consolidation. Consensual mild pleural effusion was documented by a chest radiograph (A) and high-resolution computed tomography (B). A week after hospital admission, repeat high-resolution computed tomography of the chest showed extensive and homogeneous consolidation of left upper and lower lobes, accompanied by bilateral ground-glass opacities (C and D). Courtesy of *Emerging Infectious Diseases*.

CHAPTER 76

Leishmaniasis

CLINICAL MANIFESTATIONS

The 3 main clinical syndromes are as follows:

- **Cutaneous leishmaniasis.** After inoculation by the bite of an infected female phlebotomine sand fly (approximately 2–3 mm long), parasites proliferate locally in mononuclear phagocytes, leading to an erythematous papule, which typically slowly enlarges to become a nodule and then an ulcerative lesion with raised, indurated borders. Ulcerative lesions can become dry and crusted or may develop a moist granulating base with an overlying exudate. Lesions can persist as nodules, papules, or plaques and can be single or multiple. Lesions commonly appear on exposed areas of the body (eg, face and extremities) and can be accompanied by satellite lesions, sporotrichoid-like nodules, and regional adenopathy. Clinical manifestations of Old World and New World (American) cutaneous leishmaniasis generally are similar. Spontaneous resolution of lesions may take weeks to years—depending on the *Leishmania* species/strain—and usually results in a flat, atrophic scar.

- **Mucosal leishmaniasis (espundia)** traditionally refers to a metastatic sequela of New World cutaneous infection, which results from dissemination of the parasite from the skin to the naso-oropharyngeal/laryngeal mucosa; this form of leishmaniasis typically is caused by species in the *Viannia* subgenus. Mucosal disease usually becomes evident clinically months to years after the original cutaneous lesions have healed, although mucosal and cutaneous lesions may be noted simultaneously, and some affected people have had subclinical cutaneous infection. Untreated mucosal leishmaniasis can progress to cause ulcerative destruction of the mucosa (eg, perforation of the nasal septum) and facial disfigurement.

- **Visceral leishmaniasis (kala-azar).** After cutaneous inoculation by an infected sand fly, the parasite spreads throughout the reticuloendothelial system (ie, within macrophages in spleen, liver, and bone marrow). The stereotypical clinical manifestations include fever, weight loss, hepatosplenomegaly, pancytopenia (anemia, leukopenia, and thrombocytopenia), hypoalbuminemia, and hypergammaglobulinemia. Peripheral lymphadenopathy is quite common in East Africa (eg, South Sudan). Some patients in South Asia (the Indian subcontinent) develop grayish discoloration of their skin; this manifestation gave rise to the Hindi term kala-azar ("black sickness"). Some patients develop post-kala-azar dermal leishmaniasis (referred to as PKDL) during or after treatment of visceral leishmaniasis. Untreated, advanced cases of visceral leishmaniasis almost always are fatal, either directly from the disease or from complications, such as secondary bacterial infections or hemorrhage. At the other end of the spectrum, visceral infection can be asymptomatic or oligosymptomatic. Latent visceral infection can reactivate years to decades after exposure in people who become immunocompromised (eg, because of coinfection with human immunodeficiency virus [HIV] or immunosuppressive/immunomodulatory therapy).

ETIOLOGY

In the human host, *Leishmania* species are obligate intracellular parasites of mononuclear phagocytes. Together with *Trypanosoma* species, they constitute the family *Trypanosomatidae.* Approximately 20 *Leishmania* species (in the *Leishmania* and *Viannia* subgenera) are known to infect humans. Cutaneous leishmaniasis typically is caused by Old World species *Leishmania tropica*, *Leishmania major*, and *Leishmania aethiopica* and by New World species *Leishmania mexicana*, *Leishmania amazonensis*, *Leishmania* (*Viannia*) *braziliensis*, *Leishmania* (*V*) *panamensis*, *Leishmania* (*V*) *guyanensis*, and *L* (*V*) *peruviana*. Mucosal leishmaniasis typically is caused by species in the *Viannia* subgenus (especially *L* [*V*] *braziliensis* but also *L* [*V*] *panamensis* and *L* [*V*] *guyanensis*). Most cases of visceral leishmaniasis are caused by *Leishmania donovani* or *Leishmania infantum* (*Leishmania chagasi* is synonymous). *L donovani* and *L infantum* also can cause cutaneous and

mucosal leishmaniasis, although people with typical cutaneous leishmaniasis caused by these organisms rarely develop visceral leishmaniasis.

EPIDEMIOLOGY

In most settings, leishmaniasis is a zoonosis, with mammalian reservoir hosts, such as rodents or dogs. Some transmission cycles are anthroponotic: infected humans are the primary or only reservoir hosts of *L donovani* in South Asia (potentially also in East Africa) and of *L tropica.* Congenital and parenteral transmission also have been reported.

Overall, leishmaniasis is endemic in more than 90 countries in the tropics, subtropics, and southern Europe. Visceral leishmaniasis (0.2–0.4 million new cases annually) is found in focal areas of more than 60 countries: in the Old World, in parts of Asia (particularly South, Southwest, and Central Asia), Africa (particularly East Africa), the Middle East, and southern Europe, and in the New World, particularly in Brazil, with scattered foci elsewhere. Most (>90%) of the world's cases of visceral leishmaniasis occur in South Asia (India, Bangladesh, and Nepal), East Africa (Sudan, South Sudan, and Ethiopia), and Brazil.

Cutaneous leishmaniasis is more common (0.7 to 1.2 million new cases annually) and more widespread than visceral leishmaniasis. Cutaneous leishmaniasis is found in focal areas of more than 90 countries: in the Old World, in parts of the Middle East, Asia (particularly Southwest and Central Asia), Africa (particularly North and East Africa, with some cases elsewhere), and southern Europe, and, in the New World, in parts of Mexico, Central America, and South America (not in Chile or Uruguay). In addition, cases of cutaneous leishmaniasis have been acquired in Texas and occasionally in Oklahoma, and a cryptic case was diagnosed in a child in North Dakota. In general, the geographic distribution of leishmaniasis cases identified in the United States reflects immigration from and travel patterns to endemic regions.

The **incubation periods** for the various forms of leishmaniasis range from weeks to years. In **cutaneous** leishmaniasis, the primary skin lesions typically appear within several weeks of exposure. In **visceral** infection, the incubation period usually ranges from approximately 2 to 6 months.

DIAGNOSTIC TESTS

Definitive diagnosis is made by detecting the parasite (amastigote stages) in infected tissue (eg, of aspirates, touch preparations, or histologic sections) by light-microscopic examination of slides stained with Giemsa, hematoxylin, and eosin or other stains, by in vitro culture (not readily available), or increasingly by molecular methods. In cutaneous and mucosal disease, tissue can be obtained by a 3-mm punch biopsy, lesion scrapings, or needle aspiration of the raised nonnecrotic edge of the lesion. In visceral leishmaniasis, although the sensitivity is highest (approximately 95%) for splenic aspiration, the procedure can be associated with life-threatening hemorrhage; bone marrow aspiration is safer and generally preferred. Other potential sources of specimens include liver, lymph node, and in some patients (eg, those coinfected with HIV), whole blood or buffy coat. Identification of the *Leishmania* species (eg, via isoenzyme analysis of cultured parasites or molecular approaches) may affect prognosis and influence treatment decisions. The Centers for Disease Control and Prevention (CDC) (**www.cdc.gov/parasites/leishmaniasis**) can assist in all aspects of diagnostic testing. Serologic testing usually is not helpful in the evaluation of potential cases of cutaneous leishmaniasis but can provide supportive evidence for the diagnosis of visceral or mucosal leishmaniasis, particularly if the patient is immunocompetent.

TREATMENT

Guidelines published in 2016 from the Infectious Diseases Society of America and the American Society of Tropical Medicine and Hygiene provide a detailed approach to diagnosis and treatment. Systemic antileishmanial treatment always is indicated for patients with visceral or mucosal leishmaniasis, whereas not all patients with cutaneous leishmaniasis need to be treated or require systemic therapy. Consultation with infectious disease or tropical medicine specialists is recommended. The relative merits of various treatment approaches/regimens for an individual patient should be

considered, taking into account that the therapeutic response may vary, not only for different *Leishmania* species but also for the same species in different geographic regions. In addition, special considerations apply in the United States regarding the availability of particular medications. For example, the pentavalent antimonial compound, sodium stibogluconate, is not commercially available but can be obtained through the CDC Drug Service (404-639-3670) under an investigational new drug (IND) protocol, for parenteral (intravenous or, less commonly, intramuscular) treatment of leishmaniasis. Liposomal amphotericin B is recommended for treatment of visceral leishmaniasis. The oral agent miltefosine is approved for treatment of cutaneous, mucosal, and visceral leishmaniasis; the FDA-approved indications are limited to infection caused by particular *Leishmania* species and to patients who are at least 12 years of age and are not pregnant or breastfeeding during and for 5 months after the treatment course.

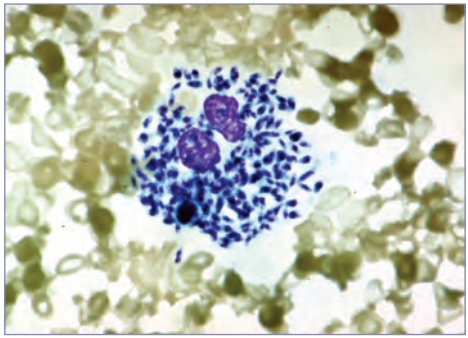


Image 76.1
Leishmania organisms in a peripheral blood smear from a young man with HIV infection who had visited a jungle in Central America. (See also Human Immunodeficiency Virus Infection.)

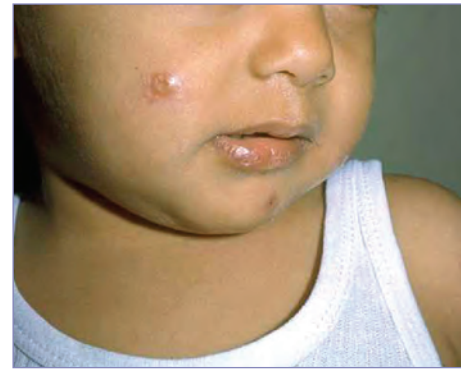


Image 76.2
Cutaneous leishmaniasis, as in this boy from India, seldom disseminates in immunocompetent persons. Multiple organisms can usually be found on biopsy of the border of a lesion.

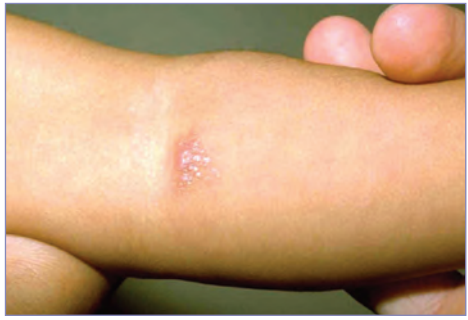


Image 76.3
Cutaneous leishmaniasis. Infected sand fly inoculation site with satellite lesions. The organism may be demonstrated by punch biopsy of the margin of a cutaneous lesion. This is the same child as in Image 76.2.

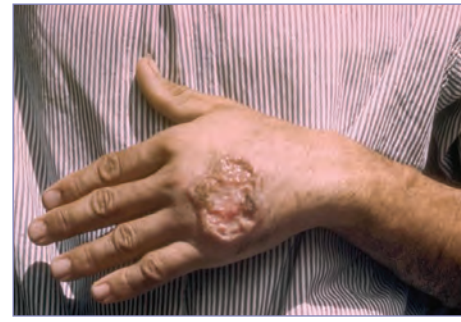


Image 76.4
Skin ulcer due to leishmaniasis; hand of Central American adult. Courtesy of Centers for Disease Control and Prevention.

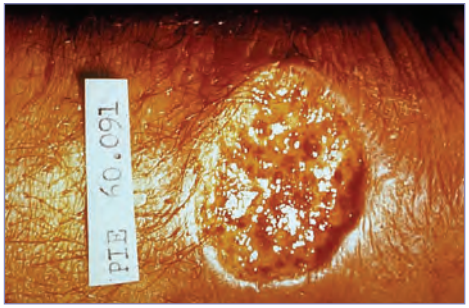


Image 76.5
Crater lesion of leishmaniasis, skin. Courtesy of Centers for Disease Control and Prevention.

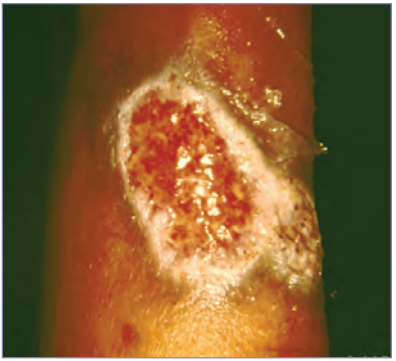


Image 76.6
Leishmaniasis of the forearm with severe cutaneous involvement. Copyright Hugh Moffet, MD.

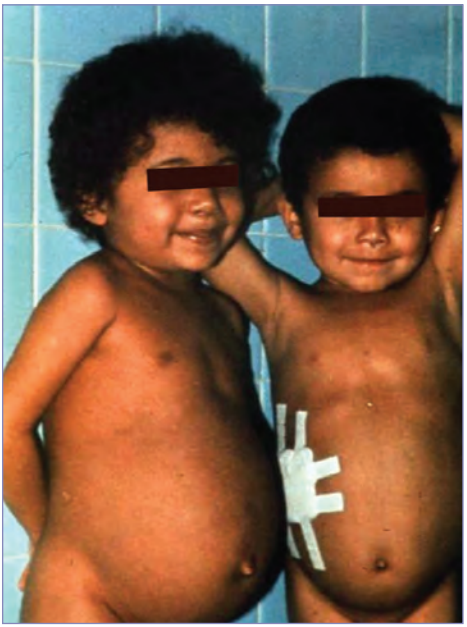


Image 76.7
Two young boys experiencing visceral leishmaniasis, with distended abdomens due to hepatosplenomegaly. Courtesy of World Health Organization/TDR/Lainson/ Wellcome Trust.

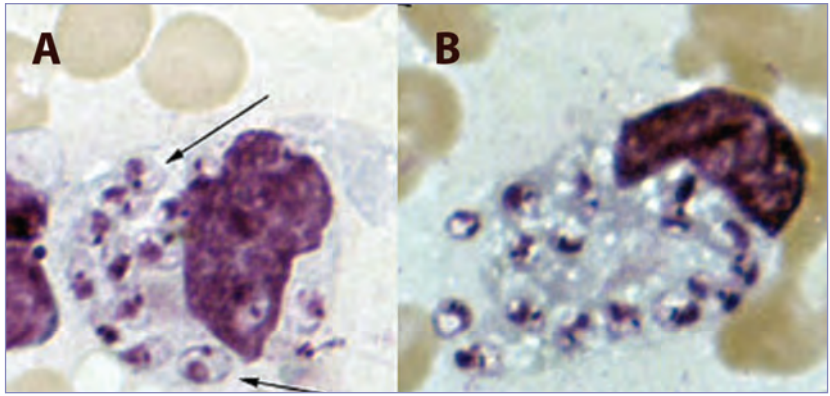


Image 76.8
Leishmania tropica amastigotes from a skin touch preparation. A, Still intact macrophage is practically filled with amastigotes, several of which have a clearly visible nucleus and a kinetoplast (arrows). B, Amastigotes are being freed from a rupturing macrophage. The patient has a history of travel to Egypt, Africa, and the Middle East. Culture in Novy-MacNeal-Nicolle medium followed by isoenzyme analysis identified the species as *L tropica* minor. Courtesy of Centers for Disease Control and Prevention.

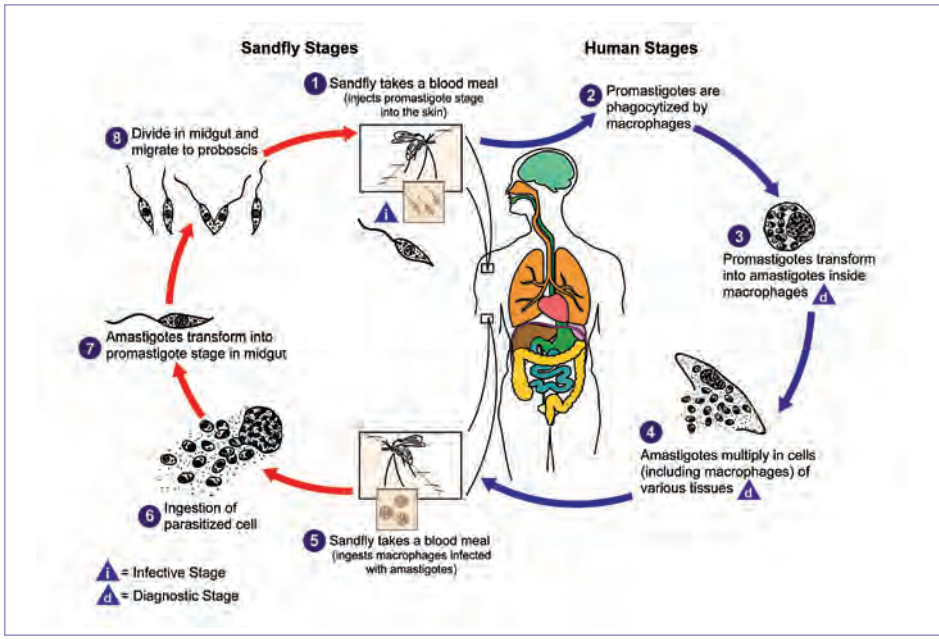


Image 76.9
Leishmaniasis is transmitted by the bite of female *Phlebotomine* species sand flies. The sand flies inject the infective stage, promastigotes, during blood meals (1). Promastigotes that reach the puncture wound are phagocytized by macrophages (2) and transform into amastigotes (3). Amastigotes multiply in infected cells and affect different tissues, depending, in part, on the *Leishmania* species (4). This originates the clinical manifestations of leishmaniasis. Sand flies become infected during blood meals on an infected host when they ingest macrophages infected with amastigotes (5, 6). In the sand fly's midgut, the parasites differentiate into promastigotes (7), which multiply and migrate to the proboscis (8). Courtesy of Centers for Disease Control and Prevention.

Image 76.10
This image depicts a mounted male *Phlebotomus* species fly, which, due to its resemblance, may be mistaken for a mosquito. *Phlebotomus* species sand flies are bloodsucking insects that are very small and sometimes act as the vectors for various diseases, such as leishmaniasis and bartonellosis (also known as Carrión disease). Courtesy of Centers for Disease Control and Prevention.

Image 76.11
A shantytown, another environment where *Leishmania* infection proliferates due to inadequate housing and lack of sanitation. Courtesy of World Health Organization.

Image 76.12
Natural uncut forests are transmission sites for leishmaniasis. People who collect rubber or clear such areas for agriculture are prone to infection. Courtesy of World Health Organization/TDR/Lainson/Wellcome Trust.

CHAPTER 77

Leprosy

CLINICAL MANIFESTATIONS

Leprosy (Hansen disease) is a curable infection primarily involving skin, peripheral nerves, and mucosa of the upper respiratory tract. The clinical forms of leprosy reflect the cellular immune response to *Mycobacterium leprae* and, in turn, the number, size, structure, and bacillary content of the lesions. The organism has unique tropism for peripheral nerves, and all forms of leprosy exhibit nerve involvement. Leprosy lesions usually do not itch or hurt. They lack sensation to heat, touch, and pain but otherwise may be difficult to distinguish from other common maladies. There may be madarosis (loss of eyelashes or eyebrows). However, the stereotypical presentations of leonine facies with nasal deformity or clawed hands with loss of digits are manifestations of late-stage untreated disease that seldom are seen today. Although the nerve injury caused by leprosy is irreversible, early diagnosis and drug therapy can prevent sequelae.

Leprosy manifests over a broad clinical and histopathologic spectrum. In the United States, the Ridley-Jopling scale is used to classify patients according to the histopathologic features of their lesions and organization of the underlying granuloma. The scale includes: (1) tuberculoid, (2) borderline tuberculoid, (3) borderline, (4) borderline lepromatous, and (5) lepromatous. A simplified scheme introduced by the World Health Organization for circumstances in which pathologic examination and diagnosis is unavailable is based purely on clinical skin examination. Under this scheme, leprosy is classified by the number of skin patches seen on skin examination, classifying disease as either paucibacillary (1–5 lesions, usually tuberculoid or borderline tuberculoid) or multibacillary (>5 lesions, usually borderline, borderline lepromatous, or lepromatous). Patients in the tuberculoid spectrum have active cell-mediated immunity with low antibody responses to *M leprae* and few well-defined lesions containing few bacilli. Lepromatous spectrum cases have high antibody responses with little cell mediated immunity to *M leprae* and several somewhat-diffuse lesions usually containing numerous bacilli.

Serious consequences of leprosy occur from immune reactions and nerve involvement with resulting anesthesia, which can lead to repeated unrecognized trauma, ulcerations, fractures, and even bone resorption. Injuries can have a significant effect on life quality. Leprosy is a leading cause of permanent physical disability among communicable diseases worldwide. Eye involvement can occur, especially corneal scarring, and patients should be examined by an ophthalmologist. A diagnosis of leprosy should be considered in any patient with hypoesthetic or anesthetic skin rash or skin patches—especially those that do not respond to ordinary therapies—who have a history of residence in areas with endemic leprosy or where they may have had contact with armadillos.

Leprosy Reactions

Acute clinical exacerbations reflect abrupt changes in the immunologic balance. They are especially common during initial years of treatment but can occur in the absence of therapy. Two major types of leprosy reactions (LRs) are seen. Type 1 (reversal reaction, LR-1) is observed predominantly in borderline tuberculoid and borderline lepromatous leprosy and is the result of a sudden increase in effective cell-mediated immunity. Acute tenderness and swelling at the site of cutaneous and neural lesions with development of new lesions are major manifestations. Ulcerations can occur, but polymorphonuclear leukocytes are absent from the LR-1 lesion. Fever and systemic toxicity are uncommon. Type 2 (erythema nodosum leprosum, LR-2) occurs in borderline and lepromatous forms as a systemic inflammatory response. Tender, red dermal papules or nodules resembling erythema nodosum can occur along with high fever, migrating polyarthralgia, painful swelling of lymph nodes and spleen, iridocyclitis, and rarely, nephritis.

ETIOLOGY

Leprosy is caused *by M leprae*, an obligate intracellular rod-shaped bacterium that can have variable findings on Gram stain and is weakly acid-fast on standard Ziehl-Neelsen

staining. It is best visualized using the Fite stain. *M leprae* has not been cultured successfully in vitro. *M leprae* is the only bacterium known to infect Schwann cells of peripheral nerves.

EPIDEMIOLOGY

Leprosy is considered a neglected tropical disease and is most prevalent in tropical and subtropical zones. It is not highly infectious. Several human genes have been identified that are associated with susceptibility to *M leprae*, and fewer than 5% of people appear to be genetically susceptible to the infection. Accordingly, spouses of leprosy patients are not likely to develop leprosy, but biological parents, children, and siblings who are household contacts of untreated patients with leprosy are at increased risk.

Transmission is thought to be most effective through long-term close contact with an infected individual and likely occurs through respiratory shedding of infectious droplets by untreated cases or individuals incubating subclinical infections. The 9-banded armadillo (*Dasypus novemcinctus*) is the only known nonhuman reservoir of *M leprae*, and zoonotic transmission is reported in the southern United States. There are unconfirmed reports of *M leprae* infection among 9-banded armadillos in Latin America as well as a 6-banded armadillo (*Euphractus sexcinctus*) in Brazil. People with human immunodeficiency virus (HIV) infection do not appear to be at increased risk of becoming infected with *M leprae.* However, concomitant HIV infection and leprosy can lead to worsening of leprosy symptoms during HIV treatment and result in immune reconstitution inflammatory syndrome. Like many other chronic infectious diseases, onset of leprosy is associated increasingly with use of anti-inflammatory autoimmune therapies and immunologic senescence among elderly patients.

There are approximately 6,500 people with leprosy living in the United States, with 3,500 under active medical management. During 1994–2011, there were 2,323 new cases of leprosy, with an average annual incidence rate of 0.45 cases per 1 million people. Over this period, a decline in the rate of new diagnoses from 0.52 (1994–1996) to 0.43 (2009–2011) per million was observed. The annual incidence rate among foreign-born people in the United States decreased from 3.66 to 2.29, whereas the rate among people born in the United States was 0.16 in both 1994–1996 and 2009–2011. Delayed diagnosis was more common among foreign-born people. Most leprosy cases reported in the United States occurred among residents of Texas, California, and Hawaii or among immigrants and other people who lived or worked in countries with endemic leprosy and likely acquired their disease while abroad. More than 65% of the world's leprosy patients reside in South and Southeast Asia, primarily India. Other areas of high endemicity include Angola, Brazil, the Central African Republic, Democratic Republic of Congo, Madagascar, Mozambique, the Republic of the Marshall Islands, South Sudan, the Federated States of Micronesia, and the United Republic of Tanzania.

The **incubation period** usually is 3 to 5 years (range from 1 to 20).

DIAGNOSTIC TESTS

There are no diagnostic tests or methods to detect subclinical leprosy. Histopathologic examination of a skin biopsy by an experienced pathologist is the best method of establishing the diagnosis and is the basis for classification of leprosy. These specimens can be sent to the National Hansen's Disease (Leprosy) Program (NHDP [800-642-2477; **https://www.hrsa.gov/hansens-disease/index.html**]) in formalin or embedded in paraffin. Acid-fast bacilli may be found in slit smears or biopsy specimens of skin lesions from patients with lepromatous forms of the disease but rarely are visualized from patients with tuberculoid and indeterminate forms of disease. A polymerase chain reaction test for *M leprae* is available to assist diagnosis after consultation with the NHDP and can be performed based on clinical suspicion. Molecular tests for mutations causing drug resistance also are available, as is strain typing based on single nucleotide polymorphism and other genomic elements.

TREATMENT

Leprosy is curable. Therapy for patients with leprosy should be undertaken in consultation with an expert in leprosy. The NHDP

(800-642-2477) provides consultation on clinical and pathologic issues and information about local Hansen disease clinics and clinicians who have experience with the disease. Combination antimicrobial multidrug therapy can be obtained free of charge from the NHDP in the United States and from the World Health Organization in other countries. Certain criteria must be met for physicians wishing to obtain the antimicrobial therapy from the NHDP (**www.hrsa.gov/hansensdisease/diagnosis/recommendedtreatment.html**).

It is important to treat *M leprae* infections with more than 1 antimicrobial agent to minimize development of antimicrobial-resistant organisms. Adults are treated with dapsone, rifampin, and clofazimine. Resistance to all 3 drugs has been documented but is extremely rare. The infectivity of leprosy patients ceases within a few days of initiating standard multidrug therapy.

Multibacillary Leprosy (6 Patches or More)

Dapsone **and** rifampin **and** clofazimine for 24 months; clarithromycin can be used in place of clofazimine for children.

Paucibacillary Leprosy (1–5 Patches)

Dapsone **and** rifampin for 12 months.

Before beginning antimicrobial therapy, patients should be tested for glucose-6-phosphate dehydrogenase deficiency, have baseline complete blood cell counts and liver function test results (eg, transaminases) documented, and be evaluated for any evidence of tuberculosis infection, especially if infected with HIV. Gastric upset and darkening of skin caused by daily clofazimine therapy are common adverse reactions to the therapy. Skin darkening typically resolves within several months of completing therapy.

Leprosy reactions should be treated aggressively to prevent peripheral nerve damage. Treatment with prednisone can be initiated. The severe type 2 reaction (erythema nodosum leprosum) occurs in patients with multibacillary leprosy. Treatment with thalidomide is available for erythema nodosum leprosum under the Celgene THALOMID REMS Program (888-771-0141) and is used under strict supervision because of its teratogenicity. Thalidomide is not approved for use in children younger than 12 years. Rehabilitative measures, including surgery and physical therapy, may be necessary for some patients.

All patients with leprosy should be educated about signs and symptoms of neuritis and cautioned to report signs and symptoms of neuritis immediately so that corticosteroid therapy can be instituted. Patients should receive counseling because of the social and psychological effects of this disease.

Relapse of disease after completing multidrug therapy is rare (0.01%–0.14%); the presentation of new skin patches usually is attributable to a late type 1 reaction. When it does occur, relapse usually is attributable to reactivation of drug-susceptible organisms. People with relapses of disease require another course of multidrug therapy.

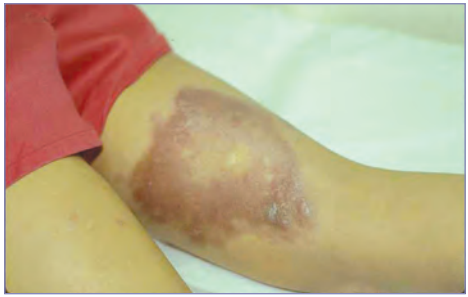


Image 77.1
Hansen disease. A young Vietnamese boy who spent 2 years in a refugee camp in the Philippines presented with the nodular violaceous skin lesion shown. The results of a biopsy of the lesion showed acid-fast organisms surrounding blood vessels. A diagnosis of lepromatous leprosy was made, and the child was treated with a multidrug regimen. Copyright Barbara Jantausch, MD, FAAP.

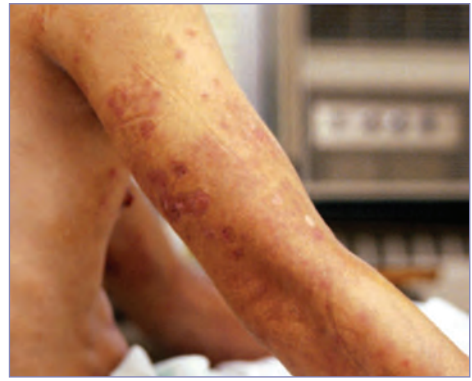


Image 77.2
Erythema nodosum leprosum in a 29-year-old man. Copyright Gary Williams.

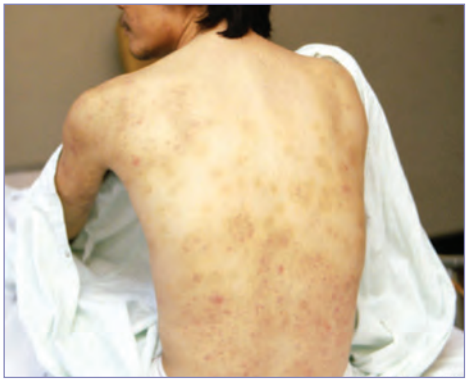


Image 77.3
Erythema nodosum leprosum in the same patient as in Image 77.2. Copyright Gary Williams.

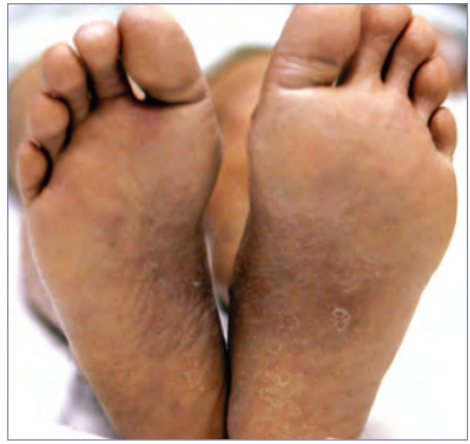


Image 77.4
Erythema nodosum leprosum in the same patient as in Images 77.2 and 77.3. Copyright Gary Williams.

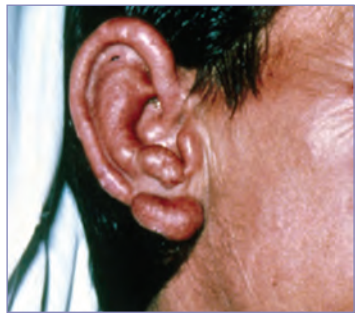


Image 77.5
Lepromatous leprosy in a man. Newly diagnosed cases are considered contagious until treatment is established and should be reported to local and state public health departments. Courtesy of Hugh Moffet, MD.

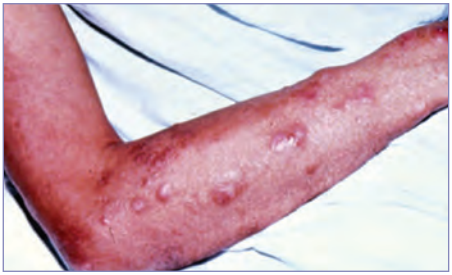


Image 77.6
An adult male with lepromatous leprosy. Courtesy of Hugh Moffet, MD.

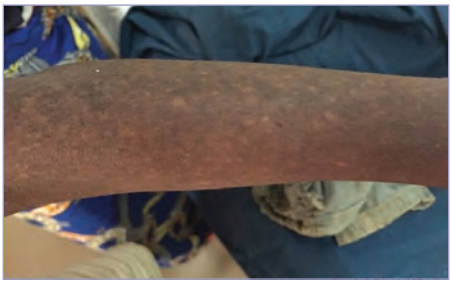


Image 77.7
Hypopigmented skin lesions in the arm of an 18-month-old boy with multibacillary leprosy. This patient experienced lack of sensation during a pinprick test performed on the lesions. Courtesy of Daniel Blatt, MD.

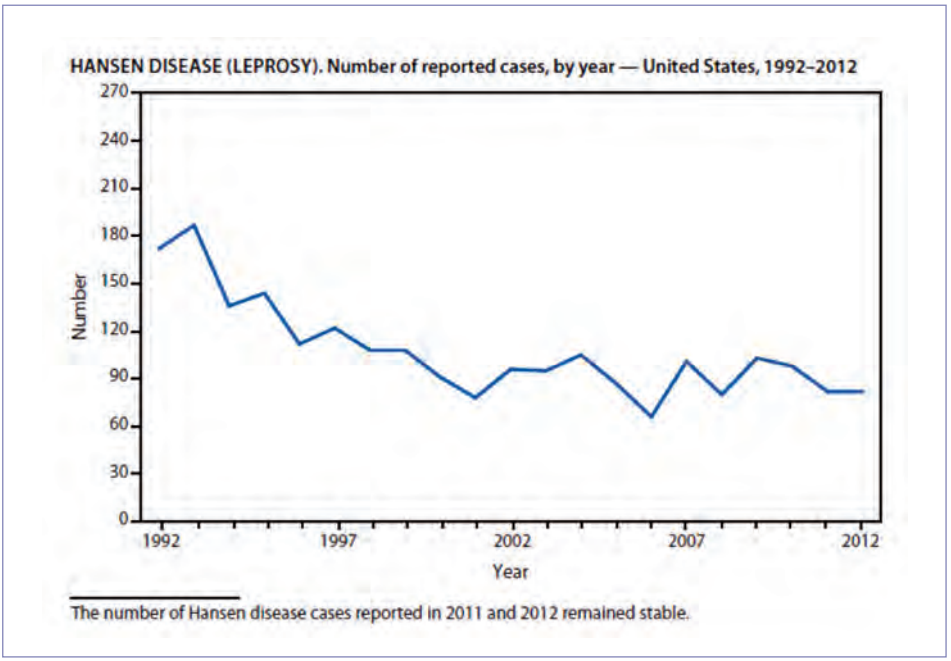


Image 77.8
Number of reported cases, by year—United States, 1992–2012. Courtesy of *Morbidity and Mortality Weekly Report*.

CHAPTER 78

Leptospirosis

CLINICAL MANIFESTATIONS

Leptospirosis is an acute febrile disease with varied manifestations. The severity of disease ranges from asymptomatic or subclinical to a self-limited febrile systemic illness (approximately 90% of patients) to a life-threatening illness that can include jaundice, renal failure (oliguric or nonoliguric), myocarditis, hemorrhage (particularly pulmonary), and refractory shock. Clinical presentation may be mono- or biphasic. Classically described biphasic leptospirosis has an acute septicemia phase usually lasting 1 week, during which time *Leptospira* organisms are present in blood, followed by a second immune-mediated phase that generally does not respond to antimicrobial therapy. Regardless of its severity, the acute phase is characterized by nonspecific symptoms, including fever, chills, headache, myalgia, nausea, vomiting, and conjunctival suffusion, occasionally accompanied by rash. Distinct clinical findings include notable conjunctival suffusion without purulent discharge (28%–99% of cases) and myalgia of the calf and lumbar regions (40%–97% of cases). Findings commonly associated with the immune-mediated phase include fever, aseptic meningitis, and uveitis; between 5% and 10% of *Leptospira*-infected patients are estimated to experience severe illness; this phase usually requires supportive therapies. Severe manifestations include jaundice and renal dysfunction (Weil syndrome), pulmonary or other hemorrhage (which may involve gastrointestinal tract or brain), cardiac arrhythmias, and circulatory collapse. Abnormal potassium (high or low) or magnesium (low) levels may require aggressive management. The estimated case-fatality rate is 5% to 15% with severe illness, although it can increase to >50% in patients with pulmonary hemorrhage syndrome. Asymptomatic or subclinical infection with seroconversion is frequent, especially in settings of endemic infection.

ETIOLOGY

Leptospirosis is caused by pathogenic spirochetes of the genus *Leptospira*. Leptospires are classified by species and subdivided into more than 300 antigenically defined serovars and grouped into serogroups on the basis of antigenic relatedness. Currently, the molecular classification divides the genus into 23 named pathogenic (n=10), intermediate (n=5), and saprophytic (nonpathogenic; n=8) genomospecies as determined by DNA-DNA hybridization, 16S ribosomal gene phylogenetic clustering, and whole genome sequencing. This newer nomenclature supersedes the former division of these organisms into 2 species: *Leptospira interrogans*, comprising all pathogenic strains, and *Leptospira biflexa*, comprising all saprophytic stains found in the environment.

EPIDEMIOLOGY

Leptospirosis is among the most globally important zoonoses, affecting people in resource-rich and resource-limited countries in both urban and rural contexts. It has been estimated that more than 1 million people annually worldwide are infected (95% CI, 434,000–1,750,000), with approximately 58,900 deaths occurring each year. The reservoirs for *Leptospira* species include a wide range of wild and domestic animals, primarily rats, dogs, and livestock (cattle, pigs) that may shed organisms asymptomatically for years. *Leptospira* organisms excreted in animal urine may remain viable in moist soil or water for weeks to months in warm climates. Humans usually become infected via entry of leptospires through contact of mucosal surfaces (especially conjunctivae) or abraded skin with urine-contaminated environmental sources such as soil and water. Infection also may be acquired through direct contact with infected animals or their tissues, urine, or other body fluids. Epidemic exposure is associated with seasonal flooding and natural disasters, including hurricanes and monsoons. Populations in regions of high endemicity in the tropics likely encounter *Leptospira* organisms commonly during routine activities of daily living. People who are predisposed by occupation include abattoir and sewer workers, miners, veterinarians, farmers, and military personnel. Recreational exposures and clusters of disease have been associated with adventure travel, sporting events including triathlons, and wading, swimming, or boating in contaminated water, particularly during flooding or following heavy rainfall. Common history includes being submerged in or

swallowing water during such activities. Person-to-person transmission is not convincingly described.

The **incubation period** usually is 5 to 14 days (range 2 to 30).

DIAGNOSTIC TESTS

Leptospira organisms can be isolated from blood during the early septicemic phase (first week) of illness, from urine specimens 14 days or more after symptom onset, and from cerebrospinal fluid when clinical signs of aseptic meningitis are present. Specialized culture media are required but are not routinely available in most clinical laboratories. *Leptospira* organisms can be subcultured to specific *Leptospira* semi-solid medium (ie, EMJH) from blood culture bottles used in automated systems within 1 week of inoculation. However, isolation of the organism may be difficult, requiring incubation for up to 16 weeks, and the sensitivity of culture for diagnosis is low. Isolated leptospires are identified by either serologic methods using agglutinating antisera or more recently by molecular methods.

For these reasons, serum specimens always should be obtained to facilitate diagnosis, and paired acute and convalescent sera are recommended. Antibodies can develop as early as 5 to 7 days after onset of illness; however, increases in antibody titer may not be detected until more than 10 days after onset, especially if antimicrobial therapy is initiated early. Antibodies can be measured by commercially available immunoassays. These assays have variable sensitivity. Further, in populations with high endemicity, background reactivity requires establishing regionally relevant diagnostic criteria and establishment of diagnostic versus background titers. Antibody increases can be transient, delayed, or absent in some patients, which may be related to antibiotic use, bacterial virulence, immunogenetics of the individual, or other unknown factors. Microscopic agglutination, the gold standard serologic test, is performed only in reference laboratories and seroconversion demonstrated between acute and convalescent specimens obtained at least 10 days apart is diagnostic.

Immunohistochemical and immunofluorescent techniques can detect leptospiral antigens in infected tissues. Polymerase chain reaction (PCR) assays for detection of *Leptospira* DNA in clinical specimens have been developed but are sensitive only in acute specimens and sometimes convalescent urine, are not approved by the FDA, and are available only in research laboratories. *Leptospira* DNA can be found after 7 days of illness in urine and may be detectable for weeks to months in the absence of antimicrobial treatment.

TREATMENT

Antimicrobial therapy should be initiated as soon as possible after symptom onset. Intravenous penicillin is the drug of choice for patients with severe infection requiring hospitalization; penicillin has been shown to be effective in shortening duration of fever as late as 7 days into the course of illness. Penicillin G decreases the duration of systemic symptoms and persistence of associated laboratory abnormalities and may prevent development of leptospiruria. As with other spirochetal infections, a Jarisch-Herxheimer reaction (an acute febrile reaction accompanied by headache, myalgia, and an aggravated clinical picture lasting less than 24 hours) can develop after initiation of penicillin therapy. Parenteral cefotaxime, ceftriaxone, and doxycycline have been demonstrated in randomized clinical trials to be equal in efficacy to penicillin G for treatment of severe leptospirosis. For patients with mild disease, oral doxycycline has been shown to shorten the course of illness and decrease occurrence of leptospiruria; doxycycline can be used for short durations (ie, 21 days or less) without regard to patient age. Ampicillin or amoxicillin also can be used to treat mild disease. Azithromycin has been demonstrated in a clinical trial to be as effective as doxycycline. Severe cases require appropriate supportive care, including fluid and electrolyte replacement. Patients with oliguric renal insufficiency require prompt dialysis, and those with pulmonary hemorrhagic syndrome may require mechanical ventilation to improve clinical outcome.

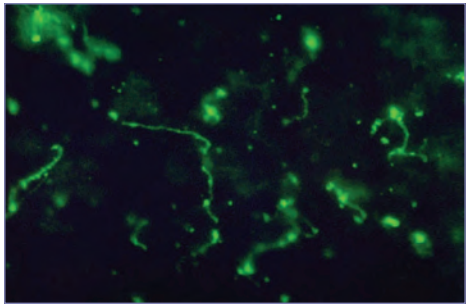


Image 78.1
Leptospira bacteria in liver impression smear (fluorescent antibody stain). Patient died of leptospirosis. Courtesy of Centers for Disease Control and Prevention.

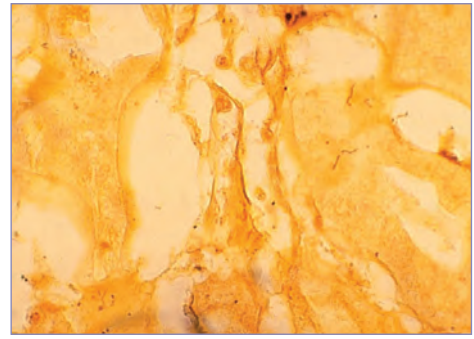


Image 78.2
Histopathology of leptospirosis, kidney. *Leptospira* bacteria are visible at right (Dieterle stain). Courtesy of Centers for Disease Control and Prevention.

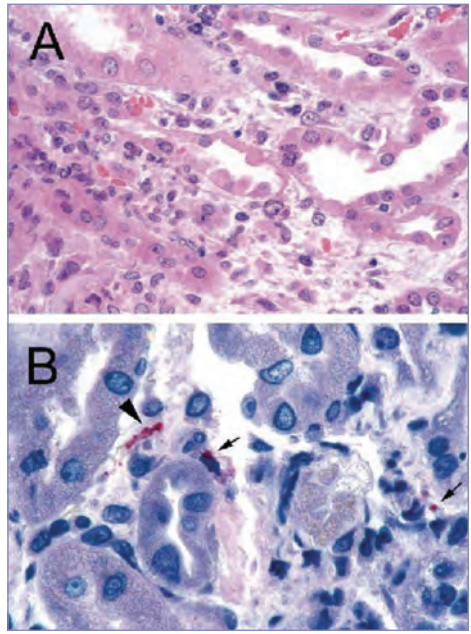


Image 78.3
A, Renal biopsy shows inflammatory cell infiltrate in the interstitium and focal denudation of tubular epithelial cells (hematoxylin-eosin, original magnification ×100).
B, Immunostaining of fragmented leptospire (arrowhead) and granular form of bacterial antigens (arrows) (original magnification ×158). Courtesy of *Emerging Infectious Diseases*.

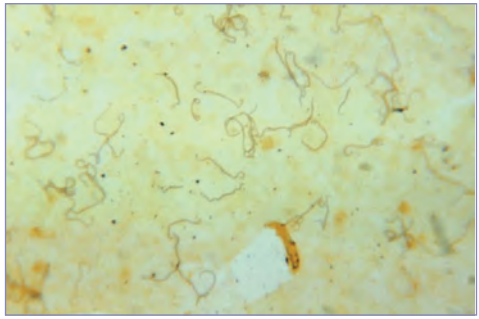


Image 78.4
A photomicrograph of a liver smear, using a silver staining technique, taken from a patient with a fatal case of leptospirosis. Humans become infected by swallowing water contaminated by infected animals or through skin contact, especially with mucosal surfaces, such as the eyes or nose, or with broken skin. The disease is not known to be spread from person to person. Courtesy of Centers for Disease Control and Prevention.

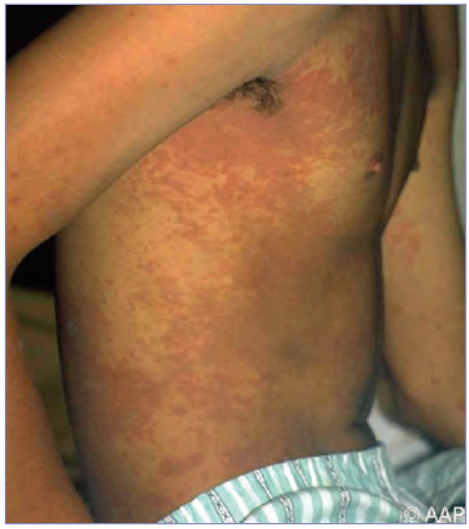


Image 78.5
Leptospirosis rash in an adolescent boy that shows the generalized vasculitis caused by this infection.

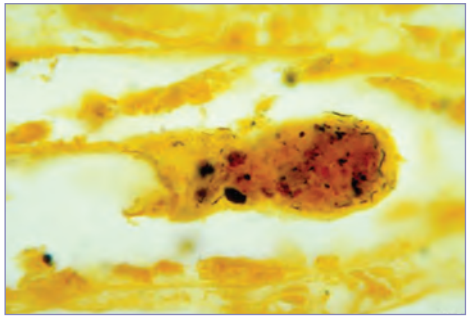


Image 78.6
Photomicrograph of kidney tissue, using a silver staining technique, revealing the presence of *Leptospira* bacteria. Courtesy of Centers for Disease Control and Prevention/Martin Hicklin, MD.

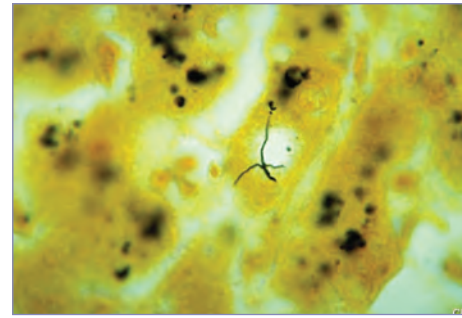


Image 78.7
Photomicrograph of liver tissue revealing the presence of *Leptospira* bacteria. Humans become infected by swallowing water contaminated by infected animals or through skin contact, especially with mucosal surfaces, such as the eyes or nose, or with broken skin. The disease is not known to be spread from person to person. Courtesy of Centers for Disease Control and Prevention/Martin Hicklin, MD.

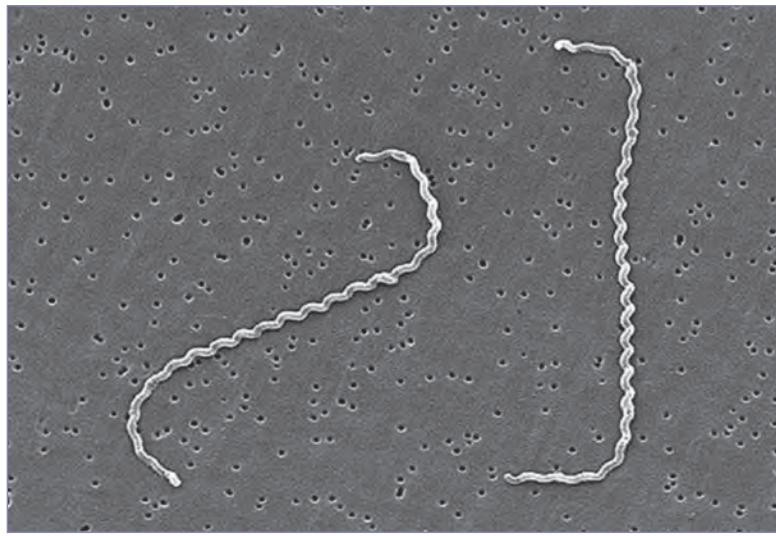


Image 78.8
Scanning electron micrograph of *Leptospira interrogans* strain RGA. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 79

Listeria monocytogenes Infections

(Listeriosis)

CLINICAL MANIFESTATIONS

Listeriosis is a relatively uncommon but severe invasive infection caused by *Listeria monocytogenes.* Transmission predominantly is foodborne, and illness, especially with severe manifestations, occurs most frequently among pregnant women and their fetuses or newborn infants, older adults, and people with impaired cell-mediated immunity resulting from underlying illness or treatment (eg, organ transplant, hematologic malignancy, immunosuppression resulting from therapy with corticosteroid or anti-tumor necrosis factor agents, or acquired immunodeficiency syndrome). Pregnancy-associated infections can result in spontaneous abortion, fetal death, preterm delivery, and neonatal illness or death. In pregnant women, infections can be asymptomatic or associated with a nonspecific febrile illness with myalgia, back pain, and occasionally, gastrointestinal tract symptoms. Fetal infection results from transplacental transmission following maternal bacteremia. Approximately 65% of pregnant women with *Listeria* infection experience a prodromal illness before the diagnosis of listeriosis in their newborn infant. Amnionitis during labor, brown staining of amniotic fluid, or asymptomatic perinatal infection can occur.

Neonates can present with early-onset and late-onset syndromes similar to those of group B streptococcal infections. Preterm birth, pneumonia, and septicemia are common in early-onset disease (within the first week), with fatality rates of 14% to 56%. An erythematous rash with small, pale papules characterized histologically by granulomas, termed "granulomatosis infantisepticum," can occur in severe newborn infection. Late-onset infections occur at 7 to 30 days following term deliveries and usually result in meningitis with fatality rates of approximately 25%. Late-onset infection may result from acquisition of the organism during passage through the birth canal or, rarely, from environmental sources. Health care-associated nursery outbreaks have been reported.

Clinical features characteristic of invasive listeriosis outside the neonatal period or pregnancy are bacteremia and meningitis with or without parenchymal brain involvement, and less commonly brain abscess or endocarditis. *L monocytogenes* also can cause rhombencephalitis (brain stem encephalitis) in otherwise healthy adolescents and young adults. Outbreaks of febrile gastroenteritis caused by food contaminated with a very large inoculum of *L monocytogenes* have been reported. The prevalence of stool carriage of *L monocytogenes* among healthy, asymptomatic adults is estimated to be 1% to 5%.

ETIOLOGY

L monocytogenes is a facultatively anaerobic, nonspore-forming, nonbranching, motile, gram-positive rod that multiplies intracellularly. It has been assigned to the family *Listeriaceae* along with 5 other traditional and several newly named species. The organism grows readily on blood agar and produces incomplete hemolysis. *L monocytogenes* serotypes 1/2a, 4b, and 1/2b cause most invasive disease. *L monocytogenes* grows well at refrigerator temperatures (4°C–10°C).

EPIDEMIOLOGY

L monocytogenes causes approximately 1,600 cases of invasive disease and 260 deaths annually in the United States. The saprophytic organism is distributed widely in the environment and is an important cause of illness in ruminants. Foodborne transmission causes outbreaks and sporadic infections in humans. Commonly incriminated foods include deli-style, ready-to-eat meats, particularly poultry; unpasteurized milk; and soft cheeses, including Mexican-style cheese. Ice cream and fresh and frozen fruits and vegetables also have been implicated in recent outbreaks. Listeriosis is a relatively rare foodborne illness (approximately 1% of US cases) but is associated with a case-fatality rate of 16% to 20% (second only to *Vibrio vulnificus* at 35% to 39%) and causes 19% to 28% of all foodborne disease-related deaths. The US incidence of listeriosis

decreased substantially during the 1990s, when US regulatory agencies began enforcing rigorous screening guidelines for *L monocytogenes* in processed foods and as better detection methods became available to identify contaminated foods.

The **incubation period** for invasive disease is longer for pregnancy-associated cases (2–4 weeks) than for nonpregnancy-associated cases (1–14 days). The incubation period for self-limiting, febrile gastroenteritis following ingestion of a large inoculum is 24 hours; illness typically lasts 2 to 3 days.

DIAGNOSTIC TESTS

L monocytogenes can be recovered readily on blood agar from cultures of blood, cerebrospinal fluid (CSF), meconium, placental or fetal tissue specimens, amniotic fluid, and other infected tissue specimens, including joint, pleural, or peritoneal fluid. Gram stain of meconium, placental tissue, biopsy specimens of the rash of early-onset infection, or CSF from an infected patient may demonstrate the organism. The organisms can be gram-variable and can resemble diphtheroids, cocci, or diplococci. Laboratory misidentification is not uncommon, and the isolation of a "diphtheroid" from blood or cerebrospinal fluid (CSF) should always alert one to the possibility that the organism is *L monocytogenes*.

At least one multiplexed PCR diagnostic panel designed to detect agents of meningitis and encephalitis in CSF contains *L monocytogenes* as one of its target organisms; however, there are limited clinical data with the use of PCR for this purpose, and parallel culture of CSF also should be performed to allow for susceptibility testing and molecular characterization, especially for outbreak detection.

TREATMENT

No controlled trials have established the drug(s) of choice or duration of therapy for listeriosis. Combination therapy using ampicillin and a second agent is recommended for severe infections, including meningitis, encephalitis, endocarditis, and infections in neonates and immunocompromised patients. Therapy with intravenous ampicillin and an aminoglycoside, usually gentamicin, has been used traditionally. Use of an alternative second agent that is active intracellularly (eg, trimethoprim-sulfamethoxazole, fluoroquinolones, linezolid, or rifampin) is supported by case reports in adults. In the penicillin-allergic patient, options including either penicillin desensitization or use of either trimethoprim-sulfamethoxazole or a fluoroquinolone, both of which have been used successfully as monotherapy for Listeria meningitis and in the setting of brain abscess. Treatment failures with vancomycin have been reported. Cephalosporins are not active against *L monocytogenes*.

For bacteremia without associated central nervous system infection, 14 days of treatment is sufficient. For *L monocytogenes* meningitis, most experts recommend 21 days of treatment. Longer courses are necessary for patients with endocarditis or parenchymal brain infection (cerebritis, rhombencephalitis, brain abscess). Diagnostic imaging of the brain near the end of the anticipated duration of therapy allows determination of parenchymal involvement of the brain and the need for prolonged therapy in neonates with complicated courses and immunocompromised patients.

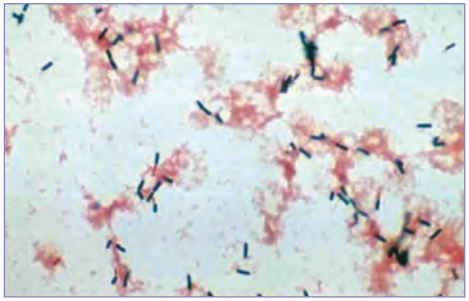


Image 79.1
Cerebrospinal fluid showing characteristic gram-positive rods (Gram stain). Listeriosis is a severe but relatively uncommon infection. Listeriosis occurs most frequently among pregnant women and their fetuses or newborns, people of advanced age, or immunocompromised people. Copyright Martha Lepow, MD.

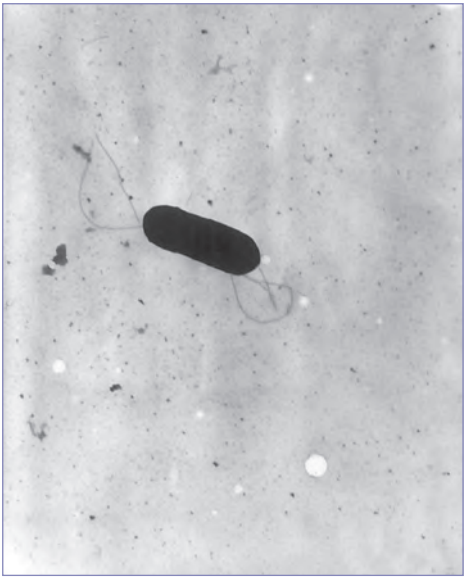


Image 79.2
Electron micrograph of a flagellated *Listeria monocytogenes* bacterium (magnification ×41,250). Courtesy of Centers for Disease Control and Prevention.

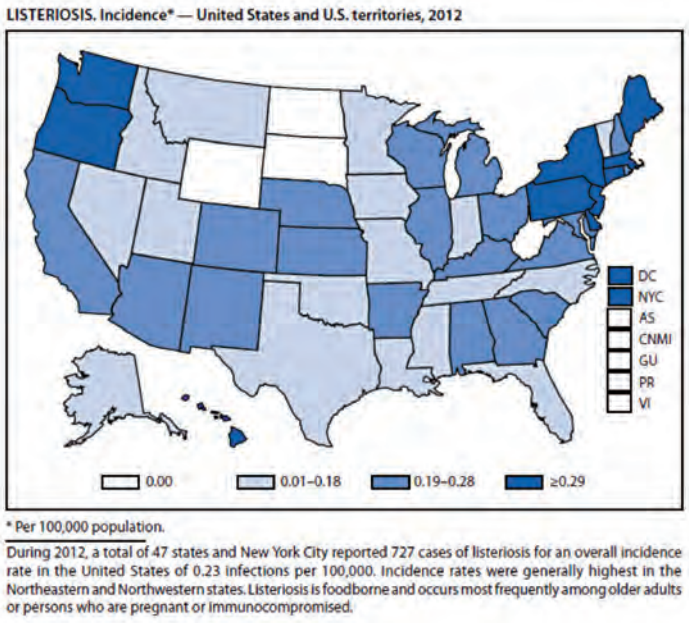


Image 79.3
Listeriosis. Incidence—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

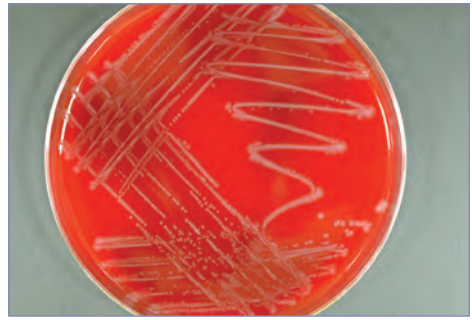


Image 79.4
Listeria monocytogenes on blood agar. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

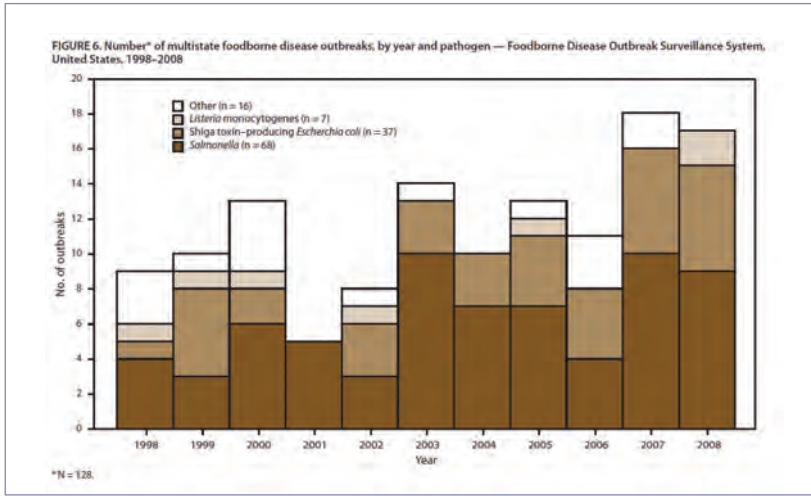


Image 79.5
Number of multistate foodborne disease outbreaks, by year and pathogen—Foodborne Disease Outbreak Surveillance System, United States, 1998–2008. Courtesy of *Morbidity and Mortality Weekly Report*.

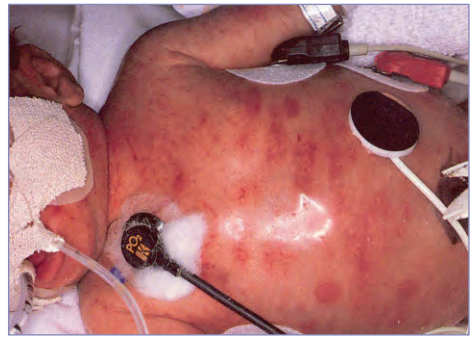


Image 79.6
Skin lesions present at birth in a neonate with congenital pneumonia. *Listeria monocytogenes* was isolated from blood and skin lesion cultures.

CHAPTER 80

Lyme Disease

(Lyme Borreliosis, *Borrelia burgdorferi* sensu lato Infection)

CLINICAL MANIFESTATIONS

Clinical manifestations of Lyme disease are divided into 3 stages: early localized, early disseminated, and late manifestations. **Early localized disease** is characterized by a distinctive lesion, erythema migrans, at the site of a recent tick bite. Erythema migrans is by far the most common manifestation of Lyme disease in children. Erythema migrans begins as a red macule or papule that usually expands over days to weeks to form a large (≥5 cm in diameter) annular, erythematous lesion, sometimes with partial central clearing. The lesion usually but not always is painless, and it usually is not pruritic. Localized erythema migrans can vary greatly in size and shape and can be confused with cellulitis; lesions may have a purplish discoloration or central vesicular or necrotic areas. A classic "bull's-eye" appearance with concentric rings appears in a minority of cases. Factors that distinguish erythema migrans from local allergic reaction to a tick bite include larger size (≥5 cm), gradual expansion, less pruritus, and slower onset. Constitutional symptoms, such as malaise, headache, mild neck stiffness, myalgia, and arthralgia, often accompany erythema migrans. Fever may be present but is not universal and generally is mild.

In **early disseminated disease,** multiple erythema migrans lesions may appear several weeks after an infective tick bite and consist of secondary annular, erythematous lesions similar to but usually smaller than the primary lesion. Other manifestations of early disseminated illness (which may occur with or without a skin lesion) are palsies of the cranial nerves (most commonly cranial nerve VII), lymphocytic meningitis (often associated with cranial neuropathy or papilledema), and radiculitis. Carditis usually manifests as various degrees of atrioventricular block and can be life threatening. Although carditis occurs less commonly in children than in adults with Lyme disease, young adult males appear to be most prone. Systemic symptoms, such as low-grade fever, arthralgia, myalgia, headache, and fatigue, may be present during the early disseminated stage.

Patients with early Lyme disease can be infected simultaneously with *Borrelia miyamotoi* and agents of babesiosis and anaplasmosis. These diagnoses should be suspected in patients who manifest high fever or hematologic abnormalities or who do not respond as expected to therapy prescribed for Lyme disease. Additionally, patients who contract Lyme disease may be coinfected with Powassan virus (deer tick virus) if bitten in the United States or with tickborne encephalitis virus if infection was acquired in Europe.

Late Lyme disease occurs in patients who are not treated at an earlier stage of illness and most commonly manifests as Lyme arthritis in children. Lyme arthritis is characterized by inflammatory arthritis that usually is mono- or pauciarticular and affects large joints, particularly the knees. Although arthralgia can be present at any stage of Lyme disease, Lyme arthritis has objective evidence of joint swelling as well as white blood cells in synovial fluid specimens. Arthritis can occur without a history of earlier stages of illness (including erythema migrans). Compared with pyogenic arthritis, Lyme arthritis tends to manifest with joint swelling/effusion out of proportion to pain or disability and with lower peripheral blood neutrophilia and erythrocyte sedimentation rate (ESR). Polyneuropathy, encephalopathy, and encephalitis are rare late manifestations. Children who are treated with antimicrobial agents in the early stage of disease almost never develop late manifestations. Other clinical manifestations include ophthalmic conditions such as conjunctivitis, optic neuritis, keratitis, and uveitis.

Lyme disease is not thought to produce a congenital infection syndrome. No causal relationship between maternal Lyme disease and abnormalities of pregnancy or congenital disease caused by *Borrelia burgdorferi* sensu lato has been documented. No evidence exists that Lyme disease can be transmitted via human milk.

ETIOLOGY

In the United States, Lyme disease is caused by the spirochete *B burgdorferi* sensu stricto (hereafter referred to as *B burgdorferi*) and rarely by the recently discovered *Borrelia mayonii*. In Eurasia, *B burgdorferi*, *Borrelia afzelii*, and *Borrelia garinii* cause borreliosis. *Borrelia* species are members of the family *Spirochaetaceae*, which also includes *Treponema* species.

EPIDEMIOLOGY

In 2015, there were 28,453 confirmed cases of Lyme disease in the United States, although the actual number of cases may be up to 10-fold greater because of underreporting. Lyme disease occurs primarily in 2 distinct geographic regions of the United States, with more than 90% of cases occurring in New England and the eastern Mid-Atlantic States, as far south as Virginia. The disease also occurs, but with lower frequency, in the upper Midwest, especially Wisconsin and Minnesota. The geographic range is not static and has expanded considerably in the eastern and Midwestern states since 2000. Transmission also occurs at a low level on the West Coast, especially northern California. The occurrence of cases in the United States correlates with the distribution and frequency of infected tick vectors—*Ixodes scapularis* in the east and Midwest and *Ixodes pacificus* in the west. In Southern states, *I scapularis* ticks are rarer than in the northeast; those ticks that are present do not commonly feed on competent reservoir mammals and are less likely to bite humans because of different questing habits. Reported cases from states without known endemic transmission may have been imported from endemic states or may be misdiagnoses resulting from false-positive serologic test results or results that are misinterpreted as positive.

Most cases of early localized and early disseminated Lyme disease occur between April and October; more than 50% of cases occur during June and July. People of all ages can be affected, but the incidence in the United States is highest among children 5 through 9 years of age and adults 55 through 59 years of age.

With lesion(s) like erythema migrans, "southern tick associated rash illness" (STARI) has been reported in south central and southeastern states without endemic *B burgdorferi* infection. The etiology is unknown. STARI results from the bite of the lone star tick, *Amblyomma americanum*, which is abundant in southern states and is biologically incapable of transmitting *B burgdorferi*. Patients with STARI may present with constitutional symptoms in addition to erythema migrans; however, STARI has not been associated with any of the disseminated complications of Lyme disease. Appropriate treatment of STARI is unknown.

B mayonii is a newly described species identified in a small number of patients from the upper Midwest with symptoms like those of Lyme disease. Patients with *B mayonii* infection can be expected to test positive for Lyme disease using the 2-tier serologic testing described below, and therapy used for Lyme disease is effective against *B mayonii*.

The **incubation period** from tick bite to appearance of single or multiple erythema migrans lesions ranges from 3 to 32 days (median 11 days). Late manifestations such as arthritis can occur months after the tick bite in people who do not receive antimicrobial therapy.

Lyme disease also is endemic in eastern Canada, Europe, states of the former Soviet Union, China, Mongolia, and Japan. The primary tick vector in Europe is *Ixodes ricinus*, and the primary tick vector in Asia is *Ixodes persulcatus*. Clinical manifestations of infection vary somewhat from manifestations seen in the United States. European Lyme disease can cause the skin lesions borrelial lymphocytoma and acrodermatitis chronica atrophicans and is more likely to produce neurologic disease; arthritis is uncommon. These differences are attributable to the different genospecies of *Borrelia* responsible for European Lyme disease.

DIAGNOSTIC TESTS

The diagnosis of Lyme disease rests first and foremost on the recognition of a consistent clinical illness in people who have had plausible geographic exposure. Early Lyme disease in patients with erythema migrans is diagnosed

clinically based on recognition of the characteristic appearance of this skin lesion, and serologic testing is not recommended. Although erythema migrans is not strictly pathognomonic for Lyme disease, it is highly distinctive and characteristic. In areas with endemic Lyme disease, it is expected that most of the erythema migrans occurring in the appropriate season is attributable to *B burgdorferi* infection, and presumptive treatment is appropriate. Current diagnostic testing is based on serology, but during early infection, the sensitivity is low. For children with solitary erythema migrans lesion, fewer than one-half will be seropositive, and diagnostic testing is not recommended. Patients who seek medical attention with one or more lesions of erythema migrans and without extracutaneous manifestations should be treated based on a clinical diagnosis of Lyme disease without serologic testing.

There is a broad differential diagnosis for extracutaneous manifestations of Lyme disease. The diagnosis of extracutaneous manifestations, including late-stage Lyme disease, requires a typical clinical illness, plausible geographic exposure, and a positive serologic test result.

The standard testing method for Lyme disease is a 2-tier serologic algorithm (**www.cdc.gov/lyme/healthcare/clinician_twotier.html**). The initial screening test identifies antibodies to a whole-cell sonicate, to peptide antigen, or to recombinant antigens of *B burgdorferi*. This test is performed using an enzyme-linked immunosorbent assay (ELISA or EIA) or immunofluorescent antibody (IFA) test. It should be noted that clinical laboratories vary somewhat in their description of this test. It may be described as "Lyme ELISA," "Lyme antibody screen," "total Lyme antibody," or "Lyme IgG/IgM." Many commercial laboratories offer EIA/IFA with reflex to Western immunoblot if the first-tier assay result is positive or equivocal.

Although the initial EIA or IFA test result may be reported quantitatively, its sole importance is to categorize the result as negative, equivocal, or positive. If the first-tier EIA result is negative, the patient is considered seronegative and no further testing is indicated. If the result is equivocal or positive, then a second-tier test is required to make the diagnosis of Lyme disease. Two-tier serologic testing increases test specificity. False-positive results are partly explained by antigenic components of *B burgdorferi* that are not specific to this species. Antibodies produced in response to other spirochetal infections, spirochetes in normal oral flora, other acute infections, and certain autoimmune diseases may be cross-reactive. In areas with endemic infection, previous subclinical infection with seroconversion may occur, and a seropositive patient's symptoms may be coincidental. Patients with active Lyme disease almost always have objective signs of infection (eg, erythema migrans, facial nerve palsy, arthritis). Nonspecific symptoms commonly accompany these specific signs but almost never are the only evidence of Lyme disease. Serologic testing for Lyme disease should not be performed for children without symptoms or signs suggestive of Lyme disease and plausible geographic exposure.

Serum specimens that yield positive or equivocal EIA or IFA results should be tested by the second-tier standardized Western immunoblot. Immunoblot testing should not be performed if the EIA or IFA test result is negative or without a prior EIA or IFA test, because specificity of immunoblot diminishes if the test is performed alone. The immunoblot assay tests for the presence of antibodies to specific *B burgdorferi* antigens, including immunoglobulin (Ig) M antibodies to 3 spirochetal antigens (the 23/24, 39, and 41 kDa polypeptides) and IgG antibodies to 10 spirochetal antigens (the 18, 23/24, 28, 30, 39, 41, 45, 60, 66, and 93 kDa polypeptides). Although some clinical laboratories report the presence of antibody to each of 13 bands, describing each band as positive or negative, a positive immunoblot result is defined as the presence of at least 2 IgM bands or 5 IgG bands. Physicians must be careful not to misinterpret a positive band as a positive test result or interpret a result as positive despite the presence of 4 or fewer IgG bands. It is noteworthy that IgG antibodies to flagella protein, the p41 band, is present in 30% to 50% of healthy people.

The IgM assay is useful only for patients in the first 30 days after symptom onset. The IgM immunoblot result should be disregarded (or, if possible, not ordered) in

patients who have had symptoms for longer than 4 to 6 weeks, or symptoms consistent with late Lyme disease, because false-positive IgM assay results are common, and because most untreated patients with disseminated Lyme disease will have a positive IgG result by week 4 to 6 after infection.

Lyme disease test results for *B burgdorferi* in patients treated for syphilis or other spirochete diseases are difficult to interpret. Consultation with an infectious diseases specialist is recommended. Although immunodeficiency theoretically could affect serologic testing results, reports have described infected patients who produced anti-*B burgdorferi* antibodies and had positive test results despite various immunocompromising conditions.

A licensed, commercially available serologic test (C6) that detects antibody to a peptide of the immunodominant conserved region of the variable surface antigen (VlsE) of *B burgdorferi* appears to have improved sensitivity for adults with early Lyme disease and Lyme disease acquired in Europe. However, when used alone, its specificity is slightly lower than that of standard 2-tier testing. Of interest, substitution of the C6 EIA for immunoblot testing in the 2-tier testing algorithm does not reduce the overall specificity.

CR testing of joint fluid from a patient with Lyme arthritis often has positive results and can be informative in establishing a diagnosis of Lyme arthritis. The role of a PCR assay on blood is not well established and is not routinely recommended. The yield of PCR testing on cerebrospinal fluid samples from patients with neuroborreliosis is too low to be useful in excluding this diagnosis.

Some patients who are treated with antimicrobial agents for early Lyme disease never develop detectable antibodies against *B burgdorferi;* they are cured and are not at risk of late disease. Development of antibodies in patients treated for early Lyme disease does not indicate lack of cure or presence of persistent infection. Ongoing infection without development of antibodies ("seronegative Lyme") has not been demonstrated. Most patients with early disseminated disease and virtually all patients with late disease have antibodies against *B burgdorferi.* Once such antibodies develop, they may persist for many years. Consequently, tests for antibodies should not be repeated or used to assess the success of treatment.

Several tests for Lyme disease have been found to be invalid based on independent testing or to be too nonspecific to exclude false-positive results. These include urine tests for *B burgdorferi*, CD57 assay, novel culture techniques, and antibody panels that differ from those recommended as part of standardized 2-tier testing. Although these tests are commercially available from some clinical laboratories, they are not FDA cleared and are not appropriate diagnostic tests for Lyme disease.

Current evidence indicates that patients with *B mayonii* infection develop a serologic response similar to that of patients infected with *B burgdorferi.* Two-tier testing can be expected to have positive results in patients with *B mayonii* infection.

TREATMENT

Consensus practice guidelines for assessment, treatment, and prevention of Lyme disease have been published by the Infectious Diseases Society of America. Care of children should follow recommendations in Table 80.1. Antimicrobial therapy for nonspecific symptoms or for asymptomatic seropositivity is not recommended. Antimicrobial agents administered for durations not specified in Table 80.1 are not recommended. Alternative diagnostic approaches or therapies without adequate validation studies and publication in peer-reviewed scientific literature are discouraged. Physicians have successfully treated patients with *B mayonii* infection with regimens used for Lyme disease.

Erythema Migrans (Single or Multiple)

Doxycycline, amoxicillin, or cefuroxime can be used to treat children of any age who present with erythema migrans. Azithromycin generally is regarded as a second-line antimicrobial agent for erythema migrans in the United States, but further research on the efficacy of this agent is warranted. Selection of an oral antimicrobial agent for treatment of erythema migrans should be based on the following considerations:

Table 80.1
Recommended Treatment of Lyme Disease in Children

Disease Category	Drug(s) and Dose
Early localized disease	
Erythema migrans (single or multiple) (any age)	Doxycycline, 4.4 mg/kg per day, orally, divided into 2 doses (maximum 200 mg/day) for 10 days[a] **OR** Amoxicillin, 50 mg/kg per day, orally, divided into 3 doses (maximum 1.5 g/day) for 14 days[a] **OR** Cefuroxime, 30 mg/kg per day, orally, in 2 divided doses (maximum 1,000 mg/day or 1 g/day) for 14 days[a] **OR,** for a patient unable to take a beta-lactam or doxycycline, Azithromycin, 10 mg/kg/day, orally, once daily for 7 days
Extracutaneous disease	
Isolated facial palsy	Doxycycline, 4.4 mg/kg per day, orally, divided into 2 doses (maximum 200 mg/day), for 14 days[a,b]
Arthritis	An oral agent as for early localized disease, for 28 days[c]
Persistent arthritis after first course of therapy	Retreat using an oral agent as for first-episode arthritis for 28 days[c] **OR** Ceftriaxone sodium, 50–75 mg/kg, IV, once a day (maximum 2 g/day) for 14–28 days
Atrioventricular heart block or carditis	An oral agent as for early localized disease, for 14 days (range 14–21 days) **OR** Ceftriaxone sodium, 50–75 mg/kg, IV, once a day (maximum 2 g/day) for 14 days (range 14–21 days for a hospitalized patient); oral therapy (using an agent as for early localized disease) can be substituted when the patient is stabilized or discharged, to complete the 14- to 21-day course
Meningitis	Doxycycline, 4.4 mg/kg per day, orally, divided into 1 or 2 doses (maximum 200 mg/day) for 14 days[a] **OR** Ceftriaxone sodium, 50–75 mg/kg, IV, once a day (maximum 2 g/day) for 14 days[a]

IV indicates intravenously.

[a] Represents a change from the 2006 Infectious Diseases Society of America (IDSA) guidelines by virtue of elimination of a longer range in duration of therapy of up to 21 days for erythema migrans, up to 21 days for facial palsy, and up to 28 days for meningitis or radiculopathy (Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review. *JAMA*. 2016;315[16]:1767–1777).

[b] Corticosteroids should not be given. Use of amoxicillin for facial palsy in children has not been studied. Treatment has no effect on the resolution of facial nerve palsy; its purpose is to prevent late disease.

[c] There are limited safety data on the use of doxycycline for >21 days in children <8 years of age.

presence of neurologic disease (for which doxycycline is the drug of choice), drug allergy, adverse effects, frequency of administration (doxycycline and cefuroxime are administered twice a day, amoxicillin is administered 3 times a day), ability to minimize sun exposure (photosensitivity may be associated with doxycycline use), likelihood of coinfection with *Anaplasma phagocytophilum* or *Ehrlichia muris*-like agent (neither is sensitive to beta-lactam antimicrobial agents), and when *Staphylococcus aureus* cellulitis cannot be distinguished easily from erythema migrans (doxycycline is effective against most strains of methicillin-sensitive and methicillin-resistant *Staphylococcus aureus*). Erythema migrans should be treated orally for 10 days if doxycycline is used and for 14 days if amoxicillin or cefuroxime is used. Because STARI may be indistinguishable from early Lyme disease and questions remain about appropriate treatment, some physicians treat STARI with the same antimicrobial agents orally as for Lyme disease.

Treatment of erythema migrans results in resolution of the skin lesion within several days of initiating therapy and almost always prevents development of later stages of Lyme disease.

Early Disseminated (Extracutaneous) Disease

Oral antimicrobial agents are appropriate and effective for most manifestations of disseminated Lyme disease, including multiple erythema migrans and for patients with Lyme carditis treated as outpatients. For patients requiring hospitalization for Lyme carditis (eg, high-grade atrioventricular block), initial therapy usually is parenteral but can be completed with oral therapy for a total course of 14 to 21 days.

Doxycycline is preferred therapy for facial nerve palsy caused by *B burgdorferi* in children of any age. The purpose of therapy for cranial nerve palsies is to reduce the risk of late disease. Amoxicillin has not been studied sufficiently for the treatment of facial nerve palsies in young children and is unlikely to reach therapeutic levels in the central nervous system.

A growing body of evidence suggests that oral doxycycline is effective for treatment of Lyme meningitis and may be used as an alternative to hospitalization and parenteral ceftriaxone therapy in children who are well enough to be treated as outpatients. In a child with a stiff neck and other symptoms of meningitis in whom the possibility of a bacterial (nonspirochetal) meningitis cannot be ruled out, a lumbar puncture is indicated. Neurologic disease is treated for 14 days.

Late Disseminated Disease

Children with Lyme arthritis are treated with oral antimicrobial agents for 28 days. Because of this duration, patients younger than 8 years should be treated with an oral agent other than doxycycline (eg, amoxicillin). For patients 8 years and older, any of the oral options, including doxycycline, may be used.

Patients who have responded incompletely or who respond and then relapse soon after stopping therapy can be given a second 28-day course of oral therapy. Patients who experience worsening of their arthritis can be treated with ceftriaxone parenterally for 14 to 28 days.

Approximately 10% to 15% of patients treated for Lyme arthritis will go on to have persistent synovitis that can last for months to years. Theories of pathophysiology include delayed resolution of inflammation because of slow clearance of nonviable bacteria following treatment versus an autoimmune mechanism. Misdiagnosis also should be considered (ie, Lyme antibodies in serum present from a previous infection or cross-reacting because of another disorder). Persisting synovitis following Lyme disease, termed “antibiotic-refractory Lyme arthritis,” is a strongly HLA-associated phenomenon. Patients with persistent synovitis despite repeat treatment initially should be managed with nonsteroidal anti-inflammatory drugs. More severe cases should be referred to a rheumatologist. Methotrexate has been used successfully in some cases. Arthroscopic synovectomy is required rarely for more disabling or refractory cases.

Persistent Post-treatment Symptoms (Mistakenly Called "Chronic Lyme Disease")

Some patients have prolonged, persistent symptoms following standard treatment for Lyme disease. However, it is not clear whether this phenomenon is unique to Lyme disease or whether it is a more general occurrence during convalescence from other systemic illnesses. Persistent, treatment-refractory infection with *B burgdorferi* has not been substantiated scientifically. Patients with persistent symptoms following Lyme disease usually respond to symptomatic treatment and recover gradually.

Several double-blinded, randomized, placebo-controlled trials have found that retreatment with additional antimicrobial agents for patients with residual post-treatment Lyme disease subjective symptoms may be associated with harm and does not offer benefit. Administration of additional antimicrobial agents to a patient with post-treatment Lyme disease symptoms following standard treatment for Lyme disease is strongly discouraged.

Retreatment is appropriate for subsequent acute infections caused by *B burgdorferi*.

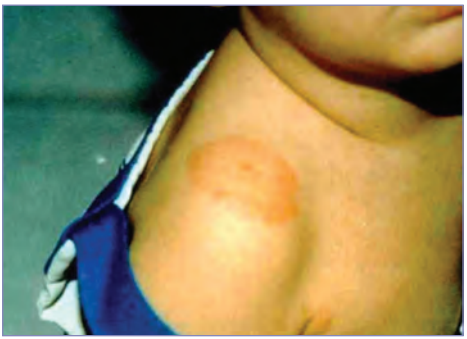


Image 80.1
Lyme disease. The rash of erythema migrans in a 4-year-old boy with infection due to *Borrelia burgdorferi*. Copyright Richard Jacobs, MD.

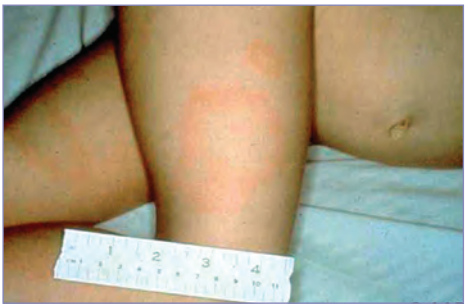


Image 80.2
Erythema migrans lesion at the site of a tick bite characteristic of early localized Lyme disease. It is annular with central clearing (ie, a target lesion), but in other cases the initial lesion can be uniformly erythematous and occasionally have a vesicular or necrotic center, as illustrated in Image 80.3. Systemic symptoms, such as fever, myalgia, headache, or malaise, can occur at this stage of infection.

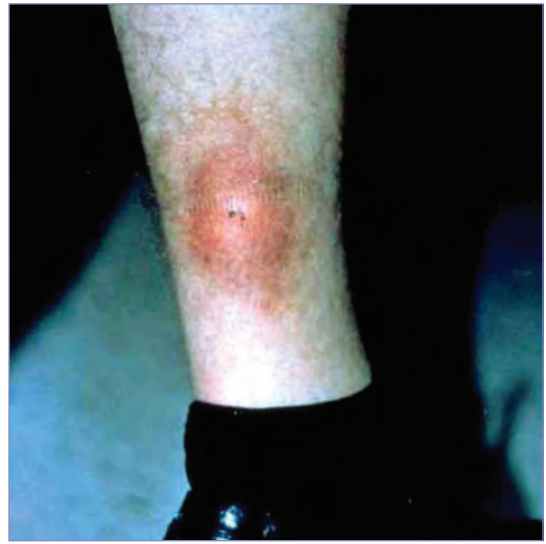


Image 80.3
The rash at the site of a tick bite on the lower leg is indicative of the variation in the initial rash of Lyme disease. Central clearing is incomplete, and a central necrotic area is apparent at the presumed site of the tick bite.

Image 80.4
A 15-month-old girl with left facial nerve palsy complicating Lyme disease. Copyright Michael Rajnik, MD, FAAP.

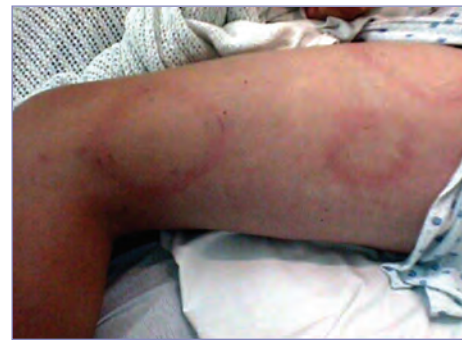


Image 80.5
Erythema migrans lesions in a 12-year-old boy who contracted Lyme disease in Maryland. Copyright Michael Rajnik, MD, FAAP.

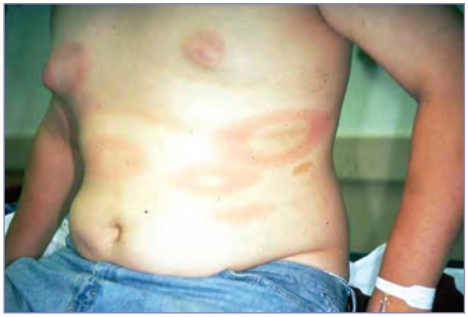


Image 80.6
A 14-year-old boy with multiple annular skin lesions and worsening headache associated with photophobia. Results from a lumbar puncture revealed a cerebrospinal fluid pleocytosis and aseptic meningitis. The characteristic erythema migrans skin lesions helped to determine the diagnosis of Lyme disease. The patient was treated with intravenous ceftriaxone. Copyright Barbara Jantausch, MD, FAAP.

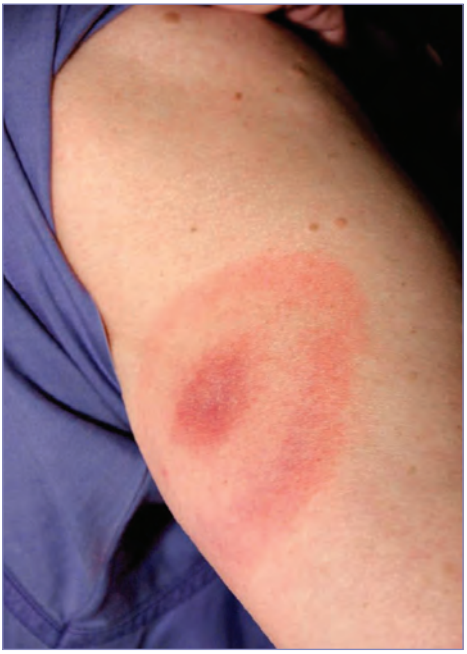


Image 80.8
This photograph depicts the pathognomonic erythematous rash in the pattern of a bull's-eye, which developed at the site of a tick bite on this Maryland woman's posterior right upper arm. Courtesy of Centers for Disease Control and Prevention/ James Gathany.

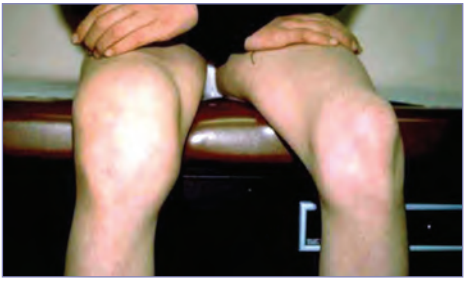


Image 80.7
Borrelia burgdorferi synovitis with marked swelling and only mild tenderness. Arthritis usually occurs within 1 to 2 months following the appearance of erythema migrans, and the knees are the most commonly affected joints.

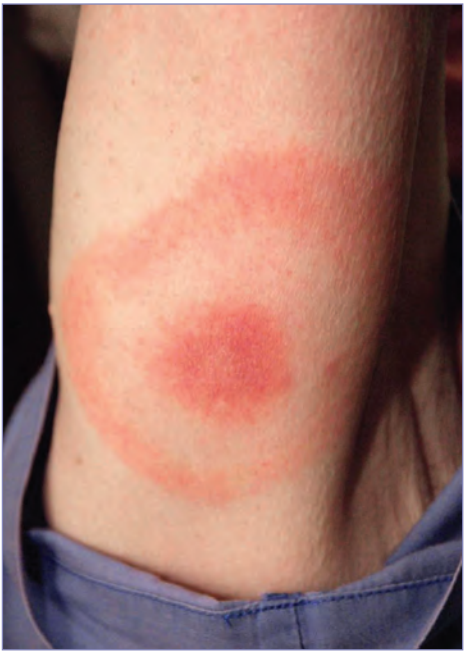


Image 80.9
This photograph depicts the pathognomonic erythematous rash (erythema migrans) in the pattern of a bull's-eye, which developed at the site of a tick bite on this Maryland woman's posterior right upper arm. The expanding rash reflects migration of the spirochetes after introduction of the organism during the tick bite. Courtesy of Centers for Disease Control and Prevention/James Gathany.

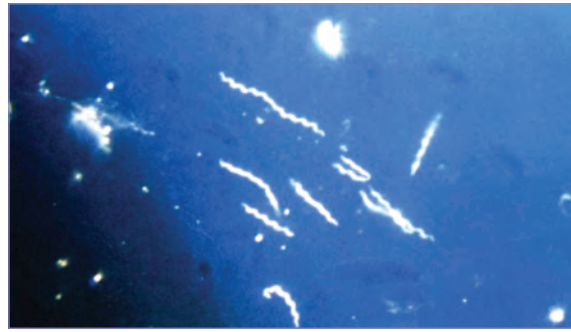


Image 80.10
Using darkfield microscopy technique, this photomicrograph reveals the presence of spirochetes, or corkscrew-shaped bacteria known as *Borrelia burgdorferi*, which is the pathogen responsible for causing Lyme disease (magnification ×400). *B burgdorferi* are helical-shaped bacteria and are about 10 to 25 µm long. These bacteria are transmitted to humans by the bite of an infected deer tick. Courtesy of Centers for Disease Control and Prevention.

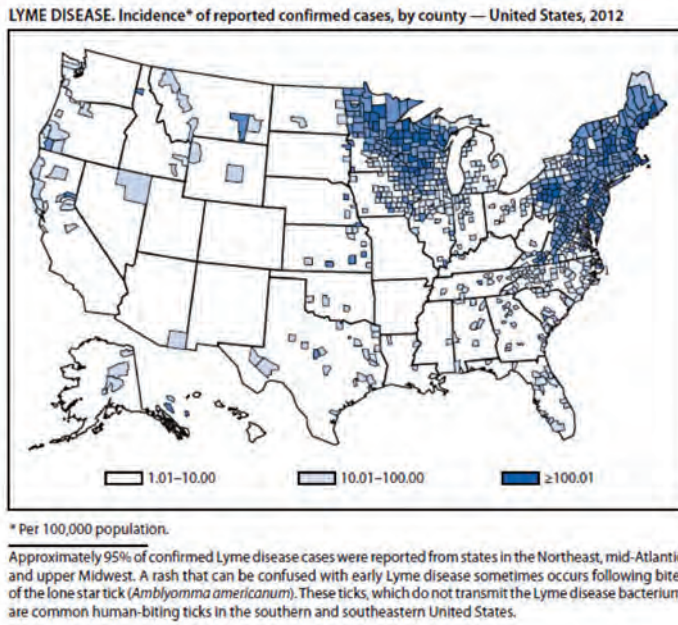


Image 80.11
Incidence of reported confirmed cases, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

Image 80.12
Two deer ticks of the *Ixodes* genus that transmit *Borrelia burgdorferi* to humans. The engorged tick on the right demonstrates increased size from a blood meal. Both are magnified for this photograph.

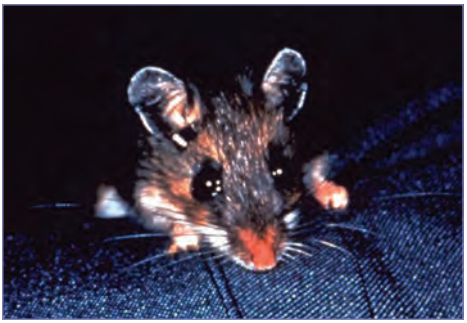


Image 80.14
This photograph depicts a white-footed mouse, *Peromyscus leucopus*, which is a wild rodent reservoir host of ticks, which are known to carry *Borrelia burgdorferi*, the bacteria responsible for Lyme disease. During their larval stage, *Ixodidae*, or hard ticks, feed on small mammals, particularly the white-footed mouse, which serves as the primary reservoir for *B burgdorferi*. Courtesy of Centers for Disease Control and Prevention.

Image 80.13
This photograph depicts a dorsal view of an immature, or nymphal, lone star tick, *Amblyomma americanum*. Nymphal ticks are much smaller than adult ticks, and people might not notice a nymph until it has been feeding for a few days. Nymphs are, therefore, more likely than adult ticks to transmit diseases to people. Courtesy of Centers for Disease Control and Prevention/ Amanda Loftis, MD; William Nicholson, MD; Will Reeves, MD; and Chris Paddock, MD.

Image 80.15
This is a male *Ixodes ricinus* tick (smaller) shown copulating with a female tick (larger). *I ricinus*, the castor-bean tick, so called because of its resemblance to the castor bean, is a vector for the *Borrelia burgdorferi* spirochete, the cause of Lyme disease, and is commonly found on farm animals and deer. Courtesy of Centers for Disease Control and Prevention/World Health Organization.

Image 80.16
This photograph depicts a dorsal view of a female lone star tick, *Amblyomma americanum*. Note the characteristic lone star marking located centrally on its dorsal surface, at the distal tip of its scutum. Courtesy of Centers for Disease Control and Prevention/Amanda Loftis, MD; William Nicholson, MD; Will Reeves, MD; and Chris Paddock, MD.

Image 80.18
These black-legged ticks, *Ixodes scapularis*, are found on a wide range of hosts, including mammals, birds, and reptiles. *I scapularis* are known to transmit the agent of Lyme disease, *Borrelia burgdorferi*, to humans and animals during feeding when they insert their mouth parts into the skin of a host and slowly take in the nutrient-rich host blood. Courtesy of Centers for Disease Control and Prevention/Michael L. Levin, PhD.

Image 80.17
This photograph depicts a dorsal view of an adult female western black-legged tick, *Ixodes pacificus*, which has been shown to transmit *Borrelia burgdorferi*, the agent of Lyme disease, and *Anaplasma phagocytophilum*, the agent of human granulocytic anaplasmosis (previously known as human granulocytic ehrlichiosis), in the western United States. The small scutum does not cover its entire abdomen, thereby allowing the abdomen to expand many times when this tick ingests its blood meal, and which identifies this specimen as a female. The 4 pairs of jointed legs place these ticks in the phylum *Arthropoda* and the class *Arachnida*. Courtesy of Centers for Disease Control and Prevention/Amanda Loftis, MD; William Nicholson, MD; Will Reeves, MD; and Chris Paddock, MD.

CHAPTER 81

Lymphatic Filariasis

(Bancroftian, Malayan, and Timorian)

CLINICAL MANIFESTATIONS

Lymphatic filariasis (LF) is caused by infection with the filarial parasites *Wuchereria bancrofti*, *Brugia malayi*, or *Brugia timori*. Adult worms cause lymphatic dilatation and dysfunction, which result in abnormal lymph flow and eventually may lead to lymphedema in the legs, scrotal area (for *W bancrofti* only), and arms. Recurrent secondary bacterial infections hasten progression of lymphedema to the more severe form known as elephantiasis. Although the infection occurs commonly in young children living in areas with endemic LF, chronic manifestations of infection, such as hydrocele and lymphedema, occur infrequently in people younger than 20 years. Most filarial infections remain clinically asymptomatic, but even then they commonly cause subclinical lymphatic dilatation and dysfunction. Lymphadenopathy, most frequently of the inguinal, crural, and axillary lymph nodes, is the most common clinical sign of lymphatic filariasis in children. There can be an acute inflammatory response that progresses from the lymph node distally (retrograde) along the affected lymphatic vessel, usually in the limbs. Accompanying systemic symptoms, such as headache or fever, generally are mild. In postpubertal males, adult *W bancrofti* organisms are found most commonly in the intrascrotal lymphatic vessels; thus, inflammation around dead or dying adult worms may present as funiculitis (inflammation of the spermatic cord), epididymitis, or orchitis. A tender granulomatous nodule may be palpable at the site of dying or dead adult worms. Chyluria can occur as a manifestation of bancroftian filariasis. Tropical pulmonary eosinophilia, characterized by cough, fever, wheezing, marked eosinophilia, and high serum immunoglobulin (Ig) E concentrations, is a rare manifestation of lymphatic filariasis.

ETIOLOGY

Filariasis is caused by 3 filarial nematodes in the family *Filaridae: W bancrofti*, *B malayi*, and *B timori*.

EPIDEMIOLOGY

The parasite is transmitted by the bite of infected mosquitoes of various genera, including *Culex*, *Aedes*, *Anopheles*, and *Mansonia*. *W bancrofti*, the most prevalent cause of lymphatic filariasis, is found in Haiti, the Dominican Republic, Guyana, northeast Brazil, sub-Saharan and North Africa, and Asia, extending from India through the Indonesian archipelago to the western Pacific islands. Humans are the only definitive host for the parasite. *B malayi* is found mostly in Southeast Asia and parts of India. *B timori* is restricted to certain islands at the eastern end of the Indonesian archipelago. Live adult worms release microfilariae into the bloodstream. Adult worms live for an average of 5 to 8 years, and reinfection is common. Microfilariae that can infect mosquitoes may be present in a patient's blood for decades, although individual microfilariae have a life span between 3 and 12 months. The adult worm is not transmissible from person to person or by blood transfusion, but microfilariae may be transmitted by transfusion.

The **incubation period** is not known; the period from acquisition to the appearance of microfilariae in blood can be 3 to 12 months, depending on the species of parasite.

DIAGNOSTIC TESTS

Microfilariae generally can be detected microscopically on blood smears obtained at night (10:00 pm–4:00 am), although variations in the periodicity of microfilaremia have been described depending on the parasite strain and the geographic location. Adult worms or microfilariae can be identified based on general morphology, size, and the presence or absence of a sheath in Giemsa-stained fluid or tissue specimens obtained at biopsy. Serologic enzyme immunoassays are available, but interpretation of results is affected by cross-reactions of filarial antibodies with antibodies against other helminths. Determination of serum antifilarial IgG is available through the Centers for Disease Control and Prevention (CDC [**www.dpd.cdc.gov/dpdx**; 404-718-4745; parasites@cdc.gov]). Assays for circulating parasite antigen of *W bancrofti* are available commercially but are not available in the United States. Ultrasonography can be used to visualize

adult worms. Patients with lymphedema may no longer have microfilariae or antifilarial antibody present.

TREATMENT

The main goal of treatment of an infected person is to kill the adult worm. Diethylcarbamazine citrate (DEC), which is both microfilaricidal and active against the adult worm, is the drug of choice for lymphatic filariasis. DEC is no longer sold in the United States but can be obtained from the CDC (404-718-4745; parasites@cdc.gov; or **www.cdc.gov/parasites/lymphaticfilariasis**). Treatment with DEC should be undertaken by a tropical medicine specialist with experience in treating lymphatic filariasis, because DEC therapy has been associated with life-threatening adverse events, including encephalopathy and renal failure, particularly in people with circulating *Loa loa* microfilaria concentrations >2,500/mm^3. Ivermectin is effective against the microfilariae of *W bancrofti* and the 2 *Brugia* species but has no effect on the adult parasite. Albendazole has demonstrated macrofilaricidal activity. Combination therapy with single-dose DEC-albendazole or ivermectin-albendazole has been shown to be more effective than any one drug alone in suppressing microfilaremia and is the basis for the Global Programme to Eliminate Lymphatic Filariasis. Doxycycline, a drug that targets the *Wolbachia* (intracellular rickettsial-like bacteria) endosymbiont in adult worms, has been shown to be macrofilaricidal as well and has been used in combination with DEC.

Antifilarial chemotherapy has been shown to have limited efficacy for reversing or stabilizing the lymphedema in its early forms. Doxycycline, in limited studies, has been shown to decrease the severity of lymphedema. Complex decongestive physiotherapy can be effective for treating lymphedema and requires strict attention to hygiene in the affected anatomical areas. Chyluria originating in the bladder responds to fulguration; chyluria originating in the kidney is difficult to correct. Prompt identification and treatment of bacterial superinfections, particularly streptococcal and staphylococcal infections, and careful treatment of intertriginous and ungual fungal infections are important aspects of therapy for lymphedema. For management of hydrocele, surgery may be indicated.

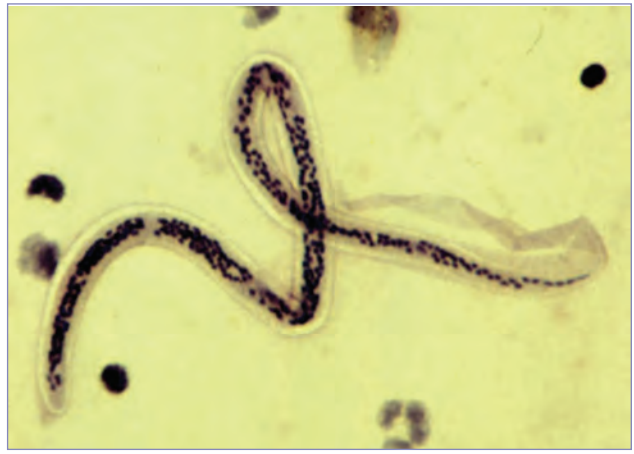


Image 81.1
Microfilaria of *Wuchereria bancrofti* from a patient in Haiti (thick blood smear; hematoxylin stain). The microfilaria is sheathed, its body is gently curved, and the tail is tapered to a point. The nuclear column (ie, the cells that constitute the body of the microfilaria) is loosely packed; the cells can be visualized individually and do not extend to the tip of the tail. The sheath is slightly stained by hematoxylin. Courtesy of Centers for Disease Control and Prevention.

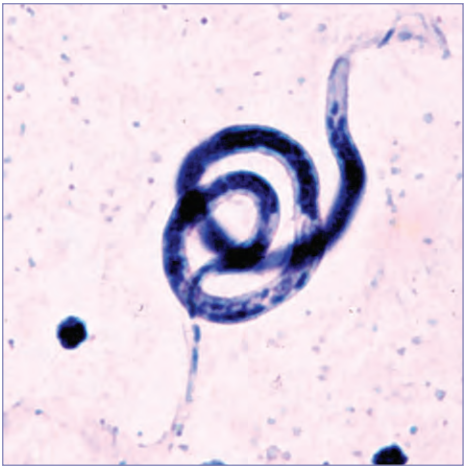


Image 81.2
Microfilaria of *Brugia malayi* (thick blood smear; hematoxylin stain). Like *Wuchereria bancrofti*, this species has a sheath (slightly stained in hematoxylin). In contrast with *W bancrofti*, the microfilariae in this species are more tightly coiled and the nuclear column is more tightly packed, preventing the visualization of individual cells. Courtesy of Centers for Disease Control and Prevention.

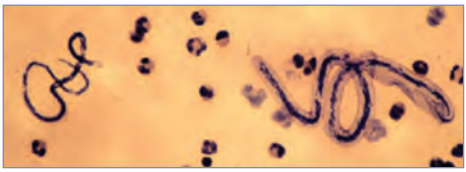


Image 81.5
Microfilariae of *Loa loa* (right) and *Mansonella perstans* (left) in a patient in Cameroon (thick blood smear; hematoxylin stain). *L loa* is sheathed, with a relatively dense nuclear column; its tail tapers and is frequently coiled, and nuclei extend to the end of the tail. *M perstans* is smaller, has no sheath, and has a blunt tail with nuclei extending to the end of the tail. Courtesy of Centers for Disease Control and Prevention.

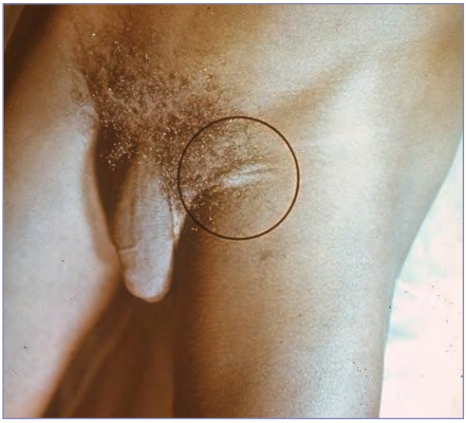


Image 81.3
Inguinal lymph nodes enlarged due to filariasis. Courtesy of Centers for Disease Control and Prevention.

Image 81.4
Microfilaria of *Onchocerca volvulus* from skin snip from a patient in Guatemala (wet preparation). Some important characteristics of the microfilariae of this species are shown here—no sheath present, and the tail is tapered and is sharply angled at the end. Courtesy of Centers for Disease Control and Prevention.

Image 81.6
Microfilaria of *Mansonella ozzardi* (thick blood smear; Giemsa stain). The microfilaria is typically small and unsheathed and has a slender, tapered tail that is hooked ("buttonhook"). The nuclei do not extend to the end of the tail. Courtesy of Centers for Disease Control and Prevention.

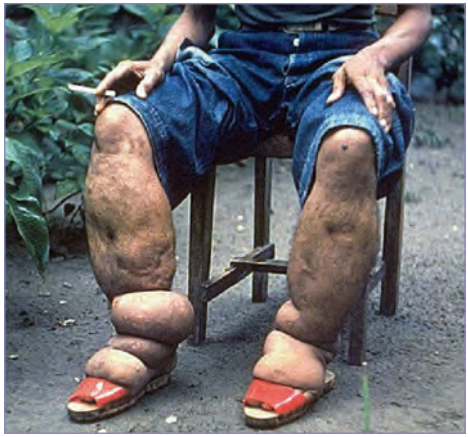


Image 81.7
Elephantiasis of both legs due to filariasis. Luzon, Philippines. Courtesy of Centers for Disease Control and Prevention.

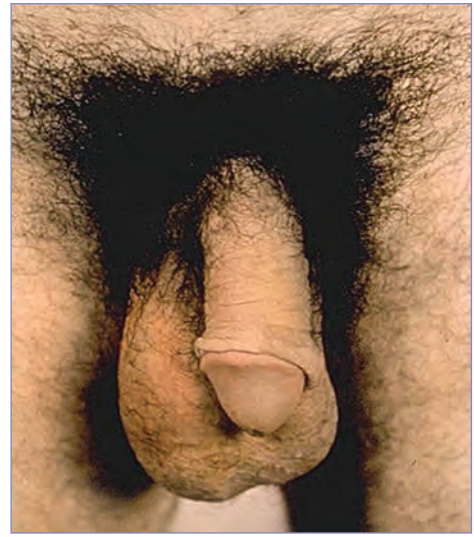


Image 81.8
Scrotal lymphangitis due to filariasis. Courtesy of Centers for Disease Control and Prevention.

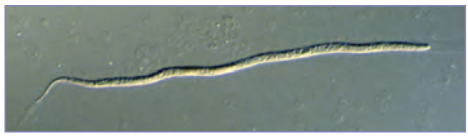


Image 81.9
Microfilaria of *Brugia malayi* collected by the Knott (centrifugation) concentration technique, in 2% formalin wet preparation. Note the erythrocyte ghosts (for size comparison) and the clearly visible sheath that extends beyond the anterior and posterior ends of the microfilaria. (There are 4 sheathed species: *Wuchereria bancrofti*, *Brugia malayi, Brugia timori,* and *Loa loa*.) Courtesy of Centers for Disease Control and Prevention.

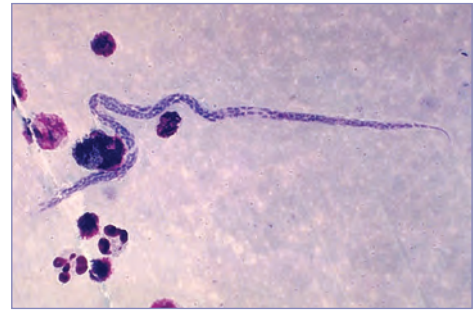


Image 81.10
Mansonella ozzardi, infectious agent of filariasis. Courtesy of Centers for Disease Control and Prevention.

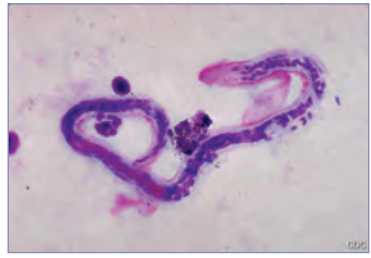


Image 81.11
This photomicrograph shows the inner body and cephalic space of a *Brugia malayi* microfilaria in a thick blood smear. *B malayi*, a nematode that can inhabit the lymphatics and subcutaneous tissues in humans, is one of the causative agents for lymphatic filariasis. The vectors for this parasite are mosquito species from the genera *Mansonia* and *Aedes*. Courtesy of Centers for Disease Control and Prevention/Mae Melvin, MD.

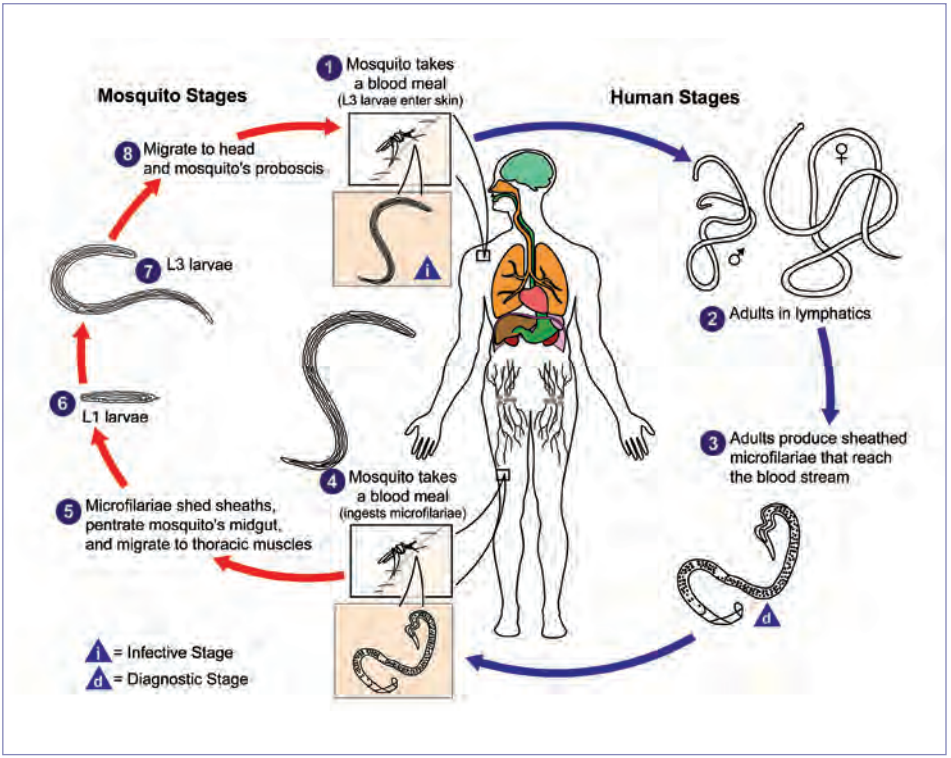


Image 81.12

The typical vector for *Brugia malayi* filariasis are mosquito species from the genera *Mansonia* and *Aedes*. During a blood meal, an infected mosquito introduces third-stage filarial larvae onto the skin of the human host, where they penetrate into the bite wound (1). They develop into adults that commonly reside in the lymphatics (2). The adult worms resemble those of *Wuchereria bancrofti* but are smaller. Female worms measure 43 to 55 mm in length by 130 to 170 µm in width, and males measure 13 to 23 mm in length by 70 to 80 µm in width. Adults produce microfilariae, measuring 177 to 230 µm in length and 5 to 7 µm in width, that are sheathed and have nocturnal periodicity. The microfilariae migrate into lymph and enter the bloodstream, reaching the peripheral blood (3). A mosquito ingests the microfilariae during a blood meal (1). After ingestion, the microfilariae lose their sheaths and work their way through the wall of the proventriculus and cardiac portion of the midgut to reach the thoracic muscles (5). There, the microfilariae develop into first-stage larvae (6) and, subsequently, into third-stage larvae (7). The third-stage larvae migrate through the hemocoel to the mosquito's proboscis (8) and can infect another human when the mosquito takes a blood meal (1). Courtesy of Centers for Disease Control and Prevention.

CHAPTER 82

Lymphocytic Choriomeningitis

CLINICAL MANIFESTATIONS

Child and adult infections with lymphocytic choriomeningitis virus (LCMV) are asymptomatic in approximately one third of cases. Symptomatic infection can result in a mild to severe illness, which can include fever, malaise, myalgia, retro-orbital headache, photophobia, anorexia, and nausea and vomiting. Sore throat, cough, arthralgia or arthritis, and orchitis also can occur. Initial symptoms may last from a few days to 3 weeks. Leukopenia, lymphopenia, thrombocytopenia, and elevation of lactate dehydrogenase and aspartate transaminase occur frequently. A biphasic febrile course is common; after a few days without symptoms, the second phase may occur in up to half of symptomatic patients, consisting of neurologic manifestations that vary from aseptic meningitis to severe encephalitis. Transverse myelitis, eighth nerve deafness, Guillain-Barré syndrome, and hydrocephalus also have been reported, but a causal link remains to be established. Extraneural disease has included reports of myocarditis and dermatitis. Rarely, LCMV has caused a disease resembling viral hemorrhagic syndrome. Transmission of LCMV through organ transplantation and infection in other immunocompromised populations can result in fatal disseminated infection with multiple organ failure.

Convalescence may take several weeks, with asthenia, poor cognitive function, headaches, and arthralgia. Recovery without sequelae is the usual outcome. LCMV infection should be suspected in presence of: (1) aseptic meningitis or encephalitis during the fall-winter season; (2) febrile illness, followed by brief remission, followed by onset of neurologic illness; and (3) cerebrospinal fluid (CSF) findings of lymphocytosis and hypoglycorrhachia.

Infection during pregnancy has been associated with spontaneous abortion. Congenital infection may cause severe abnormalities, including hydrocephalus, chorioretinitis, intracranial calcifications, microcephaly, and intellectual disability. Congenital LCMV should be included in the differential diagnosis whenever intrauterine infections with toxoplasma, rubella, cytomegalovirus, herpes simplex, enterovirus, parechovirus, Zika virus, dengue, syphilis, and parvovirus B19 are also being considered.

ETIOLOGY

LCMV is a single-stranded RNA virus that belongs to the family *Arenaviridae*. Other members of this family include Lassa virus and the Tacaribe group.

EPIDEMIOLOGY

LCMV is a chronic infection of common house mice, which often are infected asymptomatically and chronically shed virus in urine and other excretions. Congenital murine infection is common and results in a normal-appearing litter with chronic viremia and particularly high virus excretion. In addition, pet hamsters, laboratory mice, guinea pigs, and colonized golden hamsters can have chronic infection and can be sources of human infection. Humans are infected mostly by inhalation of aerosol generated by rodents shedding virus from the urine, feces, blood, or nasopharyngeal secretions. Other less likely routes of entry of infected secretions include conjunctival and other mucous membranes, ingestion, and occult cuts. The disease is observed more frequently in young adults. Human-to-human transmission has occurred during pregnancy from infected mothers to their fetus and through solid organ transplantation from an undiagnosed, acutely LCMV-infected organ donor. Several such clusters of cases have been described following transplantation, and one case was traced to a pet hamster purchased by the donor. A number of laboratory-acquired LCMV infections have occurred, both through infected laboratory animals and contaminated tissue-culture stocks.

The **incubation period** usually is 6 to 13 days (occasionally 3 weeks).

DIAGNOSTIC TESTS

Patients with central nervous system disease have a mononuclear pleocytosis with 30 to 8,000 cells in CSF. Hypoglycorrhachia, as well as mild increase in protein, may occur. LCMV usually can be isolated from CSF obtained during the acute phase of illness and, in severe disseminated infections, also from blood, urine,

and nasopharyngeal secretion specimens. Reverse transcriptase-polymerase chain reaction assays available through reference or commercial laboratories can be used on serum during the acute stage and on CSF during the neurologic phase. Serum specimens from the acute and convalescent phases of illness can be tested for increases in antibody titers by enzyme immunoassays and neutralization tests. Demonstration of virus-specific immunoglobulin M antibodies in serum or CSF specimens is useful. In congenital infections, diagnosis usually is suspected at the sequela phase, and diagnosis usually is made by serologic testing. In immunosuppressed patients, seroconversion can take several weeks. Diagnosis can be made retrospectively by immunohistochemical assay of fixed tissues obtained from necropsy.

TREATMENT

Supportive.

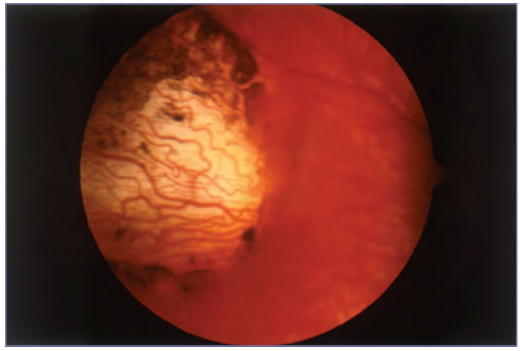


Image 82.1
Fundus photograph of a 9-month-old girl with congenital lymphocytic choriomeningitis virus infection. Extensive chorioretinal scarring is visible. Hydrocephalus and periventricular calcification were visible on computed tomography scan and magnetic resonance imaging. Copyright Leslie L. Barton, MD, FAAP.

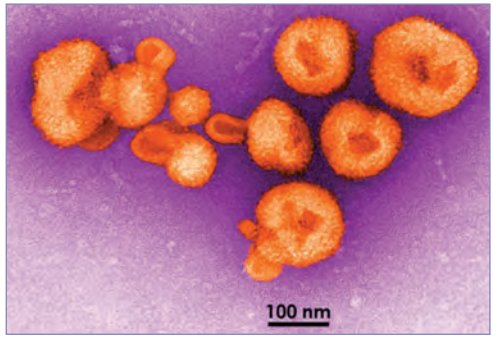


Image 82.2
This transmission electron micrograph depicted 8 virions (viral particles) of a newly discovered virus, which was determined to be a member of the genus *Arenavirus*. A cause of fatal hemorrhagic fever, it was confirmed that this virus was responsible for causing illness in 5 South Africans, 4 of whom died having succumbed to its devastating effects. Ultrastructurally, these round *Arenavirus* virions displayed the characteristic "sandy" or granular capsid (ie, outer skin), an appearance from which the Latin name, arena, was derived. Other members of the genus *Arenavirus* include the West African Lassa virus, lymphocytic choriomeningitis, and Bolivian hemorrhagic fever, also known as Machupo virus, all of which are spread to humans through their inhalation of airborne particulates originating from rodent excrement, which can occur during the simple act of sweeping a floor. Courtesy of Centers for Disease Control and Prevention/Charles Humphrey.

CHAPTER 83

Malaria

CLINICAL MANIFESTATIONS

The classic symptoms of malaria are high fever with chills, rigor, sweats, and headache, which may be paroxysmal. If appropriate treatment is not administered, fever and paroxysms may occur in a cyclic pattern. Depending on the infecting species, fever classically appears every day (*Plasmodium knowlesi*), every other day (*Plasmodium falciparum*, *Plasmodium vivax*, and *Plasmodium ovale*), or every third day (*Plasmodium malariae*), although in general practice this pattern is infrequently observed, especially in children. Other manifestations, particularly as the clinical disease progresses, can include nausea, vomiting, diarrhea, cough, tachypnea, arthralgia, myalgia, and abdominal and back pain. Anemia and thrombocytopenia, along with pallor and jaundice caused by hemolysis, are common in severe illness. Hepatosplenomegaly is frequently present in infected children in areas with endemic malaria and may be present in adults and in people not previously infected with malaria. More severe disease frequently occurs in people without immunity acquired as a result of previous infection, in young children, and in people who are pregnant or immunocompromised.

Infection with *P falciparum,* one of the 5 *Plasmodium* species that infect humans, potentially is fatal and most commonly manifests as a febrile nonspecific illness without localizing signs. Severe disease (most commonly caused by *P falciparum*) may manifest as one of the following clinical syndromes, all of which are medical emergencies and may be fatal unless treated:

- **Cerebral malaria,** characterized by coma and manifesting with a range of neurologic signs, including generalized seizures, signs of increased intracranial pressure (confusion and progression to stupor, coma), and death;
- **Hypoglycemia,** which can present with metabolic acidosis and hypotension associated with hyperparasitemia; it also can be a consequence of quinine or quinidine-induced hyperinsulinemia;
- **Renal failure** caused by acute tubular necrosis (rare in children younger than 8 years);
- **Respiratory failure,** without pulmonary edema;
- **Metabolic acidosis,** usually attributed to lactic acidosis, hypovolemia, liver dysfunction, and impaired renal function;
- **Severe anemia** attributable to high parasitemia and hemolysis, sequestration of infected erythrocytes to capillaries, and hemolysis of infected erythrocytes associated with hypersplenism; or
- **Vascular collapse and shock** associated with hypothermia and adrenal insufficiency; people with asplenia who become infected may be at increased risk of more severe illness and death.

Syndromes primarily associated with *P vivax* and *P ovale* infection are as follows:

- **Anemia** attributable to acute parasitemia;
- **Hypersplenism** with danger of splenic rupture; and
- **Relapse of infection,** for as long as 3 to 5 years after the primary infection, attributable to latent hepatic stages (hypnozoites).

Syndromes associated with *P malariae* infection include

- **Chronic asymptomatic parasitemia** for as long as decades after the primary infection; and
- **Nephrotic syndrome** resulting from deposition of immune complexes in the kidney.

Plasmodium knowlesi is a nonhuman primate malaria parasite that also can infect humans. *P knowlesi* malaria has been misdiagnosed commonly as the more benign *P malariae* malaria. Disease can be characterized by very rapid replication of the parasite and hyperparasitemia resulting in severe disease. Severe disease in patients with *P knowlesi* infection should be treated aggressively, because hepatorenal failure and subsequent death have been well documented.

Congenital malaria resulting from perinatal transmission occurs infrequently, with increased risk among primigravidae. Most congenital cases have been caused by *P vivax* and *P falciparum; P malariae* and *P ovale* account for fewer than 20% of such cases. Manifestations can resemble those of neonatal sepsis, including fever and nonspecific symptoms of poor appetite, irritability, and lethargy.

ETIOLOGY

The genus *Plasmodium* includes species of intraerythrocytic parasites that infect a wide range of mammals, birds, and reptiles. The 5 species that infect humans are *P falciparum*, *P vivax*, *P ovale*, *P malariae*, and *P knowlesi*. Coinfection with multiple species increasingly is documented in areas with endemic disease using polymerase chain reaction for diagnosis of malaria.

EPIDEMIOLOGY

Malaria is endemic throughout the tropical areas of the world and is acquired from the bite of the female nocturnal-feeding *Anopheles* genus of mosquito. Half of the world's population lives in areas where transmission occurs. Worldwide, 212 million cases and 429,000 deaths were reported in 2015. Approximately 10% of these are cases of severe malaria, with a significantly higher chance of death. Most deaths occur in young children. Infection by the malaria parasite poses substantial risks to pregnant women, especially primigravida women in areas with endemic infection, and their fetuses and may result in spontaneous abortion and stillbirth. Malaria also contributes to low birth weight in countries where *P falciparum* is endemic.

The risk of malaria is highest, but variable, for travelers to sub-Saharan Africa, Papua New Guinea, the Solomon Islands, and Vanuatu; the risk is intermediate on the Indian subcontinent and is low in most of Southeast Asia and Latin America. The potential for malaria reintroduction can occur in areas where malaria previously was eliminated if infected people return and the mosquito vector is still present. These conditions have resulted in recent cases in travelers to areas such as Jamaica, Greece, and the Bahamas.

Health care professionals should check the Centers for Disease Control and Prevention (CDC) website for the most current information (**www.cdc.gov/malaria**) to determine malaria endemicity when providing pretravel malaria advice or evaluating a febrile returned traveler. Transmission is possible in more temperate climates, including areas of the United States where *Anopheles* mosquitoes are present. Nearly all the approximately 1,500 annual reported cases in the United States result from infection acquired abroad. Uncommon modes of malaria transmission are congenital, through transfusions, or through the use of contaminated needles or syringes.

P vivax and *P falciparum* are the most prevalent species worldwide. *P vivax* malaria is prevalent on the Indian subcontinent and in Central America. *P falciparum* malaria is prevalent in Africa, Papua New Guinea, and on the island of Hispaniola (Haiti and the Dominican Republic). *P vivax* and *P falciparum* species are the most common malaria species in southern and Southeast Asia, Oceania, and South America. *P malariae*, although much less common, has a wide distribution. *P ovale* malaria occurs most frequently in West Africa but has been reported in other areas. Reported cases of human infections with *P knowlesi* have been from certain countries of Southeast Asia, specifically Borneo, Malaysia, Philippines, Thailand, the Thai-Burmese border, Singapore, and Cambodia.

Relapses may occur in *P vivax* and *P ovale* infections because of a persistent hepatic (hypnozoite) stage of infection. Recrudescence of *P falciparum* and *P malariae* infection occurs when a persistent low-concentration parasitemia produces recurrence of blood parasite replication and symptoms of the disease or when drug resistance prevents elimination of the parasite. In areas of Africa and Asia with hyperendemic transmission, repeated infection in people with partial immunity results in a high prevalence of asymptomatic parasitemia.

Drug resistance in both *P falciparum* and *P vivax* has been evolving throughout areas with endemic malaria. The spread of chloroquine-resistant *P falciparum* strains throughout the world dates to the 1960s.

P falciparum resistance to sulfadoxine-pyrimethamine is distributed throughout Africa. Mefloquine resistance has been documented in Myanmar (Burma), Lao People's Democratic Republic (Laos), Thailand, Cambodia, China, and Vietnam. Resistance to artemisinins has been reported from the 5 countries of Greater Mekong Subregions (GMS), which consist of Cambodia, Laos, Myanmar, Thailand, and Vietnam. Chloroquine-resistant *P vivax* has been reported in Indonesia, Papua New Guinea, the Solomon Islands, Myanmar, India, and Guyana.

The **incubation period** is as soon as 7 days after exposure in an area with endemic malaria to several months after departure. More than 80% of cases in the United States occur in people who have onset of symptoms after their return to the United States.

DIAGNOSTIC TESTS

Definitive parasitological diagnosis has historically been based on identification of *Plasmodium* parasites microscopically on stained blood films. Both thick and thin blood films should be examined. The thick film allows for concentration of the blood to find parasites that may be present at low density, whereas the thin film is most useful for species identification and determination of the density of red blood cells infected with parasites. If initial blood smears test negative for *Plasmodium* species but malaria remains a possibility, the smear should be repeated every 12 to 24 hours during a 72-hour period.

Confirmation and identification of the species of malaria parasites on the blood smear is essential in guiding therapy. Serologic testing generally is not helpful, except in epidemiologic surveys. Polymerase chain reaction (PCR) assay is available in reference laboratories. Species confirmation and antimalarial drug resistance testing are available free of charge at the CDC for all cases of malaria diagnosed in the United States. A rapid antigen test is available in the United States. Rapid diagnostic testing should be conducted in parallel with routine microscopy to provide further information needed for patient treatment, such as the percentage of erythrocytes harboring parasites. Both positive and negative rapid diagnostic test results should be confirmed by microscopic examination, because low-level parasitemia may not be detected (ie, false-negative result), false-positive results occur, and mixed infections may not be detected accurately. Information about the sensitivity of rapid diagnostic tests for the 2 less common species of malaria, *P ovale* and *P malariae*, is limited. Additional information is available at **www.cdc.gov/malaria/diagnosis_treatment/index.html**.

TREATMENT

The choice of malaria chemotherapy is based on the infecting species, possible drug resistance, and severity of disease. Severe malaria (largely a consideration for *P falciparum* infections) is defined as any one or more of the following: parasitemia greater than 5% of red blood cells infected, signs of central nervous system or other end-organ involvement, shock, acidosis, thrombocytopenia, and/or hypoglycemia. Patients with severe malaria require intensive care and parenteral treatment with intravenous quinidine until the parasite density decreases to less than 1% and patients can tolerate oral therapy. If quinidine is not available, intravenous artesunate should be administered. Concurrent treatment with tetracycline, doxycycline, or clindamycin should begin orally or intravenously if oral treatment is not tolerated. A recent review of available literature suggests exchange transfusion for severe disease is not efficacious in patients with end-organ involvement.

For patients with *P falciparum* malaria, sequential blood smears to determine percentage of erythrocytes infected with parasites are monitored to assess therapeutic efficacy. Assistance with management of malaria is available 24 hours a day through the CDC Malaria Hotline (770-488-7788). Guidelines for the treatment of malaria are available on the CDC website (**www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf**).

Image 83.1
The edema exhibited by this African child was brought on by nephrosis associated with malaria. Infection with one type of malaria, *Plasmodium falciparum*, if not promptly treated, may cause kidney failure. Swelling of the abdomen, eyes, feet, and hands are some of the symptoms of nephrosis brought on by the damaged kidneys. Courtesy of Centers for Disease Control and Prevention.

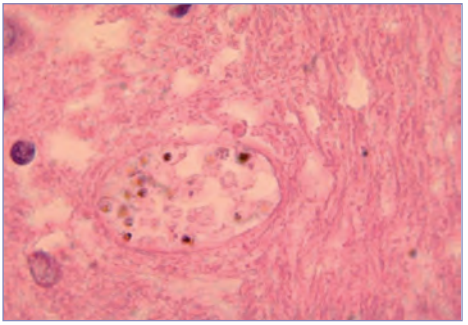


Image 83.2
Histopathology of malaria of the brain. Mature schizonts. Courtesy of Centers for Disease Control and Prevention.

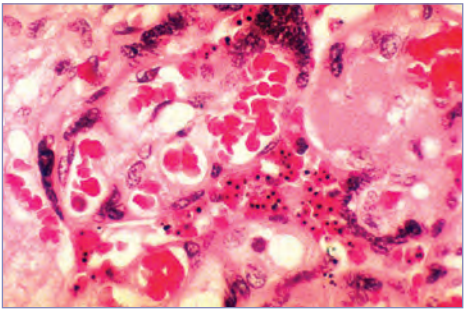


Image 83.3
A photomicrograph of placental tissue revealing the presence of the malarial parasite *Plasmodium falciparum*. Maternal or placental malaria predisposes the newborn to a low birth weight, preterm delivery, and increased mortality, and the mother to maternal anemia. Courtesy of Centers for Disease Control and Prevention.

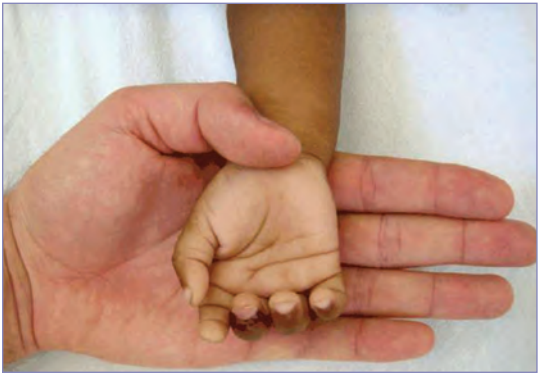


Image 83.4
Severe *Plasmodium vivax* malaria, Brazilian Amazon. Hand of a 2-year-old with severe anemia (hemoglobin level 3.6 g/dL) and showing intense pallor, compared with the hand of a healthy physician. Courtesy of *Emerging Infectious Diseases*.

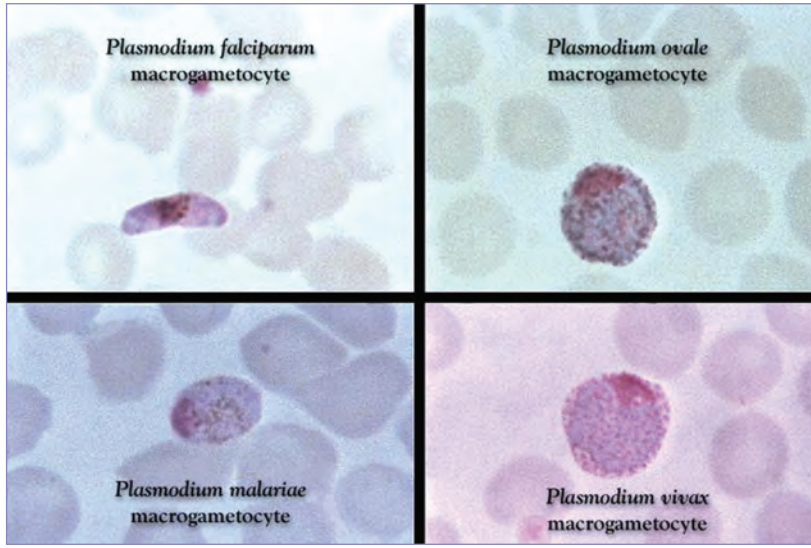


Image 83.5
This Giemsa-stained slide reveals a *Plasmodium falciparum*, *Plasmodium ovale*, *Plasmodium malariae*, and *Plasmodium vivax* gametocyte. The male (microgametocytes) and female (macrogametocytes) are ingested by an *Anopheles* mosquito during its blood meal. Known as the sporogonic cycle, while in the mosquito's stomach, the microgametes penetrate the macrogametes, generating zygotes. Courtesy of Centers for Disease Control and Prevention.

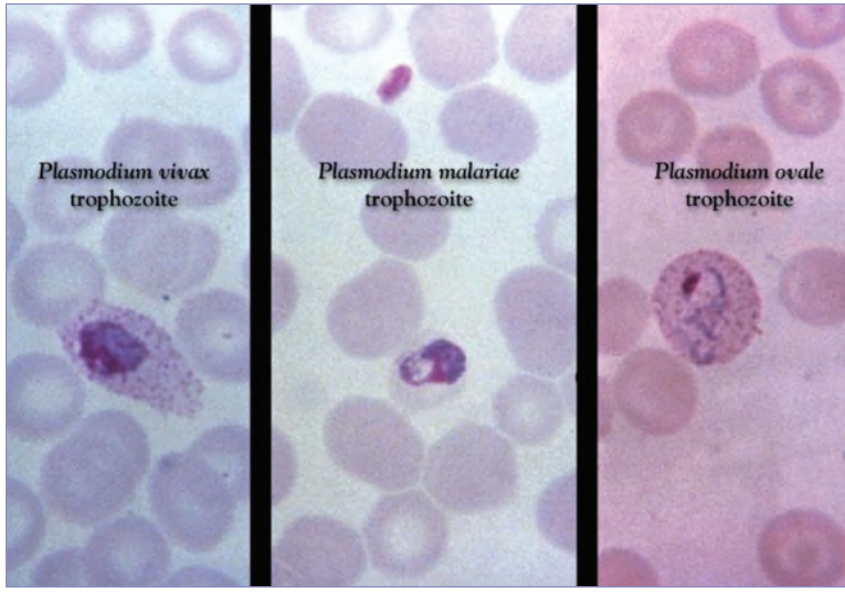


Image 83.6
This thin-film Giemsa-stained micrograph reveals growing *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale* trophozoites. As the parasite increases in size, the ring morphology of the early trophozoite disappears and becomes what is referred to as a *mature trophozoite,* which undergoes further transformation, maturing into a schizont. Courtesy of Centers for Disease Control and Prevention.

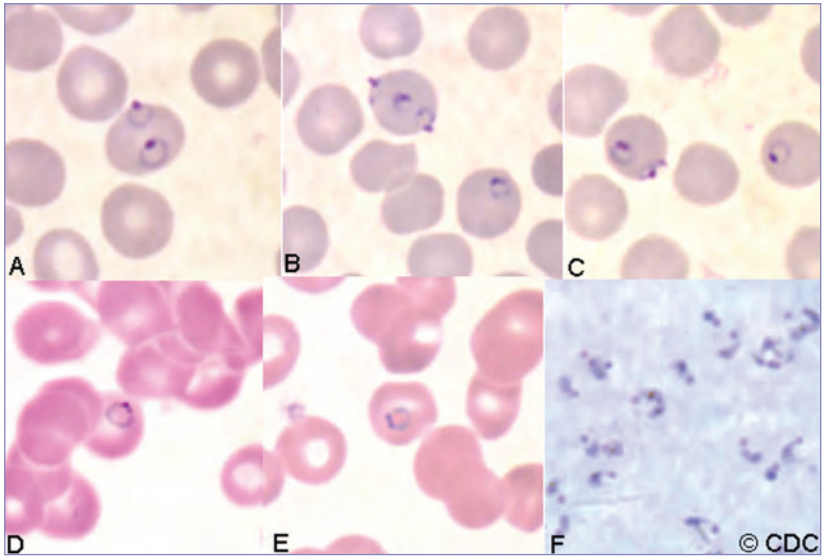


Image 83.7
Plasmodium falciparum ring-stage smears from patients. *P falciparum* rings have delicate cytoplasm and 1 or 2 small chromatin dots. Red blood cells (RBCs) that are infected are not enlarged; multiple infection of RBCs is more common in *P falciparum* than in other species. Occasional appliqué forms (rings appearing on the periphery of the RBC) can be present. A–C, Multiply infected RBCs with appliqué forms in thin blood smears. D, Signet ring form. E, Double chromatin dot. F, A thick blood smear showing many ring forms of *P falciparum*. Courtesy of Centers for Disease Control and Prevention.

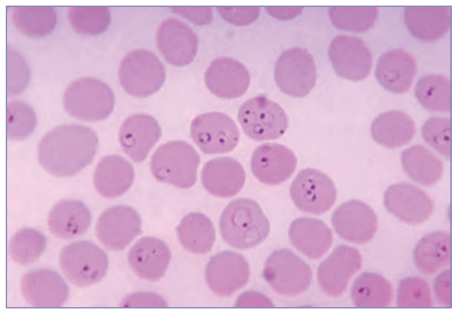


Image 83.8
Photomicrograph of a blood smear showing *Plasmodium falciparum* rings in erythrocytes. The term *ring* is derived from the morphological appearance of this stage, which includes chromatin (red) and cytoplasm (blue), often arranged in a ring shape around a central vacuole; biologically, the ring is a young trophozoite. Courtesy of Centers for Disease Control and Prevention.

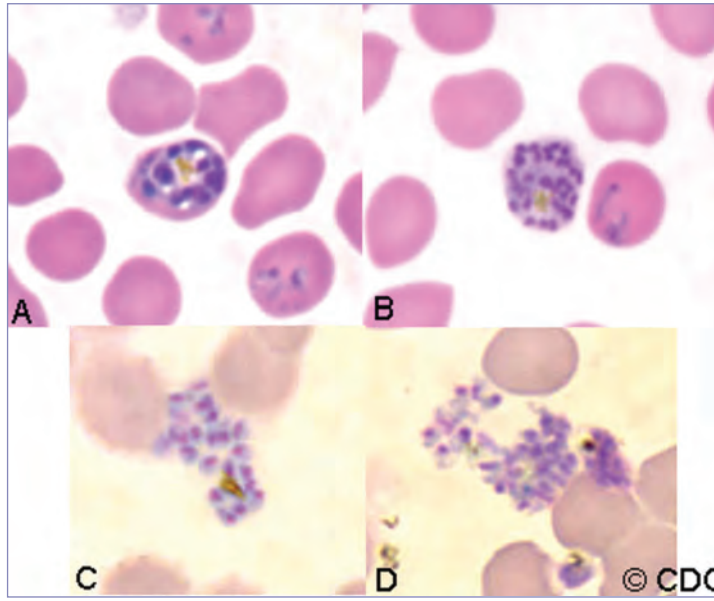


Image 83.9
Plasmodium falciparum schizont smears from patients. Schizonts are seldom seen in peripheral blood. Mature schizonts have 8 to 24 small merozoites with dark pigment and are clumped in one mass. A, Immature schizont in a thin blood smear. B, Mature schizont. C–D, Ruptured schizonts in a thin blood smear. Courtesy of Centers for Disease Control and Prevention.

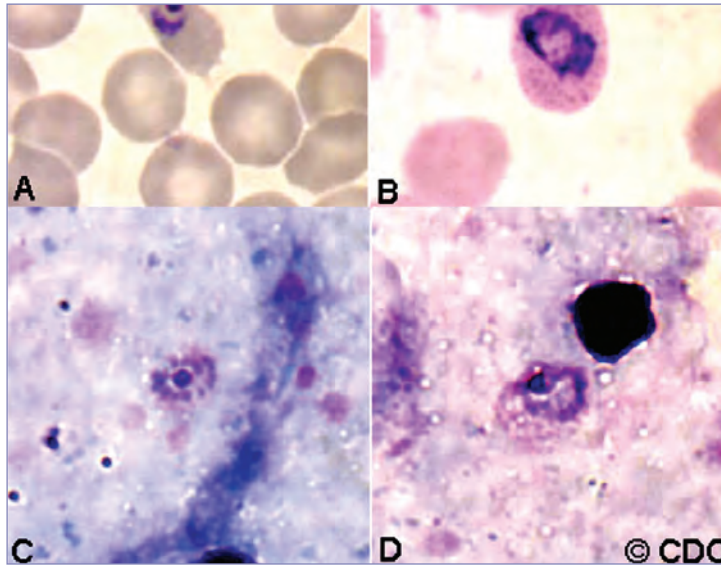


Image 83.10
Plasmodium ovale ring-stage parasites (smears from patients). *P ovale* rings have sturdy cytoplasm and large chromatin dots. Red blood cells (RBCs) are normal to slightly enlarged (×1.25), may be round to oval, and are sometimes fimbriated. Schüffner dots are visible under optimal conditions. A–B, *P ovale* rings in thin blood smears. A, Fimbriation of the infected RBC. B, Schüffner dots. C–D, Rings of *P ovale* in thick blood smears. Courtesy of Centers for Disease Control and Prevention.

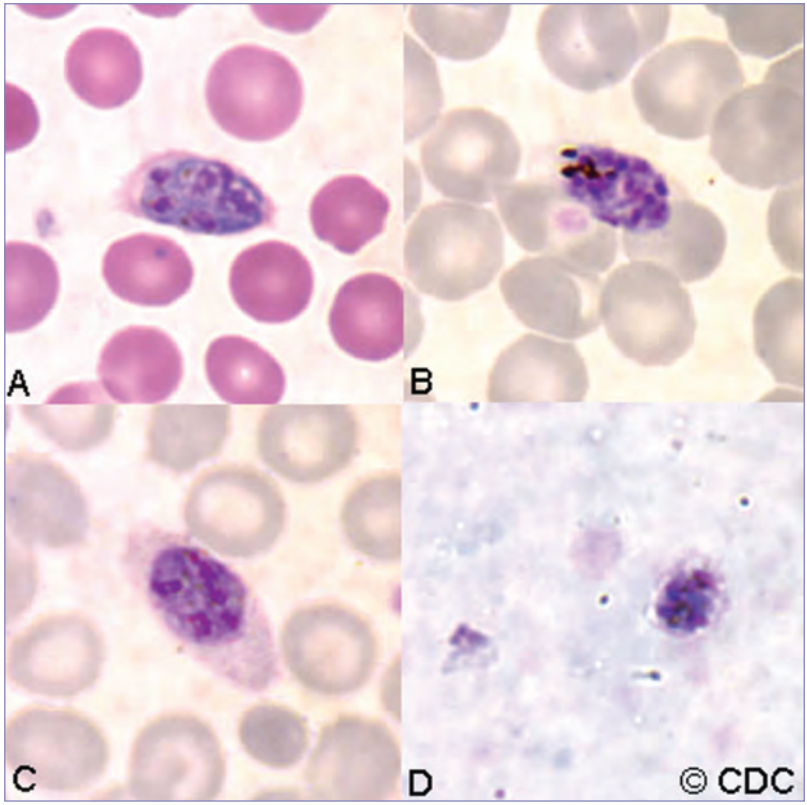


Image 83.11
Plasmodium ovale schizonts (smears from patients). *P ovale* schizonts have 6 to 14 merozoites with large nuclei, clustered around a mass of dark-brown pigment. Red blood cells are normal to slightly enlarged (×1.25), may be round to oval, and are sometimes fimbriated. Schüffner dots are visible under optimal conditions. A–C, Schizonts of *P ovale* in thin blood smears. All of these infected blood cells are oval. A and C, Minor fimbriation. D, Schizont in a thick blood smear. Courtesy of Centers for Disease Control and Prevention.

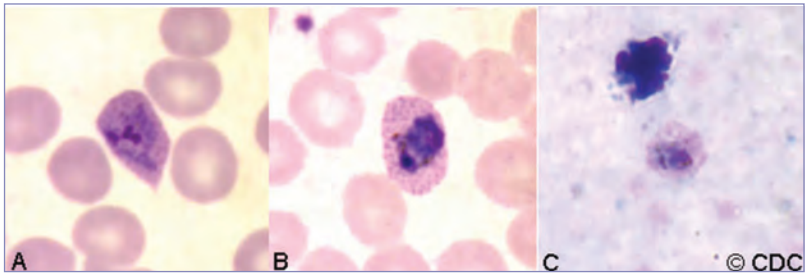


Image 83.12
Plasmodium ovale trophozoites (smears from patients). *P ovale* trophozoites have sturdy cytoplasm and large chromatin dots and can be compact to slightly amoeboid. Red blood cells are normal to slightly enlarged (×1.25), may be round to oval, and are sometimes fimbriated. Schüffner dots are visible under optimal conditions. A–B, Trophozoites of *P ovale* in thin blood smears. A, Slightly amoeboid. B, A more compact trophozoite and Schüffner dots. C, Trophozoite in a thick blood smear. Courtesy of Centers for Disease Control and Prevention.

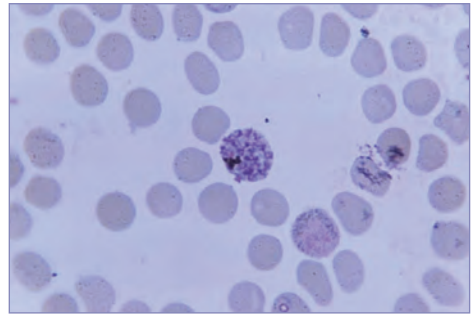


Image 83.13
This photomicrograph of a simian blood sample reveals the presence of a mature simian malarial schizont and gametocyte (magnification ×1,125). Courtesy of Centers for Disease Control and Prevention/W. A. Rogers Jr, MD.

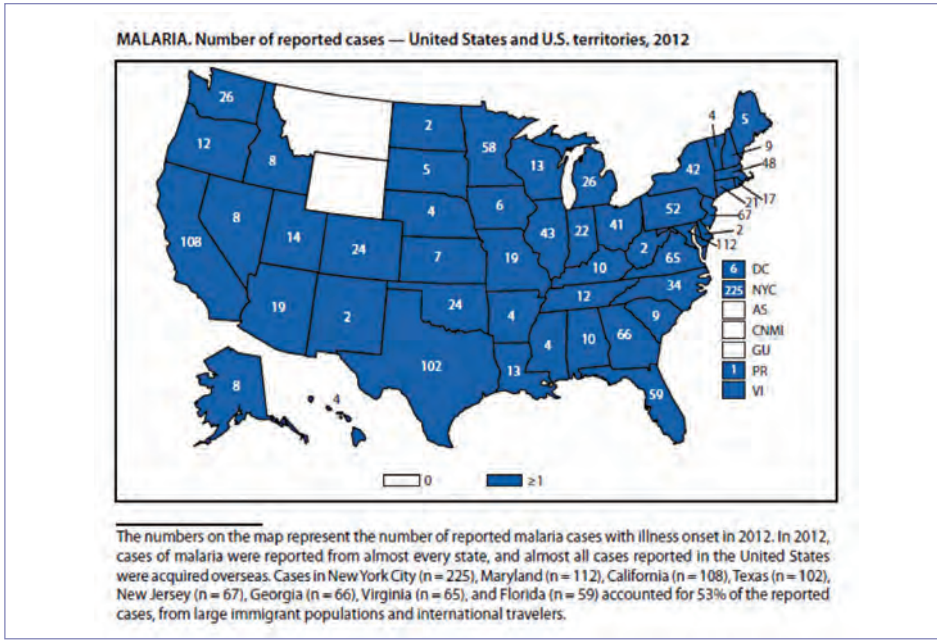


Image 83.14
Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

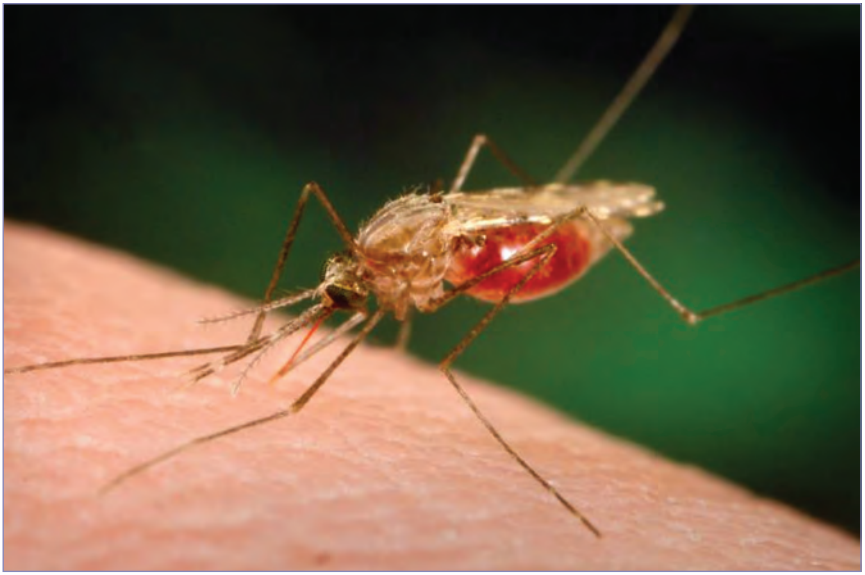


Image 83.15
This photograph depicts an *Anopheles funestus* mosquito partaking in a blood meal from its human host. Note the blood passing through the proboscis, which has penetrated the skin and entered a miniscule cutaneous blood vessel. The *A funestus* mosquito, along with *Anopheles gambiae,* is 1 of the 2 most important malaria vectors in Africa, where more than 80% of the world's malarial disease and deaths occurs. Courtesy of Centers for Disease Control and Prevention.

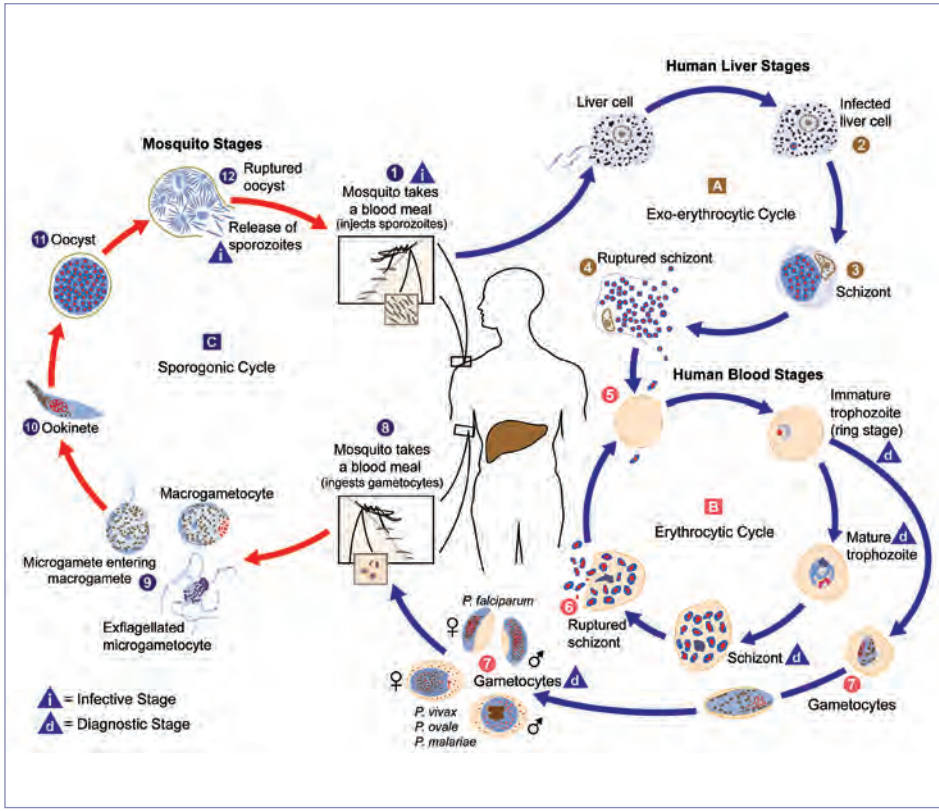


Image 83.16

The malaria parasite life cycle involves 2 hosts. During a blood meal, a malaria-infected female *Anopheles* species mosquito inoculates sporozoites into the human host (1). Sporozoites infect liver cells (2) and mature into schizonts (3), which rupture and release merozoites (4). (Of note, in *Plasmodium vivax* and *Plasmodium ovale* a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years, later.) After this initial replication in the liver (exoerythrocytic schizogony) (A), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony) (B). Merozoites infect red blood cells (5). The ring-stage trophozoites mature into schizonts, which rupture, releasing merozoites (6). Some parasites differentiate into sexual erythrocytic stages (gametocytes) (7). Blood stage parasites are responsible for the clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* species mosquito during a blood meal (8). The parasite multiplication in the mosquito is known as the *sporogonic cycle* (C). While in the mosquito's stomach, the microgametes penetrate the macrogametes, generating zygotes (9). The zygotes, in turn, become motile and elongated (ookinetes) (10) and invade the midgut wall of the mosquito, where they develop into oocysts (11). The oocysts grow, rupture, and release sporozoites (12), which make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle (1). Courtesy of Centers for Disease Control and Prevention.

CHAPTER 84

Measles

CLINICAL MANIFESTATIONS

Measles is an acute viral disease characterized by fever, cough, coryza, and conjunctivitis, followed by a maculopapular rash beginning on the face and spreading cephalocaudally and centrifugally. During the prodromal period, a pathognomonic enanthem (Koplik spots) may be present. Complications of measles, including otitis media, bronchopneumonia, laryngotracheobronchitis (croup), and diarrhea, occur commonly in young children and immunocompromised hosts. Acute encephalitis, which often results in permanent brain damage, occurs in approximately 1 of every 1,000 cases. In the post-elimination era, death, predominantly resulting from respiratory and neurologic complications, has occurred in 1 to 3 of every 1,000 cases reported in the United States. Case-fatality rates are increased in children younger than 5 years, pregnant women, and immunocompromised children, including children with leukemia, human immunodeficiency virus (HIV) infection, and severe malnutrition (including vitamin A deficiency). Sometimes the characteristic rash does not develop in immunocompromised patients. Individuals with incomplete immunity from immunization with inactivated measles vaccine may have an atypical presentation with some but not all symptoms following exposure to wild-type measles.

Subacute sclerosing panencephalitis (SSPE) is a rare degenerative central nervous system disease characterized by behavioral and intellectual deterioration and seizures that occurs 7 to 11 years after wild-type measles virus infection, occurring at a rate of 4 to 11 per 100,000 measles cases, with higher rates if measles occurs before 2 years of age. Widespread measles immunization has led to the virtual disappearance of SSPE in the United States.

ETIOLOGY

Measles virus is an enveloped RNA virus with 1 serotype, classified as a member of the genus *Morbillivirus* in the *Paramyxoviridae* family.

EPIDEMIOLOGY

The only natural host of measles virus is humans. Measles is transmitted by direct contact with infectious droplets or, less commonly, by airborne spread. Measles is one of the most highly communicable of all infectious diseases; the attack rate in a susceptible individual exposed to measles is 90%. Population immunity of greater than 95% is needed to stop ongoing transmission. In temperate areas, the peak incidence of infection usually occurs during late winter and spring. In the prevaccine era, most cases of measles in the United States occurred in preschool- and young school-aged children, and few people remained susceptible by 20 years of age. Following implementation of routine childhood vaccination in the United States at age 12 to 15 months, the age of peak measles incidence during epidemics in the United States shifted to 6 to 12 months. This susceptibility approximates the time at which transplacentally acquired maternal antibodies no longer are present if the mother has vaccine-induced immunity. The childhood and adolescent immunization program in the United States began with licensure of the measles vaccine in 1963 and has resulted in a greater than 99% decrease in the reported incidence of measles, with interruption of endemic disease transmission being declared in 2000.

From 1989 to 1991, the incidence of measles in the United States increased because of low immunization rates in preschool-aged children, especially in urban areas, and because of primary vaccine failures after one measles vaccine dose. Following improved coverage in preschool-aged children and implementation of a routine second dose of measles-mumps-rubella (MMR) vaccine for children, the incidence of measles declined to extremely low levels (<1 case per 1 million population). In 2000, an independent panel of internationally recognized experts reviewed available data and unanimously agreed that measles no longer was endemic (defined as continuous, year-round transmission) in the United States. Compared with earlier post-elimination years (2001–2008), when the annual median number of cases reported was 56 cases/year (range, 37–140), a median

of 130 measles cases were reported annually (range, 55–667) during 2009–2014. In 2011, 2013, and 2014, the numbers of reported cases were 220, 187, and 667, respectively; these larger numbers of cases were attributable to an increase in the number of importations or spread from importations. The median number of measles outbreaks (defined as 3 or more cases linked in time and space) that occurred during 2009–2014 was 10 per year (range, 4–23) and was higher than the annual median number of outbreaks that occurred in earlier post-elimination years. Of the 1,264 cases reported during 2009–2014, 1,204 (95%) were import associated (including 275 [22%] directly imported cases), and 60 (5%) cases were of an unknown source; among 1,173 cases in US residents, 74% were in unvaccinated people, 16% were in people with unknown vaccination status (83% of those were adults), and 10% were in vaccinated people (with ≥1 dose of a measles-containing vaccine). During the same period, among 917 cases in vaccine-eligible US residents, 65% were in people reported as having a philosophical or religious objection to vaccination. In 2015, 188 people from 24 states and the District of Columbia were reported to have measles. This large, multistate measles outbreak was linked to an amusement park in California. The outbreak likely started from a traveler who became infected overseas with measles, then visited the amusement park while infectious; however, no source was identified. In 2016, 86 people from 16 states had measles reported, and in 2017, 120 people from 15 states and the District of Columbia had measles reported.

Progress continues toward global control and regional measles elimination. In 2016, there were 89,780 measles deaths globally, marking the first year measles deaths have fallen below 100,000 per year. Measles vaccination resulted in an 84% drop in measles deaths between 2000 and 2016 worldwide. In 2016, approximately 85% of the world's children received one dose of measles vaccine by their first birthday through routine health services, up from 72% in 2000. During 2000–2016, measles vaccination prevented an estimated 20.4 million deaths. All World Health Organization (WHO) regions have established goals to eliminate measles by 2020.

Inadequate response to vaccine (ie, primary vaccine failure) occurs in as many as 7% of people who have received a single dose of vaccine at 12 months or older. Most cases of measles in previously immunized children seem to be attributable to primary vaccine failures, but waning immunity after immunization (ie, secondary vaccine failure) may be a factor in some cases. Primary vaccine failure was the main reason a 2-dose vaccine schedule was recommended routinely for children and high-risk adults.

Patients infected with wild-type measles virus are contagious from 4 days before the rash through 4 days after appearance of the rash. Immunocompromised patients who may have prolonged excretion of the virus in respiratory tract secretions can be contagious for the duration of the illness. Patients with SSPE are not contagious.

The **incubation period** generally is 8 to 12 days (range, 7 to 21) from exposure to onset of symptoms. In SSPE, the mean incubation period is approximately 11 years.

DIAGNOSTIC TESTS

Measles virus infection can be confirmed by: (1) detection of measles viral RNA by reverse transcriptase-polymerase chain reaction (RT-PCR); (2) detection of measles-specific immunoglobulin (Ig) M; (3) a fourfold increase in measles IgG antibody concentration in paired acute and convalescent serum specimens (collected at least 10 days apart); or (4) isolation of measles virus in cell culture. Detection of IgM in serum samples by enzyme immunoassay has been the preferred method for case confirmation; however, as the incidence of disease decreases, the positive predictive value of IgM detection also decreases. For this reason, detection of viral RNA in blood; throat, nasal, and posterior nasopharyngeal swab specimens; bronchial lavage samples; or urine samples (respiratory samples are preferred specimens) is playing an increasing role in case confirmation, especially in countries that have achieved measles elimination. A serum sample as well as a throat swab specimen should be obtained from any patient in whom measles infection is suspected. Additionally, it is ideal to obtain a urine sample, because

sampling from all 3 sites will increase the likelihood of establishing a diagnosis. State public health laboratories and the Measles Laboratory at the Centers for Disease Control and Prevention (CDC) can perform RT-PCR assays to detect measles RNA. Isolation of measles virus in cell culture is not recommended for routine case confirmation.

The sensitivity of measles IgM assays varies by timing of specimen collection, immunization status of the patient, and the assay method itself. Up to 20% of assays for IgM may have a false-negative result in the first 72 hours after rash onset. If the measles IgM result is negative and the patient has a generalized rash lasting more than 72 hours, a second serum specimen should be obtained. Measles IgM is detectable for at least 1 month after rash onset in unimmunized people but might be absent or present only transiently in people immunized with 1 or 2 vaccine doses.

Detection of viral RNA by RT-PCR provides a relatively rapid and sensitive method for case confirmation. It is important to collect samples for RNA detection as soon as possible after rash onset, because viral shedding declines with time after rash. In populations with high vaccine coverage, such as those in the United States, comprehensive serologic and virologic testing generally is not available locally and requires submitting specimens to state public health laboratories or the CDC. Individuals with a febrile rash illness who are seronegative for measles IgM and have negative RT-PCR assay results for measles should be tested for rubella using the same specimens.

TREATMENT

No specific antiviral therapy is available. Vitamin A treatment of children with measles in resource-limited countries has been associated with decreased morbidity and mortality rates. Low serum concentrations of vitamin A also have been found in children in the United States, and children with more severe measles illness have lower vitamin A concentrations. The WHO currently recommends vitamin A for all children with acute measles. Even in countries where measles is not usually severe, vitamin A should be given to all children with severe measles (eg, requiring hospitalization). Parenteral and oral formulations of vitamin A are available in the United States.

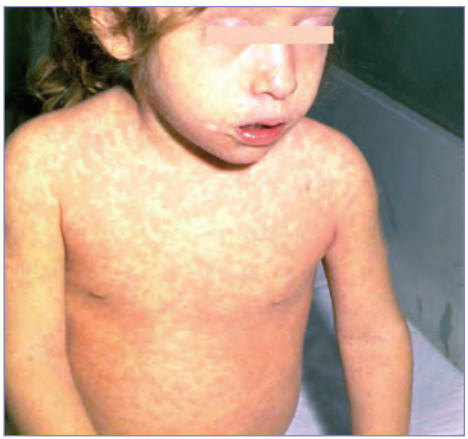


Image 84.1
Child with measles who exhibited an appearance of feeling miserable.

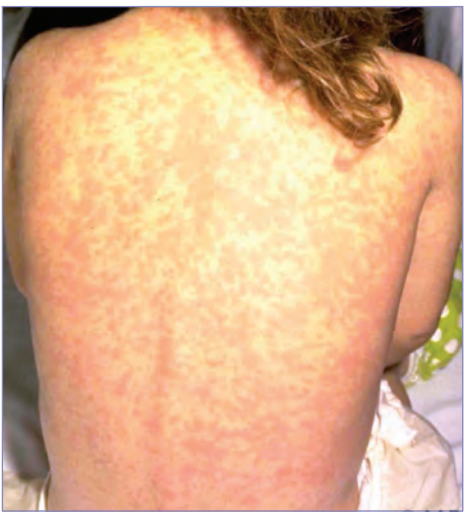


Image 84.2
Measles. This is the same patient as in Image 84.1.

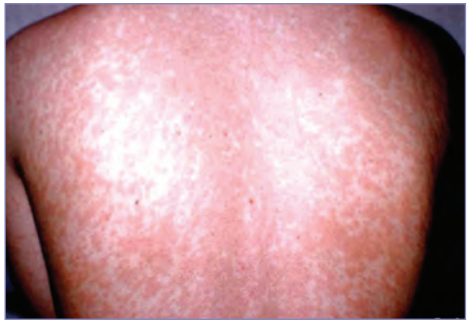


Image 84.3
Characteristic confluent measles rash over the back of this child.

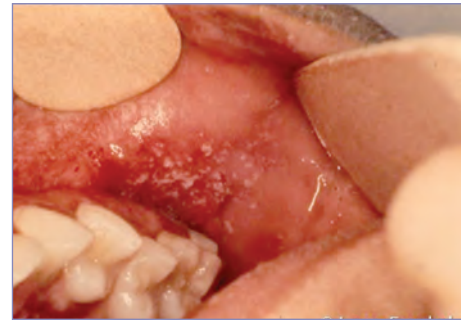


Image 84.4
Koplik spots of measles in a 7-year-old boy. Courtesy of Larry Frenkel, MD.

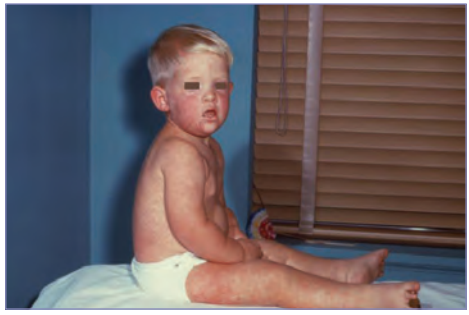


Image 84.5
This child with measles is displaying the characteristic red, blotchy pattern on his face and body during the third day of the rash. Courtesy of Centers for Disease Control and Prevention.

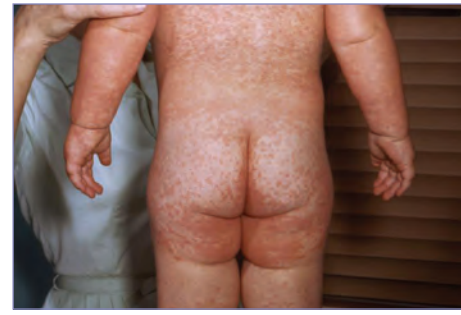


Image 84.6
This child with measles is showing the characteristic red, blotchy rash on his buttocks and back during the third day of the rash. Measles is an acute, highly communicable viral disease with prodromal fever, conjunctivitis, coryza, cough, and Koplik spots on the buccal mucosa. A red, blotchy rash appears around day 3 of the illness, first on the face and then becoming generalized. Courtesy of Centers for Disease Control and Prevention.

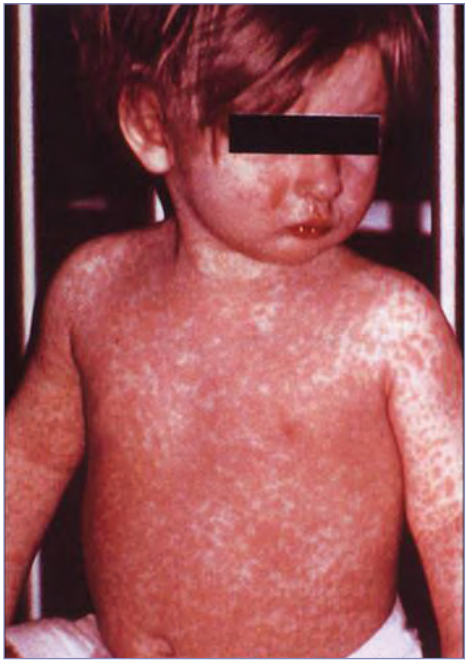


Image 84.7
A 2-year-old boy with the confluent rash of measles. Courtesy of Larry Frenkel, MD.

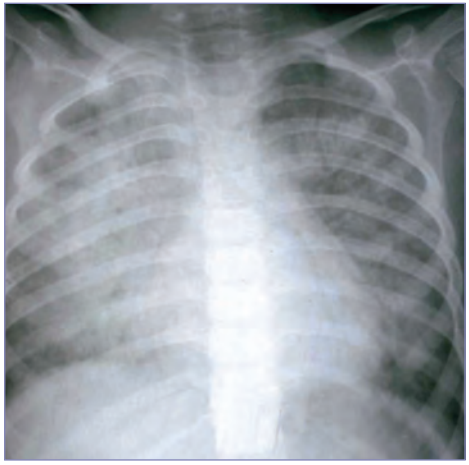


Image 84.9
Measles pneumonia in a 6-year-old with acute lymphoblastic leukemia. The child died of respiratory failure.

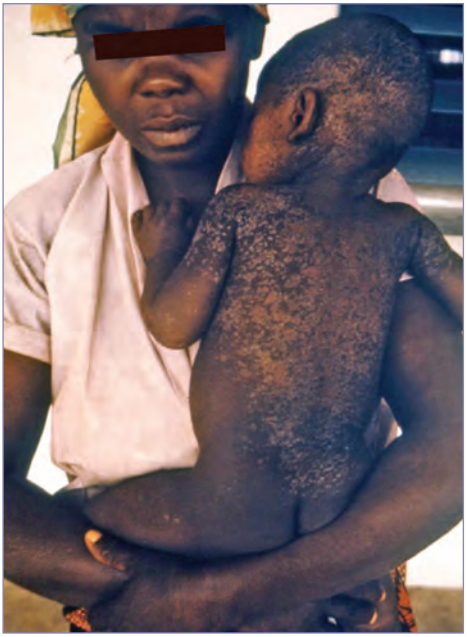


Image 84.8
This photograph shows a Nigerian mother and her child, who was recovering from measles. Note that the skin is sloughing on the child as he heals from his measles infection. Sloughing of the skin in recovering patients is often extensive and resembles that of a burn victim. Due to their weakened state, children like the one shown here need nursing care to avoid subsequent infections. Courtesy of Centers for Disease Control and Prevention.

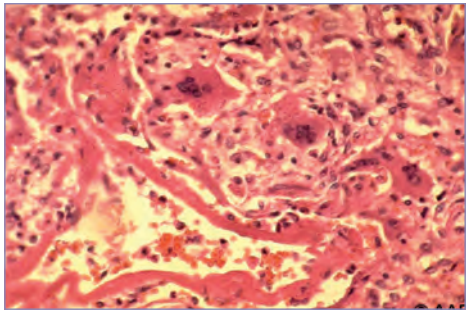


Image 84.10
Measles pneumonia with interstitial mononuclear cell infiltration, multinucleated giant cells, and hyaline membranes (hematoxylin-eosin stain, original magnification ×250). This is the same patient as in Image 84.9.

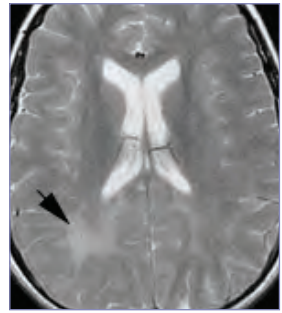


Image 84.11
This axial T2-weighted magnetic resonance image demonstrates an asymmetrical right peri-trigonal focus of white matter hyperintensity consistent with early demyelination in a patient with measles encephalitis.

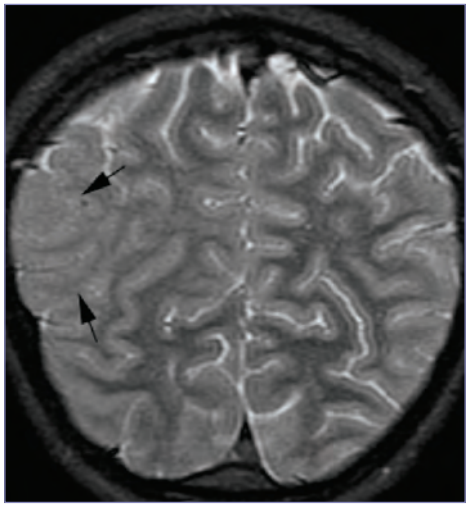


Image 84.12
This coronal T2-weighted magnetic resonance image shows swelling and hyperintensity of the right parietal occipital cortex (arrows) in a patient with measles encephalitis.

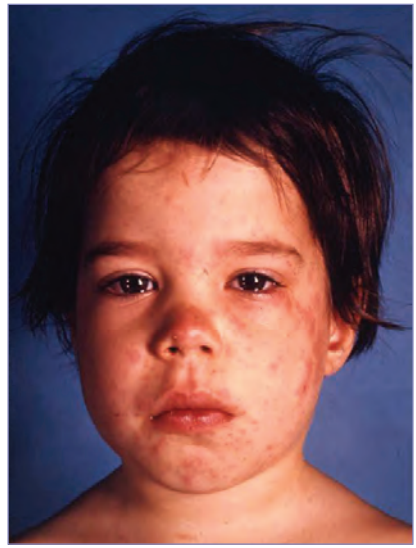


Image 84.13
A 6-year-old girl with the early facial rash and conjunctivitis of measles. Courtesy of Larry Frenkel, MD.

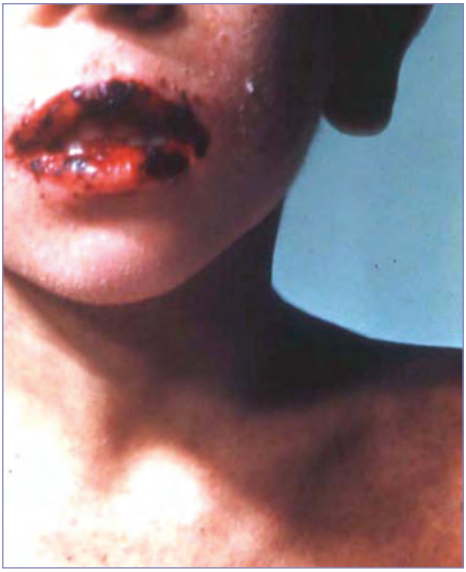


Image 84.14
Hemorrhagic measles (black measles). Although uncommon, hemorrhagic measles may result in bleeding from the mouth, nose, and gastrointestinal tract. Courtesy of Edgar O. Ledbetter, MD, FAAP.

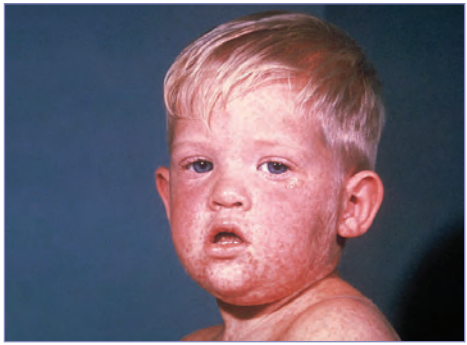


Image 84.15
The face of a boy with measles on the third day of the rash. Courtesy of Centers for Disease Control and Prevention.

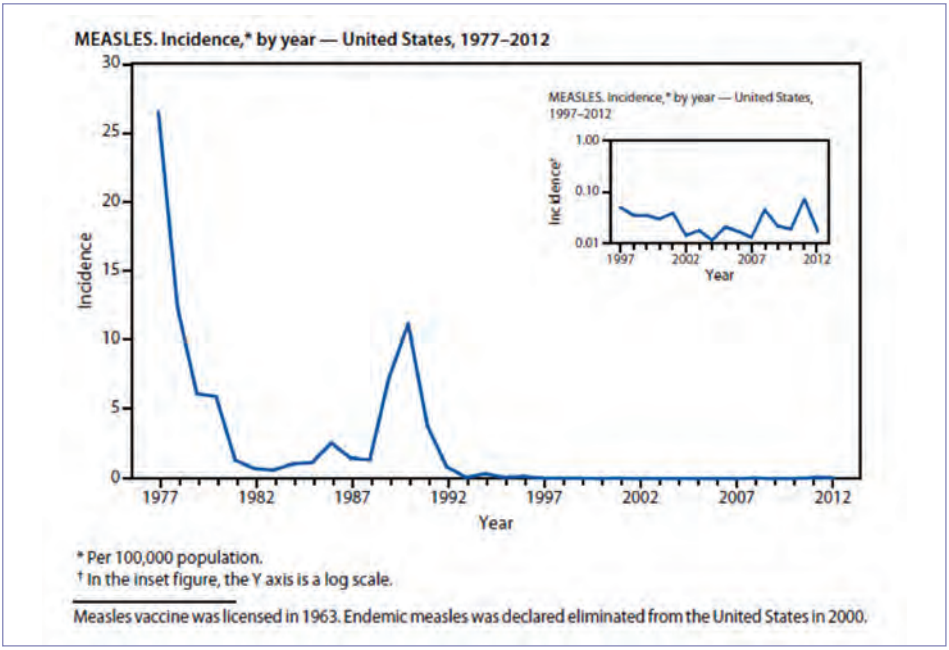


Image 84.16
Measles. Incidence, by year—United States, 1977–2012. *Courtesy of Morbidity and Mortality Weekly Report.*

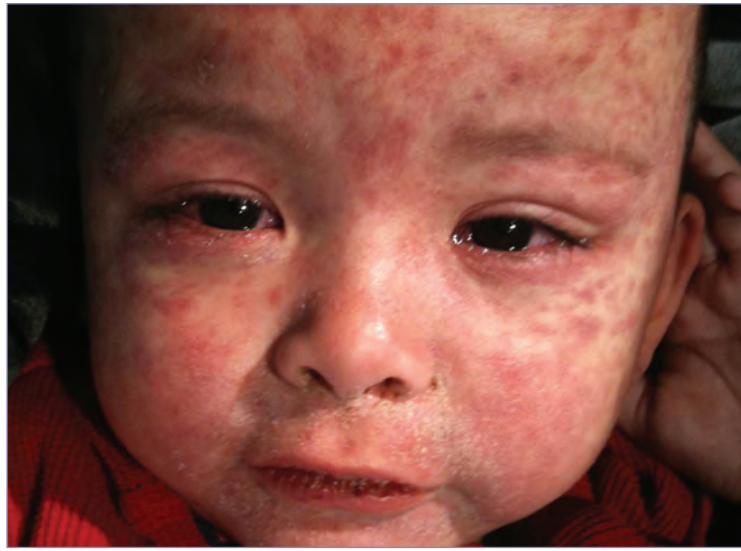


Image 84.17
This unvaccinated 11-month-old acquired measles while traveling to the Philippines to visit relatives. Note the bilateral conjunctivitis, crusting rhinorrhea, and morbilliform rash; he also had a prominent staccato cough. Courtesy of Carol J. Baker, MD.

CHAPTER 85

Meningococcal Infections

CLINICAL MANIFESTATIONS

Invasive infection usually results in septicemia (~35%–40% of cases), meningitis (~50% of cases), or both. Bacteremic pneumonia is less common (~9% of cases). Rarely, young children have occult bacteremia. Onset of invasive infections can be insidious and nonspecific, but onset of septicemia (meningococcemia) typically is abrupt, with fever, chills, malaise, myalgia, limb pain, prostration, and a rash that initially can be macular or maculopapular but typically becomes petechial or purpuric within hours. A similar rash can occur with viral infections or with severe sepsis attributable to other bacterial pathogens. In fulminant cases, purpura, limb ischemia, coagulopathy, pulmonary edema, shock, coma, and death can ensue within hours despite appropriate management. Signs and symptoms of meningococcal meningitis are indistinguishable from those associated with pneumococcal meningitis. In severe and fatal cases of meningococcal meningitis, raised intracranial pressure is a predominant presenting feature. Invasive infections can be complicated by arthritis, myocarditis, pericarditis, and endophthalmitis. The overall case-fatality rate for meningococcal disease is ~15% and is somewhat higher in late adolescence and in adults. Mortality is higher with infection caused by serogroup C and Y strains than serogroup B strains. Risk factors for mortality include coma, hypotension, leukopenia, thrombocytopenia, and absence of meningitis. Less common manifestations of meningococcal infection include conjunctivitis, septic arthritis, and chronic meningococcemia. A self-limiting postinfectious inflammatory syndrome occurs in fewer than 10% of cases, begins a minimum 4 days after onset of meningococcal infection, and most commonly presents as fever and arthritis or vasculitis with less common manifestations including iritis, scleritis, conjunctivitis, pericarditis, and polyserositis.

Sequelae associated with meningococcal disease occur in up to 19% of survivors and include hearing loss, neurologic disability, digit or limb amputations, and skin scarring. In addition, patients may experience subtle long-term neurologic deficits, such as impaired school performance, behavioral problems, and attention-deficit/hyperactivity disorder.

ETIOLOGY

Neisseria meningitidis is a gram-negative diplococcus with 13 serogroups based on capsular type.

EPIDEMIOLOGY

In the United States, *N meningitidis* is the leading cause of bacterial meningitis in children 11 through 17 years of age and remains an important cause of septicemia. *N meningitidis* disease rates are highest in infants, adolescents, young adults 16 through 21 years of age, and adults older than 65 years. Household contacts of cases have 500 to 800 times the rate of disease for the general population. A predominance of US cases is observed in the winter, often noted 2 to 3 weeks following onset of influenza season, with peak of cases in January, February, and March. Patients with persistent complement component deficiencies (eg, C3, C5–C9, properdin, or factor D or factor H deficiencies), with anatomic or functional asplenia, or treated with eculizumab are at increased risk of invasive and recurrent meningococcal disease. Asymptomatic colonization of the upper respiratory tract is most common in older adolescents and young adults and is the reservoir from which the organism is spread. Transmission occurs from person to person through droplets from the respiratory tract and requires close contact. Patients should be considered capable of transmitting the organism for up to 24 hours after initiation of effective antimicrobial treatment.

Distribution of meningococcal serogroups in the United States has shifted in the past 2 decades. Serogroups B, C, and Y each account for approximately 30% of reported cases, but serogroup distribution varies by age, location, and time. Approximately 90% of cases among adolescents and adults are caused by serogroups B, C, Y, or W and, therefore, potentially are preventable with available vaccines. In infants and children younger than 60 months, approximately two-thirds of cases are caused by serogroup B.

During the past 60 years, the annual incidence of meningococcal disease in the United States has varied from ≤0.3 to 1.5 cases per 100,000 population. Since the early 2000s, annual incidence rates have decreased, and during 2012 to 2014, rates were at a historic low, with fewer than 600 cases annually in the United States; 375 cases were reported in 2015. The decrease in cases in the United States started before the 2005 introduction of meningococcal vaccine into the routine immunization schedule and the 2011 recommendation for a booster vaccine for age 16 years. Reasons for this decrease are postulated to be related to the increased use of influenza vaccine, reduction in the carriage rates, the use of meningococcal conjugate vaccines in preadolescents and adolescents, immunity of the population to circulating meningococcal strains unrelated to vaccination, and changes in behavioral risk factors (eg, decreases in smoking and exposure to secondhand smoke among adolescents and young adults).

Strains belonging to groups A, B, C, Y, and W are implicated most commonly in invasive disease worldwide. Serogroup A has been associated frequently with epidemics outside the United States, primarily in sub-Saharan Africa. A serogroup A meningococcal conjugate vaccine was introduced in the "meningitis belt" of sub-Saharan Africa in December 2010, and its widespread use has been associated with a marked reduction in serogroup A disease rates; recent outbreaks in the meningitis belt have been associated with serogroups C, W, and most recently, the rarely reported serogroup X. In Europe, Australia, and South America, the incidence of meningococcal disease ranged from 0.3 to 3 cases per 100,000 population in recent years. Serogroups B and C are the most commonly reported in these regions, although increased rates of serogroups W and Y have been observed in some countries.

Most cases of meningococcal disease are sporadic, with fewer than 5% associated with outbreaks. Outbreaks occur in communities and institutions, including child care centers, schools, colleges, and military recruit camps. More recently, several outbreaks of serogroup B meningococcal disease have occurred on college campuses, and clusters/outbreaks of serogroup C meningococcal disease have been reported among men who have sex with men.

The **incubation period** is 1 to 10 days, typically less than 4 days.

DIAGNOSTIC TESTS

Cultures of blood and cerebrospinal fluid (CSF) are indicated for patients with suspected invasive meningococcal disease. Cultures of a petechial or purpuric lesion scraping, synovial fluid, and other usually sterile body fluid specimens sometimes are positive. Specimens for culture should be plated onto both sheep blood and chocolate agar and incubated at 35°C to 37°C with 5% carbon dioxide in a moist atmosphere. The organism is readily identified with standard biochemical tests as well as by the newer method of mass spectrometry of bacterial cell components. Isolates should be submitted to a reference laboratory for serogrouping for epidemiologic purposes. A Gram stain of a petechial or purpuric scraping, CSF, and buffy coat smear of blood can be positive. Because *N meningitidis* can be a component of the nasopharyngeal flora, isolation of *N meningitidis* from this site is not helpful diagnostically. A serogroup-specific polymerase chain reaction (PCR) test to detect *N meningitidis* from clinical specimens is used routinely in the United Kingdom and some European countries, where up to 56% of cases are confirmed by PCR testing alone. PCR testing is useful particularly in patients who receive antimicrobial therapy before cultures are obtained. In the United States, PCR-based assays are available in some research and public health laboratories. A multiplex PCR assay has been developed for CSF specimens that appears to have a sensitivity and specificity approaching 100% for detection of serogroups A, B, C, W, and Y.

Surveillance case definitions for invasive meningococcal disease are provided in Table 85.1. Serologic typing, multilocus sequence typing, multilocus enzyme electrophoresis, pulsed-field gel electrophoresis of enzyme-restricted DNA fragments, and whole genome sequencing can

Table 85.1
Surveillance Case Definitions for Invasive Meningococcal Disease

Confirmed case
A clinically compatible case and isolation of *Neisseria meningitidis* from a usually sterile site, for example:

- Blood
- Cerebrospinal fluid (CSF)
- Synovial fluid
- Pleural fluid
- Pericardial fluid
- Isolation from skin scraping of petechial or purpuric lesions

OR

Detection of *N meningitidis*-specific nucleic acid in a specimen obtained from a normally sterile body site (eg, blood or CSF), using a validated polymerase chain reaction (PCR) assay

Probable case
A clinically compatible case with EITHER a positive result of antigen test OR immunohistochemistry of formalin-fixed tissue

Suspect
- A clinically compatible case and gram-negative diplococcic in any sterile fluid, such as CSF, synovial fluid, or scraping from a petechial or purpuric lesion
- Clinical purpura fulminans without a positive culture

be useful epidemiologic tools during a suspected outbreak to detect concordance among invasive strains.

TREATMENT

The priority in management of meningococcal disease is treatment of shock in meningococcemia and of raised intracranial pressure in severe meningitis. Empirical therapy for suspected meningococcal disease should include cefotaxime or ceftriaxone. Once the microbiologic diagnosis is established, definitive treatment with penicillin G, ampicillin, cefotaxime, or ceftriaxone is recommended. Five to 7 days of antimicrobial therapy is adequate. Some experts recommend susceptibility testing before switching to penicillin, although resistance of *N meningitidis* to penicillin is rare in the United States. Additionally, susceptibility testing is not standardized, and the clinical significance of intermediate susceptibility to penicillin is unknown. Ceftriaxone clears nasopharyngeal carriage effectively after 1 dose. For patients with a life-threatening penicillin allergy characterized by anaphylaxis, meropenem or ceftriaxone can be used with caution as the rate of cross-reactivity in penicillin-allergic adults is very low. In meningococcemia, early and rapid fluid resuscitation and early use of inotropic and ventilator support may reduce mortality. The postinfectious inflammatory syndromes associated with meningococcal disease often respond to nonsteroidal anti-inflammatory drugs. Treating physicians should consider evaluating for conditions that increase risk of disease, such as underlying complement component deficiencies.

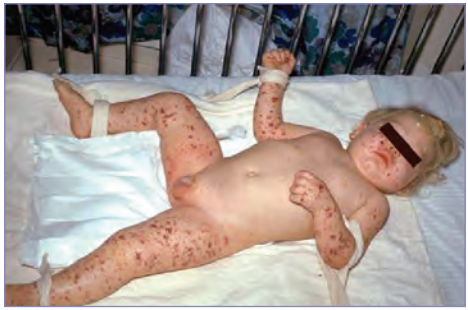


Image 85.1
Young boy with meningococcemia that demonstrates striking involvement of the extremities with sparing of the trunk. Copyright Martin G. Myers.

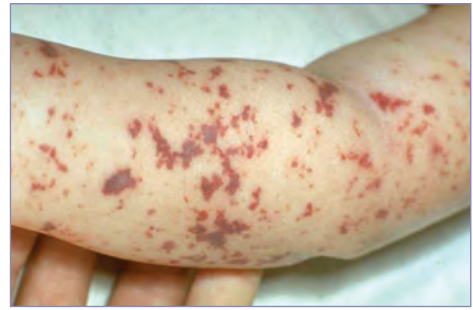


Image 85.2
The arm of the boy shown in Image 85.1, which demonstrates striking extremity involvement and characteristic angular lesions. Copyright Martin G. Myers, MD.

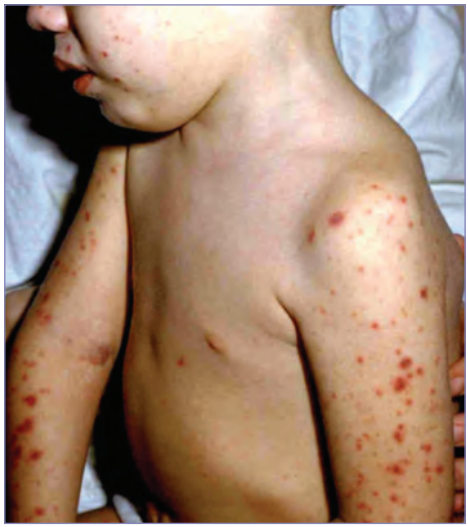


Image 85.3
Meningococcemia showing striking involvement of the extremities with relative sparing of the skin of the child's body surface.

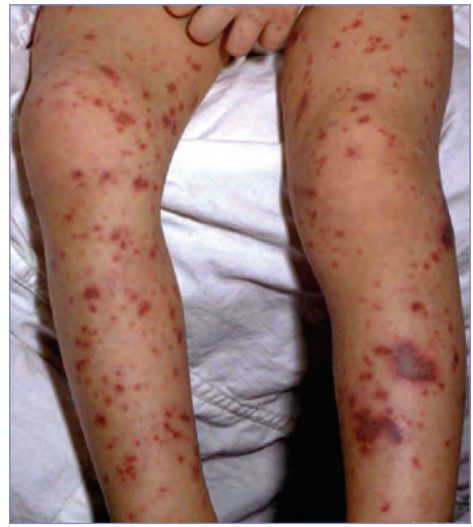


Image 85.4
Meningococcemia. This image shows the lower extremities of the patient in Image 85.3.

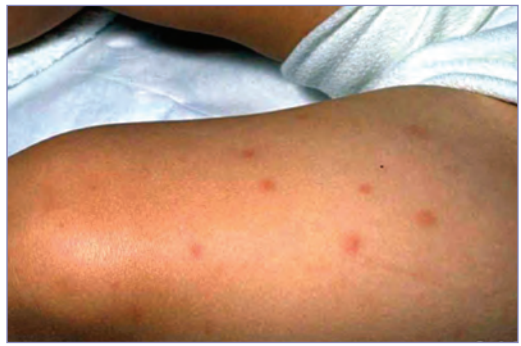


Image 85.5
Papular skin lesions of early meningococcemia.

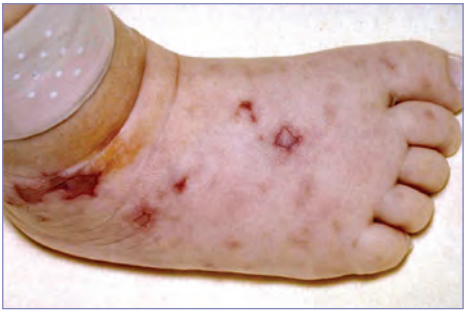


Image 85.6
Characteristic, angular, necrotic lesions on the foot of infant boy with meningococcemia (after 2 days of intravenous penicillin treatment).

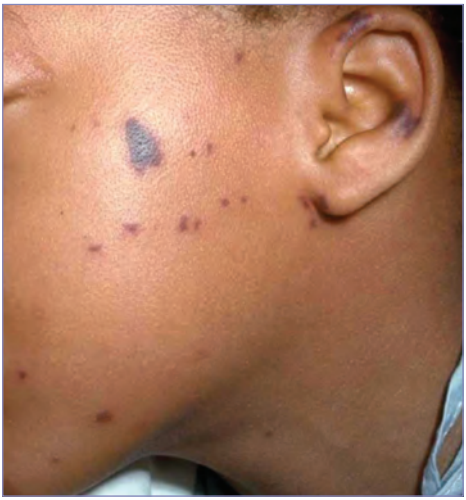


Image 85.8
Meningococcemia in an adolescent girl with disseminated intravascular coagulation.

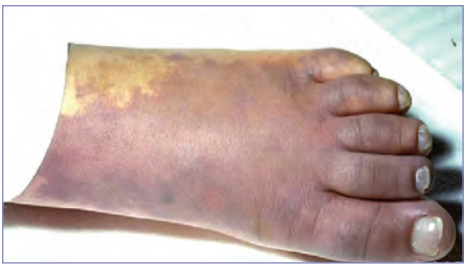


Image 85.10
Patient shown in Images 85.8 and 85.9 with marked purpura of the left foot.

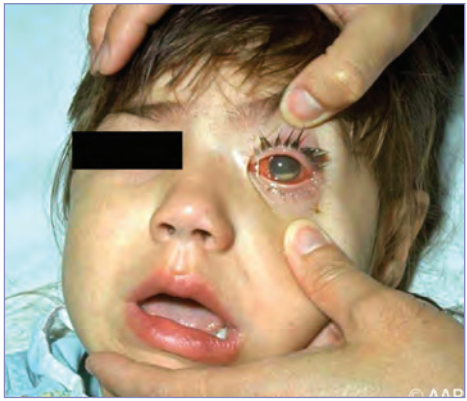


Image 85.7
Preschool-aged girl with meningococcal panophthalmitis. An infant sibling had meningococcal meningitis 1 week prior to the onset of this child's illness.

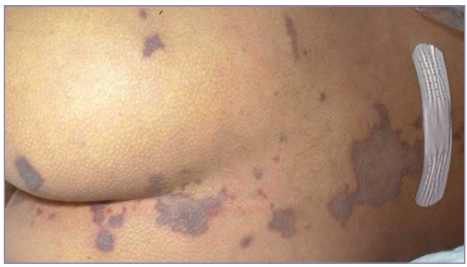


Image 85.9
Meningococcemia in the same patient as in Image 85.8.

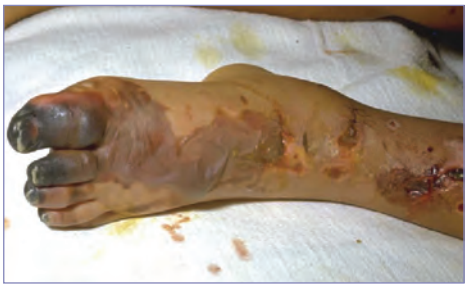


Image 85.11
Patient shown in Images 85.8, 85.9, and 85.10 with gangrene of the toes.

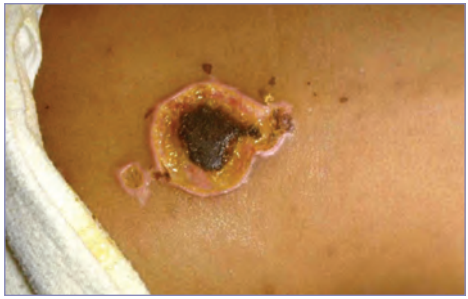


Image 85.12
Patient shown in Images 85.8 through 85.11 with cutaneous necrosis.

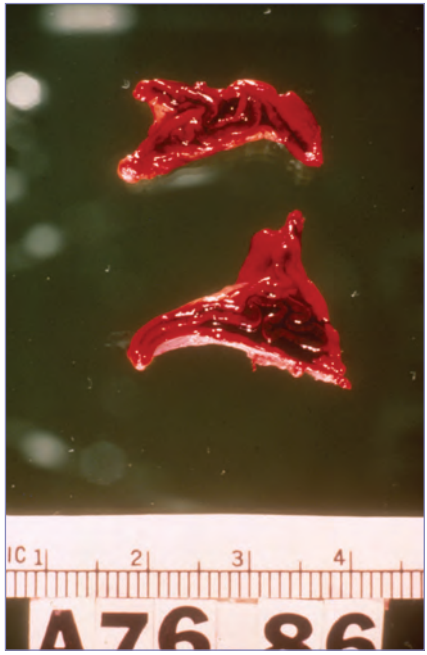


Image 85.14
Hemorrhagic adrenal glands from the 2-year-old child in Image 85.13 who had the characteristic histopathology of Waterhouse-Friderichsen syndrome at autopsy. Courtesy of George Nankervis, MD.

Image 85.13
A 2-year-old boy with acute meningococcemia with septic shock and purpura fulminans. Courtesy of George Nankervis, MD.

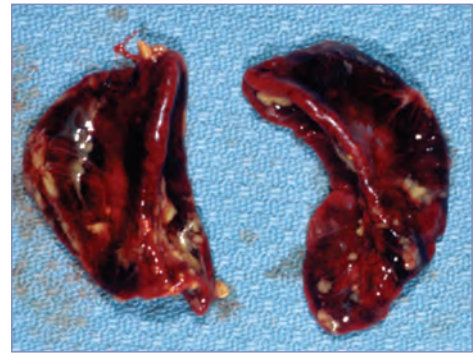


Image 85.15
Adrenal hemorrhage in a patient with gram-negative sepsis, a major complication of meningococcal disease with increased mortality. Courtesy of Dimitris P. Agamanolis, MD.

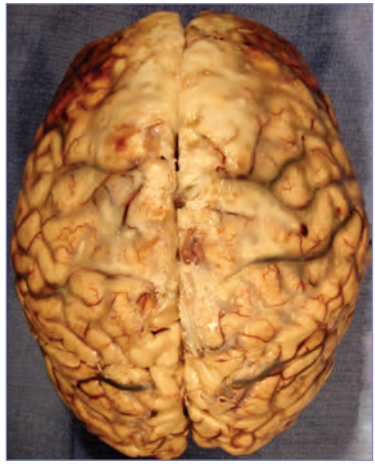


Image 85.16
Fatal meningococcal meningitis with purulent exudate in the subarachnoid space covering the cerebral convexities. Courtesy of Dimitris P. Agamanolis, MD.

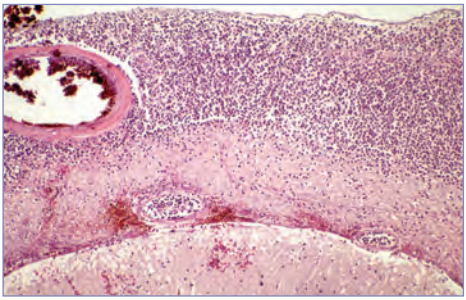


Image 85.17
Suppurative meningococcal meningitis. The subarachnoid space is filled with neutrophils. Courtesy of Dimitris P. Agamanolis, MD.

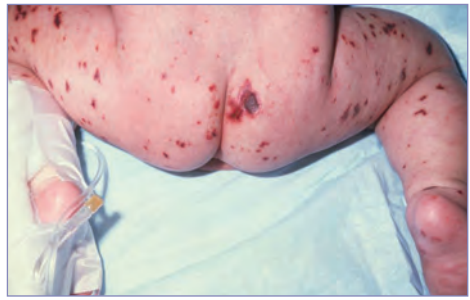


Image 85.18
Petechial rash with a necrotic lesion over the right buttock of an infant girl with *Neisseria meningitidis* septicemia and meningitis. Courtesy of Ed Fajardo, MD.

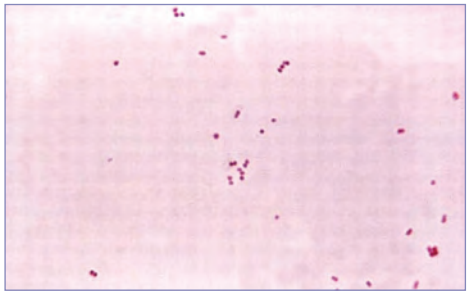


Image 85.19
This micrograph depicts the presence of aerobic gram-negative *Neisseria meningitidis* diplococcal bacteria (magnification ×1,150). Meningococcal disease is an infection caused by a bacterium called *N meningitidis* or meningococcus. Courtesy of Centers for Disease Control and Prevention.

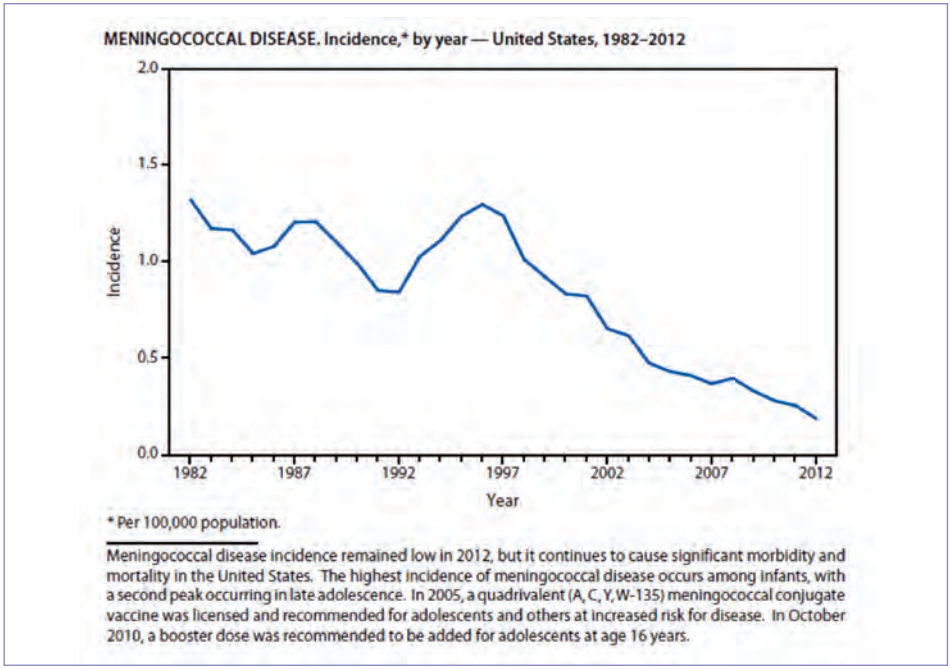


Image 85.20
Meningococcal disease. Incidence, by year—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 85.21
Neisseria meningitidis on chocolate agar. Isolation of this species requires chocolate or Thayer-Martin agar. Colonies are gray-brown and can appear moist to mucoid or dry. *N meningitidis* can be distinguished from *Neisseria gonorrhoeae* by the fact that it ferments glucose and maltose. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

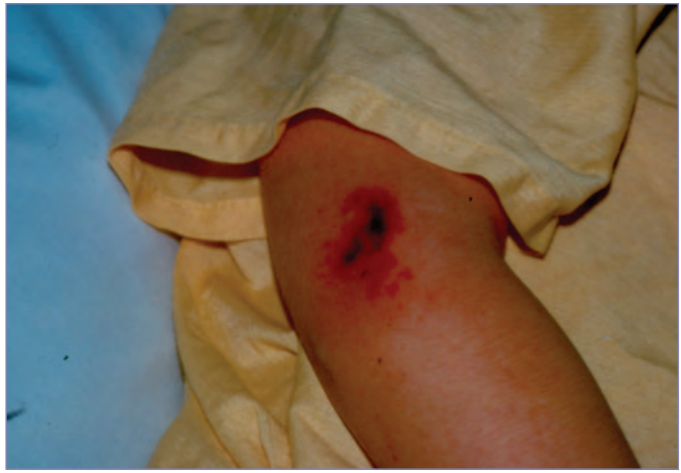


Image 85.22
Purpuric lesion on day 5 of therapy in a 6-year-old with group C *Neisseria meningitidis* sepsis and meningitis. Fever returned on day 6 with swelling of the left knee and mild discomfort. This represents the immune-mediated complication, which resolves with oral nonsteroidal medication. Courtesy of Carol J. Baker, MD.

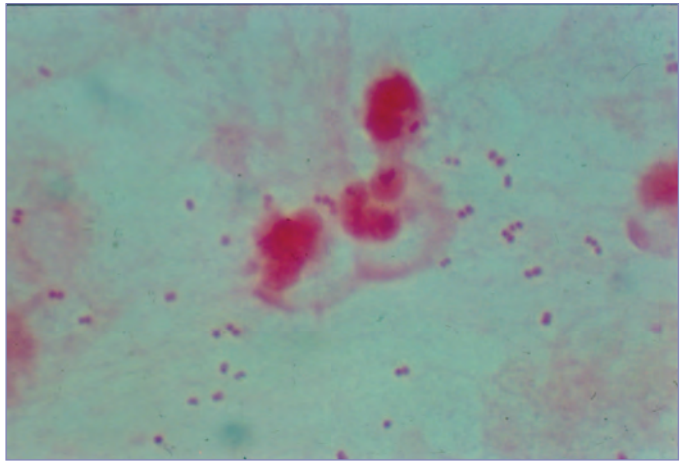


Image 85.23
Gram stain from the cerebrospinal fluid at admission from the patient in Image 85.22. Note the gram-negative cocci in pairs, typical of *Neisseria meningitides* morphology. Courtesy of Carol J. Baker, MD.

CHAPTER 86

Human Metapneumovirus

CLINICAL MANIFESTATIONS

Human metapneumovirus (hMPV) causes acute respiratory tract illness in people of all ages and is one of the leading causes of bronchiolitis in infants. hMPV also causes pneumonia, asthma exacerbations, croup, and upper respiratory tract infections with concomitant acute otitis media in children. Similar to influenza, infection with hMPV has been associated with invasive secondary bacterial infections, including *Streptococcus pneumoniae*, that can result in severe disease. hMPV is associated with acute exacerbations of chronic obstructive pulmonary disease and pneumonia in adults. Otherwise healthy young children infected with hMPV usually have mild or moderate respiratory symptoms, but some young children have severe disease requiring hospitalization. hMPV infection in immunosuppressed people may result in severe disease, and fatalities have been reported in hematopoietic stem cell or lung transplant recipients. Preterm birth and underlying cardiopulmonary disease are risk factors for more severe disease and hospitalization. Preterm birth also is associated with more severe disease in later years of life. Recurrent infection occurs throughout life and, in previously healthy people, usually is mild or asymptomatic.

ETIOLOGY

hMPV is an enveloped single-stranded negative-sense RNA virus in the genus *Metapneumovirus* of the family *Paramyxoviridae*. hMPV comprises at least 4 genetic lineages in 2 major antigenic subgroups (designated A1, A2, B1, and B2) based on sequence differences in the fusion (F) and attachment (G) surface glycoproteins. Viruses from these different lineages cocirculate each year in varying proportions.

EPIDEMIOLOGY

Humans are the only source of infection. Spread occurs by direct or close contact with contaminated secretions. Health care-associated infections have been reported. hMPV infections usually occur annually during late winter and early spring in temperate climates, overlapping with parts of the respiratory syncytial virus (RSV) season, but typically 1 to 2 months later than RSV. Sporadic infection may occur throughout the year. In otherwise healthy infants, the duration of viral shedding is 1 to 2 weeks. Prolonged shedding (weeks to months) has been reported in severely immunocompromised hosts.

Serologic studies suggest that most children are infected at least once by 5 years of age. The population incidence of hospitalizations attributable to hMPV is lower than that attributable to RSV but comparable to that of influenza and parainfluenza 3 in children younger than 5 years. Large studies have shown that hMPV is detected in 6% to 12% of children with lower respiratory tract illnesses who are hospitalized or seen in outpatient settings and emergency departments. Overall annual rates of hospitalization associated with hMPV infection are about 1 per 1,000 children 1 to 5 years of age, 2 per 1,000 children 6 to 11 months of age, and 3 per 1,000 infants younger than 6 months. Coinfection with RSV and other respiratory viruses occurs.

The **incubation period** is estimated to be 3 to 5 days.

DIAGNOSTIC TESTS

Reverse transcriptase-polymerase chain reaction (RT-PCR) assays are the diagnostic method of choice for hMPV. Several RT-PCR assays for hMPV are available commercially. These include a test for hMPV alone and multiplexed tests for hMPV and other diverse respiratory pathogens. hMPV can be difficult to isolate in cell culture. Immunofluorescence assays using monoclonal antibodies for hMPV antigen for direct detection in respiratory tract specimens are available; sensitivities vary from 65% to 95%.

TREATMENT

Treatment is supportive. Antimicrobial agents are not indicated in the treatment of infants hospitalized with uncomplicated hMPV bronchiolitis or pneumonia unless evidence exists for the presence of a concurrent bacterial infection.

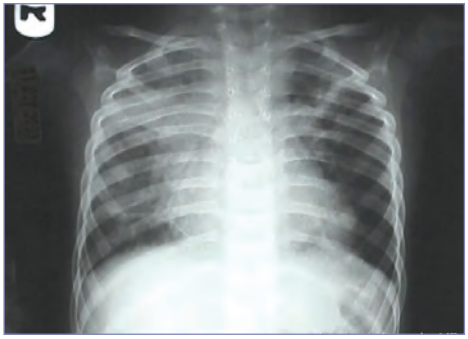


Image 86.1
Bilateral human metapneumovirus pneumonia in a 3-year-old boy. Courtesy of Benjamin Estrada, MD.

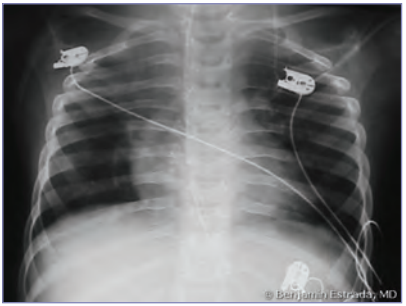


Image 86.2
Human metapneumovirus bronchiolitis in a 12-month-old boy. Courtesy of Benjamin Estrada, MD.

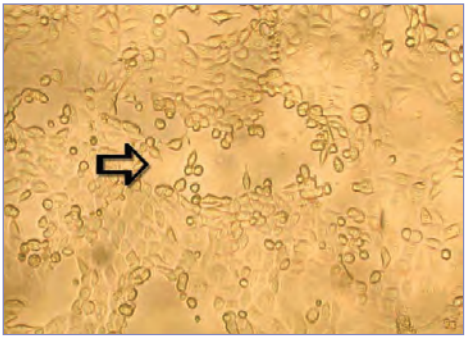


Image 86.3
Late cytopathic effect of human metapneumovirus in rhesus monkey kidney cell monolayers. Infected cells progressed slowly from focal rounding to detachment from cell monolayer (arrow) (magnification ×100). Courtesy of *Emerging Infectious Diseases*.

CHAPTER 87

Microsporidia Infections

(Microsporidiosis)

CLINICAL MANIFESTATIONS

Microsporidia infections can be asymptomatic and may be more common than previously believed. Patients with symptomatic intestinal infection have watery, nonbloody diarrhea, generally without fever. Abdominal cramping can occur. Symptomatic intestinal infection, often protracted diarrhea, is most common in immunocompromised people, especially in organ transplant recipients and people who are infected with human immunodeficiency virus (HIV) with low CD4+ lymphocyte counts (<100 cells/μL). Complications include malnutrition, progressive weight loss, and failure to thrive. Different infecting microsporidia species may result in different clinical manifestations, including ocular, muscle, and genitourinary involvement (Table 87.1). Chronic infection in immunocompetent people is rare.

ETIOLOGY

Microsporidia are obligate intracellular, spore-forming organisms classified as fungi. *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are the most commonly reported pathogens in humans and are most often associated with chronic diarrhea in HIV-infected people. Multiple genera, including *Encephalitozoon*, *Enterocytozoon*, *Nosema*, *Pleistophora*, *Trachipleistophora*, *Anncaliia*, *Vittaforma*, and *Microsporidium*, have been implicated in human infection, as have unclassified species.

EPIDEMIOLOGY

Most microsporidia infections are transmitted by oral ingestion of spores. *Microsporidium* spores commonly are found in surface water, and strains responsible for human infection have been identified in municipal water supplies and ground water. Several studies indicate that waterborne transmission occurs. Donor-derived infections in organ transplant recipients have been documented. Person-to-person

Table 87.1
Clinical Manifestations of Microsporidia Infections

Microsporidia Species	Clinical Manifestation
Anncaliia algerae	Keratoconjunctivitis, skin and deep muscle infection
Enterocytozoon bieneusi	Diarrhea, acalculous cholecystitis
Encephalitozoon cuniculi and *Encephalitozoon hellem*	Keratoconjunctivitis, infection of respiratory and genitourinary tract, disseminated infection
Encephalitozoon intestinalis (synonym *Septata intestinalis*)	Infection of the gastrointestinal tract causing diarrhea, and dissemination to ocular, genitourinary, and respiratory tracts
Microsporidium (*M ceylonensis* and *M africanum*)	Infection of the cornea
Nosema species (*N ocularum*), *Anncaliia connori*	Ocular infection
Pleistophora species	Muscular infection
Trachipleistophora anthropophthera	Disseminated infection
Trachipleistophora hominis	Muscular infection, stromal keratitis (probably disseminated infection)
Tubulinosema acridophagus	Disseminated infection
Vittaforma corneae (synonym *Nosema corneum*)	Ocular infection, urinary tract infection

Source: **www.cdc.gov/dpdx/microsporidiosis.**

spread by the fecal-oral route also occurs. Spores also have been detected in other body fluids, but their role in transmission is unknown. Data suggest the possibility of zoonotic transmission.

The **incubation period** is unknown.

DIAGNOSTIC TESTS

Infection with gastrointestinal tract microsporidia can be documented by identification of organisms in biopsy specimens from the small intestine. Microsporidia spores can be detected in formalin-fixed stool specimens or duodenal aspirates stained with a chromotrope-based stain (a modification of the trichrome stain) and examined by an experienced microscopist. Several histologic stains, including calcofluor, hematoxylin-eosin, Gram, acid-fast, periodic acid-Schiff, Warthin-Starry silver, and Giemsa stains, can be used to detect organisms in tissue sections. Organisms often are not noticed because they are small (0.8–4 μm), stain poorly, and evoke minimal inflammatory response. Use of stool concentration techniques does not seem to improve the ability to detect *E bieneusi* spores. Identification and diagnostic confirmation of species requires transmission electron microscopy or molecular techniques. The value of serologic testing, when available, has not been substantiated.

TREATMENT

Restoration of immune function is critical for control of any microsporidia infection. Effective antiretroviral therapy is the primary initial treatment for these infections in people infected with HIV. Albendazole is the drug of choice for infections caused by microsporidia other than *E bieneusi* and *Vittaforma corneae* infections, which may respond to fumagillin. However, fumagillin is associated with bone marrow toxicity, recurrence of diarrhea is common after therapy is discontinued, and the drug for systemic use is not available in the United States. None of these therapies have been studied in children with microsporidia infection. Supportive care for malnutrition and dehydration may be necessary. Antimotility agents may be useful to control chronic diarrhea.

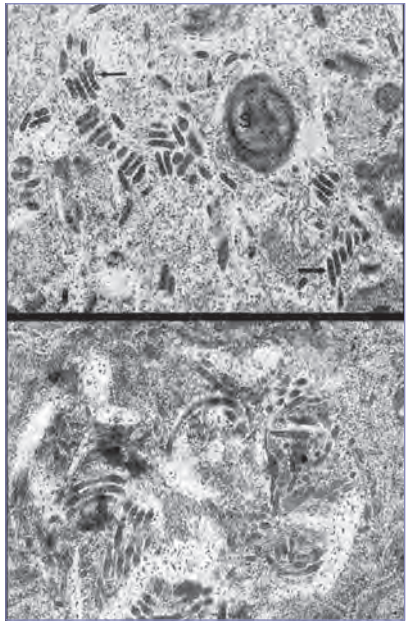


Image 87.1
Transmission electron micrographs showing developmental intracellular stages of microsporidia. Courtesy of Centers for Disease Control and Prevention.

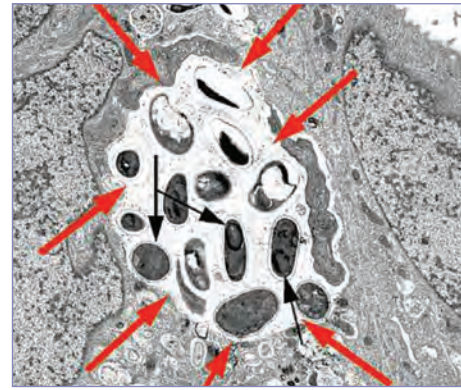


Image 87.2
Transmission electron micrograph showing developing forms of *Encephalitozoon intestinalis* inside a parasitophorous vacuole (red arrows) with mature spores (black arrows). Microsporidiosis, parasite. Courtesy of Centers for Disease Control and Prevention.

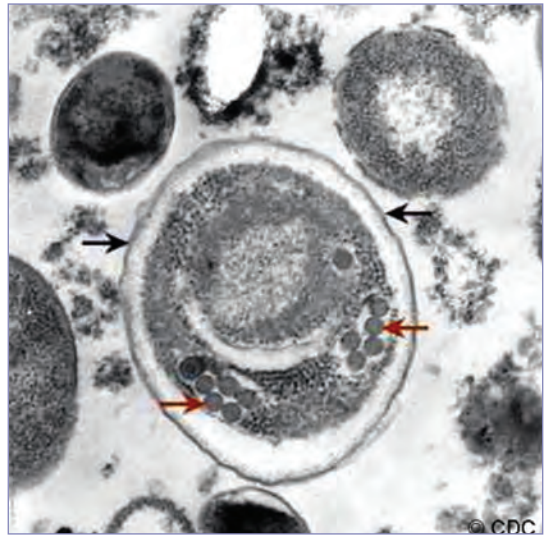


Image 87.3
Transmission electron micrograph of a mature microsporidian spore. Black arrows indicate the electron dense cell wall and red arrows, the coils of polar tubule. Although polymerase chain reaction can be used for diagnosis, serologic tests are unreliable. Courtesy of Centers for Disease Control and Prevention.

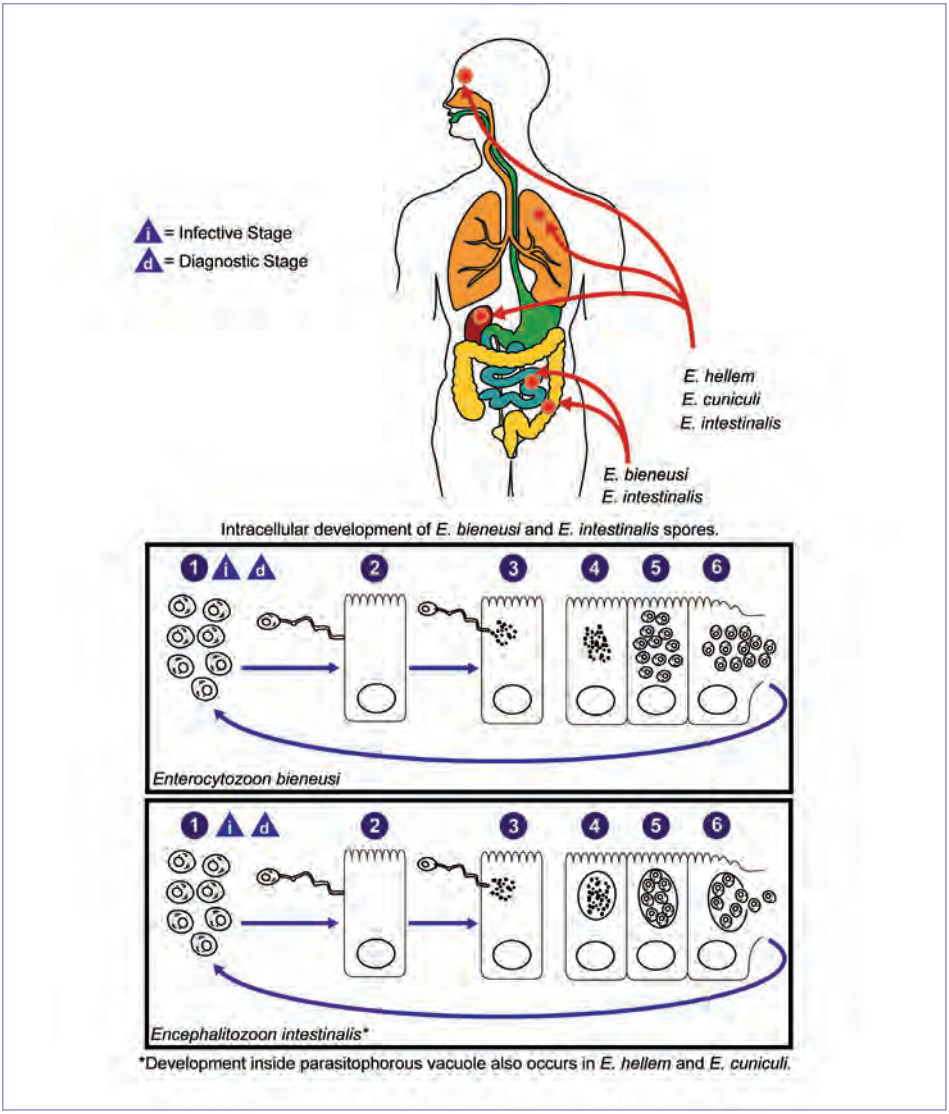


Image 87.4

The infective form of microsporidia is the resistant spore and it can survive for a long time in the environment (1). The spore extrudes its polar tubule and infects the host cell (2). The spore injects the infective sporoplasm into the eukaryotic host cell through the polar tubule (3). Inside the cell, the sporoplasm undergoes extensive multiplication either by merogony (binary fission) (4) or schizogony (multiple fission). This development can occur either in direct contact with the host cell cytoplasm (eg, *Enterocytozoon bieneusi*) or inside a vacuole termed parasitophorous vacuole (eg, *Enterocytozoon intestinalis*). Free in the cytoplasm or inside a parasitophorous vacuole, microsporidia develop by sporogony to mature spores (5). During sporogony, a thick wall is formed around the spore that provides resistance to adverse environmental conditions. When the spores increase in number and completely fill the host cell cytoplasm, the cell membrane is disrupted and releases the spores to the surroundings (6). These free mature spores can infect new cells, thus continuing the cycle. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 88

Molluscum Contagiosum

CLINICAL MANIFESTATIONS

Molluscum contagiosum is a benign viral infection of the skin with no systemic manifestations. It usually is characterized by 1 to 20 discrete, 2- to 5-mm-diameter, flesh-colored to translucent, dome-shaped papules, some with central umbilication. Lesions commonly occur on the trunk, face, and extremities but rarely are generalized. Molluscum contagiosum is a self-limited epidermal infection that usually resolves spontaneously in 6 to 12 months but may take as long as 4 years to disappear completely. The average duration for a single lesion is approximately 2 months. An eczematous reaction encircles lesions in approximately 10% of patients. People with atopic dermatitis and immunocompromising conditions, including human immunodeficiency virus infection and patients with congenital DOCK8 deficiency, tend to have more widespread and prolonged eruptions, which often are recalcitrant to therapy.

ETIOLOGY

Molluscum contagiosum virus (MCV) is the sole member of the genus *Molluscipoxvirus*, family *Poxviridae*. Other poxviruses include the agents of smallpox, monkeypox, vaccinia, and cowpox.

EPIDEMIOLOGY

Humans are the only known source of the virus, which is spread by direct contact, scratching, shaving, sexual contact, or fomites. Vertical transmission has been linked with neonatal molluscum contagiosum infection. Lesions can be disseminated by autoinoculation. Infectivity generally is low, but occasional outbreaks may occur in facilities such as child care centers. The period of communicability is unknown.

The **incubation period** varies between 2 and 7 weeks (can be up to 6 months).

DIAGNOSTIC TESTS

The diagnosis usually can be made clinically from the characteristic appearance of umbilicated papules. Wright or Giemsa staining of cells expressed from the central core of a lesion reveals characteristic intracytoplasmic inclusions. Electron microscopic examination of these cells identifies typical poxvirus particles. If questions persist, nucleic acid testing by polymerase chain reaction is available at certain reference centers. Adolescents and young adults with genital molluscum contagiosum should have screening tests for other sexually transmitted infections.

TREATMENT

There is no consensus on management of molluscum contagiosum in children and adolescents. Genital lesions should be treated to prevent spread to sexual contacts. Treatment of nongenital lesions is sometimes provided for cosmetic reasons. Lesions in healthy people typically are self-limited, so treatment may be unnecessary. However, therapy may be warranted to alleviate discomfort, reduce autoinoculation, limit transmission to close contacts, reduce cosmetic concerns, and prevent secondary infection. Physical destruction of the lesions is the most rapid and effective means of curing molluscum contagiosum. Modalities available include curettage, cryodestruction with liquid nitrogen, electrodesiccation, and chemical agents designed to initiate a local inflammatory response (podophyllin, tretinoin, cantharidin, 25%–50% trichloroacetic acid, liquefied phenol, silver nitrate, tincture of iodine, or potassium hydroxide). Because physical destruction of the lesions is painful, appropriate local anesthesia may be required, particularly in young children. Data from large randomized, vehicle-controlled, double-blind trials have failed to demonstrate efficacy of imiquimod cream. Cidofovir is a cytosine nucleotide analogue with in vitro activity against molluscum contagiosum; successful intravenous treatment of immunocompromised adults with severe involvement has been reported. Successful treatment using topical cidofovir, in a combination vehicle, has been reported in both adult and pediatric cases, most of whom were immunocompromised.

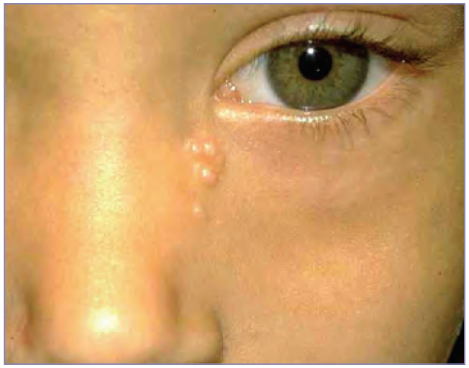


Image 88.1
Molluscum contagiosum lesions adjacent to the nasal bridge. Copyright Edgar K. Marcuse, MD.

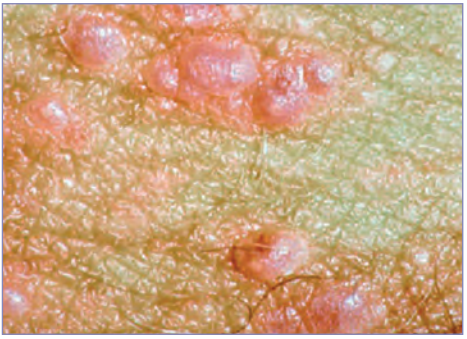


Image 88.2
A central dimple or umbilication is the hallmark of molluscum contagiosum. The lesions of molluscum contagiosum vary in size from 1 to 6 mm and, unlike venereal warts, are smooth and pearly and have an umbilicated center.

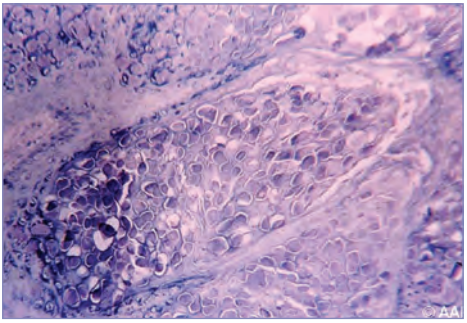


Image 88.3
Molluscum contagiosum lesions in a skin biopsy specimen (Giemsa stain, original magnification ×40). Courtesy of Edgar O. Ledbetter, MD, FAAP.

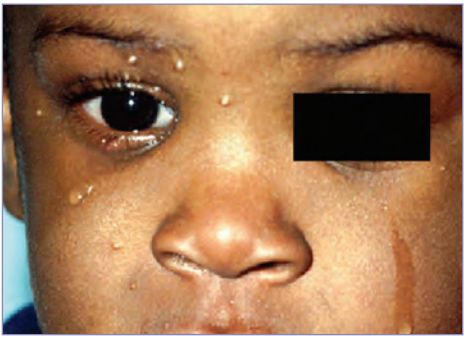


Image 88.4
Molluscum contagiosum is characterized by one or more translucent or white papules. Intracytoplasmic inclusions may be seen with Wright or Giemsa staining of material expressed from the core of a lesion.

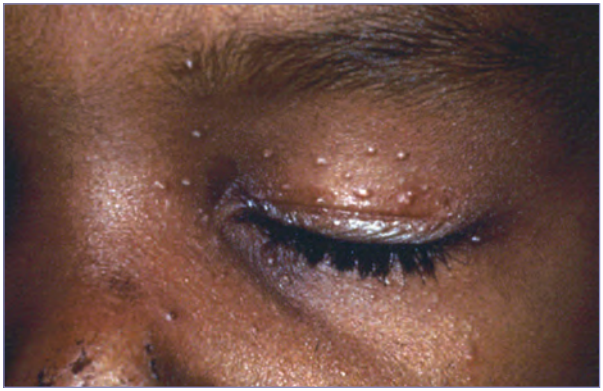


Image 88.5
Pearly papules on the forehead and eyelid in a child with molluscum contagiosum lesions, which commonly occur on the face.

Image 88.6
This 10-year-old girl has had multiple small bumps on the face for the past month. These started as a solitary papule on her eyebrow but spread over several weeks. They have developed a small pointed core and are an embarrassment to the child. School pictures are pending. The family demands treatment. There is a family history of keloids. The family was counseled on the limited treatment options due to the potential for permanent scarring and keloid formation. Consultation with a dermatologist was arranged at the parents' request. Courtesy of Will Sorey, MD.

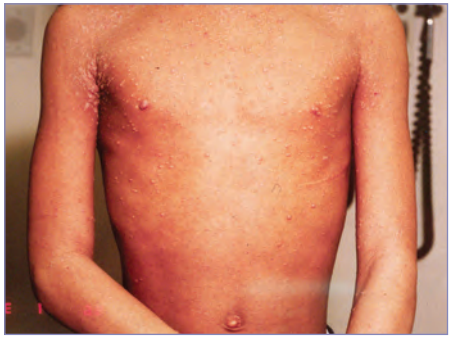


Image 88.7
A 15-year-old boy with HIV with numerous and widespread molluscum contagiosum lesions. Courtesy of Larry Frenkel, MD.

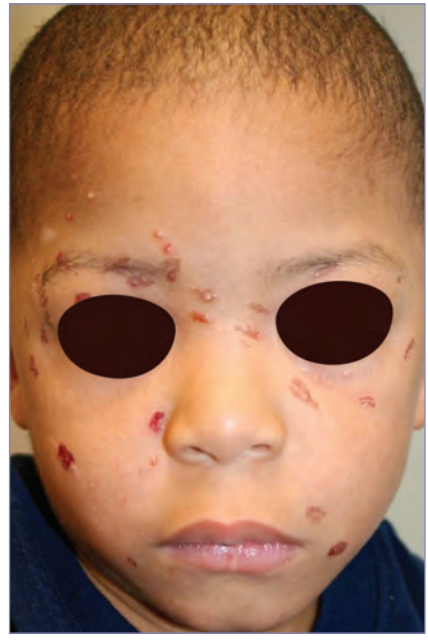


Image 88.8
This healthy 5-year-old boy with widespread molluscum was started on home treatment with a topical liquid salicylic acid preparation. He developed itchy crusted erosions around the treated lesions. Topical therapy was discontinued and a topical antibiotic ointment was prescribed with rapid clearing of the irritant dermatitis. Courtesy of H. Cody Meissner, MD, FAAP

CHAPTER 89

Moraxella catarrhalis Infections

CLINICAL MANIFESTATIONS

Moraxella catarrhalis commonly is implicated in acute otitis media (AOM), otitis media with effusion, and sinusitis. AOM caused by *M catarrhalis* occurs predominantly in younger infants and frequently is recovered in mixed infections. Since introduction of 13-valent pneumococcal conjugate vaccine (PCV13), *M catarrhalis* appears to be recovered in a greater proportion of children undergoing tympanocentesis; however, it is unclear whether this represents an increase in cases attributable to *M catarrhalis* or a decrease in pneumococcal disease. *M catarrhalis* can cause pneumonia and bacteremia in healthy children but is more commonly reported in children with chronic lung disease or impaired host defenses, such as leukemia with neutropenia or congenital immunodeficiency. In immunocompetent patients, bacteremia usually is associated with a respiratory tract focus; in immunocompromised children, most often no focus of infection is identified. Other clinical manifestations include hypotension with or without a rash indistinguishable from that observed in meningococcemia, neonatal meningitis, and focal infections, such as preseptal cellulitis, bacterial tracheitis, urethritis, osteomyelitis, or septic arthritis. Rare manifestations include endocarditis, peritonitis, shunt-associated ventriculitis, meningitis, and mastoiditis.

ETIOLOGY

M catarrhalis is a gram-negative aerobic diplococcus. Nearly 100% of strains produce beta-lactamase that mediates resistance to the penicillins, including amoxicillin.

EPIDEMIOLOGY

M catarrhalis is part of the normal microbiota of the upper respiratory tract of humans. Two thirds of children are colonized within the first year of life. The mode of transmission is presumed to be direct contact with contaminated respiratory tract secretions or droplet spread. Infection is most common in infants and young children but also occurs in immunocompromised people at all ages. The duration of carriage by children with infection or colonization and the period of communicability are unknown. Recent studies suggest early colonization with *M catarrhalis* is associated with a stable microbiome and low risk for recurrent respiratory tract infection.

DIAGNOSTIC TESTS

The organism can be isolated on blood or chocolate agar culture media after incubation in air or with increased carbon dioxide. On Gram stain, *Moraxella* species are short and plump gram-negative rods, usually occurring in pairs or short chains, and are mostly catalase and cytochrome oxidase positive. Culture of middle ear or sinus aspirates is indicated for patients with unusually severe infection, for patients with infection that fails to respond to treatment, and for immunocompromised children. *M catarrhalis* often is recovered as part of mixed infections. Polymerase chain reaction tests for *M catarrhalis* have been developed but currently are used for research purposes only.

TREATMENT

Almost all strains of *Moraxella* species produce beta-lactamase and are resistant to amoxicillin. When beta-lactamase–producing *M catarrhalis* is isolated from appropriately obtained specimens (middle ear fluid, sinus aspirates, or lower respiratory tract secretions), cefotaxime and ceftriaxone are likely to be effective if parenteral antimicrobial therapy is needed. For oral therapy, amoxicillin-clavulanate, cefixime, azithromycin, cefdinir, cefpodoxime, trimethoprim-sulfamethoxazole, or a fluoroquinolone can be administered. Cefuroxime axetil, high-dose amoxicillin, and cefaclor are likely to be ineffective. The organism is resistant to clindamycin, vancomycin, and oxacillin.

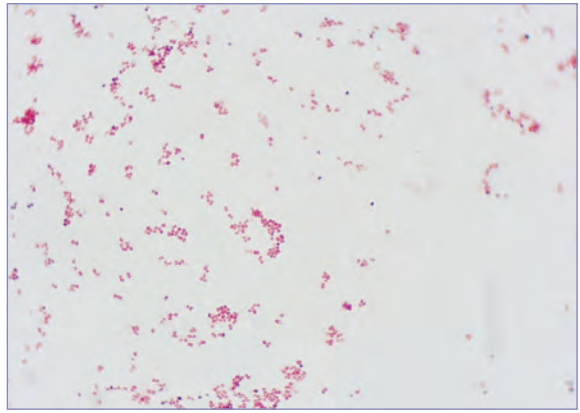


Image 89.1
Gram stain of *Moraxella catarrhalis* showing characteristic gram-negative diplococci morphology (magnification ×100). Courtesy of Rita Yee, MT(ASCP)SM.

Image 89.2
Moraxella catarrhalis on blood and chocolate agar plates, both inoculated simultaneously. Courtesy of Rita Yee, MT(ASCP)SM.

Image 89.3
Moraxella catarrhalis on chocolate agar. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 90

Mumps

CLINICAL MANIFESTATIONS

Mumps is a systemic disease characterized by swelling of one or more of the salivary glands, usually the parotid glands. Approximately one third of infections do not cause clinically apparent salivary gland swelling and may be asymptomatic (subclinical) or manifest primarily as respiratory tract infection. More than 50% of people with mumps have cerebrospinal fluid pleocytosis, but fewer than 10% have symptoms of viral meningitis. Orchitis is a commonly reported complication after puberty, although sterility rarely results. Rare complications include arthritis, thyroiditis, mastitis, glomerulonephritis, myocarditis, endocardial fibroelastosis, thrombocytopenia, cerebellar ataxia, transverse myelitis, encephalitis, pancreatitis, oophoritis, and permanent hearing impairment. In the absence of an immunization program, mumps typically occurs during childhood. Infection in adults is more likely to result in complications. Although mumps virus can cross the placenta, no evidence exists that this transmission results in congenital malformation.

ETIOLOGY

Mumps is an RNA virus in the genus *Rubulavirus* in the family *Paramyxoviridae*. The genus also includes human parainfluenza virus types 2 and 4. Other infectious causes of parotitis include Epstein-Barr virus, cytomegalovirus, parainfluenza virus types 1 and 3, influenza A virus, enteroviruses, lymphocytic choriomeningitis virus, human immunodeficiency virus (HIV), nontuberculous mycobacterium, gram-positive bacteria, and less often, gram-negative bacteria.

EPIDEMIOLOGY

Mumps occurs worldwide, and humans are the only known natural hosts. The virus is spread by contact with infectious respiratory tract secretions and saliva. Mumps virus is the only known cause of epidemic parotitis. Historically, the peak incidence of mumps was between January and May and among children younger than 10 years. Mumps vaccine was licensed in the United States in 1967 and recommended for routine childhood immunization in 1977. After implementation of the 2-dose measles-mumps-rubella (MMR) vaccine recommendation in 1989 for measles control in the United States, mumps further declined to extremely low levels, with an incidence of 0.1/100,000 by 1999. From 2000 to 2005, seasonality no longer was evident, and there were fewer than 300 reported cases per year (incidence, 0.1/100,000), representing a greater than 99% reduction in disease incidence compared with the prevaccine era. In early 2006, a large-scale mumps outbreak occurred in the Midwestern United States, with 6,584 reported cases (incidence of 2.2/100,000). Most of the cases occurred among people 18 through 24 years of age, many of whom were college students who had received 2 doses of mumps vaccine. Another outbreak in 2009–2010 affected more than 3,500 people, mainly students in grades 6 through 12 who were members of traditional observant religious communities in New York and New Jersey and who also had received 2 doses of vaccine. Beginning in 2016, even larger outbreaks of mumps have occurred in the United States. In 2016, there were 6,353 cases. There were 67 mumps outbreaks reported in 2016, including 35 university outbreaks, 7 outbreaks in close-knit communities, 21 outbreaks in other close-contact settings (eg, churches, workplaces, fitness centers, etc), and 4 community-wide outbreaks. Available data from 1 outbreak indicate that cases occurred primarily in young adults with high 2-dose MMR vaccination coverage. Two doses of vaccine are approximately 88% effective in preventing disease. In settings of high immunization coverage, such as the United States, it is predictable that most mumps cases will occur in people who have received 2 doses of vaccine.

The **incubation period** is 16 to 18 days after exposure (range, 12–25 days). The period of maximum communicability begins several days before parotitis onset. The virus has been isolated from saliva from 7 days before through 8 days after onset of swelling.

DIAGNOSTIC TESTS

Despite localized outbreaks, mumps remains an uncommon infection in the United States, and most parotitis has other infectious etiologies. Mumps can be confirmed by detection of

mumps virus nucleic acid by reverse transcriptase-polymerase chain reaction (RT-PCR) assay in specimens from buccal swabs (Stenson duct exudates), throat washings, saliva, or cerebrospinal fluid. The mumps RT-PCR test, as developed and available at the Centers for Disease Control and Prevention (CDC), is sensitive and specific. Other RT-PCR assays for mumps may be available, but none are US Food and Drug Administration approved. Failure to detect mumps virus RNA by RT-PCR in samples from a person with clinically compatible mumps symptoms does not rule out mumps as a diagnosis. Mumps can be diagnosed by testing for mumps-specific immunoglobulin (Ig) M antibody or by a significant increase between acute and convalescent serum mumps IgG antibody titer determined by standard quantitative or semiquantitative serologic assay. In highly immunized populations, confirming the diagnosis of mumps by serologic testing can be challenging, because the IgM response may be absent or short lived; acute IgG titers already might be high, so no significant increase can be detected between acute and convalescent specimens. In immunized people or previously infected individuals presenting with clinically compatible mumps, a negative IgM result does not rule out acute mumps.

TREATMENT

Supportive.

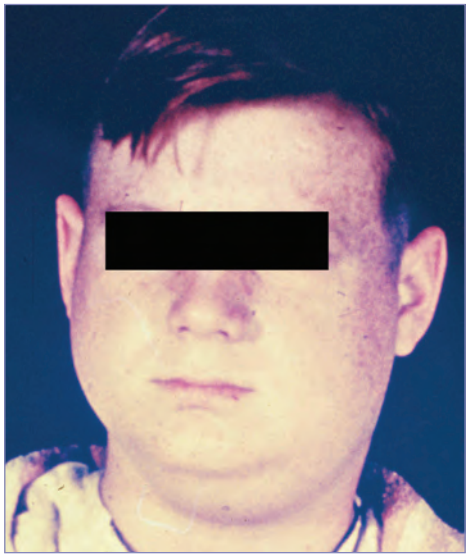


Image 90.1
A 10-year-old boy with bilateral mumps parotitis and submandibular edema. Courtesy of Paul Wehrle, MD.

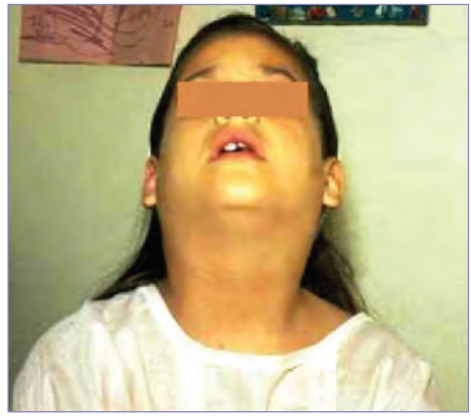


Image 90.2
Mumps with parotid and submandibular involvement bilaterally. The differential diagnosis for acute infectious parotitis includes cytomegalovirus, parainfluenza viruses, lymphocytic choriomeningitis, coxsackieviruses and other enteroviruses, HIV, nontuberculous mycobacterium, and certain bacteria. Copyright Martha Lepow.

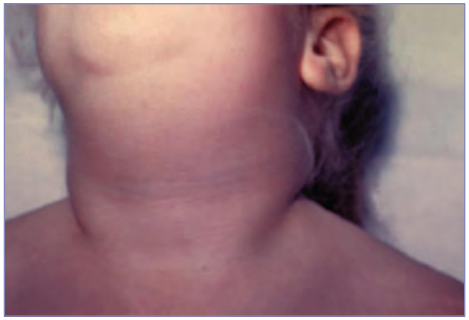


Image 90.3
This is a photograph of a patient with bilateral swelling in the submaxillary regions due to mumps. Prior to vaccine licensure in 1967, 100,000 to 200,000 mumps cases are estimated to have occurred in the United States each year. Courtesy of Centers for Disease Control and Prevention.

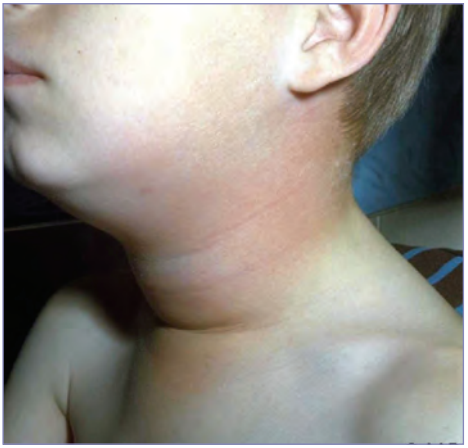


Image 90.4
Mumps parotitis with cervical and presternal edema and erythema that resolved spontaneously.

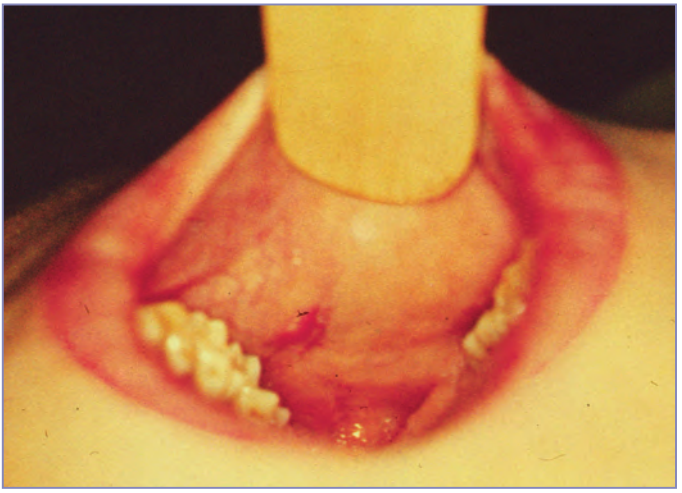


Image 90.5
Swelling and erythema of the Stensen duct in a 10-year-old boy with mumps parotitis. Courtesy of Paul Wehrle, MD.

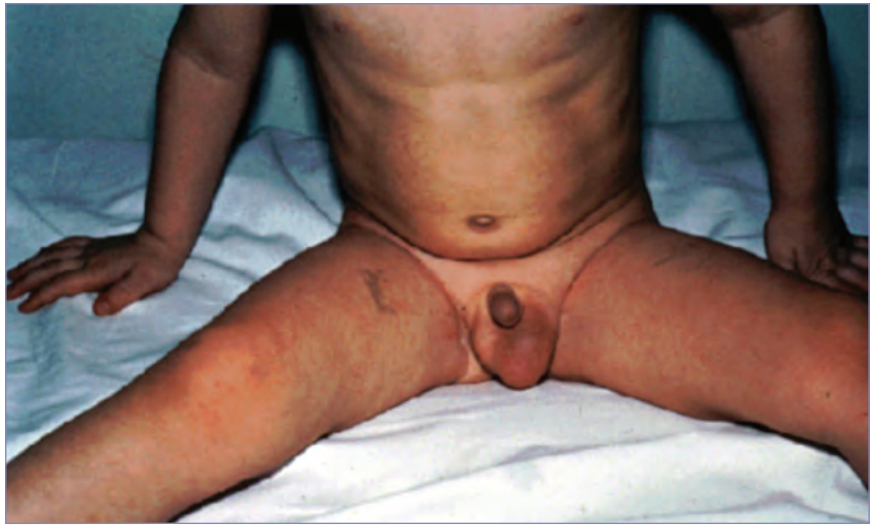


Image 90.6
Mumps orchitis in a 6-year-old boy. This complication is unusual in prepubertal boys. The highest risk for orchitis is in men between 15 and 29 years of age.

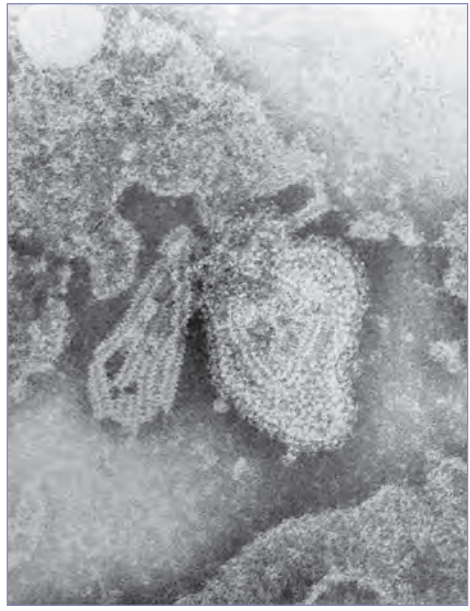


Image 90.7
Electron micrograph of the mumps virus. The mumps virus is a member of the *Paramyxoviridae* family and is enveloped by a helical ribonucleic-protein capsid, which has a Herring-body–like appearance. Courtesy of Centers for Disease Control and Prevention.

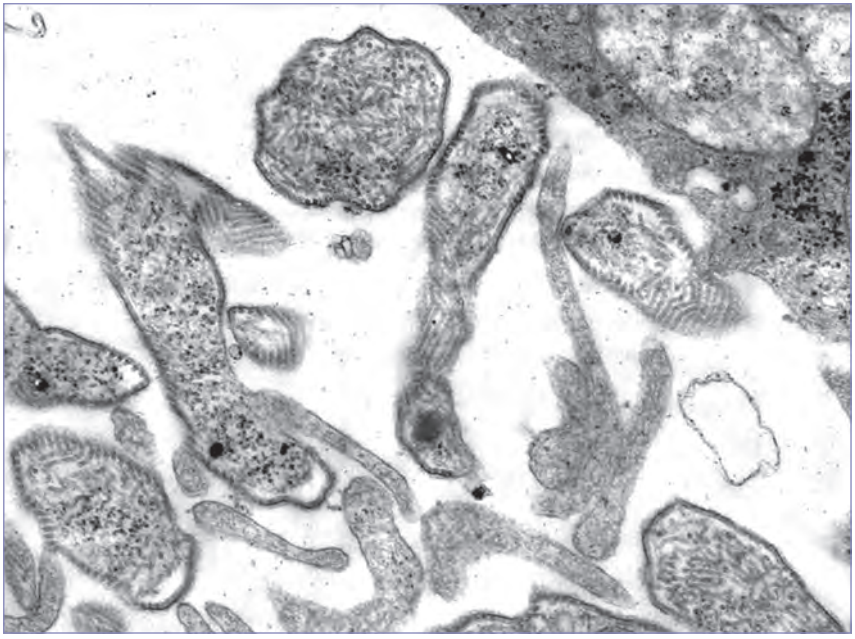


Image 90.8
Thin-section electron micrograph of mumps virus. Filamentous nucleocapsids can be seen within viral particles and juxtaposed along the viral envelope. Courtesy of Centers for Disease Control and Prevention.

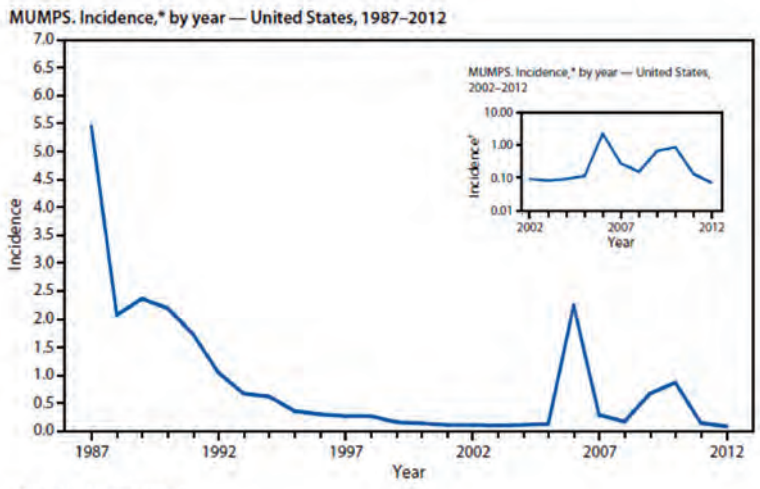


Image 90.9
Mumps. Incidence, by year—United States, 1987–2012. Courtesy of *Morbidity and Mortality Weekly Report*.

CHAPTER 91

Mycoplasma pneumoniae and Other *Mycoplasma* Species Infections

CLINICAL MANIFESTATIONS

Mycoplasma pneumoniae is a frequent cause of upper and lower respiratory tract infections in children, including pharyngitis, acute bronchitis, and pneumonia. Acute otitis media is uncommon. Bullous myringitis, once considered pathognomonic for mycoplasma, now is known to occur with other pathogens as well. Sinusitis and croup are rare. Symptoms are variable and include cough, malaise, fever, and occasionally headache. Acute bronchitis and upper respiratory tract illness caused by *M pneumoniae* generally are mild and self-limited. Approximately 10% of infected school-aged children will develop pneumonia with cough and rales on physical examination within days after onset of constitutional symptoms. Cough, initially nonproductive, can become productive, persist for 3 to 4 weeks, and be accompanied by wheezing. Approximately 10% of children with *M pneumoniae* infection can exhibit a rash, which most often is maculopapular. Radiographic abnormalities are variable; bilateral diffuse infiltrates or focal abnormalities, such as consolidation, effusion, or hilar adenopathy, can occur.

Unusual manifestations include nervous system disease (eg, aseptic meningitis, encephalitis, acute disseminated encephalomyelitis, cerebellar ataxia, transverse myelitis, and peripheral neuropathy) as well as myocarditis, pericarditis, arthritis, erythema nodosum, polymorphous mucocutaneous eruptions (including classic and atypical Stevens-Johnson syndrome), hemolytic anemia, thrombocytopenic purpura, and hemophagocytic syndromes. Severe pneumonia with pleural effusion can occur, particularly in patients with sickle cell disease, Down syndrome, immunodeficiencies, and chronic cardiorespiratory disease. Acute chest syndrome and pneumonia have been associated with *M pneumoniae* in patients with sickle cell disease. Infection also has been associated with exacerbations of asthma.

Several other *Mycoplasma* species colonize mucosal surfaces of humans and can produce disease in children. *Mycoplasma hominis* infection has been reported in neonates (especially at scalp electrode monitor site) and children (both immunocompetent and immunocompromised). Intra-abdominal abscess, septic arthritis, endocarditis, pneumonia, meningoencephalitis, brain abscess, and surgical wound infection have been reported to be attributable to *M hominis*.

ETIOLOGY

Mycoplasmas, including *M pneumoniae*, are pleomorphic bacteria that lack a cell wall. They are classified in the family *Mycoplasmataceae*, which includes the *Mycoplasma* and *Ureaplasma* genera.

EPIDEMIOLOGY

Mycoplasmas are ubiquitous in animals and plants, but *M pneumoniae* causes disease only in humans. *M pneumoniae* is transmissible by respiratory droplets during close contact with a symptomatic person. Outbreaks have been described in hospitals, military bases, colleges, and summer camps. Occasionally, *M pneumoniae* causes ventilator-associated pneumonia. *M pneumonia*e is a leading cause of pneumonia in school-aged children and young adults but is an infrequent cause of community-acquired pneumonia in children younger than 5 years. In the United States, an estimated 2 million infections are caused by *M pneumoniae* each year. Overall, approximately 20% of hospitalized community-acquired pneumonia is thought to be caused by *M pneumoniae*. Infections occur throughout the world, in any season, and in all geographic settings. In family studies, approximately 30% of household contacts develop pneumonia. Asymptomatic carriage after infection may occur for weeks to months. Immunity after infection is not long lasting.

The **incubation period** usually is 2 to 3 weeks (range, 1–4 weeks).

DIAGNOSTIC TESTS

Nucleic acid amplification tests (NAATs), including polymerase chain reaction (PCR) tests for *M pneumoniae*, are available commercially and increasingly are replacing other

tests, because PCR tests performed on respiratory tract specimens (nasal wash, nasopharyngeal swab, pharyngeal swab) are rapid, have sensitivity and specificity between 80% and 100%, and yield positive results earlier in the course of illness. Identification of *M pneumoniae* by NAAT or culture in a patient with compatible clinical manifestations suggests causation. However, attributing a nonclassic clinical disorder to *M pneumoniae* is problematic, because the organism can colonize the respiratory tract for several weeks after acute infection (even after appropriate antimicrobial therapy) and has been detected by PCR in 17% to 25% of asymptomatic children 3 months to 16 years of age. Performance characteristics of PCR assays that have not been cleared by the US Food and Drug Administration are not generalizable. PCR assay of body fluids for *M hominis* is available at reference laboratories and may be helpful diagnostically. Serologic tests using immunofluorescence and enzyme immunoassays that detect *M pneumoniae*-specific immunoglobulin (Ig) M and IgG antibodies are available commercially. IgM antibodies generally are not detectable within the first 7 days after onset of symptoms. Although the presence of IgM antibodies may indicate recent *M pneumoniae* infection, false-positive test results occur, and antibodies persist in serum for several months and may not indicate current infection. Serologic diagnosis is best accomplished by demonstrating a fourfold or greater increase in antibody titer between acute and convalescent serum specimens. IgM antibody titer peaks at approximately 3 to 6 weeks and persists for 2 to 3 months after infection but should be interpreted cautiously because of frequent false-positive results. Measurement of serum cold hemagglutinin titer has limited value.

The diagnosis of mycoplasma-associated central nervous system disease is challenging, both because disease may not be the result of direct invasion and because there is no reliable single test for cerebrospinal fluid to establish a diagnosis.

TREATMENT

Mycoplasma infection is an infrequent cause of community-acquired pneumonia (CAP) in preschool-aged children. Evidence of benefit of antimicrobial therapy for nonhospitalized children with lower respiratory tract disease attributable to *M pneumoniae* is limited. Antimicrobial therapy is not recommended for preschool-aged children with CAP, because viral pathogens are responsible for the great majority of cases. There is no evidence that treatment of other possible manifestations of *M pneumoniae* infection (eg, upper respiratory tract infection, extrapulmonary infection) with antimicrobial agents alters the course of illness.

Because *Mycoplasma* organisms lack a cell wall, they inherently are resistant to beta-lactam agents. Macrolides, including azithromycin, clarithromycin, and erythromycin, are the preferred antimicrobial agents for treatment of *Mycoplasma* pneumonia in school-aged children who have moderate to severe infection and those with underlying conditions, such as sickle cell disease. Fluoroquinolones and doxycycline are active in vitro. Macrolide-resistant strains are increasingly common, although the effect of resistance on treatment outcome is not known. The usual course of antimicrobial therapy for pneumonia is 7 to 10 days, except for azithromycin, for which it usually is 5 days.

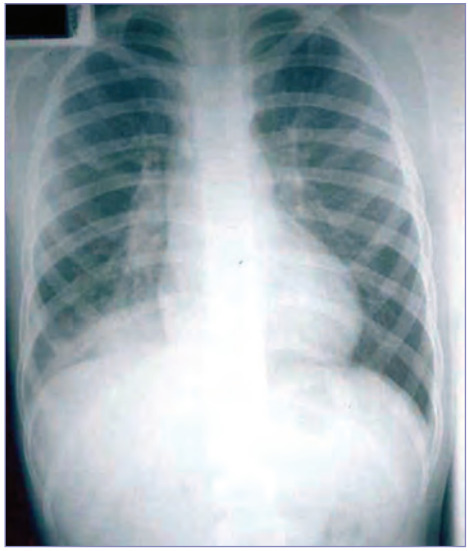


Image 91.1
A preadolescent boy with bilateral perihilar infiltration and right lower lobe pneumonia and pleural effusion due to *Mycoplasma pneumoniae*. Courtesy of Edgar O. Ledbetter, MD, FAAP.

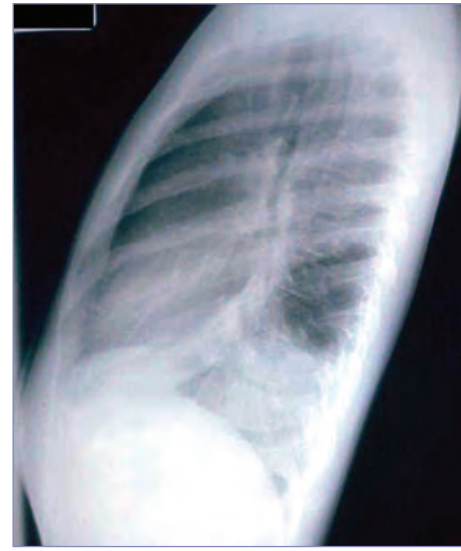


Image 91.2
Right lateral radiograph of the patient in Image 91.1 with pneumonia and pleural effusion. Pleural effusions associated with *Mycoplasma pneumoniae* infections generally resolve spontaneously without drainage. Courtesy of Edgar O. Ledbetter, MD, FAAP.

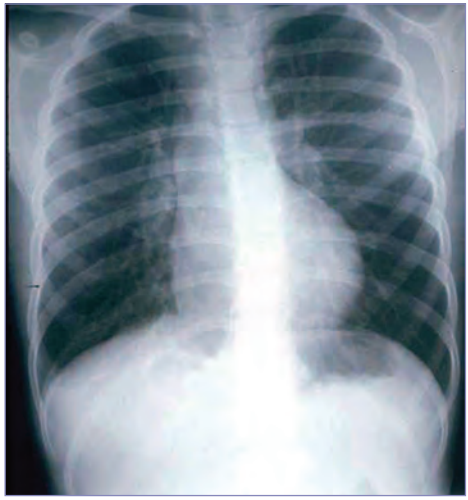


Image 91.3
Preadolescent boy with bilateral perihilar infiltrates caused by *Mycoplasma pneumoniae*.

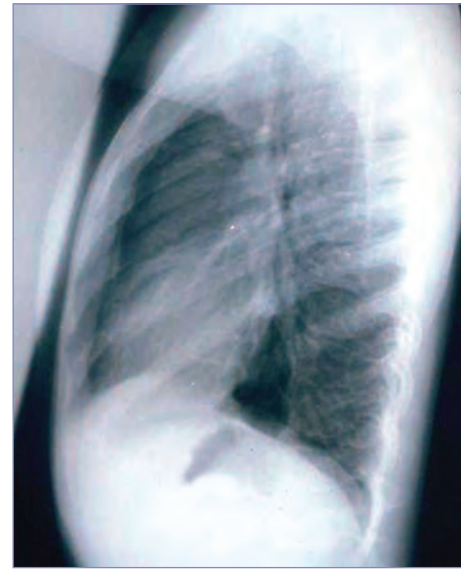


Image 91.4
Lateral radiograph of the patient in Image 91.3 with pneumonia caused by *Mycoplasma pneumoniae*.

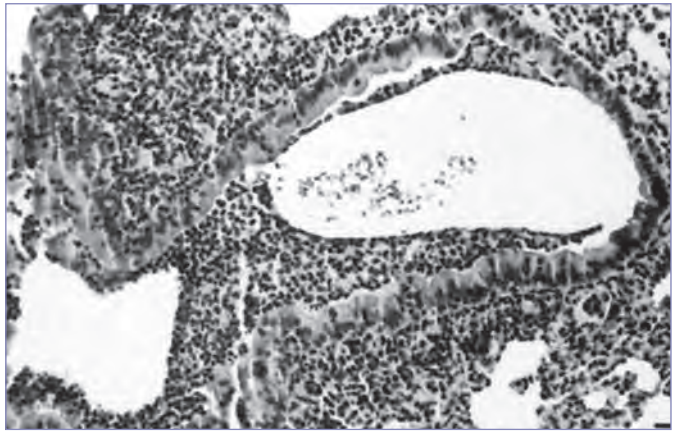


Image 91.5
Histopathologic study of *Mycoplasma pneumoniae*–infected lung tissue. The respiratory bronchiole is surrounded by an inflammatory mononuclear cell response. The intraluminal site is approximately 30% occluded by mucus and white blood cells. *M pneumoniae* is a common cause of pneumonia and tracheobronchitis in school-aged children and adolescents.

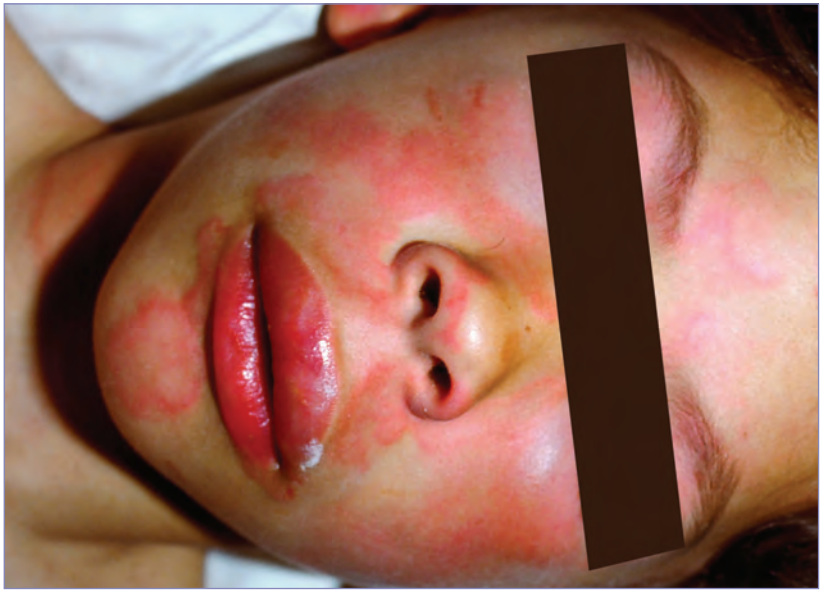


Image 91.6
Erythema multiforme associated with mycoplasma infection. This 10-year-old boy presented with fever and macular lesions on the face, chest, arms, and back, as well as facial swelling. He had a 4-day period of increasing cough and low-grade fever prior to the onset of the skin lesions and facial swelling. Chest radiograph revealed mild increased infiltrates in the right lung. Cold agglutinins were markedly elevated and he had a greater than 4-fold rise in complement fixation antibody to *Mycoplasma pneumoniae*. Courtesy of Neal Halsey, MD.

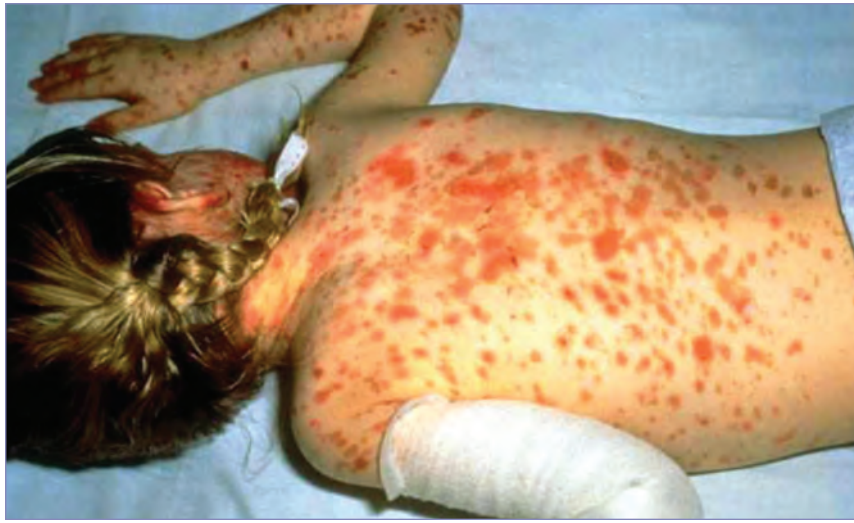


Image 91.7
Erythema multiforme rash (Stevens-Johnson syndrome) associated with *Mycoplasma pneumoniae* infection in a preadolescent girl.

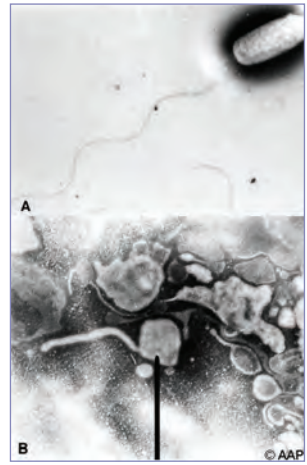


Image 91.8
A, Typical structure of a common gram-negative bacterium (*Pseudomonas aeruginosa*) and its flagellum, as seen on electron microscopy. B, Pleomorphic structure of *Mycoplasma pneumoniae*, as seen on electron microscopy. The bacterium is indicated by the black pointer. Mycoplasmas, including *M pneumoniae*, lack a cell wall.

CHAPTER 92

Nocardiosis

CLINICAL MANIFESTATIONS

Immunocompetent children typically develop cutaneous or lymphocutaneous disease with pustular or ulcerative lesions following soil contamination of a skin injury. Deep-seated tissue infection may follow traumatic soil-contaminated wounds. Immunocompromised people may develop invasive disease (pulmonary disease, which may disseminate). At-risk people include those with chronic granulomatous disease, human immunodeficiency virus infection, or disease requiring long-term systemic corticosteroid therapy or organ transplantation, or people having received tumor necrosis factor inhibitors, especially infliximab. Pulmonary disease commonly manifests as rounded nodular infiltrates that can undergo cavitation; the infection may be acute, subacute, or chronic. Hematogenous spread may occur from the lungs to the brain (single or multiple abscesses), to the skin (pustules, pyoderma, abscesses, mycetoma), or occasionally to other organs. Some experts recommend cerebrospinal fluid examination and/or neuroimaging in patients with pulmonary disease, even with a nonfocal neurologic examination, given the propensity of these organisms to infect the central nervous system. *Nocardia* organisms can be recovered from respiratory specimens of patients with cystic fibrosis, but the clinical significance of this pathogen in these patients is unclear.

ETIOLOGY

Nocardia are gram-positive, filamentous bacteria that belong to a group informally known as the aerobic actinomycetes. The cell walls of *Nocardia* organisms contain mycolic acid and thus may be described as “acid fast” or “partially acid fast” using special staining techniques and light microscopy.

EPIDEMIOLOGY

Nocardia species are ubiquitous environmental saprophytes, living in soil, organic matter, and water. Infections caused by *Nocardia* species typically are the result of environmental exposure through inhalation of soil or dust particles or through traumatic inoculation with a soil-contaminated object. The most prevalent species reported from human clinical sources in the United States are the *Nocardia asteroides* complex, which includes *Nocardia nova*, *Nocardia farcinica*, *Nocardia cyriacigeorgica*, and *Nocardia abscessus*. Primary cutaneous infection most often is associated with *Nocardia brasiliensis*. Other less common pathogenic species include *Nocardia brevicatena*, *Nocardia otitidiscaviarum*, *Nocardia pseudobrasiliensis*, *Nocardia transvalensis* complex, and *Nocardia veterana*.

Person-to-person and animal-to-human transmission is not known to occur.

The **incubation period** is unknown.

DIAGNOSTIC TESTS

Isolation of *Nocardia* species from clinical specimens can require extended incubation periods because of their slow growth. Specimens from sterile sites can be inoculated directly onto solid media. Specimens from nonsterile or contaminated sites, such as tissue or sputum, should be inoculated onto selective media, with a minimum incubation of 3 weeks. Recovery of *Nocardia* species from tissue can be improved if the laboratory is requested to observe cultures for up to 4 weeks in an appropriate liquid medium. Stained smears of sputum, body fluids, or pus demonstrating beaded, branching rods that stain weakly gram-positive and partially acid-fast by the modified Kinyoun method suggest the diagnosis. Because of the difficulty in interpretation of the acid-fast stain, positive and negative staining controls are suggested. The Brown-Brenn tissue gram-stain method and Grocott-Gomori methenamine silver stains are recommended to demonstrate microorganisms in tissue specimens.

Accurate identification of *Nocardia* isolates paired with antimicrobial susceptibility testing (the latter usually requires a specialty laboratory) greatly enhances the selection of appropriate antimicrobial therapy, thereby increasing the likelihood of favorable patient care outcomes. For *Nocardia* species, 16S rRNA gene sequence analysis of a nearly full-length (~1,440 bp) sequence can identify the isolate to the species level. Serologic tests for *Nocardia* species are not useful.

TREATMENT

Trimethoprim-sulfamethoxazole (TMP/SMX) or a sulfonamide alone (eg, sulfisoxazole or sulfamethoxazole) is the drug of choice for mild infections. Sulfonamides that are less urine soluble, such as sulfadiazine, should be avoided. Certain *Nocardia* species including *N farcinica*, *N nova*, and *N otitidiscaviarum* may demonstrate resistance to TMP/SMX. If infection does not respond to TMP/SMX, imipenem, meropenem, and fluoroquinolones may be considered. Other agents with specific *Nocardia* activity include clarithromycin (*N nova*) and amoxicillin-clavulanate (*N brasiliensis* and *N abscessus*). Linezolid has excellent activity against all *Nocardia* species. Pediatric data are lacking for many of these agents in treatment of nocardiosis. Immunocompetent patients with lymphocutaneous disease usually respond after 6 to 12 weeks of monotherapy.

Drainage of abscesses is beneficial, and removal of infected foreign bodies is recommended.

Combination drug therapy is recommended for patients with serious disease (pulmonary infection, disseminated disease, central nervous system involvement) and immunocompromised hosts. Initial combination treatment should include imipenem (resistance noted for some strains of *N brasiliensis*), amikacin, and TMP/SMX. Linezolid, ceftriaxone or cefotaxime (resistance noted for some strains of *N farcinica*, *N transvalensis*, and *N otitidiscaviarum*), meropenem, or minocycline are alternative agents. Immunocompromised patients and patients with serious disease should be treated for 6 to 12 months and for at least 3 months after apparent cure because of the propensity for relapse.

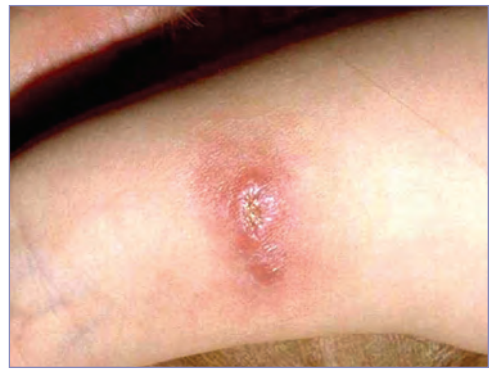


Image 92.1
Cutaneous nocardiosis of forearm in an immunocompetent preschool-aged boy.

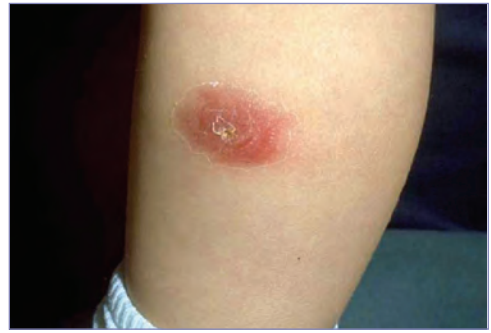


Image 92.2
Cutaneous nocardiosis of lower leg of immunocompetent preschool-aged girl.

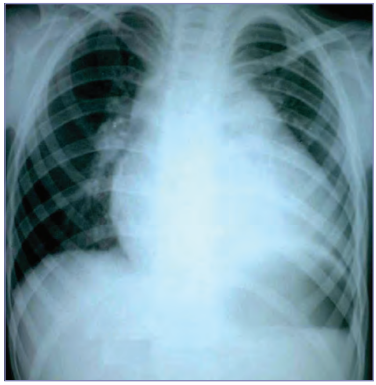


Image 92.3
Nocardia mediastinitis following surgical repair of ventricular septal defect (nosocomial infection). Courtesy of Edgar O. Ledbetter, MD, FAAP.

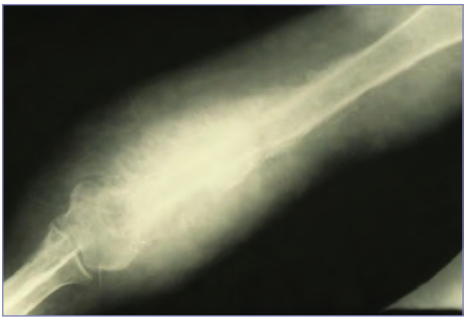


Image 92.5
This radiograph of a patient's right arm reveals the effects of actinomycotic mycetoma caused by *Nocardia asteroides,* which is among the most common actinomycetes that cause mycetoma worldwide. Mycetoma is a slowly progressive, destructive infection of the cutaneous and subcutaneous tissues and fascia, and, as seen here, it affects bone as well. Courtesy of Centers for Disease Control and Prevention.

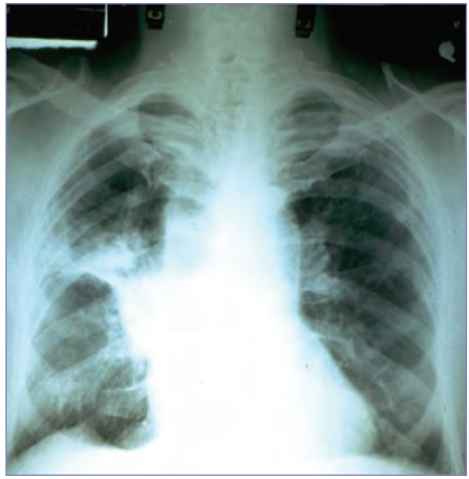


Image 92.4
Nocardia pneumonia, bilateral, in an immunocompromised child. Invasive nocardiosis is unusual in immunocompetent children.

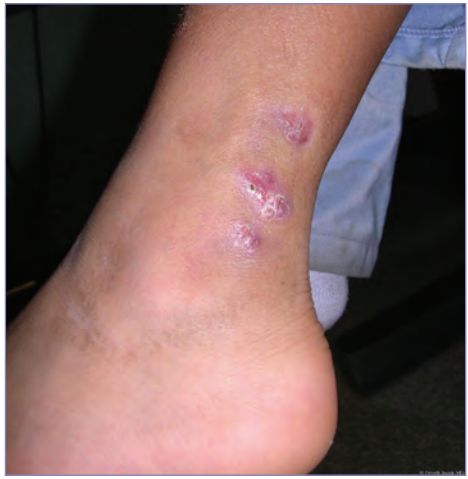


Image 92.6
A school-aged child with chronic rash on the lower left ankle. Histopathology confirmed *Nocardia brasiliensis*. Courtesy of Preeti Jaggi, MD.

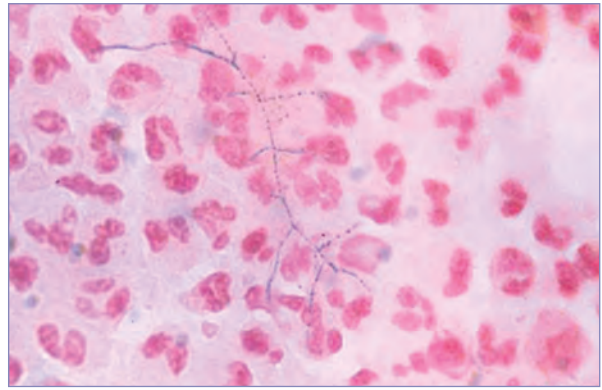


Image 92.7
Nocardia asteroides (Gram stain). Courtesy of Edgar O. Ledbetter, MD, FAAP.

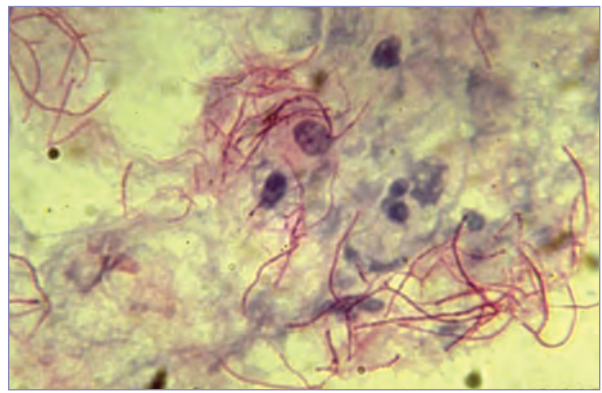


Image 92.8
Nocardia asteroides colony (tissue acid-fast stain).

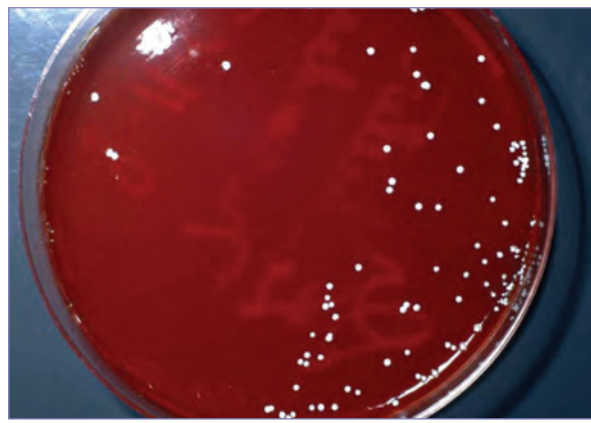


Image 92.9
Nocardia asteroides colonies (white, chalklike colonies on blood agar plate).

CHAPTER 93

Norovirus and Sapovirus Infections

CLINICAL MANIFESTATIONS

Abrupt onset of vomiting accompanied by watery diarrhea, abdominal cramps, and nausea are characteristic of norovirus gastroenteritis. Acute diarrhea without vomiting may also occur, most notably in children. Symptoms can last from 24 to 60 hours but usually no more than 48 hours. However, more prolonged courses of illness can occur, particularly among elderly people, young children, and hospitalized patients. Norovirus illness also is recognized as an important cause of chronic gastroenteritis in immunocompromised patients. Systemic manifestations, including fever, myalgia, malaise, anorexia, and headache, may accompany gastrointestinal tract symptoms. Since the introduction of rotavirus vaccines, noroviruses have become the leading cause of gastroenteritis in the United States.

ETIOLOGY

Noroviruses are 27- to 40-nm, nonenveloped, single-stranded RNA viruses of the family *Caliciviridae*. This family is classified into 5 known genera (*Lagovirus*, *Nebovirus*, *Vesivirus*, *Sapovirus*, and *Norovirus*) and 5 additional proposed genera (*Valovirus*, *Secalivirus*, *Recovirus*, *Nacovirus*, and *Bavovirus*). *Norovirus* and *Sapovirus* are the genera known to cause human infection. Noroviruses are genetically diverse, with 6 known (I–VI) and 3 proposed genogroups (VII–IX). Viruses from 4 genogroups (I, II, IV, and VIII) can cause human illness. Sapoviruses are divided into 5 major genogroups (I–V), of which viruses from 4 (GI, GII, GIV, and GV) cause disease in humans.

EPIDEMIOLOGY

Norovirus causes an estimated 1 in 15 US residents to become ill each year as well as 56,000 to 71,000 hospitalizations and 570 to 800 deaths, predominantly among young children and the elderly. Because of the success of rotavirus vaccines, noroviruses have become the predominant agent of pediatric viral gastroenteritis in the United States, causing both sporadic cases and outbreaks. Norovirus genogroup II, genotype 4 (GII.4) has been predominant worldwide during the past decade. Sapovirus infections also cause outbreaks, albeit significantly fewer than norovirus, and are a contributor to sporadic acute diarrhea in children. Asymptomatic norovirus excretion is common across all age groups, with the highest prevalence in children. Outbreaks with high attack rates tend to occur in semiclosed populations, such as long-term care facilities, schools, and cruise ships. Transmission is by person-to-person spread via the fecal-oral or vomitus-oral routes, through contaminated food or water, or by touching surfaces contaminated with norovirus and then touching the mouth. Norovirus is recognized as the most common cause of foodborne illness and foodborne disease outbreaks in the United States. Common-source outbreaks have been described after ingestion of ice, shellfish, and a variety of ready-to-eat foods, including salads, berries, and bakery products, usually contaminated by infected food handlers.

Norovirus recognizes and binds to histo-blood group antigens, which are expressed by the fucosyltransferase 2 (*FUT2*) gene, and individuals with a functional *FUT2* gene are referred to as "secretors." *FUT2* polymorphisms have been associated with increased host susceptibility to certain norovirus strains.

The **incubation period** is 12 to 48 hours. Viral shedding may start before onset of symptoms, peaks several days after exposure, and may persist for 4 weeks or more. Prolonged shedding (>6 months) can occur in immunocompromised hosts.

DIAGNOSTIC TESTS

Molecular diagnostic methods are the most sensitive way to detect norovirus or sapovirus. In children, interpretation of test results may be complicated by the frequent detection of viruses in fecal samples from asymptomatic children and the detection of multiple viruses in a single sample. Multiple multiplex nucleic acid-based assays for the detection of gastrointestinal pathogens are cleared by the US Food and Drug Administration, with the majority including norovirus testing and a select few including sapovirus. State and local public health laboratories use

real-time reverse transcriptase-polymerase chain reaction (RT-PCR) for detection of norovirus and sapovirus RNA in stool.

Norovirus was recently able to be cultured using human B cells and commensal bacteria; however, this diagnostic approach is not commercially available.

TREATMENT

Supportive therapy includes oral or intravenous rehydration solutions to replace and maintain fluid and electrolyte balance.

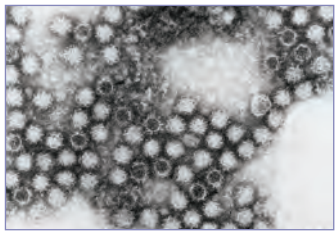


Image 93.1
Transmission electron micrograph of a feline calicivirus. Virions average 35 to 40 nm in diameter. Cuplike surface depressions sometimes manifest in a Star of David array. Courtesy of Centers for Disease Control and Prevention.

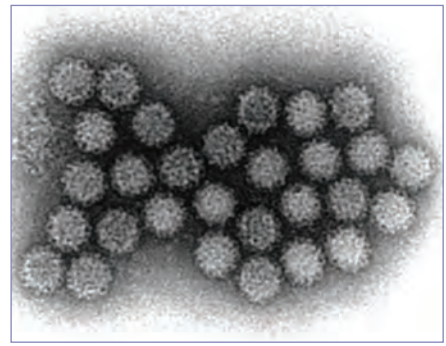


Image 93.2
This is a norovirus in a stool specimen from a patient with acute gastroenteritis, visualized by negative contrast staining and transmission electron microscopy. Particles frequently appear in clumps. Noroviruses are small, round-structured viruses (particle size, 28–32 nm) with a rough surface that contrasts with the smooth edge of astroviruses and picornaviruses, which also can be found in stool specimens. Copyright David O. Matson, MD, PhD, FAAP.

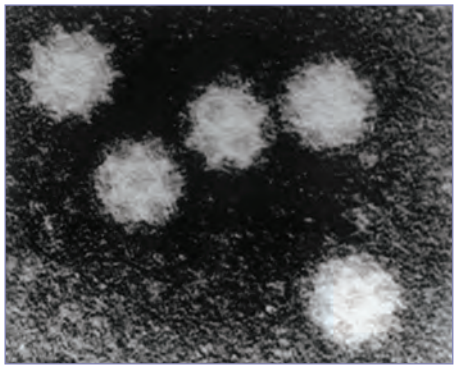


Image 93.3
Calicivirus from clinical specimens and after cryoelectronic image reconstruction. This is *Sapovirus* species in a stool specimen from a patient with acute gastroenteritis, visualized by negative contrast staining and transmission electron microscopy. *Sapovirus* species are typical caliciviruses because they manifest as a particle with 10 surface spikes (top left particle) or a Star of David (bottom left particle), depending on the particle orientation, as do many animal caliciviruses.

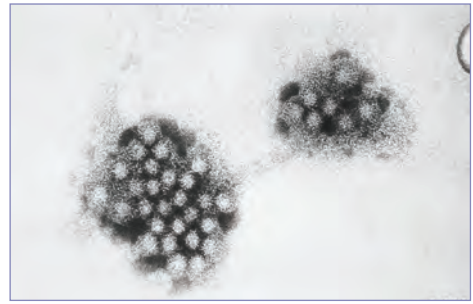


Image 93.4
An electron micrograph of a norovirus, with 27- to 32-nm viral particles. Noroviruses (and related caliciviruses) are important causes of nonbacterial gastroenteritis in the United States. An estimated 181,000 cases of this type of food poisoning occur annually.

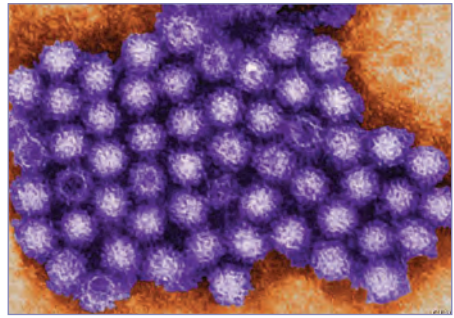


Image 93.5
This transmission electron micrograph revealed some of the ultrastructural morphology displayed by norovirus virions (virus particles). Noroviruses belong to the genus *Norovirus* and the family *Caliciviridae*. They are a group of related, single-stranded RNA, nonenveloped viruses that cause acute gastroenteritis in humans. Courtesy of Centers for Disease Control and Prevention/Charles D. Humphrey.

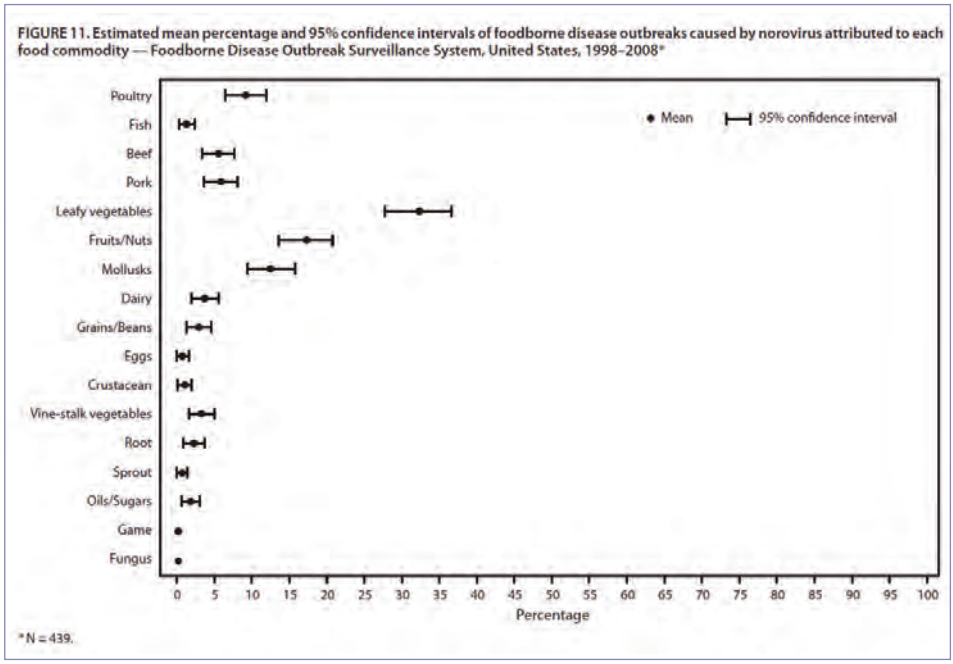


Image 93.6
Estimated mean percentage and 95% confidence intervals of foodborne disease outbreaks caused by norovirus attributed to each food commodity—Foodborne Disease Outbreak Surveillance System, United States, 1998–2008. Courtesy of *Morbidity and Mortality Weekly Report*.

CHAPTER 94

Onchocerciasis

(River Blindness, Filariasis)

CLINICAL MANIFESTATIONS

The disease involves skin, subcutaneous tissues, lymphatic vessels, and eyes. Subcutaneous, nontender nodules that can be up to several centimeters in diameter containing male and female worms develop 6 to 12 months after initial infection. In patients in Africa, nodules tend to be found on the lower torso, pelvis, and lower extremities, whereas in patients in Central and South America, the nodules more often are located on the upper body (the head and trunk) but also can occur on the extremities. After the worms mature, fertilized females produce embryos called microfilariae that migrate to the dermis and may cause a papular dermatitis. Pruritus often is highly intense, resulting in patient-inflicted excoriations over the affected areas. After a period of years, skin can become lichenified and hypo- or hyperpigmented. Microfilariae may invade ocular structures, leading to inflammation of the cornea, iris, ciliary body, retina, choroid, and optic nerve. Loss of visual acuity and blindness can result over time if the disease is left untreated.

ETIOLOGY

Onchocerca volvulus is a filarial nematode and 1 of 8 species of filarial worms that commonly infect humans.

EPIDEMIOLOGY

O volvulus has no significant animal reservoir. Microfilariae in human skin infect *Simulium* species flies (black flies) when they take a blood meal; microfilariae then, in 10 to 14 days, develop in the vector into infectious larvae that are transmitted with subsequent bites. Black flies breed in fast-flowing streams and rivers (hence, the colloquial name for the disease, "river blindness"). The disease occurs primarily in equatorial Africa, but small foci are found in Venezuela, Brazil, and Yemen. Prevalence is greatest among people who live near vector breeding sites. Person-to-person or blood transfusion transmission does not occur.

The **incubation period** from larval inoculation to microfilariae in the skin usually is 12 to 18 months (sometimes 3 years).

DIAGNOSTIC TESTS

Direct examination of a 1- to 2-mg shaving or biopsy specimen of the epidermis and upper dermis (usually taken from the posterior iliac crest area) can reveal microfilariae. Microfilariae are not found in blood. Adult worms may be demonstrated in excised nodules that have been sectioned and stained. A slit-lamp examination of an involved eye may reveal motile microfilariae in the anterior chamber or "snowflake" corneal lesions. Eosinophilia is common. Specific serologic tests and polymerase chain reaction techniques for detection of microfilariae in skin are available in the United States in research and public health laboratories, including the Centers for Disease Control and Prevention.

TREATMENT

Ivermectin, a microfilaricidal agent, is the drug of choice for treatment of onchocerciasis. Treatment decreases dermatitis and the risk of developing severe ocular disease but does not kill the adult worms (which can live for more than a decade) and, thus, is not curative. One single oral dose of ivermectin should be given every 6 to 12 months until asymptomatic. Adverse reactions to treatment are caused by death of microfilariae and can include rash, edema, fever, myalgia, and rarely, asthma exacerbation and hypotension. Such reactions are more common in people with higher skin loads of microfilaria and decrease with repeated treatment in the absence of reexposure. Precautions to ivermectin treatment include pregnancy, central nervous system disorders, and high levels of circulating *Loa* microfilaremia. Treatment of patients with high levels of circulating *Loa loa* microfilaremia with ivermectin rarely can result in fatal encephalopathy. Referral to a tropical medicine specialist would be indicated for people coinfected with *Onchocerca volvulus* and *L loa*. The American Academy of Pediatrics notes that ivermectin usually is compatible with breastfeeding. Because low levels of drug are found in human milk after maternal treatment, some experts recommend delaying maternal treatment until

the infant is 7 days of age. Safety and effectiveness of ivermectin in pediatric patients weighing less than 15 kg have not been established.

A 6-week course of doxycycline can be used to kill adult worms through depletion of the endosymbiotic rickettsia-like bacteria *Wolbachia*, which appear to be required for survival of *O volvulus*. Doxycycline can be used for short durations (ie, 21 days or less) without regard to patient age, but for the longer treatment durations required in for treatment of *O volvulus*, for whom the alternative treatment of ivermectin exists, doxycycline is not recommended for children younger than 8 years. Doxycycline may be used for children 8 years or older and nonpregnant adults to obviate the need for years of ivermectin treatment. Doxycycline treatment may be initiated 1 week after treatment with ivermectin; for patients without symptoms, a 6-week course of doxycycline may be given, followed by a dose of ivermectin.

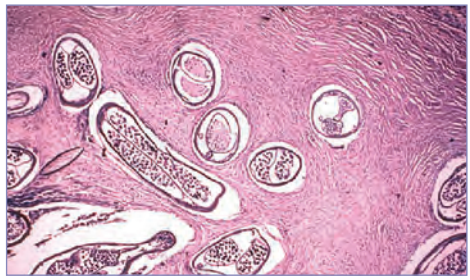


Image 94.1
Histopathologic features of *Onchocerca* nodule in onchocerciasis. Courtesy of Centers for Disease Control and Prevention.

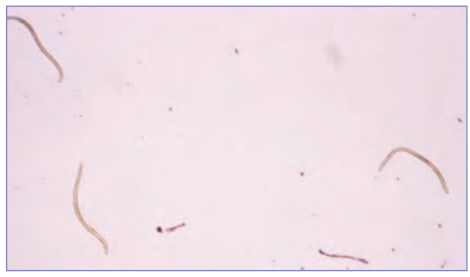


Image 94.2
This is a glycerin mount photomicrograph of the microfilarial pathogen *Onchocerca volvulus* in its larval form. Courtesy of Centers for Disease Control and Prevention.

Image 94.3
As an adult, this *Simulium* species larva, or blackfly, is a vector of the disease onchocerciasis, or river blindness. The blackfly larva is usually a filter-feeder, feeding on nutrients extracted from passing currents. Prior to entering the pupal stage, a *Simulium* species larva passes through 6 larval stages and then encases itself in a silken, submerged cocoon. Courtesy of Centers for Disease Control and Prevention.

Image 94.4
These are *Simulium* species of flies, or blackflies, a vector of the disease onchocerciasis, or river blindness. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 95

Human Papillomaviruses

CLINICAL MANIFESTATIONS

Most human papillomavirus (HPV) infections are subclinical, and 90% resolve spontaneously within 2 years. However, persistent HPV infection can cause benign epithelial proliferation (warts) of the skin and mucous membranes as well as cancers of the lower anogenital tract and the head and neck. HPVs can be grouped into cutaneous and mucosal types. The cutaneous types cause common skin warts, plantar warts, flat warts, and threadlike (filiform) warts. Cutaneous warts are benign. Certain mucosal types (low risk) are associated with warts or papillomas of mucous membranes, including the upper respiratory tract and anogenital, oral, nasal, and conjunctival areas. Other mucosal types (high risk) are associated with precancers and cancers, including cervical, anogenital, and oropharyngeal cancers.

Common skin warts are dome-shaped with conical projections that give the surface a rough appearance. Skin warts usually are painless and multiple, occurring commonly on the hands and around or under the nails. When small dermal vessels become thrombosed, black dots appear in the warts.

Plantar warts on the foot often are larger than warts at other sites and may not project through much of the skin surface. They can be painful when walking and are characterized by marked hyperkeratosis, sometimes with black dots. **Flat warts** ("juvenile warts") commonly are found on the face and extremities of children and adolescents. Flat warts usually are small, multiple, and flat topped, seldom exhibit papillomatosis, and rarely cause pain. **Filiform warts** occur on the face and neck.

Anogenital warts, also called **condylomata acuminata,** are skin-colored warts with a papular, flat or cauliflower-like surface that range in size from a few millimeters to several centimeters; these warts often occur in groups. In males, these warts may be found on the penis, scrotum, or anal or perianal area. In females, these lesions may occur on the vulvar, anal, or perianal areas and less commonly in the vagina or on the cervix. Warts usually are painless, although they may cause itching, burning, local pain, or bleeding.

Invasive cancers attributable to HPV include those of cervix, vagina, vulva, penis, anus, and oropharynx (back of throat, base of tongue, and tonsils). Cervical cancer is the most common HPV-attributable cancer among women, and oropharyngeal cancer is the most common HPV-attributable cancer among men. Anogenital **low-grade squamous intraepithelial lesions** (**LSILs**) can result from persistent infection with low-risk or high-risk HPV types, whereas **high-grade squamous intraepithelial lesions** (**HSILs**) can result from persistent infection with high-risk HPV types. In the cervix, HSILs typically indicate the presence of **cervical intraepithelial neoplasia** (**CIN**) grades 2 or 3, which are precancerous lesions. These lesions are detected through routine screening with cytologic testing (Papanicolaou [Pap] test) and/or clinical HPV tests; tissue biopsy is required to make the diagnosis. Endocervical glandular precancer, **adenocarcinoma in situ** (**AIS**), also can result from persistent infection with high-risk HPV types.

Recurrent respiratory papillomatosis is a rare condition characterized by recurring papillomas in the larynx or other areas of the upper respiratory tract. Recurrent respiratory papillomatosis is called juvenile onset when it occurs before 18 years of age; adult onset also occurs. Juvenile onset recurrent respiratory papillomatosis is believed to result from vertical transmission of HPV types 6 or 11 from a mother to her infant at the time of delivery and is diagnosed most commonly in children between 2 and 5 years of age, with manifestations of voice change (eg, hoarseness), stridor, or abnormal cry. Respiratory papillomas can cause respiratory tract obstruction in young children, and repeated surgeries often are needed.

Epidermodysplasia verruciformis is a rare, inherited disorder believed to be a consequence of a deficiency of cell-mediated immunity resulting in an abnormal susceptibility to certain HPV types and manifesting as chronic cutaneous lesions and skin cancers. Lesions may resemble flat warts or pigmented plaques

covering the torso and upper extremities. Most appear during the first decade of life, but malignant transformation, which occurs in 30% to 60% of affected people, usually is delayed until adulthood.

ETIOLOGY

HPVs are small, nonenveloped, double-stranded DNA viruses of the *Papillomaviridae* family, which can be grouped into types based on DNA sequence variation. Different types display different specific tissue tropism. Types 6 and 11 cause condylomata acuminata, recurrent respiratory papillomatosis, and conjunctival papillomas but rarely are found in cancer; they are referred to as low-risk types. High-risk types (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68, which are included in HPV clinical tests) can cause low-grade cervical cell abnormalities, high-grade cervical cell abnormalities that are precursors to cancer, and anogenital cancers. High-risk HPV types are detected in 99% of cervical precancers and 90% of invasive cervical cancer. Approximately 50% of cervical cancers worldwide are attributable to HPV type 16, and 70% are attributable to types 16 and 18. The majority of other HPV-related cancers—anogenital cancers (vulvar, vaginal, penile, anal) and oropharyngeal cancers—are attributable to HPV type 16. Risk of developing cancer precursors or cancers is greater in people with certain immunocompromising conditions, such as human immunodeficiency virus (HIV) infection.

EPIDEMIOLOGY

Virtually all adults will be infected with some type of HPV during their lives. In the United States, HPV infection prevalence is 79 million, and annual incidence is 14 million infections. HPV types involved in common hand and foot warts are quite different from mucosal types. Nongenital hand and foot warts occur commonly among school-aged children, in whom prevalence is as high as 50%. Acquisition can occur through casual contact and is facilitated by minor skin trauma. Autoinoculation can result in spread of lesions. The intense and often widespread appearance of cutaneous warts in people with compromised cellular immunity (particularly those who have undergone transplantation or who have HIV infection) suggests that alterations in T-lymphocyte immunity may impair clearance of infection.

Genital HPV infections are transmitted primarily by skin-to-skin contact, usually through sexual intercourse and other close genital contact. In US females, the highest prevalence of infection is in 20- to 24-year-olds. Most infections are subclinical and clear spontaneously within 2 years. Cancer is an uncommon outcome of infection that generally requires decades of persistent infection with high-risk HPV types. There are nearly 31,000 cases of HPV-attributable cancers annually in the United States. Cervical cancer accounts for approximately 12,000 new cases and 4,000 deaths annually in the United States. HPV also is the cause of most vulvar, vaginal, penile, and anal cancers as well as 70% of oropharyngeal cancers.

Rarely, HPV infection is transmitted to a child through the birth canal during delivery or transmitted from nongenital sites. When anogenital warts are identified in a child, sexual abuse must be considered while noting the possibility of vertical transmission to neonates.

The **incubation period** for symptoms of HPV infection is estimated from 3 months to several years.

DIAGNOSTIC TESTS

Most cutaneous and anogenital warts can be diagnosed through clinical inspection. Routine cervical cancer screening guidelines direct the interval at which cytologic screening (Pap testing) should be performed, when HPV clinical tests ("co-testing") should be added, and when colposcopic evaluation with biopsy should be performed. Vulvar, vaginal, penile, and anal lesions may be identified using visual inspection, sometimes using magnification; in some cases, cytologic screening is used and suspicious lesions are biopsied, but there is no routine screening recommended for cancers at these sites. For all anogenital lesions, diagnosis is made on the basis of histologic findings. Respiratory papillomatosis is diagnosed using endoscopy and biopsy.

Although cytologic and histologic changes can be suggestive of HPV, these findings are not diagnostic of HPV. Detection of HPV infection is based on detection of viral nucleic acid (DNA or RNA). Clinical tests for high-risk HPV types may be used in combination with Pap testing for cervical cancer screening in women 30 years or older and for triage of equivocal Pap test abnormalities (atypical squamous cells of undetermined significance [ASCUS]) in women 21 years or older. The benefit of adding HPV testing to the Pap test is that the rate of false-negative results with the Pap test is reduced with a negative test result for high-risk HPV types, allowing longer intervals (eg, 5 years) between routine Pap test screenings.

A number of HPV DNA or mRNA detection and genotyping assays have been approved by the FDA. Liquid-based cytology collection and transport kits permit performance of Pap smear cytology and HPV detection and genotyping on the same specimen. There are differences in the appropriate clinical applications for each of these assays, including whether they can be used as an initial standalone test (ie, without cervical cytology) or in a primary screening algorithm; none is recommended for use in women younger than 21 years or for men.

TREATMENT

There is no treatment for HPV infection. Treatment may be directed toward lesions caused by HPV. Regression of **nongenital and genital warts** occurs in approximately 30% of cases within 6 months. Most methods of treatment of **cutaneous warts** use chemical or physical destruction of the infected epithelium, including cryotherapy with liquid nitrogen, laser or surgical removal of warts, application of salicylic acid products, or application of topical immune-modulating agents. Daily treatment with tretinoin has been useful for widespread flat warts in children. Care should be taken to avoid deleterious cosmetic results with therapy. Systemic treatments for refractory warts, including cimetidine, have been used with varying success.

Treatments for genital warts are characterized as patient-applied or provider administered. Interventions include ablational/excisional treatments or topical antiproliferative or immune-modulating medications. Oral warts can be removed through cryotherapy, electrocautery, or surgical excision. Although most forms of therapy are successful for initial removal of warts, treatment may not eradicate HPV infection from the surrounding tissue. Recurrences are common and may be attributable to reactivation rather than reinfection.

Cancer precursor lesions that are identified in the cervix (HSILs, AIS) or elsewhere in the genital tract may require excision or destruction. Treatment of cervical lesions can cause substantial economic, emotional, and reproductive adverse effects, including higher risk of preterm birth. Management of invasive cervical and other anogenital and oropharyngeal cancers requires a specialist and should be conducted according to current guidance.

Respiratory papillomatosis is difficult to treat and is best managed by an experienced otolaryngologist. Local recurrence is common, and repeated surgical debulking procedures are necessary to relieve airway obstruction. Extension or dissemination of respiratory papillomas from the larynx into the trachea, bronchi, or lung parenchyma is rare but can result in increased morbidity and mortality; malignant transformation occurs rarely.

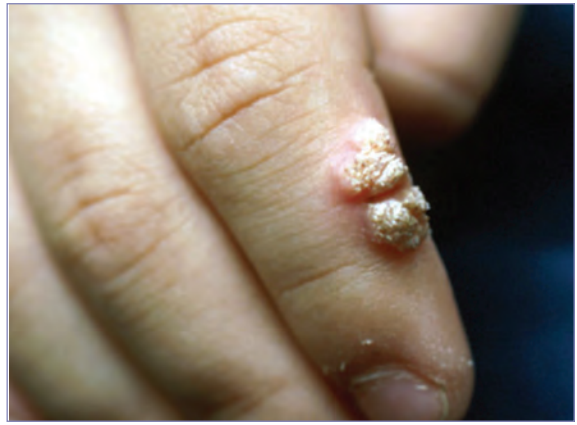


Image 95.1
Digitate human papillomavirus wart with fingerlike projections on a child's index finger. Copyright Gary Williams.

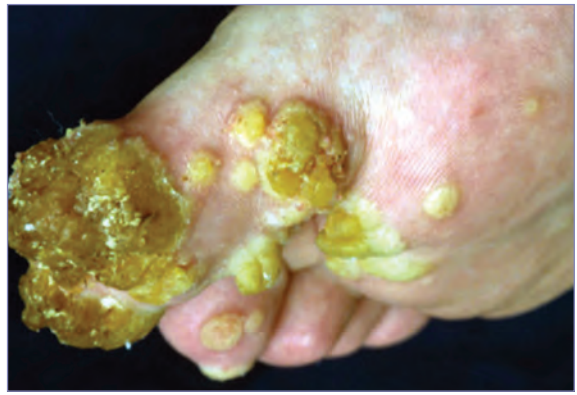


Image 95.2
Human papillomavirus warts on the foot of an immunocompromised 14-year-old boy. Copyright Gary Williams.

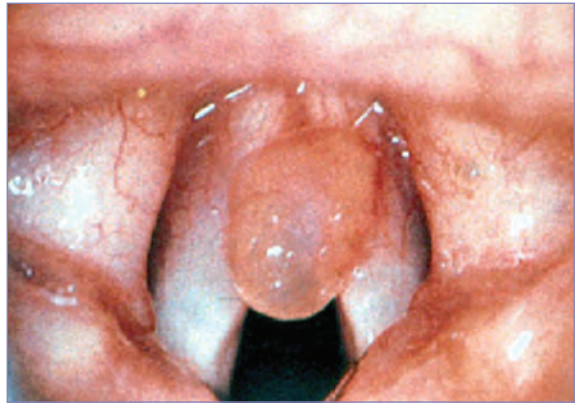


Image 95.3
Laryngeal papillomas may cause hoarseness. Although rare, they can occur in infants of mothers infected with human papillomavirus.

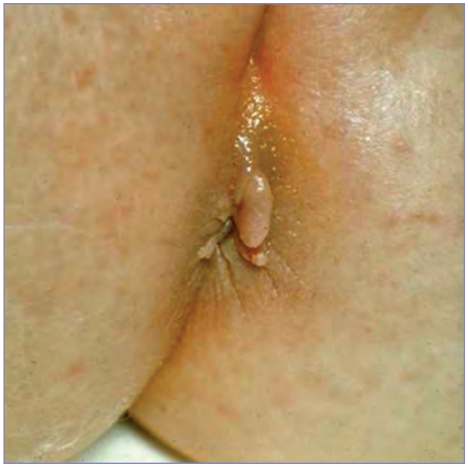


Image 95.4
A 13-month-old girl with condyloma acuminata around the anus from sexual abuse (sodomy). Copyright Martin G. Myers, MD.

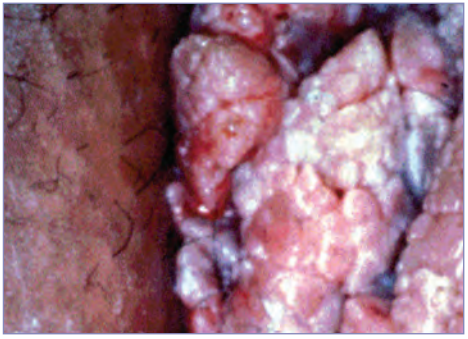


Image 95.5
Massive condyloma acuminata (genital warts) in a 10-year-old girl who had been sexually abused. These genital warts are commonly caused by human papillomavirus, especially types 6 and 11.

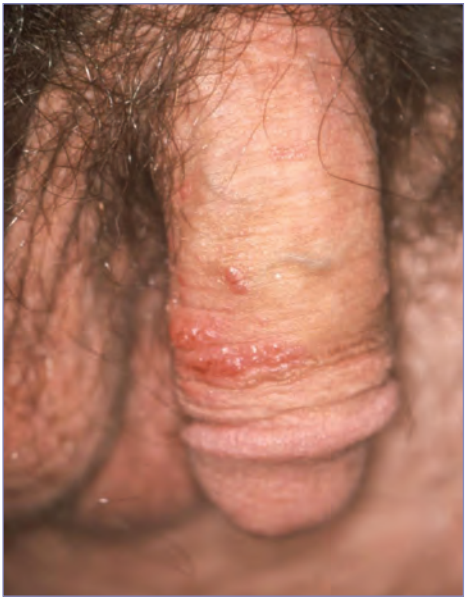


Image 95.6
This patient with condylomata acuminata presented with soft, wartlike growths on the penis (12 hours postpodophyllin application). Condylomata acuminata refers to an epidermal manifestation caused by epidermotropic human papillomavirus. The most commonly affected areas are the penis, vulva, vagina, cervix, perineum, and perianal area. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 96

Paracoccidioidomycosis

(Formerly Known as South American Blastomycosis)

CLINICAL MANIFESTATIONS

Disease occurs primarily in adults, in whom the site of initial infection is the lungs. Disease is infrequent in children, in whom approximately 5% to 10% of all cases occur. Clinical patterns can include subclinical infection or progressive disease that can be either acute-subacute (juvenile type) or chronic (adult type). In both adult and juvenile forms, constitutional symptoms, such as fever, malaise, anorexia, and weight loss, are common. In the juvenile form, the initial pulmonary infection usually is asymptomatic, and manifestations are related to dissemination of infection to the reticuloendothelial system, resulting in enlarged lymph nodes and involvement of liver, spleen, and bone marrow. Skin lesions are observed regularly and are located typically on the face, neck, and trunk. Involvement of bones, joints, and mucous membranes is less common. Enlarged lymph nodes occasionally coalesce and form abscesses or fistulas. The chronic form of the illness can be localized to the lungs or can disseminate. Oral mucosal lesions are observed in half of the cases. Skin involvement is common but occurs in a smaller proportion than in patients with the acute-subacute form. Infection can be latent for years before causing illness.

ETIOLOGY

Paracoccidioides brasiliensis is a thermally dimorphic fungus with yeast and mycelia (mold) phases. A new species, *Paracoccidioides lutzii*, also causes paracoccidioidomycosis.

EPIDEMIOLOGY

The infection occurs in Latin America, from Mexico to Argentina, with 80% of cases in Brazil. The natural reservoir is unknown, although soil is suspected. The mode of transmission is unknown but most likely occurs via inhalation of contaminated soil or dust; person-to-person transmission does not occur.

The **incubation period** is variable (range, 1 month to decades); prior residence in Latin America is critical.

DIAGNOSTIC TESTS

A number of serologic tests are available; quantitative immunodiffusion is the preferred test. The antibody titer by immunodiffusion usually is ≥1:32 in acute infection. Round, multiple-budding yeast cells with a distinguishing pilot's wheel appearance can be seen in preparations of sputum, bronchoalveolar lavage specimens, scrapings from ulcers, and material from lesions or in tissue biopsy specimens. Several procedures, including wet or KOH wet preparations, or histologic staining with hematoxylin and eosin, silver, or periodic-acid Schiff, are adequate for visualization of fungal elements. The mycelia form of *P brasiliensis* can be cultured on most enriched media, including blood agar and Sabouraud dextrose agar. Cultures should be held at least 4 weeks.

TREATMENT

Amphotericin B is preferred by many experts for initial treatment of severe paracoccidioidomycosis. An alternative is intravenous trimethoprim-sulfamethoxazole. Children treated initially by the intravenous route can transition to orally administered therapy after clinical improvement has been observed, usually after 3 to 6 weeks, and the duration of total acute treatment usually lasts for 6 to 12 months.

Oral therapy with itraconazole is the treatment of choice for less severe or localized infection and to complete treatment when amphotericin B is used initially. Itraconazole oral solution is preferred to capsules. Serum trough concentrations of itraconazole should be 1 to 2 μg/mL. Concentrations should be checked after 1 to 2 weeks of therapy to ensure adequate drug exposure.

Prolonged therapy for 6 to 12 months is necessary to minimize the relapse rate. Children with severe disease can require a longer course. Voriconazole is as well tolerated and as effective as itraconazole in adults, but data for its use in children with paracoccidioidomycosis are not available. Serial serologic testing by quantitative immunodiffusion is useful for monitoring the response to therapy. The expected response is a progressive decline in titers after 1 to 3 months of treatment with stabilization at a low titer for years or even lifelong.

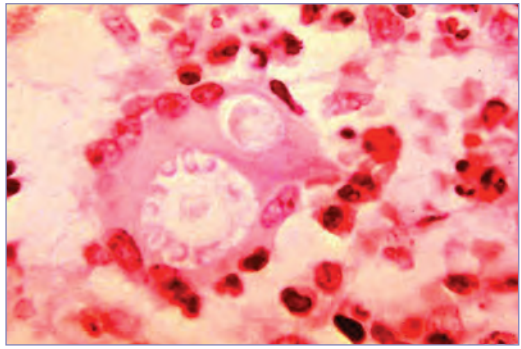


Image 96.1
Histopathologic features of paracoccidioidomycosis, skin. Budding cell of *Paracoccidioides brasiliensis* within multinucleated giant cell. Courtesy of Centers for Disease Control and Prevention.

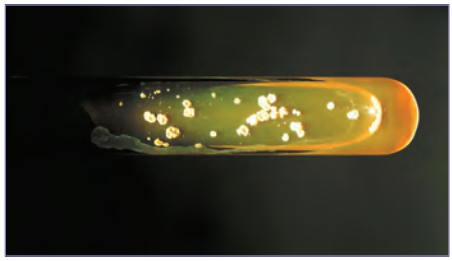


Image 96.2
Pictured is a Sabouraud dextrose agar slant culture of the fungus *Paracoccidioides brasiliensis* grown at 37°C (98.6°F). This is the only etiological agent for the disease paracoccidioidomycosis. *P brasiliensis* is geographically restricted to areas of South and Central America. Courtesy of Centers for Disease Control and Prevention.

Image 96.3
This is a slant culture growing the fungus *Paracoccidioides brasiliensis* during its yeast phase. Inhalation of *P brasiliensis* conidia is presumably the route of acquisition. The primary infection is asymptomatic in most cases and can remain dormant for years within lymph nodes, reappearing later, usually due to some type of immunodeficiency. Courtesy of Centers for Disease Control and Prevention.

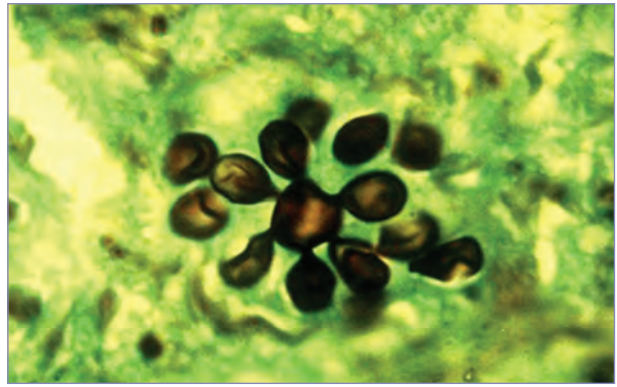


Image 96.4
Histopathologic features of paracoccidioidomycosis. Budding cell of *Paracoccidioides brasiliensis* (methenamine silver stain). Courtesy of Centers for Disease Control and Prevention.

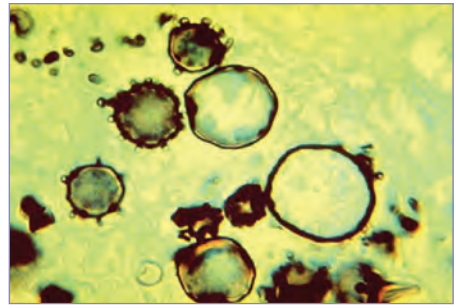


Image 96.5
Histopathologic features of paracoccidioidomycosis, liver. Minute buds on several cells of *Paracoccidioides brasiliensis* (methenamine silver stain). Courtesy of Centers for Disease Control and Prevention.

Image 96.6
Histopathology of paracoccidioidomycosis. Budding cells of *Paracoccidioides brasiliensis* (methenamine silver stain). Courtesy of Centers for Disease Control and Prevention.

CHAPTER 97

Paragonimiasis

CLINICAL MANIFESTATIONS

There are 2 major forms of paragonimiasis: (1) disease principally attributable to *Paragonimus westermani*, *Paragonimus heterotremus*, *Paragonimus africanus*, *Paragonimus uterobilateralis*, and *Paragonimus kellicotti*, causing primary pulmonary disease with or without extrapulmonary manifestations, and (2) disease attributable to other species of *Paragonimus*, most notably *Paragonimus skrjabini*, for which humans are accidental hosts and manifestations generally are extrapulmonary, resulting in a larva migrans syndrome similar to that caused by *Toxocara canis*. The former disease is especially likely to have an insidious onset and a chronic course. Pulmonary disease is associated with chronic cough and dyspnea, but most infections probably are inapparent or result in mild symptoms. During worm migration in the lungs, migratory infiltrates may be noted on serial imaging. Heavy infestations cause paroxysms of coughing, which often produce blood-tinged sputum that is brown because of the presence of the pigmented *Paragonimus* eggs and hemosiderin. Hemoptysis can be severe. Eosinophilic pleural effusion, pneumothorax, bronchiectasis, and pulmonary fibrosis with clubbing can develop.

Extrapulmonary manifestations may involve the liver, spleen, abdominal cavity, intestinal wall, intra-abdominal lymph nodes, skin, and central nervous system, with meningoencephalitis, seizures, and space-occupying tumors attributable to invasion of the brain by adult flukes, usually occurring within a year of pulmonary infection. Symptoms tend to subside after approximately 5 years but can persist for as many as 20 years. Extrapulmonary paragonimiasis also is associated with migratory allergic subcutaneous nodules, which contain juvenile worms.

ETIOLOGY

Paragonimiasis is caused by the lung fluke (trematode, flat worm) *Paragonimus*. In Asia, classical paragonimiasis is caused by adult flukes and eggs of *P westermani* and *P heterotremus*. In Africa, the adult flukes and eggs of *P africanus* and *P uterobilateralis* produce the disease, whereas in North America the endemic species is *P kellicotti*. In North America, disease also has been caused by *P westermani*, present in imported crab. The adult flukes of *P westermani* are up to 12 mm long and 7 mm wide and occur throughout Asia. A triploid parthenogenetic form of *P westermani*, which is larger, produces more eggs, and elicits greater disease, has been described in Japan, Korea, Taiwan, and parts of eastern China. *P heterotremus* occurs in Southeast Asia and adjacent parts of China.

Extrapulmonary paragonimiasis (ie, visceral larva migrans) is caused by larval stages of *P skrjabini* and *Paragonimus miyazakii*. The worms rarely mature in infected human tissues. *P skrjabini* occurs in China, whereas *P miyazakii* occurs in Japan. *Paragonimus mexicanus* and *Paragonimus ecuadoriensis* occur in Mexico, Costa Rica, Ecuador, and Peru. *P kellicotti*, a lung fluke of mink, opossums, and other animals in the United States, can cause infection in humans.

EPIDEMIOLOGY

Transmission occurs when raw or undercooked freshwater crabs or crayfish containing larvae (metacercariae) are ingested. Numerous cases have been associated with ingestion of uncooked or undercooked crawfish and during exposure to river water during canoeing or camping trips in the Midwestern United States. The metacercariae excyst in the small intestine and penetrate the abdominal cavity, where they remain for a few days before migrating through the diaphragm to the lungs. *P westermani* and *P heterotremus* mature within the lungs over 6 to 10 weeks, when they then begin egg production. Eggs escape from pulmonary capsules into the bronchi and exit from the human host in sputum or feces. Eggs hatch in freshwater within 3 weeks, giving rise to miracidia. Miracidia penetrate freshwater snails and emerge several weeks later as cercariae, which encyst within the muscles and viscera of freshwater crustaceans before maturing into infective metacercariae. A less common mode of transmission that also may occur is human infection through ingestion of raw pork, usually

from wild pigs, containing the juvenile stages of *Paragonimus* species (described as occurring in Japan).

Humans are accidental ("dead-end") hosts for *P skrjabini* and *P miyazakii* in visceral larva migrans. These flukes cannot mature in humans and, hence, do not produce eggs. *Paragonimus* species infect a variety of other mammals, such as canids, mustelids, felids, and rodents, which serve as animal reservoir hosts.

The incubation period is variable. Egg production begins approximately 8 weeks after ingestion of *P westermani* metacercariae.

DIAGNOSIS

Microscopic examination of stool, sputum, pleural fluid, cerebrospinal fluid, and other tissue specimens may reveal eggs. A Western blot serologic antibody test based on *P westermani* antigen, available at the Centers for Disease Control and Prevention (CDC), is sensitive and specific, and specific antibody concentrations detected by immunoblot decrease slowly after the infection is cured by treatment. Charcot-Leyden crystals and eosinophils in sputum are useful diagnostic elements. Peripheral blood eosinophilia is characteristic. Chest radiographs may appear normal or may resemble radiographs from patients with tuberculosis or malignancy.

TREATMENT

Praziquantel in a 2- to 3-day course is the treatment of choice and is associated with high cure rates with disappearance of egg production and radiographic lesions in the lungs. The drug also is effective for some extrapulmonary manifestations. An alternative drug for patients unable to take praziquantel is triclabendazole, given in 1 or 2 doses. Triclabendazole is available to US-licensed physicians through the CDC Drug Service, under a special protocol. For patients with central nervous system paragonimiasis, a short course of steroids may be beneficial in addition to the praziquantel, to reduce the inflammatory response associated with the dying flukes.

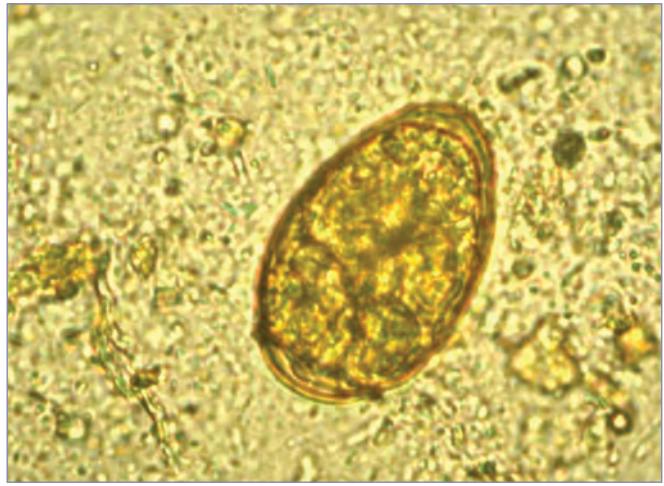


Image 97.1
Paragonimus westermani ova in stool preparation (original magnification ×400).

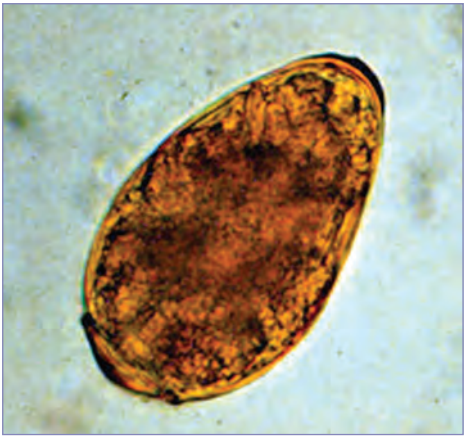


Image 97.2
Ovum of *Paragonimus westermani*. The average ovum size is 85 by 53 µm (range, 68–118 µm by 39–67 µm). They are yellow-brown and ovoid or elongate, with a thick shell, and often asymmetrical, with one end slightly flattened. At the large end, the operculum is clearly visible. The opposite (abopercular) end is thickened. The ova of *P westermani* are excreted unembryonated and may be found in the stool or sputum. Courtesy of Centers for Disease Control and Prevention.

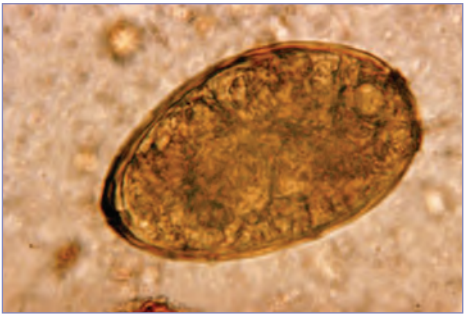


Image 97.3
This micrograph depicts an egg from the trematode parasite *Paragonimus westermani*. This parasite's eggs range in size from 68 to 118 µm by 39 to 67 µm. They are yellow-brown and ovoidal or elongated, with a thick shell, and often asymmetrical, with one end slightly flattened. At the large end, the operculum (ie, lid or covering) is visible. Courtesy of Centers for Disease Control and Prevention.

Image 97.4
Eating raw or undercooked crabs or crayfish can result in human paragonimiasis, a parasitic disease caused by *Paragonimus westermani* and *Paragonimus heterotrema*. Courtesy of Centers for Disease Control and Prevention.

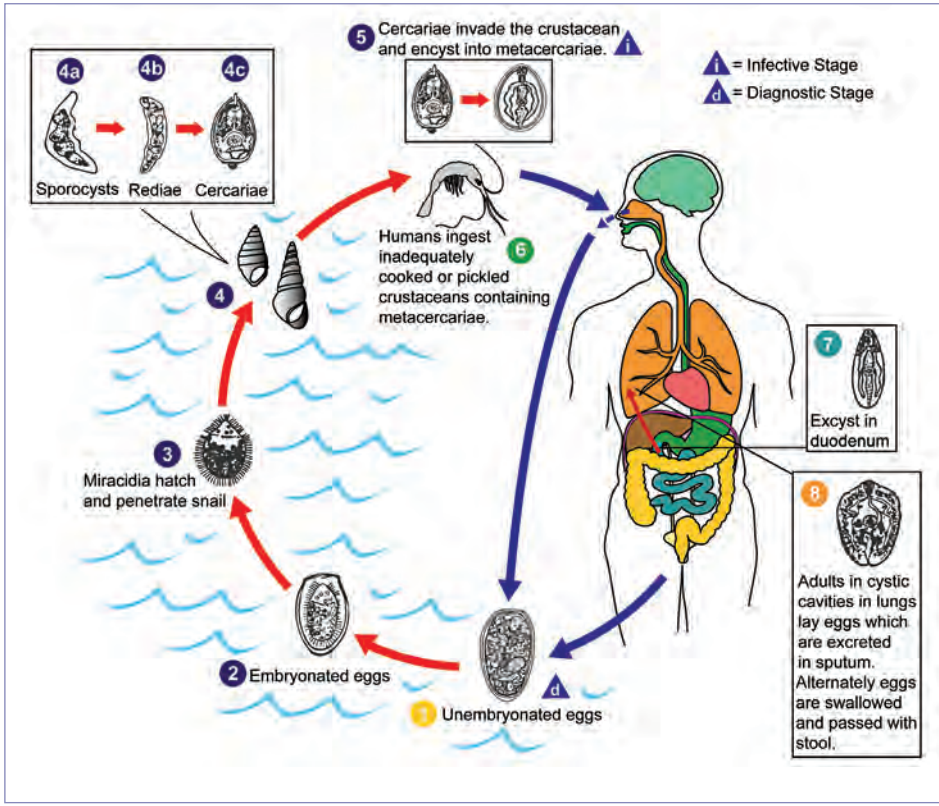


Image 97.5

Life cycle of *Paragonimus westermani*. The eggs are excreted unembryonated in the sputum or, alternately, they are swallowed and passed with stool (1). In the external environment, the eggs become embryonated (2), and miracidia hatch and seek the first intermediate host, a snail, and penetrate its soft tissues (3). Miracidia go through several developmental stages inside the snail (4): sporocysts (4a), rediae (4b), with the latter giving rise to many cercariae (4c), which emerge from the snail. The cercariae invade the second intermediate host, a crustacean such as a crab or crayfish, where they encyst and become metacercariae. This is the infective stage for the mammalian host (5). Human infection with *P westermani* occurs by eating inadequately cooked or pickled crab or crayfish that harbor metacercariae of the parasite (6). The metacercariae excyst in the duodenum (7), penetrate through the intestinal wall into the peritoneal cavity, then through the abdominal wall and diaphragm into the lungs, where they become encapsulated and develop into adults (8) (7.5–12 mm by 4–6 mm). The worms can also reach other organs and tissues, such as the brain and striated muscles, respectively. However, when this takes place, completion of the life cycles is not achieved because the eggs laid cannot exit these sites. Time from infection to oviposition is 65 to 90 days. Infections may persist for 20 years in humans. Animals such as pigs, dogs, and a variety of feline species can also harbor *P westermani*. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 98

Parainfluenza Infections

CLINICAL MANIFESTATIONS

Parainfluenza viruses (PIVs) are the major cause of laryngotracheobronchitis (croup) and may cause bronchiolitis and pneumonia as well as upper respiratory tract infection. PIV type 1 (PIV1) and, to a lesser extent, PIV type 2 (PIV2) are the most common pathogens associated with croup. PIV type 3 (PIV3) most commonly is associated with bronchiolitis and pneumonia in infants and young children. Infections with PIV type 4 (PIV4) are less well characterized but have been associated with mild upper respiratory tract infections as well as lower respiratory tract infections. Rarely, PIVs have been isolated from patients with parotitis, myopericarditis, aseptic meningitis, encephalitis, or Guillain-Barré syndrome. PIV infections can exacerbate symptoms of chronic lung disease and asthma in children and adults. In children with immunodeficiency and recipients of hematopoietic stem cell transplants, PIVs can cause refractory infections with persistent shedding, severe pneumonia with viral dissemination, and even fatal disease, most commonly caused by PIV3. PIV infections do not confer complete protective immunity; therefore, reinfections can occur with all serotypes and at any age, but reinfections usually are mild and limited to the upper respiratory tract.

ETIOLOGY

PIVs are enveloped single-stranded negative-sense RNA viruses classified in the family *Paramyxoviridae.* Four antigenically distinct types—1 through 4 (with 2 subtypes, 4A and 4B)—that infect humans have been identified.

EPIDEMIOLOGY

PIVs are transmitted from person to person by direct contact and exposure to contaminated nasopharyngeal secretions through respiratory tract droplets and fomites. PIV infections can be sporadic or associated with outbreaks of acute respiratory tract disease. Seasonal patterns of infection are distinct, predictable, and cyclic in temperate regions. Different serotypes have distinct epidemiologic patterns. PIV1 tends to produce outbreaks of respiratory tract illness, usually croup, in the autumn of every other year. A major increase in the number of cases of croup in the autumn usually indicates a PIV1 outbreak. PIV2 also can cause outbreaks of respiratory tract illness in the autumn, often in conjunction with PIV1 outbreaks, but PIV2 outbreaks tend to be less severe, irregular, and less common. PIV3 is endemic and usually is prominent during spring and summer in temperate climates but often continues into autumn, especially in years when autumn outbreaks of PIV1 or PIV2 are absent. PIV4 seasonal patterns are not as well characterized, but a recent study has shown that infections with PIV4 had year-round prevalence with peaks during the fall of odd-numbered years.

The age of primary infection varies with serotype. Primary infection with all types usually occurs by 5 years of age. Infection with PIV3 more often occurs in infants and is a frequent cause of bronchiolitis and pneumonia in this age group. By 12 months of age, 50% of infants have acquired PIV3 infection. Infections between 1 and 5 years of age more commonly are associated with PIV1 and, to a lesser extent, PIV2. Acquisition of PIV4 also occurs during preschool years following the pattern observed with PIV1 and PIV2. Rates of PIV-associated hospitalizations for children vary depending on clinical syndrome, PIV type, and patient age.

Immunocompetent children with primary PIV infection may shed virus for up to 1 week before onset of clinical symptoms and for 1 to 3 weeks after symptoms have disappeared, depending on serotype. Severe lower respiratory tract disease with prolonged shedding of the virus can develop in immunodeficient people. In these patients, infection may spread beyond the respiratory tract to the liver and lymph nodes.

The **incubation period** is from 2 to 6 days.

DIAGNOSTIC TESTS

Reverse transcriptase-polymerase chain reaction (RT-PCR) assays are the preferred diagnostic method for detection and differentiation of PIVs. PIVs may be isolated from nasopharyngeal

secretions in cell culture, usually within 4 to 7 days of culture inoculation. Time to detection in cell culture may be decreased with fluorescein-labeled antibodies or use of centrifugation of the specimen onto a monolayer of susceptible cells with subsequent staining for viral antigen (rapid shell vial assay). In general, such antigen-based culture identification methods detect PIV1, -2, and -3 but not PIV4. Similarly, rapid direct antigen detection techniques, including immunofluorescence assays, can be used to detect the virus directly in nasopharyngeal secretions, but sensitivities of the tests vary compared with cell culture, and PIV4 generally is not detected. PIVs are included in many respiratory pathogen panels. Serologic diagnosis, made retrospectively by a significant increase in antibody titer between serum specimens obtained during acute infection and convalescence, is less useful.

TREATMENT

Specific antiviral therapy is not available, although several antiviral agents with activity against PIVs currently are in development. Most infections are self-limited and require no treatment. Monitoring for hypoxia and hypercapnia in more severely affected children with lower respiratory tract disease may be helpful. Racemic epinephrine aerosol commonly is given to severely affected hospitalized patients with laryngotracheobronchitis to decrease airway obstruction. Parenteral, oral, and nebulized corticosteroids have been demonstrated to lessen the severity and duration of symptoms and hospitalization in patients with moderate to severe laryngotracheobronchitis. Oral steroids also are effective for outpatients with less severe croup. Management otherwise is supportive.

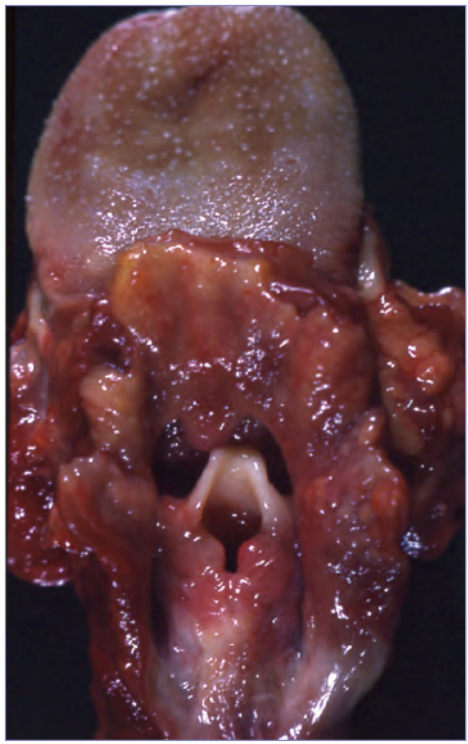


Image 98.1
Fatal croup. Edema, congestion, and inflammation of larynx and pharynx. Courtesy of Dimitris P. Agamanolis, MD.

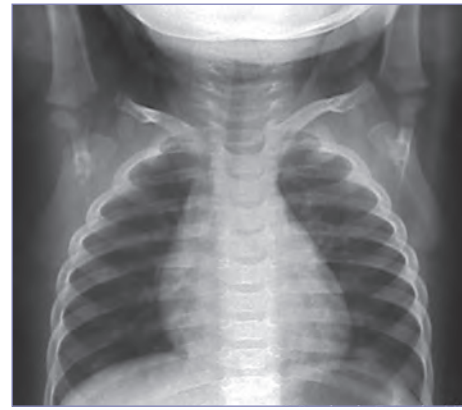


Image 98.2
Parainfluenza laryngotracheitis in a 2-year-old boy. Courtesy of Benjamin Estrada, MD.

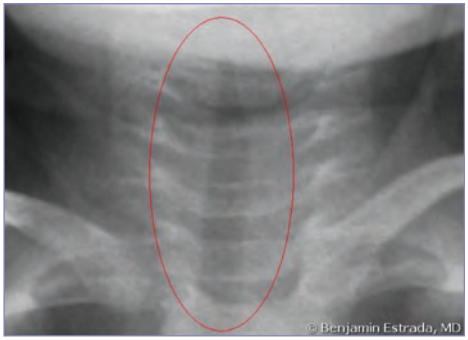


Image 98.3
Parainfluenza laryngotracheitis with the steeple sign in a 2-year-old. Courtesy of Benjamin Estrada, MD.

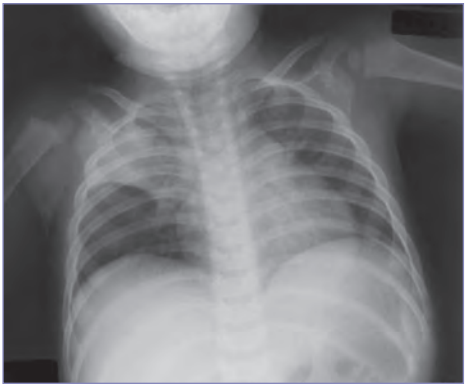


Image 98.4
Parainfluenza pneumonia in a 2-year-old boy. Courtesy of Benjamin Estrada, MD.

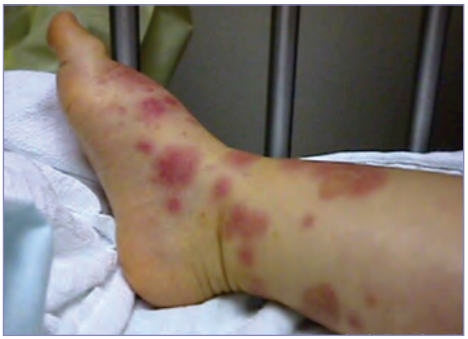


Image 98.5
Erythema multiforme minor in a 2-year-old boy with parainfluenza. Courtesy of Larry Frenkel, MD.

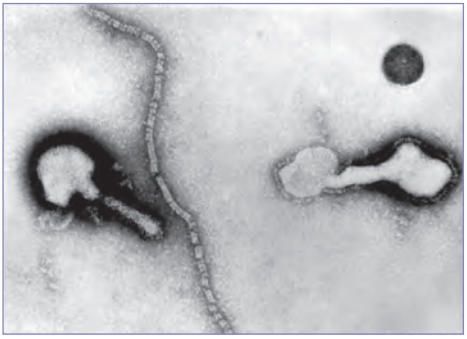


Image 98.6
Transmission electron micrograph of parainfluenza virus showing 2 intact particles and a free filamentous nucleocapsid. Courtesy of Centers for Disease Control and Prevention.

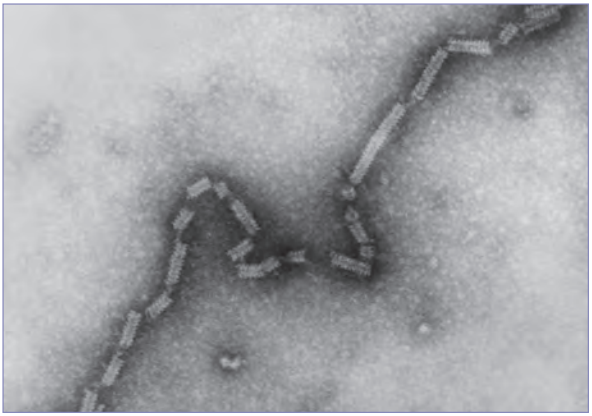


Image 98.7
This electron micrograph depicts the paramyxovirus 4A nucleocapsid with its herringbone-shaped RNA core. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 99

Parasitic Diseases

Parasites are among the most common causes of morbidity and mortality in various and diverse geographic locations worldwide. Outside the tropics and subtropics, parasitic diseases are common among travelers, immigrants, and immunocompromised people. Toxocariasis may be quite common in the southern United States and can affect impoverished populations in this region. Malaria infections in the United States occur among people who have traveled to regions with ongoing malaria transmission, and the diagnosis should be considered when evaluating fever in a returned traveler. Certain infections, such as Chagas disease, neurocysticercosis, schistosomiasis, and *Strongyloides stercoralis*, have long latency periods and are commonly encountered in immigrants from regions with endemic infection. Physicians and clinical laboratory personnel need to be aware of where these infections may be acquired, their clinical presentations, and methods of diagnosis and should advise people on how to prevent infection. Table 99.1 provides details on some infrequently encountered parasitic diseases.

Consultation and assistance in diagnosis and management of parasitic diseases are available from the Centers for Disease Control and Prevention (CDC), state health departments, and university departments or hospitals that have divisions of geographic medicine, tropical medicine, pediatric infectious diseases, international health, and public health.

Through authorized investigational new drug mechanisms, the CDC distributes several drugs that are not available commercially in the United States for treatment of parasitic diseases. To request these drugs, a physician must contact the CDC Parasitic Diseases Hotline (404-718-4745; email: parasites@cdc.gov).

Important human parasitic infections are discussed in individual chapters arranged alphabetically, and the discussions include recommendations for drug treatment.

Table 99.1
Selected Parasitic Diseases Not Covered Elsewhere

Disease and/or Agent	Where Infection May Be Acquired	Definitive Host	Intermediate Host	Modes of Human Infection	Directly Communicable (Person to Person)	Diagnostic Laboratory Tests in Humans	Causative Form of Parasite	Manifestations in Humans
Angiostrongylus cantonensis (neurotropic disease)	Widespread in the tropics, particularly Pacific Islands, Southeast Asia, Central and South America, the Caribbean, and the United States	Rodents	Snails and slugs	Eating improperly cooked infected mollusks or food contaminated by mollusk secretions containing larvae; prawns, fish, and land crabs that have ingested infected mollusks also may be infectious	No	Eosinophils in CSF; rarely, identification of larvae in CSF or at autopsy; RT-PCR of CSF, serologic testing–ELISA	Larval worms	Eosinophilia, eosinophilic meningoencephalitis
Angiostrongylus costaricensis (gastrointestinal tract disease)	Central and South America	Rodents	Snails and slugs	Eating improperly cooked infected mollusks or food contaminated by mollusk secretions containing larvae	No	Gel diffusion; identification of larvae and eggs in tissue	Larval worms	Abdominal pain, eosinophilia
Anisakiasis	Cosmopolitan, most common where eating raw fish is practiced	Marine mammal	Certain saltwater fish, squid, and octopus	Eating uncooked or inadequately treated infected marine fish	No	Identification of recovered larvae on endoscopy or identified in granulomas	Larval worms	Acute gastrointestinal tract disease

Table 99.1 (*continued*)

Disease and/or Agent	Where Infection May Be Acquired	Definitive Host	Intermediate Host	Modes of Human Infection	Directly Communicable (Person to Person)	Diagnostic Laboratory Tests in Humans	Causative Form of Parasite	Manifestations in Humans
Clonorchis sinensis, Opisthorchis viverrini, Opisthorchis felineus (flukes)	East Asia, Eastern Europe, Russian Federation	Humans, cats, dogs, other mammals	Certain freshwater snails	Eating uncooked infected freshwater fish	No	Eggs in stool or duodenal fluid Serologic testing–ELISA	Larvae and mature flukes	Abdominal pain; hepatobiliary disease; cholangiocarcinoma
Dracunculiasis (*Dracunculus medinensis*) (guinea worm)	Foci in Africa; global eradication nearly achieved	Humans	Crustacea (copepods)	Drinking water infested with infected copepods	No	Identification of emerging or adult worm in subcutaneous tissues	Adult female worm	Emerging roundworm; inflammatory response; systemic and local blister or ulcer in skin
Fascioliasis (liver fluke; *Fasciola hepatica*)	Worldwide; predominantly in the tropics	Sheep and cattle most important; other mammals	Snails	Freshwater plants; watercress; drinking contaminated water	No	Identifying eggs in stool, duodenal fluid, or bile; serologic testing; examination of surgical specimens	Migrating metacercariae cause liver parenchymal destruction; adult worms can obstruct bile ducts	Acute: fever, right upper quadrant pain, hepatosplenomegaly; anorexia, nausea, vomiting, myalgia, cough, urticaria; eosinophilia Chronic: bile duct obstruction; gastrointestinal tract symptoms

(*continued*)

Table 99.1 (*continued*)

Disease and/or Agent	Where Infection May Be Acquired	Definitive Host	Intermediate Host	Modes of Human Infection	Directly Communicable (Person to Person)	Diagnostic Laboratory Tests in Humans	Causative Form of Parasite	Manifestations in Humans
Fasciolopsiasis (*Fasciolopsis buski*)	East Asia	Humans, pigs, dogs	Certain freshwater snails, plants	Eating uncooked infected plants	No	Eggs or worm in feces or duodenal fluid; serologic testing–ELISA	Larvae and mature worms	Diarrhea, constipation, vomiting, anorexia, edema of face and legs, ascites
Intestinal capillariasis (*Capillaria philippinensis*)	Philippines, Thailand	Humans, fish-eating birds	Fish	Ingestion of uncooked infected fish	Uncertain	Eggs and parasite in feces	Larvae and mature worms	Protein-losing enteropathy, diarrhea, malabsorption, ascites, emaciation

CSF indicates cerebrospinal fluid; RT-PCR, reverse-transcriptase polymerase chain reaction; ELISA, enzyme-linked immunosorbent assay.

Image 99.1
Dracunculiasis. The female *Dracunculus medinensis* (guinea worm) induces a painful blister (A); after rupture of the blister, the worm emerges as a whitish filament (B) in the center of a painful ulcer, which is often secondarily infected. Courtesy of Centers for Disease Control and Prevention.

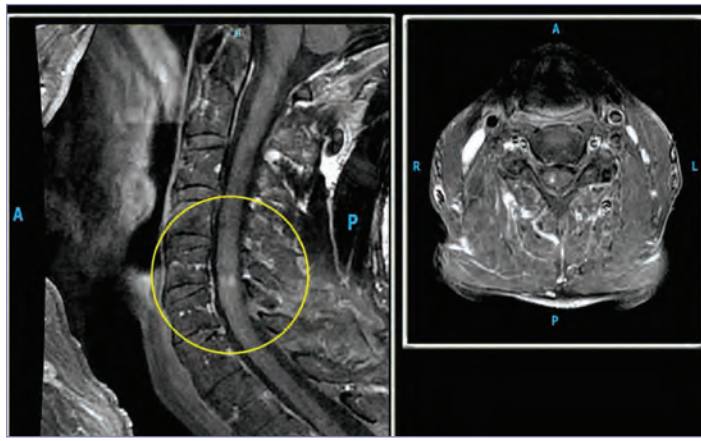


Image 99.2
Sagittal and axial T2-weighted magnetic resonance images of a focal lesion of the cervical spine in an 18-year-old patient with spinal cord involvement of infection with *Gnathostoma spinigerum*, a nematode found throughout Asia that can be acquired by humans through consumption of undercooked shellfish or meat. Courtesy of James Sejvar, MD.

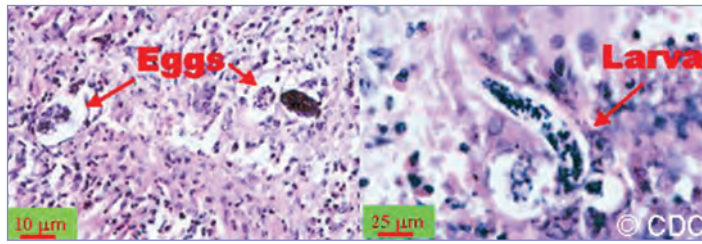


Image 99.3
Eggs and larva of *Angiostrongylus costaricensis*. In humans, eggs and larvae are not normally excreted but remain sequestered in tissues. Eggs and larvae (occasionally adult worms) of *A costaricensis* can be identified in biopsy or surgical specimens of intestinal tissue. The larvae need to be distinguished from larvae of *Strongyloides stercoralis;* however, the presence of granulomas containing thin-shelled eggs and/or larvae serve to distinguish *A costaricensis* infections. The larval infection can cause mesenteric arteritis and abdominal pain, occurring primarily in people in Central and South America. Courtesy of Centers for Disease Control and Prevention.

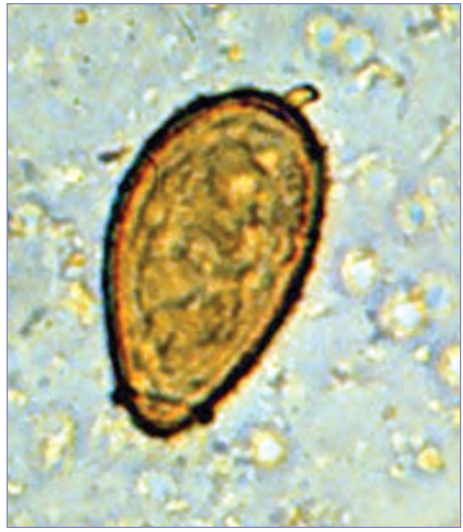


Image 99.4
Opisthorchis (formerly *Clonorchis*) *sinensis* (Chinese liver fluke) egg. These are small, operculated eggs, 27 to 35 µm by 11 to 20 µm. The operculum, at the smaller end of the egg, is convex and rests on a visible "shoulder." At the opposite (larger, abopercular) end, a small knob or hooklike protrusion is often visible (as is the case here). The miracidium is visible inside the egg. (Also referred to as opisthorchiasis.) Courtesy of Centers for Disease Control and Prevention.

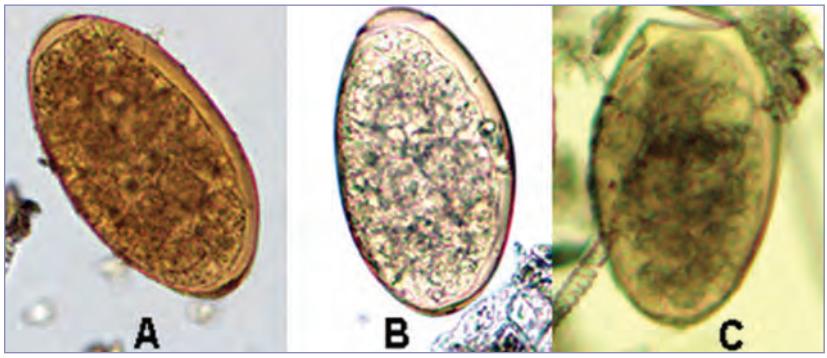


Image 99.5
Fasciola hepatica eggs (wet mounts with iodine). The eggs are ellipsoidal. They have a small, barely distinct operculum (A, B, upper end of the eggs). The operculum can be opened (egg C), for example, when a slight pressure is applied to the coverslip. The eggs have a thin shell that is slightly thicker at the abopercular end. They are passed unembryonated. The size ranges from 120 to 150 µm by 63 to 90 µm. Fascioliasis is caused by the sheep liver fluke infecting the liver and biliary system. Courtesy of Centers for Disease Control and Prevention.

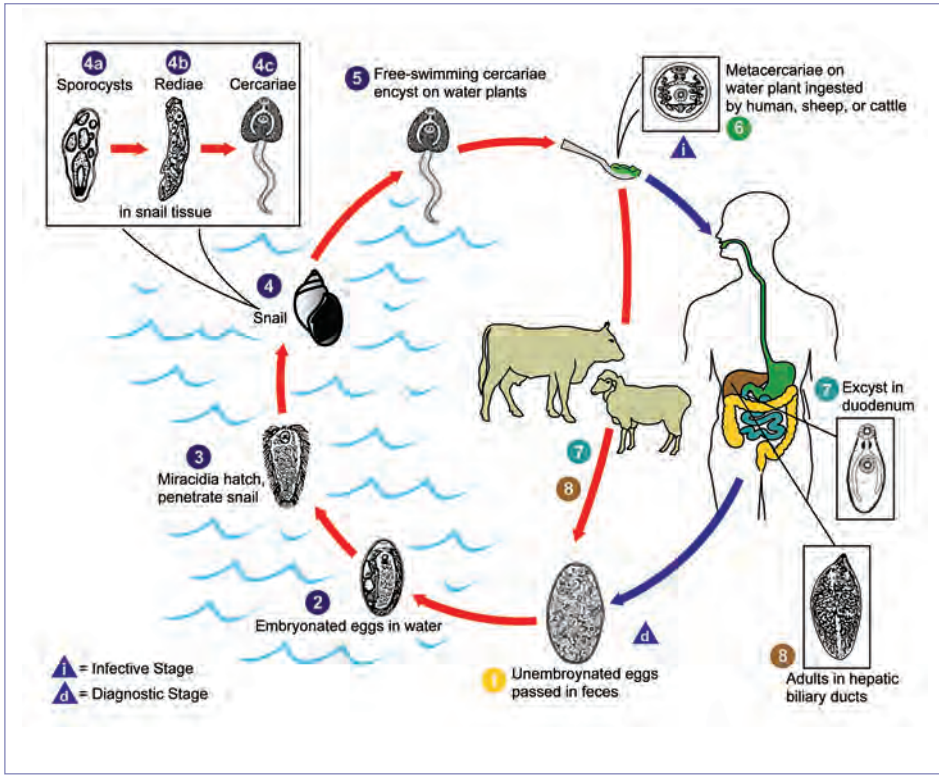


Image 99.6

Fasciola hepatica (life cycle). Immature eggs are discharged in the biliary ducts and in the stool (1). Eggs become embryonated in water (2) and release miracidia (3), which invade a suitable snail intermediate host (4), including many species of the genus *Lymnaea*. In the snail, the parasites undergo several developmental stages (sporocysts [4a], rediae [4b], and cercariae [4c]). The cercariae are released from the snail (5) and encyst as metacercariae on aquatic vegetation or other surfaces. Mammals acquire the infection by eating vegetation containing metacercariae. Humans can become infected by ingesting metacercariae-containing freshwater plants, especially watercress (6). After ingestion, the metacercariae excyst in the duodenum (7) and migrate through the intestinal wall, the peritoneal cavity, and the liver parenchyma into the biliary ducts, where they develop into adults (8). In humans, maturation from metacercariae into adult flukes takes approximately 3 to 4 months. The adult flukes (*F hepatica,* up to 30 by 13 mm; *Fasciola gigantica,* up to 75 mm) reside in the large biliary ducts of the mammalian host. *F hepatica* infect various animal species, mostly herbivores. Courtesy of Centers for Disease Control and Prevention.

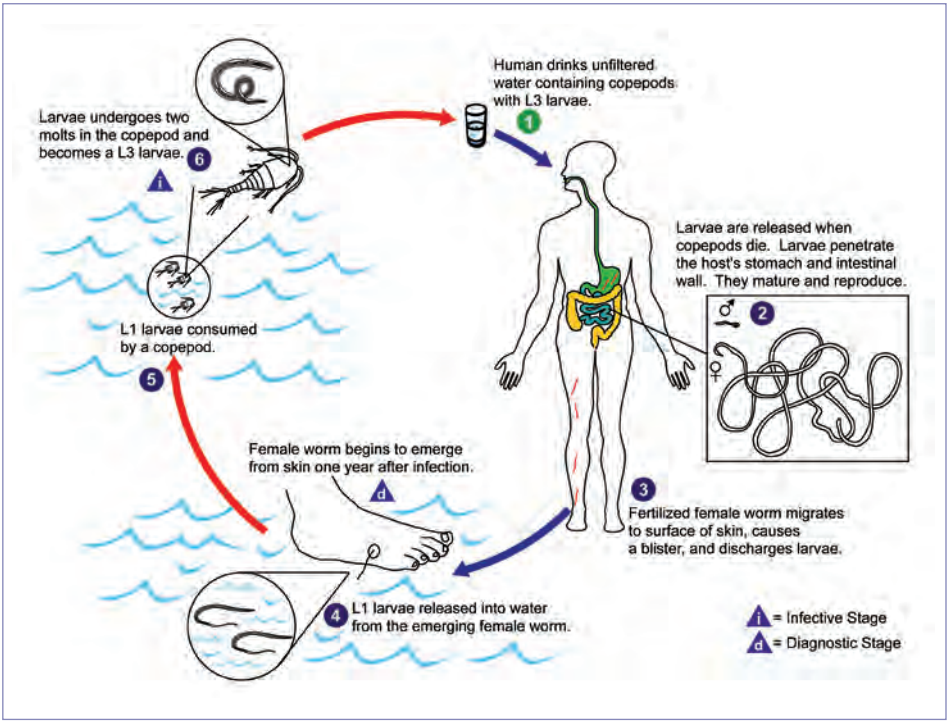


Image 99.7

Dracunculus medinensis. Humans become infected by drinking unfiltered water containing copepods (small crustaceans) that are infected with larvae of *D medinensis* (1). Following ingestion, the copepods die and release the larvae, which penetrate the host stomach and intestinal wall and enter the abdominal cavity and retroperitoneal space (2). After maturation into adults and copulation, the male worms die and the females (length, 70–120 cm) migrate in the subcutaneous tissues toward the skin surface (3). Approximately 1 year after infection, the female worm induces a blister on the skin, generally on the distal lower extremity, which ruptures. When this lesion comes into contact with water, a contact that the patient seeks to relieve the local discomfort, the female worm emerges and releases larvae (4). The larvae are ingested by a copepod (5) and after 2 weeks (and 2 molts) have developed into infective larvae (6). Ingestion of the copepods closes the cycle. Courtesy of Centers for Disease Control and Prevention.

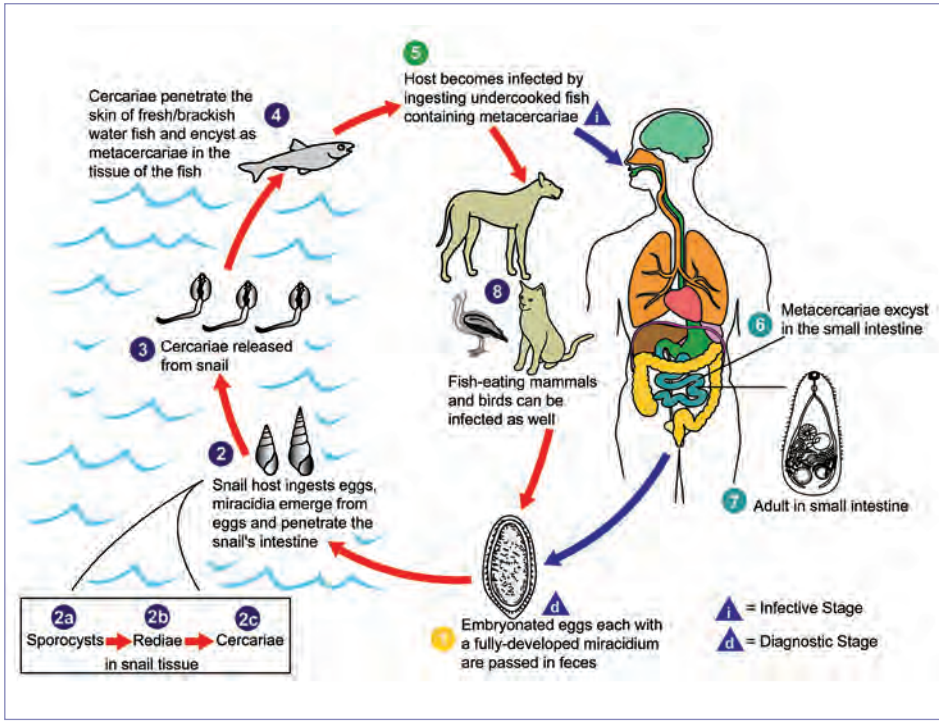


Image 99.8

Heterophyes heterophyes. Adults release embryonated eggs each with a fully developed miracidium, and eggs are passed in the host's feces (1). After ingestion by a suitable snail (first intermediate host), the eggs hatch and release miracidia, which penetrate the snail's intestine (2). Genera *Cerithidia* and *Pironella* are important snail hosts in Asia and the Middle East, respectively. The miracidia undergo several developmental stages in the snail (sporocysts [2a], rediae [2b], and cercariae [2c]). Many cercariae are produced from each redia. The cercariae are released from the snail (3) and encyst as metacercariae in the tissues of a suitable freshwater or brackish water fish (second intermediate host) (4). The definitive host becomes infected by ingesting undercooked or salted fish containing metacercariae (5). After ingestion, the metacercariae excyst, attach to the mucosa of the small intestine (6), and mature into adults (measuring 1.0–1.7 mm by 0.3–0.4 mm) (7). In addition to humans, various fish-eating mammals (eg, cats, dogs) and birds can be infected by *H heterophyes* (8). Geographic distribution: Egypt, the Middle East, and Far East. Courtesy of Centers for Disease Control and Prevention.

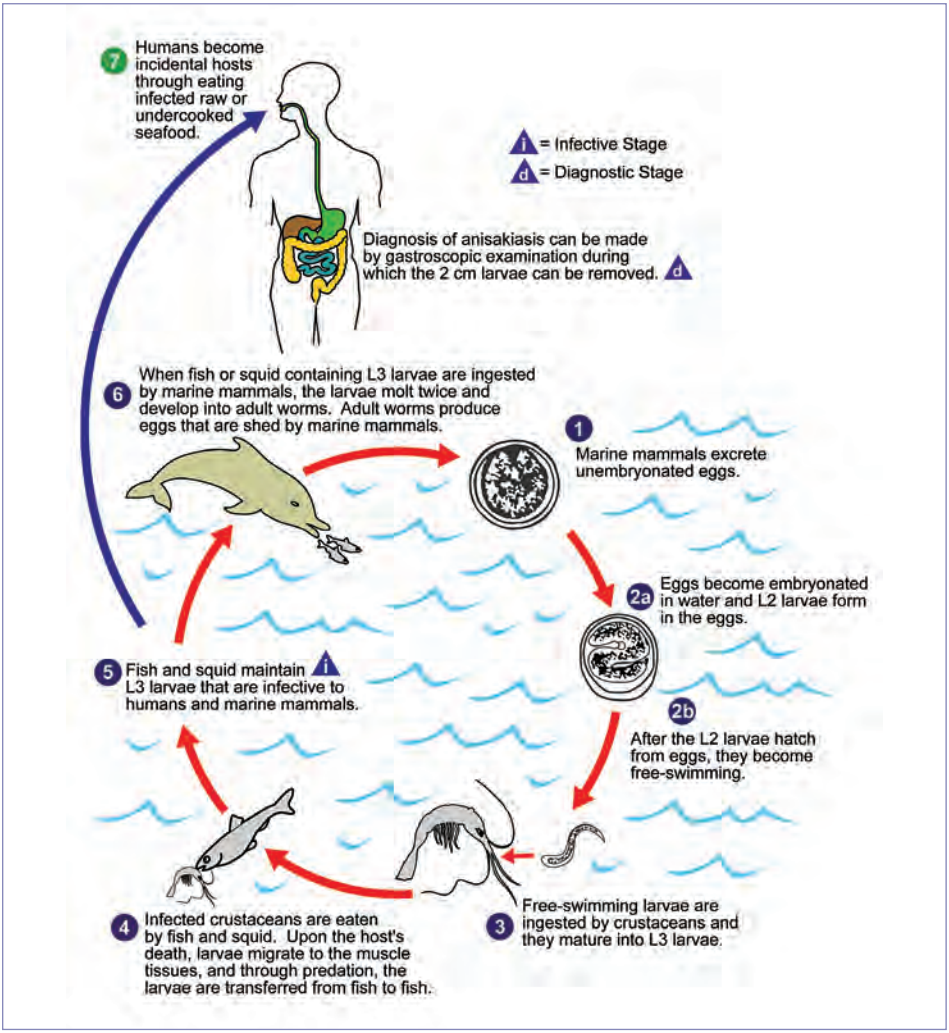


Image 99.9

Anisakiasis is caused by the accidental ingestion of larvae of the nematodes (roundworms) *Anisakis* simplex or *Pseudoterranova decipiens*. Adult stages of *Anisakis* simplex or *P decipiens* reside in the stomach of marine mammals, where they are embedded in the mucosa, in clusters. Unembryonated eggs produced by adult females are passed in the feces of marine mammals (1). The eggs become embryonated in water, and first-stage larvae are formed in the eggs. The larvae molt, becoming second-stage larvae (2a), and, after the larvae hatch from the eggs, they become free-swimming (2b). Larvae released from the eggs are ingested by crustaceans (3). The ingested larvae develop into third-stage larvae that are infective to fish and squid (4). The larvae migrate from the intestine to the tissues in the peritoneal cavity and grow up to 3 cm in length. On the host's death, larvae migrate to the muscle tissues and, through predation, are transferred from fish to fish. Fish and squid maintain third-stage larvae that are infective to humans and marine mammals (5). When fish or squid containing third-stage larvae are ingested by marine mammals, the larvae molt twice and develop into adult worms. The adult females produce eggs that are shed by marine mammals (6). Humans become infected by eating raw or undercooked infected marine fish (7). After ingestion, the *Anisakis* larvae penetrate the gastric and intestinal mucosa, causing the symptoms of anisakiasis. Courtesy of Centers for Disease Control and Prevention.

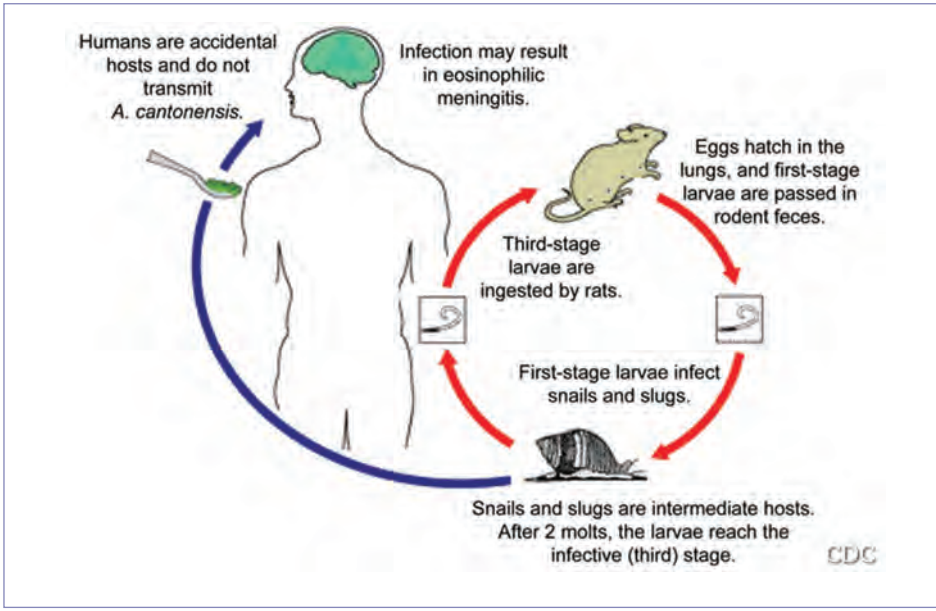


Image 99.10
Life cycle of *Angiostrongylus cantonensis*. Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases*.

CHAPTER 100

Human Parechovirus Infections

CLINICAL MANIFESTATIONS

Human parechoviruses (HPeVs) primarily cause disease in young infants and present in a similar manner to enterovirus or disseminated herpes simplex virus infection, with a febrile illness, exanthem, sepsis-like syndrome, and/or central nervous system manifestations such as meningitis (typically with little or no pleocytosis), encephalitis, intractable seizures, and paralytic disease, often with brain imaging abnormalities. Infections (particularly with HPeV type 3) may be severe and include sepsis, hepatitis and coagulopathy, myocarditis, pneumonia, and/or meningoencephalitis, with long-term sequelae. HPeV infections have been associated with respiratory and gastrointestinal tract disease and a variety of other less severe manifestations, although causation has not been established consistently.

ETIOLOGY

HPeVs are a group of small, nonenveloped, single-stranded, positive-sense RNA viruses in the family *Picornaviridae*. The *Parechovirus* genus includes at least 16 HPeV types (designated 1–16). HPeV types 1 and 2 previously were classified as echoviruses 22 and 23, respectively.

EPIDEMIOLOGY

Humans are the primary reservoir for HPeV, although infection in primates has been demonstrated. HPeV infections have been reported worldwide. Seroepidemiologic studies suggest that HPeV infections occur commonly during early childhood. In some studies, most school-aged children have serologic evidence of prior infection, but seroprevalence appears to vary by geographic region and specific HPeV type. Infections frequently are asymptomatic. Clinical reports suggest that most severe disease occurs in infants and young children. Transmission appears to occur via the fecal-oral and respiratory routes, and on the basis of reports of very early onset neonatal disease, in utero transmission also may occur. HPeVs may circulate throughout the year, but infections by certain types occur more commonly during summer and fall months. Multiple HPeV types may circulate in a community during the same time period. Community outbreaks and health care-associated transmission in neonatal and pediatric hospital units have been described. Virus is shed from the upper respiratory tract for 1 to 3 weeks and in stool for less than 2 weeks to 5 months. Shedding may occur in the absence of illness.

The **incubation period** for HPeV infections is unknown.

DIAGNOSTIC TESTS

Reverse-transcriptase polymerase chain reaction (RT-PCR) assays that detect HPeVs, available at the Centers for Disease Control and Prevention and select reference and hospital-based laboratories, represent the best diagnostic modality. Some of the assays may not detect all 16 serotypes. Enterovirus PCR assays will not detect HPeV. A multiplexed, multiple-pathogen assay designed to detect a number of bacterial and viral agents of meningitis and encephalitis in cerebrospinal fluid will detect HPeV, but data are limited. HPeVs can be detected by RT-PCR in stool, throat swab specimens, nasopharyngeal aspirates, tracheal secretions, cerebrospinal fluid, and blood. HPeVs can be shed in throat and particularly from the gastrointestinal tract for prolonged periods, so detection does not necessarily represent a current invasive disease attributable to HPeVs. Viral culture can be used, but recovery in culture is less sensitive than PCR assay.

TREATMENT

Supportive. No specific therapy is available for HPeV infections. Immune Globulin Intravenous (IGIV) has been used in some published case reports of neonates with severe HPeV infections, often complicated by myocarditis, but efficacy is unknown.

CHAPTER 101

Parvovirus B19

(Erythema Infectiosum, Fifth Disease)

CLINICAL MANIFESTATIONS

Infection with human parvovirus B19 is recognized most often as erythema infectiosum (EI), or fifth disease, which is characterized by a distinctive rash that may be preceded by mild systemic symptoms, including fever in 15% to 30% of patients. The facial rash can be intensely red with a "slapped cheek" appearance that often is accompanied by circumoral pallor. A symmetric, macular, lacelike, and often pruritic rash occurs on the trunk, moving peripherally to involve the arms, buttocks, and thighs. The rash can fluctuate in intensity and recur with environmental changes, such as temperature and exposure to sunlight, for weeks to months. A brief, mild, nonspecific illness consisting of fever, malaise, myalgia, and headache often precedes the characteristic exanthem by approximately 7 to 10 days. Arthralgia and arthritis occur in fewer than 10% of infected children but commonly occur among adults, especially women. Knees are involved most commonly in children, but a symmetric polyarthropathy of knees, fingers, and other joints is common in adults.

Human parvovirus B19 can cause asymptomatic or subclinical infections. Other manifestations (Table 101.1) include a mild respiratory tract illness with no rash, a rash atypical for EI that may be rubelliform or petechial, papular-purpuric gloves-and-socks syndrome (PPGSS; painful and pruritic papules, petechiae, and purpura of hands and feet, often with fever and an enanthem), polyarthropathy syndrome (arthralgia and arthritis in adults in the absence of other manifestations of EI), chronic erythroid hypoplasia with severe anemia in immunodeficient patients (eg, patients with human immunodeficiency virus [HIV] infection), and transient aplastic crisis lasting 7 to 10 days in patients with hemolytic anemias (eg, sickle cell disease and autoimmune hemolytic anemia). For children with other conditions associated with low hemoglobin concentrations, including hemorrhage and severe anemia, parvovirus B19 infection usually will not result in aplastic crisis but might result in prolongation of recovery from the anemia. Patients with transient aplastic crisis may have a prodromal illness with fever, malaise, and myalgia, but rash usually is absent. In addition, human parvovirus B19 infection sometimes has been associated with decreases in numbers of platelets, lymphocytes, and neutrophils. In rare cases, parvovirus B19 infection has been associated with acute hepatitis and myocarditis in children.

Human parvovirus B19 infection occurring during pregnancy can cause fetal hydrops, intrauterine growth restriction, isolated pleural and pericardial effusions, and death, but the virus is not a proven cause of congenital anomalies. The risk of fetal death is between 2% and 6% when infection occurs during pregnancy. The greatest risk appears to occur during the first half of pregnancy.

Table 101.1
Clinical Manifestations of Human Parvovirus B19 Infection

Conditions	Usual Hosts
Erythema infectiosum (fifth disease, EI)	Immunocompetent children
Polyarthropathy syndrome	Immunocompetent adults (more common in women)
Chronic anemia/pure red cell aplasia	Immunocompromised hosts
Transient aplastic crisis	People with hemolytic anemia (ie, sickle cell anemia)
Hydrops fetalis/congenital anemia	Fetus (first 20 weeks of pregnancy)
Petechial, papular-purpuric gloves-and-socks syndrome (PPGSS)	Immunocompetent children and young adults

ETIOLOGY

Human parvovirus B19 is a small, nonenveloped, single-stranded DNA virus in the family *Parvoviridae*, genus *Erythroparvovirus*. Parvovirus B19 replicates in human erythrocyte precursors, and human parvovirus B19-associated red blood cell aplasia is related to caspase-mediated apoptosis of erythrocyte precursors.

EPIDEMIOLOGY

Parvovirus B19 is distributed worldwide and is a common cause of infection in humans, who are the only known hosts. Modes of transmission include contact with respiratory tract secretions, percutaneous exposure to blood or blood products, and vertical transmission from mother to fetus. Human parvovirus B19 infections are ubiquitous, and cases of EI can occur sporadically or in outbreaks in elementary or junior high schools during late winter and early spring. Secondary spread among susceptible household members is common, with infection occurring in approximately 50% of susceptible contacts in some studies. The transmission rate in schools is lower, but infection can be an occupational risk for school and child care personnel, with approximately 20% of susceptible contacts becoming infected. In young children, antibody seroprevalence generally is 5% to 10%. In most communities, approximately 50% of young adults and often more than 90% of elderly people are seropositive.

The **incubation period** from acquisition to symptom onset symptoms is 4 to 14 days but can be 21 days. People with EI are infectious before rash onset and are unlikely to be infectious after rash onset. Patients with aplastic crises are contagious from before the onset of symptoms through 7 days after onset of symptoms.

DIAGNOSTIC TESTS

In the immunocompetent host, detection of serum parvovirus B19-specific immunoglobulin (Ig) M antibodies is the preferred diagnostic test for an acute or recent parvovirus B19-associated rash illness. A positive IgM test result indicates that infection probably occurred within the previous 2 to 3 months. IgM antibodies may be detected in 90% or more of patients at the time of the EI rash and by the third day of illness in patients with transient aplastic crisis. Serum IgG antibodies appear by approximately day 2 of EI and persist for life. IgM assays have variable sensitivity and specificity.

Serum IgM and IgG assays are not reliable in immunocompromised patients. The optimal method for detecting transient aplastic crisis or chronic infection in the immunocompromised patient is demonstration of high titer of viral DNA by polymerase chain reaction (PCR) assays. Such patients generally have >106 parvovirus B19 DNA copies/mL of plasma. With the availability of a World Health Organization (WHO) nucleic acid standard for parvovirus B19 DNA, assay results can be reported in international units per mL (IU/mL) to allow for straightforward comparison across assays. The WHO also offers an International Reference Panel for parvovirus B19 nucleic acid amplification assays to allow laboratories to ensure that all 3 genotypes are detected in their assays. Because parvovirus B19 DNA can be detected at low levels by PCR assay in serum for months and even years after the acute viremic phase, detection does not necessarily indicate acute infection. Qualitative PCR may be used on amniotic fluid as an aid to diagnosis of hydrops fetalis. Parvovirus B19 cannot be propagated in standard cell culture.

TREATMENT

For most patients, only supportive care is indicated. Patients with aplastic crisis may require transfusions of blood products. For treatment of chronic infection in immunodeficient patients, Immune Globulin Intravenous (IGIV) therapy often is effective and should be considered. Some cases of parvovirus B19 infection concurrent with hydrops fetalis have been treated successfully with intrauterine blood transfusions of the fetus.

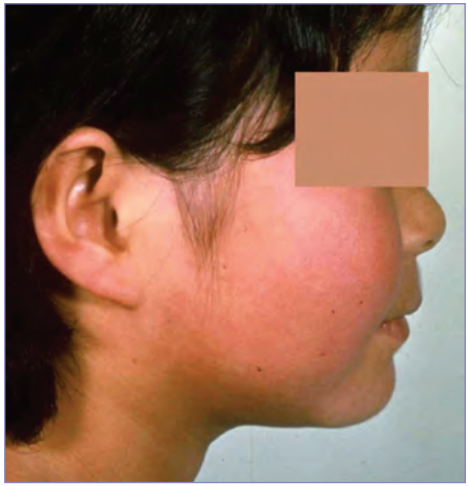


Image 101.1
Parvovirus B19 infection (erythema infectiosum, fifth disease) with typical facial erythema, commonly referred to as the "slapped cheek" sign.

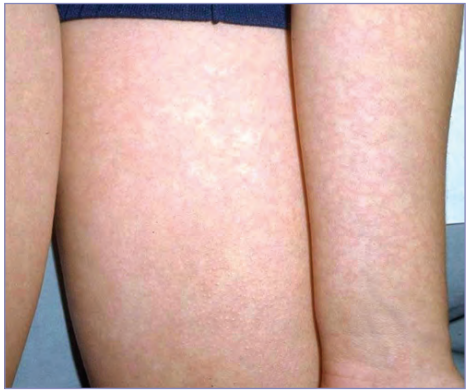


Image 101.3
Parvovirus B19 infection (erythema infectiosum, fifth disease). Three preschool-aged female siblings manifested the rash on the same day.

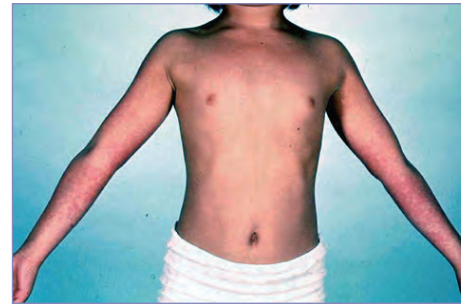


Image 101.2
Parvovirus B19 infection. Note lacelike pattern of the rash on the volar aspect of the child's arms. This is the same patient as in Image 101.1.

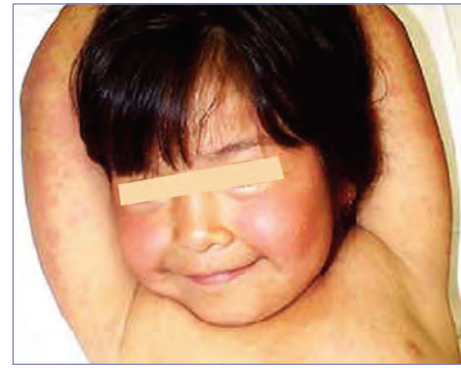


Image 101.4
Characteristic "slapped cheek" appearance of the face in a child who has fifth disease. The characteristic rash also is present on the arms.

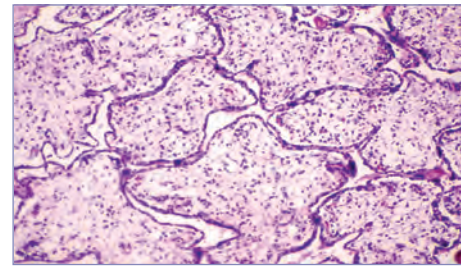


Image 101.5
Parvovirus infection in pregnancy. Hydropic placental villi. Courtesy of Dimitris P. Agamanolis, MD.

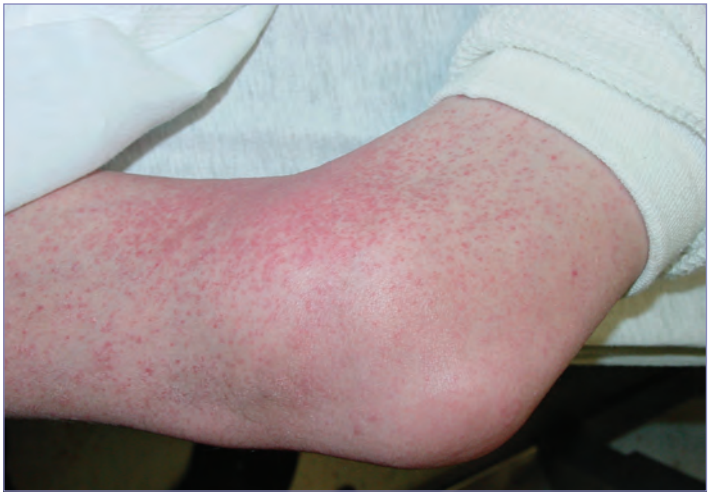


Image 101.6
Parvovirus B19 infection with a rash in a 10-year-old boy. Courtesy of Benjamin Estrada, MD.

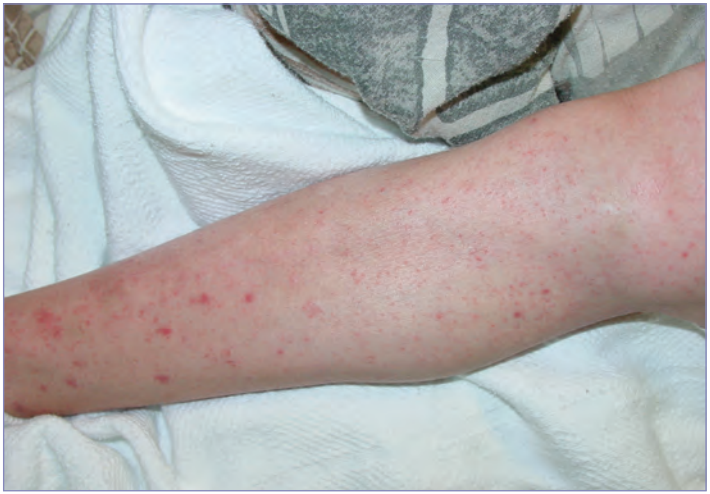


Image 101.7
Parvovirus B19 infection with a rash in a 10-year-old boy. Courtesy of Benjamin Estrada, MD.

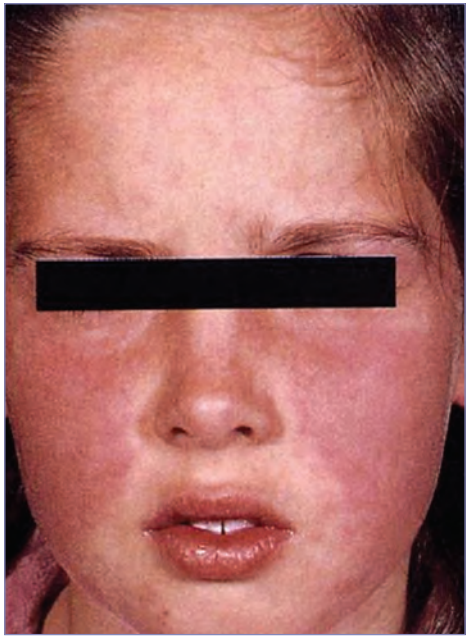


Image 101.8
An 8-year-old girl with the facial erythema of erythema infectiosum. Courtesy of Larry Frenkel, MD.

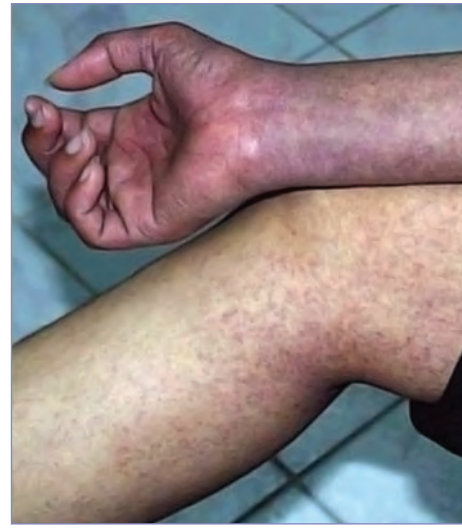


Image 101.9
Stocking glove purpura. This 18-year-old girl awoke one morning with asymptomatic symmetrical purpura of the hands and feet, which spread to involve the proximal extremities. The exanthem faded over 7 to 10 days. Although an enanthem is not usually reported with parvovirus infection, she also developed some erythema of the buccal mucosa and white plaques on a red base on the dorsum of the tongue. Courtesy of H. Cody Meissner, MD, FAAP.

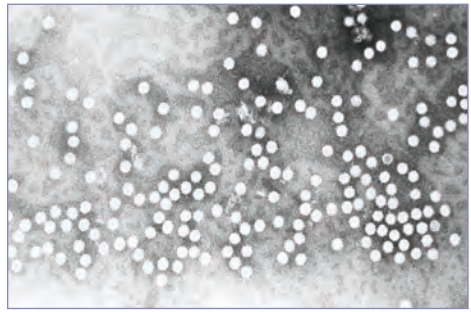


Image 101.10
This electron micrograph depicts a number of parvovirus H1 virions of the *Parvoviridae* family. These are nonenveloped single-strand DNA viruses. The *Parvoviridae* family of viruses also contains the parvovirus B19 virion, which is responsible for causing erythema infectiosum, or fifth disease. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 102

Pasteurella Infections

CLINICAL MANIFESTATIONS

The most common manifestation is cellulitis at the site of a bite or scratch of a cat, dog, or other domestic or wild animal. Cellulitis typically develops within 24 hours of the injury and includes swelling, erythema, tenderness, and serosanguinous to purulent drainage at the wound site. Regional lymphadenopathy, chills, and fever can occur. The most frequent local complications are abscesses and tenosynovitis, but septic arthritis and osteomyelitis also are reported. Other less common manifestations of infection include septicemia, central nervous system infections (meningitis is the most common; however, brain abscess and subdural empyema have been observed), ocular infections (eg, conjunctivitis, corneal ulcer, endophthalmitis), endocarditis, respiratory tract infections (eg, pneumonia, pulmonary abscesses, pleural empyema, epiglottitis), appendicitis, hepatic abscess, peritonitis, and urinary tract infection. People with liver disease, solid organ transplant, or underlying host defense abnormalities are predisposed to bacteremia with *Pasteurella multocida*.

ETIOLOGY

The genus *Pasteurella* is one of 4 genera of human pathogens classified in the family *Pasteurellaceae;* the other genera are *Actinobacillus*, *Aggregatibacter*, and *Haemophilus*. Members of the genus *Pasteurella* are nonmotile, facultatively anaerobic, mostly catalase and oxidase positive, gram-negative coccobacilli that are primarily respiratory tract colonizers and pathogens in animals. The most common human pathogen is *Pasteurella multocida; P multocida* subspecies *multocida* causes more than 50% of infections.

EPIDEMIOLOGY

Pasteurella species have a worldwide distribution. They colonize the upper respiratory tract of 70% to 90% of cats, 25% to 50% of dogs, and many other wild and domestic animals. Transmission most frequently occurs from the bite or scratch or licking of a previous wound by a cat or dog. Infected cat bite wounds contain *Pasteurella* species more often than do dog bite wounds. Rarely, respiratory tract spread occurs from animals to humans, and in a significant proportion of cases, no animal exposure can be identified. Human-to-human transmission has been documented vertically from mother to neonate, horizontally from colonized humans, and by contaminated blood products.

The **incubation period** usually is less than 24 hours.

DIAGNOSTIC TESTS

The isolation of *Pasteurella* species from a normally sterile body site (eg, blood, joint fluid, cerebrospinal fluid, pleural fluid, or suppurative lymph nodes) is diagnostic. Recovery of the organism from a superficial site, such as drainage from a skin lesion subsequent to an animal bite, must be interpreted in the context of other potential pathogens isolated; however, mixed infection may occur. *Pasteurella* species are somewhat fastidious but may be cultured on several media generally used in clinical laboratories, including blood and chocolate agar. Although they resemble several other organisms morphologically, laboratory identification to the genus level generally is not difficult. Newer laboratory methods, including polymerase chain reaction amplification of the 16S rRNA gene followed by sequencing, and identification of cellular components by matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectroscopy, have significantly improved specific identification.

TREATMENT

The drug of choice is penicillin. Penicillin resistance is rare, but beta-lactamase–producing strains have been recovered, especially from adults with pulmonary disease. Other oral agents that usually are effective include amoxicillin, amoxicillin/clavulanate, cefuroxime, cefixime, cefpodoxime, doxycycline, and fluoroquinolones. Oral and parenteral antistaphylococcal penicillins and first-generation cephalosporins are not recommended for treatment. *Pasteurella* species are usually resistant to vancomycin, clindamycin, and erythromycin. For patients who are allergic to beta-lactam agents, azithromycin, trimethoprim-sulfamethoxazole, and the

fluoroquinolones are alternative choices. For suspected polymicrobial infected bite wounds, oral amoxicillin-clavulanate or, for severe infection, intravenous ampicillin-sulbactam or piperacillin-tazobactam can be given. The duration of therapy usually is 7 to 10 days for local infections and 10 to 14 days for more severe infections. Antimicrobial therapy should be continued for 4 to 6 weeks for bone and joint infections. Wound drainage or débridement may be necessary.

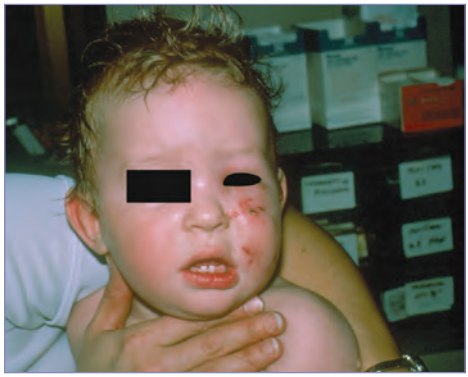


Image 102.1
Pasteurella multocida cellulitis secondary to multiple cat bites about the face of a 1-year-old. Courtesy of George Nankervis, MD.

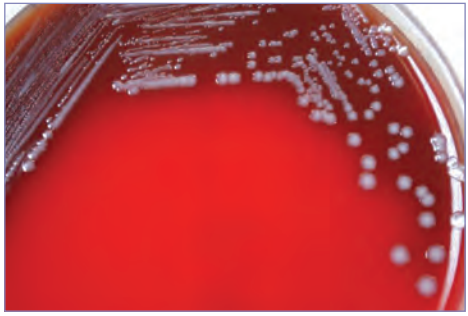


Image 102.3
This photograph depicts the colonial morphology displayed by gram-negative *Yersinia pestis* bacteria, which was grown on a medium of sheep blood agar for a 72-hour period at a temperature of 37°C (98.6°F). Courtesy of Centers for Disease Control and Prevention/Todd Parker, MD, and Audra Marsh.

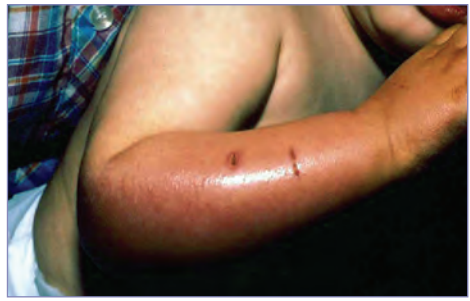


Image 102.2
Right forearm of 1-year-old boy bitten by a stray cat. The child developed fever, redness, and swelling 10 hours after the bite. He was taking amoxicillin for otitis media at the time of the bite. The child responded to treatment with intravenous cefuroxime, although the fever persisted for 36 hours. *Pasteurella multocida* was cultured from purulent material obtained from the wound the day after admission. Courtesy of Larry I. Corman, MD.

Image 102.4
Pasteurella multocida on chocolate agar. Colonies are small, gray, smooth, and nonhemolytic. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 103

Pediculosis Capitis

(Head Lice)

CLINICAL MANIFESTATIONS

Itching is the most common symptom of head lice infestation, but many children are asymptomatic. Adult lice (2–3 mm long, tan to grayish-white) or eggs (match hair color) and nits (empty egg shells, white) are found on the hair and are most readily apparent behind the ears and near the nape of the neck. Excoriations and crusting caused by secondary bacterial infection may occur and often are associated with regional lymphadenopathy. Head lice usually deposit their eggs on a hair shaft 4 mm or less from the scalp. Because hair grows at a rate of approximately 1 cm per month, the duration of infestation can be estimated by the distance of the nit from the scalp.

ETIOLOGY

Pediculus humanus capitis is the head louse. Both nymphs and adult lice feed on human blood.

EPIDEMIOLOGY

In the United States, head lice infestation is most common in children attending child care and elementary school. Head lice infestation is not a sign of poor hygiene. All socioeconomic groups are affected. Head lice infestation is not influenced by hair length or frequency of shampooing or brushing. Head lice are not a health hazard and are not responsible for spread of any disease. Head lice are only able to crawl; therefore, transmission occurs mainly by direct head-to-head contact with hair of infested people. Transmission by contact with personal belongings, such as combs, hairbrushes, sporting gear, and hats, is uncommon. Away from the scalp, head lice survive <1 day at room temperature, and their eggs generally become nonviable within a week and cannot hatch at a lower ambient temperature than that near the scalp.

The **incubation period** from the laying of eggs to hatching of the first nymph usually is about 1 week (6 to 9 days). Lice mature to the adult stage approximately 7 days later. Adult females then may lay eggs (nits), but these will develop only if the female has mated.

DIAGNOSTIC TESTS

Identification of eggs, nymphs, and adult lice with the naked eye is possible; diagnosis can be confirmed by using a hand lens, dermatoscope (epiluminescence microscope), or traditional microscope. Nymphal and adult lice shun light and move rapidly to conceal themselves. Wetting the hair with water, oil, or a conditioner may "slow down" the movement of the lice. In combination with using a fine-tooth comb, examiners may improve their ability to diagnose infestation and shorten inspection time. It is important to differentiate nits from dandruff, hair casts (a layer of follicular cells that slide easily off the hair shaft), plugs of desquamated cells, external hair debris, and fungal infections of the scalp. Because nits remain firmly affixed to hair, their mere presence is not a sign of an active infestation.

TREATMENT

Several effective pediculicidal agents are available to treat head lice. Costs vary by product (Table 103.1). Safety is a major concern with pediculicides, because the lice infestation itself presents minimal risk to the host. Pediculicides should be used only as directed and with care. Instructions on proper use of any product should be explained carefully. Therapy can be initiated with over-the-counter 1% permethrin lotion or with pyrethrin combined with piperonyl butoxide, both of which have good safety profiles. Resistance to these compounds has been documented in the United States; health care providers should be aware of regional patterns of clinical resistance. For treatment failures not attributable to improper use of an over-the-counter pediculicide, malathion, benzyl alcohol lotion, spinosad suspension, or ivermectin lotion should be used. When lice are resistant to all topical agents, oral ivermectin may be used in children weighing more than 15 kg. Drugs that have residual activity may kill nymphs as they emerge from eggs. No treatment is 100% ovicidal. Retreatment (with benzyl alcohol lotion, spinosad suspension, or malathion lotion) is performed commonly 7 to 10 days after treatment—that is, after eggs

Table 103.1
Pediculicides for the Treatment of Head Lice

Product	Brand Name	Recommended Age Range	Retreatment Interval (if Needed)	Availability	Cost Estimate[a]
Permethrin 1% lotion	Nix (Prestige Brands, Greenburgh, NY)	≥2 mo	9–10 days	Over the counter	$
Pyrethrins + piperonyl butoxide	Rid (Bayer Group, Leverkusen, Germany)	≥24 mo	9–10 days	Over the counter	$
Malathion 0.5%	Ovide (Taro Pharmaceutical Industries Ltd, Haifa Bay, Israel)	≥2 y	7–9 days if live lice are seen after initial dose	Prescription	$$$$
Benzyl alcohol 5%	Ulesfia (Contract Pharmaceuticals Ltd, Mississauga, Ontario, Canada)	≥6 mo	9–10 days	Prescription	$$–$$$$[b]
Spinosad 0.9% suspension	Natroba (ParaPRO, Carmel, IN)	≥6 mo	7 days if live lice are seen after initial dose	Prescription	$$$$
Ivermectin 0.5% lotion	Sklice (Arbor Pharmaceuticals, Atlanta, GA)	≥6 mo	Single use	Prescription	$$$$
Ivermectin (oral)	Stromectol (Merck & Co Inc, Whitehouse Station, NJ)	Any age, if weight >15 kg	9–10 days	Prescription	$$$$

[a] $ = ≤$25; $$ = $26–$99; $$$ = $100–$199; $$$$ = $200–$299.
[b] Cost varies by length of hair, which impacts number of units of product required.

present at the time of initial treatment have hatched but before new eggs are produced. Rinsing of hair after topical pediculicide application should always be done over a sink rather than during a shower or bath to limit skin exposure and with warm water rather than hot water to minimize skin absorption attributable to vasodilatation.

Because pediculicides kill lice shortly after application, detection of living lice on scalp inspection 24 hours or more after treatment suggests either incorrect use of pediculicide, hatching of lice after treatment, reinfestation, or resistance to therapy. In such situations, after excluding incorrect use, immediate retreatment with a different pediculicide followed by a second application 7 to 10 days later is recommended.

Itching or mild burning of the scalp caused by inflammation of the skin in response to topical therapeutic agents can persist for many days after lice are killed; this is not a reason for retreatment. Topical corticosteroid and oral antihistamine agents may be beneficial for relieving these signs and symptoms.

Manual removal of nits after successful treatment with a pediculicide is helpful to decrease diagnostic confusion and to decrease the small risk of self-reinfestation and social stigmatization. Fine-toothed nit combs designed for this purpose are available. Other products, such as vinegar, should not be used to help remove nits, because these may interfere with effectiveness of the pediculicide.

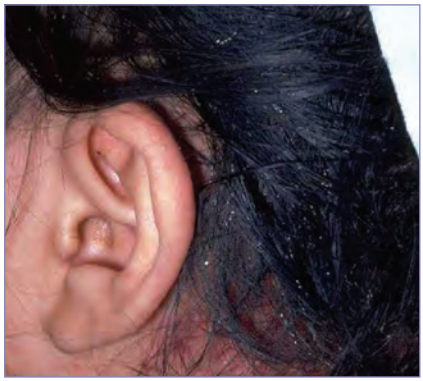


Image 103.1
Nits on the hair shafts. Copyright Edgar K. Marcuse, MD.

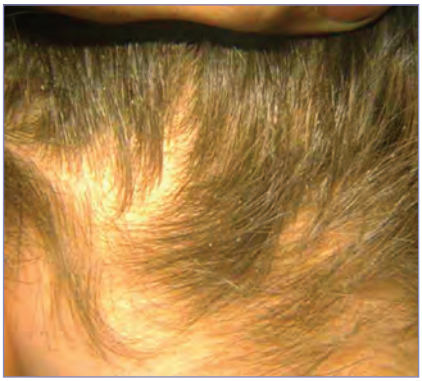


Image 103.2
Nits on the hair shaft. Copyright Edgar K. Marcuse, MD.

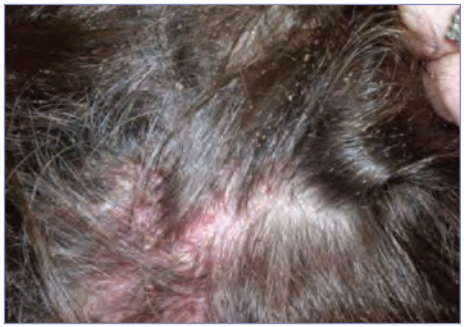


Image 103.3
An 8-year-old girl with an earache. This child complained of otalgia. During the course of otoscopic evaluation, she was noted to have a very large number of nits in her hair as well as active lice. On questioning, she stated she has had itching of the scalp. She was treated with topical permethrin with temporary resolution. Reinfestation occurred after sharing a riding helmet with a cousin. Courtesy of Will Sorey, MD.

Image 103.4
Head louse, baby louse, and hair. Copyright Gary Williams, MD.

Image 103.5
Lice nit. Copyright James Brien, DO.

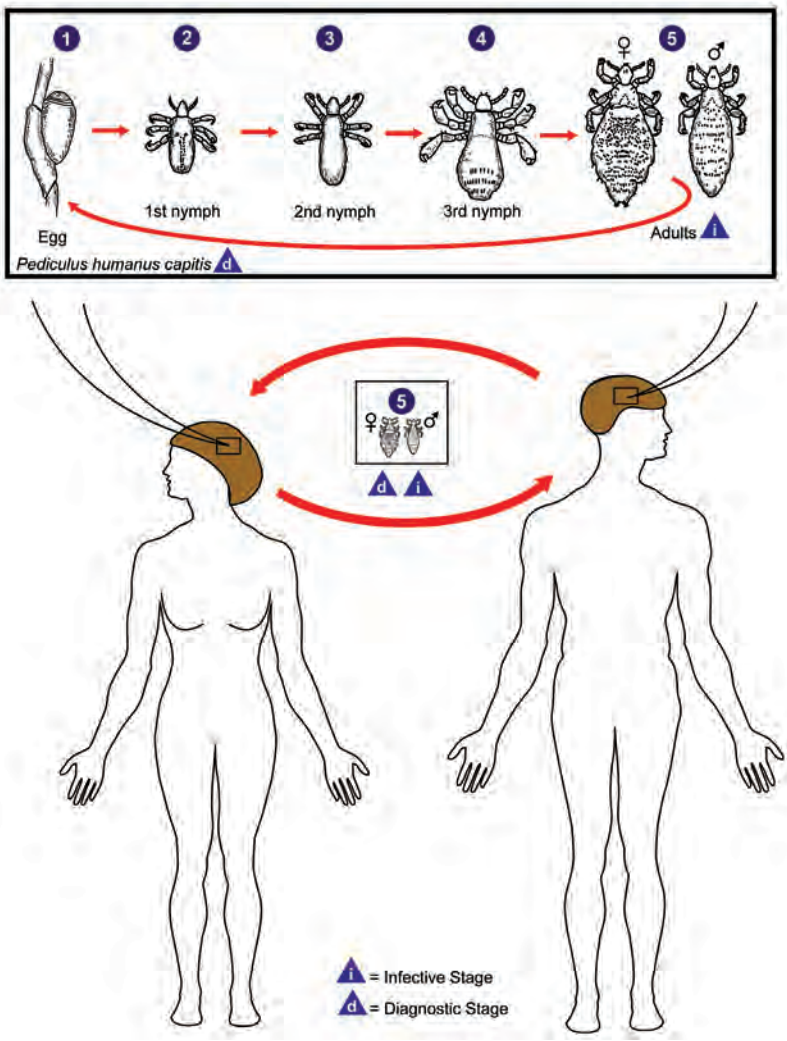


Image 103.6

The life cycle of the head louse has 3 stages: egg, nymph, and adult. Eggs: Nits are head lice eggs. They are hard to see and are often confused for dandruff or hair spray droplets. Nits are laid by the adult female and are cemented at the base of the hair shaft nearest the scalp (1). They are 0.8 by 0.3 mm, oval, and usually yellow to white. Nits take about 1 week to hatch (range, 6–9 days). Viable eggs are usually located within 6 mm of the scalp. Nymphs: The egg hatches to release a nymph (2). The nit shell then becomes a more visible dull yellow and remains attached to the hair shaft. The nymph looks like an adult head louse but is about the size of a pinhead. Nymphs mature after 3 molts (3, 4) and become adults about 7 days after hatching. Adults: The adult louse is about the size of a sesame seed, has 6 legs (each with claws), and is tan to grayish-white (5). In persons with dark hair, the adult louse will appear darker. Females are usually larger than males and can lay up to 8 nits per day. Adult lice can live up to 30 days on a person's head. To live, adult lice need to feed on blood several times daily. Without blood meals, the louse will die within 1 to 2 days off the host. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 104

Pediculosis Corporis

(Body Lice)

CLINICAL MANIFESTATIONS

Patients affected with pediculosis corporis characteristically come to medical attention because of intense itching, particularly at night. Bites manifest as small erythematous macules, papules, and excoriations, primarily on the trunk. In heavily bitten areas, typically around the midsection of the body (waist, groin, upper thighs), the skin can become thickened and discolored. Secondary bacterial infection of the skin (pyoderma) caused by scratching is common.

ETIOLOGY

Pediculus humanus corporis (or *humanus*) is the body louse. Both nymphs and adult lice feed on human blood.

EPIDEMIOLOGY

Body lice generally are restricted to people living in crowded conditions without access to regular bathing or changes of clothing (refugees, victims of war or natural disasters, homeless people). Under these conditions, body lice can spread rapidly through direct contact or contact with contaminated clothing or bedding. Body lice live in clothes or bedding, lay their eggs on or near the seams of clothing, and only move to the skin to feed. Body lice cannot survive away from a blood source for longer than approximately 5 to 7 days at room temperature. In contrast with head and pubic lice, body lice are well-recognized vectors of disease (eg, epidemic typhus, trench fever, epidemic relapsing fever, and bacillary angiomatosis).

The **incubation period** from laying eggs to hatching of the first nymph is 1 to 2 weeks. Lice mature and capable of reproducing 9 to 19 days after hatching.

DIAGNOSTIC TESTS

Seams of clothing should be examined for eggs (nits), nymphs, and adult lice (2–4 mm) if body louse infestation is suspected. Nits and lice may be seen with the naked eye; diagnosis can be confirmed by using a hand lens, dermatoscope (epiluminescence microscope), or a traditional microscope. Adult and nymphal body lice seldom are seen on the body, because they generally are sequestered in clothing.

TREATMENT

Treatment consists of improving hygiene, including bathing and regular changes of clean clothes and bedding. Infested materials can be discarded or decontaminated by washing in hot water (at least 128°F–130°F), by machine drying at hot temperatures, by dry cleaning, or by pressing with a hot iron. Temperatures exceeding 128°F for 5 minutes are lethal to lice and eggs. Pediculicides usually are not necessary if materials are laundered at least weekly. People with abundant body hair may require full-body treatment with a pediculicide, because lice and eggs may occasionally adhere to body hair. The only US Food and Drug Administration-approved treatment is pyrethrin with piperonyl butoxide.

Image 104.1
These body lice, *Pediculus humanus humanus,* family *Pediculidae*, are parasitic insects that live on the body and in the clothing or bedding of infested humans. Infestation is common and is found worldwide. Itching and rash are common with lice infestation. Courtesy of Centers for Disease Control and Prevention.

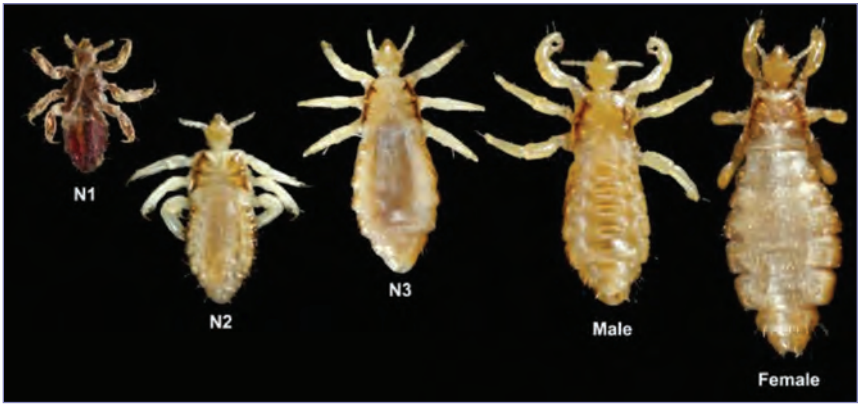


Image 104.2
This image depicts 5 body lice, *Pediculus humanus humanus,* which, from left to right, include 3 nymphal-staged lice, beginning with a stage N1, then N2, and, thirdly, an N3-staged nymph, followed by an adult male louse and, finally, an adult female louse. Courtesy of Centers for Disease Control and Prevention/Joseph Strycharz, PhD; Kyong Sup Yoon, PhD; and Frank Collins, PhD.

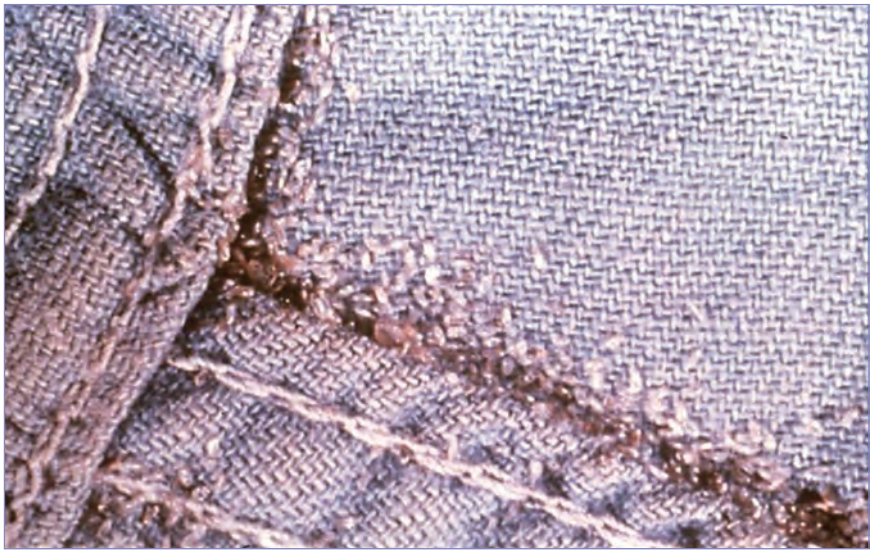


Image 104.3
This is a piece of clothing, the seams of which contained lice eggs from the body louse *Pediculus humanus humanus.* The most important factor in the control of body lice infestation is the ability to change and wash clothing. Courtesy of Centers for Disease Control and Prevention/Reed & Carnrick Pharmaceuticals.

CHAPTER 105

Pediculosis Pubis

(Pubic Lice, Crab Lice)

CLINICAL MANIFESTATIONS

Pruritus of the anogenital area is a common symptom in pubic lice infestations ("crabs" or "phthiriasis"). Adult lice (1–2 mm long and flattened, tan to grayish-white) or eggs (match hair color) and nits (empty egg shells, white) are found on hair. The parasite most frequently is found in the pubic region, but infestation can involve the eyelashes, eyebrows, beard, axilla, perianal area, and rarely, the scalp. A characteristic sign of heavy pubic lice infestation is the presence of bluish or slate-colored macules (maculae ceruleae) on the chest, abdomen, or thighs.

ETIOLOGY

Phthirus pubis is the pubic or crab louse. Both nymphs and adult lice feed on human blood. Pubic lice are not a health hazard and are not responsible for the spread of any disease.

EPIDEMIOLOGY

Pubic lice infestations are more prevalent in adults and usually are transmitted through sexual contact. Transmission by contact with contaminated items, such as towels, is uncommon. Pubic lice on the eyelashes or eyebrows of children may be evidence of sexual abuse, although other modes of transmission are possible. Adult pubic lice can survive away from a host for up to 48 hours, and their eggs can remain viable for up to 10 days under suitable environmental conditions.

The **incubation period** from the laying of eggs to the hatching of the first nymph is approximately 6 to 10 days.

DIAGNOSTIC TESTS

Identification of eggs (nits), nymphs, and lice with the naked eye is possible; the diagnosis can be confirmed by using a hand lens, traditional microscope, or dermatoscope (epiluminescence microscope). Pubic lice may be difficult to find because of low numbers. If crawling lice are not seen, finding nits in the pubic area strongly suggests infestation and should lead to treatment.

TREATMENT

All areas of the body with coarse hair should be examined for evidence of pubic lice infestation. Lice and their eggs can be removed manually, or the hairs can be shaved to eliminate infestation immediately. Caution should be used when inspecting, removing, or treating lice on or near the eyelashes. Pediculicides used to treat other kinds of louse infestations are effective for treatment of pubic lice, although treatment is off-label for all products except pyrethrin with piperonyl butoxide. Topical pediculicides should not be used for treatment of pubic lice infestation of eyelashes; an ophthalmic-grade petrolatum ointment (only available by prescription) applied to the eyelashes 2 to 4 times daily for 10 days is effective.

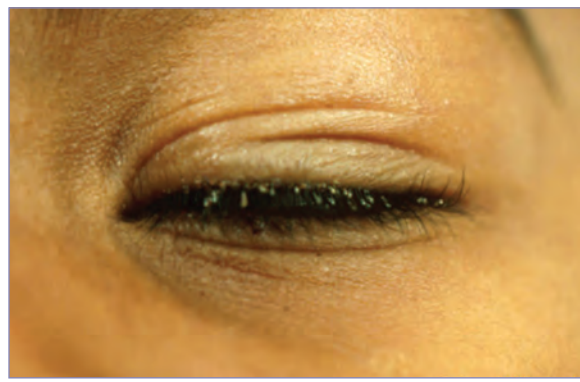


Image 105.1
Pubic lice (*Phthirus pubis*) in the eyelashes of a 3-year-old boy. The diagnosis can be confirmed by the use of a hand lens or microscope. Copyright Gary Williams.

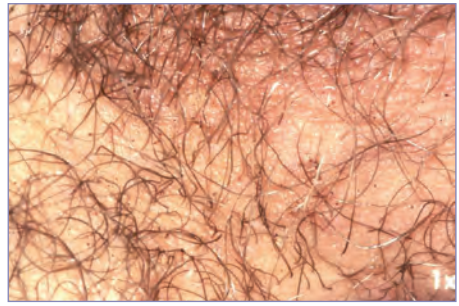


Image 105.2
This photograph reveals the presence of pubic or crab lice, *Phthirus pubis*, with reddish-brown feces. Pubic lice are generally found in the genital area on pubic hair but may occasionally be found on other coarse body hair, such as leg hair, armpit hair, mustache, beard, eyebrows, and eyelashes. Courtesy of Centers for Disease Control and Prevention/ Reed & Carnrick Pharmaceuticals.

Image 105.3
Pediculosis, the infestation of humans by lice, has been documented for millennia. Three species of lice infest humans: *Pediculus humanus humanus,* the body louse; *Pediculus humanus capitis,* the head louse; and *Phthirus pubis*, the pubic or crab louse. The hallmark of louse infestation is pruritus at the site of bites. Lice are more active at night, frequently disrupting the sleep of the host, which is the derivation of the term "feeling lousy." Adult pubic lice can survive without a blood meal for 36 hours. Unlike head lice, which may travel up to 23 cm per minute, pubic lice are sluggish, traveling a maximum of 10 cm per day. Viable eggs on pubic hairs may hatch up to 10 days later. Pubic louse infestation is localized most frequently to the pubic and perianal regions but may spread to the mustache, beard, axillae, eyelashes, or scalp hair. Infestation usually is acquired through sexual contact, and the finding of pubic lice in children (often limited to the eyelashes) should raise concern for possible sexual abuse. Courtesy of H. Cody Meissner, MD, FAAP.

CHAPTER 106

Pelvic Inflammatory Disease

CLINICAL MANIFESTATIONS

Pelvic inflammatory disease (PID) comprises a spectrum of inflammatory disorders of the female upper genital tract, including any combination of endometritis, parametritis, salpingitis, oophoritis, tubo-ovarian abscess, and pelvic peritonitis. Acute PID is difficult to diagnose because of the wide variation in symptoms and signs. Symptoms of acute PID include unilateral or bilateral lower abdominal or pelvic pain, fever, vomiting, abnormal vaginal discharge, irregular vaginal bleeding, and pain with intercourse. The severity of symptoms varies widely and may range from indolent to severe. Patients occasionally present with right upper quadrant abdominal pain resulting from perihepatitis (Fitz-Hugh-Curtis syndrome). Many episodes of PID go undiagnosed and untreated because the patient or health care professional fails to recognize the implications of mild or nonspecific symptoms and signs. Subclinical PID is a term that can be applied to females with very minimal or no symptoms, and there is a growing body of evidence that this represents a large proportion of all PID cases. In both clinically apparent and subclinical PID, inflammation occurs within the reproductive tract that scars or damages the fallopian tubes or surrounding structures. Clinicians need to recognize the implication of mild or nonspecific findings, particularly in a young female who might provide an incomplete or inaccurate sexual history.

Examination findings vary but may include oral temperature >101°F (>38.3°C), lower abdominal tenderness with or without peritoneal signs, abnormal cervical or vaginal discharge, tenderness with lateral motion of the cervix, uterine tenderness, unilateral or bilateral adnexal tenderness, and adnexal fullness. Pyuria (presence of white blood cells [WBCs] on urine microscopy), abundant WBCs on saline microscopy of vaginal fluid, an elevated erythrocyte sedimentation rate, elevated C-reactive protein, and/or an adnexal mass demonstrated by abdominal or transvaginal ultrasonography are findings that support a diagnosis of PID.

Complications of PID include perihepatitis (Fitz-Hugh-Curtis syndrome) and tubo-ovarian abscess/complex formation. Long-term sequelae include tubal scarring that can cause infertility in an estimated 20% of females, ectopic pregnancy in an estimated 9%, and chronic pelvic pain in an estimated 18%. Factors that may increase the likelihood of infertility are delay in diagnosis or delay in initiation of antimicrobial therapy, younger age at time of infection, chlamydial infection, recurrent PID, and PID determined to be severe by laparoscopic examination.

Any prepubertal girl with PID needs to be assessed for sexual abuse.

ETIOLOGY

Neisseria gonorrhoeae and *Chlamydia trachomatis* are the pathogens most commonly associated with PID, although the proportion of PID cases attributable to these pathogens is declining. Polymicrobial infection is common. Numerous organisms have been isolated from upper genital tract cultures of females with PID, including anaerobes, *Gardnerella vaginalis*, *Haemophilus influenzae*, *Streptococcus agalactiae*, enteric gram-negative rods, cytomegalovirus, *Mycoplasma genitalium*, *Mycoplasma hominis*, and *Ureaplasma urealyticum*. However, in more than half of cases, no organism is identified in lower genital tract swab specimens (ie, endocervical or vaginal specimens). More recent data suggest that *M genitalium* may play a role in the pathogenesis of PID, although there currently is no direct detection assay such as antigen or nucleic acid detection for *M genitalium*.

EPIDEMIOLOGY

Although many of the issues pertaining to high-risk sexual behavior and acquisition of sexually transmitted infections (STIs) are common to both adolescents and adults, they often are intensified among adolescents because of both behavioral and biological predispositions. Adolescents and young women can be at higher risk of STIs and PID because of behavioral factors such as inconsistent barrier contraceptive use, douching, greater number of current and lifetime sexual partners, and use of alcohol and other substances that may impair judgment while engaging in sexual activity. Latex condoms

may reduce the risk of PID. Adolescent and young adult females also have an increased biologic susceptibility to STIs. Cervical ectopy increases risk of chlamydia and gonorrhea infection by exposing columnar epithelium to a potential infectious inoculum. Although the risk of developing PID is minimally elevated during the initial 20 days following intrauterine device (IUD) insertion, the Centers for Disease Control and Prevention (CDC) advises that the benefits of IUDs in adolescents generally outweigh the risks.

The **incubation period** for PID is unknown.

DIAGNOSTIC TESTS

Diagnostic criteria recommended by the CDC are presented in Table 106.1. No single symptom, sign, or laboratory or imaging finding is sensitive and specific for the diagnosis of acute PID. The diagnosis of PID typically is accomplished by using a combination of clinical symptoms and signs, physical examination, and laboratory tests. A clinical diagnosis of symptomatic PID has a positive predictive value (PPV) for salpingitis of 65% to 90% but generally is higher among populations at risk, such as sexually active females 25 years and younger, females attending STI clinics, and females who live in communities with high gonorrhea or chlamydia rates.

The minimum clinical criteria on pelvic examination to make the diagnosis of PID include cervical motion tenderness, or uterine or adnexal tenderness. Additional criteria can be used to make the diagnosis of PID more specific (see Table 106.1). Most females with PID have either mucopurulent cervical discharge or evidence of WBCs on a microscopic evaluation of a saline preparation of vaginal fluid (ie, wet prep). If a patient's cervical discharge appears normal and no WBCs are observed on the wet prep of vaginal fluid, the diagnosis of PID is unlikely, and alternative causes of pain should be considered. A cervical or vaginal swab specimen should be obtained from all patients with suspected PID to perform a nucleic acid amplification test (NAAT) for *C trachomatis* and *N gonorrhoeae*. A swab specimen for culture of *N gonorrhoeae* may be collected from the cervix or vagina to allow susceptibility testing to be performed. When the diagnosis of PID is in doubt, there is concern for a tubo-ovarian abscess, or the patient is not responding to conventional therapy, further diagnostic evaluation using transvaginal ultrasonography or magnetic resonance imaging (MRI) may be helpful to evaluate for thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex or using Doppler ultrasonography to evaluate for evidence of increased fallopian tube blood flow suggestive of infection (eg, tubal hyperemia). Laparoscopy is the gold standard for diagnosis, allowing direct visualization of the adnexal structures as well as allowing bacteriologic specimens to be obtained directly from tubal exudate or the cul-de-sac. Endometrial biopsy may demonstrate histopathologic evidence of endometritis and may be the only sign of PID in some females. Because of their high cost and invasive nature, however, these procedures are not indicated for diagnosis of most PID cases. Pregnancy must be ruled out in all patients evaluated for PID. In addition to determining whether WBCs are present in cervicovaginal secretion, wet mount will assist in the diagnosis or exclusion of the commonly associated trichomonas or bacterial vaginosis. Serologic testing for human immunodeficiency virus (HIV) and syphilis also should be performed.

TREATMENT

A sexually active adolescent or young adult female with lower abdominal pain who exhibits uterine, adnexal, or cervical motion tenderness on bimanual examination should be treated for PID if no other cause is identified. To minimize risks of progressive infection and subsequent infertility, treatment should be initiated at the time of clinical diagnosis, and therapy should be completed, regardless of the STI test results.

Among females with mild to moderate PID, there is no difference in clinical course, recurrent PID, chronic pelvic pain, or infertility rates between females hospitalized and those treated as outpatients for PID. The decision to hospitalize adolescents with acute PID should be made by the same criteria used for older women and should be based on the provider's judgment and whether the patient meets any of the following suggested criteria:

Table 106.1
Criteria for Clinical Diagnosis of Pelvic Inflammatory Disease (PID)[a]

Minimum Criteria

Empiric treatment of PID should be initiated in sexually active young women if they are experiencing pelvic or lower abdominal pain, if one or more of the following **minimum criteria** are present, and no other cause(s) for the illness can be identified:

- Uterine tenderness
  or
- Adnexal tenderness
  or
- Cervical motion tenderness

Additional Criteria

These criteria may be used to enhance the specificity of the minimum criteria. Additional criteria that support a diagnosis of PID include the following:

- Oral temperature greater than 38.3°C (101°F)
- Mucopurulent cervical or vaginal discharge
- Presence of white blood cells (WBCs) on saline microscopy of vaginal secretions
- Elevated erythrocyte sedimentation rate
- Elevated C-reactive protein
- Laboratory documentation of cervical infection with *Neisseria gonorrhoeae* or *Chlamydia trachomatis*

Most females with PID have mucopurulent cervical discharge or evidence of WBCs on a microscopic evaluation of a saline preparation of vaginal fluid. If the cervical discharge appears normal **and** no WBCs are found on the wet preparation, the diagnosis of PID is unlikely, and alternative causes of pain should be sought.

The **most specific criteria** for diagnosing PID include the following:

- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal ultrasonography or magnetic resonance imaging techniques showing thickened, fluid-filled tubes with or without free pelvic fluid or tubo-ovarian complex, or Doppler ultrasonography suggests increased fallopian tube blood flow suggestive of infection (eg, tubal hyperemia)
- Laparoscopic findings consistent with PID

A diagnostic evaluation that includes some of these more extensive studies may be warranted in some cases.

[a] Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR-1):1–137.

- The patient is experiencing a surgical emergency, such as ectopic pregnancy or appendicitis, or another serious condition cannot be excluded;
- The patient's illness is severe (eg, vomiting, severe pain, overt peritonitis, or high fever);
- The patient has a tubo-ovarian abscess;
- The patient is pregnant;
- The patient is unable to follow or tolerate an outpatient regimen; or
- The patient has failed to respond clinically to outpatient therapy.

The antimicrobial regimen chosen should provide empiric, broad-spectrum coverage directed against the most common causative agents, including *N gonorrhoeae* and *C trachomatis*, even if these pathogens are not identified in lower genital tract specimens (Tables 106.2 and 106.3). As a result of the emergence of quinolone-resistant *N gonorrhoeae*, fluoroquinolones no longer are recommended as first-line treatment of PID.

For patients with severe cephalosporin allergy, the use of a fluoroquinolone with metronidazole for 14 days can be considered, provided the community prevalence as well as individual risk for gonococcal infection are low and patient follow-up is likely. If the *N gonorrhoeae* culture is positive, antimicrobial susceptibility testing should guide therapy. If the isolate is determined to be a quinolone-resistant strain of *N gonorrhoeae* or if antimicrobial susceptibility cannot be assessed (eg, if only NAAT testing is available), consultation with an infectious disease specialist and the local or state health department is recommended. Clinicians should follow public health reporting guidelines for positive *N gonorrhoeae* results.

A critical component to the outpatient management is short-term follow-up, especially in the adolescent population. Outpatients should be reevaluated after 72 hours of therapy, including repeating the bimanual examination of the pelvis; hospitalization and/or further diagnostics should be considered in females without clinical improvement.

Pregnant women with PID are at high risk for preterm delivery and severe infection. They should be hospitalized to receive intravenous antibiotic therapy. Doxycycline should not be used during pregnancy unless it is essential for the mother's welfare.

Patients with tubo-ovarian abscesses should be treated with inpatient parenteral treatment that includes anaerobic coverage, and antimicrobial therapy can be switched to the oral route after 24 hours of clinical improvement; at the time of discharge, patients should complete a 14-day course of doxycycline (100 mg, twice a day) or clindamycin (450 mg, orally, 4 times a day). If an IUD user receives a diagnosis of PID, the IUD does not need to be removed. However, the woman should receive treatment according to these recommendations and should have close clinical follow-up. If no clinical improvement occurs within 48 to 72 hours of initiating treatment, providers should consider removing the IUD.

Table 106.2
Recommended Parenteral Treatment of Pelvic Inflammatory Disease (PID)[a]

Cefotetan, IV, every 12 h **OR Cefoxitin,** IV, every 6 h

PLUS

Doxycycline, orally or IV, every 12 h to complete 14 days

OR

Clindamycin, IV, every 8 h

PLUS

Gentamicin: loading dose, IV or IM, followed by maintenance dose every 8 h. Single daily dosing can be substituted.

NOTE
Parenteral therapy may be discontinued 24 h after clinical improvement; continuing oral therapy should consist of doxycycline or clindamycin to complete a total of 14 days of therapy. If tubo-ovarian abscess is present, clindamycin, orally, 4 times daily, or metronidazole should be used to complete at least 14 days of therapy with doxycycline to provide more effective anaerobic coverage than doxycycline alone.

IV indicates intravenous; IM, intramuscular.

[a] Additional regimens may be found in: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR-3):1–137 (see **www.cdc.gov/std/treatment**).

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR-3):1-137.

Table 106.3
Recommended Intramuscular/Oral Regimens for Treatment of Pelvic Inflammatory Disease (PID)[a]

Ceftriaxone, IM, once **OR Cefoxitin,** IM, and **probenecid,** orally, in a single dose concurrently **OR** other parenteral third-generation **cephalosporin** (eg, **ceftizoxime** or **cefotaxime**) PLUS **Doxycycline,** orally, twice a day for 14 days WITH or WITHOUT **Metronidazole,** orally, twice a day for 14 days

IV indicates intravenous; IM, intramuscular.

[a] Additional regimens may be found in: Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR-3):1–137 (see **www.cdc.gov/std/treatment**).

Adapted from Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. *MMWR Recomm Rep.* 2015;64(RR-3):1–137

CHAPTER 107

Pertussis (Whooping Cough)

CLINICAL MANIFESTATIONS

Pertussis begins with mild upper respiratory tract symptoms similar to the common cold (catarrhal stage) and progresses to cough, usually paroxysms of cough (paroxysmal stage), characterized by inspiratory whoop (gasping) after repeated cough on the same breath, which commonly is followed by vomiting. Fever is absent or minimal. Symptoms wane gradually over weeks to months (convalescent stage). Cough illness in immunized children and adults can range from typical to mild and unrecognized. The duration of classic pertussis is 6 to 10 weeks. Approximately half of adolescents with pertussis cough for 10 weeks or longer. Complications among adolescents and adults include syncope, weight loss, sleep disturbance, incontinence, rib fractures, and pneumonia; among adults, complications increase with age. Pertussis is most severe when it occurs during the first 6 months of life, particularly in preterm and unimmunized infants. Disease in infants younger than 6 months can be atypical with a short catarrhal stage, followed by gagging, gasping, bradycardia, or apnea (67%) as prominent early manifestations; absence of whoop; and prolonged convalescence. Sudden unexpected death can be caused by pertussis. Complications among infants include pneumonia (23%) and pulmonary hypertension as well as complications related to severe coughing spells, such as conjunctival bleeding, hernia, and severe coughing spells leading to hypoxia and complications such as seizures (2%), encephalopathy (less than 0.5%), apnea, and death. More than two thirds of infants with pertussis are hospitalized. Case-fatality rates are approximately 1% in infants younger than 2 months and less than 0.5% in infants 2 through 11 months of age. Maternal immunization during pregnancy and an infant's previous immunization reduce morbidity and mortality in young infants.

ETIOLOGY

Pertussis is caused by a fastidious, gram-negative, pleomorphic bacillus, *Bordetella pertussis*. Other causes of sporadic prolonged cough illness include *Bordetella parapertussis*, *Mycoplasma pneumoniae*, *Chlamydia trachomatis*, *Chlamydia pneumoniae*, *Bordetella bronchiseptica* (the cause of kennel cough), *Bordetella holmesii*, and certain respiratory tract viruses, particularly adenoviruses and respiratory syncytial viruses.

EPIDEMIOLOGY

Humans are the only known hosts of *B pertussis*. Transmission occurs by close contact with cases via large respiratory droplets generated by coughing or sneezing. Cases occur year-round, typically with a late summer-autumn peak. Neither infection nor immunization provides lifelong immunity. Waning immunity, particularly when acellular pertussis vaccine is used for the entire immunization series, is predominantly responsible for increased cases reported in school-aged children, adolescents, and adults. Additionally, waning maternal immunity of mothers who have not received Tdap vaccine during that pregnancy results in low concentrations of transplacentally transmitted antibody and an increase in pertussis in very young infants. Reports of pertussis increased in the United States in recent years with notable epidemic peaks in disease; more than 48,000 cases of pertussis were reported in 2012, the highest number in over 50 years. Pertussis is highly contagious. As many as 80% of previously immunized household contacts of symptomatic infant cases are infected with *B pertussis*, with symptoms in these contacts varying from mild to classic pertussis. Siblings and adults with cough illness are important sources of pertussis infection for young infants. Infected people are most contagious during the catarrhal stage through the third week after onset of paroxysms. Factors affecting the length of communicability include age, immunization status or previous infection, and receipt of appropriate antimicrobial therapy.

The **incubation period** is 7 to 10 days (range, 5 to 21 days).

DIAGNOSTIC TESTS

Culture was considered the "gold standard" for laboratory diagnosis of pertussis but is not optimally sensitive, because *B pertussis* is a fastidious organism. Culture requires collection of an appropriate nasopharyngeal specimen, obtained either by aspiration or with polyester or flocked rayon swabs or calcium alginate swabs. Specimens must be placed into special transport media (such as Regan-Lowe) immediately and not allowed to dry during prompt transport to the laboratory. Culture results can be negative if taken from a previously immunized person, if antimicrobial therapy has been started, if more than 2 weeks has elapsed since cough onset, or if the specimen is not collected or handled appropriately.

Nucleic acid amplification tests (NAATs), including polymerase chain reaction (PCR) assay, now are commercially available as standalone tests or as multiplex assays, and are the most commonly used laboratory method for detection of *B pertussis* because of greater sensitivity and more rapid results. The PCR test requires collection of an adequate nasopharyngeal specimen using a Dacron swab or nasopharyngeal wash or aspirate. Calcium alginate swabs can be inhibitory to PCR and should not be used for PCR tests. The PCR test has optimal sensitivity during the first 3 weeks of cough, is unlikely to be useful if antimicrobial therapy has been given for more than 5 days, and has lower sensitivity in previously immunized people, but still is more sensitive than culture. Some PCR assays target only a multicopy insertion gene sequence (IS 481) found in *B pertussis* as well as the less commonly encountered *B holmesii* and some strains of *B bronchiseptica*. Multiple DNA target sequences are required to distinguish among *Bordetella* species. Direct fluorescent antibody (DFA) testing no longer is recommended.

Commercial serologic tests for pertussis infection can be helpful for diagnosis, especially late in illness and in adolescents and adults. Most assays are formulated as enzyme immunoassays. In the absence of recent immunization, an elevated serum immunoglobulin (Ig) G antibody to pertussis toxin (PT) present 2 to 8 weeks after onset of cough is suggestive of recent *B pertussis* infection. For single serum specimens, an IgG anti-PT value of approximately 100 IU/mL or greater has been recommended. Positive paired serologic results based on the World Health Organization pertussis case definition may also be considered diagnostic.

An increased white blood cell count attributable to absolute lymphocytosis is suggestive of pertussis in infants and young children but often is absent in older people with pertussis and can be only mildly abnormal in some young infants at the time of presentation. A markedly elevated white blood cell count is associated with a poor prognosis in young infants.

TREATMENT

Antimicrobial therapy administered during the catarrhal stage may ameliorate the disease. Antimicrobial therapy is indicated before test results are available if the clinical history is strongly suggestive of pertussis or the patient is at high risk of severe or complicated disease (eg, an infant). A 5-day course of azithromycin is the appropriate first-line choice for treatment and for postexposure prophylaxis. After the paroxysmal cough is established, antimicrobial agents have no discernible effect on the course of illness but are recommended to limit spread of organisms to others. Resistance of *B pertussis* to macrolide antimicrobial agents has been reported, but rarely. Penicillins and first- and second-generation cephalosporins are not effective.

Azithromycin should be used with caution in people with prolonged QT interval and proarrhythmic conditions. An association between orally administered erythromycin and azithromycin with infantile hypertrophic pyloric stenosis (IHPS) has been reported, but azithromycin remains the drug of choice for treatment or prophylaxis of pertussis in very young infants because the risk of developing severe pertussis and life-threatening complications outweighs the potential risk of pyloric stenosis. Health care providers should be alert to the possible

development of pyloric stenosis in infants from birth up to 6 weeks of age who have received azithromycin.

Trimethoprim-sulfamethoxazole is an alternative for patients older than 2 months who cannot tolerate macrolides or who are infected with a macrolide-resistant strain, but studies evaluating trimethoprim-sulfamethoxazole as treatment for pertussis are limited.

Young infants are at increased risk of respiratory failure attributable to apnea or secondary bacterial pneumonia and are at risk of cardiopulmonary failure and death from severe pulmonary hypertension. Hospitalized young infants with pertussis should be managed in a setting/facility where these complications can be recognized and managed urgently.

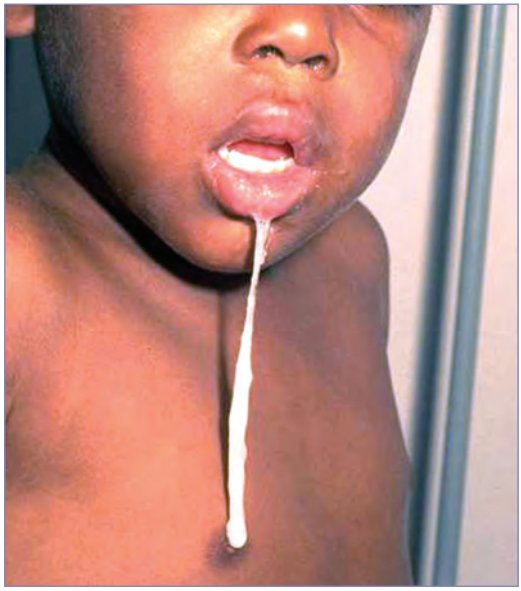


Image 107.1
A preschool-aged boy with pertussis. Thick respiratory secretions were produced by a paroxysmal coughing spell. Courtesy of Edgar O. Ledbetter, MD, FAAP.

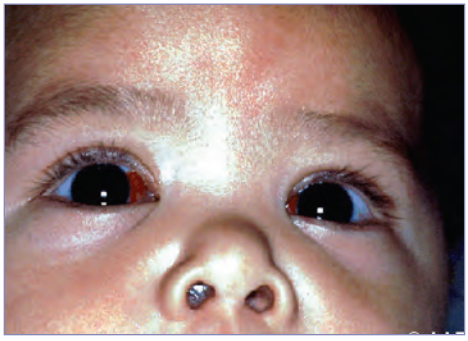


Image 107.2
Bilateral subconjunctival hemorrhages and thick nasal mucus in an infant with pertussis.

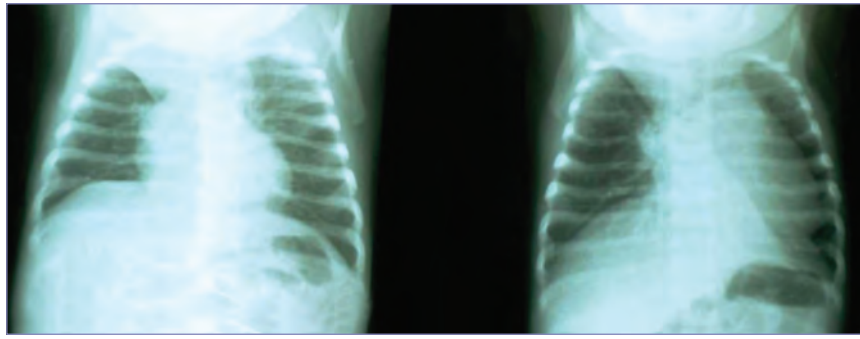


Image 107.3
A 4-week-old with pertussis pneumonia with pulmonary air trapping and progressive atelectasis confirmed at autopsy. The neonate acquired the infection from the mother shortly after birth. Segmented and lobar atelectasis are not uncommon complications of pertussis.

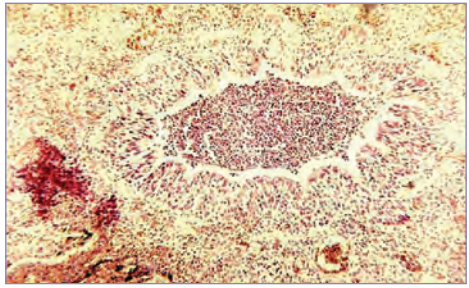


Image 107.4
Bronchiolar plugging in the neonate in Image 107.3 who died of pertussis pneumonia. Neonates, infants, and children often acquire pertussis from an infected adult or sibling contact.

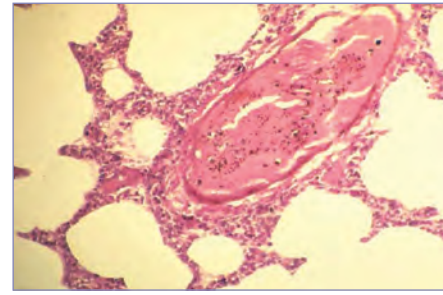


Image 107.5
Plugging and alveolar dilatation of pertussis pneumonia in an infant who died. Courtesy of Edgar O. Ledbetter, MD, FAAP.

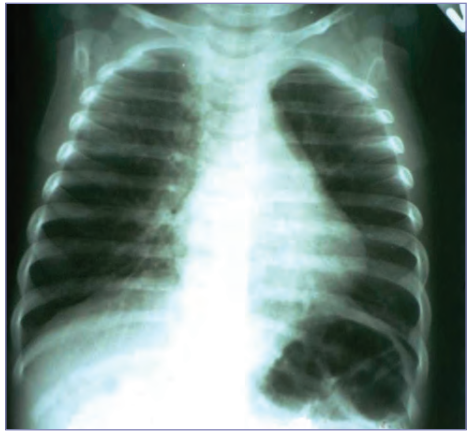


Image 107.6
Pertussis pneumonia with hyperaeration (air trapping) due to inability to cough out thick pulmonary secretions.

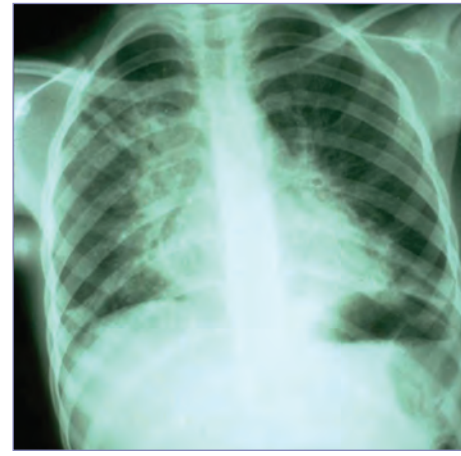


Image 107.7
Pertussis pneumonia in a 7-year-old who was exhausted from persistent coughing. Obliteration of cardiac borders on the chest radiograph is a common radiographic change of pertussis pneumonia.

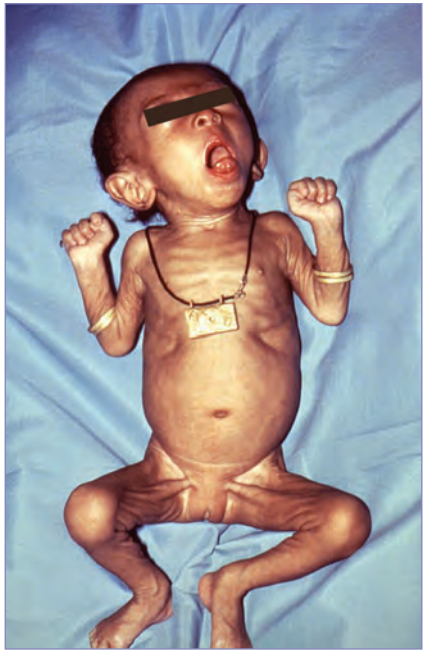


Image 107.8
This image depicts a malnourished infant girl who presented to a clinic with what was diagnosed as pertussis. Pertussis is a highly communicable, vaccine-preventable disease caused by *Bordetella pertussis*, a gram-negative coccobacillus, that lasts for many weeks and typically afflicts children with severe coughing, whooping, and posttussive vomiting. Courtesy of Centers for Disease Control and Prevention.

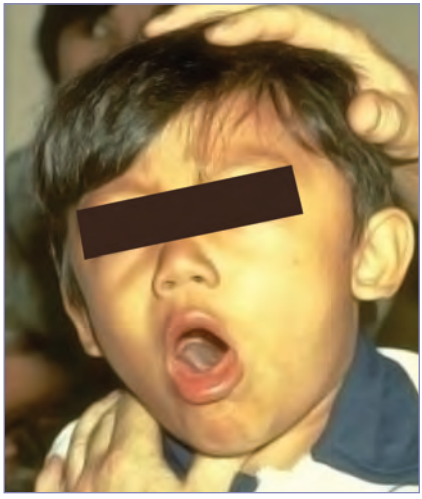


Image 107.9
This child has pertussis (whooping cough). He has severe coughing spasms, which are often followed by a whooping sound. It is difficult for him to stop coughing and catch his breath. Courtesy of Centers for Disease Control and Prevention.

Image 107.10
This child has broken blood vessels in his eyes and bruising on his face because of coughing from pertussis. Courtesy of Thomas Schlenker, MD, MPH, chief medical officer, Children's Hospital of Wisconsin.

Image 107.11
Colonies of *Bordetella pertussis* growing on Bordet-Gengou media. Courtesy of Edgar O. Ledbetter, MD, FAAP.

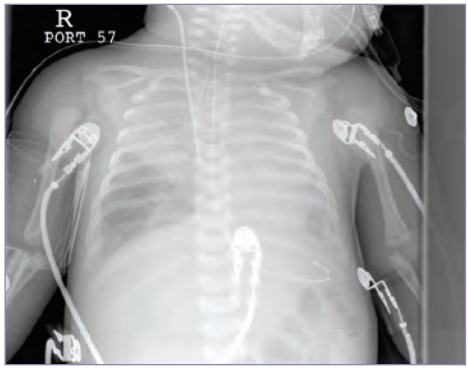


Image 107.12
Pertussis pneumonia in a 2-month-old 2 days after hospital admission. His mother had been coughing since shortly after delivery. Courtesy of Carol J. Baker, MD, FAAP.

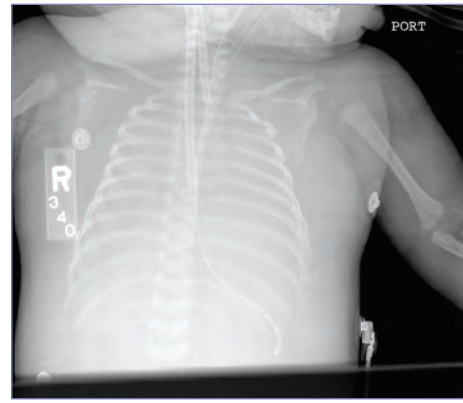


Image 107.13
The infant in Image 107.12 required mechanical ventilation because of respiratory failure. Courtesy of Carol J. Baker, MD, FAAP.

CHAPTER 108

Pinworm Infection

(*Enterobius vermicularis*)

CLINICAL MANIFESTATIONS

Although some people are asymptomatic, pinworm infection (enterobiasis) may cause pruritus ani and, rarely, pruritus vulvae. Bacterial superinfections can result from scratching and excoriation of the area. Pinworms have been found in the lumen of the appendix, and in some cases, these intraluminal parasites have been associated with signs of acute appendicitis; they also have been observed in histologically normal appendices removed for incidental reasons. Many clinical findings, such as grinding of teeth at night, weight loss, and enuresis, have been attributed to pinworm infections, but a causal relationship has not been established. Urethritis, vaginitis, salpingitis, or pelvic peritonitis may occur from aberrant migration of an adult worm from the perineum. Peripheral eosinophilia generally is not seen.

ETIOLOGY

Enterobius vermicularis is a nematode or roundworm.

EPIDEMIOLOGY

Enterobiasis occurs worldwide and commonly clusters within families. Prevalence rates are higher in preschool- and school-aged children, in primary caregivers of infected children, and in institutionalized people; up to 50% of these populations may be infected.

The adult female and eggs induce intense perianal pruritus, leading to transmission by the fecal-oral route via contaminated hands. Alternative modes of transmission include person-to-person or sexual transmission. Female pinworms usually die after depositing up to 100,00 fertilized eggs within 24 hours on perianal skin. Eggs adhere to the anal region and embryonate within 6 hours, becoming infective, leading to person-to-person spread or reinfection by autoinfection. A person remains infectious while female nematodes are discharging eggs on perianal skin. Eggs remain infective in an indoor environment usually for 2 to 3 weeks. Humans are the only known natural hosts.

The **incubation period** from ingestion of an egg until an adult gravid female migrates to the perianal region is 1 to 2 months or longer.

DIAGNOSTIC TESTS

Diagnosis is established via the classic cellulose tape (clear adhesive cellophane tape) test or with a commercially available pinworm paddle test, which is a clear plastic paddle coated with an adhesive surface on one side that is pressed in the perianal region during the night or upon waking, prior to bathing. The paddle then is pressed on a slide and eggs can be visualized by microscopy. Eggs are 50 x 25 microns and flattened on one side, giving them a "bean-shaped" appearance. Testing on 3 different days will increase the yield. Adult females, which are white and measure 8 to 13 mm, also can be seen in the perineal region. Stool examinations are of limited value. Peripheral eosinophilia is unusual.

TREATMENT

Several drugs of choice are available for treatment of pinworms, including pyrantel pamoate, which is available over the counter; albendazole; and mebendazole. Albendazole and mebendazole cost more than pyrantel pamoate. Each medication is recommended to be given in a single dose and repeated in 2 weeks, because these drugs are not completely effective against the egg or developing larvae stages. Ivermectin has been evaluated and is effective. Despite effective therapy, reinfection is common; therefore, treatment of the entire household should be considered, given the high transmission rate in families. Hygienic prevention, such as bathing in the morning to remove eggs, frequent hand hygiene, and clipping of fingernails, all are helpful for decreasing the risk of autoinfection and continued transmission. Repeated infections should be treated the same as the first infection. All household members should be treated as a group in situations in which multiple or repeated symptomatic infections occur. Vaginitis is self-limited and does not require separate treatment.

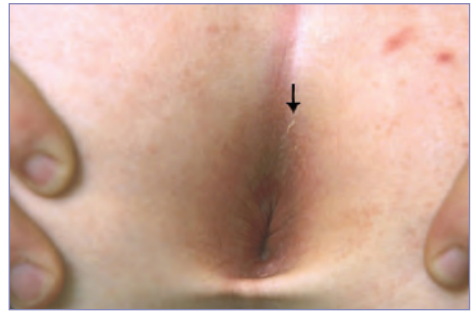


Image 108.1
Adult pinworm (*Enterobius vermicularis*) in the perianal area of a 14-year-old boy. Perianal inspection 2 to 3 hours after the child goes to sleep may reveal pinworms that have migrated outside of the intestinal tract. Copyright Gary Williams.

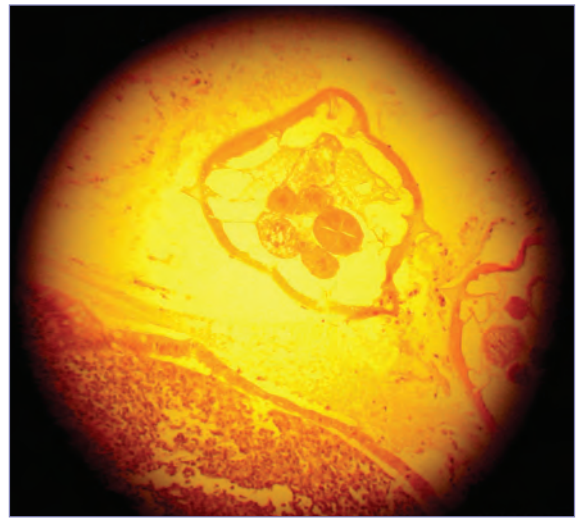


Image 108.2
Enterobius vermicularis in the lumen of the appendix of a 10-year-old. Pinworms can be found in the lumen of the appendix, but most evidence indicates that they do not cause acute appendicitis. Courtesy of Benjamin Estrada, MD.

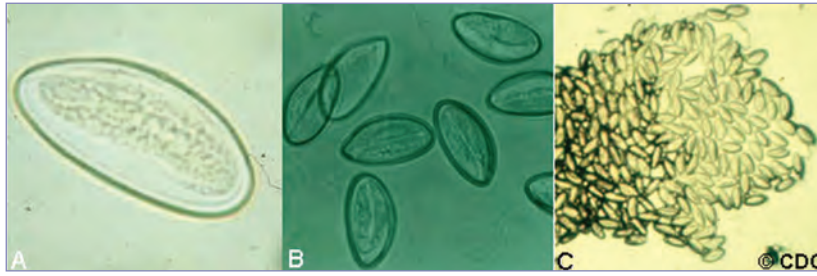


Image 108.3
A–B, Enterobius egg(s). C, Enterobius eggs on cellulose tape prep. Courtesy of Centers for Disease Control and Prevention.

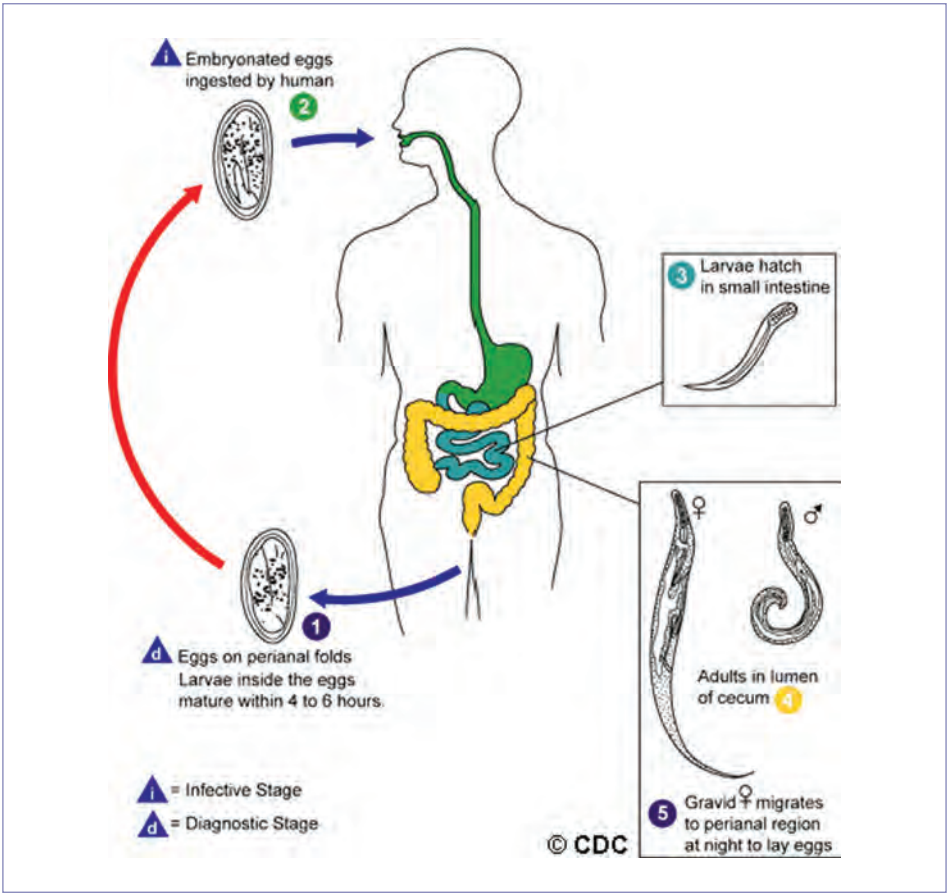


Image 108.4

Eggs are deposited on perianal folds (1). Self-infection occurs by transferring infective eggs to the mouth with hands that have scratched the perianal area (2). Person-to-person transmission can also occur through handling of contaminated clothes or bed linens. Enterobiasis may also be acquired through surfaces in the environment that are contaminated with pinworm eggs (eg, curtains, carpeting). Some small number of eggs may become airborne and inhaled. These could be swallowed and follow the same development as ingested eggs. Following ingestion of infective eggs, the larvae hatch in the small intestine (3) and the adults establish themselves in the colon (4). The time interval from ingestion of infective eggs to oviposition by the adult females is about 1 month. The life span of the adults is about 2 months. Gravid females migrate nocturnally outside the anus and oviposit while crawling on the skin of the perianal area (5). The larvae contained inside the eggs develop (the eggs become infective) in 4 to 6 hours under optimal conditions (1). Retroinfection, or the migration of newly hatched larvae from the anal skin back into the rectum, may occur, but the frequency with which this happens is unknown. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 109

Pityriasis Versicolor

(Formerly Tinea Versicolor)

CLINICAL MANIFESTATIONS

Pityriasis versicolor (formerly tinea versicolor) is a common and benign superficial infection of the skin, classically manifesting on the upper trunk and neck. In infants and children, the infection is likely to involve the face, particularly the bilateral temples. Infection can include other areas, including the scalp, genital area, and thighs. Symmetrical involvement with ovoid discrete or coalescent lesions of varying size is typical; these macules or patches vary in color, even in the same person. White, pink, tan, or brown coloration is often surmounted by faint dusty scales. Lesions fail to tan during the summer and are relatively darker than the surrounding skin during the winter, hence the term versicolor. The differential diagnosis includes pityriasis alba, vitiligo, seborrheic dermatitis, pityriasis rosea, progressive macular hypopigmentation, and pityriasis lichenoides. Folliculitis also can occur, particularly in immunocompromised patients. Systemic infections can occur in neonates, particularly those receiving total parenteral nutrition with lipids.

ETIOLOGY

The cause of pityriasis versicolor is a number of species of the *Malassezia furfur* complex, a group of lipid-dependent yeasts that exist on healthy skin in yeast phase and cause clinical lesions only when substantial growth of hyphae occurs. Moisture, heat, and the presence of lipid-containing sebaceous secretions encourage rapid overgrowth of hyphae.

EPIDEMIOLOGY

Pityriasis versicolor can occur in any climate or age group but tends to favor adolescents and young adults, particularly in tropical climates.

The **incubation period** is unknown.

DIAGNOSTIC TESTS

The presence of symmetrically distributed faintly scaling macules and patches of varying color concentrated on the upper back and chest is close to diagnostic. The "evoked scale" sign consists of stretching or scraping the involved skin, which readily elicits a visible layer of thin scale. Involved areas fluoresce yellow-green under Wood lamp evaluation. Potassium hydroxide wet mount prep of scraped scales reveals the classic "spaghetti and meatballs" short hyphae and clusters of yeast forms. Because this yeast is a common inhabitant of the skin, culture from the skin surface is nondiagnostic. Samples from pustules or sterile sites should be placed in media enriched with olive oil or another long-chain fatty acid.

TREATMENT

Multiple topical and systemic agents are efficacious, and recommendations vary substantially. For uncomplicated cases, most experts recommend initiating therapy with topical agents. The most cost-effective treatments are selenium sulfide shampoo/lotion and clotrimazole cream. Selenium sulfide shampoo is used for 3 to 7 days; application is once daily for 5 to 10 minutes, followed by rinsing. Topical azole therapy (eg, clotrimazole cream) is applied twice daily for 2 to 3 weeks. Adherence with these agents may be low because of unpleasant adverse effects (the shampoo has a sulfur-like odor) or duration and anatomic extent of required therapy. Other effective topical agents include ketoconazole, bifonazole, miconazole, econazole, oxiconazole, clotrimazole, terbinafine, and ciclopirox, as well as zinc pyrithione shampoo. Shampoos are easier to disperse, particularly on wet skin, than topical creams and may increase compliance.

Recurrence following discontinuation of therapy may approach 60% to 80%, and preventive treatments sometimes are used to decrease recurrences. The family must be counseled that return of pigment to the previously affected sites can take months.

Systemic therapy is reserved for resistant infection or extensive involvement. Medications, including fluconazole, ketoconazole, itraconazole, and pramiconazole, are used, but single oral doses do not appear to be as efficacious as multiple doses over several days or weeks. Fluconazole can be administered for 2 to 4 weeks, and ketoconazole for 10 days. Although oral agents may be easier to use than topical agents, they are not necessarily more effective and have possible serious adverse effects.

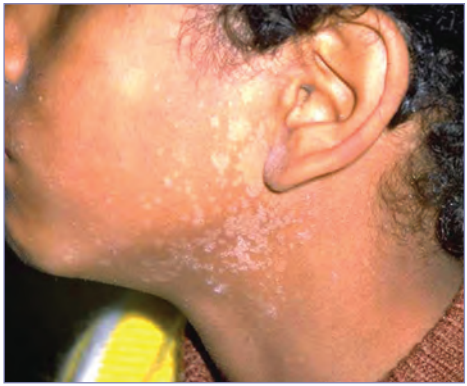


Image 109.1
Pityriasis versicolor.

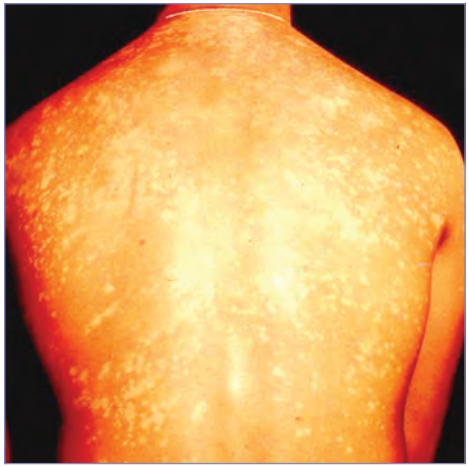


Image 109.2
Pityriasis versicolor of the posterior surface of the neck and trunk.

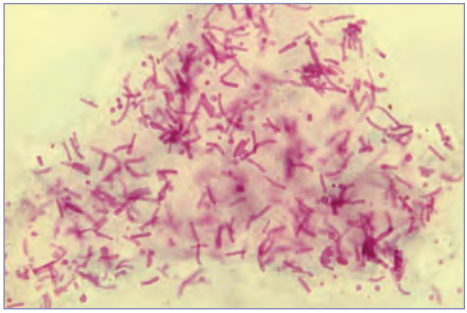


Image 109.3
This photomicrograph of a skin scale reveals the presence of the fungus *Malassezia furfur*. Usually *M furfur* grows sparsely without causing a rash. In some individuals, it grows more actively for reasons unknown, resulting in pale brown, flaky patches on the trunk, neck, or arms, a condition called pityriasis versicolor (formerly called tinea versicolor).

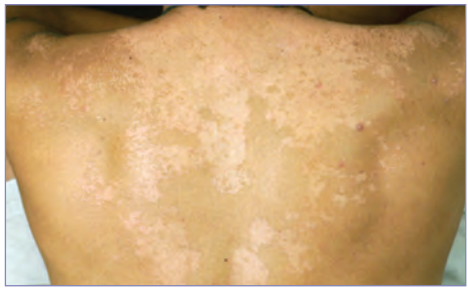


Image 109.4
Pityriasis versicolor in a 16-year-old boy.

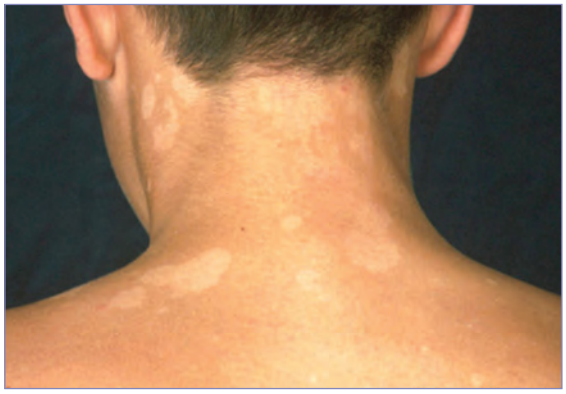


Image 109.5
Pityriasis versicolor in a 14-year-old boy.

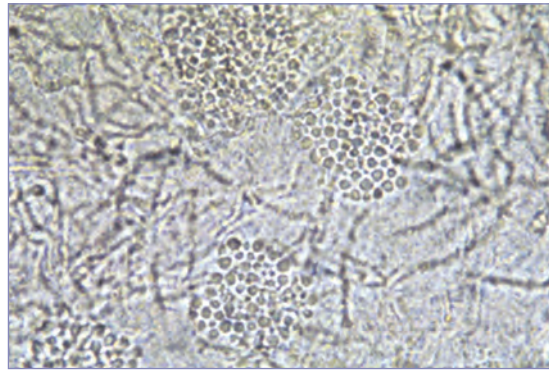


Image 109.6
The spores and pseudohyphae of *Malassezia furfur* (a yeast that can cause pityriasis versicolor) resemble spaghetti and meatballs on a potassium hydroxide slide.

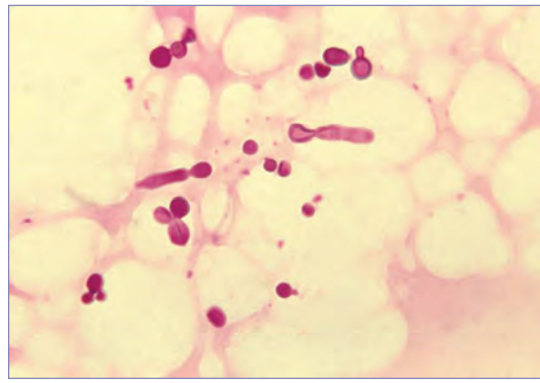


Image 109.7
Note the yeastlike fungal cells and short hyphae of *Malassezia furfur* in skin scale from a patient with pityriasis versicolor. Usually, *M furfur* grows sparsely without causing a rash. In some individuals, it grows more actively for reasons unknown, resulting in pale brown, flaky patches on the trunk, neck, or arms, a condition called pityriasis versicolor (formerly called tinea versicolor). Courtesy of Centers for Disease Control and Prevention.

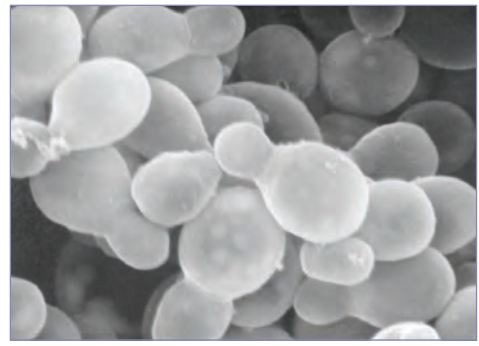


Image 109.8
Scanning electron micrograph of *Malassezia furfur*. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 110

Plague

CLINICAL MANIFESTATIONS

Naturally acquired plague most commonly manifests in the **bubonic form,** with acute onset of high fever and a painful swollen regional lymph node (bubo). Buboes develop most commonly in the inguinal region but also occur in axillary or cervical areas. Less commonly, plague manifests in the **septicemic form** (hypotension, acute respiratory distress, purpuric skin lesions, intravascular coagulopathy, organ failure) or as **pneumonic plague** (cough, fever, dyspnea, and hemoptysis) and rarely as **meningeal, pharyngeal, cutaneous, ocular,** or **gastrointestinal plague**. Abrupt onset of fever, chills, headache, and malaise are characteristic in all cases. Occasionally, patients have symptoms of mild lymphadenitis or prominent gastrointestinal tract symptoms, which may obscure the correct diagnosis. Untreated, plague often progresses to overwhelming sepsis and death. Plague has been referred to as the Black Death.

ETIOLOGY

Plague is caused by *Yersinia pestis*, a pleomorphic, bipolar-staining (with Giemsa, Wright, and Watson stains), gram-negative coccobacillus. *Y pestis* is a member of the *Enterobacteriaceae* family, along with more common *Yersinia* species and other enteric bacteria.

EPIDEMIOLOGY

Plague is a zoonotic infection primarily maintained in rodents and their fleas. Humans are incidental hosts who develop bubonic or primary septicemic manifestations typically through the bite of infected rodent fleas or through direct contact with tissues of infected animals. Secondary pneumonic plague arises from hematogenous seeding of the lungs with *Y pestis* in patients with untreated bubonic or septicemic plague. Primary pneumonic plague is acquired by inhalation of respiratory tract droplets from a human or animal with pneumonic plague. Only the pneumonic form has been shown to be transmitted from person to person. Plague occurs worldwide with enzootic foci in parts of Asia, Africa, and the Americas. Most human plague cases are reported from rural, underdeveloped areas and mainly occur as isolated cases or in small, focal clusters. In the United States, plague is endemic in western states, with most cases reported from New Mexico, Colorado, Arizona, and California. Cases of plague have been identified in travelers returning to states without endemic plague.

The **incubation period** is 2 to 8 days for bubonic plague and 1 to 6 days for primary pneumonic plague.

DIAGNOSTIC TESTS

Diagnosis of plague usually is confirmed by culture of *Y pestis* from blood, bubo aspirate, sputum, or another clinical specimen. The organism is slow growing but not fastidious and can be isolated on sheep blood and chocolate agars with typical "fried-egg" colonies appearing after 48 to 72 hours of incubation. *Y pestis* has a bipolar (safety-pin) appearance when stained with Wright-Giemsa or Wayson stains. A positive direct fluorescent antibody test result for the presence of *Y pestis* in direct smears or cultures of blood, bubo aspirate, sputum, or another clinical specimen provides presumptive evidence of *Y pestis* infection. Automated, commercially available biochemical identification systems are not recommended, because they can misidentify *Y pestis.* Polymerase chain reaction assay and immunohistochemical staining for rapid diagnosis of *Y pestis* are available in some reference or public health laboratories.

A single positive serologic test result from a passive hemagglutination assay or enzyme immunoassay also provides presumptive evidence of infection. Seroconversion, defined as a fourfold increase in antibody titer between serum specimens obtained at least 2 weeks apart, also confirms the diagnosis of plague.

TREATMENT

For children, gentamicin or streptomycin, administered intramuscularly or intravenously, appear to be equally effective. Alternative drugs include ciprofloxacin, levofloxacin, moxifloxacin, tetracycline, doxycycline, chloramphenicol, and trimethoprim-sulfamethoxazole. Fluoroquinolones have been shown to be highly effective in animal and in vitro studies. Trimethoprim-sulfamethoxazole should not be

considered a first-line treatment option when treating bubonic plague and should not be used as monotherapy to treat pneumonic or septicemic plague because of higher treatment failure rates than with other antimicrobial agents. The usual duration of antimicrobial treatment is 10 to 14 days or until several days after resolution of fever. Drainage of abscessed buboes may be necessary; drainage material is infectious until effective antimicrobial therapy has been administered.

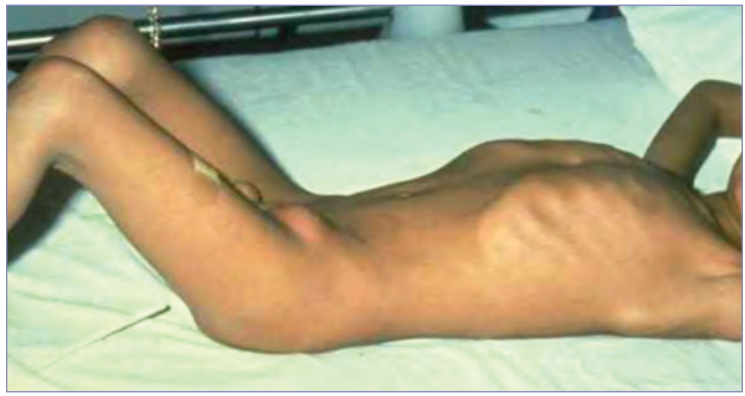


Image 110.1
Inguinal plague buboes in an 8-year-old boy. If left untreated, bubonic plague often becomes septicemic, with meningitis occurring in 6% of cases.

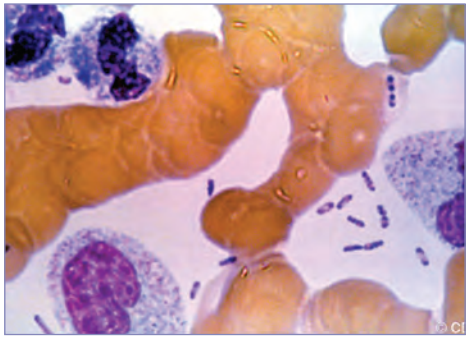


Image 110.2
Dark-stained bipolar ends of *Yersinia pestis* can clearly be seen in this Wright stain of blood from a plague victim. The actual cause of the disease is the plague bacillus, *Y pestis*. It is a nonmotile, nonspore-forming, gram-negative, nonlactose-fermenting, bipolar, ovoid, safety-pin–shaped bacterium. Courtesy of Centers for Disease Control and Prevention.

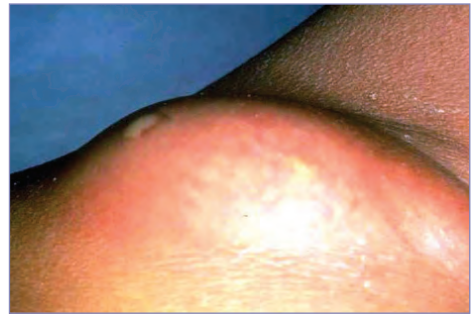


Image 110.3
Close-up view of inguinal buboes of the patient in Image 110.1. Surgical excision of infected lymph nodes without appropriate antimicrobial treatment may result in septicemic plague. When left untreated, plague often will progress to overwhelming sepsis and death.

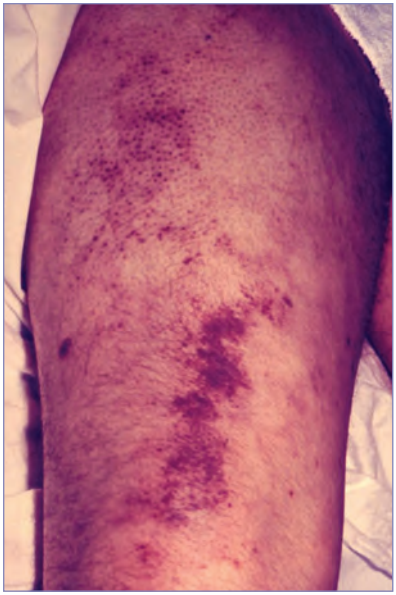


Image 110.4
This patient acquired a plague infection through abrasions on his upper right leg. Bubonic plague is transmitted through the bite of an infected flea or, as in this case, exposure to inoculated material through a break in the skin. Symptoms include swollen, tender lymph glands known as buboes. Courtesy of Centers for Disease Control and Prevention.

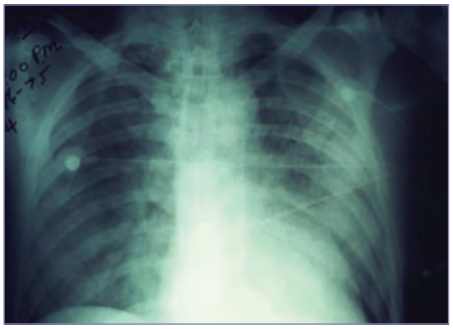


Image 110.6
This anteroposterior radiograph demonstrates a bilaterally progressive plague infection involving both lung fields. The first signs of plague are fever, headache, weakness, and rapidly developing pneumonia with shortness of breath, chest pain, cough, and, sometimes, bloody or watery sputum, eventually progressing for 2 to 4 days into respiratory failure and shock. Courtesy of Centers for Disease Control and Prevention.

Image 110.5
This patient presented with symptoms of plague that included gangrene of the right hand, causing necrosis of the fingers. Courtesy of Centers for Disease Control and Prevention.

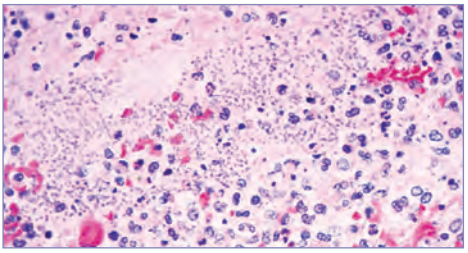


Image 110.7
Photomicrograph of lung tissue (Giemsa stain) from a patient with fatal human plague, revealing pneumonia and an abundance of *Yersinia pestis* organisms. Courtesy of Centers for Disease Control and Prevention.

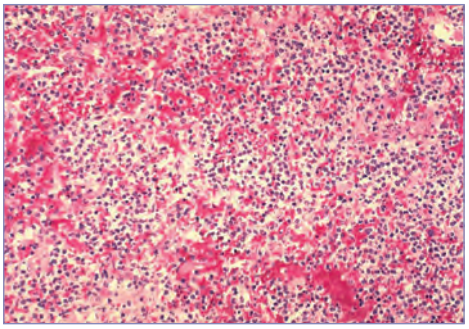


Image 110.8
Histopathology of lung in fatal human plague. Area of marked fibrinopurulent pneumonia. Courtesy of Centers for Disease Control and Prevention.

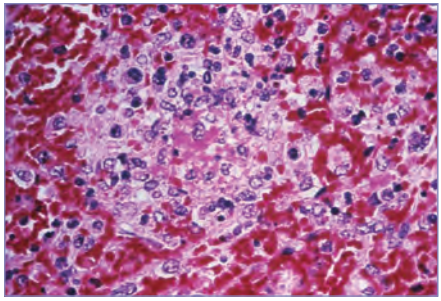


Image 110.9
This photomicrograph depicts the histopathologic changes in splenic tissue in a case of fatal human plague (hematoxylin-eosin stain, magnification ×400). Note the presence of general arteriolar inflammation, or arteriolitis, and an accompanying surrounding hemorrhage indicative of an acute infection associated with fatal human plague. Courtesy of Centers for Disease Control and Prevention.

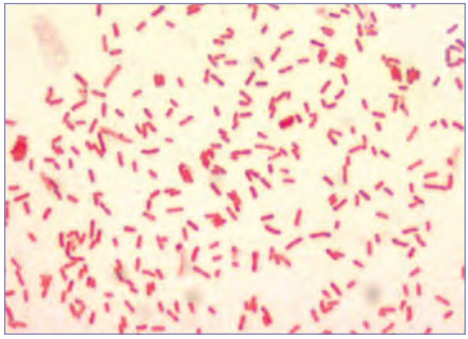


Image 110.11
Yersinia pestis is a small (0.5 × 1.0 µm) gram-negative bacillus (magnification ×1,000). Bipolar staining occurs when using Wayson, Wright, Giemsa, or methylene blue stain and may occasionally be seen in Gram-stained preparations. Courtesy of Centers for Disease Control and Prevention.

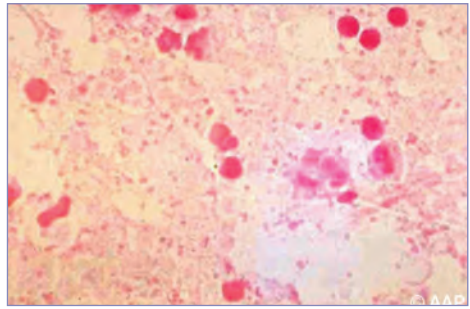


Image 110.10
Bubo aspirate (Gram stain) showing many gram-negative bacilli, *Yersinia pestis*.

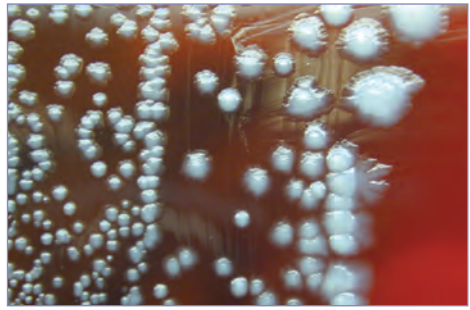


Image 110.12
Yersinia pestis on sheep blood agar, 72 hours. *Y pestis* grows well on most standard laboratory media, after 48 to 72 hours, gray-white to slightly yellow opaque raised, irregular "fried egg" morphology; alternatively, colonies may have a "hammered copper" shiny surface. Courtesy of Centers for Disease Control and Prevention.

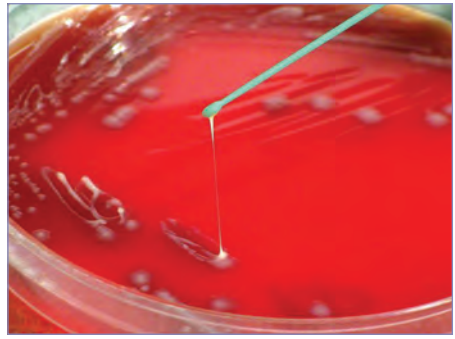


Image 110.13
This photograph depicts the colonial morphology displayed by gram-negative *Yersinia pestis* bacteria, which were grown on a medium of sheep blood agar for a 48-hour period at a temperature of 37°C (98.6°F). There is a tenacious nature of these colonies when touched by an inoculation loop, and they tend to form "stringy," sticky strands. Morphologic characteristics after 48 hours of *Y pestis* colonial growth include an average colonial diameter of 1.0 to 2.0 mm and an opaque coloration that ranges from gray-white to yellowish. If permitted to continue growing, *Y pestis* colonies take on what is referred to as a "fried egg" appearance, which becomes more prominent as the colonies age. Older colonies also display what is termed a "hammered copper" texture to their surfaces. Courtesy of Centers for Disease Control and Prevention.

Image 110.14
This photograph depicts an adult male *Diamanus montana* flea, formerly known as *Oropsylla montana*. This flea is a common ectoparasite of the rock squirrel, *Citellus variegatus*, and in the western United States, is an important vector for the bacterium *Yersinia pestis*, the pathogen responsible for causing plague. Courtesy of Centers for Disease Control and Prevention.

Image 110.15
This photograph shows a ground squirrel that died due to a plague infection, *Yersinia pestis*. Field rodents, such as western ground squirrels and prairie dogs, may be a threat when their burrows are beside labor camps and residential areas because they and their fleas are carriers of the plague bacteria. Courtesy of Centers for Disease Control and Prevention.

Image 110.16
The bobcat, *Felis rufus*, can be a source of plague infection for humans. People involved in trapping and skinning wild carnivores, especially bobcats, should be extremely cautious about exposure to *Yersinia pestis* vectors. Courtesy of Centers for Disease Control and Prevention.

Image 110.17
The bushy-tailed wood rat, *Neotoma cinerea,* is known to carry fleas inoculated with the plague bacteria *Yersinia pestis*. All wood rat species are quick to occupy and construct nests in human habitations or outbuildings within their range, thereby bringing vector fleas into close contact with humans and their pets. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 111

Pneumococcal Infections

CLINICAL MANIFESTATIONS

Streptococcus pneumoniae is a common bacterial cause of acute otitis media, sinusitis, community-acquired pneumonia, and pediatric conjunctivitis; pleural empyema, mastoiditis, and periorbital cellulitis occur. It is the most common cause of bacterial meningitis in infants and children ages 2 months to 11 years in the United States. *S pneumoniae* also may cause endocarditis, pericarditis, peritonitis, pyogenic arthritis, osteomyelitis, soft tissue infection, and neonatal septicemia. Overwhelming septicemia in patients with splenic dysfunction is noted, and hemolytic-uremic syndrome can accompany pneumococcal pneumonia with or without pleural empyema or meningitis.

ETIOLOGY

S pneumoniae organisms (pneumococci) are lancet-shaped, gram-positive, catalase-negative diplococci. More than 90 pneumococcal serotypes have been identified based on unique polysaccharide capsules.

EPIDEMIOLOGY

Nasopharyngeal carriage rates in children range from 21% in industrialized countries to more than 90% in resource-limited countries. Transmission is from person to person by respiratory droplet contact. Viral upper respiratory tract infections, including influenza, can predispose to pneumococcal infection and transmission. Pneumococcal infections are most prevalent during winter months. The period of communicability is unknown and may be as long as the organism is present in respiratory tract secretions but probably is less than 24 hours after effective antimicrobial therapy is begun. Before the pneumococcal conjugate vaccine era, among young children who acquired a new pneumococcal serotype in the nasopharynx, otitis media or other pneumococcal infection occurred in approximately 15%, usually within a few days of acquisition.

The incidence and severity of infections are increased in people with congenital or acquired humoral immunodeficiency, human immunodeficiency virus (HIV) infection, absent or deficient splenic function (eg, sickle cell disease, congenital or surgical asplenia), certain complement deficiencies, diabetes mellitus, chronic liver disease, chronic renal failure or nephrotic syndrome, or abnormal innate immune responses. Children with cochlear implants, particularly those who had placement of an older model that involved a cochlear electrode, have high rates of pneumococcal meningitis, as do children with congenital or acquired cerebrospinal fluid (CSF) leaks. Other categories of children at presumed high risk or at moderate risk of developing invasive pneumococcal disease are outlined in Table 111.1. Infection rates are highest in infants, young children, elderly people, and black, Alaska Native, and some American Indian populations. Since introduction of the heptavalent pneumococcal conjugate vaccine (PCV7), which included the most common serotypes associated with invasive infection (4, 6B, 9V, 14, 18C, 19F, and 23F), in 2000 and 13-valent pneumococcal conjugate vaccine (PCV13), which includes the additional serotypes 1, 3, 5, 6A, 7F, and 19A, in 2010, racial disparities have diminished; however, rates of invasive pneumococcal disease (IPD) among some American Indian (Alaska Native, Navajo, and White Mountain Apache) populations remain more than fivefold higher than the rate among children in the general US population, especially for serotypes not included in the vaccine. Factors associated with this increased risk include household crowding, poverty, and lack of in-home piped water.

By 7 years after the introduction of PCV7 in 2000, the incidence of vaccine-type invasive pneumococcal infections decreased by 99%, and the incidence of all IPD decreased by 76% in children younger than 5 years. In adults 65 years and older, IPD caused by PCV7 serotypes decreased 92% compared with baseline and all IPD decreased by 37%. The reduction in cases in these latter groups indicates the significant indirect benefits of PCV7 immunization by interruption of transmission of pneumococci from children to adults. After introduction of PCV13, further reductions in IPD disease in children younger than 5 years occurred, in large part because of reductions in IPD caused

Table 111.1
Underlying Medical Conditions That Are Indications for Immunization With 23-Valent Pneumococcal Polysaccharide Vaccine (PPSV23)[a] Among Children, by Risk Group[b]

Risk Group	Condition
Immunocompetent children	Chronic heart disease[c]
	Chronic lung disease[d]
	Diabetes mellitus
	Cerebrospinal fluid leaks
	Cochlear implant
Children with functional or anatomic asplenia	Sickle cell disease and other hemoglobinopathies
	Chronic or acquired asplenia, or splenic dysfunction
Children with immunocompromising conditions	HIV infection
	Chronic renal failure and nephrotic syndrome
	Diseases associated with treatment with immunosuppressive drugs or radiation therapy, including malignant neoplasms, leukemias, lymphomas, and Hodgkin disease; or solid organ transplantation
	Congenital immunodeficiency[e]

[a]PPSV23 is indicated starting at 24 months of age.
[b]Centers for Disease Control and Prevention. Licensure of a 13-valent pneumococcal conjugate vaccine (PCV13) and recommendations for use among children. Advisory Committee on Immunization Practices (ACIP). *MMWR Morb Mortal Wkly Rep.* 2010;59(9):258–261.
[c]Particularly cyanotic congenital heart disease and cardiac failure.
[d]Including asthma if treated with prolonged high-dose oral corticosteroids.
[e]Includes B- (humoral) or T-lymphocyte deficiency; complement deficiencies, particularly C_1, C_2, C_3, and C_4 deficiency; and phagocytic disorders (excluding chronic granulomatous disease).

by serotype 19A. There have also been reductions in IPD in unvaccinated older children and adults, indicative of herd protection.

The **incubation period** varies by type of infection but can be as short as 1 to 3 days.

DIAGNOSTIC TESTS

Recovery of *S pneumoniae* from a normally sterile site (eg, blood, CSF, peritoneal fluid, middle ear fluid, joint fluid) or from a suppurative focus confirms the diagnosis. The finding of lancet-shaped gram-positive organisms and white blood cells in expectorated sputum (older children and adults) or pleural exudate suggests pneumococcal pneumonia. Recovery of pneumococci by culture of an upper respiratory tract swab specimen is not sufficient to assign an etiologic diagnosis of pneumococcal disease involving the middle ear, upper or lower respiratory tract, or sinus. The organism is isolated readily on sheep blood agar, where it produces a zone of "alpha" hemolysis (greening of the agar). Definitive identification requires determination of optochin susceptibility (optochin disk test) or bile solubility (sodium deoxycholate lysis).

Two multiplexed nucleic acid amplification tests have been designed to identify *S pneumoniae* and other bacterial and fungal pathogens directly from positive blood culture bottles. One real-time polymerase chain reaction (PCR) assay is available for detection of *S pneumoniae* in CSF. There is limited clinical experience with this assay, and this assay should be used cautiously and be accompanied by culture of CSF to obtain an isolate. Other PCR tests designed to detect *lyt*A or other gene targets are investigational but may be specific and significantly more sensitive than culture of pleural fluid, CSF, blood, or other normally sterile body fluid particularly in patients who have received recent antimicrobial therapy.

Detection of C-polysaccharide (common to all pneumococci) in urine for diagnosis of pneumococcal pneumonia may have some utility in adults but is not useful in children. Commercially available antigen detection tests performed on CSF or blood are not recommended for routine use because of low sensitivity.

Susceptibility Testing

All *S pneumoniae* isolates from normally sterile body fluids (eg, CSF, blood, middle ear fluid, mastoid, pleural, joint fluid, pericardial fluid) should be tested for antimicrobial susceptibility to determine the minimum inhibitory concentration (MIC) of penicillin, cefotaxime or ceftriaxone, and clindamycin. CSF isolates also should be tested for susceptibility to vancomycin, meropenem, and rifampin. *Nonsusceptibility* includes both *intermediate* and *resistant* isolates. Breakpoints vary depending on whether an isolate is from a nonmeningeal or meningeal site; in children with meningitis presentations, the breakpoints for meningeal isolates should be used (eg, a blood isolate in a patient with meningitis). Susceptibility and nonsusceptibility are provided in Table 111.2 for nonmeningeal and meningitis presentations. *S pneumoniae* strains that are nonsusceptible to penicillin G, cefotaxime, ceftriaxone, and other antimicrobial agents using meningitis breakpoints have been identified throughout the United States and worldwide.

For patients with meningitis caused by an organism that is nonsusceptible to penicillin, susceptibility testing of rifampin also should be performed. If the patient has a nonmeningeal infection caused by an isolate that is nonsusceptible to penicillin, cefotaxime, and ceftriaxone, susceptibility testing to other agents such as clindamycin, erythromycin, trimethoprim-sulfamethoxazole, linezolid, meropenem, and vancomycin should be performed.

Quantitative MIC testing using reliable methods, such as broth microdilution or antimicrobial gradient strips, should be performed on isolates from children with invasive infections. For isolates from noninvasive infections, quantitative MIC testing or a qualitative screening testing can be used; the latter uses a 1-μg oxacillin disk on an agar plate to reliably identify all penicillin-*susceptible* pneumococci using meningitis breakpoints (ie, disk-zone diameter of 20 mm or greater). Organisms with an oxacillin disk-zone size of less than 20 mm potentially are nonsusceptible to penicillins and cephalosporins for treatment of meningitis and require quantitative susceptibility testing.

Table 111.2

Clinical and Laboratory Standards Institute Definitions of in Vitro Susceptibility and Nonsusceptibility of Pneumococcal Isolates in Nonmeningeal and Meningeal Cases[a,b]

Drug and Isolate Location	Susceptible, μg/mL	Nonsusceptible, μg/mL	
		Intermediate	Resistant
Penicillin (oral)[c]	≤0.06	0.12–1.0	≥2.0
Penicillin (intravenous)[d]			
Nonmeningeal cases	≤2.0	4.0	≥8.0
Meningitis cases	≤0.06	None	≥0.12
Cefotaxime **OR** ceftriaxone			
Nonmeningeal cases	≤1.0	2.0	≥4.0
Meningitis cases	≤0.5	1.0	≥2.0

[a] Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing: 27th Informational Supplement.* CLSI Publication No. M100-S27. Wayne, PA: Clinical and Laboratory Standards Institute; 2016.
[b] Centers for Disease Control and Prevention. Effects of new penicillin susceptibility breakpoints for *Streptococcus pneumoniae*—United States, 2006–2007. *MMWR Morb Mortal Wkly Rep.* 2008;57(50):1353–1355.
[c] Without meningitis.
[d] Treated with intravenous penicillin.

TREATMENT

Bacterial Meningitis Possibly or Proven to Be Caused by *S pneumoniae*

For all children with bacterial meningitis presumed to be caused by *S pneumoniae*, vancomycin should be administered in addition to cefotaxime (or ceftriaxone for those >1 month) because of the possibility of *S pneumoniae* resistant to penicillin, cefotaxime, and ceftriaxone.

For children with serious hypersensitivity reactions to beta-lactam antimicrobial agents (ie, penicillins and cephalosporins), the combination of vancomycin and rifampin should be considered. Vancomycin should not be given alone, because bactericidal concentrations in CSF are difficult to sustain, and clinical experience to support use of vancomycin as monotherapy is minimal. Rifampin also should not be given as monotherapy, because resistance can develop during therapy. Meropenem is an alternative drug in a patient with hypersensitivity to other beta-lactam antimicrobial agents. Penicillin desensitization can be considered.

A repeat lumbar puncture should be considered after 48 hours of therapy in the following circumstances:

- The organism is penicillin nonsusceptible by oxacillin disk or quantitative (MIC) testing, and results from cefotaxime and ceftriaxone quantitative susceptibility testing are not yet available or the isolate is cefotaxime and ceftriaxone nonsusceptible; or
- The patient's condition has not improved or has worsened; or
- The child has received dexamethasone, which can interfere with the ability to interpret the clinical response, such as resolution of fever.

If the organism is nonsusceptible to penicillin and cefotaxime or ceftriaxone, vancomycin should be continued. Addition of rifampin to the combination of vancomycin and cefotaxime or ceftriaxone after 24 to 48 hours of therapy should be considered if the organism is susceptible to rifampin and: (1) after 24 to 48 hours, despite therapy with vancomycin and cefotaxime or ceftriaxone, the clinical condition has worsened; (2) the subsequent culture of CSF indicates failure to eradicate or to decrease substantially the number of organisms; or (3) the organism has a high cefotaxime or ceftriaxone MIC ($\geq$2 μg/mL or $\geq$4 μg/mL) indicating resistance. Consultation with an infectious disease specialist should be considered for all children with bacterial meningitis.

Dexamethasone

For infants and children 6 weeks and older, adjunctive therapy with dexamethasone may be considered after weighing the potential benefits and risks. Some experts recommend use of corticosteroids in pneumococcal meningitis, but this issue is controversial, and data are not sufficient to make a routine recommendation for children. If used, dexamethasone should be administered before or concurrently with the first dose of antimicrobial agents.

Nonmeningeal Invasive Pneumococcal Infections Requiring Hospitalization

For nonmeningeal invasive infections in previously healthy children who are not critically ill, antimicrobial agents currently used to treat infections with *S pneumoniae* and other potential pathogens should be initiated at the usually recommended dosages. For critically ill infants and children with invasive infections potentially attributable to *S pneumoniae*, vancomycin, in addition to empiric antimicrobial therapy (eg, cefotaxime or ceftriaxone or others), can be considered. Such patients include those with presumed septic shock, severe pneumonia with empyema, or significant hypoxia or myopericardial involvement. If vancomycin is administered, it should be discontinued as soon as antimicrobial susceptibility test results demonstrate effective alternative agents. If the organism has in vitro resistance to penicillin, cefotaxime, and ceftriaxone, consultation with an infectious disease specialist should be considered.

Acute Otitis Media

According to clinical practice guidelines of the American Academy of Pediatrics (AAP) and the American Academy of Family Physicians (AAFP) on acute suppurative otitis media (AOM), amoxicillin is recommended for infants <6 months of age and for those 6 through 23 months of age with bilateral disease. A watch-and-wait option can be considered for older children and those with non-severe disease. Optimal duration of therapy is uncertain. For younger children and children with severe disease at any age, a 10-day course is recommended; for children 6 years and older with mild or moderate disease, a duration of 5 to 7 days is appropriate. Otalgia should be treated in all cases.

Patients who fail to respond to initial management should be reassessed at 48 to 72 hours to confirm the diagnosis of AOM and exclude other causes of illness. If AOM is confirmed in the patient managed initially with observation, amoxicillin should be administered. If the patient has failed initial antibacterial therapy, a change in antibacterial agent is indicated. Suitable alternative agents should be active against penicillin-nonsusceptible pneumococci as well as beta-lactamase–producing *Haemophilus influenzae* and *Moraxella catarrhalis*. Such agents include high-dose oral amoxicillin-clavulanate; oral cefdinir, cefpodoxime, or cefuroxime; or intramuscular ceftriaxone in a 3-day course. Patients who continue to fail to respond to therapy with one of the aforementioned oral agents should be treated with a 3-day course of parenteral ceftriaxone. Macrolide resistance among *S pneumoniae* is high, so clarithromycin and azithromycin are not appropriate alternatives for initial therapy. In such cases, treatment with clindamycin (if susceptibility is known) or levofloxacin is preferred. For patients with a history of non-type I allergic reaction to penicillin, agents such as cefdinir, cefuroxime, or cefpodoxime can be used orally.

Myringotomy or tympanocentesis should be considered for children failing to respond to second-line therapy, for severe cases to obtain cultures to guide therapy, and for patients with invasive pneumococcal infection. For multidrug-resistant strains of *S pneumoniae*, use of levofloxacin or other agents should be considered in consultation with an infectious diseases expert and based on the specific susceptibility profile.

Sinusitis

Antimicrobial agents effective for treatment of AOM also are likely to be effective for acute sinusitis and are recommended when a child meets clinical criteria for diagnosis.

Pneumonia

Oral amoxicillin in 3 equally divided doses is likely to be effective in ambulatory children with pneumonia caused by susceptible and relatively resistant pneumococci (MICs of 2.0 μg/mL), respectively. Ampicillin is used for intravenous therapy of community acquired pneumonia. Cefotaxime or ceftriaxone is used for treatment of inpatients infected with pneumococci suspected or proven to be penicillin resistant, for serious infections including empyema, or in those not fully immunized with PCV13. Vancomycin should be included in those with life-threatening infection. For patients with isolates resistant to penicillin (MICs of 4.0 μg/mL or higher) or significant allergy to beta lactam antimicrobials, treatment with clindamycin (if susceptible) or levofloxacin should be considered, assuming that concurrent meningitis has been excluded.

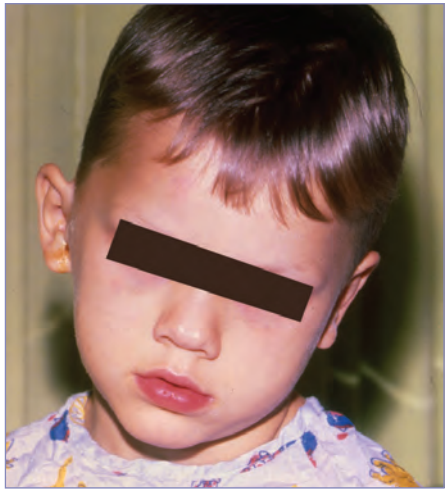


Image 111.1
A 3½-year-old boy with acute suppurative otitis media and mastoiditis due to *Streptococcus pneumoniae*. Note the protuberance of the right external ear secondary to mastoid swelling. Courtesy of George Nankervis, MD.

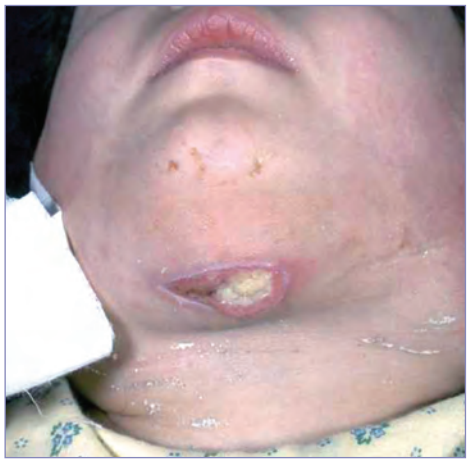


Image 111.3
Streptococcus pneumoniae submental abscess in a 5-year-old girl with dysgammaglobulinemia. There is an increased incidence of pneumococcal disease in immunocompromised children. Courtesy of Edgar O. Ledbetter, MD, FAAP.

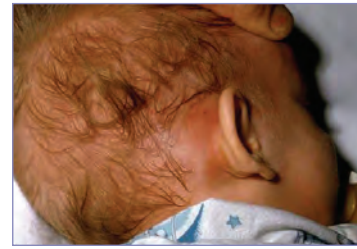


Image 111.2
Child with acute mastoiditis caused by *Streptococcus pneumoniae*.

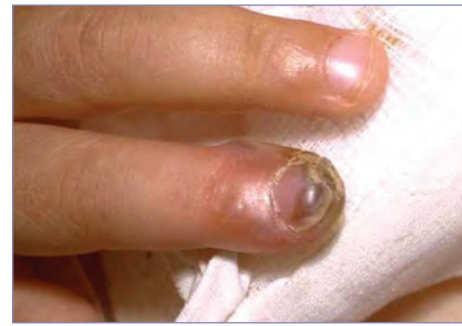


Image 111.4
Perionychial abscess caused by *Streptococcus pneumoniae* in a child with acute lymphoblastic leukemia.

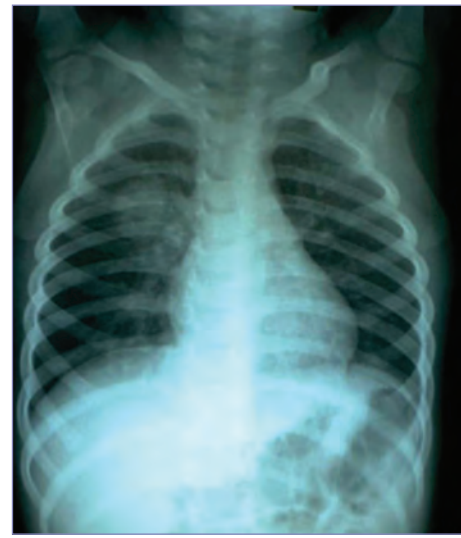


Image 111.5
Segmental (nodular) pneumonia due to *Streptococcus pneumoniae*.

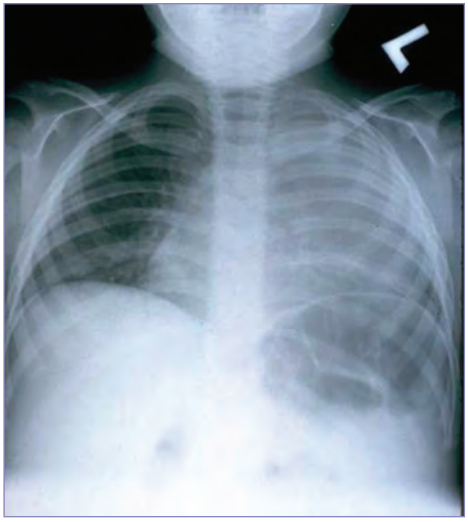


Image 111.6
Acute pneumococcal pneumonia of the left upper lobe proven by a positive blood culture result. Courtesy of Edgar O. Ledbetter, MD, FAAP.

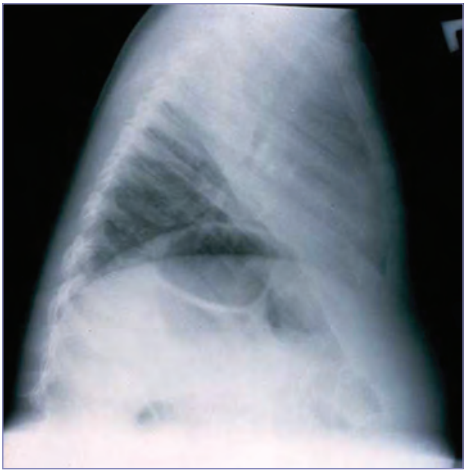


Image 111.7
Acute pneumococcal pneumonia of the left upper lobe proven by a positive blood culture result. This is the same patient as in Image 111.6. Courtesy of Edgar O. Ledbetter, MD, FAAP.

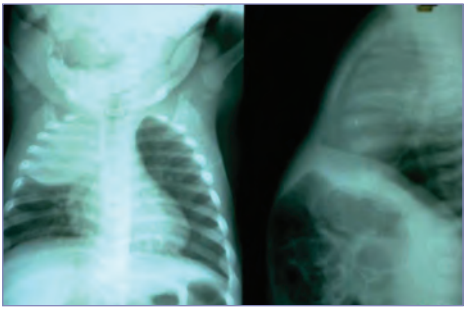


Image 111.8
Streptococcus pneumoniae pneumonia of the upper lobe of the right lung. The blood culture result was positive, and the infant had a prompt response to penicillin therapy.

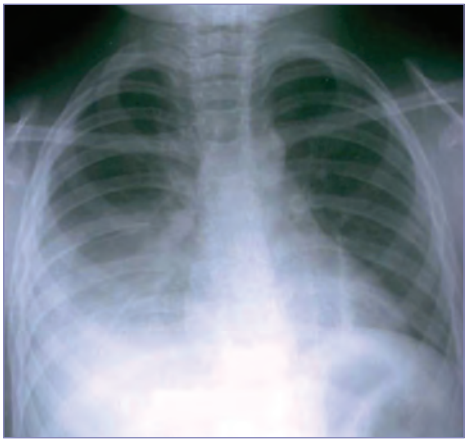


Image 111.9
Pneumococcal pneumonia with pleural effusion on the right. Courtesy of Edgar O. Ledbetter, MD, FAAP.

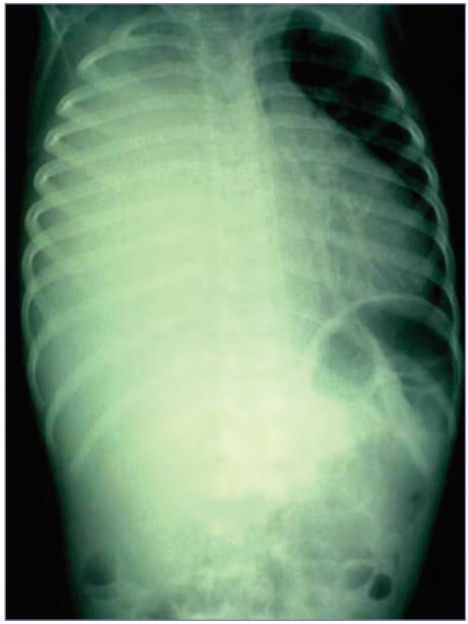


Image 111.10
Pneumococcal pneumonia with massive effusion pushing the mediastinal structures into the left area of the chest. A delayed clinical response to treatment was not surprising. Courtesy of Edgar O. Ledbetter, MD, FAAP.

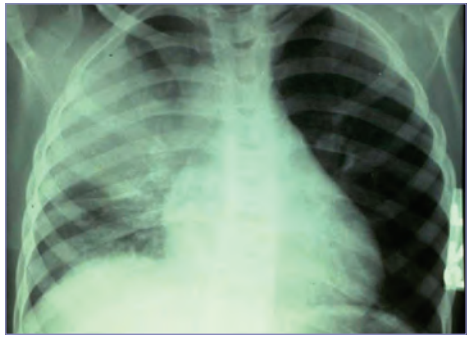


Image 111.12
Pneumonia with right subpleural empyema due to *Streptococcus pneumoniae* in a child with sickle cell disease.

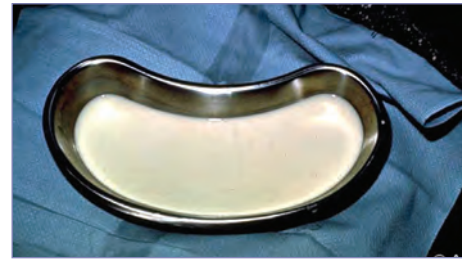


Image 111.11
Purulent pleural fluid of pneumococcal empyema removed from patient in Image 111.10. Courtesy of Edgar O. Ledbetter, MD, FAAP.

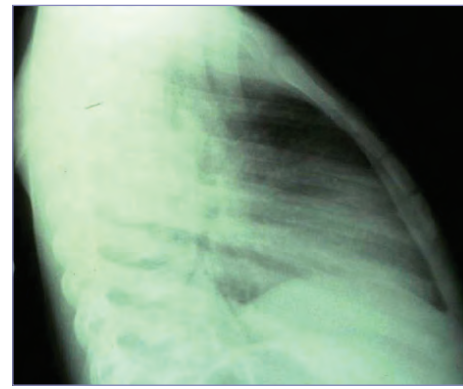


Image 111.13
Pneumonia with subpleural empyema due to *Streptococcus pneumoniae* evident on lateral chest radiograph. This is the same patient as in Image 111.12. Note the difference in the level of the right and left hemidiaphragms.

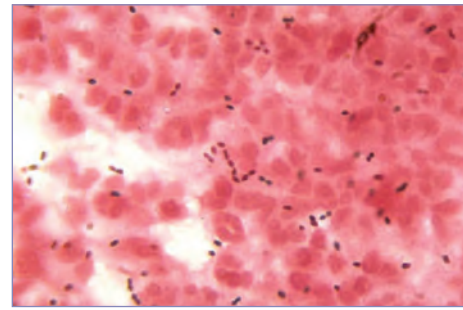


Image 111.14
Streptococcus pneumoniae in pleural exudate (Gram stain).

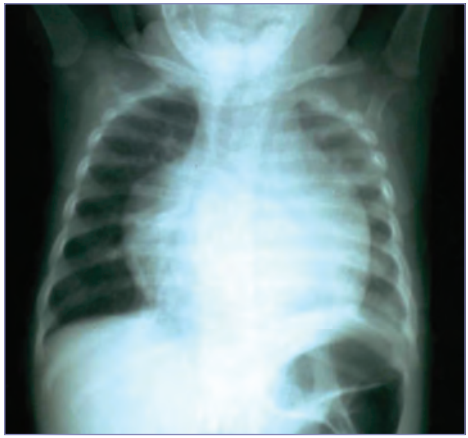


Image 111.15
Pneumonia and purulent pericarditis due to *Streptococcus pneumoniae* in a previously healthy infant. Despite clinical improvement with penicillin therapy and repeated needle aspiration of the pericardial space, the infant died of constrictive pericarditis.

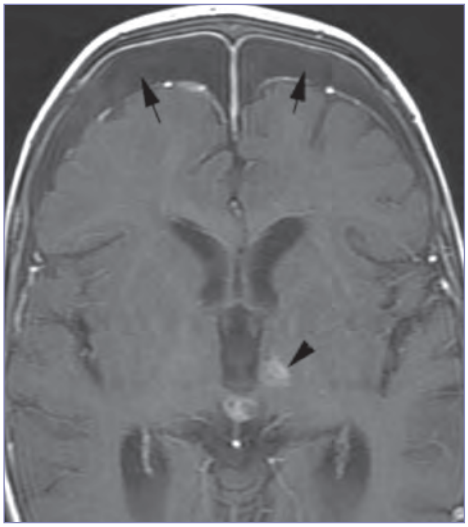


Image 111.17
An axial T1-weighted magnetic resonance image following contrast shows frontal subdural hygromas (arrows). Also note the enhancing left thalamic infarction secondary to penetrating artery spasm (arrowhead) in a patient with pneumococcal meningitis.

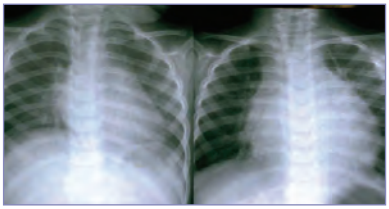


Image 111.16
Pneumonia and pericarditis due to *Streptococcus pneumoniae*. Despite pericardial drainage by needle aspiration followed by pericardiostomy drainage, the child died. Surgical drainage is imperative in the management of purulent pericarditis.

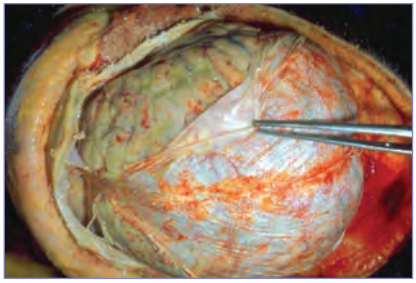


Image 111.18
Skull opened at autopsy revealing purulent inflammation of leptomeninges beneath reflected dura in a patient who died of pneumococcal meningitis. Courtesy of Centers for Disease Control and Prevention.

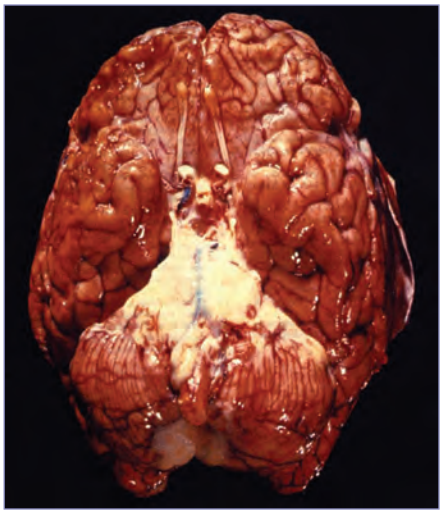


Image 111.19
A ventral view of the brain depicting purulent exudate from fatal *Streptococcus pneumoniae* meningitis. Courtesy of Centers for Disease Control and Prevention.

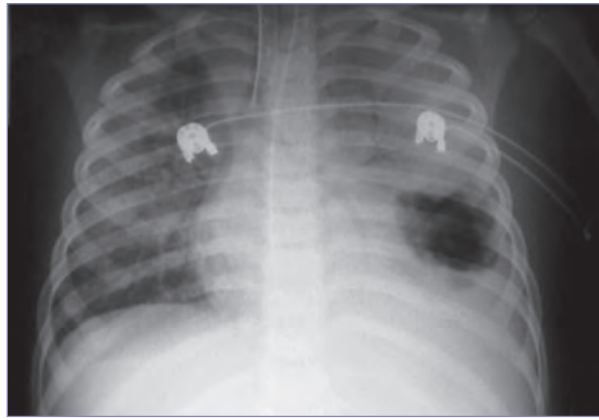


Image 111.20
Streptococcus pneumoniae pneumonia with pneumatocele formation in the left lung. Courtesy of Benjamin Estrada, MD.

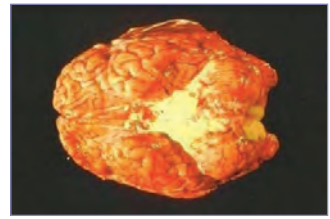


Image 111.21
This is a photo of the brain of a person who died from pneumococcal meningitis. Note the purulence (pus) that covers the brain surface. Courtesy of Centers for Disease Control and Prevention.

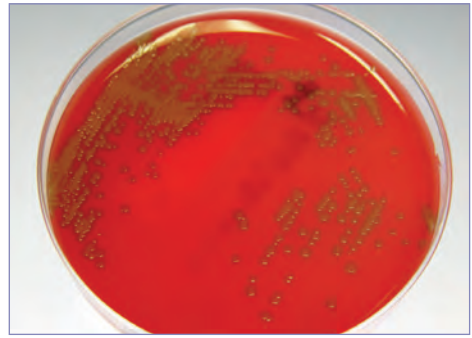


Image 111.22
Streptococcus pneumoniae, 24-hour sheep blood agar plate, with alpha hemolysis. Courtesy of Robert Jerris, MD.

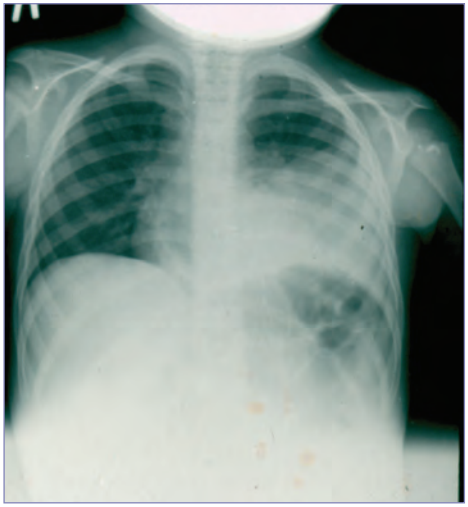


Image 111.23
A 3-year-old boy who presented with high fever, tachypnea, left-sided chest pain, and his chest radiograph. Note the left lower consolidation, pleural fluid, and rounded air-filled cavities. Courtesy of Carol J. Baker MD.

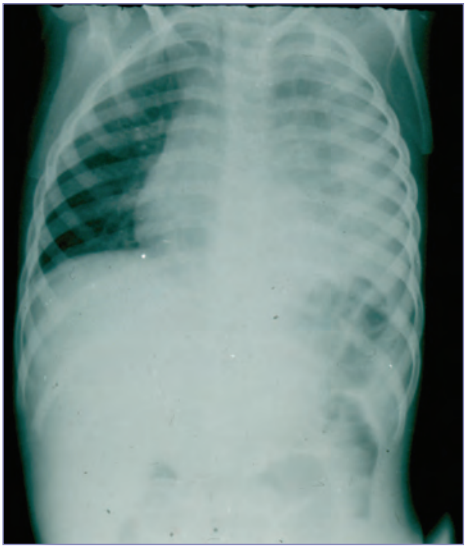


Image 111.24
Same patient as in Image 111.23 after 48 hours of antibiotic therapy. He had continued high fever, tachypnea, and no audible breath sounds in the left chest. Courtesy of Carol J. Baker, MD.

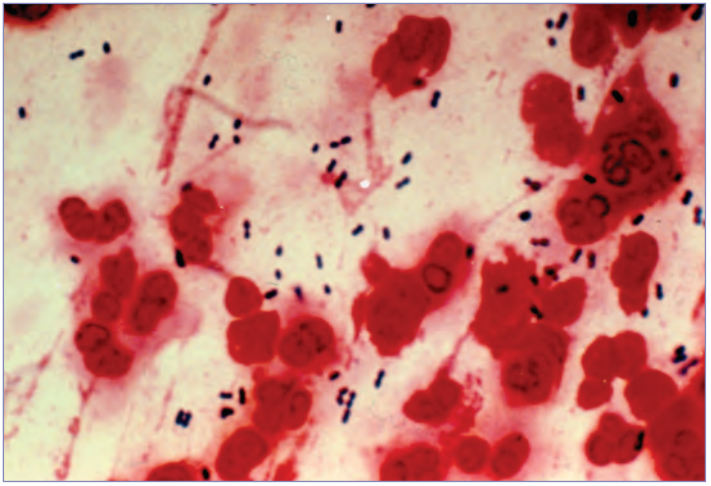


Image 111.25
Gram stain from pleural fluid on day 5 of antibiotic therapy for the patient in Images 111.23 and 111.24. The gram-positive, lancet-shaped diplococci are abundant in this empyema fluid, which grew *Streptococcus pneumoniae,* as did his admission blood culture. Two days after chest tube drainage, he became afebrile. Courtesy of Carol J. Baker, MD

CHAPTER 112

Pneumocystis jiroveci Infections

CLINICAL MANIFESTATIONS

Symptomatic infection is extremely rare in healthy people. Disease in immunocompromised infants and children is a respiratory illness characterized by dyspnea, tachypnea, significant hypoxemia, nonproductive cough, and fever. The intensity of these signs and symptoms may vary, and in some immunocompromised children and adults, the onset may be acute and fulminant. Most children with *Pneumocystis* pneumonia are significantly hypoxic. Chest radiographs often show bilateral diffuse interstitial or alveolar disease but may appear normal in early disease. Atypical radiographic findings may include lobar, miliary, cavitary, and nodular lesions. The mortality rate in immunocompromised patients ranges from 5% to 40% in treated patients and approaches 100% without therapy.

ETIOLOGY

Human *Pneumocystis* is called *Pneumocystis jiroveci*, although the familiar acronym PCP (originally *Pneumocystis carinii* pneumonia) still is used commonly among clinicians. *P jiroveci* is an atypical fungus (based on DNA sequence analysis) with several morphologic and biologic similarities to protozoa, including susceptibility to several antiprotozoal agents but resistance to most antifungal agents. In addition, the organism exists as 2 distinct morphologic forms: the 5- to 7-μm-diameter cysts, which contain up to 8 intracystic bodies or sporozoites, and the smaller, 1- to 5-μm-diameter trophozoite or trophic form.

EPIDEMIOLOGY

Pneumocystis species are ubiquitous in mammals worldwide and have a tropism for respiratory tract epithelium. *Pneumocystis* isolates recovered from mice, rats, and ferrets differ genetically from each other and from human *P jiroveci*. Asymptomatic or mild human infection occurs early in life, with more than 85% of healthy children showing seropositivity by 20 months of age. Animal models and studies of patients with acquired immunodeficiency syndrome (AIDS) do not support the existence of latency and suggest that disease after the age 2 is likely reinfection.

The single most important factor in susceptibility to PCP is the status of cell-mediated immunity of the host, reflected by a marked decrease in percentage and numbers CD4+ T-lymphocytes, or a decrease in CD4+ T-lymphocyte function. In resource-limited countries and in times of famine, *Pneumocystis* pneumonia can occur in epidemics, primarily affecting malnourished infants and children. In industrialized countries, PCP occurs almost entirely in immunocompromised people, particularly people with human immunodeficiency virus (HIV) infection, recipients of immunosuppressive therapy after solid organ transplantation or during treatment for malignancy, and children with primary immunodeficiency syndromes. Although decreasing in frequency because of effective prophylaxis and antiretroviral therapy, PCP remains one of the most common serious opportunistic infections in infants and children with perinatally acquired HIV infection and adolescents with advanced immunosuppression. Although onset of disease can occur at any age, PCP most commonly occurs in HIV-infected children in the first year of life, with peak incidence at 3 through 6 months of age. In patients with cancer, the disease can occur during remission or relapse of the malignancy.

Animal studies have demonstrated animal-to-animal transmission by the airborne route; human-to-human transmission has been suggested by molecular epidemiology and global clustering of PCP cases in several studies. Vertical transmission has been postulated but remains unproven. The period of communicability is unknown.

The **incubation period** is unknown; outbreaks in transplant recipients have demonstrated a median of 53 days from exposure to clinical infection.

DIAGNOSTIC TESTS

A definitive diagnosis of PCP is made by visualization of organisms (*Pneumocystis* cysts) in lung tissue or respiratory tract secretion specimens. The most sensitive and specific diagnostic procedures involve specimen collection from open lung biopsy and, in older children, transbronchial biopsy. However, bronchoscopy with bronchoalveolar lavage, induction of sputum in older children and adolescents, and intubation with deep endotracheal aspiration are less invasive, can be diagnostic, and are sensitive in patients with HIV infection, who tend to have heavier organism burdens. Methenamine silver stain, toluidine blue stain, and fluorescently conjugated monoclonal antibody are useful tools for identifying the thick-walled cysts of *P jiroveci*. Sporozoites (within cysts) and trophozoites are identified with Giemsa or modified Wright-Giemsa stain. The sensitivity of all microscopy-based methods depends on the skill of the laboratory technician.

Pneumocystis species cannot be cultivated continuously outside the mammalian lung. Polymerase chain reaction (PCR) assays have been shown to be highly sensitive with a variety of respiratory tract specimens. Because highly sensitive PCR assays may detect colonization with these organisms, results from such assays must be interpreted in the context of clinical presentation.

Limited data suggest that serum 1,3-β-D-glucan (BG) assay may be a potential marker for *Pneumocystis* infection. This compound is a component of the cell wall of the cyst stage of the organism and may be found in high concentrations in serum of patients infected with *P jiroveci;* however, most other fungi also secrete the compound during infection, so correlation with clinical presentation is imperative.

TREATMENT

The drug of choice is trimethoprim-sulfamethoxazole (TMP-SMX), usually administered intravenously. Oral therapy should be reserved for patients with mild disease who do not have malabsorption or diarrhea, and for patients with a favorable clinical response to initial intravenous therapy. Duration of therapy is 21 days.

The rate of adverse reactions to TMP-SMX (eg, rash, neutropenia, anemia, thrombocytopenia, renal toxicity, hepatitis, nausea, vomiting, and diarrhea) is higher in HIV-infected children than in non–HIV-infected patients. Desensitization to TMP-SMX may be considered after the acute reaction has abated.

Pentamidine, administered intravenously, is an alternative drug for children and adults who cannot tolerate TMP-SMX or who have severe disease and have not responded to TMP-SMX after 4 to 8 days of therapy. The therapeutic efficacy of intravenous pentamidine in adults with PCP is like that of TMP-SMX. Pentamidine is associated with a high incidence of adverse reactions, including pancreatitis, diabetes mellitus, renal toxicity, electrolyte abnormalities, hypoglycemia, hyperglycemia, hypotension, cardiac arrhythmias, fever, and neutropenia. Aerosolized pentamidine should not be used for treatment, because its efficacy is limited. Atovaquone is approved for oral treatment of mild to moderate PCP in adults who are intolerant of TMP-SMX. Adverse reactions to atovaquone are limited to rash, nausea, and diarrhea.

Other potentially useful drugs in adults include clindamycin with primaquine (adverse reactions are rash, nausea, and diarrhea), dapsone with trimethoprim (associated with neutropenia, anemia, thrombocytopenia, methemoglobinemia, rash, and transaminase elevation), and trimetrexate with leucovorin. Experience with the use of these combinations in children is limited. Based on studies in both adults and children, a course of corticosteroids is recommended in patients with moderate to severe PCP (as defined by an arterial oxygen pressure [Pao_2] of less than 70 mm Hg in room air or an arterial-alveolar gradient ≥35 mm Hg).

Coinfection with other organisms, such as cytomegalovirus or pneumococcus, has been reported in HIV-infected children. Children with dual infections may have more severe disease.

Chemoprophylaxis is highly effective in preventing PCP among high-risk groups. Prophylaxis against a first episode of PCP is indicated for many patients with significant

immunosuppression, including people with HIV infection and people with primary or acquired cell-mediated immunodeficiency.

Prophylaxis for PCP is recommended for children who have received hematopoietic stem cell transplants (HSCTs) or solid organ transplants; children with hematologic malignancies (eg, leukemia or lymphoma) and some nonhematologic malignancies; children with severe cell-mediated immunodeficiency, including children who received adrenocorticotropic hormone for treatment of infantile spasm; and children who otherwise are immunocompromised and who have had a previous episode of PCP. For this diverse group of immunocompromised hosts, the risk of PCP varies with duration and intensity of chemotherapy, with other immunosuppressive therapies, with coinfection with immunosuppressive viruses (eg, cytomegalovirus), and local epidemiologic rates of PCP. Guidelines for allogeneic HSCT recipients recommend that PCP prophylaxis be initiated at engraftment (or before engraftment, if engraftment is delayed) and administered for at least 6 months. It should be continued in all children receiving ongoing or intensified immunosuppressive therapy (eg, prednisone or cyclosporine) or in children with chronic graft-versus-host disease. Guidelines for PCP prophylaxis for solid organ transplant recipients are less definitive, but some authorities suggest durations ranging from 6 months to 1 year following renal transplantation, and from 1 year to lifelong following heart, lung, liver, and intestinal transplantation.

The recommended drug regimen for PCP prophylaxis for all immunocompromised patients is TMP-SMX.

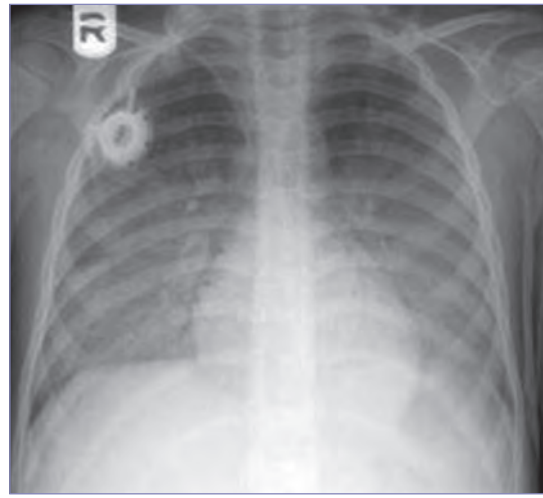


Image 112.1

Pneumocystis jiroveci pneumonia. This pathogen is an important cause of pulmonary infections in patients who are immunocompromised. Characteristic signs and symptoms include dyspnea at rest, tachypnea, nonproductive cough, fever, and hypoxia with an increased oxygen requirement. The intensity of the signs and symptoms can vary, and onset may be acute and fulminant. Chest radiographs frequently demonstrate diffuse bilateral interstitial or alveolar disease. This is a chest radiograph from a 5-year-old boy demonstrating bilateral perihilar infiltrates due to *P jiroveci*. Courtesy of Beverly P. Wood, MD, FAAP, MSEd, PhD.

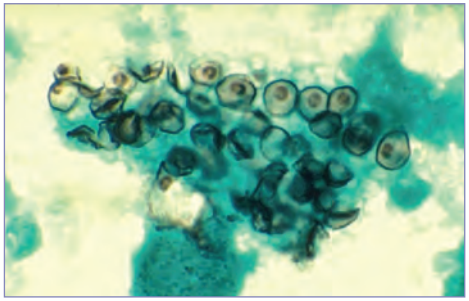


Image 112.2
Cysts of *Pneumocystis jiroveci* in a smear from bronchoalveolar lavage (Gomori methenamine silver stain). Courtesy of Russell Byrnes.

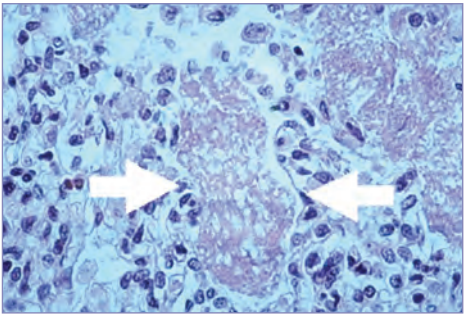


Image 112.3
Foamy intra-alveolar exudate in lung biopsy specimen from a patient with *Pneumocystis jiroveci* pneumonia (hematoxylin-eosin stain).

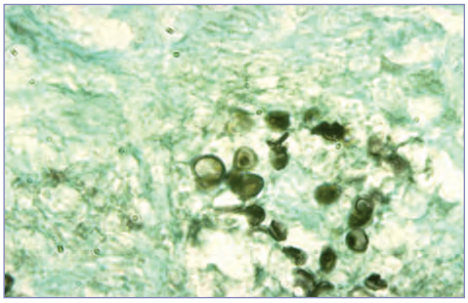


Image 112.4
Pneumocystis jiroveci organisms in lung biopsy specimen (Gomori methenamine silver stain).

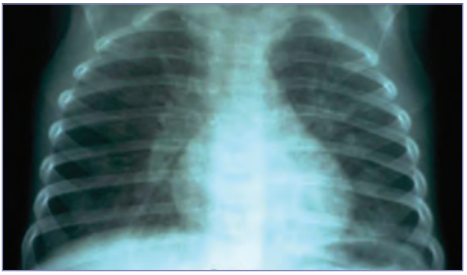


Image 112.5
Pneumocystis jiroveci pneumonia with hyperaeration in an infant with congenital agammaglobulinemia.

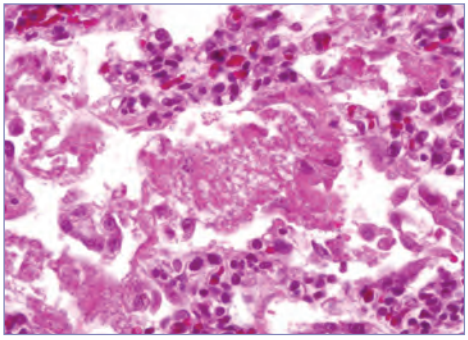


Image 112.6
Pneumocystis jiroveci in the lung. Frothy exudate in alveolar spaces. Courtesy of Dimitris P. Agamanolis, MD.

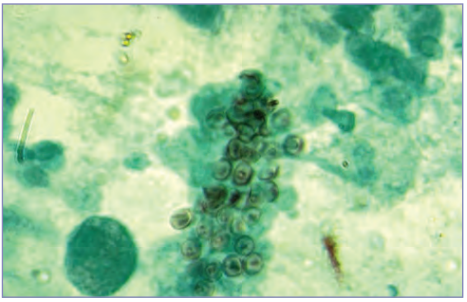


Image 112.7
Pneumocystis jiroveci organisms in tracheal aspirate (Gomori methenamine silver stain).

CHAPTER 113

Poliovirus Infections

CLINICAL MANIFESTATIONS

Approximately 70% of poliovirus infections in susceptible children are asymptomatic. Nonspecific illness with low-grade fever and sore throat (minor illness) occurs in approximately 25% of infected people, and viral meningitis (nonparalytic polio), sometimes accompanied by paresthesias, occurs in 1% to 5% of patients a few days after the minor illness has resolved. Rapid onset of asymmetric acute flaccid paralysis with areflexia of the involved limb (paralytic poliomyelitis) occurs in fewer than 1% of infections, with residual paresis in approximately two thirds of patients. Classical paralytic polio begins with a minor illness characterized by fever, sore throat, headache, nausea, constipation, and/or malaise for several days, followed by a symptom-free period of 1 to 3 days. Rapid onset of paralysis then follows. Typically, paralysis is asymmetric and affects the proximal muscles more than the distal muscles. Cranial nerve involvement (bulbar poliomyelitis) and paralysis of the diaphragm and intercostal muscles may lead to impaired respiration requiring assisted ventilation. Sensation usually is intact. The cerebrospinal fluid (CSF) profile is characteristic of viral meningitis, with mild pleocytosis and lymphocytic predominance.

Adults who contracted paralytic poliomyelitis during childhood may develop the noninfectious post-polio syndrome 15 to 40 years later, characterized by slow and irreversible exacerbation of weakness in the muscle groups affected during the original infection. Muscle and joint pain also are common manifestations. The estimated incidence of post-polio syndrome in poliomyelitis survivors is 25% to 40%.

ETIOLOGY

Polioviruses are classified as members of the family *Picornaviridae*, genus *Enterovirus*, in the species enterovirus C, and include 3 serotypes. They are nonenveloped, positive-sense, single-stranded RNA viruses that are highly stable in a liquid environment. Acute paralytic disease may be caused by naturally occurring (wild) polioviruses, by oral poliovirus (OPV) vaccine viruses that cause rare cases of vaccine-associated paralytic poliomyelitis (VAPP) in vaccine recipients or their close contacts, or by circulating vaccine-derived polioviruses (cVDPVs) that have acquired virulence properties (neurovirulence and transmissibility) that are indistinguishable from naturally occurring polioviruses as a result of sustained person-to-person circulation in the absence of adequate population immunity. People with primary B-lymphocyte immunodeficiencies are at increased risk both of VAPP and of chronic infection (immunodeficiency-associated vaccine-derived polioviruses, or iVDPVs) from vaccine virus. With ongoing progress in the World Health Organization (WHO) Global Polio Eradication Initiative, more cases of paralytic disease are caused by vaccine-related viruses (VAPP and cVDPV) than by wild polioviruses.

EPIDEMIOLOGY

Humans are the only natural reservoir for poliovirus. Spread is by contact with feces and/or respiratory secretions. Infection is more common in infants and young children and occurs at an earlier age among children living in poor hygienic conditions. In temperate climates, poliovirus infections are most common during summer and autumn; in the tropics, the seasonal pattern is less pronounced.

The last reported case of poliomyelitis attributable to indigenously acquired, naturally occurring wild poliovirus in the United States occurred in 1979 during an outbreak among unimmunized people that resulted in 10 paralytic cases. Except for very rare imported cases, all poliomyelitis cases acquired in the United States have been attributable to VAPP, which, until 1998, occurred in an average of 6 to 8 people annually. Fewer VAPP cases were reported in 1998 and 1999, after a shift in US immunization policy in 1997 from use of OPV to a sequential inactivated poliovirus (IPV) vaccine/OPV schedule. Implementation of an all-IPV vaccine schedule in 2000 halted the occurrence of VAPP cases in the United States.

Circulation of indigenous wild poliovirus strains ceased in the United States several decades ago, and the risk of contact with imported wild polioviruses and cVDPV viruses has decreased in parallel with the success of the global eradication program. Of the

3 poliovirus serotypes, type 2 wild poliovirus has been declared eradicated globally by the Global Certification Commission, with the last naturally occurring case detected in 1999 in India. No cases of type 3 wild poliovirus have been detected since 2012, suggesting this type may also be eradicated. Type 1 poliovirus now accounts for all polio cases attributable to wild poliovirus. Because the only source of disease from type 2 poliovirus is related to vaccine use, the world switched from trivalent OPV (tOPV) to bivalent OPV (bOPV) on April 1, 2016, thus ending all routine immunization with live type 2 poliovirus-containing oral vaccines. Similarly, following this vaccine change, the only remaining risk of type 2 infection would come from vaccine manufacturers and laboratories. For this reason, containment of all type 2 poliovirus infectious and potentially infectious materials into accredited essential facilities has been initiated globally.

Communicability of poliovirus is greatest shortly before and after onset of clinical illness, when the virus is present in the throat and excreted in high concentrations in feces. Virus persists in the throat for approximately 1 to 2 weeks after onset of illness and is excreted in feces for 3 to 6 weeks. Patients potentially are contagious while fecal excretion persists. In recipients of OPV, virus also persists in the throat for 1 to 2 weeks and is excreted in feces for several weeks, although in rare cases, excretion for more than 2 months can occur. Immunocompromised patients with significant primary B-lymphocyte immune deficiencies have excreted iVDPV for periods of more than 25 years.

The **incubation period of nonparalytic poliomyelitis** is 3 to 6 days. For the onset of poliomyelitis, the **incubation period to paralysis** usually is 7 to 21 days (range, 3–35 days).

DIAGNOSTIC TESTS

Poliovirus can be detected in specimens from the pharynx and feces, less commonly from urine, and rarely from CSF by isolation in cell culture. The relatively low sensitivity of isolation in cell culture from CSF is likely attributable to low viral load, presence of neutralizing antibodies, and an inadequate volume of CSF for optimal recovery on cell culture. Fecal material and pharyngeal swab specimens are most likely to yield virus in cell culture.

The diagnostic test of choice for confirming poliovirus disease is viral culture of stool specimens and throat swab specimens obtained as early in the course of illness as possible. Nucleic acid amplification tests (NAATs) are available for detection of enteroviruses from CSF and at least one multiplexed assay that detects enteroviruses, in addition to a number of other bacterial and viral agents causing meningitis or encephalitis. Such commonly used molecular tests for enteroviruses will detect poliovirus but will not differentiate poliovirus from other enteroviruses and, therefore, are insufficient to demonstrate that poliovirus is the etiology of disease. In these situations, additional virus testing will be necessary to confirm the diagnosis of poliovirus-related disease. Interpretation of acute and convalescent serologic test results can be difficult because of high levels of population immunity.

Real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assays generally have sensitivity that is nearly comparable to or better than cell culture and may be more likely to identify polioviruses in CSF. Two or more stool and throat swab specimens for enterovirus isolation or detection by RT-PCR should be obtained at least 24 hours apart from patients with suspected paralytic poliomyelitis as early in the course of illness as possible, ideally within 14 days of onset of symptoms. Poliovirus may be excreted intermittently, and a single negative test result does not rule out infection.

TREATMENT

Supportive.

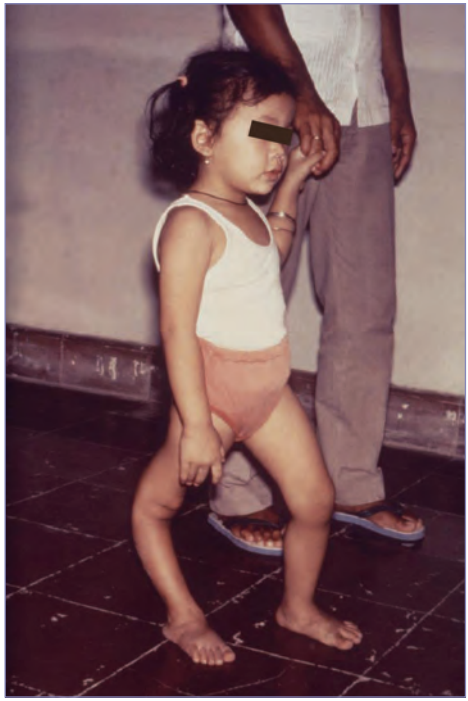


Image 113.1
This child is displaying a deformity of her right lower extremity caused by the poliovirus. Courtesy of Centers for Disease Control and Prevention.

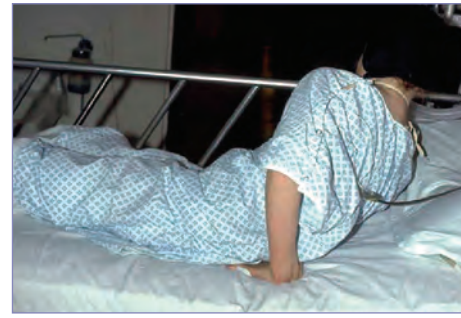


Image 113.2
A young girl with bulbar polio with tripod sign attempts to sit upright. Copyright Martin G. Myers, MD.

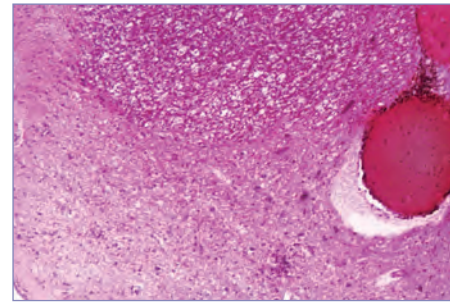


Image 113.3
Pontine histopathology due to the effects of poliomyelitis. Photomicrograph of the pons at the level of the sixth cranial nerve nucleus (abducens nerve) from a patient with type 3 poliomyelitis. Courtesy of Centers for Disease Control and Prevention.

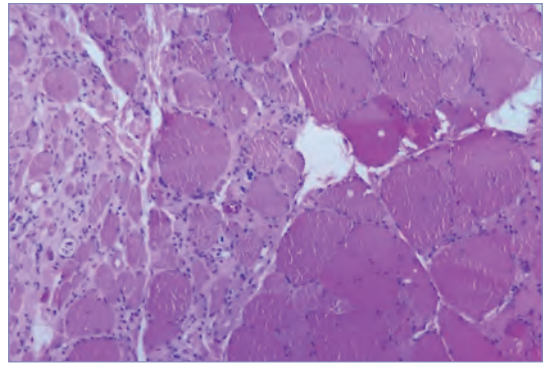


Image 113.4
A photomicrograph of skeletal muscle tissue revealing myotonic dystrophic changes as a result of poliovirus type 3. When spinal neurons die, wallerian degeneration takes place, resulting in muscle weakness of those muscles once innervated by the now-dead neurons (denervated). The degree of paralysis is directly correlated to the number of deceased neurons. Courtesy of Centers for Disease Control and Prevention.

Image 113.5
Patients whose respiratory muscles were affected by polio were placed in an iron lung machine to enable them to breathe. Courtesy of World Health Organization.

Image 113.6
Cheshire Home for Handicapped Children, Freetown, Sierra Leone. Courtesy of World Health Organization/Immunization Action Coalition.

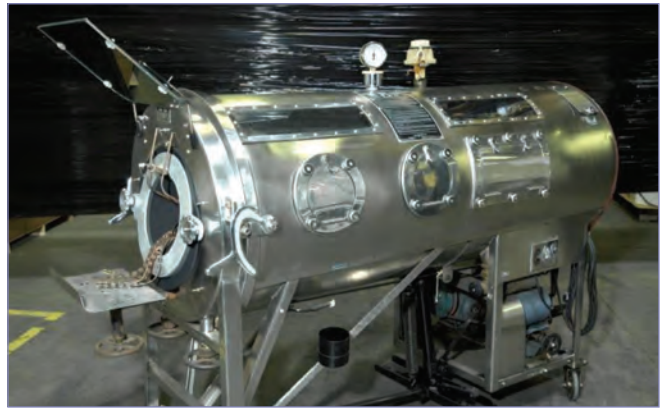


Image 113.7
Made of stainless steel and still in good working order, this Emerson Respirator, also known as an iron lung, was used by polio patients whose ability to breath was paralyzed due to this crippling viral disease. This iron lung was donated to the David J. Spencer Centers for Disease Control and Prevention Museum by the family of polio patient Barton Hebert of Covington, LA, who had used the device from the late 1950s until his death in 2003. Iron lungs encase the thoracic cavity externally in an airtight chamber. The chamber is used to create a negative pressure around the thoracic cavity, thereby causing air to rush into the lungs to equalize intrapulmonary pressure. Courtesy of Centers for Disease Control and Prevention.

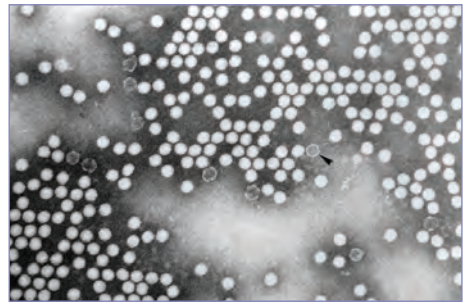


Image 113.8
Transmission electron micrograph of poliovirus type 1. Virions are 20 to 30 nm in diameter and have icosahedral symmetry. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 114

Polyomaviruses

(BK, JC, and Other Polyomaviruses)

CLINICAL MANIFESTATIONS

BK virus (BKV) infection and JC virus (JCV) infection in humans usually occur in childhood and seemingly result in lifelong persistence. Primary infection with BKV in immunocompetent children generally is asymptomatic. However, because of the tropism of BKV for the genitourinary tract epithelium, it may occasionally cause asymptomatic hematuria or cystitis in healthy children. More than 90% of adults are seropositive for BKV. BKV is more likely to cause disease in immunocompromised people, including hemorrhagic cystitis in hematopoietic stem cell transplant recipients and interstitial nephritis and ureteral stenosis in renal transplant recipients. The primary symptom of BKV-associated hemorrhagic cystitis among immunocompromised children is painful hematuria. Passage of blood clots in the urine and secondary obstructive nephropathy can occur in patients with BKV-associated hemorrhagic cystitis. BKV-associated nephropathy occurs in 3% to 8% of renal transplant recipients and less frequently in other solid organ transplant recipients. BKV-associated nephropathy should be suspected in any renal transplant recipient with allograft dysfunction. More than half of renal allograft patients with BKV-associated nephropathy can experience allograft loss.

JCV is the cause of progressive multifocal leukoencephalopathy (PML), a demyelinating disease of the central nervous system that occurs in severely immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS), patients receiving intensive chemotherapy, bone marrow or solid organ transplant recipients, and patients receiving various monoclonal antibody therapies for treatment of autoimmune, oncologic, and neurologic diseases. PML, the only known disease caused by JCV, occurs in approximately 3% to 5% of untreated adults with AIDS but is rare in children with AIDS. Symptoms include cognitive disturbance, hemiparesis, ataxia, cranial nerve dysfunction, and aphasia. Lytic infection of oligodendrocytes by JCV is the primary mechanism of pathogenesis for PML. In the absence of restored T-lymphocyte function, PML almost always is fatal. Currently, 13 polyomaviruses have been detected in humans, but only a few have been associated with disease,

ETIOLOGY

Polyomaviruses are members of the family *Polyomaviridae*, which has a single genus, *Polyomavirus*. They are nonenveloped viruses with a circular double-stranded DNA genome with icosahedral symmetry of the capsid ranging 40 to 50 nm in diameter. The genome of the polyomaviruses encodes 5 major proteins: 3 for capsid proteins VP1, VP2, and VP3, and 2 for large T and small t antigens. One of the biological characteristics of the polyomaviruses is the maintenance of a chronic viral infection with little or no symptoms.

EPIDEMIOLOGY

Humans are the only known natural hosts for BKV and JCV. The mode of transmission of BKV and JCV is uncertain, but the respiratory route and the oral route by water or food have been postulated for their transmission. BKV and JCV are ubiquitous in the human population, with BKV infection occurring in early childhood and JCV infection occurring primarily in adolescence and adulthood. BKV persists in the kidney and gastrointestinal tract of healthy subjects, with urinary excretion occurring in 3% to 5% of healthy adults. JCV persists in the kidney and brain of healthy people.

DIAGNOSTIC TESTS

Detection of BKV T-antigen by immunohistochemical analysis of renal biopsy material is the gold standard for diagnosis of BKV-associated nephropathy, but nucleic acid-based polymerase chain reaction (PCR) assays are the most sensitive tools for rapid viral screening for polyomaviruses and quantification of viral load. Prospective monitoring of BK viral load in plasma using PCR commonly is used after renal transplantation to monitor for BKV-associated nephropathy. Detection of BKV nucleic acid in plasma by PCR assay is associated with an increased risk of BKV-associated nephropathy, especially when BKV viral loads exceed 10,000 genomes/mL. However, detection of BKV in urine of renal transplant recipients is common and does not predict BKV disease after renal transplantation. Both BKV and JCV

can be propagated in cell culture. However, culture plays no role in the laboratory diagnosis of infection.

The diagnosis of BKV-associated hemorrhagic cystitis is made clinically when other causes of urinary tract bleeding are excluded. Among hematopoietic stem cell transplant recipients, detection of BKV by PCR in urine is common (more than 50%), but BKV-associated hemorrhagic cystitis is much less common (10%–15%). Prolonged urinary shedding of BKV and detection of BKV in plasma after hematopoietic stem cell transplantation has been associated with increased risk of developing BKV-associated hemorrhagic cystitis. Urine cytologic testing may suggest urinary shedding of BKV on the basis of presence of decoy cells, which resemble renal carcinoma cells. However, decoy cells do not have high sensitivity or specificity for BKV disease.

A confirmed diagnosis of PML attributable to JCV requires a compatible clinical syndrome and magnetic resonance imaging or computed tomographic findings showing lesions in the brain white matter coupled with brain biopsy findings. JCV can be demonstrated by in situ hybridization, electron microscopy, or immunohistochemistry of brain biopsy or autopsy material. Diagnosis of PML can be facilitated when JCV DNA is detected in cerebrospinal fluid by a nucleic acid amplification test, which may obviate the need for a brain biopsy. Early in the course of PML, false-negative PCR assay results have been reported, so repeat testing is warranted when clinical suspicion of PML is high.

TREATMENT

In patients with biopsy-confirmed BKV-associated nephropathy, reduction of immune suppression may prevent allograft loss. The use of fluoroquinolones or Immune Globulin Intravenous (IGIV) in the treatment of BKV-associated nephropathy provide little to no benefit. In renal transplant patients with BKV plasma viral loads greater than 10,000 genomes/mL, judicious reduction of immune suppression has been shown to prevent development of BKV-associated nephropathy without increasing the risk of rejection.

Most patients with BKV-hemorrhagic cystitis after hematopoietic stem cell transplantation require only supportive care, because restoration of immune function by stem cell engraftment ultimately will control BKV replication. In severe cases, surgical intervention may be required to stop bladder hemorrhage. Cidofovir has been used for treatment; however, definitive data on its efficacy and safety are lacking.

Restoration of immune function (eg, combination antiretroviral therapy for patients with AIDS) is necessary for survival of patients with PML. Cidofovir sometimes is used for the treatment of PML but has not been shown to be effective in producing clinical improvement. For patients with monoclonal antibody-associated PML, plasmapheresis or immune stimulatory agents (eg, granulocyte colony-stimulating factor) may be useful to improve outcomes.

CHAPTER 115

Prion Diseases: Transmissible Spongiform Encephalopathies

CLINICAL MANIFESTATIONS

Transmissible spongiform encephalopathies (TSEs or prion diseases) constitute a group of rare, rapidly progressive, universally fatal neurodegenerative diseases of humans and animals that are characterized by neuronal degeneration, spongiform vacuolation in the cerebral gray matter, reactive proliferation of astrocytes and microglia, and accumulation of abnormal misfolded protease-resistant prion protein (PrP^{res}). This PrP^{res}, variably called prion, scrapie prion protein (PrP^{sc}), or as suggested by the World Health Organization, TSE-associated PrP (PrP^{TSE}), distributes diffusely throughout the brain or forms plaques of various morphology.

Human prion diseases include several diseases: Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler-Scheinker disease, fatal familial and sporadic fatal insomnia, kuru, and variant CJD (vCJD, presumably caused by the agent of bovine spongiform encephalopathy [BSE], commonly called "mad cow" disease). Classic CJD can be sporadic (approximately 85% of cases), familial (approximately 15% of cases), or iatrogenic (fewer than 1% of cases). Sporadic CJD most commonly is a disease of older adults (median age of death in the United States, 68 years) but also rarely has been described in adolescents older than 13 years and young adults. Iatrogenic CJD has been acquired through intramuscular injection of contaminated cadaveric pituitary hormones (growth hormone and human gonadotropin), dura mater allografts, corneal transplantation, and use of contaminated instrumentation at neurosurgery or during depth-electrode electroencephalographic recording. In 1996, an outbreak of vCJD linked to exposure to tissues from BSE-infected cattle was reported in the United Kingdom. Since the end of 2003, 4 presumptive cases of transfusion-transmitted vCJD have been reported: 3 clinical cases as well as 1 asymptomatic case in which PrP^{TSE} was detected in the spleen and lymph nodes but not brain tissues. A fifth possible iatrogenic vCJD infection in a hemophiliac patient in the United Kingdom, also asymptomatic, with a finding of PrP^{TSE} in spleen, was attributed to treatment with potentially vCJD-contaminated, United Kingdom-sourced fractionated plasma products. The best-known prion diseases affecting animals include scrapie of sheep and goats BSE and a chronic wasting disease (CWD) of North American deer, elk, and moose (**www.cdc.gov/prions/index.html**). CWD recently was detected in reindeer and a European elk (moose) in Norway. Except for vCJD, no other human prion disease has been attributed to infection with an agent of animal origin.

CJD manifests as a rapidly progressive neurologic disease with escalating defects in memory, personality, and other higher cortical functions. At presentation, approximately one third of patients have cerebellar dysfunction, including ataxia and dysarthria. Iatrogenic CJD also may manifest as dementia with cerebellar signs. Myoclonus develops in at least 80% of affected patients at some point in the course of disease. Death usually occurs in weeks to months (median, 4–5 months); approximately 10% to 15% of patients with sporadic CJD survive for more than 1 year.

CJD is distinguished from classic CJD by younger age of onset (median age at death around 28 years), early "psychiatric" manifestations, and other features, such as painful sensory symptoms, delayed onset of overt neurologic signs, relative absence of diagnostic electroencephalographic changes, and a more prolonged duration of illness (median, 13–14 months). In vCJD, but not in classic CJD, a high proportion of people exhibit high signal abnormalities on T2-weighted brain magnetic resonance imaging in the pulvinar region of the posterior thalamus (known as the "pulvinar sign"). In vCJD, the neuropathologic examination reveals highly reproducible pathology with spongiform vacuolation and numerous "florid" plaques (compact amyloid plaque surrounded by vacuoles) and exceptionally striking punctate deposition of PrP^{TSE} in the basal ganglia. In addition, PrP^{TSE} is detectable in the tonsils, appendix, spleen, and lymph nodes of patients with vCJD.

ETIOLOGY

The infectious particle or prion responsible for human and animal prion diseases is believed to consist of a misfolded form (PrP^{TSE}) of a normal ubiquitous cellular prion protein (PrP^{C}) found in high quantities on the surfaces of cells of the central nervous system and in spermatogenetic cells in both humans and animals. The precise protein structure and mechanism of propagation is unknown. It has been postulated that sporadic CJD arises from a spontaneous structural change of a host-encoded sialoglycoprotein, PrP^{C}, into the pathogenic PrP^{TSE} form. Prion propagation is proposed to occur by a "recruitment" reaction (the nature of which is under investigation), in which abnormal PrP^{TSE} serves as a template or lattice for the conversion of neighboring PrP^{C} molecules into misfolded protein with high potential to aggregate.

EPIDEMIOLOGY

Classic CJD is rare, occurring in the United States at a rate of approximately 1 to 1.5 cases per million people annually. The onset of disease peaks in the 60- through 74-year age group. Case-control studies of sporadic CJD have not identified any consistent environmental risk factor. No statistically significant increase in cases of sporadic CJD has been observed in people previously treated with blood, blood components, or plasma derivatives. The incidence of sporadic CJD is not increased in patients with several diseases associated with frequent exposure to blood or blood products, specifically hemophilia A and B, thalassemia, and sickle cell disease, suggesting that the risk of transfusion transmission of classic CJD, if any, must be very low and appropriately regarded as theoretical. CJD has not been reported in infants born to infected mothers. Familial forms of prion diseases are expressed as autosomal-dominant disorder with variable penetrance associated with a variety of mutations of the PrP-encoding gene (PRNP) located on chromosome 20. Onset of familial CJD occurs approximately 10 years earlier than sporadic CJD.

As of June 2016 (**www.cjd.ed.ac.uk/surveillance**), the total number of vCJD cases reported was in 178 patients in the United Kingdom, 27 in France, 5 in Spain, 4 in Ireland, 4 in the United States, 3 in the Netherlands, 3 in Italy, 2 in Portugal, 2 in Canada, and 1 each in Taiwan, Japan, and Saudi Arabia. Two of the 4 patients in the United States, 2 of the 4 in Ireland, and 1 each of the patients in France, Canada, and Taiwan are believed to have acquired vCJD during residence in the United Kingdom. The Centers for Disease Control and Prevention (CDC) and Health Canada have concluded that one of the vCJD patients in the United States and another in Canada probably were infected during their childhood residencies in Saudi Arabia. Another US patient might have been infected while a student in Kuwait. Authorities suspect that the Japanese patient was infected during a short visit of 24 days to the United Kingdom in 1990, 12 years before the onset of vCJD. Most patients with vCJD were younger than 30 years, and several were adolescents. All but 3 of the primary 174 United Kingdom patients with noniatrogenic vCJD died before 60 years of age. All but 14 patients died before 50 years of age, and 151 patients (87%) died before the age of 40. The median age at death of the 174 primary vCJD cases was 27 years. The ages at death of the 3 iatrogenic vCJD transfusion transmission cases were 32, 69, and 75 years. Based on animal inoculation studies, comparative PrP immunoblotting, and epidemiologic investigations, almost all cases of vCJD are believed to have resulted from exposure to tissues from cattle infected with BSE. As noted, 3 clinically symptomatic patients and 1 patient with no clinical signs of neurologic disease are believed to have been infected with vCJD through transfusion of non-leukoreduced red blood cells, and 1 hemophiliac patient, also with no clinical signs of prion disease, was probably infected through injections of human plasma-derived clotting factors.

The **incubation period** for iatrogenic CJD varies by route of exposure and ranges from about 14 months to up to at least 42 years.

DIAGNOSTIC TESTS

The diagnosis of human prion diseases can be made with certainty only by neuropathologic examination of affected brain tissue, usually obtained at autopsy. Immunodetection methods such as immunohistochemistry and Western blot can be used to test brain tissues.

Electroencephalography (EEG), magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) testing can be used to diagnose prion disease in live patients. In most patients with classic CJD, a characteristic 1-cycle to 2-cycles per second triphasic sharp-wave discharge on EEG tracing is regarded as indicative of CJD. The likelihood of finding this abnormality is enhanced when serial EEG recordings are obtained. Validated assays that detect 2 protein markers, 14-3-3 and Tau, in CSF showed 83% to 90% sensitivity and 78% diagnostic accuracy. These proteins are surrogate and nonspecific markers found in CSF as a result of the death of neurons. Specific disease marker PrP^{TSE} was demonstrated in CSF of 80% of CJD cases. Testing for this marker now is performed in a few laboratories using sophisticated techniques that detect minute amounts of the protein. No validated blood test is available, but a prototype test for vCJD that captures, enriches, and detects disease-associated prion protein from whole blood using stainless steel powder is being developed. A progressive neurologic syndrome in a person bearing a pathogenic mutation of the PRNP gene (not a normal polymorphism) is presumed to be prion disease. Because no unique nucleic acid has been detected in prions (the infectious particles) causing TSEs, nucleic acid amplification studies such as polymerase chain reaction tests are not possible. Consideration of brain biopsies for patients with possible CJD should be given when other potentially treatable diseases remain in the differential diagnosis.

TREATMENT

No treatment has been shown in humans to slow or stop the progressive neurodegeneration in prion diseases. Experimental treatments are being studied. Supportive therapy is necessary to manage dementia, spasticity, rigidity, and seizures occurring during the illness.

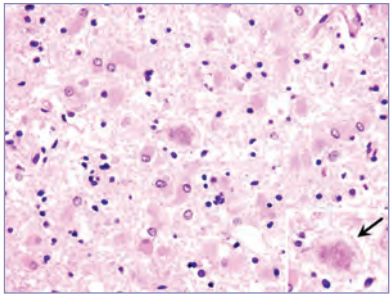


Image 115.1
Histopathologic changes in frontal cerebral cortex of the patient who died of variant Creutzfeldt-Jakob disease in the United States. Marked astroglial reaction is shown, occasionally with relatively large florid plaques surrounded by vacuoles (arrow in inset) (hematoxylin-eosin stain, original magnification ×40). Courtesy of *Emerging Infectious Diseases.*

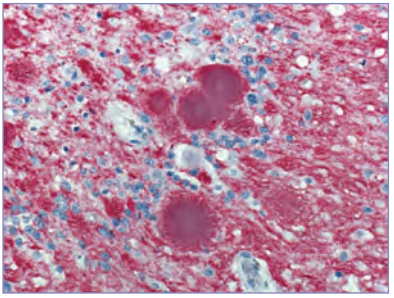


Image 115.2
Immunohistochemical staining of cerebellar tissue of the patient who died of variant Creutzfeldt-Jakob disease in the United States. Stained amyloid plaques are shown with surrounding deposits of abnormal prion protein (immunoalkaline phosphatase stain, naphthol fast red substrate with light hematoxylin counterstain; original magnification ×158). Courtesy of *Emerging Infectious Diseases.*

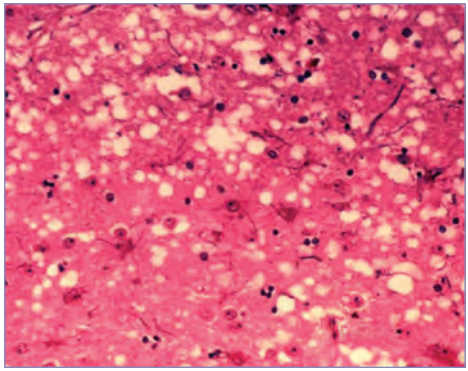


Image 115.3
This micrograph of brain tissue reveals the cytoarchitectural histopathologic changes found in bovine spongiform encephalopathy (BSE). The presence of vacuoles (ie, microscopic "holes" in the gray matter) gives the brain of BSE-affected cows a spongelike appearance when tissue sections are examined in the laboratory. Courtesy of Centers for Disease Control and Prevention.

Image 115.5
Cattle affected by bovine spongiform encephalopathy (BSE) experience progressive degeneration of the nervous system. Behavioral changes in temperament (eg, nervousness, aggression), abnormal posture, incoordination and difficulty in rising, decreased milk production, and/or weight loss despite continued appetite are followed by death in cattle affected by BSE. Courtesy of Centers for Disease Control and Prevention.

Image 115.4
These cattle will be inspected by the US Department of Agriculture (USDA) Food Safety and Inspection Service prior to slaughter. USDA Animal and Plant Health Inspection Service leads an ongoing, comprehensive interagency surveillance program for bovine spongiform encephalopathy in the United States to ensure the health of America's cattle herd. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 116

Q Fever (*Coxiella burnetii* Infection)

CLINICAL MANIFESTATIONS

Approximately half of acute Q fever infections result in symptoms. Acute and persistent (chronic) forms of the disease exist and both can present as fever of unknown origin. Q fever in children typically is characterized by abrupt onset of fever, often accompanied by chills, headache, weakness, cough, and other nonspecific systemic symptoms. Illness typically is self-limited, although a relapsing febrile illness lasting for several months has been documented in children. Gastrointestinal tract symptoms, such as diarrhea, vomiting, abdominal pain, and anorexia, are reported in 50% to 80% of children. Rash has been observed in some patients with Q fever. Q fever pneumonia usually manifests with a mild cough and shortness of breath but can progress to respiratory distress. Chest radiographic patterns are variable; chest computed tomography may show multilobar airspace consolidation. In immunocompromised patients, a nodular pattern accompanied by a halo of ground-glass opacification and vessel connection, or findings suggestive of a necrotizing process, may be seen. More severe manifestations of acute Q fever are rare but include hepatitis, hemolytic-uremic syndrome, myocarditis, pericarditis, cerebellitis, encephalitis, meningitis, hemophagocytosis, lymphadenitis, acalculous cholecystitis, and rhabdomyolysis. Persistent, localized (chronic) Q fever is rare in children but can present as blood culture-negative endocarditis, chronic relapsing or multifocal osteomyelitis, or chronic hepatitis. Children who are immunocompromised or have underlying valvular heart disease may be at higher risk of persistent, localized Q fever.

ETIOLOGY

Coxiella burnetii, the cause of Q fever, previously was formerly considered a rickettsial organism but is a gram-negative intracellular bacterium that belongs to the order *Legionellales*, family *Coxiellaceae*. The infectious form of *C burnetii* is highly resistant to heat, desiccation, and disinfectant chemicals and can persist for long periods of time in the environment. *C burnetii* is classified as a category B bioterrorism agent.

EPIDEMIOLOGY

Q fever is a zoonotic infection that has been reported worldwide, including in every state in the United States. The "Q" comes from "query" fever, the name of the disease until its etiologic agent was identified in the 1930s. *C burnetii* infection usually is asymptomatic in animals. Many different species can be infected, although cattle, sheep, and goats are the primary reservoirs for human infection. Tick vectors may be important for maintaining animal and bird reservoirs but are not thought to be important in transmission to humans. Humans most often acquire infection by inhalation of fine-particle aerosols of *C burnetii* generated from birthing fluids or other excreta of infected animals or through inhalation of dust contaminated by these materials. Infection can occur by exposure to contaminated materials, such as wool, straw, bedding, or laundry. Windborne particles containing infectious organisms can travel prolonged distances, contributing to sporadic cases for which no apparent animal contact can be demonstrated. Unpasteurized dairy products can contain the organism. Seasonal trends occur in farming areas with predictable frequency, and the disease often coincides with the livestock birthing season in spring.

The **incubation period** is 14 to 22 days (range, 9 to 39 days), depending on the inoculum size. Persistent, localized (chronic) Q fever can develop months to years after initial infection.

DIAGNOSTIC TESTS

Serologic evidence of a fourfold increase in phase II immunoglobulin (Ig) G via immunofluorescent assay (IFA) tests between paired sera taken 3 to 6 weeks apart is the diagnostic gold standard to confirm diagnosis of acute Q fever. A single high serum phase II IgG titer (≥1:128) by IFA in the convalescent stage may be considered as evidence of probable infection. Confirmation of persistent (chronic) Q fever is based on an increasing phase I IgG titer (typically ≥1:1,024) that often is higher than the phase II IgG titer *and* an identifiable nidus of infection (eg, endocarditis, vascular infection, osteomyelitis, chronic hepatitis).

Polymerase chain reaction (PCR) testing on whole blood or serum may be useful in the first 2 weeks of symptom onset and before antimicrobial administration. Although a positive PCR assay result can confirm the diagnosis, a negative PCR test result will exclude Q fever. PCR testing generally is available only in select reference or public health laboratories. Detection of *C burnetii* in tissues (eg, heart valve) by immunohistochemistry or PCR assay can also confirm a diagnosis of chronic Q fever. However, PCR test results may be negative in up to 66% of patients with endocarditis attributable to Q fever.

TREATMENT

Acute Q fever generally is a self-limited illness, and many patients recover without antimicrobial therapy. However, early treatment is effective in shortening illness duration and symptom severity and should be initiated in all symptomatic patients. For patients with suspected disease, immediate empiric therapy should be given, because laboratory results are often negative early in illness onset pending production of quantifiable antibody. Doxycycline orally, divided 2 times a day for children ≥8 years, administered for 14 days, is the drug of choice for severe infections in patients and can be used for acute Q fever regardless of patient age. Children younger than 8 years with mild illness, pregnant women, and patients allergic to doxycycline can be treated with trimethoprim-sulfamethoxazole.

Persistent (chronic) Q fever is much more difficult to treat, and relapses can occur despite appropriate therapy, necessitating repeated courses of therapy. The recommended therapy for Q fever endocarditis is a combination of doxycycline and hydroxychloroquine for a minimum of 18 months. Surgical replacement of the infected valve may be necessary in some patients.

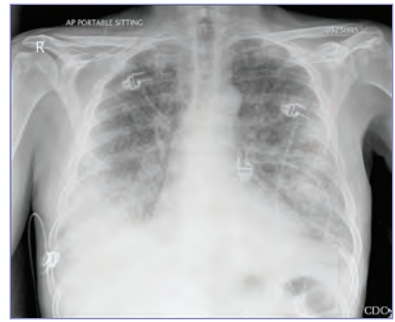


Image 116.1
Chest radiograph of patient at time of admission to hospital, before intubation, demonstrating extensive bilateral airspace disease. The first cases of Q fever in Nova Scotia were recognized in 1979 during a study of atypical pneumonia. This observation led to a series of studies that showed Q fever was common in Nova Scotia (50–60 cases per year in a population of approximately 950,000) and the epidemiology was unique; exposure to infected parturient cats or newborn kittens was the major risk factor for infection. At about the same time, cat-related outbreaks were noted in neighboring Prince Edward Island and New Brunswick. In the early 1990s, cases began to decline but, to our knowledge, since 1999, Q fever in this area has not been systematically studied. Courtesy of *Emerging Infectious Diseases.*

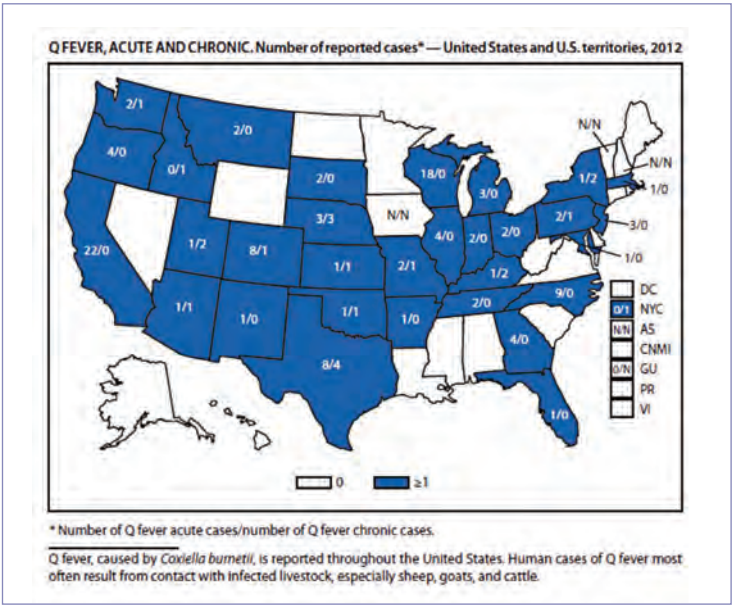


Image 116.2
Q fever, acute and chronic. Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 116.3
These domestic sheep were lying on a hillside in Glencolumbkille, County Donegal, Ireland, with the Atlantic Ocean in the background. In 2004, Ireland had almost 7 million domestic sheep. That year, the Irish state exported approximately 51,500 tons of sheep meat valued at 165 million euros. While important to national economies, livestock industries can present health hazards for producers and consumers. Diseases that can be transmitted from animals to humans are called zoonoses. Q fever, *Coxiella burnetii*, is a disease passed to humans from sheep. People working around domestic sheep should consider getting vaccinated against this disease. The disease can be acquired from the inhalation of aerosolized barnyard dust should it contain infected dried urine, manure particles, or dried fluids from the birth of calves or lambs. Domestic animals present problems not only for their handlers (ie, farmers) but also for consumers when animals are used for food. Food products made from animals include not only meat but meat derivatives that are added to sweets and other foods and, therefore, are less obvious to consumers. Courtesy of Centers for Disease Control and Prevention/Edwin P. Ewing Jr, MD.

CHAPTER 117

Rabies

CLINICAL MANIFESTATIONS

Infection with rabies virus and other lyssaviruses characteristically produces an acute illness with rapidly progressive central nervous system manifestations, including anxiety, radicular pain, dysesthesia or pruritus, hydrophobia, and dysautonomia. Some patients may have paralysis. Illness almost invariably progresses to death. The differential diagnosis of acute encephalitic illnesses of unknown cause or with features of Guillain-Barré syndrome should include rabies.

ETIOLOGY

Rabies virus is a single-stranded RNA virus classified in the *Rhabdoviridae* family, *Lyssavirus* genus. The genus *Lyssavirus* currently contains 14 species divided into 3 phylogroups.

EPIDEMIOLOGY

Understanding the epidemiology of rabies has been aided by viral variant identification using monoclonal antibodies and nucleotide sequencing. In the United States, human cases have decreased steadily since the 1950s, reflecting widespread immunization of dogs and the availability of effective prophylaxis after exposure to a rabid animal. From 2000 through 2014, 31 of 44 cases of human rabies reported in the United States were acquired indigenously. Among the 31 indigenously acquired cases, all but 4 were associated with bats. Despite the large focus of rabies in raccoons in the eastern United States, only 3 human deaths have been attributed to the raccoon rabies virus variant. Historically, 2 cases of human rabies were attributable to probable aerosol exposure in laboratories, and 2 unusual cases have been attributed to possible airborne exposures in caves inhabited by millions of bats, although alternative infection routes cannot be discounted. Transmission also has occurred by transplantation of organs, corneas, and other tissues from patients dying of undiagnosed rabies. Person-to-person transmission by bite has not been documented in the United States, although the virus has been isolated from saliva of infected patients.

Wildlife rabies perpetuates throughout all of the 50 United States except Hawaii, which remains "rabies free." Wildlife, including bats, raccoons, skunks, foxes, coyotes, bobcats, and mongoose, are the most important potential sources of infection for humans and domestic animals in the United States and its territories. Rabies in small rodents (squirrels, hamsters, guinea pigs, gerbils, chipmunks, rats, and mice) and lagomorphs (rabbits, pikas, and hares) is rare. Rabies may occur in woodchucks or other large rodents in areas where raccoon rabies is common. The virus is present in saliva and is transmitted by bites or, rarely, by contamination of mucosa or skin lesions by saliva or other potentially infectious material (eg, neural tissue). Worldwide, most rabies cases in humans result from dog bites in areas where canine rabies is enzootic. Most rabid dogs, cats, and ferrets shed virus for a few days before there are obvious signs of illness. No case of human rabies in the United States has been attributed to a dog, cat, or ferret that has remained healthy throughout the standard 10-day period of confinement after an exposure.

The **incubation period** in humans averages 1 to 3 months (range, days to years).

DIAGNOSTIC TESTS

Infection in animals can be diagnosed by demonstration of the presence of rabies virus antigen in brain tissue using a direct fluorescent antibody (DFA) test. Suspected rabid animals should be euthanized in a manner that preserves brain tissue for appropriate laboratory diagnosis. Virus can be isolated in suckling mice or in tissue culture from saliva, brain, and other specimens and can be detected by identification of viral antigens by immunofluorescence or immunoperoxidase staining or nucleotide sequences by reverse transcriptase-polymerase chain reaction (RT-PCR) in affected tissues. Diagnosis in suspected human cases can be made postmortem by either immunofluorescent or immunohistochemical examination of brain tissue or by detection of viral nucleotide sequences. The latter generally is performed by RT-PCR, but only after DFA testing has failed to confirm the diagnosis of a suspected case. Antemortem diagnosis can be made by DFA testing on skin biopsy specimens

from the nape of the neck, by isolation of the virus from saliva, by detection of antibody in serum (neutralization or IFA methods generally are used) in unvaccinated people and in cerebrospinal fluid (CSF) in all infected people, and by detection of viral nucleotide sequences in saliva, skin, or other tissues. RT-PCR plays a greater role in the diagnosis of rabies in such antemortem specimens in the absence of a brain biopsy specimen. No single test is sufficiently sensitive because of the unique nature of rabies pathobiology. Laboratory personnel and state health or local health departments should be consulted before submission of specimens to the Centers for Disease Control and Prevention (CDC) so appropriate collection and transport of materials can be arranged.

TREATMENT

Once symptoms have developed, neither rabies vaccine nor Rabies Immune Globulin (RIG) improves the prognosis. A combination of sedation and intensive medical intervention may be valuable adjunctive therapy. Details of one management protocol used can be found at **www.mcw.edu/rabies**. Eleven people have survived rabies in association with incomplete rabies vaccine schedules. Eight people who had not received rabies postexposure prophylaxis survived rabies. Approximately half of survivors have normal cognition.

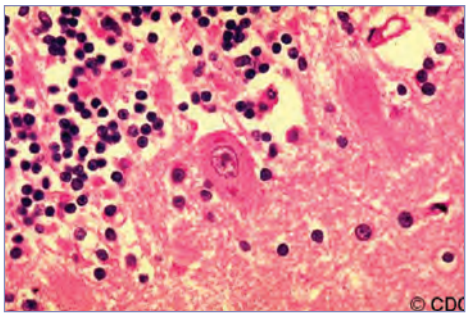


Image 117.1
Characteristic Negri bodies are present within a Purkinje cell of the cerebellum in this patient who died of rabies. Courtesy of Centers for Disease Control and Prevention.

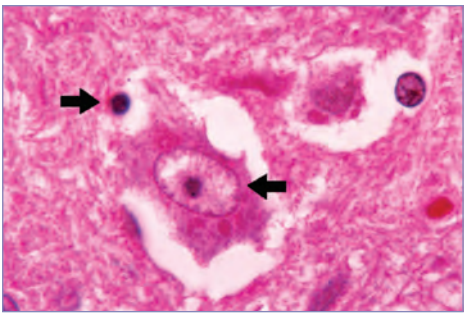


Image 117.2
Photomicrograph of brain tissue from a rabies encephalitis patient (hematoxylin-eosin stain). Histopathologic brain tissue from a rabies patient displaying the pathognomonic finding of Negri bodies within the neuronal cytoplasm (hematoxylin-eosin stain). Courtesy of Centers for Disease Control and Prevention.

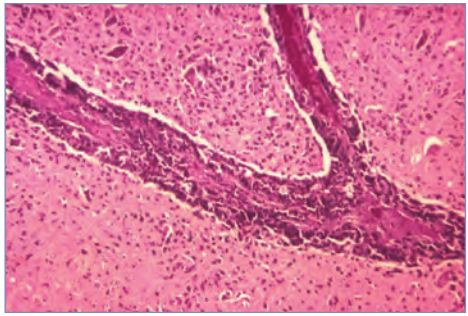


Image 117.3
This micrograph depicts the histopathologic changes associated with rabies encephalitis (hematoxylin-eosin stain). Note the perivascular cuffing due to the accumulation of inflammatory cell infiltrates, including lymphocytes and polymorphonuclear leukocytes. Courtesy of Centers for Disease Control and Prevention.

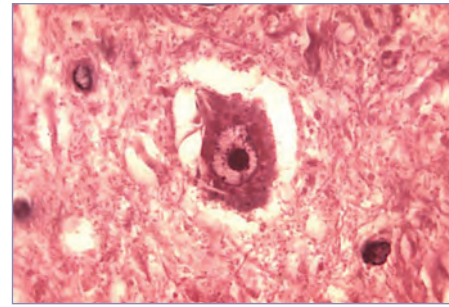


Image 117.4
This micrograph depicts the histopathologic changes associated with rabies encephalitis (hematoxylin-eosin stain). Note the Negri bodies, which are cellular inclusions found most frequently in the pyramidal cells of hippocampus proper, and the Purkinje cells of the cerebellum. They are also found in the cells of the medulla and various other ganglia. Courtesy of Centers for Disease Control and Prevention.

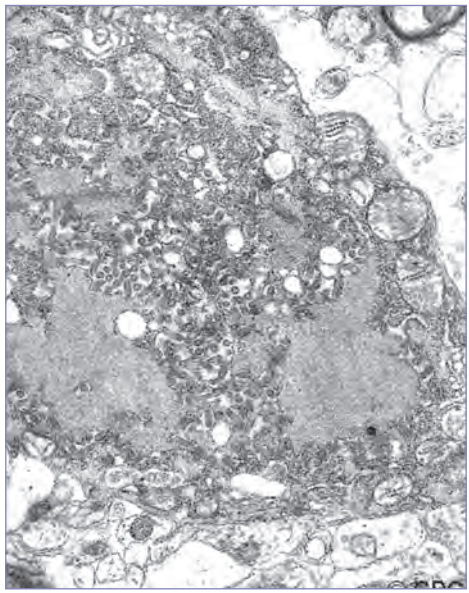


Image 117.5
Electron micrograph of the rabies virus. This electron micrograph shows the rabies virus as well as Negri bodies, or cellular inclusions. Courtesy of Centers for Disease Control and Prevention.

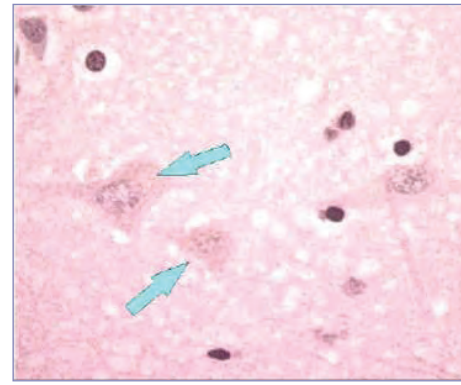


Image 117.6
Neurons without Negri bodies in hematoxylin-eosin stained tissue. Courtesy of Centers for Disease Control and Prevention.

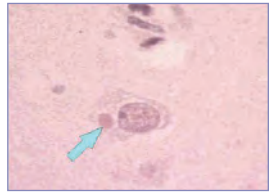
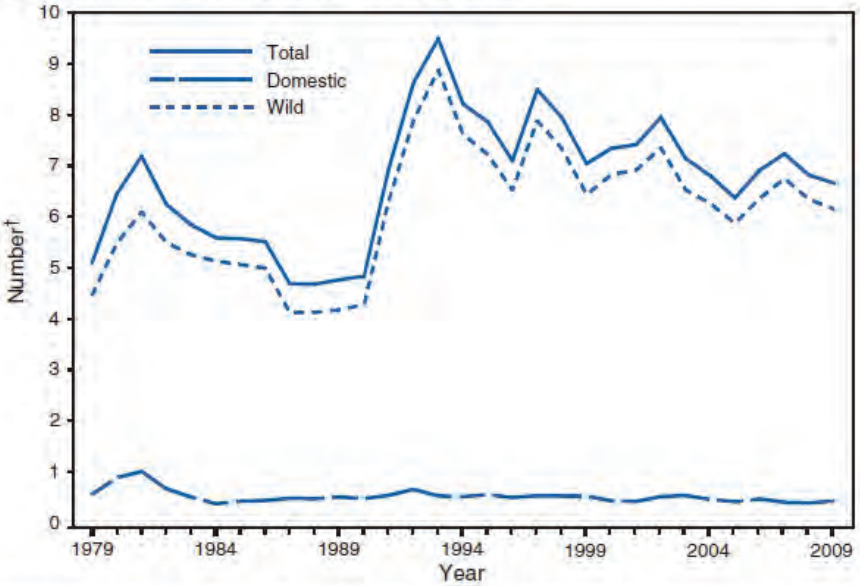


Image 117.7
Negri body in infected tissue in hematoxylin-eosin stained tissue. Courtesy of Centers for Disease Control and Prevention.

RABIES, ANIMAL. Number of reported cases among wild and domestic animals,* by year — United States and Puerto Rico, 1979–2009



* Data from the Division of Vector-Borne Infectious Diseases, National Center for Emerging and Zoonotic Infectious Diseases (NCZVED).
† In thousands.

The proportion of rabid animals among those tested has demonstrated a downward trend from 6.1% in 2006 to 5.6% in 2009. Despite an overall decrease in the number of rabid animals submitted for testing during 2009, bats remained the second most submitted animals for rabies testing and behind only raccoons in total reported rabid animals. The raccoon rabies virus variant remains responsible for the majority of reported rabid animals, but increases in rabid animals attributable to skunk rabies virus variants were reported during 2009.

Image 117.8
Rabies, animal. Number of reported cases among wild and domestic animals, 1979–2009. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 117.9
Aerial distribution of rabies vaccine bait has been a feasible tactic for controlling rabies in foxes in some urban areas, including Toronto, Canada. Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases* and R. C. Rosatte.

Image 117.10
Raccoons can be vectors of the rabies virus, transmitting the virus to humans and other animals. Rabies virus belongs to the order *Mononegavirales.* Raccoons continue to be the most frequently reported rabid wildlife species and involved 37.7% of all animal-transmitted cases during 2000. Courtesy of Centers for Disease Control and Prevention.

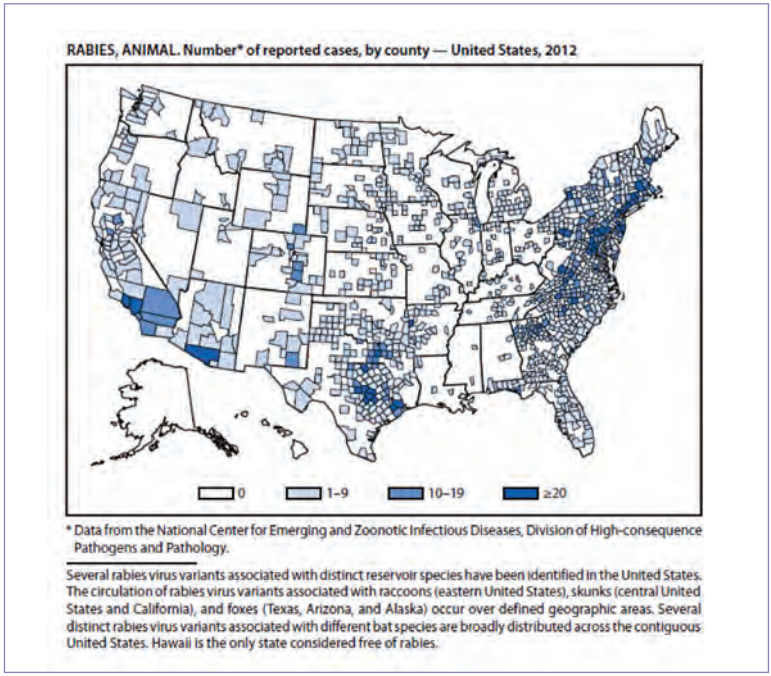


Image 117.11
Rabies, animal. Number of reported cases, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 117.12
This bat, *Artibeus jamaicensis*, is also known as the Jamaican fruit bat. Most of the recent human rabies cases in the United States have been caused by rabies virus that was transmitted through a bat vector. Courtesy of Centers for Disease Control and Prevention.

Image 117.13
This wild fox exhibited symptoms including agitation and excessive salivation and was diagnosed as having rabies. Courtesy of Centers for Disease Control and Prevention.

Image 117.14
Close-up of a dog's face during late-stage "dumb" paralytic rabies. Animals with dumb rabies appear depressed, lethargic, and uncoordinated. Gradually, they become completely paralyzed. When their throat and jaw muscles are paralyzed, the animals will drool and have difficulty swallowing. Courtesy of Centers for Disease Control and Prevention

CHAPTER 118

Rat-Bite Fever

CLINICAL MANIFESTATIONS

Rat-bite fever is caused by *Streptobacillus moniliformis* or *Spirillum minus*. *S moniliformis* infection (streptobacillary fever or Haverhill fever) is characterized by relapsing fever, rash, and migratory polyarthritis. There is an abrupt onset of fever, chills, muscle pain, vomiting, headache, and rarely (unlike *S minus*), lymphadenopathy. A maculopapular, purpuric, or petechial rash develops, predominantly on the peripheral extremities including the palms and soles, typically within a few days of fever onset. The skin lesions may become purpuric or confluent and may desquamate. The bite site usually heals promptly and exhibits no or minimal inflammation. Nonsuppurative migratory polyarthritis or arthralgia follows in approximately 50% of patients. Symptoms of untreated infection resolve within 2 weeks, but fever occasionally can relapse for weeks or months. Complications include soft tissue and solid-organ abscesses, septic arthritis, pneumonia, endocarditis, myocarditis, pericarditis, sepsis, and meningitis. The case-fatality rate is 7% to 13% in untreated patients, and fatal cases have been reported in young children.

With *S minus* infection ("sodoku"), a period of initial apparent healing at the site of the bite usually is followed by fever and ulceration, discoloration, swelling, and pain at the site (about 1 to 4 weeks later), regional lymphangitis and lymphadenopathy, and a distinctive rash of red or purple plaques. Arthritis is rare. Infection with *S minus* is rare in the United States.

ETIOLOGY

The causes of rat-bite fever are *S moniliformis*, a microaerophilic, facultatively anaerobic, gram-negative, pleomorphic bacillus, and *S minus*, a small, gram-negative, spiral-shaped bacterium with bipolar flagellar tufts.

EPIDEMIOLOGY

Rat-bite fever is a zoonotic illness. The natural habitat of *S moniliformis* and *S minus* is the upper respiratory tract of rodents. *S moniliformis* is transmitted by bites or scratches from or exposure to oral secretions of infected rats (eg, kissing pet rodents), other rodents (eg, mice, gerbils, squirrels, weasels), and rodent-eating animals, including cats and dogs. Haverhill fever refers to infection after ingestion of unpasteurized milk, water, or food contaminated with *S moniliformis* and may be associated with an outbreak of disease. *S minus* is transmitted by bites of rats and mice. *S moniliformis* infection accounts for most cases of rat-bite fever in the United States; *S minus* infections occur primarily in Asia.

The **incubation period** for *S moniliformis* usually is less than 7 days (range, 3 days to 3 weeks); for *S minus*, the **incubation period** is 7 to 21 days.

DIAGNOSTIC TESTS

S moniliformis is a fastidious, slow-growing organism isolated from specimens of blood, synovial fluid, abscesses, or aspirates from the bite lesion. Growth is best in bacteriologic media enriched with blood (15% rabbit blood seems optimal), serum, and ascitic fluid, and kept in 5% to 10% carbon dioxide atmosphere. Cultures should be held for 1 week if *S moniliformis* is suspected. Sodium polyanethol sulfonate (SPS), present in most commercially available aerobic blood culture media, is inhibitory to *S moniliformis*. Therefore, SPS-free media (as is found in anaerobic blood culture bottles) should be used, and the laboratory should be alerted to process the specimen aerobically and hold the culture for a longer interval. A terminal blind subculture of blood culture broth to enriched media should be performed after the standard incubation time is completed. Alternatively, the addition of fastidious organism supplement (FOS) to standard SPS-containing aerobic blood culture media can improve the yield of *S moniliformis*. *S moniliformis* also has been detected using a nucleic acid amplification-based assay, available in research laboratories.

S minus has not been recovered on artificial media but can be visualized by darkfield microscopy in wet mounts of blood, exudate of a lesion, and lymph nodes. Blood specimens also should be viewed with Giemsa or Wright

stain. *S minus* can be recovered from blood, lymph nodes, or local lesions by intraperitoneal inoculation of mice or guinea pigs.

TREATMENT

Penicillin G procaine administered intramuscularly or penicillin G administered intravenously for 7 to 10 days is the treatment for rat-bite fever caused by either agent; currently in the United States and other countries, intravenous administration is the more acceptable route.

Initial intravenous penicillin G therapy for 5 to 7 days followed by oral penicillin V for 7 days also has been successful. Limited experience exists for ampicillin, cefuroxime, and cefotaxime. Doxycycline or streptomycin (limited availability) can be substituted when a patient has a serious allergy to penicillin. Patients with endocarditis should receive intravenous high-dose penicillin G for at least 4 weeks. The addition of streptomycin or gentamicin for initial therapy may be useful in severe infections.

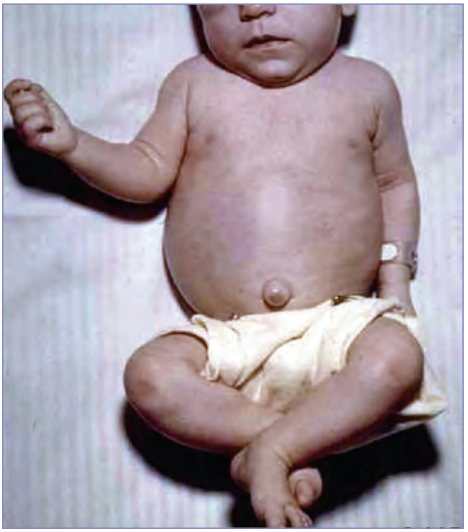


Image 118.1
The rash of rat-bite fever (*Streptobacillus moniliformis*) in an infant bitten by a rat on the right side of the face while sleeping.

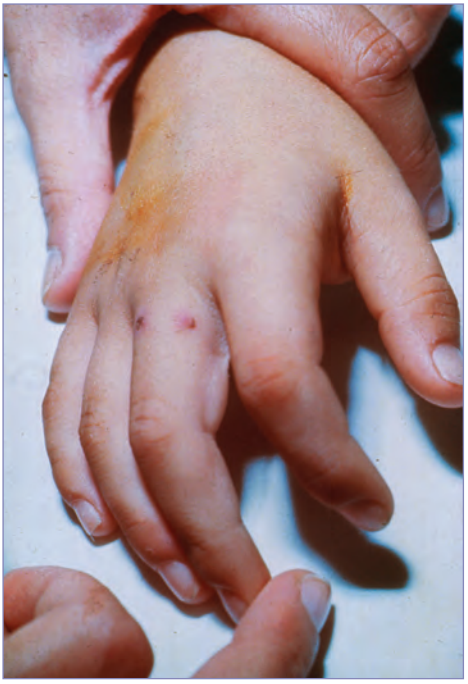


Image 118.2
Rat-bite wounds on the finger of a 5-year-old boy 12 hours after the bite appear non-inflammatory. Because of fever, chills, headache, and rash 5 days later, blood cultures were obtained that grew *Streptobacillus moniliformis*. Courtesy of George Nankervis, MD.

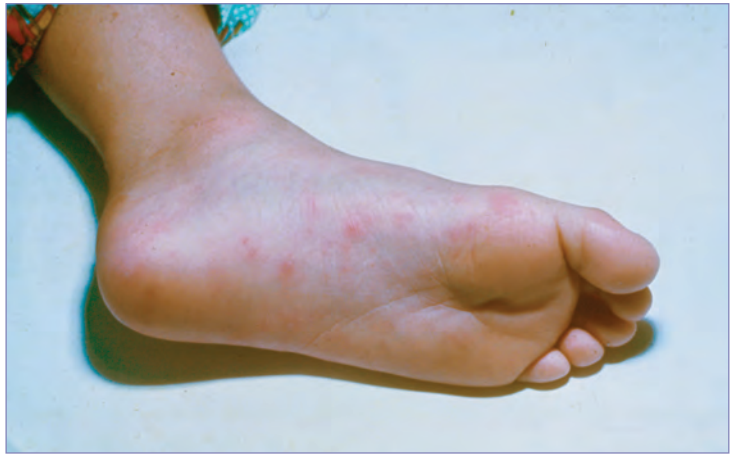


Image 118.3
Five days after being bitten by a rat, the child in Image 118.2 developed fever, chills, and headache, followed 5 days later by a papulovesicular rash on the hands and feet. *Streptobacillus moniliformis* was isolated from blood cultures, and the patient responded to intravenous penicillin therapy without complication. Courtesy of George Nankervis, MD.

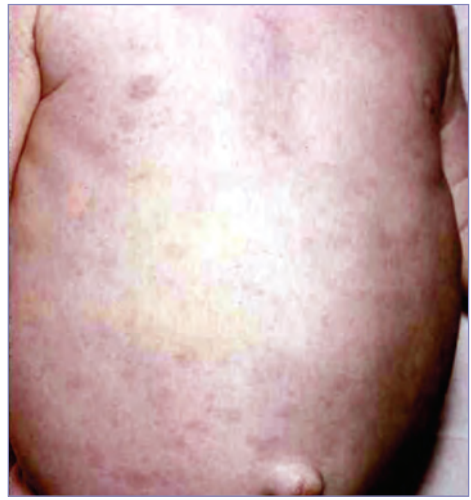


Image 118.4
Close-up view of the rash of the same infant as in Image 118.1 who was bitten on the right cheek by a rat. Sodoku, or rat-bite fever caused by *Spirillum minus,* rarely occurs in the United States.

CHAPTER 119

Respiratory Syncytial Virus

CLINICAL MANIFESTATIONS

Respiratory syncytial virus (RSV) causes acute respiratory tract infections in people of all ages and is one of the most common diseases of early childhood. Most infants infected with RSV experience upper respiratory tract symptoms, and 20% to 30% develop lower respiratory tract disease (eg, bronchiolitis and/or pneumonia) with the first infection. Signs of bronchiolitis typically begin with rhinitis and cough, which progress to increased respiratory effort with tachypnea, wheezing, rales, crackles, intercostal and/or subcostal retractions, grunting, and nasal flaring. Infection with RSV during the first few weeks of life, particularly among preterm infants, may produce minimal respiratory tract signs, lethargy, irritability, and poor feeding, sometimes accompanied by apneic episodes. These infants are at particular risk of life-threatening apnea even in the absence of any other severe respiratory symptoms. Most previously healthy infants who develop RSV bronchiolitis do not require hospitalization, and most who are hospitalized improve with supportive care and are discharged after 2 or 3 days. However, approximately 1% to 3% of all children in the first 12 months of life will be hospitalized because of RSV lower respiratory tract disease, with most RSV hospitalizations occurring in the first 6 months of life. RSV hospitalization rates are highest between 30 and 60 days of age. Factors that increase the risk of severe RSV lower respiratory tract illness include prematurity, especially infants born before 29 weeks' gestation; chronic lung disease of prematurity (CLD [formerly called bronchopulmonary dysplasia]); certain types of hemodynamically significant congenital heart disease (CHD), especially conditions associated with pulmonary hypertension; and certain immunodeficiency states. Additional risk factors for severe RSV lower respiratory tract infections in children worldwide include low birth weight, having siblings, maternal smoking during pregnancy, exposure to secondhand smoke in the household, history of atopy, not breastfeeding, and household crowding.

Mortality is rare when supportive care is available. Fewer than 125 deaths in children <2 years of age are associated with RSV infection annually in the United States, and fewer than 50 deaths occur in those with a primary diagnosis of RSV.

The association between RSV infection early in life and subsequent asthma remains poorly understood. Children who experience lower respiratory tract disease (eg, bronchiolitis or pneumonia) from RSV have an increased risk of developing asthma later in life. This association, which also is seen with other viruses including rhinovirus, may reflect an underlying anatomic or genetic predisposition to both severe bronchiolitis and to asthma rather than a direct consequence of RSV infection.

Almost all children are infected by RSV at least once by 24 months of age, and reinfection throughout life is common. Subsequent infections usually are less severe than primary infections. Particularly among older children and adults, recurrent RSV infection manifests as mild upper respiratory tract illness. Serious disease involving the lower respiratory tract may develop in older children and adults, especially in immunocompromised people, people with cardiopulmonary disease, and elderly people, particularly those with comorbidities.

ETIOLOGY

RSV is an enveloped, nonsegmented, negative strand RNA virus of the genus *Pneumovirus* of the family *Paramyxoviridae.* RSV F and G surface proteins likely promote virus attachment, although a virus constructed without the G surface protein was able to infect and replicate in tissue culture. Numerous genotypes have been identified in each RSV subgroup based on the G protein gene, and strains of both subgroups often circulate concurrently in a community.

EPIDEMIOLOGY

Humans are the only source of infection. RSV usually is transmitted by direct or close contact with contaminated secretions, which may occur from exposure to large-particle droplets at short distances (typically <6 feet) or from fomites. Viable RSV can persist on environmental surfaces for several hours and for 30 minutes

or more on hands. Infection among health care personnel and others may occur by hand-to-eye or hand-to-nasal epithelium self-inoculation with contaminated secretions. Enforcement of infection-control policies is critical to decrease the risk of health care-associated transmission of RSV. Health care-associated spread of RSV to hematopoietic stem cell or solid organ transplant recipients or to patients with cardiopulmonary abnormalities or immunocompromised conditions has been associated with severe and fatal disease in children and adults. Other immunocompromised children, such as those with human immunodeficiency virus (HIV) infection, experience extended viral shedding and sometimes prolonged illness but usually do not exhibit enhanced disease.

RSV occurs in annual epidemics during winter and early spring in temperate climates. Spread among household and child care contacts, including adults, is common. The period of viral shedding usually is 3 to 8 days but may last longer, especially in young infants and in immunosuppressed people, in whom shedding may continue for 3 to 4 weeks or longer.

The **incubation period** ranges from 2 to 8 days; 4 to 6 days is most common.

DIAGNOSTIC TESTS

Rapid diagnostic assays, including direct fluorescent antibody (DFA) assay and enzyme or chromatographic immunoassay techniques for detection of viral antigen in nasopharyngeal specimens, are available commercially for RSV and generally are reliable in infants and young children. In children, the sensitivity of these assays in comparison with culture varies between 53% and 96%, with most in the 80% to 90% range. The sensitivity may be lower in older children and is quite poor in adults, because adults typically shed low concentrations of RSV. As with all antigen detection assays, the predictive value is high during the peak season, but false-positive test results are more likely to occur when the incidence of disease is low, such as in the summer in temperate areas. Therefore, antigen detection assays should not be the only basis on which the beginning and end of monthly RSV immunoprophylaxis is determined.

Molecular diagnostic tests using reverse transcriptase-polymerase chain reaction (RT-PCR) are available widely and increase RSV detection rates over viral isolation or antigen detection assays, especially in older children and adults. Many tests are designed as multiplex assays to facilitate testing for multiple respiratory viruses with a single assay. Because of the increased sensitivity of RT-PCR assay, these tests may be preferred. However, results of these tests should be interpreted with caution, especially when a multiplex assay identifies more than one virus, because some viruses (eg, RSV, rhinovirus, adenovirus, and bocavirus) may persist in the airway for many weeks after the acute infection has resolved. As many as 25% of asymptomatic children test positive for respiratory viruses using RT-PCR assays in population-based studies. Up to 30% of children with RSV bronchiolitis may be coinfected with another respiratory tract pathogen, such as human metapneumovirus, rhinovirus, bocavirus, adenovirus, coronavirus, influenza virus, or parainfluenza virus. Whether children with bronchiolitis who are coinfected with more than one virus experience more severe or even less severe disease is not clear.

RSV isolation from respiratory tract secretions in cell culture requires 1 to 5 days (rapid, centrifugation-enhanced, shell vial techniques can produce results within 24–48 hours), but results and sensitivity vary among laboratories; therefore, molecular diagnostic methods are preferred.

Palivizumab may interfere with immunologic-based RSV diagnostic tests, such as some antigen detection-based assays. In addition, palivizumab inhibits virus replication in cell culture and may interfere with viral culture assays. Palivizumab does not interfere with RT-PCR assays. Assay interference could lead to false-negative RSV diagnostic test results. Therefore, diagnostic test results, when obtained in patients receiving palivizumab immunoprophylaxis, should be used in conjunction with clinical findings to guide medical decisions.

In most outpatient settings for children with bronchiolitis, routine specific respiratory viral testing has little effect on management and testing is not recommended. Specific

respiratory viral testing in hospitalized patients has been associated with fewer diagnostic tests in general once RSV or another virus is identified, use of fewer antibiotics, and in some hospitals, better cohorting and less health care-associated infection.

TREATMENT

No available treatment shortens the course of bronchiolitis or hastens the resolution of symptoms. The variable course of bronchiolitis and the inability to predict whether supportive care will be needed often results in hospital admission, even when symptoms are not severe. Management of young children hospitalized with bronchiolitis is supportive and should include hydration, careful assessment of respiratory status, suction of the upper airway, and if necessary, intubation and mechanical ventilation. Clinicians may choose not to administer supplemental oxygen if the oxyhemoglobin saturation exceeds 90% in infants and children hospitalized with bronchiolitis. Clinicians may choose not to use continuous pulse oximetry for children with bronchiolitis. Continuous measurement of oxygen saturation may detect transient fluctuations in oxygenation that are not clinically significant, prolong oxygen use, and delay discharge. Transient desaturation to <90% is a normal occurrence among healthy infants. Among patients with bronchiolitis, pulse oximetry should not be used as a proxy for respiratory distress. The correlation between respiratory distress and oxygen saturation is poor among infants with lower respiratory tract infection. Supplemental oxygen is recommended only when oxyhemoglobin saturation persistently falls below 90% in a previously healthy infant.

Aerosolized ribavirin therapy has been associated with a small but statistically significant increase in oxygen saturation during the acute infection in several small studies. However, a consistent decrease in need for mechanical ventilation, decrease in length of stay in the pediatric intensive care unit, reduction in days of hospitalization, or decrease in mortality among ribavirin recipients has not been demonstrated. The aerosol route of administration, concern about potential toxic effects among exposed health care personnel, conflicting results of efficacy trials, and high cost have led to infrequent use of this drug. Aerosolized ribavirin is not recommended for routine use because of the lack of a clinically significant effect on outcome. However, it may be considered for use in selected patients with severe, life-threatening disease.

Alpha- and Beta-Adrenergic Agents

Beta-adrenergic agents are not recommended for care of first-time wheezing associated with RSV bronchiolitis. Randomized clinical trials have demonstrated that bronchodilators do not affect disease resolution, need for hospitalization, or length of stay. Bronchodilators do not improve oxygen saturation, hospital admission rates after outpatient treatment, or time to resolution of illness at home. For these reasons, a trial of albuterol no longer is included as a recommended option in the management of RSV bronchiolitis. Evidence does not support the use of nebulized epinephrine in children hospitalized with bronchiolitis. Insufficient data are available to recommend routine use of epinephrine for outpatient management of children with bronchiolitis.

Glucocorticoid Therapy

Controlled clinical trials among children with bronchiolitis have demonstrated that corticosteroids do not reduce hospital admissions and do not reduce length of stay for inpatients. Corticosteroid treatment should not be used for infants and children with RSV bronchiolitis. Evidence for potential benefit from combined use of corticosteroids and agents with alpha- or beta-adrenergic activity is insufficient to support a recommendation.

Antimicrobial Therapy

Antimicrobial therapy is not indicated for infants with RSV bronchiolitis or pneumonia unless there is evidence of concurrent bacterial infection. Bacterial lung infections and bacteremia are uncommon in this setting. Acute otitis media (AOM) caused by RSV or bacterial superinfection may occur in infants with RSV bronchiolitis. Oral antimicrobial therapy for treatment of otitis media may be considered if bulging of the tympanic membrane is present.

Other Therapies

Chest physiotherapy should not be used in infants and children with a diagnosis of bronchiolitis. Suctioning of the nasopharynx to remove secretions may provide temporary relief. If indicated, nasogastric or intravenous fluids may be used to maintain hydration. Nebulized hypertonic saline (3%) appears to be safe and effective at improving the symptoms of mild to moderate bronchiolitis after 24 hours of use and in reducing hospital length of stay in cases in which the duration of stay is likely to exceed 3 days. Hypertonic saline has not been shown to be effective over the short term for patients managed in the emergency department or when length of hospitalization is brief.

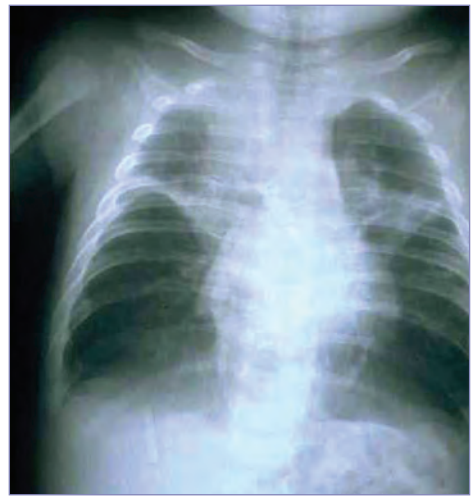


Image 119.1
Respiratory syncytial virus bronchiolitis and pneumonia. Note the bilateral infiltrates and striking hyperaeration. Copyright Martha Lepow.

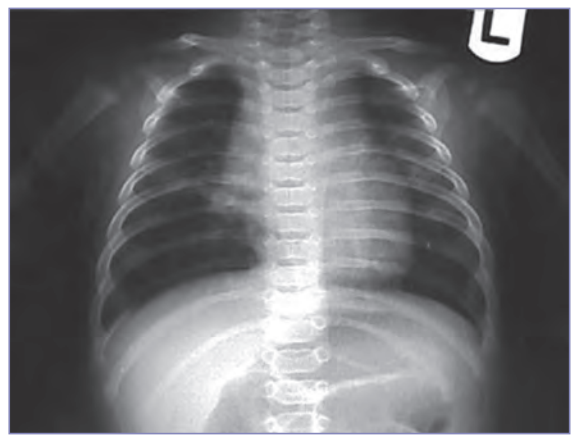


Image 119.2
An anteroposterior radiograph of a 2-month-old girl with respiratory syncytial virus bronchiolitis. Note the wide intercostal spaces, hyperaeration of the lung fields, and flattening of the diaphragm. Courtesy of Benjamin Estrada, MD.

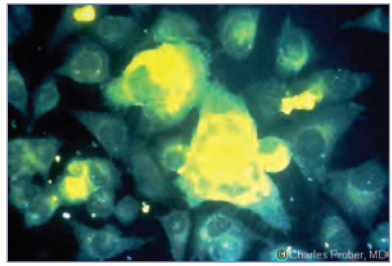


Image 119.3
Direct fluorescent antibody staining of respiratory syncytial virus in cell culture. Copyright Charles Prober.

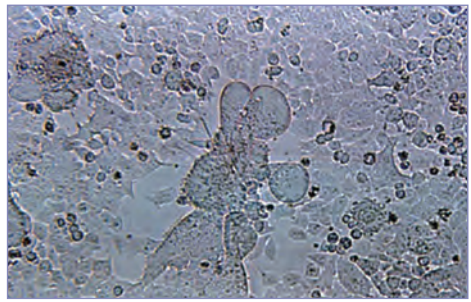


Image 119.4
The characteristic cytopathic effect of respiratory syncytial virus in tissue culture includes the formation of large multinucleated syncytial cells.

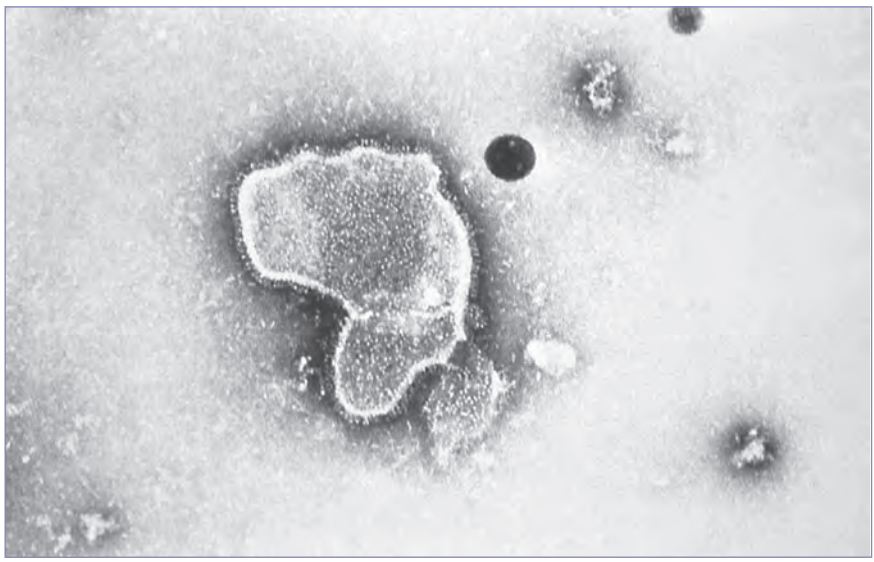


Image 119.5
Electron micrograph of a respiratory syncytial virus. The virion is variable in shape and size (average diameter between 120 and 300 nm). Respiratory syncytial virus is the most common cause of bronchiolitis and pneumonia among infants younger than 1 year. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 120

Rhinovirus Infections

CLINICAL MANIFESTATIONS

Rhinoviruses are a frequent cause of the common cold, or rhinosinusitis. Typical clinical manifestations include sore throat, nasal congestion, and nasal discharge that initially is watery and clear but often becomes mucopurulent and viscous after a few days. Malaise, headache, myalgia, low-grade fever, cough, and sneezing may occur. Symptoms typically peak in severity after 3 to 4 days and have a median duration of 7 days but may persist for more than 10 days in approximately 25% of illnesses. Rhinoviruses also cause otitis media and lower respiratory tract infections (eg, bronchiolitis, pneumonia) in infants, and they are increasingly recognized as an important cause of community-acquired pneumonia in both children and adults. Rhinoviruses also are associated with 60% to 70% of acute exacerbations of asthma in school-aged children.

ETIOLOGY

Human rhinoviruses (HRVs) are small, nonenveloped, single, positive-stranded RNA viruses classified into 3 species (HRV-A, HRV-B, and HRV-C) in the family *Picornaviridae*, genus *Enterovirus*. More than 150 rhinovirus types have been identified by immunologic and molecular methods. Infection confers type-specific immunity, but this protection is temporary.

EPIDEMIOLOGY

Rhinovirus infection is ubiquitous in human populations. Children have an average of 2 rhinovirus infections each year, and 93% of adults experience at least 1 rhinovirus infection, which may be either symptomatic or asymptomatic, each year. Rhinoviruses are detected commonly in adults and children with upper and lower respiratory infections and usually are self-limited. Rhinoviruses are the most common cause of pneumonia in immunocompromised people.

Transmission occurs predominantly by person-to-person contact via self-inoculation by contaminated secretions on hands or by large-particle aerosol spread. Infections occur throughout the year, but peak activity occurs during autumn and spring. Multiple serotypes circulate simultaneously, and the prevalent serotypes circulating in a given population change from season to season. HRV-A and HRV-C induce more severe illnesses than HRV-B. In addition, HRV-C infections are more commonly associated with wheezing and lower respiratory illnesses compared with the other 2 serotypes. Viral shedding in nasopharyngeal secretions is most abundant during the first 2 to 3 days of infection and usually ceases by 7 to 10 days. However, virus shedding detectable by polymerase chain reaction testing may continue for as long as 7 weeks or more.

The **incubation period** usually is 2 to 3 days.

DIAGNOSTIC TESTS

Reverse transcriptase-polymerase chain reaction (RT-PCR) assays are the preferred way to identify rhinovirus infections, with several commercial assays available. Most of these assays are designed as multiplexed tests that detect a wide variety of viral and, in some cases, bacterial respiratory pathogens. In general, these assays cannot clearly distinguish human rhinoviruses from enteroviruses because of the genetic similarity of the 2 groups and primers that target genetically conserved regions. Specific viral diagnosis generally is not useful clinically, and isolation of virus in cell culture is insensitive. Given the prevalence of rhinovirus infection and the occurrence of shedding following infection, rhinovirus detected, even in symptomatic patients, may not be causal.

TREATMENT

Treatment is supportive. Antimicrobial agents should not be used for prevention of secondary bacterial infection, because their use may promote the emergence of resistant bacteria and subsequently complicate treatment for a bacterial infection, and because of the risk of antibiotic-associated side effects.

CHAPTER 121

Rickettsial Diseases

Rickettsial diseases comprise infections caused by bacterial species of the genera *Rickettsia* (endemic and epidemic typhus and spotted fever group rickettsioses), *Orientia* (scrub typhus), *Ehrlichia* (ehrlichiosis), *Anaplasma* (anaplasmosis), *Neoehrlichia*, and *Neorickettsia*.

CLINICAL MANIFESTATIONS

The early signs and symptoms can be nonspecific and often mimic other viral illnesses. Rickettsial infections have many features in common, including the following:

- Fever, rash (especially in spotted fever and typhus group rickettsiae), headache, myalgia, and respiratory tract symptoms are prominent features. The classic rash in Rocky Mountain spotted fever (RMSF) may not appear for 1 week after onset of symptoms, and 10% to 15% of patients do not present with the rash.
- One or more inoculation eschars occur with many rickettsial diseases, especially most spotted fever group rickettsioses, rickettsialpox, and scrub typhus.
- Systemic endothelial damage of small blood vessels resulting in increased vascular permeability is the hallmark pathologic feature of most severe spotted fever and typhus group rickettsial infections.
- Some rickettsial diseases, particularly RMSF and Mediterranean spotted fever, can become life-threatening rapidly. Risk factors for severe disease include glucose-6-phosphate dehydrogenase deficiency, male gender, and antecedent exposure to sulfonamides.

Immunity against reinfection by the same agent after natural infection is not well studied, but some anecdotal information suggests that prior infection confers immunity for at least 1 year. Documented reinfections with *Rickettsia* and *Ehrlichia* species have been described only rarely.

ETIOLOGY

Currently recognized rickettsial pathogens of humans include more than 20 species of *Rickettsia*, 5 species of *Ehrlichia*, *Anaplasma phagocytophilum*, *Orientia tsutsugamushi*, and *Neorickettsia sennetsu*. Tickborne neoehrlichiosis caused by *Candidatus Neoehrlichia mikurensis*, which features rodents as the primary host, is an emerging disease in Asia and Europe. Rickettsiae are small, coccobacillary gram-negative bacteria that are obligately intracellular pathogens and cannot be grown in cell-free media. *Orientia* and *Rickettsia* organisms reside free within the cytoplasm and *Anaplasmataceae* organisms in phagosomes.

EPIDEMIOLOGY

Rickettsial diseases have various hematophagous arthropod vectors that include ticks, fleas, mites, and lice. Except in the case of *Rickettsia prowazekii*, the cause of epidemic typhus, humans are incidental hosts for rickettsial pathogens. Rickettsial life cycles typically involve one or more arthropod species as well as various mammalian reservoir or amplifying hosts, and transmission to humans occurs during environmental or occupational exposures to infected arthropods. Geographic and seasonal occurrences of each rickettsial disease are related directly to the distributions and life cycles of the specific vector.

Other Global Rickettsial Spotted Fever Infections

A number of other epidemiologically distinct fleaborne and tickborne spotted fever infections caused by rickettsiae have been recognized. These diseases are of importance among people traveling to or returning from areas where these agents are endemic and among people living in these areas. These infections have clinical and pathologic features that vary widely in severity. Many present with an eschar at the site of the tick bite and without rash. The causative agents of some of these infections share the same group antigen as *R rickettsii* and include the following:

- *Rickettsia africae*, the causative agent of African tick bite fever that is endemic in sub-Saharan Africa, Oceania, and some Caribbean islands.

- *Rickettsia conorii* and subspecies, the causative agents of Mediterranean spotted fever, India tick typhus, Marseilles fever, Israeli tick typhus, and Astrakhan spotted fever, that are endemic in southern Europe, Africa, the Middle East, and the Indian subcontinent.
- *Rickettsia parkeri*, a causative agent of eschar-associated infections in the Americas.
- *Rickettsia sibirica*, the causative agent of Siberian tick typhus (or North Asian tick typhus), endemic in central Asia.
- *Rickettsia australis*, the causative agent of North Queensland tick typhus, endemic in eastern Australia.
- *Rickettsia japonica*, the causative agent of Japanese spotted fever, endemic in Japan.
- *Rickettsia honei*, the causative agent of Thai tick typhus and Flinders Island spotted fever, endemic throughout Southeast Asia.
- *Rickettsia slovaca*, the causative agent of tickborne lymphadenopathy (TIBOLA), also known as *Dermacentor*-borne necrosis-erythema-lymphadenopathy (DEBONEL) or the more overarching term scalp eschars and neck lymphadenopathy (SENLAT), endemic in European countries; *Rickettsia raoultii* infections have a similar presentation and distribution.
- *Rickettsia felis*, the causative agent of cat flea rickettsiosis that occurs worldwide; reports on the severity of illness vary widely.
- *Rickettsia aeschlimannii*, a causative agent of disease with an eschar-associated illness reported from Africa and Europe.
- *Rickettsia heilongjiangensis*, reported from the Russian Far East and China.
- *Rickettsia sibirica* subspecies *mongolitimonae*, reported from Europe, Africa, and Asia, which causes a rickettsiosis with eschar and lymphangitis.
- *Rickettsia massiliae* is widespread in Africa and Europe; the Bar 29 type agent has been found in the United States and is implicated as a cause of illness in Argentina.
- *Rickettsia* species 364D causes eschar, headache, and fever on the US Pacific coast.
- *Rickettsia monacensis* causes a syndrome similar to that caused by *R conorii* and is found in Spain and southern Italy.

DIAGNOSTIC TESTS

Group-specific antibodies are detectable in the serum of most patients by 7 to 14 days after onset of illness, but slower antibody responses may occur, particularly in some diseases of lesser severity. The utility of serologic testing during the acute illness is generally of limited value, and a negative serologic test result during the initial stage of the illness should never be used to exclude a diagnosis of rickettsial disease. Nonetheless, serologic assays provide an excellent method of retrospective confirmation when paired serum samples collected during the illness and approximately 2 to 4 weeks later are tested in tandem. Treatment early in the course of illness can blunt or delay serologic responses. Polymerase chain reaction (PCR) assays can detect rickettsiae in whole blood or tissues collected during the acute stage of illness and before administration of antimicrobial agents; availability of these tests often is limited to reference and research laboratories. PCR assays and sequencing of DNA collected during acute infection provide more accurate identification of the etiologic agent than serologic testing.

TREATMENT

Prompt initiation of treatment is indicated for all patients in all age groups with suspected RMSF or ehrlichiosis, without waiting for confirmative diagnostic testing. The drug of choice for all rickettsioses is doxycycline for 7 to 14 days. Antimicrobial treatment is most effective when people are treated appropriately during the first week of illness. If the disease remains untreated during the second week, therapy is less effective in preventing complications.

CHAPTER 122

Rickettsialpox

CLINICAL MANIFESTATIONS

Rickettsialpox is a febrile, eschar-associated illness that is characterized by generalized, relatively sparse, erythematous, papulovesicular eruptions on the trunk, face, and extremities (less often on palms and soles) or on mucous membranes of the mouth. The rash develops 1 to 4 days after onset of fever and 3 to 10 days after appearance of an eschar at the site of the bite of a house mouse mite. Regional lymph nodes in the area of the primary eschar typically become enlarged. Without specific antimicrobial therapy, systemic disease lasts approximately 7 to 10 days; manifestations include fever, headache, malaise, and myalgia. Less frequent manifestations include anorexia, vomiting, conjunctivitis, hepatitis, nuchal rigidity, and photophobia. The disease is mild compared with Rocky Mountain spotted fever, and no rickettsialpox-associated deaths have been described; however, disease occasionally is severe enough to warrant hospitalization.

ETIOLOGY

Rickettsialpox is caused by *Rickettsia akari*, a gram-negative intracellular bacillus, which is classified with the spotted fever group rickettsiae and related antigenically to other members of that group.

EPIDEMIOLOGY

The natural host for *R akari* in the United States is *Mus musculus*, the common house mouse. The organism is transmitted by the house mouse mite, *Liponyssoides sanguineus*. Disease risk is heightened in areas infested with mice and rats. The disease can occur wherever the hosts, pathogens, and humans coexist but most frequently is reported in large urban settings. In the United States, rickettsialpox has been described predominantly in northeastern metropolitan centers, especially in New York City. It also has been confirmed in many other countries, including the Netherlands, Croatia, Ukraine, Turkey, Russia, South Korea, South Africa, and Mexico. All age groups can be affected. No seasonal pattern of disease occurs. The disease is not communicable but occurs occasionally among families or people cohabiting a house mouse mite-infested dwelling.

The **incubation period** is 6 to 15 days.

DIAGNOSTIC TESTS

R akari can be isolated in cell culture from blood and eschar biopsy specimens during the acute stage of disease, but culture is not attempted routinely. Because antibodies to *R akari* have extensive cross-reactivity with antibodies against *Rickettsia rickettsii* (the cause of Rocky Mountain spotted fever) and other spotted fever-group rickettsiae, an indirect immunofluorescence antibody assay for *R rickettsii* can be used to demonstrate a fourfold or greater change in antibody titers between acute and convalescent serum specimens taken 2 to 6 weeks apart. Use of *R akari* antigen is recommended for a more accurate serologic diagnosis but may be available only in specialized research laboratories. Immunoglobulin (Ig) M and IgG are detected 7 to 15 days after illness onset. Immunohistochemical testing of formalin-fixed, paraffin-embedded eschars or papulovesicle biopsy specimens can detect rickettsiae in the samples and are useful diagnostic techniques, but because of cross-reactivity, these assays are not able to confirm the etiologic agent. A real-time polymerase chain reaction assay for detection of rickettsial DNA with subsequent sequence identification can confirm *R akari* infection but is not cleared by the US Food and Drug Administration for use in the United States.

TREATMENT

Doxycycline is the drug of choice in all age groups and is effective when administered for 5 to 7 days. Doxycycline shortens the course of disease, and symptoms typically resolve within 12 to 48 hours after initiation of therapy. Chloramphenicol is an alternative drug but is not available as an oral formulation in the United States. Use of chloramphenicol should be considered only in rare cases, such as for patients with severe doxycycline allergies, because rickettsialpox usually is mild and self-limited. Untreated rickettsialpox usually resolves within 2 to 3 weeks.

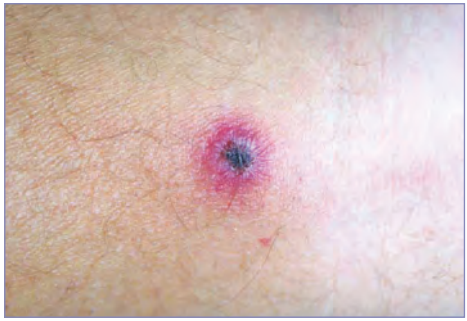


Image 122.1
Eschar on the posterior right calf of patient with rickettsialpox. This type of lesion is not seen with Rocky Mountain spotted fever. Courtesy of *Emerging Infectious Diseases.*

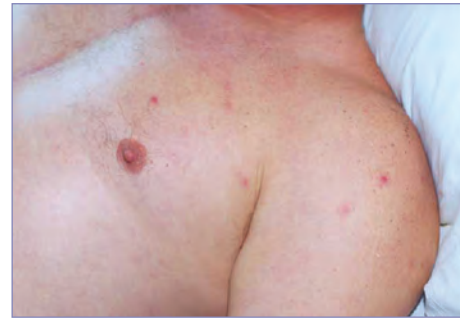


Image 122.2
Multiple papulovesicular lesions involving the upper trunk on a patient with rickettsialpox. Courtesy of *Emerging Infectious Diseases.*

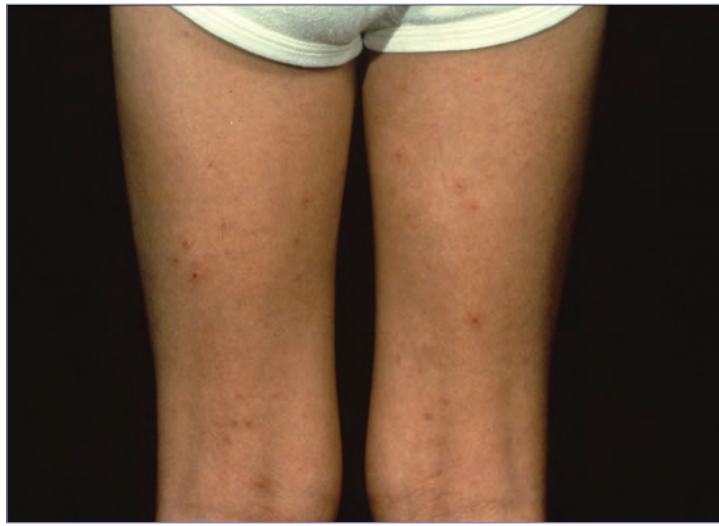


Image 122.3
Rickettsialpox on the legs. Copyright James Brien, DO.

CHAPTER 123

Rocky Mountain Spotted Fever

CLINICAL MANIFESTATIONS

Rocky Mountain spotted fever (RMSF) is a systemic, small-vessel vasculitis that often involves a characteristic rash. Fever, myalgia, severe headache (less common in young children), photophobia, nausea, vomiting, and anorexia are typical presenting symptoms. Abdominal pain and diarrhea often are present and can obscure the diagnosis. The rash usually begins within the first 2 to 4 days of symptoms as erythematous macules or maculopapules. The rash usually appears first on the wrists and ankles, often spreading within hours proximally to the trunk and distally to the palms and soles. Although early development of a rash is a useful diagnostic sign, the rash can be atypical or absent altogether in a small portion of patients. It may be difficult to visualize in patients with dark skin. A petechial rash typically is a late finding and indicates progression to severe disease. Lack of a typical rash is a risk factor for misdiagnosis and poor outcome. Hepatomegaly and splenomegaly occur in 10% to 20% of patients and may be reported more frequently in children. Meningeal signs with a positive Kernig and Brudzinski sign may occur. Pediatric cases may additionally experience peripheral or periorbital edema.

Thrombocytopenia, hyponatremia (serum sodium concentrations <130 mg/dL are observed in 20%–50% of cases), and elevated liver transaminase concentrations develop in many cases, are frequently mild in the early stages of disease, and worsen as disease progresses. White blood cell count typically is normal, but leukopenia and anemia can occur. If not treated, the illness can be severe, with prominent central nervous system, cardiac, pulmonary, gastrointestinal tract, and renal involvement; disseminated intravascular coagulation; and shock leading to death. RMSF can progress rapidly, even in previously healthy people. Delay in appropriate antimicrobial treatment past the fifth day of symptoms is associated with severe disease and poor outcomes. The median time to death in untreated cases is 8 days. Significant long-term sequelae are common in patients with severe RMSF, including neurologic (paraparesis; hearing loss; peripheral neuropathy; bladder and bowel incontinence; and cerebellar, vestibular, and motor dysfunction) and nonneurologic (disability from limb or digit amputation) sequelae. Patients treated early in the course of symptoms may have a mild illness, with fever resolving in the first 48 hours of treatment.

ETIOLOGY

The family *Rickettsiaceae* compromises 2 genera, *Rickettsia* and *Orientia*. *Rickettsia rickettsii*, an obligate, intracellular, gram-negative bacillus and a member of the spotted fever group of rickettsiae, is the causative agent. The primary targets of infection in mammalian hosts are endothelial cells lining the small blood vessels of all major tissues and organs. Diffuse small vessel vasculitis leads to increased permeability.

EPIDEMIOLOGY

The pathogen is transmitted to humans by the bite of a tick of the *Ixodidae* family (hard ticks). Ticks and their small mammal hosts serve as reservoirs of the pathogen in nature. Other wild animals and dogs have been found with antibodies to *R rickettsii*, but their role as natural reservoirs is not clear. People with occupational or recreational exposure to the tick vector (eg, pet owners, animal handlers, and people who spend more time outdoors) are at increased risk of exposure to the organism. People of all ages can be infected. The period of highest incidence in the United States is from April to September, although RMSF can occur year-round in certain areas with endemic disease. Transmission has occurred on rare occasions by blood transfusion. RMSF is the most frequently fatal rickettsial illness in the United States; the case-fatality rate in the preantibiotic era was approximately 25%. Present-day case-fatality rates, estimated at 5% to 10% overall, depend in part on the timing of initiation of appropriate treatment. Mortality is highest in males, people older than 50 years, children younger than 10 years, and people with no recognized tick bite or attachment. In approximately half of pediatric RMSF cases, there is no recall of a recent tick bite. Delay in disease recognition and initiation of antirickettsial therapy after the fifth day of symptoms

increase the risk of death. Factors contributing to delayed diagnosis include absence of rash or difficulty in its recognition, especially in individuals with darker complexions; initial presentation before the fourth day of illness; and onset of illness during months of low incidence.

RMSF is widespread in the United States, with a reported annual incidence that has increased sixfold, from 1.8 cases per million people in 2000 to 13.0 cases per million in 2015, or approximately 3,700 cases per year between 2011 and 2015. Despite its name, RMSF is not common in the Rocky Mountain area. Most cases are reported in the south Atlantic, southeastern, and south central states, although most states in the contiguous United States record cases each year. The principal recognized vectors of *R rickettsii* are *Dermacentor variabilis* (the American dog tick) in the eastern and central United States and *Dermacentor andersoni* (the Rocky Mountain wood tick) in the western United States. Another common tick throughout the world that feeds on dogs, *Rhipicephalus sanguineus* (the brown dog tick) has been confirmed as a vector of *R rickettsii* in Arizona and Mexico and may play a role in other regions. Transmission parallels periods of tick host-seeking activity in a given geographic area. RMSF also occurs in Canada, Mexico, Central America, and South America.

The **incubation period** is approximately 1 week (range, 3–12 days).

DIAGNOSTIC TESTS

The diagnosis of RMSF must be made on the basis of clinical signs and symptoms and can be confirmed later using confirmatory diagnostic tests. Treatment should never be delayed while awaiting laboratory confirmation. The gold standard for serologic diagnosis of RMSF is the indirect immunofluorescence antibody (IFA) test. A negative serologic test result from the acute phase does not exclude the diagnosis of RMSF. Both immunoglobulin (Ig) G and IgM antibodies begin to increase around day 7 to 10 after onset of symptoms; however, an elevated acute titer may represent prior infection rather than acute infection. Low-level elevated antibody titers can be an incidental finding in a significant proportion of the population in some regions. IgM antibodies may remain elevated for months and are not highly specific for acute RMSF. A fourfold or greater increase in antigen-specific IgG between acute and convalescent sera obtained 2 to 4 weeks apart confirms the diagnosis (6 weeks for convalescent serum for *Rickettsia africae*). Cross-reactivity may be observed between antibodies to other spotted fever group rickettsiae, including *Rickettsia parkeri* and *R africae.* Enzyme-linked immunosorbent assays also can be used for assessing antibody presence in acute and convalescent sera but are less useful for quantifying changes in titer.

RMSF may be diagnosed by the detection of *R rickettsii* DNA in acute whole blood and serum specimens by polymerase chain reaction (PCR) assay. *R rickettsii* typically do not circulate in the whole blood until advanced stages of disease; therefore, detection of *R rickettsii* DNA in whole blood by PCR testing is possible, but it may be considered a less sensitive diagnostic assay in the absence of advanced illness. The specimen should be obtained preferably before (or within 24 hours of) doxycycline administration; a negative result does not exclude RMSF infection. Diagnosis may be confirmed by the detection of rickettsial DNA in biopsy or autopsy specimens by PCR assay or immunohistochemical (IHC) visualization of rickettsiae in tissues.

TREATMENT

Doxycycline is the drug of choice for treatment of RMSF in patients of any age and should be started as soon as RMSF is suspected. Use of antimicrobial agents other than doxycycline increases the risk of mortality. Doxycycline is administered twice per day, orally or intravenously. Treatment is most effective if initiated in the first few days of symptoms, and treatment started after the fifth day of symptoms is less likely to prevent death or other adverse outcomes. Chloramphenicol sometimes is listed as an alternative treatment; however, its use is associated with a higher risk of fatal outcome. Antimicrobial treatment should be continued until the patient has been afebrile for at least 3 days and has demonstrated clinical improvement; the usual duration of therapy is 5 to 7 days.

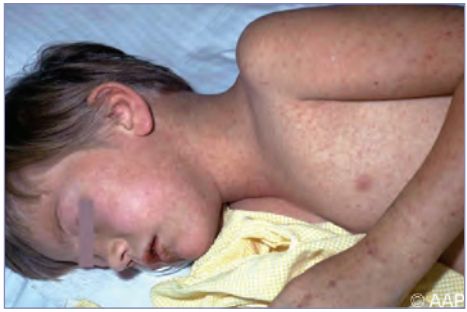


Image 123.1
Rocky Mountain spotted fever in an 8-year-old boy. Sixth day of rash without treatment.

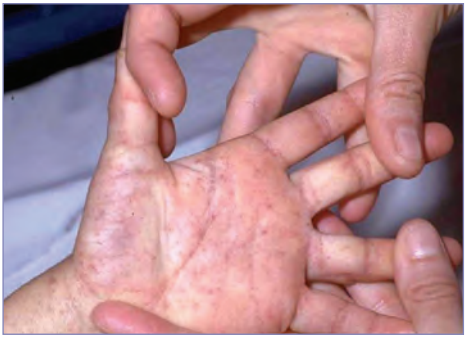


Image 123.2
Rocky Mountain spotted fever. Sixth day of rash without treatment. This is the same patient as in Image 123.1.

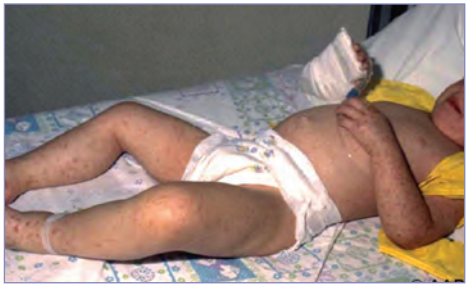


Image 123.3
A 2-year-old boy with obtundation, disorientation, and petechial rash of Rocky Mountain spotted fever, with facial and generalized edema secondary to generalized vasculitis. Rocky Mountain spotted fever is the most severe and frequently reported rickettsial illness in the United States.

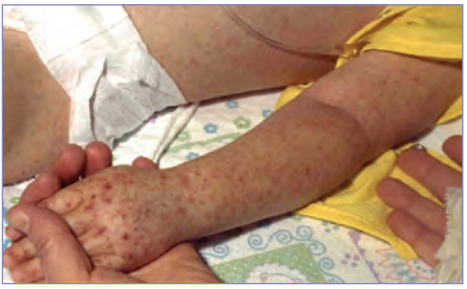


Image 123.4
This is the same patient as in Image 123.3, showing petechial rash and edema of the upper extremity. The rickettsiae multiply in the endothelial cells of small blood vessels, resulting in vasculitis.

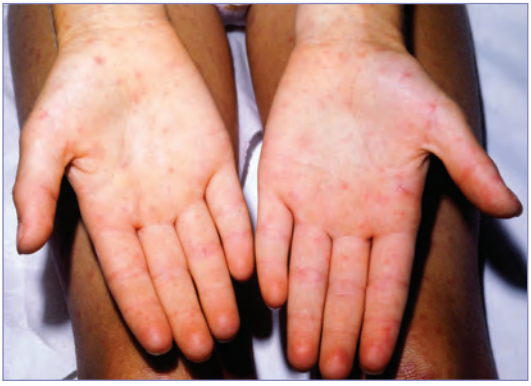


Image 123.5
This 8-year-old girl presented with a history of "chickenpox" for 11 days. She had numerous lesions on her chest, face, arms, and proximal legs. There were subcutaneous erythematous lesions on the hands, and she had 5 or 6 lesions on her feet. The diagnosis of Rocky Mountain spotted fever was confirmed serologically, and she was treated without any complications. Courtesy of Neal Halsey, MD.

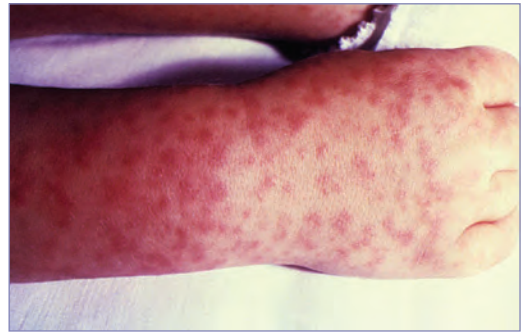


Image 123.6
A child's right hand and wrist displaying the spotted rash and edema of Rocky Mountain spotted fever. Courtesy of Centers for Disease Control and Prevention.

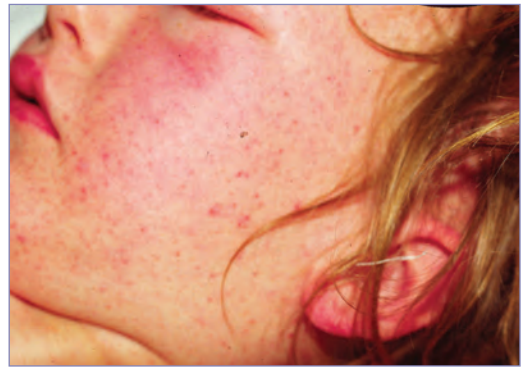


Image 123.7
A 7-year-old girl with severe Rocky Mountain spotted fever. Note the rash and edema secondary to diffuse vasculitis. Courtesy of Larry Frenkel, MD.

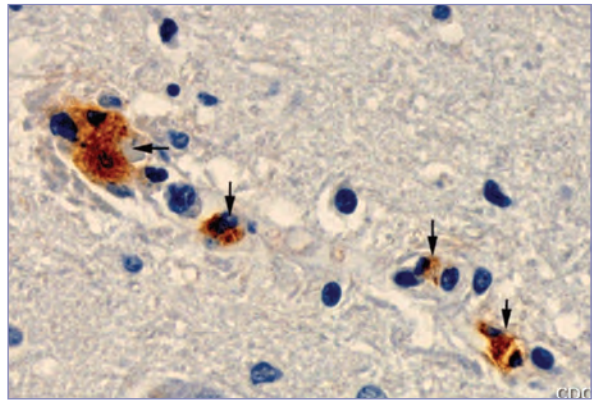


Image 123.8
Immunohistochemical analysis shows the presence of spotted fever group rickettsiae (brown) in vessels of the brain of a patient with fatal Rocky Mountain spotted fever (magnification ×400). Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases* and Marylin Hidalgo.

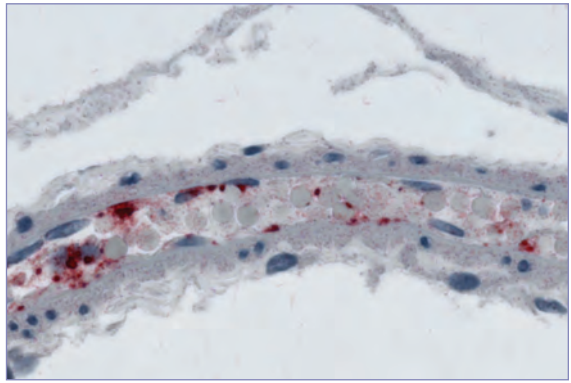


Image 123.9
Immunohistochemical staining of *Rickettsia rickettsii* in vascular endothelial cells in the cerebellum of a child with fatal Rocky Mountain spotted fever. Immunoalkaline phosphatase with naphthol fast red and hematoxylin counterstain (original magnification ×158). Courtesy of Christopher Paddock, MD.

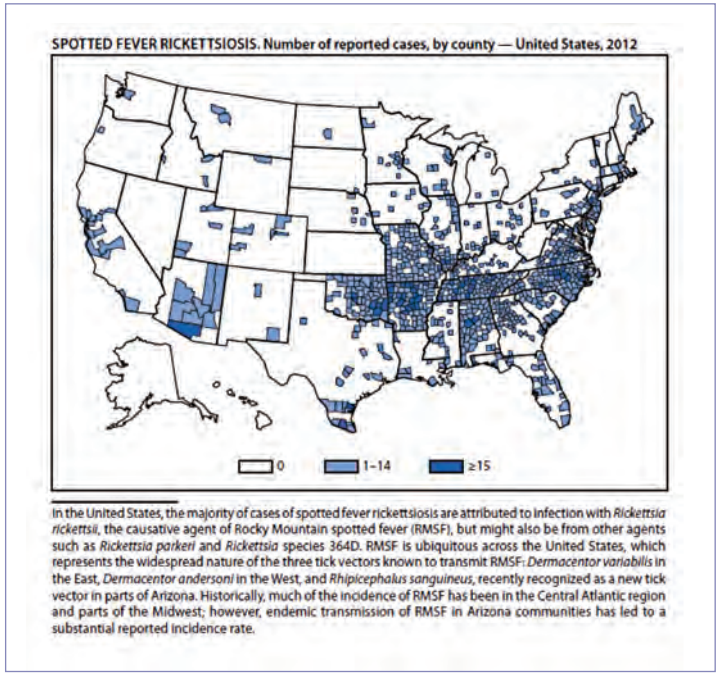


Image 123.10
Spotted fever rickettsiosis. Number of reported cases, by county—United States, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 123.11
This is a female lone star tick, *Amblyomma americanum*, and is found in the southeastern and mid-Atlantic United States. This tick is a vector of several zoonotic diseases, including human monocytic ehrlichiosis and Rocky Mountain spotted fever. Courtesy of Centers for Disease Control and Prevention.

Image 123.12
This image depicts a male brown dog tick, *Rhipicephalus sanguineus*, from a superior, or dorsal, view looking down on this hard tick's scutum, which entirely covers its back, identifying it as a male. In the female, the dorsal abdomen is only partially covered, thereby, offering room for abdominal expansion when she becomes engorged with blood while ingesting her blood meal obtained from her host. Courtesy of Centers for Disease Control and Prevention/James Gathany; William Nicholson.

CHAPTER 124

Rotavirus Infections

CLINICAL MANIFESTATIONS

The clinical manifestations vary and depend on whether it is the first infection or reinfection. After 3 months of age, the first infection generally is the most severe. Infection begins with acute onset of vomiting followed 24 to 48 hours later by watery diarrhea; up to one third of the patients will have high fevers. Signs generally persist for 3 to 7 days. In moderate to severe cases, dehydration, electrolyte abnormalities, and acidosis may occur. In certain immunocompromised children, including children with congenital cellular immunodeficiencies or severe combined immunodeficiency (SCID) and children who are hematopoietic stem cell or solid organ transplant recipients, severe, prolonged, and sometimes fatal rotavirus diarrhea may occur. The presence of rotavirus RNA in cerebrospinal fluid (CSF) has been detected in children with rotavirus-associated seizures.

ETIOLOGY

Rotaviruses are segmented, nonenveloped, double-stranded RNA viruses belonging to the family *Reoviridae*, with at least 8 distinct groups (A through H). Group A viruses are the major causes of rotavirus diarrhea worldwide. Genotyping is based on the 2 outer capsid proteins, VP7 glycoprotein (G) and VP4 protease-cleaved hemagglutinin (P). Before introduction of the rotavirus vaccine, genotypes G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] were the most common genotypes circulating in the United States. However, in 2012 and 2013, G12P[8] was the most common genotype identified.

EPIDEMIOLOGY

Rotavirus is present in high titer in stools of infected patients several days before and several days after onset of clinical disease. Transmission occurs via the fecal-oral route. Rotavirus is very stable and may remain infectious in the environment for weeks to months. Rotavirus can be found on toys and hard surfaces in child care centers, indicating that fomites may serve as a mechanism of transmission. Respiratory transmission may play a minor role in disease transmission. Spread within families and institutions is common. Rarely, common-source outbreaks from contaminated water or food have been reported.

In temperate climates, rotavirus disease is most prevalent during the cooler months. Before licensure of rotavirus vaccines in North America in 2006 and 2008, the annual rotavirus epidemic usually started during the fall in Mexico and the southwest United States and moved eastward, reaching the northeast United States and Maritime Provinces by spring. The seasonal pattern of disease is less pronounced in tropical climates, with rotavirus infection being more common during the cooler, drier months.

The epidemiology and burden of rotavirus disease in the United States has changed dramatically following the introduction of rotavirus vaccines in 2006 and 2008. Before widespread use of these vaccines, rotavirus was the most common cause of gastroenteritis in young children, the most common cause of health care-associated diarrhea in young children, and an important cause of acute gastroenteritis in children attending child care. Now, a biennial pattern has emerged, with small, short seasons beginning in late winter/early spring (eg, 2009, 2011, 2013, 2015) alternating with years with extremely low circulation (eg, 2008, 2010, 2012, 2014). Beginning in 2008, annual hospitalizations for rotavirus disease among US children younger than 5 years declined by approximately 75%, with an estimated 40,000 to 50,000 fewer rotavirus hospitalizations nationally each year. In case-control evaluations in the United States, the rotavirus vaccines (full series) have been found to be approximately 80% to 90% effective against rotavirus disease resulting in hospitalization. The vaccines also are highly effective in preventing rotavirus disease resulting in emergency department care.

The **incubation period** for rotavirus is short, usually less than 48 hours.

DIAGNOSTIC TESTS

It is not possible to diagnose rotavirus infection by clinical presentation or nonspecific laboratory tests. Enzyme immunoassays (EIAs), chromatographic immunoassays, and latex agglutination assays for group A rotavirus

antigen detection in stool are available commercially. EIAs are used most widely because of their high sensitivity and specificity and ease of use. A variety of multiplex nucleic acid-based assays for the detection of gastrointestinal pathogens, including rotavirus, are available for diagnosis. The major advantages of molecular diagnostic methods are increased sensitivity and the ability to detect viruses, including rotavirus, that are difficult to isolate in cell culture. Interpretation of assay results may be complicated by the frequent detection of viruses in fecal samples from asymptomatic children and the detection of multiple gastrointestinal pathogens in a single sample. Several standard or real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assays for detection of rotaviral-specific genomic RNA also are available.

The following tests are available in some research and reference laboratories: electron microscopy, polyacrylamide gel electrophoresis (PAGE) of viral RNA with silver staining, and viral culture. However, these tests generally are not used for rapid, acute diagnosis of rotaviral disease.

TREATMENT

Oral or parenteral fluids and electrolytes are given to prevent or correct dehydration. Orally administered Human Immune Globulin, administered as an investigational therapy in immunocompromised patients with prolonged infection, has decreased viral shedding and shortened the duration of diarrhea.

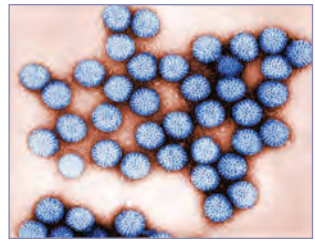


Image 124.1
Electron micrograph of intact rotavirus particles, double-shelled. Note the characteristic wheel-like appearance. Courtesy of Centers for Disease Control and Prevention.

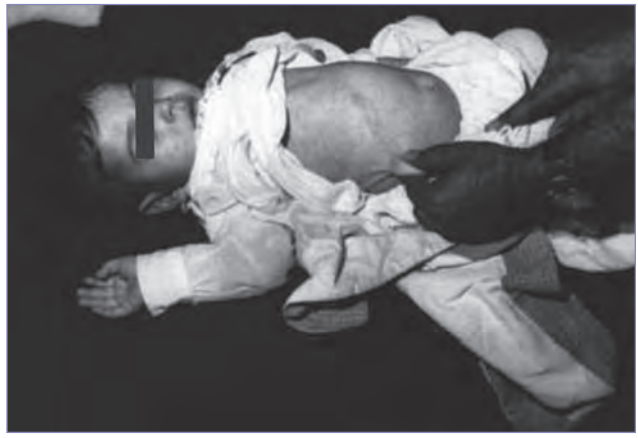


Image 124.2
Doctor examining a child dehydrated from rotavirus infection. In developing countries, rotavirus causes approximately 600,000 deaths each year in children younger than 5 years. Courtesy of World Health Organization.

CHAPTER 125

Rubella

CLINICAL MANIFESTATIONS

Postnatal Rubella

Many cases of postnatal rubella are subclinical. Clinical disease usually is mild and characterized by a generalized erythematous maculopapular rash, lymphadenopathy, and slight fever. The rash starts on the face, becomes generalized in 24 hours, and lasts a median of 3 days. Lymphadenopathy, which may precede rash, often involves posterior auricular or suboccipital lymph nodes, can be generalized, and lasts between 5 and 8 days. Conjunctivitis and palatal enanthem have been noted. Transient polyarthralgia and polyarthritis rarely occur in children but are common in adolescents and adults, especially among females. Encephalitis (1 in 6,000 cases) and thrombocytopenia (1 in 3,000 cases) are uncommon complications.

Congenital Rubella Syndrome

Maternal rubella during pregnancy can result in miscarriage, fetal death, or a constellation of congenital anomalies (congenital rubella syndrome [CRS]). The most commonly described anomalies/manifestations associated with CRS are ophthalmologic (cataracts, pigmentary retinopathy, microphthalmos, congenital glaucoma), cardiac (patent ductus arteriosus, peripheral pulmonary artery stenosis), auditory (sensorineural hearing impairment), or neurologic (behavioral disorders, meningoencephalitis, microcephaly, mental retardation). Neonatal manifestations of CRS include growth restriction, interstitial pneumonitis, radiolucent bone lesions, hepatosplenomegaly, thrombocytopenia, and dermal erythropoiesis (so-called "blueberry muffin" lesions); death may occur. Mild forms of the disease can be associated with few or no obvious clinical manifestations at birth. Congenital defects occur in up to 85% if maternal infection occurs during the first 12 weeks of gestation, 50% if infection occurs during 13 to 16 weeks of gestation, and 25% if infection occurs during the end of the second trimester. CRS is one of the few known causes of autism.

ETIOLOGY

Rubella virus is an enveloped, positive-stranded RNA virus classified as a *Rubivirus* in the *Togaviridae* family.

EPIDEMIOLOGY

Humans are the only source of infection. Postnatal rubella is transmitted primarily through direct or droplet contact from nasopharyngeal secretions. The peak incidence of infection is during late winter and early spring. Approximately 25% to 50% of infections are asymptomatic. Immunity from wild-type or vaccine virus usually is lifelong, but reinfection on rare occasions has been demonstrated and rarely has resulted in CRS. The period of maximal communicability extends from a few days before to 7 days after onset of rash. Rubella virus has been recovered in high titer from lens aspirates in children with congenital cataracts for several years, and a small proportion of infants with congenital rubella continue to shed virus in nasopharyngeal secretions and urine for 1 year or more, with transmission to susceptible contacts.

Before widespread use of rubella vaccine, rubella was an epidemic disease, occurring in 6- to 9-year cycles, with most cases occurring in children. In the postvaccine era, most cases in the mid-1970s and 1980s occurred in young unimmunized adults during outbreaks on college campuses and in occupational settings. More recent outbreaks have occurred in people born outside the United States or among underimmunized populations. The incidence of rubella in the United States has decreased by more than 99% from the prevaccine era.

The United States was determined no longer to have endemic rubella in 2004, and from 2004 through 2014, 94 cases of rubella and 9 cases of CRS were reported in the United States; all the cases were import associated or from unknown sources. A national serologic survey from 1999–2004 indicated that among children and adolescents 6 through 19 years of age, seroprevalence was approximately 95%. However, approximately 10% of adults 20 through 49 years of age lacked antibodies to rubella, although 92% of women were seropositive. The risk of CRS is highest in infants of

women born outside the United States, because these women are more likely to be susceptible to rubella.

In 2003, the Pan American Health Organization (PAHO) adopted a resolution calling for elimination of rubella and CRS in the Americas by the year 2010. The strategy consisted of achieving high levels of measles-rubella vaccination coverage in the routine immunization program and in the supplemental vaccination campaigns to rapidly reduce the number of people in the country susceptible to acute infection. The last confirmed endemic rubella case in the Americas was diagnosed in Argentina in February 2009.

The **incubation period** for postnatally acquired rubella ranges from 14 to 21 days, usually 16 to 18 days.

DIAGNOSTIC TESTS

Rubella

Detection of rubella-specific immunoglobulin (Ig) M antibody usually indicates recent postnatal infection, but both false-negative and false-positive results occur, requiring additional specialized testing in a reference laboratory. Most postnatal cases are IgM-positive by 5 days after symptom onset. For diagnosis of postnatally acquired rubella, a fourfold or greater increase in antibody titer between acute and convalescent periods or seroconversion between acute and convalescent IgG serum titers indicates infection. Acute serum must be collected as close to rash onset as possible.

CRS

CRS can be confirmed by detection of rubella-specific IgM antibody usually within the first 6 months of life. Congenital infection also can be confirmed by stable or increasing serum concentrations of rubella-specific IgG over the first 7 to 11 months of life. Diagnosis of congenital rubella infection in children older than 1 year is difficult because of routine vaccination with measles-mumps-rubella (MMR) vaccine; serologic testing usually is not diagnostic, and viral isolation, although confirmatory, is possible in only the small proportion of congenitally infected children who are still shedding virus at this age.

The most commonly used methods of serologic screening for previous rubella infection are enzyme immunoassays (EIAs) and latex agglutination tests. As a rule, both IgM and IgG antibody testing should be performed for suspected cases of both congenital and postnatal rubella, because both results may contribute to the diagnosis.

A false-positive IgM test result may be caused by several factors including rheumatoid factor, parvovirus IgM, and heterophile antibodies. The use of IgM-capture EIA may reduce the occurrence of false-positive IgM results. The presence of high-avidity IgG or a lack of increase in IgG titers can be useful in identifying false-positive rubella IgM results. Low-avidity IgG is associated with recent primary rubella infection, whereas high-avidity IgG is associated with past infection or reinfection or with previous vaccination. The avidity assay is not a routine test and should be performed at reference laboratories like the Centers for Disease Control and Prevention (CDC).

Rubella virus can be isolated most consistently from throat or nasal swab specimens (and less consistently urine) by inoculation of appropriate cell culture. Detection of rubella virus RNA by real-time reverse-transcriptase polymerase chain reaction (RT-PCR) from a throat/nasal swab or urine sample with subsequent genotyping of strains may be valuable for diagnosis and molecular epidemiology. There are currently no RT-PCR assays cleared by the US Food and Drug Administration for rubella, but testing generally is available in commercial and public health laboratories. In most postnatal cases, viral detection is possible by culture or RT-PCR assay on the day of symptom onset, and in most congenital cases, viral detection is possible at birth and in some cases for up to 12 months. Laboratory personnel should be notified immediately that rubella is suspected, because specialized cell culture methods are required to isolate and identify the virus. Blood, urine, and cataract specimens also may yield virus, particularly in infants with congenital infection. With the successful elimination of indigenous rubella and CRS in the Western Hemisphere,

molecular typing of viral isolates is critical in defining a source in outbreak scenarios as well as for sporadic cases.

TREATMENT

Supportive.

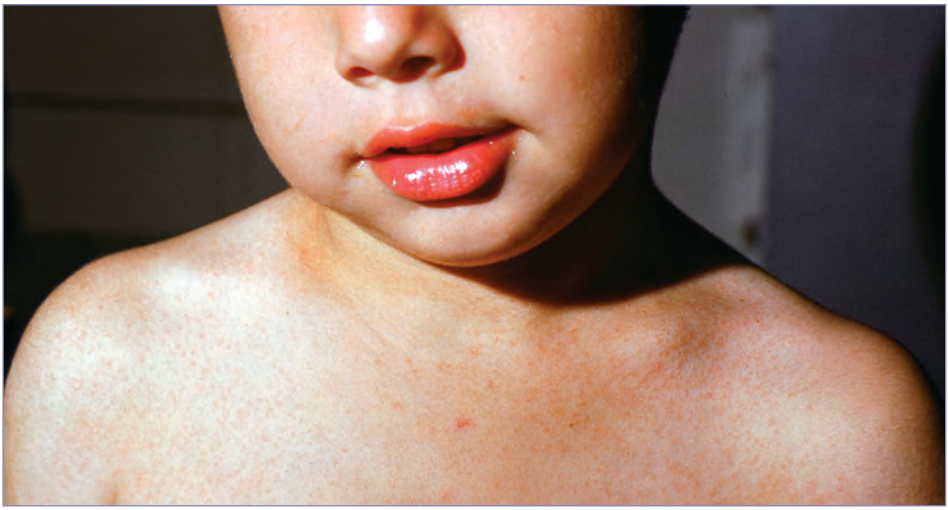


Image 125.1
This 5-year-old Hawaiian boy developed the fine macular rash noted on his face and chest. He had serologically confirmed rubella. Courtesy of Neal Halsey, MD.

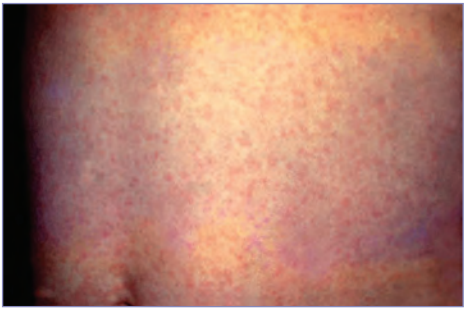


Image 125.2
This patient presented with a generalized rash on the abdomen caused by rubella. The rash usually lasts about 3 days and may be accompanied by a low-grade fever. Rubella is caused by a different virus than the one that causes regular measles. Immunity to rubella does not protect a person from measles or vice versa. Courtesy of Centers for Disease Control and Prevention

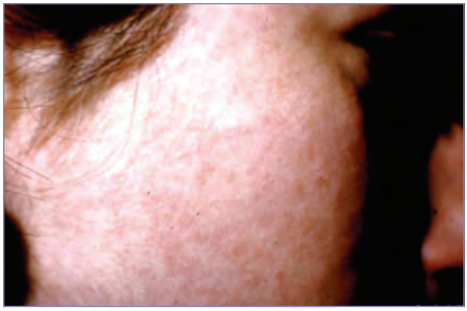


Image 125.3
Rubella rash (face) in a previously unimmunized female. Adenovirus and enterovirus infections can cause exanthema that mimics rubella. Serologic testing is important if the patient is pregnant.

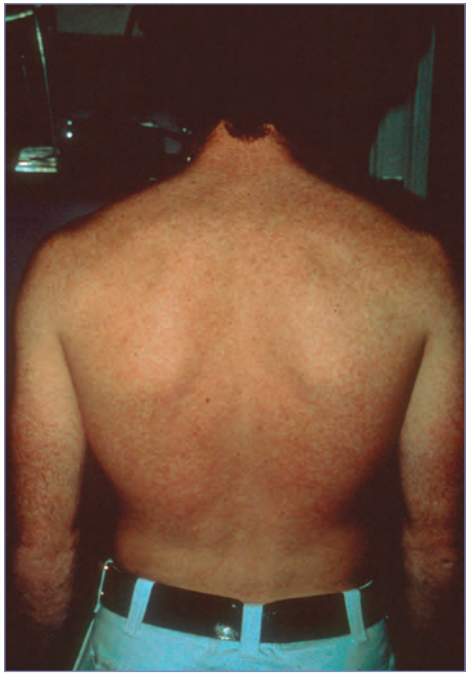


Image 125.4
A generalized, non-pruritic rash of rubella over the posterior trunk and arms of a 17-year-old boy with rubella. Courtesy of George Nankervis, MD.

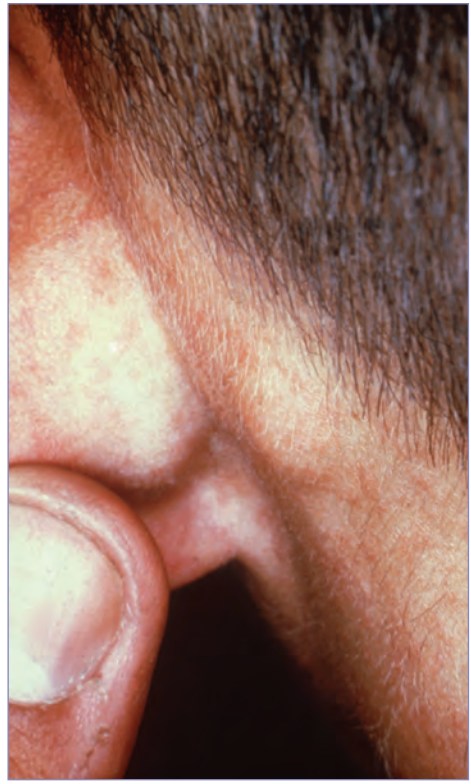


Image 125.5
Postauricular lymphadenopathy in the same 17-year-old with rubella as in Image 125.4. Courtesy of George Nankervis, MD.

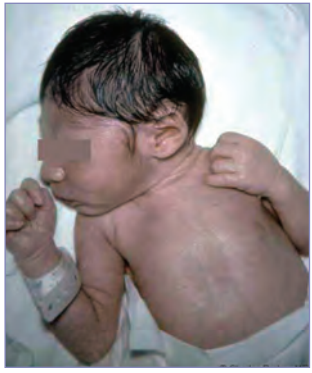


Image 125.6
Infant boy with congenital rubella with microcephaly. Copyright Charles Prober.

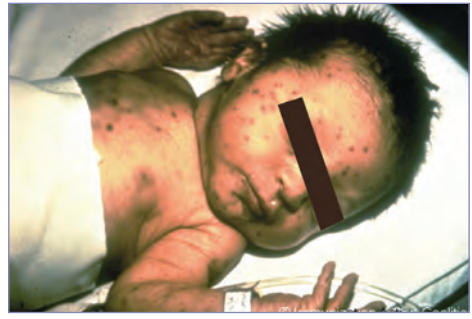


Image 125.7
Newborn with congenital rubella rash. Courtesy of Immunization Action Coalition.

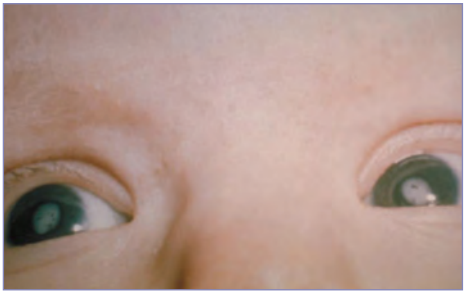


Image 125.8
This photograph shows the cataracts in an infant's eyes due to congenital rubella syndrome. Rubella is a viral disease that can affect susceptible persons of any age. Although generally a mild rash, if contracted in early pregnancy, there can be a high rate of fetal wastage or birth defects, known as congenital rubella syndrome. Courtesy of Centers for Disease Control and Prevention.

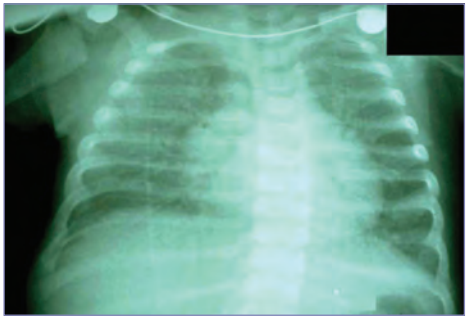


Image 125.10
Radiograph of the chest and upper abdomen of an infant with congenital rubella pneumonia with hepatosplenomegaly.

Image 125.12
A 1-month-old with congenital rubella syndrome with bilateral cataracts. Courtesy of Larry Frenkel, MD.

Image 125.9
A 4-year-old boy with congenital rubella syndrome with unilateral microphthalmos and cataract formation in the left eye.

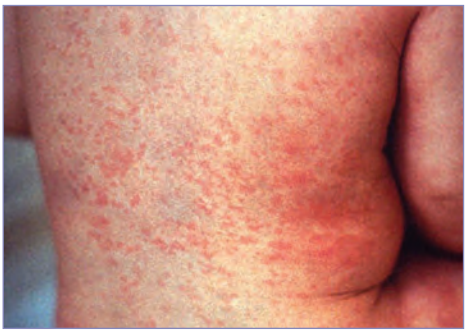


Image 125.11
Rubella rash on a child's back. The distribution is similar to that of measles, although the lesions are less intensely red. Courtesy of Centers for Disease Control and Prevention.

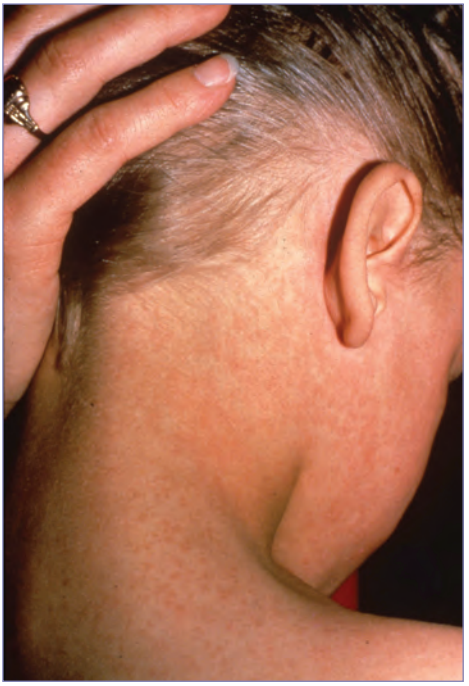


Image 125.13
Rubella on the neck. Courtesy of James Brien, DO.

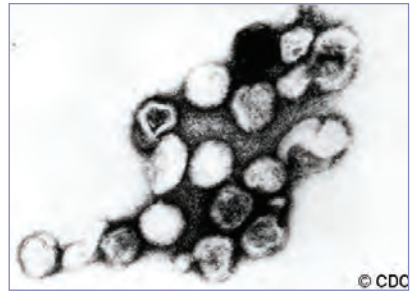


Image 125.14
Transmission electron micrograph of rubella virus. Rubella virus is an enveloped, positive-strand RNA virus classified as a *Rubivirus* in the *Togaviridae* family. Courtesy of Centers for Disease Control and Prevention.

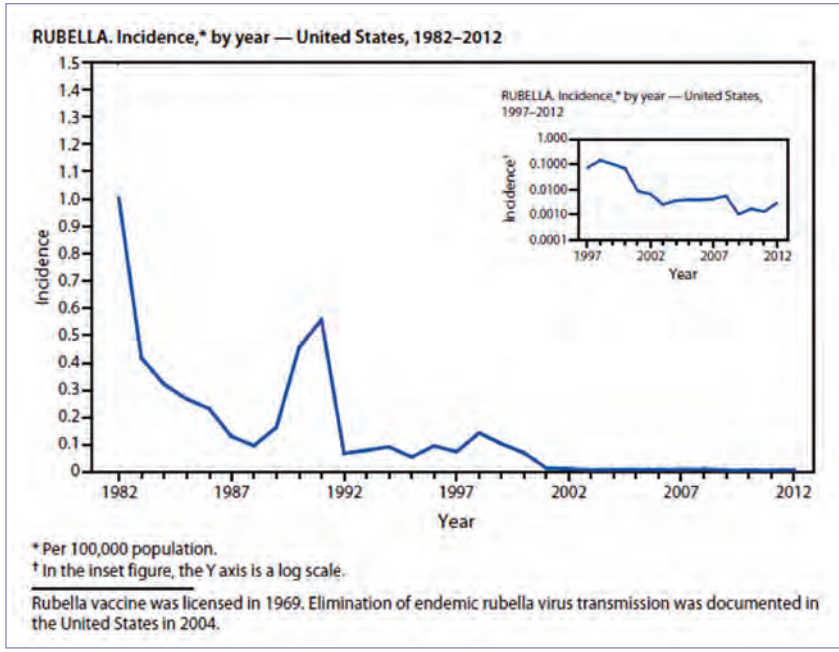


Image 125.15
Rubella. Incidence, by year—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 126

Salmonella Infections

CLINICAL MANIFESTATIONS

Nontyphoidal *Salmonella* Infection

Nontyphoidal *Salmonella* (NTS) infection is associated with a spectrum of illness ranging from asymptomatic gastrointestinal tract carriage to gastroenteritis, urinary tract infection, bacteremia, and focal infections, including meningitis, brain abscess, and osteomyelitis (to which people with sickle cell anemia are predisposed). The most common illness associated with NTS infection is gastroenteritis, with manifestations of diarrhea, abdominal cramps, and fever. The site of infection usually is the distal small intestine as well as the colon. Sustained or intermittent bacteremia can occur, and focal infections are recognized in up to 10% of patients with NTS bacteremia. In the United States, the incidence of invasive *Salmonella* infection is highest among infants.

Enteric Fever

Salmonella enterica serovars Typhi, Paratyphi A, Paratyphi B, and (rarely) Paratyphi C can cause a protracted bacteremic illness referred to, respectively, as typhoid and paratyphoid fever and collectively as **enteric fevers.** In older children, the onset of enteric fever typically is gradual, with manifestations such as fever, constitutional symptoms (eg, headache, malaise, anorexia, lethargy), abdominal pain, hepatomegaly, splenomegaly, dactylitis, and rose spots (present in approximately 30%); change in mental status and shock may ensue. Myocarditis or endocarditis occur rarely. In infants and toddlers, invasive infection with enteric fever serovars can manifest as a mild, nondescript febrile illness accompanied by self-limited bacteremia, or invasive infection can occur in association with more severe clinical symptoms and signs, sustained bacteremia, and meningitis. Either diarrhea (resembling pea soup) or constipation can be early features. Gastrointestinal tract bleeding occurs in approximately 10%. Relative bradycardia (pulse rate slower than would be expected for a given body temperature) has been considered a common feature of typhoid fever in adults but in children is not a discriminating feature.

ETIOLOGY

Salmonella organisms are gram-negative bacilli that belong to the family *Enterobacteriaceae.* Current taxonomy recognizes 2 *Salmonella* species: *S enterica* with 6 subspecies and *Salmonella bongori. S enterica* subspecies enterica is responsible for the vast majority of infections in humans and other warm-blooded animals; the other *S enterica* subspecies and *S bongori* usually are isolated from cold-blooded animals. More than 2,500 *Salmonella* serovars have been described; most serovars causing human disease are classified within O serogroups A through E. *Salmonella* serovar Typhi is classified in O serogroup D, along with many other common serovars including Enteritidis and Dublin. In 2011, the most commonly reported human isolates in the United States were *Salmonella* serovars Enteritidis, Typhimurium, Newport, and Javiana; these 5 serovars generally account for nearly half of all *Salmonella* infections in the United States.

The relative prevalence of other serovars varies by country. Approximately 75% to 95% of the serovars associated with invasive pediatric disease in sub-Saharan Africa are *Salmonella* serovar Typhimurium.

EPIDEMIOLOGY

Every year, NTS organisms are among the most common causes of laboratory-confirmed cases of enteric disease. The principal reservoirs for NTS organisms include birds, mammals, reptiles, and amphibians. The major food vehicles of transmission to humans in industrialized countries include food of animal origin, such as poultry, beef, eggs, and dairy products. Multiple other food vehicles (eg, fruits, vegetables, peanut butter, frozen pot pies, powdered infant formula, cereal, and bakery products) have been implicated in outbreaks in the United States and Europe, presumably when the food was contaminated by contact with an infected animal product or a human carrier. Other modes of transmission include ingestion of contaminated water or contact with infected animals, mainly poultry (eg, chicks, chickens, ducks), reptiles or amphibians (eg, pet turtles, iguanas, geckos, bearded dragons, lizards, snakes, frogs, toads, newts, salamanders), and

rodents (eg, hamsters, mice) or other mammals (eg, hedgehogs, guinea pigs). Reptiles and amphibians that live in tanks or aquariums can contaminate the water with bacteria, which can spread to people. Small turtles with a shell length of less than 4 inches are a well-known source of human *Salmonella* infections. Because of this risk, the US Food and Drug Administration (FDA) has banned the interstate sale and distribution of these turtles since 1975. Animal-derived pet foods and treats also have been linked to *Salmonella* infections, especially among young children.

Unlike NTS serovars, the enteric fever serovars (*Salmonella* serovars Typhi, Paratyphi A, Paratyphi B [*sensu stricto*]) are restricted to human hosts, in whom they cause clinical and subclinical infections. Chronic human carriers (mostly involving chronic infection of the gall bladder but occasionally involving infection of the urinary tract) constitute the reservoir in areas with endemic infection. Infection with enteric fever serovars implies ingestion of a food or water vehicle contaminated by a chronic carrier or person with acute infection. Although typhoid fever (300–400 cases annually) and paratyphoid fever (~150 cases annually) are uncommon in the United States, these infections are highly endemic in many resource-limited countries, particularly in Asia. Consequently, most typhoid fever and paratyphoid fever infections in US residents are acquired during international travel.

The incidence of NTS infection is highest in children younger than 4 years. In the United States, rates of invasive infections and mortality are higher in infants, elderly people, and people with hemoglobinopathies (including sickle cell disease) and immunocompromising conditions (eg, malignant neoplasms, HIV infection). Most reported cases are sporadic, but widespread outbreaks, including health care-associated and institutional outbreaks, have been reported. The incidence of foodborne cases of NTS gastroenteritis has diminished slightly in recent years.

A risk of transmission of infection to others persists for as long as an infected person excretes NTS organisms. Twelve weeks after infection with the most common NTS serovars, approximately 45% of children younger than 5 years excrete organisms compared with 5% of older children and adults; antimicrobial therapy can prolong excretion. Approximately 1% of adults continue to excrete NTS organisms for more than 1 year.

The **incubation period** for NTS gastroenteritis is 6 to 48 hours (a week or more has been reported). For enteric fever, the **incubation period** is 7 to 14 days (range, 3–60 days).

DIAGNOSTIC TESTS

Isolation of *Salmonella* organisms from cultures of stool, blood, urine, bile (including duodenal fluid containing bile), and material from foci of infection is diagnostic. Gastroenteritis is diagnosed by stool culture; stool cultures should be obtained in all children with unexplained persistent or severe diarrhea and or those with bloody diarrhea. Optimum recovery of *Salmonella* from stool is achieved with the use of enrichment broth and multiple selective agar plate media. Definitive identification requires confirmation by either phenotypic methods (biochemical profiling) or mass spectrometry of cellular components and O serogroup determination. Serovar (serotype) determination is helpful and is usually performed at public health laboratories.

Diagnostic tests to detect *Salmonella* antigens by enzyme immunoassay, latex agglutination, and monoclonal antibodies have been developed, as have commercial immunoassays that detect antibodies to antigens of enteric fever serovars. The latter tests are more important in areas of the world where typhoid fever is endemic.

Gene-based polymerase chain reaction (PCR) diagnostic tests also are available in research laboratories. Several multiplex PCR platforms for detection of multiple viral, parasitic, and bacterial pathogens, including *Salmonella*, directly in stool are available, but there is limited clinical experience with these assays. In general, laboratories should maintain culture capabilities for *Salmonella* species and other bacterial enteric pathogens, because antimicrobial susceptibility testing and serotyping generally are important for treatment and epidemiologic surveillance. In addition, state public

health laboratories require isolates for genomic characterization of strains, which is needed for outbreak detection and investigation.

If enteric fever is suspected, blood, bone marrow, or bile culture is diagnostic, because organisms often are absent from stool. The sensitivity of blood culture and bone marrow culture in children with enteric fever is approximately 60% and 90%, respectively. The combination of a single blood culture plus culture of bile (collected from a bile-stained duodenal string) is 90% sensitive in detecting *Salmonella* serovar Typhi infection in children with clinical enteric fever.

TREATMENT

Antimicrobial therapy usually is not indicated for patients with either asymptomatic infection or uncomplicated gastroenteritis caused by NTS serovars, because therapy does not shorten the duration of diarrheal disease and can prolong duration of fecal excretion. Although of unproven benefit, antimicrobial therapy is recommended for gastroenteritis caused by NTS serovars in people at increased risk for invasive disease, including infants younger than 3 months and people with chronic gastrointestinal tract disease, malignant neoplasms, hemoglobinopathies, HIV infection, or other immunosuppressive illnesses or therapies.

If antimicrobial therapy is initiated in patients in the United States with presumed or proven NTS gastroenteritis, a blood culture should be obtained prior to antibiotic administration and an initial dose of ceftriaxone should be given. The patient who does not appear ill or have evidence of disseminated infection can be discharged with oral azithromycin pending blood culture results. Ampicillin or trimethoprim-sulfamethoxazole (TMP/SMX) may be considered for susceptible strains, once susceptibilities are available. A fluoroquinolone is an alternative option. For those who appear ill or have evidence of disseminated infection, hospitalization is required.

For bacteremia caused by NTS, disseminated disease (meningitis, osteoarticular infection, endocarditis) should be excluded. Blood cultures should be repeated until negative. Initial therapy with ceftriaxone should be given. Transition from intravenous ceftriaxone to oral azithromycin or a fluoroquinolone may be considered after the blood culture has cleared and focal disease has been excluded, for a total 7- to 10-day course.

For meningitis, the duration of treatment should be 4 weeks, and for osteomyelitis or other focal metastatic infections, a duration of 4 to 6 weeks is recommended. Evaluation for underlying immunodeficiency (eg, asplenia, HIV) should be considered.

For enteric fever caused by *Salmonella* serovar Typhi that is known or likely to be multidrug resistant, empiric therapy with azithromycin or a parenteral third-generation cephalosporin should be initiated. A fluoroquinolone is an alternative option depending on the region of acquisition. Drugs of choice, route of administration, and duration of therapy are based on susceptibility of the organism, knowledge of the antimicrobial susceptibility patterns of prevalent strains, site of infection, host, and clinical response. The optimal duration of therapy is unclear, but most experts would treat for at least 7 days for people with uncomplicated disease. Notably, in some highly endemic regions of South and Southeast Asia, the proportion of multidrug-resistant *Salmonella* serovar Typhi strains is diminishing, and strains susceptible to amoxicillin and TMP/SMX are becoming increasingly common; if amoxicillin or TMP/SMX is considered based on susceptibility testing, a 14-day course of therapy should be considered. Relapse of typhoidal *Salmonella* infection can occur in up to 17% of patients within 4 weeks and is a particular risk for immunocompromised patients, who may require longer duration of treatment and retreatment. Relapse rates appear to be lower in those treated with azithromycin than with fluoroquinolones or ceftriaxone. Aminoglycosides are not recommended for treatment of invasive *Salmonella* infections. For enteric fever caused by *Salmonella* serovar Typhi acquired from overseas travel, culture should be performed on stool samples from all people who traveled with the index case(s), and if results are positive, treatment should be initiated with azithromycin or a fluoroquinolone and the patient should be monitored for development of any symptoms.

Asymptomatic people in the United States who had contact with the index case(s) but did not travel overseas with them do not require culture of stool samples. Blood and stool cultures (positive in 30%) should be obtained for all children who present with unexplained fever after travel to resource poor countries.

The propensity to become a chronic *Salmonella* serovar Typhi carrier (excretion longer than 1 year) following acute typhoid infection correlates with prevalence of cholelithiasis, increases with age, and is greater in females than males. Chronic carriage in children is uncommon. The chronic carrier state may be eradicated by 4 weeks of oral therapy with ciprofloxacin or norfloxacin, which are antimicrobial agents that are highly concentrated in bile. High-dose parenteral ampicillin also can be used if 4 weeks of oral fluoroquinolone therapy is not well tolerated and if the strain is susceptible. Cholecystectomy followed by another course of antimicrobial agents may be indicated in some adults if antimicrobial therapy alone fails.

Corticosteroids may be beneficial in children with severe enteric fever, which is characterized by delirium, obtundation, stupor, coma, or shock. These drugs should be reserved for critically ill patients in whom relief of manifestations of toxemia may be lifesaving. The usual regimen is high-dose dexamethasone administered intravenously every 6 hours for 48 hours.

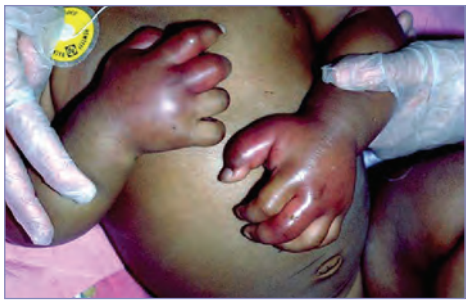


Image 126.1
A young child with sickle cell disease and *Salmonella* sepsis with swelling of the hands. Probable diagnosis: acute sickle cell dactylitis with septicemia. Copyright Martin G. Myers, MD.

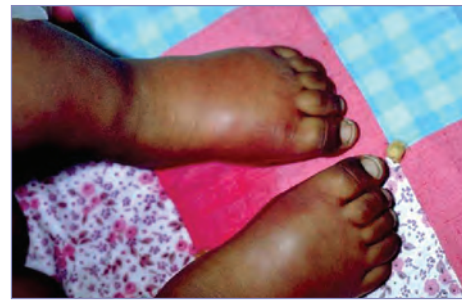


Image 126.2
A young child with sickle cell dactylitis of the foot and *Salmonella* sepsis. This is the same patient as in Image 126.1. Copyright Martin G. Myers, MD.

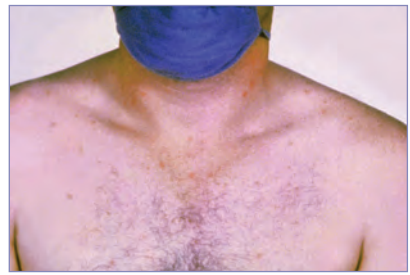


Image 126.3
Rose spots on the chest of a patient with typhoid fever due to the bacterium *Salmonella* ser Typhi. Symptoms of typhoid fever may include a sustained fever as high as 39.4°C to 40.0°C (103°F–104°F), weakness, stomach pains, headache, and loss of appetite. In some cases, patients have a rash of flat, rose-colored spots. Courtesy of Centers for Disease Control and Prevention.

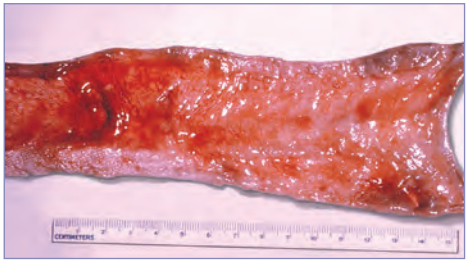


Image 126.4
Typhoid fever cholecystitis with an ulceration and perforation of the gallbladder into the jejunum. *Salmonella* ser Typhi, the bacterium responsible for causing typhoid fever, has a preference for the gallbladder and, if present, will colonize the surface of gallstones, which is how people become long-term carriers of the disease. Courtesy of Centers for Disease Control and Prevention.

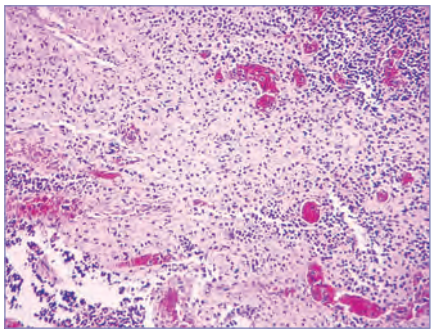


Image 126.5
Histopathology of the gallbladder in a case of typhoid fever. *Salmonella* ser Typhi, the bacterium responsible for causing typhoid fever, has a preference for the gallbladder and, if present, will colonize the surface of gallstones, which is how people become long-term carriers of the disease. Courtesy of Centers for Disease Control and Prevention.

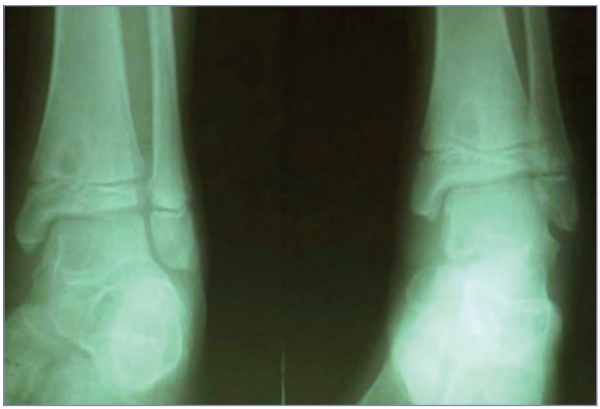


Image 126.6
Osteomyelitis due to *Salmonella* infection of the distal tibia.

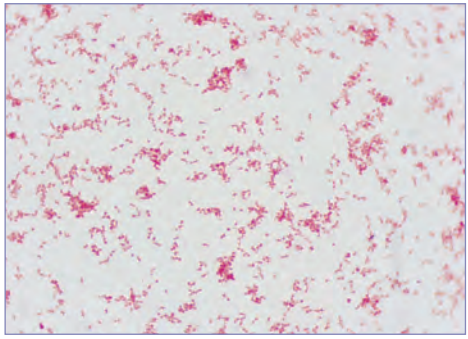


Image 126.7
Gram stain of *Salmonella* species. Courtesy of Rita Yee, MT(ASCP)SM.

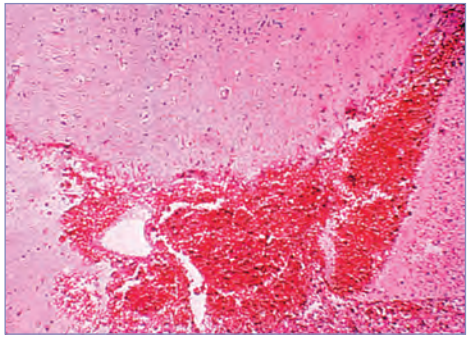


Image 126.9
Histopathologic changes in brain tissue due to *Salmonella* ser Typhi meningitis. *Salmonella* septicemia has been associated with subsequent infection of virtually every organ system, and the nervous system is no exception. Courtesy of Centers for Disease Control and Prevention.

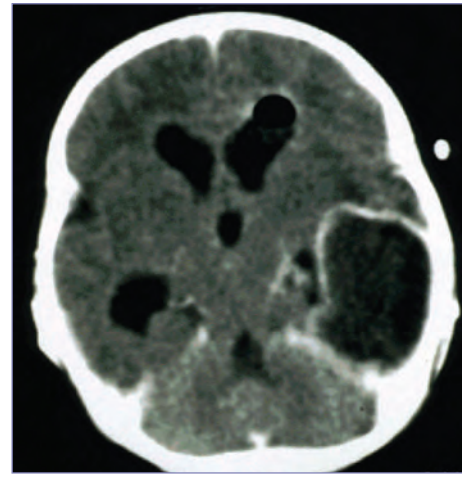


Image 126.8
A computed tomography scan showing a large brain abscess in the posterior parietal region as a complication of *Salmonella* meningitis in a neonate.

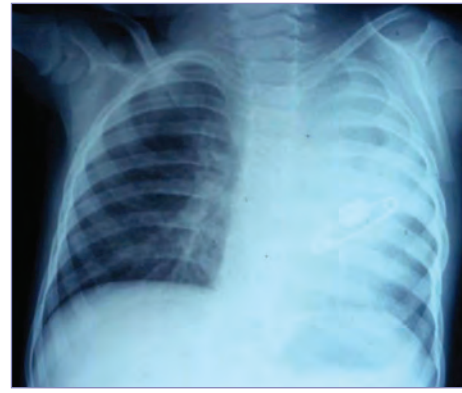


Image 126.10
Salmonella pneumonia with empyema in a 3-year-old girl with congenital neutropenia who required chest tube drainage and prolonged antibiotic treatment to control extensive pneumonia due to a nontyphoidal *Salmonella* species. Courtesy of Edgar O. Ledbetter, MD, FAAP.

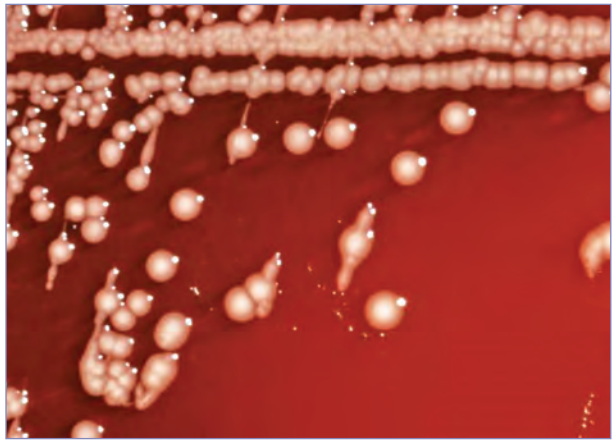


Image 126.11
This image depicts the colonial growth pattern displayed by *Salmonella enterica* subsp *arizonae* grown on blood agar, also known as *S arizonae* or *Arizona hinshawii*. *Salmonella* species are gram-negative, aerobic, rod-shaped, zoonotic bacteria that can infect people, birds, reptiles, and other animals. Courtesy of Centers for Disease Control and Prevention.

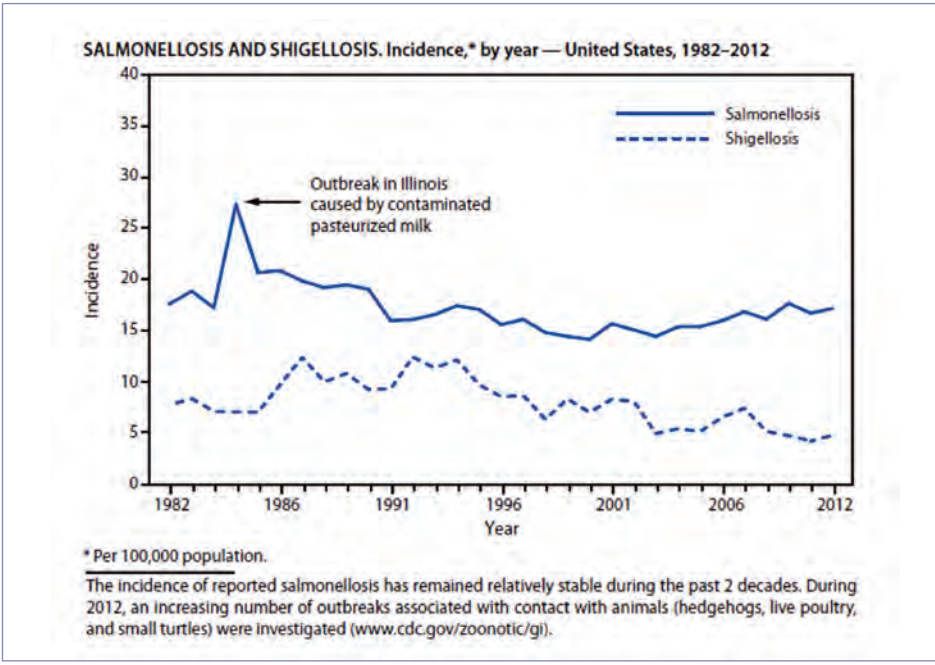


Image 126.12
Salmonellosis and shigellosis. Incidence, by year—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report* .

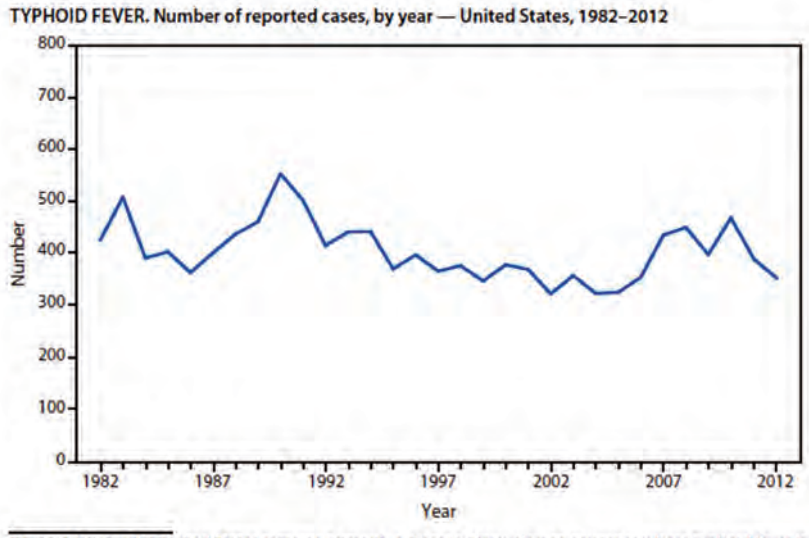


Image 126.13
Typhoid fever. Number of reported cases, by year, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report* .

Image 126.14
African dwarf frog. *Salmonella* infection can be acquired through contact with reptiles and amphibians in homes, petting zoos, parks, child care facilities, and other locations. Courtesy of Centers for Disease Control and Prevention.

Image 126.15
Turtles carry *Salmonella*. The sale of turtles less than 4 inches in length has been banned in the United States since 1975. The ban by the US Food and Drug Administration has prevented an estimated 100,000 cases of salmonellosis annually in children. Courtesy of Centers for Disease Control and Prevention/James Gathany.

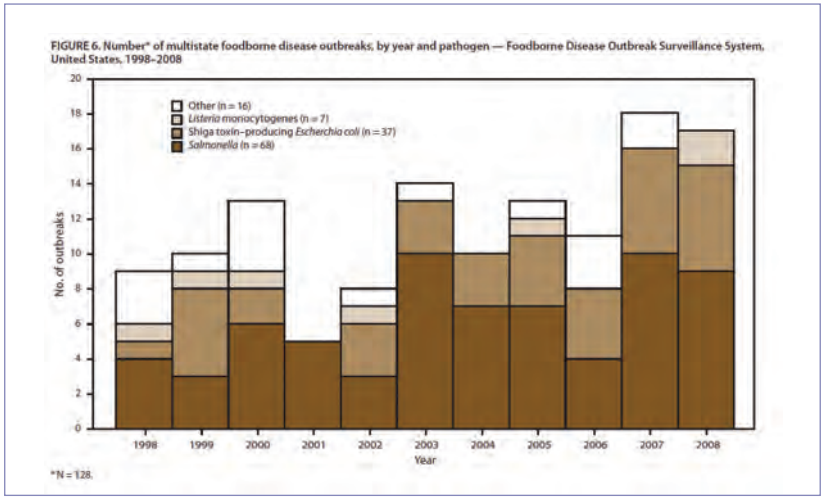


Image 126.16
Number of multistate foodborne disease outbreaks, by year and pathogen—Foodborne Disease Outbreak Surveillance System, United States, 1998–2008. Courtesy of *Morbidity and Mortality Weekly Report*.

CHAPTER 127

Scabies

CLINICAL MANIFESTATIONS

Scabies is characterized by an intensely pruritic, erythematous eruption that may include papules, nodules, vesicles, or bullae and is caused by burrowing of adult female mites in upper layers of the epidermis, creating serpiginous burrows. Itching is most intense at night. In older children and adults, the sites of predilection are interdigital folds, flexor aspects of wrists, extensor surfaces of elbows, anterior axillary folds, waistline, thighs, navel, genitalia, areolae, abdomen, intergluteal cleft, and buttocks. In children younger than 2 years, the eruption more often is vesicular and often occurs in areas usually spared in older children and adults, such as the scalp, face, neck, palms, and soles. The eruption is caused by a hypersensitivity reaction to the proteins of the parasite.

Characteristic scabietic burrows appear as thin, gray or white, serpiginous, threadlike lines. Excoriations are common, and most burrows are obliterated by scratching before a patient seeks medical attention. Occasionally, 2- to 5-mm red-brown nodules are present, particularly on covered parts of the body, such as the genitalia, groin, and axilla. These scabies nodules are a granulomatous response to dead mite antigens and feces; the nodules can persist for weeks and even months after effective treatment. Cutaneous secondary bacterial infection is a frequent complication and usually is caused by *Streptococcus pyogenes* or *Staphylococcus aureus.* Studies have demonstrated a correlation between poststreptococcal glomerulonephritis and scabies.

Crusted (formerly called Norwegian) scabies is an uncommon clinical syndrome characterized by a large number of mites and widespread, crusted, hyperkeratotic lesions. Crusted scabies usually occurs in people with debilitating conditions, people with developmental disabilities, or people who are immunocompromised, including patients receiving biologic response modifiers. It also can occur in healthy children using prolonged topical corticosteroid therapy.

Post-scabietic pustulosis is a reactive phenomenon that may follow successful treatment of primary infestation with scabies. Affected infants and young children have episodic crops of sterile, pruritic papules and pustules predominantly in an acral distribution, but lesions may extend to a lesser degree onto the torso.

ETIOLOGY

The mite *Sarcoptes scabiei* subspecies *hominis* is the cause of scabies. The adult female burrows in the stratum corneum of the skin and lays eggs. Larvae emerge from the eggs in 2 to 4 days, molt to nymphs, and then to adults, which mate and produce new eggs. The entire cycle takes about 10 to 17 days. *S scabiei* subspecies *canis,* acquired from dogs (with mange), can cause a self-limited and mild infestation in humans usually involving the area in direct contact with the infested animal.

EPIDEMIOLOGY

Humans are the source of infestation. Transmission usually occurs through prolonged close, personal contact. Because of the large number of mites in exfoliating scales, even minimal contact with patients with crusted scabies or their immediate environment can result in transmission. Infestation acquired from dogs and other animals is uncommon; these mites do not replicate in humans. Scabies of human origin can be transmitted as long as the patient remains infested and untreated, including during the interval before symptoms develop. Scabies is endemic in many countries and occurs worldwide in cycles thought to be 15 to 30 years long. Scabies affects people from all socioeconomic levels without regard to age, gender, or standards of personal hygiene. Scabies in adults often is acquired sexually.

The **incubation period** in naive people usually is 4 to 6 weeks. People who previously were infested are sensitized and develop symptoms 1 to 4 days after exposure to the mite; however, these reinfestations usually are milder than the original episode.

DIAGNOSTIC TESTS

Diagnosis of scabies typically is made by clinical examination. Diagnosis can be confirmed by identification of the mite or mite eggs or scybala (feces) from scrapings of papules or

intact burrows, preferably from the terminal portion where the mite generally is found. Mineral oil, microscope immersion oil, or water applied to skin facilitates collection of scrapings. A broad-blade scalpel is used to scrape the burrow. Scrapings and oil can be placed on a slide under a glass coverslip and examined microscopically under low power. Adult female mites average 330 to 450 μm in length. Skin scrapings provide definitive evidence of infection but have low sensitivity. Handheld dermoscopy (epiluminescence microscopy) has been used to identify in vivo the pigmented mite parts or air bubbles corresponding to infesting mites within the stratum corneum. Reflectance in vivo microscopy and polymerase chain reaction assays on swabbed skin material are promising techniques with improved sensitivity and specificity.

TREATMENT

Topical permethrin 5% cream or off-label use of oral ivermectin both are effective agents. Most experts recommend topical 5% permethrin cream as the drug of choice, particularly for infants, young children, and pregnant or nursing women. Permethrin cream should be removed by bathing after 8 to 14 hours. Children and adults with infestation should apply lotion or cream containing this scabicide over their entire body below the head. Permethrin kills the scabies mite and eggs. Two (or more) applications, each about a week apart, may be necessary to eliminate all mites. Because scabies can affect the face, scalp, and neck in infants and young children, treatment of the entire head, neck, and body in this age group is required. Fingernails should be trimmed, and medication should be applied to head, neck and body.

Because ivermectin is not ovicidal, it is given as 2 doses, 7 to 14 days apart. Oral ivermectin should be considered for patients who have failed treatment or who cannot tolerate topical treatment. The safety of ivermectin in children weighing less than 15 kg (33 lb) has not been determined. Ivermectin is not recommended for pregnant or lactating women.

Alternative drugs include 10% crotamiton cream or lotion, or 5% to 10% precipitated sulfur compounded into petrolatum. Because scabietic lesions are the result of a hypersensitivity reaction to the mite, itching may not subside for several weeks despite successful treatment. The use of oral antihistamines and topical corticosteroids can help relieve this itching. Topical or systemic antimicrobial therapy is indicated for secondary bacterial infections of the excoriated lesions. Lindane lotion should not be used in the treatment of scabies.

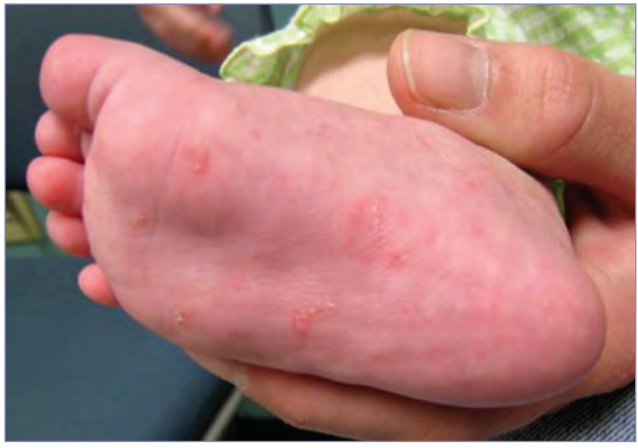


Image 127.1
A 2-year-old girl with scabies who was adopted from an orphanage in Eastern Europe. Courtesy of Daniel P. Krowchuk, MD, FAAP.

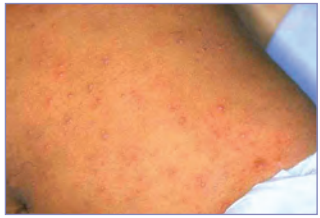


Image 127.2
Scabies rash in an infant. Copyright James Brien, DO.

Image 127.4
Scabies in an infant with striking hand involvement. Copyright James Brien, DO.

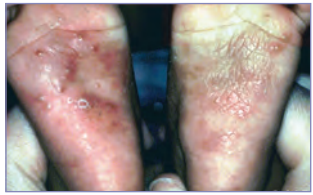


Image 127.6
Papulopustules and excoriation of the soles of the feet of an infant with severe scabies.

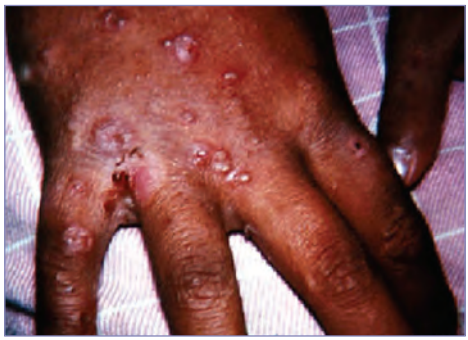


Image 127.8
Older children, adolescents, and adults with scabies exhibit erythematous papules, nodules, or burrows in the interdigital webs, as in this patient.

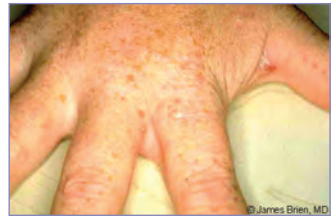


Image 127.3
Scabies in the hands of the mother of the infant in Image 127.2. Copyright James Brien, DO.

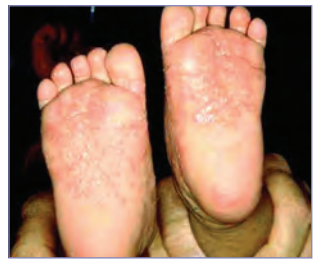


Image 127.5
Scabies in an infant with striking involvement of the feet. Copyright James Brien, DO.

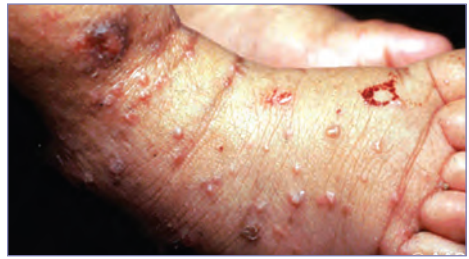


Image 127.7
Papulopustules and a widespread eczematous eruption, which represents a hypersensitivity reaction to a scabies infestation.

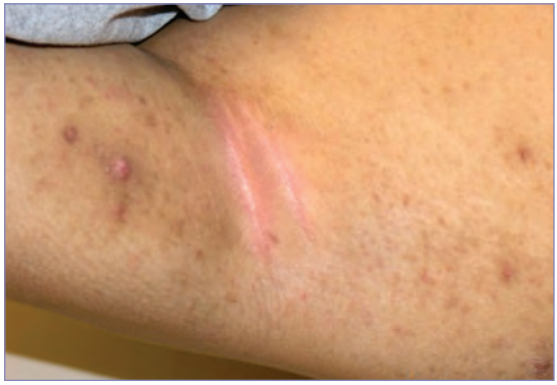


Image 127.9
A 12-year-old with itching in the axillae and groin for 2 weeks. She recently returned from a family camping trip, where she shared a tent with "dozens of cousins." Since returning home, she has had itching in the armpits and in her pubic area. She now has papules and pustules on the fingers, toes, and her gluteal furrow. The family is reluctant to inquire about relatives with similar lesions. Examination of scrapings of the lesions indicated a few oval structures suggestive of scabies eggs. She responded to treatment with topical sulfur and oil in lieu of pesticide-based therapy. Courtesy of Will Sorey, MD.

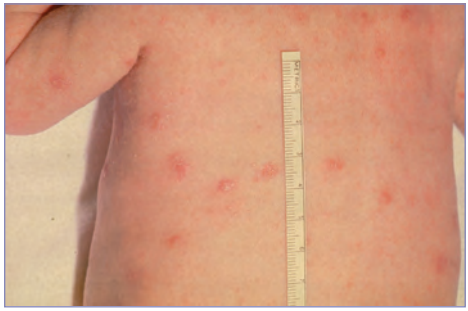


Image 127.10
A 9-month-old boy with atypical, eczema-like papulovesicular lesions of scabies on the trunk and extremities. Courtesy of George Nankervis, MD.

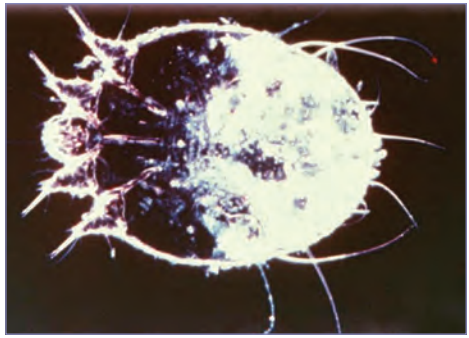


Image 127.11
This is a *Sarcoptes scabiei* subsp *hominis,* or itch mite, which is the cause of scabies. Females are 0.3- to 0.4-mm long and 0.25- to 0.35-mm wide. Male mites are slightly more than half that size. Scabies is a highly contagious infestation of the skin caused by a mite affecting humans and animals. Scabies is usually transmitted by intimate interpersonal contact, often sexual in nature, but transmission through casual contact can occur. Courtesy of Centers for Disease Control and Prevention.

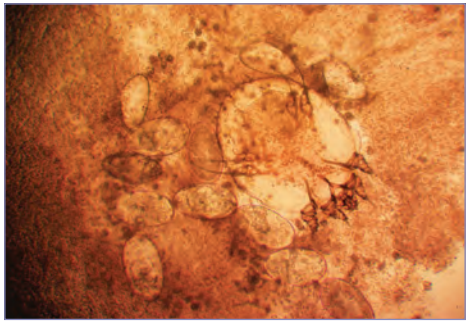


Image 127.12
The mite *Sarcoptes scabiei* subsp *hominis* is responsible for scabies in humans. Courtesy of Larry Frenkel, MD.

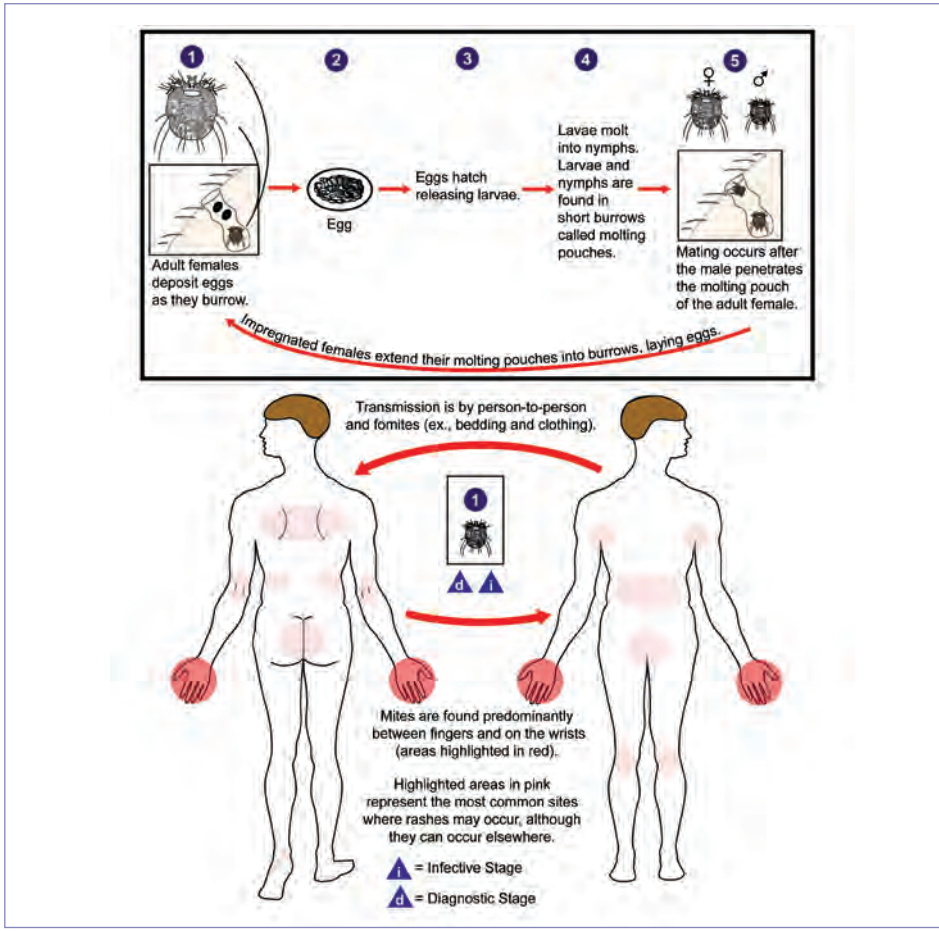


Image 127.13

Life cycle. *Sarcoptes scabiei* undergoes 4 stages in its life cycle: egg, larva, nymph, and adult. Females deposit eggs at 2- to 3-day intervals as they burrow through the skin (1). Eggs are oval and 0.1 to 0.15 mm in length (2) and incubation time is 3 to 8 days. After the eggs hatch, the larvae migrate to the skin surface and burrow into the intact stratum corneum to construct almost invisible, short burrows called *molting pouches.* The larval stage, which emerges from the eggs, has only 3 pairs of legs (3), and this form lasts 2 to 3 days. After larvae molt, the resulting nymphs have 4 pairs of legs (4). This form molts into slightly larger nymphs before molting into adults. Larvae and nymphs may often be found in molting pouches or in hair follicles and look similar to adults, only smaller. Adults are round, sac-like eyeless mites. Females are 0.3- to 0.4-mm long and 0.25- to 0.35-mm wide, and males are slightly more than half that size. Mating occurs after the nomadic male penetrates the molting pouch of the adult female (5). Impregnated females extend their molting pouches into the characteristic serpentine burrows, laying eggs in the process. The impregnated females burrow into the skin and spend the remaining 2 months of their lives in tunnels under the surface of the skin. Males are rarely seen. They make a temporary gallery in the skin before mating. Transmission occurs by the transfer of ovigerous females during personal contact. Mode of transmission is primarily person-to-person contact, but transmission may also occur via fomites (eg, bedding, clothing). Mites are found predominantly between the fingers and on the wrists. The mites hold onto the skin using suckers attached to the 2 most anterior pairs of legs. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 128

Schistosomiasis

CLINICAL MANIFESTATIONS

Infections are established by skin penetration of infecting larvae (cercariae, shed by freshwater snails). Initial infections often are asymptomatic but repeat exposures may be accompanied by a hypersensitivity reaction consisting of a transient, pruritic, papular rash (cercarial dermatitis; "swimmer's itch"). After penetration, the parasites enter the bloodstream, migrate through the lungs, and eventually mature into adult worms that reside in the venous plexus that drains the intestines or, in the case of *Schistosoma haematobium*, the urogenital tract. Four to 8 weeks after exposure, worms develop into adults and females begin egg deposition, which can lead to an acute serum sickness-like illness (Katayama syndrome) that manifests as fever, malaise, cough, rash, abdominal pain, hepatosplenomegaly, diarrhea, nausea, lymphadenopathy, and eosinophilia. This syndrome is most common among nonimmune hosts, such as travelers. Adult worms survive 7 to 10 years in the absence of treatment, although several cases have been documented of people having infections decades after leaving an area of endemicity. The severity of symptoms associated with chronic infection is related to the worm burden. People with low to moderate worm burdens may have only subclinical disease or relatively mild manifestations, such as growth stunting or anemia. Higher worm burdens are associated with a range of symptoms caused primarily by inflammation and local fibrosis triggered by the immune response to eggs produced by adult worms. Severe forms of chronic intestinal schistosomiasis (*Schistosoma mansoni* and *Schistosoma japonicum* infections) can result in hepatosplenomegaly, abdominal pain, bloody diarrhea, portal hypertension, ascites, esophageal varices, and hematemesis. Urogenital schistosomiasis (*S haematobium* infections) can result in the bladder becoming inflamed and fibrotic. Urinary tract symptoms and signs include dysuria, urgency, terminal microscopic and gross hematuria, secondary urinary tract infections, hydronephrosis, and nonspecific pelvic pain. *S haematobium* is associated with lesions of the lower genital tract (vulva, vagina, and cervix) in women, prostatitis and hematospermia in men, and certain forms of bladder cancer. Other organ systems can be involved—for example, eggs can embolize to the lungs, causing pulmonary hypertension. Less commonly, eggs can lodge in the central nervous system, causing severe neurologic complications.

Cercarial dermatitis (swimmer's itch) often is caused by larvae of schistosome parasites of birds or other wildlife. These larvae can penetrate human skin but eventually die in the dermis and do not cause systemic disease. Skin manifestations include pruritus at the penetration site a few hours after water exposure, followed in 5 to 14 days by an intermittent pruritic, sometimes papular, eruption. In previously sensitized people, more intense papular eruptions may occur more quickly and last for 7 to 10 days after exposure.

ETIOLOGY

The trematodes (flukes) *S mansoni*, *S japonicum*, *Schistosoma mekongi*, and *Schistosoma intercalatum* cause intestinal schistosomiasis, and *S haematobium* causes urogenital disease. All species have similar life cycles.

EPIDEMIOLOGY

Persistence of schistosomiasis depends on the presence of an appropriate snail as an intermediate host. Eggs excreted in stool (*S mansoni*, *S japonicum*, *S mekongi*, and *S intercalatum*) or urine (*S haematobium*) into fresh water hatch into motile miracidia, which infect snails. After development and asexual replication in snails, cercariae emerge and penetrate the skin of humans in contact with water. Children commonly are first infected when they accompany their mothers to lakes, ponds, and other open fresh water sources. School-aged children typically are the most heavily infected people in the community because of prolonged wading and swimming in infected waters. In addition, children have greater susceptibility to infection than older people because of a lack of high preexisting immunity to these parasites. Children also are important in maintaining transmission through behaviors such as uncontrolled defecation and urination. Communicability lasts as long as infected

snails are in the environment or live eggs are excreted in the urine and feces of humans into fresh water sources with appropriate snails. In the case of *S japonicum*, animals play an important zoonotic role (as a source of eggs) in maintaining the life cycle. Infection is not transmissible by person-to-person contact or blood transfusion.

The distribution of schistosomiasis is focal and limited by the presence of appropriate snail vectors, infected human reservoirs, and fresh water sources. *S mansoni* occurs throughout tropical Africa, in parts of several Caribbean islands, and in areas of Venezuela, Brazil, Suriname, and the Arabian Peninsula. *S japonicum* is found in China, the Philippines, and Indonesia. *S haematobium* occurs in Africa and the Middle East; in 2014, local transmission was reported in Corsica. *S mekongi* is found in Cambodia and Laos. *S intercalatum* is found in Central Africa. Adult worms of *S mansoni* usually survive for 5 to 7 years but can live as long as 30 years in the human host. Thus, schistosomiasis can be diagnosed in patients many years after they have left an area with endemic infection. Immunity is incomplete, and reinfection occurs commonly. Swimmer's itch can occur in all regions of the world after exposure to fresh water, brackish water, or salt water.

The **incubation period** is variable but is approximately 4 to 6 weeks for *S japonicum*, 6 to 8 weeks for *S mansoni*, and 10 to 12 weeks for *S haematobium*.

DIAGNOSTIC TESTS

Eosinophilia is common and may be intense in Katayama syndrome (acute schistosomiasis). Infection with *S mansoni* and other species (except *S haematobium*) is determined by microscopic examination of stool specimens to detect characteristic eggs containing fully differentiated larvae, but results may be negative if performed too early in the course of infection. In light infections, several stool specimens examined by a concentration technique may be needed before eggs are found, or eggs may be seen in a biopsy of the rectal mucosa. *S haematobium* is diagnosed by examining urine for eggs, with centrifugation and examination of the urinary sediment required for optimum sensitivity. Egg excretion in urine often peaks between noon and 3:00 pm. Biopsy of the bladder mucosa may be used to diagnose this infection. Urine reagent dipsticks commonly will be positive for hematuria. Serologic tests, available through the Centers for Disease Control and Prevention and some commercial laboratories, may be helpful for detecting light infections; results of these antibody-based tests remain positive for many years and are not useful in differentiating ongoing infection from past infection or reinfection. Serologic tests become positive 6 to 12 weeks or more after infection and may be positive before eggs are detectable. Antibody tests are most useful in travelers from geographic areas where the disease is endemic. Polymerase chain reaction and antigen tests for detection of schistosomes have been developed but are considered to be research tools.

Swimmer's itch can be difficult to differentiate from other causes of dermatitis. A skin biopsy may demonstrate larvae, but their absence does not exclude the diagnosis. A history of exposure to water used by waterfowl may be helpful in making the diagnosis.

TREATMENT

The drug of choice for schistosomiasis caused by any species is praziquantel. The alternative drug for *S mansoni* is oxamniquine, although this drug no longer is available. Praziquantel does not kill developing worms; therapy given within 4 to 8 weeks of exposure should be repeated 1 to 2 months later to improve parasitologic cure. Initial management of acute schistosomiasis and neuroschistosomiasis includes reduction of inflammation with steroids. Initial treatment with praziquantel may exacerbate symptoms. The optimal timing of adding praziquantel is unknown; treating with this drug when inflammation has subsided generally is favored. For acute schistosomiasis, repeating the dose of praziquantel 4 to 6 weeks later may be beneficial. Swimmer's itch is a self-limited disease that may require symptomatic treatment of the rash. More intense reactions may require a course of oral corticosteroids.

Image 128.1
A boy with swollen abdomen due to schistosomiasis with hepatosplenomegaly. Courtesy of Immunization Action Coalition.

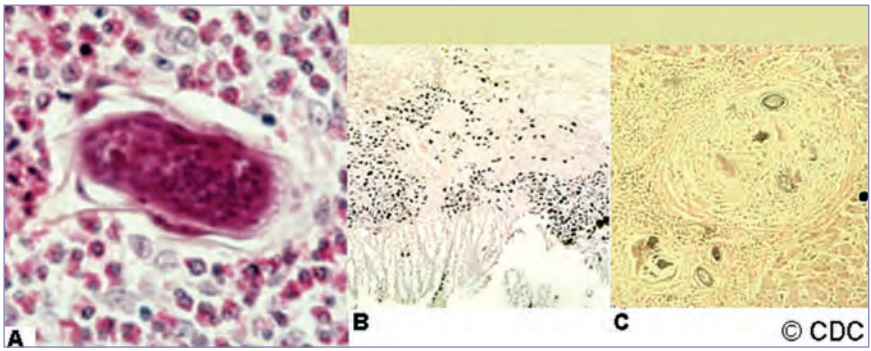


Image 128.2
A–C, Cross section of different human tissues showing *Schistosoma* species eggs. A, *Schistosoma mansoni* eggs in intestinal wall. B, *Schistosoma japonicum* eggs in colon. C, *S japonicum* eggs in liver. Courtesy of Centers for Disease Control and Prevention.

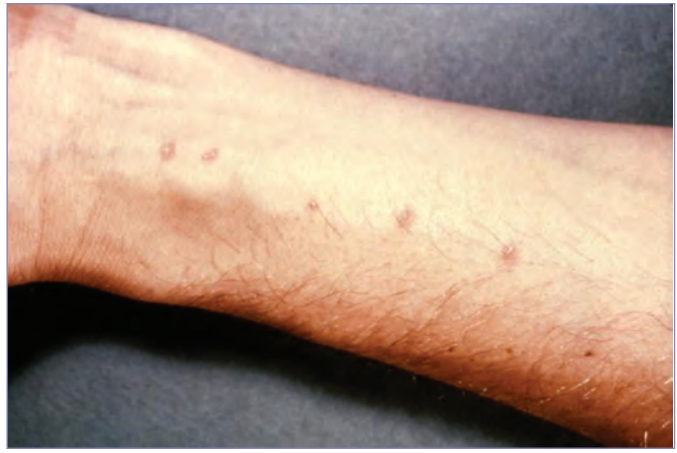


Image 128.3
Schistosome dermatitis, or swimmer's itch, occurs when skin is penetrated by a free-swimming, fork-tailed infective cercaria. On release from the snail host, the infective cercariae swim, penetrate the skin of the human host, and shed their forked tail, becoming schistosomula. The schistosomula migrate through several tissues and stages to their residence in the veins. Courtesy of Centers for Disease Control and Prevention.

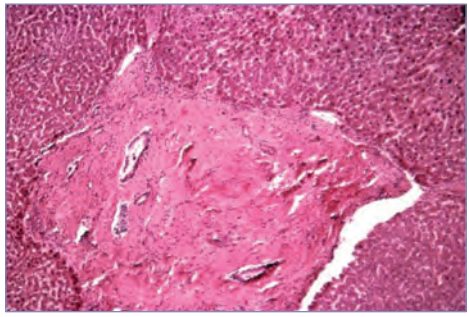


Image 128.4
This micrograph reveals signs of schistosomiasis infection of the liver, also known as pipestem cirrhosis (magnification ×500). Pipestem cirrhosis occurs when schistosomes infect the liver (ie, hepatic schistosomiasis), which causes scarring to occur, thereby entrapping parasites and their ova in and around the hepatic portal circulatory vessels. Courtesy of Centers for Disease Control and Prevention.

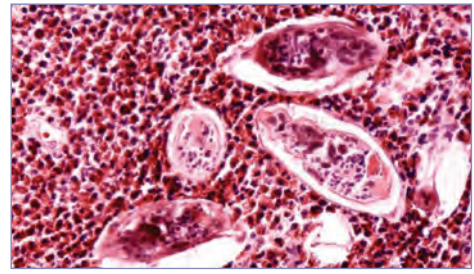


Image 128.5
Histopathology of *Schistosoma haematobium,* bladder. Histopathology of the bladder shows eggs of *S haematobium* surrounded by intense infiltrates of eosinophils. Courtesy of Centers for Disease Control a nd Prevention/Edwin P. Ewing Jr, MD.

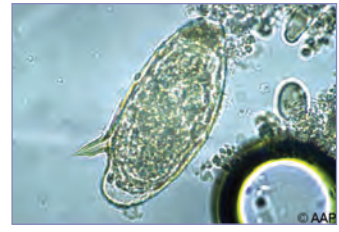


Image 128.6
Schistosoma haematobium ova (original magnification ×400).

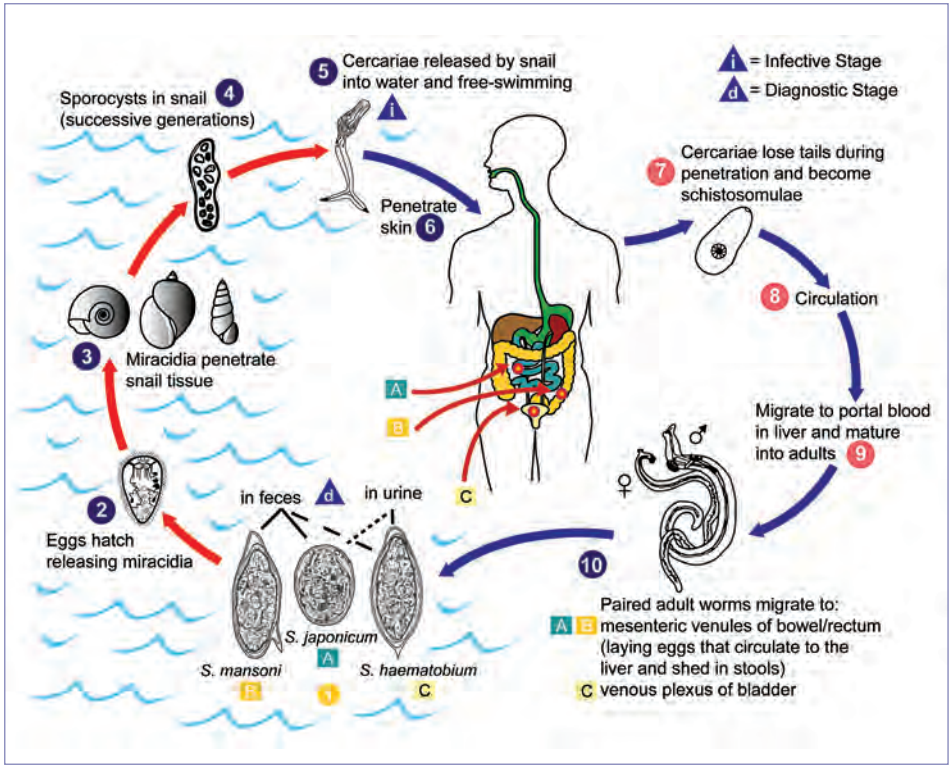


Image 128.7

Life cycle. Eggs are eliminated with feces or urine (1). Under optimal conditions, the eggs hatch and release miracidia (2), which swim and penetrate specific snail intermediate hosts (3). The stages in the snail include 2 generations of sporocysts (4) and the production of cercariae (5). On release from the snail, the infective cercariae swim, penetrate the skin of the human host (6), and shed their forked tail, becoming schistosomulae (7). The schistosomulae migrate through several tissues and stages to their residence in the veins (10). Adult worms in humans reside in the mesenteric venules in various locations, which, at times, seem to be specific for each species (10). For instance, *Schistosoma japonicum* is more frequently found in the superior mesenteric veins draining the small intestine (A), and *Schistosoma mansoni* occurs more often in the superior mesenteric veins draining the large intestine (B). However, both species can occupy either location, and they are capable of moving between sites, so it is not possible to state unequivocally that one species only occurs in one location. *Schistosoma haematobium* most often occurs in the venous plexus of the bladder (C), but it can also be found in the rectal venules. The females (size 7–20 mm; males slightly smaller) deposit eggs in the small venules of the portal and perivesical systems. The eggs are moved progressively toward the lumen of the intestine (*S mansoni* and *S japonicum*) and of the bladder and ureters (*S haematobium*) and are eliminated with feces or urine, respectively (1). Pathology of *S mansoni* and *S japonicum* schistosomiasis includes Katayama fever, presinusoidal egg granulomas, Symmers pipestem periportal fibrosis, portal hypertension, and occasional embolic egg granulomas in the brain or spinal cord. Pathology of *S haematobium* schistosomiasis includes hematuria, scarring, calcification, squamous cell carcinoma, and occasional embolic egg granulomas in the brain or spinal cord. Human contact with water is, thus, necessary for infection by schistosomes. Various animals, such as dogs, cats, rodents, pigs, horses, and goats, serve as reservoirs for *S japonicum,* and dogs for *S mekongi.* Courtesy of Centers for Disease Control and Prevention.

Image 128.8
Geographic distribution of schistosomiasis. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 129

Shigella Infections

CLINICAL MANIFESTATIONS

Shigella species primarily infect the large intestine, causing clinical manifestations that range from watery or loose stools with minimal or no constitutional symptoms to more severe symptoms, including high fever, abdominal cramps or tenderness, tenesmus, and mucoid stools with or without blood. *Shigella dysenteriae* serotype 1 often causes a more severe illness than other shigellae with a higher risk of complications, including septicemia, pseudomembranous colitis, toxic megacolon, intestinal perforation, hemolysis, and hemolytic-uremic syndrome (HUS). Infection attributable to *S dysenteriae* type 1 has become rare in industrialized countries. Generalized seizures have been reported among young children with shigellosis attributable to any serotype; although the pathophysiology and incidence are poorly understood, such seizures usually are self-limited and usually are associated with high fever or electrolyte abnormalities. Septicemia is rare during the course of illness and is caused either by *Shigella* organisms or by other gut flora that gain access to the bloodstream through intestinal mucosa damaged during shigellosis. Septicemia occurs most often in neonates, malnourished children, and people with *S dysenteriae* serotype 1 infection but may occur in healthy children with non-dysenteriae shigellosis. Reactive arthritis with possible extraarticular manifestations is a rare complication that can develop weeks or months after shigellosis, especially in patients expressing HLA-B27.

ETIOLOGY

Shigella species are facultative aerobic, gram-negative bacilli in the family *Enterobacteriaceae*. Four species have been identified. Among *Shigella* isolates reported in the United States in 2012, approximately 85% were *Shigella sonnei*, 14% were *Shigella flexneri*, 1% were *Shigella boydii*, and less than 1% were other species. Shiga toxin, a potent cytotoxin produced by *S dysenteriae* serotype 1, enhances virulence of this serotype at the colonic mucosa and can cause small blood vessel and renal damage, leading to HUS. The genes encoding Shiga toxin are phage encoded and have been found in a few strains belonging to other *Shigella* serotypes, including *S flexneri* type 2a, *S dysenteriae* type 4, and *S sonnei*. To date, HUS has not been associated with infections attributable to these serotypes.

EPIDEMIOLOGY

Humans are the natural host for *Shigella* organisms, although other primates can be infected. The primary mode of transmission is the fecal-oral route, although transmission also can occur via contact with a contaminated inanimate object, ingestion of contaminated food or water, or sexual contact. Houseflies also may be vectors through physical transport of infected feces. Ingestion of as few as 10 organisms, depending on the species, is sufficient for infection to occur. Prolonged organism survival in water (up to 6 months) and food (up to 30 days) can occur with *Shigella* species. Children 5 years or younger in child care settings and their caregivers and people living in crowded conditions are at increased risk of infection. Men who have sex with men also are at increased risk of *Shigella*, including infections with multidrug-resistant strains. Infections attributable to *S flexneri*, *S boydii*, and *S dysenteriae* are slightly more common among adults than among children; however, infections attributable to *S sonnei* in the United States predominate among both children and adults. Travel to resource-limited countries with inadequate sanitation can place travelers at risk of infection. Even without antimicrobial therapy, the carrier state usually ceases within 1 to 4 weeks after onset of illness; long-term carriage is uncommon.

In 2014 in the United States, 33.9% of *Shigella* species were resistant to ampicillin, 40.9% were resistant to trimethoprim-sulfamethoxazole (TMP/SMX), 4.7% were resistant to azithromycin, 2.4% were resistant to ciprofloxacin, and 0.4% were resistant to ceftriaxone. In 2017, the Centers for Disease Control and Prevention identified an increase in *Shigella* isolates with minimum inhibitory concentration (MIC) values of 0.12 to 1 μg/mL for ciprofloxacin; preliminary data suggest that all *Shigella* isolates MICs in this range harbor at least 1 quinolone resistance gene known to confer reduced susceptibility in enteric bacteria. Fluoroquinolone

resistance is of particular concern since isolates with a quinolone resistance gene also are resistant to many other commonly used treatment agents, such as azithromycin, TMP/SMX, amoxicillin-clavulanic acid, and ampicillin.

The **incubation period** varies from 1 to 7 days (typically, 1 to 3 days).

DIAGNOSTIC TESTS

Isolation of *Shigella* organisms from feces or rectal swab specimens containing feces is diagnostic; sensitivity is improved by testing stool as soon as possible after it is passed, along with the use of enrichment broth media and selective agar plate media. If specimens cannot be transported to the testing laboratory within 2 hours, they should be transferred to appropriate transport media (eg, Cary-Blair or similar media) at 4°C. Definitive identification of the organism requires both biochemical profiling and serogrouping to differentiate *Shigella* from *Escherichia* species. The presence of fecal lactoferrin (or fecal leukocytes) demonstrated on a methylene-blue stained stool smear is fairly sensitive for the diagnosis of colitis but is not specific for shigellosis. Although bacteremia is rare, blood should be cultured in severely ill, immunocompromised, or malnourished children. Multiplex polymerase chain reaction (PCR) platforms for detection of multiple bacterial, viral, and parasitic pathogens including *Shigella* have high sensitivity but may yield false-positive results (eg, detecting nonviable organisms). To guide treatment, stool cultures are recommended if shigellosis is diagnosed using multiplex PCR platforms or other nonculture-based diagnostic tests.

TREATMENT

Although severe dehydration is rare, correction of fluid and electrolyte losses, preferably by oral rehydration solutions, is the mainstay of treatment. Most clinical infections with *S sonnei* are self-limited (48 to 72 hours), and mild episodes do not require antimicrobial therapy. Antimicrobial treatment is recommended for patients with severe disease or with underlying immunosuppressive conditions; empiric therapy should be given while awaiting culture and susceptibility results. Available evidence suggests that antimicrobial therapy is somewhat effective in shortening duration of diarrhea and hastening eradication of organisms from feces. Antimicrobial susceptibility testing of clinical isolates is indicated, because resistance to antimicrobial agents is common and may be increasing and because susceptibility data can guide appropriate therapy. Fluoroquinolones should be avoided if the *Shigella* strain has a minimum inhibitory concentration (MIC) of $\geq$0.12 μg/mL for ciprofloxacin. Azithromycin susceptibility testing is not performed widely for *Shigella* species. Ciprofloxacin and ceftriaxone resistance are increasing around the world.

For cases in which treatment is required and susceptibilities are unknown or an ampicillin- and TMP/SMX-resistant strain is isolated, parenteral ceftriaxone for 2 to 5 days, a fluoroquinolone (eg, ciprofloxacin) for 3 days, or azithromycin for 3 days should be administered. For susceptible strains, oral ampicillin or TMP/SMX for 5 days is effective; amoxicillin is not effective because of its rapid absorption from the gastrointestinal tract. The oral route of therapy is recommended, except for seriously ill patients.

Antidiarrheal compounds that inhibit intestinal peristalsis are contraindicated, because they can prolong the clinical and bacteriologic course of disease and can increase the rate of complications.

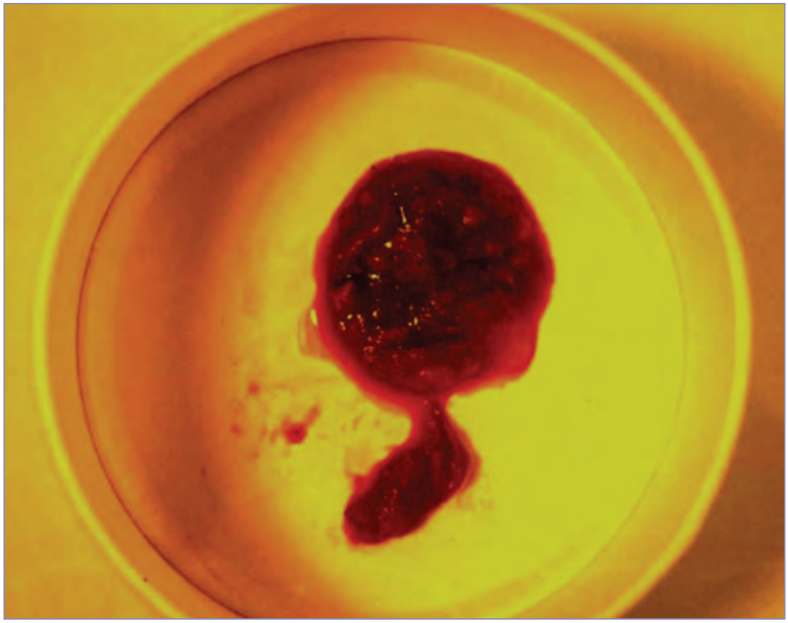


Image 129.1
Characteristic bloody mucoid stool of a child with shigellosis.

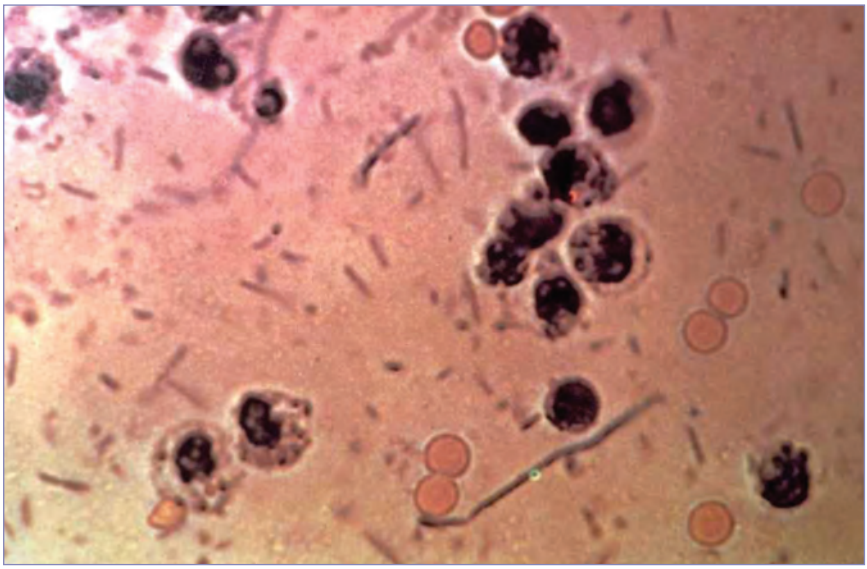


Image 129.2
Fecal leukocytes (shigellosis) (methylene-blue stain). The presence of fecal leukocytes suggests a bacterial diarrhea, although not specific for *Shigella* infection. Courtesy of Edgar O. Ledbetter, MD, FAAP.

Image 129.3
Culture of *Shigella sonnei* grown on a blood agar plate. Courtesy of Rita Yee, MT(ASCP) SM.

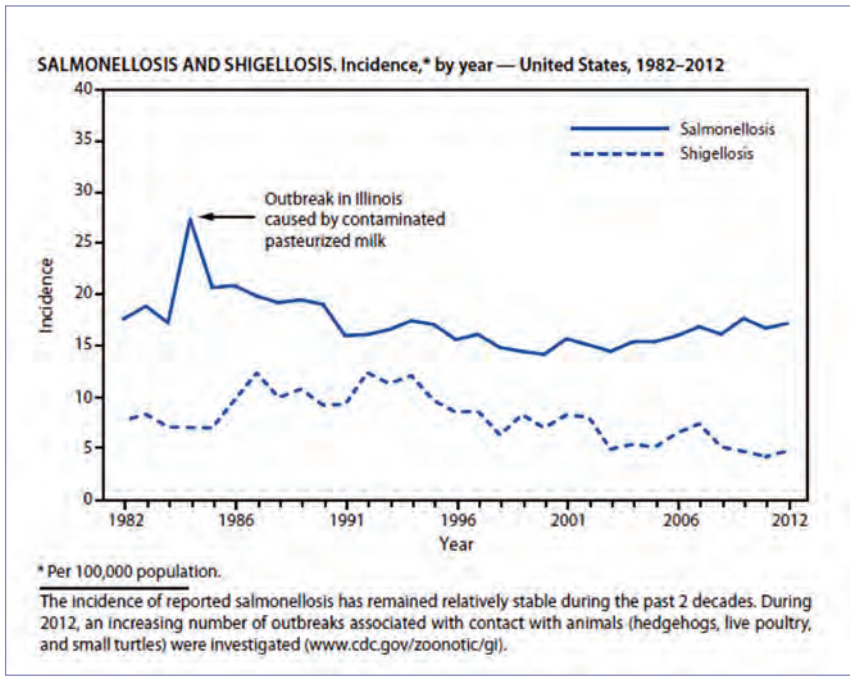


Image 129.4
Salmonellosis and shigellosis. Incidence, by year—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 130

Smallpox (Variola)

The last naturally occurring case of smallpox occurred in Somalia in 1977, followed by 2 cases in 1978 after a photographer was infected during a laboratory exposure and later transmitted smallpox to her mother in the United Kingdom. In 1980, the World Health Assembly declared that smallpox (variola virus) had been eradicated successfully worldwide, and no subsequent cases have been confirmed. The United States discontinued routine childhood immunization against smallpox in 1972 and routine immunization of health care professionals in 1976. Immunization of US military personnel continued until 1990. Following eradication, 2 World Health Organization reference laboratories were authorized to maintain stocks of variola virus. As a result of terrorism events on September 11, 2001, and concern that the virus might be used as a weapon of bioterrorism, the smallpox immunization policy was revisited. In 2002, the United States resumed immunization of military personnel deployed to certain areas of the world and in 2003 initiated a civilian smallpox immunization program for first responders to facilitate preparedness and response to a possible smallpox bioterrorism event.

CLINICAL MANIFESTATIONS

People infected with variola major strains develop a severe prodromal illness characterized by high fever (102°F–104°F [38.9°C–40.0°C]) and constitutional symptoms, including malaise, severe headache, backache, abdominal pain, and prostration, lasting for 2 to 5 days. Infected children may suffer from vomiting and seizures during this prodromal period. Most patients with smallpox are severely ill and bedridden during the febrile prodrome. The prodromal period is followed by development of lesions on mucosa of the mouth or pharynx, which may not be noticed by the patient. This stage occurs less than 24 hours before onset of rash, which usually is the first recognized manifestation of smallpox. With onset of oral lesions, the patient becomes infectious and remains so until all skin crust lesions have separated. The rash typically begins on the face and rapidly progresses to involve the forearms, trunk, and legs, with the greatest concentration of lesions on the face and distal extremities. The majority of patients will have lesions on the palms and soles. With rash onset, fever decreases but does not resolve. Lesions begin as macules that progress to papules, followed by firm vesicles and then deep-seated, hard pustules described as "pearls of pus." Each stage lasts 1 to 2 days. By the sixth or seventh day of rash, lesions may begin to umbilicate or become confluent. Lesions increase in size for approximately 8 to 10 days, after which they begin to crust. Once all the crusts have separated, 3 to 4 weeks after the onset of rash, the patient no longer is infectious. Variola major in unimmunized people is associated with case-fatality rates of approximately 30% during epidemics of smallpox. The mortality rate is highest in pregnant women, children younger than 1 year, and adults older than 30 years. The potential for modern supportive therapy to improve outcome is not known. Variola minor strains cause a disease that is indistinguishable clinically from variola major, except that it causes less severe systemic symptoms and has more rapid rash evolution, reduced scarring, and fewer fatalities.

In addition to the typical presentation of smallpox (90% of cases or greater), there are 2 uncommon forms of variola major: **hemorrhagic** (characterized either by a hemorrhagic diathesis before onset of the typical smallpox rash [early hemorrhagic smallpox] or by hemorrhage into skin lesions and disseminated intravascular coagulation [late hemorrhagic smallpox]) and **malignant or flat type** (in which the skin lesions do not progress to the pustular stage but remain flat and soft). Each variant occurs in approximately 5% of cases and is associated with a 95% to 100% mortality rate. Pregnancy is a risk factor for hemorrhagic variola. Defects in cellular immunity may be responsible for flat type variola major, which is seen more commonly in children than adults.

Varicella (chickenpox) is the condition most likely to be mistaken for smallpox. Generally, children with varicella do not have a febrile prodrome, but adults may have a brief, mild prodrome. Although the 2 diseases are confused easily in the first few days of the rash, smallpox lesions develop into pustules that

are firm and deeply embedded in the dermis, whereas varicella lesions develop into superficial vesicles.

ETIOLOGY

Variola is a member of the *Poxviridae* family (genus *Orthopoxvirus*). Other members of this genus that can infect humans include monkeypox virus, cowpox virus, and vaccinia virus. Cowpox virus was used by Benjamin Jesty in 1774 and by Edward Jenner in 1796 as material for the first smallpox vaccine. Later, cowpox virus was replaced with vaccinia virus.

EPIDEMIOLOGY

Humans are the only natural reservoir for variola virus (smallpox). Smallpox is spread most commonly in droplets from the oropharynx of infected people, although rare transmission from aerosol spread has been reported. Infection from direct contact with lesion material or indirectly via fomites, such as clothing and bedding, also has been reported. Because most patients with smallpox are extremely ill and bedridden, spread generally is limited to household contacts, hospital workers, and other health care professionals. Secondary household attack rates for smallpox were considerably lower than for measles and similar to or lower than rates for varicella.

The **incubation period** is 7 to 17 days (mean, 10–12 days).

DIAGNOSTIC TESTS

Variola virus can be detected in vesicular or pustular fluid by a number of different methods, including electron microscopy, immunohistochemistry, culture, or polymerase chain reaction (PCR) assay. Only PCR assay can diagnose infection with variola virus definitively; all other methods simply screen for orthopoxviruses. Screening is available through select state health departments. Final, confirmatory variola-specific laboratory testing is available only at the Centers for Disease Control and Prevention (CDC). Diagnostic evaluation includes exclusion of varicella-zoster virus or other common conditions that cause a vesicular/pustular rash illness.

TREATMENT

Infected patients should receive supportive care. Cidofovir, a nucleotide analogue of cytosine, has demonstrated antiviral activity against certain orthopoxviruses in vitro and in animal models. Its effectiveness in treatment of variola in humans is unknown. Investigational agents, such as brincidofovir (a lipophilic derivative of cidofovir) and tecovirimat (ST-246, an investigational agent with antiviral activity against orthopoxviruses), are being evaluated in animal models; however, benefit in infected humans cannot be tested in the absence of disease.

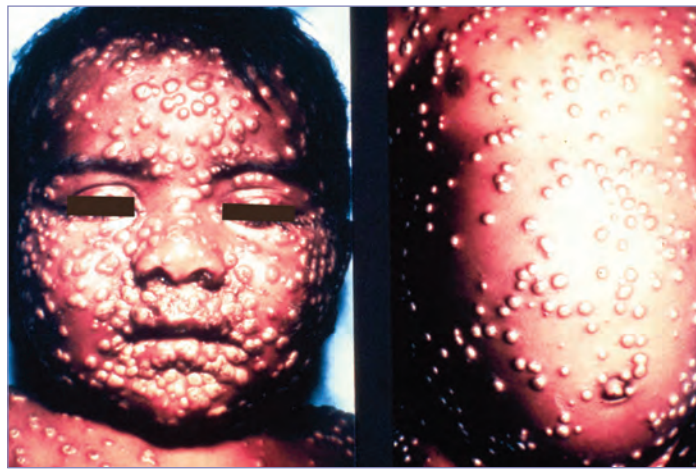


Image 130.1
Smallpox in a 2-year-old boy demonstrating commonplace greater density of lesions on the face as compared with the child's body. Courtesy of Paul Wehrle, MD.

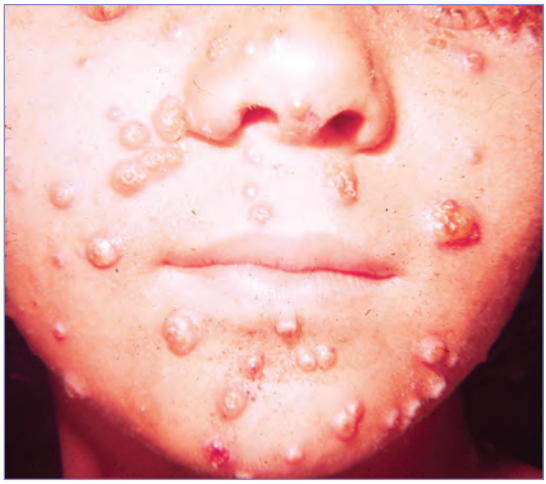


Image 130.2
Variola minor lesions on the face of a 2-year-old Latin American boy. Courtesy of Paul Wehrle, MD.

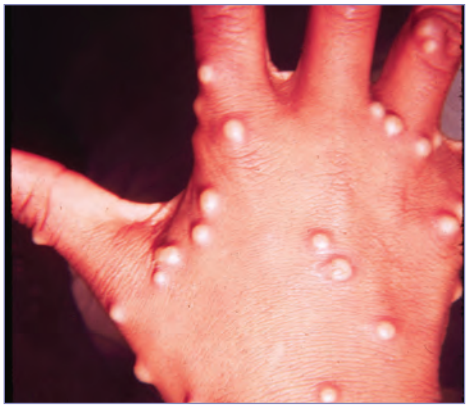


Image 130.3
Variola minor lesions on the hand of the Latin American boy in Image 130.2. Courtesy of Paul Wehrle, MD.

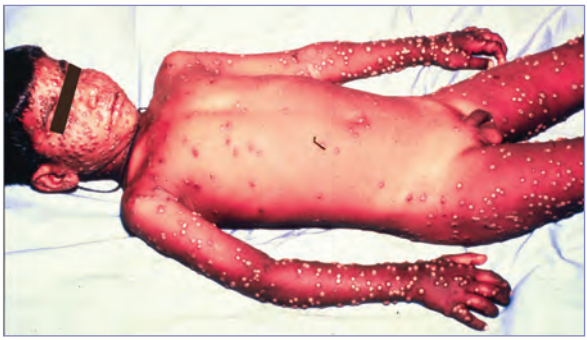


Image 130.4
A 7-year-old boy residing in India with smallpox lesions in a typical centripetal distribution. Courtesy of Paul Wehrle, MD.

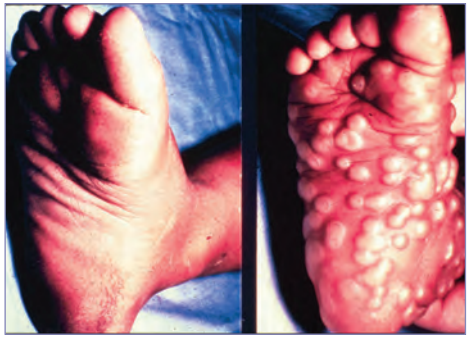


Image 130.5
The right foot of two 6-year-old boys, one (right) with smallpox, the other (left) with varicella. The palms and soles are characteristically involved in smallpox patients and infrequently involved in varicella. Courtesy of Paul Wehrle, MD.

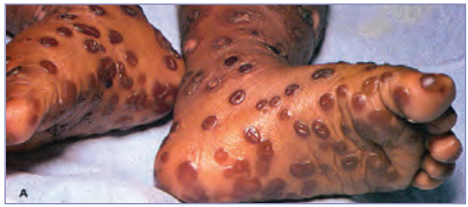


Image 130.7
Numerous healing smallpox lesions on the feet of a young child. Courtesy of Edgar O. Ledbetter, MD, FAAP.

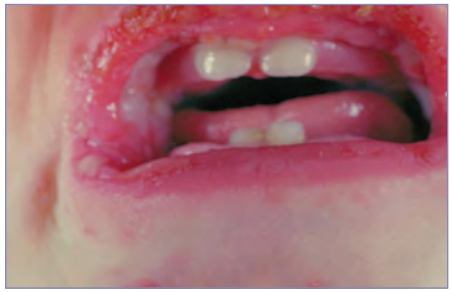


Image 130.9
Subsequent to receiving a vaccination, this 1-year-old developed erythema multiforme. Erythema multiforme major, also referred to as Stevens-Johnson syndrome, is a toxic or allergic rash in response to the smallpox vaccine that can take various forms and range from moderate to severe. Courtesy of Centers for Disease Control and Prevention.

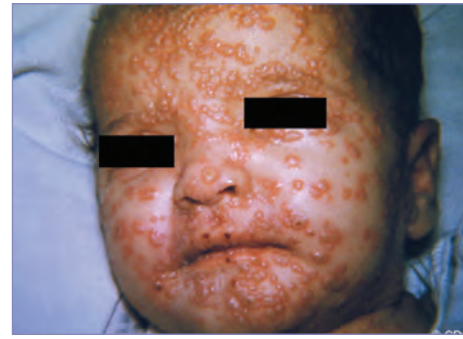


Image 130.6
Early smallpox pustules on the face of an infant. If this infant survives, smallpox lesions, or pustules, will eventually form scabs that will fall off, leaving marks on the skin. The patient is contagious to others until all of the scabs have fallen off. Courtesy of Centers for Disease Control and Prevention.

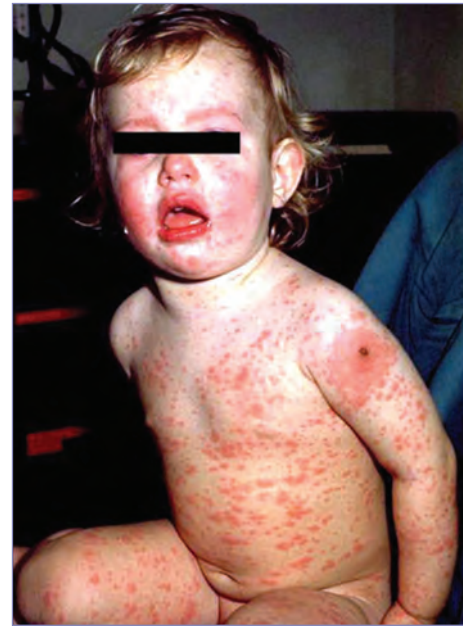


Image 130.8
Generalized vaccinia reaction secondary to smallpox vaccination. No vaccinia immunoglobulin treatment was required for resolution. Note the primary vaccination reaction on the left deltoid area. Courtesy of Edgar O. Ledbetter, MD, FAAP.

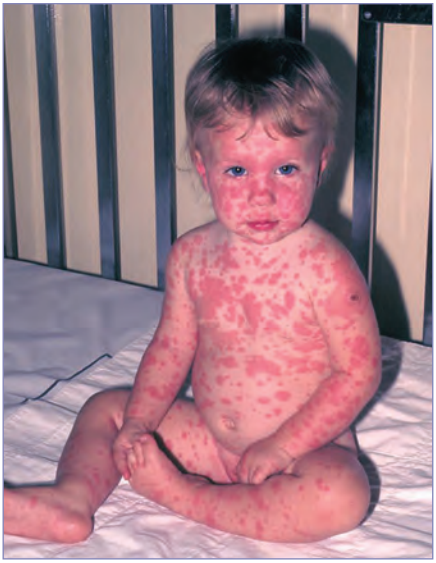


Image 130.10
After receiving a smallpox vaccination, this 1-year-old developed erythema multiforme. Erythema multiforme major, also referred to as Stevens-Johnson syndrome, is a toxic or allergic rash in response to the smallpox vaccine that can take various forms and range from moderate to severe. Courtesy of Centers for Disease Control and Prevention.

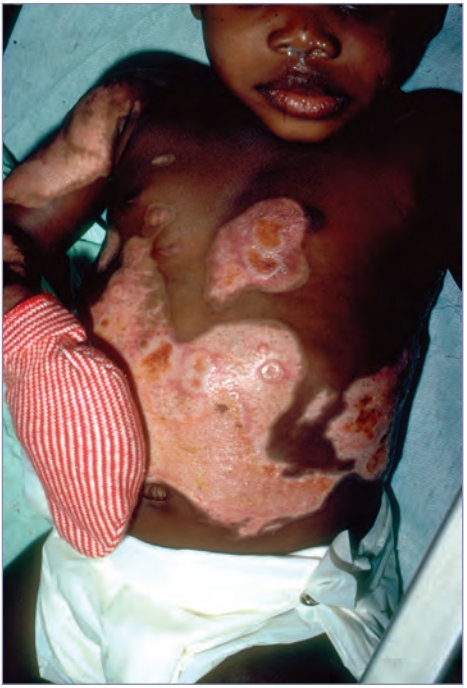


Image 130.11
Generalized vaccinia in a 6-month-old black boy; he had experienced burns and then was accidentally inoculated by contact with a vaccinated sibling. Courtesy of George Nankervis, MD.

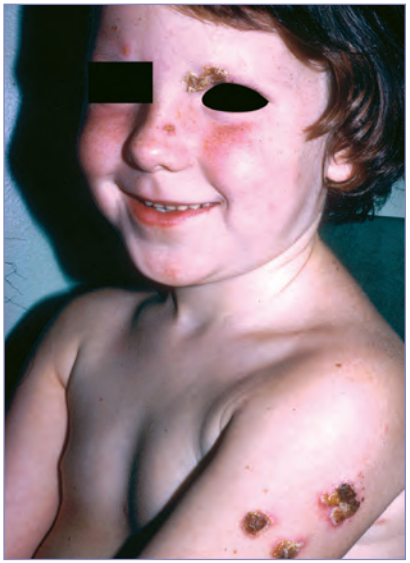


Image 130.12
Multiple secondary vaccinia lesions from autoinoculation in a 5-year-old white girl, one of the more common complications of smallpox vaccination. Courtesy of George Nankervis, MD.

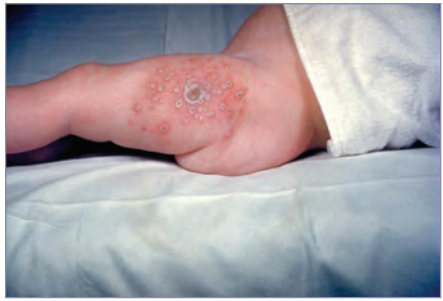


Image 130.13
After receiving a smallpox vaccination, this child developed a cluster of satellite lesions surrounding the vaccination site. Courtesy of Centers for Disease Control and Prevention.

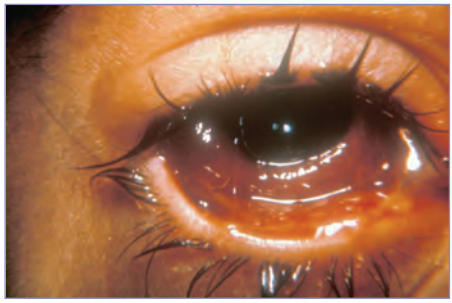


Image 130.15
This conjunctivitis was caused by the accidental implantation of vaccinia virus on the eyelid of this 6-year-old primary vaccinee. Vaccinia vaccine is a highly effective immunizing agent that brought about the global eradication of smallpox. However, because the smallpox vaccine is live, it can be spread to other people, as well as to other parts of one's own body. Courtesy of Centers for Disease Control and Prevention.

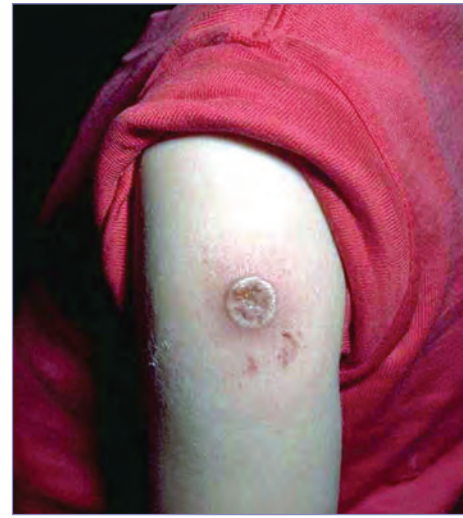


Image 130.14
Primary smallpox vaccination site with satellite vaccinia lesions in an 18-month-old girl. No treatment was required for resolution in conjunction with the primary vaccination lesion.

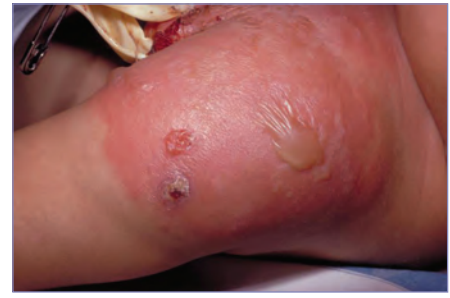


Image 130.16
This child developed a secondary staphylococcal infection at the smallpox vaccination site. Note the signs of cellulitis, including spreading erythema that envelopes the smallpox vaccination site, swelling, and accompanying areas of cutaneous purulence. Courtesy of Centers for Disease Control and Prevention.

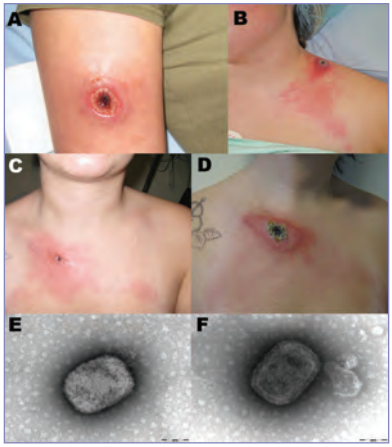


Image 130.17
Cowpox virus infection in a person in northern France caused by transmission from infected pet rats. Courtesy of Centers for Disease Control and Prevention.

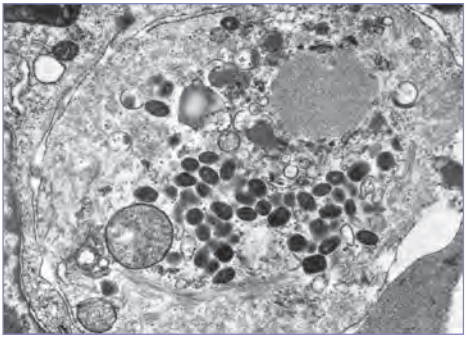


Image 130.18
A transmission electron micrograph of a tissue section containing variola virus. Smallpox is a serious, highly contagious, and, sometimes, fatal infectious disease. There is no specific treatment for smallpox disease, and the only prevention is vaccination. Courtesy of Centers for Disease Control and Prevention.

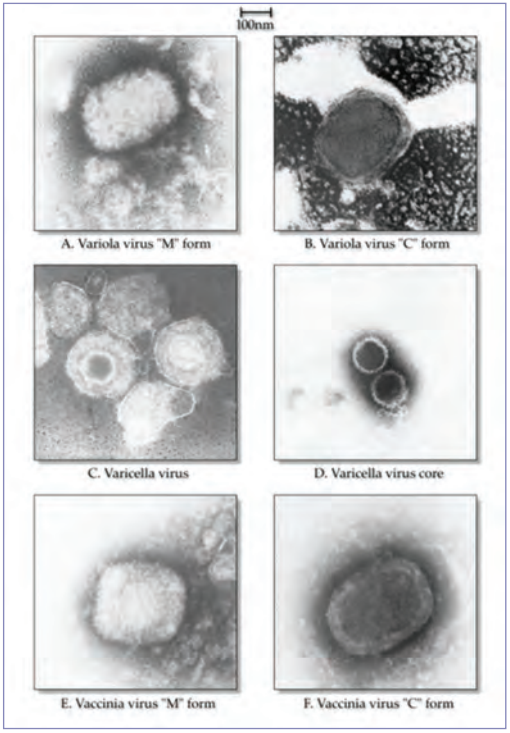


Image 130.19
Electron micrographs of variola, varicella, and vaccinia virions. Electron micrographs from top to bottom: variola virion (forms M and C), varicella virion and virion core, vaccinia virion (forms M and C). Courtesy of Centers for Disease Control and Prevention.

CHAPTER 131

Sporotrichosis

CLINICAL MANIFESTATIONS

There are 3 cutaneous patterns described for sporotrichosis. The classic **lymphocutaneous** process with multiple nodules is seen most commonly in adults. Inoculation occurs at a site of minor trauma, causing a painless papule that enlarges slowly to become a firm slightly tender subcutaneous nodule that can develop a violaceous hue or can ulcerate. Secondary lesions follow the same evolution and develop along the lymphatic distribution proximal to the initial lesion. A **localized cutaneous** form of sporotrichosis, also called fixed cutaneous form, is seen most commonly in children and presents as a solitary crusted papule or papuloulcerative or nodular lesion in which lymphatic spread is not observed. The extremities and face are the most common sites of infection. A **disseminated cutaneous** form with multiple lesions is rare, usually occurring in immunocompromised children.

Extracutaneous sporotrichosis is uncommon, with cases occurring primarily in immunocompromised patients or, in adults, those who are alcoholic or have chronic obstructive pulmonary disease. Osteoarticular infection results from hematogenous spread or local inoculation. The most commonly affected joints are the knees, elbows, wrists, and ankles. **Pulmonary sporotrichosis** clinically resembles tuberculosis and occurs after inhalation or aspiration of aerosolized conidia. Disseminated disease generally occurs after hematogenous spread from primary skin or lung infection. **Disseminated sporotrichosis** can involve multiple foci (eg, eyes, pericardium, genitourinary tract, central nervous system) and occurs predominantly in immunocompromised patients. Pulmonary and disseminated forms of sporotrichosis are uncommon in children.

ETIOLOGY

Sporothrix schenckii is a thermally dimorphic fungus that grows as a mold or mycelial form at room temperature and as a budding yeast at 35°C to 37°C and in host tissues. *S schenckii* is a complex of at least 6 species. Within this complex, *S schenckii sensu stricto* is responsible for most infections, but in South America, *Sporothrix brasiliensis* is a major cause of infection.

EPIDEMIOLOGY

S schenckii is a ubiquitous organism that has worldwide distribution but is most common in tropical and subtropical regions of Central and South America and parts of North America and Asia. Cases in the United States appear to cluster in the Midwest, particularly along the Mississippi and Missouri river areas. The fungus has been isolated from soil and plant material, including hay, straw, sphagnum moss, and decaying vegetation. Thorny plants, such as rose bushes and pine trees, commonly are implicated, because pricks from their thorns or needles inoculate the organism from the soil or moss around the bush or tree. People who handle contaminated plant matter are at risk of infection. Zoonotic spread from infected cats or scratches from digging animals, such as armadillos, has led to cutaneous disease.

The **incubation period** is 7 to 30 days after inoculation (uncommonly, up to 6 months).

DIAGNOSTIC TESTS

Culture of *Sporothrix* species from a tissue, wound drainage, or sputum specimen is diagnostic. The mold phase of the organism can be isolated on a variety of fungal media including Sabouraud dextrose agar at 25°C to 30°C. Filamentous colonies generally appear within 1 week. Definitive identification requires conversion to the yeast phase by subculture to enriched media such as brain-heart infusion agar with 5% blood and incubation at 35°C to 37°C. Culture of *Sporothrix* species from a blood specimen is definite evidence for the disseminated form of infection. Histopathologic examination of tissue may be helpful but not often, because the organism is seldom abundant. Special fungal stains including periodic acid-Schiff and Gomori methenamine silver to visualize the oval or cigar-shaped organism are required. Serologic testing and polymerase chain reaction assay show promise for accurate and specific diagnosis but are available only in research laboratories.

TREATMENT

Sporotrichosis usually does not resolve without treatment. Itraconazole is the drug of choice for children with lymphocutaneous and localized cutaneous disease; many experts prefer using the oral solution, which has no issues with food and appears to achieve better concentrations. The duration of therapy is 2 to 4 weeks after all lesions have resolved, usually for a total duration of 3 to 6 months. Serum trough concentrations of itraconazole should be 1 to 2 μg/mL. Concentrations should be checked after 1 to 2 weeks of therapy to ensure adequate drug exposure. Saturated solution of potassium is an alternative therapy. Oral fluconazole should be used only if the patient cannot tolerate other agents.

Amphotericin B is recommended as the initial therapy for visceral or disseminated sporotrichosis in children. After clinical response to amphotericin B therapy is documented, itraconazole can be substituted and should be continued for at least 12 months. Itraconazole may be required for lifelong therapy in children with human immunodeficiency virus infection. Pulmonary and disseminated infections respond less well than cutaneous infection, despite prolonged therapy.

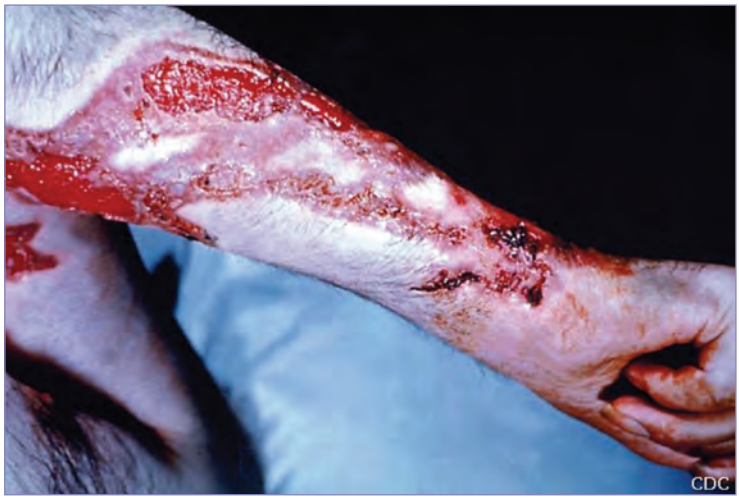


Image 131.1
This patient's arm shows the effects of the fungal disease sporotrichosis, caused by the fungus *Sporothrix schenckii*. Courtesy of Centers for Disease Control and Prevention.

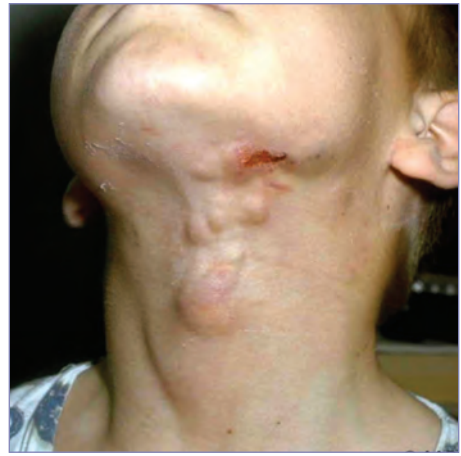


Image 131.2
Sporothrix schenckii was cultured from the biopsy specimen from an abscessed cervical lymph node of this 10-year-old boy. Test results on stained smears of purulent material aspirated from a cervical lymph node were negative.

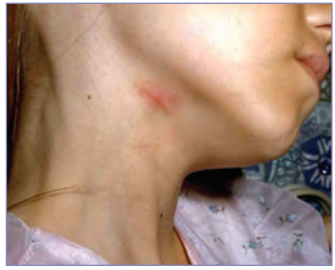


Image 131.3
The cervical lesions of a younger sister of the patient in Image 131.2 also responded to an oral-saturated solution of potassium iodide. There was no evidence of systemic sporotrichosis in these 3 siblings. The origin of their infections was not determined.

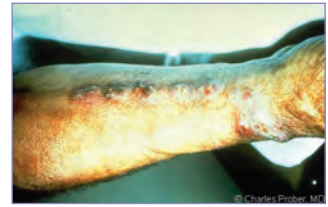


Image 131.4
Linear lymphadenitis secondary to sporotrichosis infection of the foot and foreleg. Copyright Charles Prober.

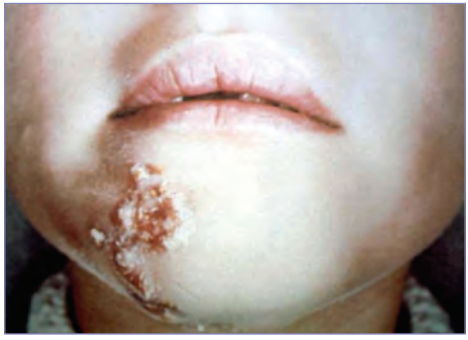


Image 131.5
Cutaneous sporotrichosis of the face in a preschool-aged child. Courtesy of Edgar O. Ledbetter, MD, FAAP.

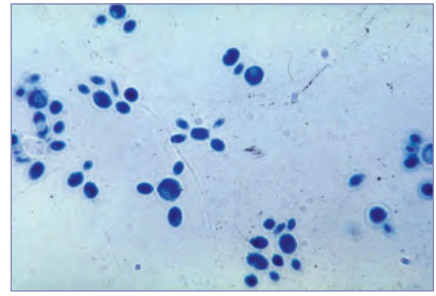


Image 131.6
This micrograph is taken from a slant culture of *Sporothrix schenckii* during its yeast phase. Courtesy of Centers for Disease Control and Prevention.

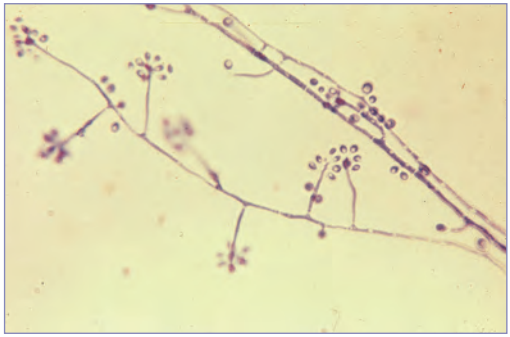


Image 131.7
Sporothrix schenckii, mold phase (48-hour potato dextrose agar, lactophenol cotton blue preparation); small tear-shaped conidia forming rosette-like clusters. Courtesy of Centers for Disease Control and Prevention.

Image 131.8
Sporothrix schenckii on Sabouraud agar slant (specimen from the patient in Image 131.2).

Image 131.9
This is an image of a Sabhi agar plate culture of *Sporothrix schenckii* grown at 20°C (68°F). *S schenckii* is the causative agent for the fungal infection sporotrichosis, also known as rose handler's disease, which affects individuals who handle thorny plants, sphagnum moss, or baled hay. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 132

Staphylococcal Food Poisoning

CLINICAL MANIFESTATIONS

Staphylococcal foodborne illness is characterized by abrupt and sometimes violent onset of severe nausea, abdominal cramps, vomiting, and prostration, often accompanied by diarrhea. Low-grade fever or mild hypothermia can occur. The illness typically lasts 1 to 2 days, but symptoms are intense and can require hospitalization. The short incubation period, brevity of illness, and usual lack of fever help distinguish staphylococcal from other types of food poisoning, with the exception of the vomiting syndrome caused by *Bacillus cereus.* Chemical food poisoning usually has a shorter, and *Clostridium perfringens* food poisoning usually a longer incubation period. Patients with foodborne *Salmonella* or *Shigella* infection are more likely to have fever and a longer incubation period.

ETIOLOGY

Enterotoxins produced by strains of *Staphylococcus aureus* and, rarely, *Staphylococcus epidermidis* and *Staphylococcus intermedius* elicit the symptoms of staphylococcal food poisoning.

EPIDEMIOLOGY

Illness is caused by ingestion of food containing heat-stable staphylococcal enterotoxins. The most commonly implicated foods are meats, poultry, pastries, custards, and other milk- or egg-based products served after inadequate heating or refrigeration. These foods may be contaminated by enterotoxigenic strains of *S aureus* via direct contact with the hands of food handlers, with the organism sometimes originating from purulent discharge from an infected finger or abscess or from nasopharyngeal secretions. When contaminated foods remain at room temperature for several hours, the toxin-producing staphylococcal organisms multiply and produce toxins that are not inactivated by reheating. Less commonly, the toxigenic staphylococci are of bovine origin (eg, cows with mastitis) from contaminated milk or milk products, especially cheeses.

The **incubation period** ranges from 0.5 to 8 hours after ingestion, typically 2 to 4 hours.

DIAGNOSTIC TESTS

In most cases, given the short duration of illness and rapid recovery with supportive care, diagnostic testing to confirm the diagnosis is not necessary. Recovery of large numbers of staphylococci from stool or vomitus and detection of enterotoxin in foods by commercially available kits support the diagnosis. In an outbreak, demonstration of either one or more enterotoxins or ≥105 colony-forming units/g in an epidemiologically implicated food confirms the diagnosis. Identification of the same subtype of *S aureus* from the stool or vomitus of 2 or more ill people also confirms the diagnosis. Strain identification is performed commonly by molecular methods including pulsed field gel electrophoresis or sequence-based typing methods and generally is available through public health laboratories for outbreak investigations.

TREATMENT

Treatment is supportive. Antimicrobial agents are not indicated.

CHAPTER 133

Staphylococcus aureus

CLINICAL MANIFESTATIONS

Staphylococcus aureus causes a variety of localized and invasive suppurative infections and 3 toxin-mediated syndromes: toxic shock syndrome, scalded skin syndrome, and food poisoning. Localized infections include cellulitis, skin and soft tissue abscesses, orbital cellulitis/abscess, pustulosis, impetigo (bullous and nonbullous), paronychia, mastitis, hordeola, furuncles, carbuncles, peritonsillar abscesses (Quinsy), omphalitis, parotitis, lymphadenitis, and wound infections. Bacteremia can be associated with focal complications including osteomyelitis; arthritis; endocarditis; pneumonia; pleural empyema; pericarditis; soft tissue, muscle, or visceral abscesses; and septic thrombophlebitis of small and large vessels. In neutropenic patients, ecthyma gangrenosum may occur. Primary *S aureus* pneumonia also can occur after aspiration of organisms from the upper respiratory tract and typically is associated with mechanical ventilation or as a secondary complication of viral infections in the community (eg, influenza). Meningitis rarely may occur in preterm infants; otherwise meningitis is accompanied by an intradermal foreign body (eg, ventriculoperitoneal shunt) or a congenital or acquired defect in the dura. *S aureus* also causes invasive infections with bacteremia associated with foreign bodies, including intravascular catheters or grafts, peritoneal catheters, cerebrospinal fluid shunts, spinal instrumentation or intramedullary rods, pressure equalization tubes, pacemakers and other intracardiac devices, and prosthetic joints. *S aureus* infections can be fulminant. Certain chronic diseases, such as diabetes mellitus, malignancy, prematurity, immunodeficiency, nutritional disorders, surgery, and transplantation, increase the risk for severe *S aureus* infections. Metastatic foci and abscesses should be drained and foreign bodies should be removed. Prolonged antimicrobial therapy often is necessary to achieve cure.

Staphylococcal toxic shock syndrome (TSS), a toxin-mediated disease, usually is caused by strains producing TSS toxin-1 or possibly other related staphylococcal enterotoxins. Characterized by acute onset of fever, generalized erythroderma, rapid-onset hypotension, and signs of multisystem organ involvement, including profuse watery diarrhea, vomiting, conjunctival injection, and severe myalgia (Table 133.1), TSS can occur in menstruating females using tampons, following childbirth or abortion, after surgical procedures, and in association with cutaneous lesions. TSS also can occur in males and females without a readily identifiable focus of infection. Prevailing clones of community-associated methicillin-resistant *S aureus* (MRSA) rarely produce TSS toxin. People with TSS, especially menses-associated illness, are at risk of a recurrent episode.

Staphylococcal scalded skin syndrome (SSSS) is a toxin-mediated disease caused by circulation of exfoliative toxins A and B. The manifestations of SSSS are age related and include Ritter disease (generalized exfoliation) in the neonate, a tender scarlatiniform eruption and localized bullous impetigo in older children, or a combination of these with thick white/brown flaky desquamation of the entire skin, especially on the face and neck, in older infants and toddlers. The hallmark of SSSS is the toxin-mediated cleavage of the stratum granulosum layer of the epidermis (ie, Nikolsky sign). Healing occurs without scarring. Bacteremia is rare, but dehydration and superinfection can occur with extensive exfoliation.

ETIOLOGY

Staphylococci are catalase-positive, gram-positive cocci that appear microscopically as grape-like clusters. Staphylococci are ubiquitous and can survive extreme conditions of drying, heat, and low-oxygen and high-salt environments. *S aureus* has many surface proteins, including the microbial surface components recognizing adhesive matrix molecule (MSCRAMM) receptors, which allow the organism to bind to tissues and foreign bodies coated with fibronectin, fibrinogen, and collagen. This permits a low inoculum of organisms to adhere to sutures, catheters, prosthetic valves, and other devices.

Table 133.1
Staphylococcus aureus Toxic Shock Syndrome: Clinical Case Definition[a]

Clinical Findings
- Fever: temperature 38.9°C (102.0°F) or greater
- Rash: diffuse macular erythroderma
- Desquamation: 1–2 weeks after onset, particularly on palms, soles, fingers, and toes
- Hypotension: systolic pressure 90 mm Hg or less for adults; lower than fifth percentile for age for children younger than 16 years; orthostatic drop in diastolic pressure of 15 mm Hg or greater from lying to sitting; orthostatic syncope or orthostatic dizziness
- Multisystem organ involvement: 3 or more of the following:
  1. Gastrointestinal tract: vomiting or diarrhea at onset of illness
  2. Muscular: severe myalgia or creatinine phosphokinase concentration greater than twice the upper limit of normal
  3. Mucous membrane: vaginal, oropharyngeal, or conjunctival hyperemia
  4. Renal: serum urea nitrogen or serum creatinine concentration greater than twice the upper limit of normal or urinary sediment with 5 white blood cells/high-power field or greater in the absence of urinary tract infection
  5. Hepatic: total bilirubin, aspartate transaminase, or alanine transaminase concentration greater than twice the upper limit of normal
  6. Hematologic: platelet count 100,000/mm^3 or less
  7. Central nervous system: disorientation or alterations in consciousness without focal neurologic signs when fever and hypotension are absent

Laboratory Criteria
- *Negative* results on the following tests, if obtained:
  1. Blood, throat, or cerebrospinal fluid cultures; blood culture rarely may be positive for *S aureus*
  2. Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles

Case Classification
- **Probable:** a case that meets the laboratory criteria and in which 4 of 5 clinical findings are present
- **Confirmed:** a case that meets laboratory criteria and all 5 of the clinical findings, including desquamation, unless the patient dies before desquamation occurs.

[a] Adapted from Wharton M, Chorba TL, Vogt RL, Morse DL, Buehler JW. Case definitions for public health surveillance. *MMWR Recomm Rep.* 1990;39(RR-13):1–43.

EPIDEMIOLOGY

S aureus is the most common cause of skin and soft tissue infections and musculoskeletal infections in otherwise healthy children. *S aureus* colonizes the skin and mucous membranes of 30% to 50% of healthy adults and children. *S aureus* is second only to coagulase-negative staphylococci (CoNS) as a cause of health care-associated bacteremia, is one of the most common causes of health care-associated pneumonia in children, and is responsible for most health care-associated surgical site infections.

S aureus-mediated TSS was recognized in 1978, and many early cases were associated with tampon use. Although changes in tampon composition and use have resulted in a decreased proportion of cases associated with menses, menstrual and nonmenstrual cases of TSS continue to occur and are reported with similar frequency. Risk factors for TSS include absence of antibody to TSS toxin-1 and focal *S aureus* infection with a TSS toxin-1–producing strain. TSS toxin-1–producing strains can be part of normal flora of the anterior nares or vagina, and colonization at these sites is believed to result in protective antibody in more

than 90% of adults. Health care-associated TSS can occur and most often follows surgical procedures. In postoperative cases, the organism generally originates from the patient's own flora.

Transmission of *S aureus*

The anterior nares, throat, axilla, perineum, vagina, or rectum are usual sites of colonization. Rates of skin carriage of more than 50% occur in children with desquamating skin disorders or burns and in people with frequent needle use (eg, diabetes mellitus, hemodialysis, illicit drug use, allergy shots). Although domestic animals can be colonized, data suggest that colonization is acquired from humans. Adults who carry MRSA in the nose preoperatively are more likely to develop surgical site infections after general, cardiac, orthopedic, or solid organ transplant surgery than are patients who are not carriers. Hospitalized children who are colonized with MRSA on admission or acquire MRSA colonization in the hospital are at increased risk for subsequent MRSA infection compared with noncolonized children.

S aureus is transmitted most often by direct contact in community settings and indirectly from patient to patient via transiently colonized hands of health care professionals in health care settings. Health care professionals and family members who are colonized with *S aureus* in the nares or on skin also can serve as a reservoir for transmission. Contaminated environmental surfaces and objects also can play a role in transmission of *S aureus*, although their relative contribution for spread is unknown. Although not transmitted by the droplet route routinely, *S aureus* can be dispersed into the air over short distances. Dissemination of *S aureus* from people with nasal carriage, including infants, is related to density of colonization, and increased dissemination occurs during viral upper respiratory tract infections. Additional risk factors for health care-associated acquisition of *S aureus* include illness requiring care in neonatal or pediatric intensive care or burn units, surgical procedures, prolonged hospitalization, local epidemic of *S aureus* infection, and the presence of indwelling catheters or prosthetic devices.

Health Care-Associated MRSA

MRSA has been endemic in most US hospitals since the 1980s and recently accounted for more than 40% of health care-associated *S aureus* infections in inpatients reported to the Centers for Disease Control and Prevention (CDC). Risk factors for nasal carriage of health care-associated MRSA strains include hospitalization within the previous year, recent (within 60 days) antimicrobial use, prolonged hospital stay, frequent contact with a health care environment, presence of an intravascular or peritoneal catheter or endotracheal tube, increased number of surgical procedures, or frequent contact with a person with one or more of the preceding risk factors. Carriage can persist for years.

MRSA, both health care- and community-associated strains, and methicillin-resistant CoNS are responsible for a large portion of infections acquired in health care settings. Health care-associated MRSA strains are difficult to treat, because they usually are multidrug resistant and are often susceptible only to vancomycin, linezolid, and agents not approved for use in children.

Community-Associated MRSA

Community-associated MRSA infections emerged in the late 1990s; skin and soft tissue abscesses are noted most commonly. Clinical infections are more common in settings where there is crowding; frequent skin-to-skin contact; sharing of personal items, such as towels and clothing; and poor personal hygiene and among those with body piercings. Outbreaks have been reported among athletic teams, in correctional facilities, and in military training facilities. Community-associated MRSA clones have been implicated as a common cause of health care-associated MRSA infections.

Vancomycin-Intermediately Susceptible *S aureus*

Strains of MRSA with intermediate susceptibility to vancomycin (minimum inhibitory concentration [MIC], 4–8 μg/mL) have been isolated from people (historically dialysis patients) who had received multiple courses of vancomycin for a MRSA infection. Strains of MRSA can be heterogeneous for vancomycin resistance (see

Diagnostic Tests). Extensive vancomycin use allows vancomycin-intermediately susceptible *S aureus* (VISA) strains to develop. These strains may emerge during therapy. Control measures have included using proper methods to detect VISA and infection control measures, and adopting protocols to ensure appropriate vancomycin use.

Vancomycin-Resistant *S aureus* (VRSA)

VRSA infections (MIC >8 μg/mL) are very rare. All reported patients had underlying medical conditions, a history of MRSA infections, and prolonged exposure to vancomycin.

The **incubation period** is variable. A long delay can occur between acquisition of the organism and onset of disease. For toxin-mediated SSSS, the **incubation period** usually is 1 to 10 days; for postoperative TSS, it can be as short as 12 hours.

DIAGNOSTIC TESTS

Gram-stained smears of material from skin lesions or pyogenic foci showing gram-positive cocci in clusters can provide presumptive evidence of infection. Isolation of organisms from culture of otherwise sterile body fluid is the method for definitive diagnosis. Molecular assays are available for direct detection of *S aureus* from blood culture bottles. Nonamplified molecular assays, such as peptide nucleic acid fluorescent in situ hybridization (PNA-FISH), and nucleic acid amplification tests, such as BD GenOhm Staph SR (BD Molecular diagnostics) and Xpert MRSA/SA BC (Cepheid), can identify *S aureus*, including MRSA, in positive blood cultures. Matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF) can rapidly identify *S aureus* colonies on culture plates or from growth in blood cultures. *S aureus* almost never is a contaminant when isolated from a blood culture.

S aureus-mediated TSS is a clinical diagnosis (Table 133.1). *S aureus* grows in culture of blood specimens from fewer than 5% of patients with TSS. Specimens for culture should be obtained from an identified focal site of infection, because these sites usually will yield the organism. Because approximately one third of isolates of *S aureus* from nonmenstrual cases produce toxins other than TSS toxin-1, and TSS toxin-1–producing organisms can be present as normal flora, TSS toxin-1 production by an isolate is not useful diagnostically.

Quantitative antimicrobial susceptibility testing should be performed for all *S aureus* specimens isolated from normally sterile sites. Laboratory practice includes routine screening (D-testing) to exclude inducible clindamycin resistance. Health care-associated MRSA heterogeneous or heterotypic strains appear susceptible by disk testing. However, when a parent strain is cultured on methicillin-containing media, resistant subpopulations are apparent. When these resistant subpopulations are cultured on methicillin-free media, they can continue as stable resistant mutants or revert to susceptible strains (heterogeneous resistance). Cells expressing heteroresistance grow more slowly than the oxacillin-susceptible cells and can be missed at growth conditions above 35°C (95°F).

S aureus strain genotyping has become a necessary adjunct for determining whether several isolates from one patient or from different patients are the same. Typing, in conjunction with epidemiologic information, can facilitate identification of the source, extent, and mechanism of transmission in an outbreak. Antimicrobial susceptibility testing is the most readily available method for typing by a phenotypic characteristic. A number of molecular typing methods are available for *S aureus*, including pulsed-field gel electrophoresis, spa typing, and whole genome sequencing.

TREATMENT

Skin and Soft Tissue Infection

Skin and soft tissue infections, such as diffuse impetigo or cellulitis attributable to methicillin-susceptible *S aureus* (MSSA), optimally are treated with oral penicillinase-resistant beta-lactam drugs, such as a first- or second-generation cephalosporin. For the penicillin-allergic patient and in cases in which MRSA is considered, trimethoprim-sulfamethoxazole, doxycycline, or clindamycin can be used if the isolate is susceptible. Topical mupirocin is recommended for localized impetigo.

The most frequent manifestation of community-associated MRSA infection is skin and soft tissue infection. Figure 133.1 shows the initial management of skin and soft tissue infections suspected to be caused by community-associated MRSA. A randomized placebo-controlled study that included children with simple abscesses ≤3 cm (6–11 months of age), ≤4 cm (1–8 years of age), or ≤5 cm (>8 years of age) in diameter showed that drainage plus systemic oral therapy with clindamycin or trimethoprim-sulfamethoxazole is associated with better outcomes compared with drainage alone, and that treatment with clindamycin was associated with fewer recurrences. In ill patients and for those with complicated skin and soft tissue infection with abscess, drainage/débridement and systemic antimicrobial therapy are warranted; therapy should be focused on the pathogen identified and based on the results of susceptibility testing.

Invasive Staphylococcal Infections

Empirical therapy for suspected invasive staphylococcal infection, including pneumonia, osteoarticular infection, visceral abscesses, and foreign body-associated infection with bacteremia, is vancomycin and a semisynthetic penicillin (eg, nafcillin, oxacillin). Subsequent therapy should be determined by antimicrobial susceptibility results. Clindamycin is bacteriostatic and should not be used for treatment of endovascular infection. Serious MSSA infections require intravenous therapy with a beta-lactamase–resistant beta-lactam antimicrobial agent, such as nafcillin or oxacillin, because most *S aureus* strains produce beta-lactamase enzymes and are resistant to penicillin and ampicillin (Table 133.2). The addition of rifampin may be considered for those with invasive disease related to an indwelling foreign body, especially if removal of the infected implant is not feasible. Vancomycin is not recommended for treatment of serious MSSA infections, because outcomes are inferior compared with cases in which antistaphylococcal beta lactams are used and to minimize emergence of vancomycin resistance. First- or second-generation cephalosporins (eg, cefazolin) or vancomycin are less effective than nafcillin or oxacillin for treatment of MSSA endocarditis or meningitis.

A patient with MSSA infection (and no evidence of endocarditis or central nervous system [CNS] infection) who has a nonserious allergy to penicillin can be treated with a first- or second-generation cephalosporin or with clindamycin, if the *S aureus* strain is susceptible. Clindamycin is bacteriostatic and should not be used for treatment of endovascular infection.

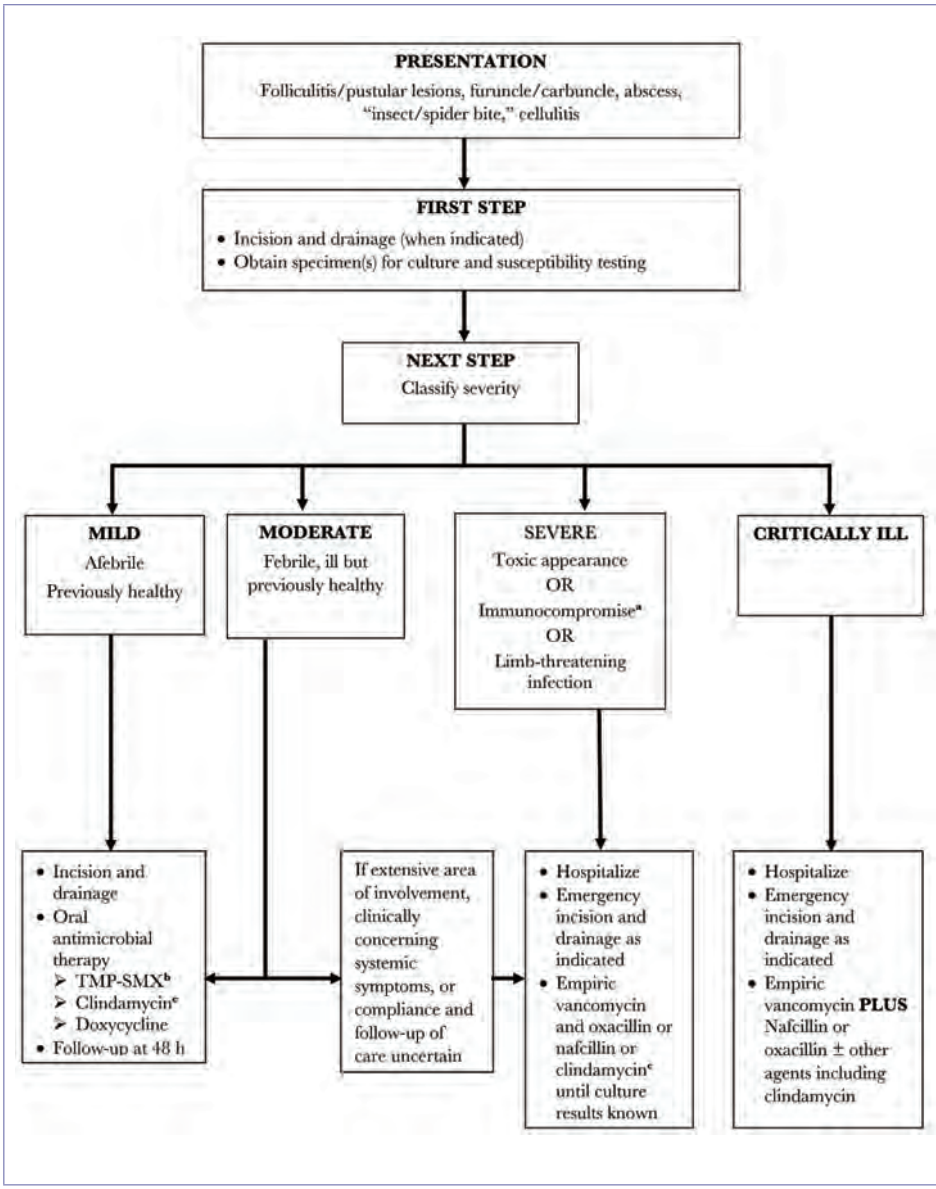
VISA infection is rare in children. For seriously ill patients with a history of recurrent MRSA infections or for patients failing vancomycin therapy in whom VISA strains are a consideration, initial therapy could include linezolid or trimethoprim-sulfamethoxazole, with or without gentamicin. If antimicrobial susceptibility results document multidrug resistance, alternative agents, such as quinupristin-dalfopristin, daptomycin (not effective for pneumonia), ceftaroline, or tigecycline, could be considered.

Duration of therapy for serious MSSA or MRSA infections depends on the site and severity of infection but usually is 4 weeks or more for endocarditis, osteomyelitis, necrotizing pneumonia, or disseminated infection, assuming a documented clinical and microbiologic response. The duration of bacteremia for pediatric patients with staphylococcal infection can be up to 3 to 4 days for MSSA and 7 to 9 days for MRSA. In assessing whether modification of therapy is necessary, clinicians should consider whether the patient is improving, should identify and drain sequestered foci of infection and remove foreign material (such as a central catheter) when possible, and for MRSA strains, should consider the vancomycin MIC and the achievable vancomycin trough concentrations.

Completion of therapy with an oral drug can be considered in children if an endovascular infection (ie, endocarditis or infected thrombus) or CNS infection has been excluded. For endocardiovascular and CNS infections, parenteral therapy is recommended for the entire treatment. Drainage of abscesses and removal of foreign bodies are desirable and almost always are required for medical treatment to be effective. In some cases, multiple drainage and débridement procedures are necessary for children with MRSA osteoarticular infection.

Figure 133.1

Algorithm for Initial Management of Skin and Soft Tissue Infections Caused by Community-Associated *Staphylococcus aureus*



[a] Immunocompromise any chronic condition except asthma or eczema.
[b] TMP-SMX = trimethoprim-sulfamethoxazole, if group A *Streptococcus* unlikely.
[c] Consider prevalence of clindamycin-susceptible methicillin-susceptible *S aureus* and "D" test-negative community-associated methicillin-resistant *S aureus* strains in the community.

Table 133.2
Parenteral Antimicrobial Agent(s) for Treatment of Bacteremia and Other Serious *Staphylococcus aureus* Infections

	Antimicrobial Agents	Comments
I. Initial empiric therapy (organism of unknown susceptibility)		
Drugs of choice:	Vancomycin plus nafcillin or oxacillin	For life-threatening infections (ie, septicemia, endocarditis, CNS infection); ceftaroline or linezolid are alternatives, but there are limited efficacy data in children
	Vancomycin[a]	For non–life-threatening infection without signs of sepsis (eg, skin infection, cellulitis, osteomyelitis, pyarthrosis) when rates of MRSA colonization and infection in the community are substantial; ceftaroline or linezolid are alternatives
	Clindamycin	For non–life-threatening infection without signs of sepsis when rates of MRSA colonization and infection in the community are substantial and prevalence of clindamycin resistance is <15%
II. Methicillin-susceptible *S aureus* (MSSA)		
Drugs of choice:	Nafcillin or oxacillin[b]	
	Cefazolin	
Alternatives:	Clindamycin	Only for patients with a serious penicillin allergy and clindamycin-susceptible strain
	Vancomycin	Only for patients with a serious penicillin and cephalosporin allergy
	Ampicillin-sulbactam	For patients with polymicrobial infections caused by susceptible isolates

Table 133.2 (*continued*)

	Antimicrobial Agents	Comments
III. Methicillin-resistant *S aureus* (MRSA; oxacillin MIC, 4 µg/mL or greater)		
A. Health care-associated (multidrug resistant)		
Drugs of choice:	Vancomycin ± gentamicin[b]	
Alternatives: susceptibility testing results available before alternative drugs are used	Trimethoprim-sulfamethoxazole Linezolid[c] Quinupristin-dalfopristin[c]	
B. Community-associated (not multidrug resistant)		
Drugs of choice:	Vancomycin ± gentamicin[b]	For life-threatening infections or endovascular infections including those complicated by venous thrombosis
	Clindamycin (if strain susceptible)	For pneumonia, septic arthritis, osteomyelitis, skin or soft tissue infections
	Trimethoprim-sulfamethoxazole	For skin or soft tissue infections
	Doxycycline (if strain susceptible)	
Alternative:	Vancomycin	For serious infections
	Linezolid	For serious infections caused by clindamycin resistant isolates in patients with renal dysfunction or those intolerant of vancomycin

(*continued*)

Table 133.2 (*continued*)

	Antimicrobial Agents	Comments
IV. Vancomycin-intermediately susceptible *S aureus* (VISA; MIC, 4 to 16 µg/mL)[c]		
Drugs of choice:	Optimal therapy is not known	Dependent on in vitro susceptibility test results
	Linezolid[c]	
	Ceftaroline	
	Daptomycin[d]	
	Quinupristin-dalfopristin[c]	
	Tigecycline	
Alternatives:	Vancomycin plus linezolid ± gentamicin	
	Vancomycin plus trimethoprim-sulfamethoxazole[b]	

CNS indicates central nervous system; MIC, minimum inhibitory concentration.

[a]Some experts prefer 15 mg/kg every 6 hours for empiric therapy for any invasive infections including osteomyelitis, pyoarthritis, or pneumonia.

[b]Gentamicin and rifampin for the first 2 weeks should be added for endocarditis of a prosthetic device. Addition of rifampin is recommended for other device-related infections (spinal instrumentation, prosthetic joint). Consultation with an infectious diseases specialist should be considered to determine which agent to use and duration of use.

[c]Linezolid, ceftaroline, quinupristin-dalfopristin, and tigecycline are agents with activity in vitro and efficacy in adults with multidrug-resistant, gram-positive organisms, including *S aureus*. Because experience with these agents in children is limited, consultation with an infectious diseases specialist should be considered before use.

[d]Daptomycin is active in vitro against multidrug-resistant, gram-positive organisms, including *S aureus*. Daptomycin is approved by the US Food and Drug Administration only for treatment of complicated skin and skin structure infections and for *S aureus* bloodstream infections. Daptomycin is ineffective for treatment of pneumonia.

Duration of therapy for central line-associated bloodstream infections is controversial and depends on consideration of a number of factors—the type and location of the catheter, the site of infection (exit site vs tunnel vs line), the feasibility of using an alternative vascular access site at a later date, and the presence or absence of a catheter-related thrombus. Infections are more difficult to treat when associated with a thrombus, thrombophlebitis, or intra-atrial thrombus, and a longer course is suggested if the patient is immunocompromised. Experts differ on recommended duration, but many suggest a minimum of 14 days provided there is no evidence of a metastatic focus and the patient responds to antimicrobial therapy with immediate resolution of the *S aureus* bacteremia. If the patient requires a new central line, waiting 48 to 72 hours after bacteremia has been documented to be resolved before insertion is optimal. If a tunneled catheter is needed for ongoing care, in situ treatment of the infection can be attempted. Vegetations or a thrombus in the heart or great vessels always should be considered when a central line becomes infected and should be suspected more strongly if blood cultures remain positive for more than 2 days during appropriate antimicrobial therapy or if there are other clinical manifestations associated with endocarditis. Transesophageal echocardiography, if feasible, is the most sensitive technique for identifying vegetations, but transthoracic echocardiography generally is adequate for children younger than 10 years and those weighing <60 kg.

Management of *S aureus* Toxin-Mediated Diseases

The principles of therapy for TSS include aggressive fluid management to maintain adequate venous return and cardiac filling to prevent end organ damage, source control that includes prompt identification and removal of any indwelling foreign body (eg, tampon) or drainable focus, and anticipation and management of the commonly observed multiorgan complications of TSS (eg, acute respiratory distress syndrome, renal dysfunction). Initial antimicrobial therapy should include a parentally administered beta-lactam antistaphylococcal antimicrobial agent and a protein synthesis-inhibiting drug, such as clindamycin, at maximum dosages. Vancomycin should be added to beta lactamase-resistant penicillins or cephalosporins in regions where MRSA infections are common, although MRSA-associated TSS is rare in the United States. Once the organism is identified and susceptibilities are known, therapy for *S aureus* should be modified, but an active antimicrobial agent should be continued for 10 to 14 days. Administration of antimicrobial agents can be changed to the oral route once the patient is tolerating oral alimentation. The total duration of therapy is based on the usual duration of established foci of infection (eg, pneumonia, osteomyelitis). SSSS in infants should be treated with a parenteral beta lactamase-resistant beta-lactam antimicrobial agent, or if MRSA is a consideration, vancomycin can be used. Transition to an oral agent can be considered in older infants, children, and adolescents who have demonstrated excellent clinical and microbiologic response to parenteral therapy.

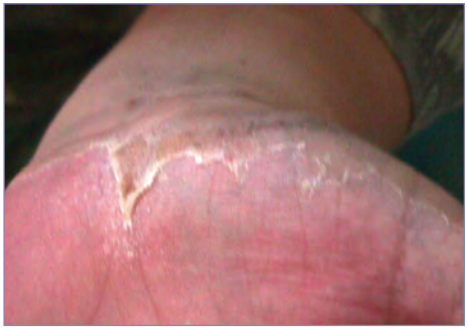


Image 133.1
Skin desquamation of the hand in a 7-year-old boy with staphylococcal scalded skin syndrome. Courtesy of Benjamin Estrada, MD.

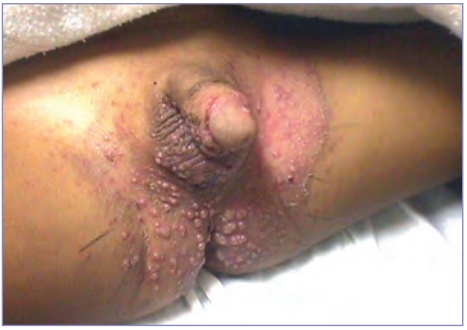


Image 133.2
Newborn with pustulosis of the perineum and genitalia due to *Staphylococcus aureus*. Copyright Michael Rajnik, MD, FAAP.

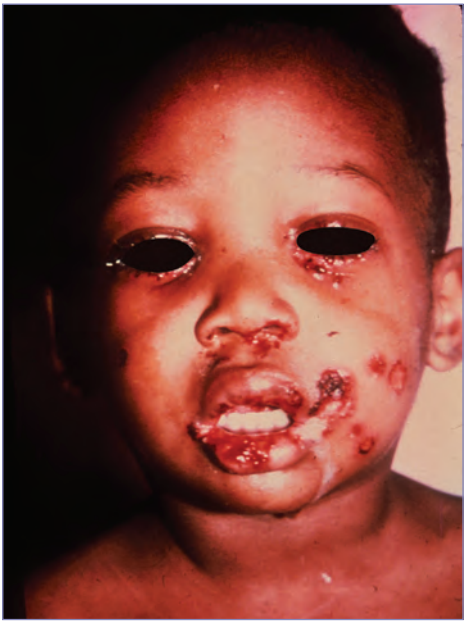


Image 133.3
Staphylococcal bullous impetigo lesions about the eyes, nose, and mouth in a 6-year-old black boy. Also note the secondary anterior cervical lymphadenopathy. Courtesy of George Nankervis, MD.

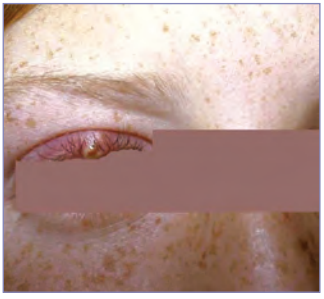


Image 133.4
Staphylococcus aureus hordeolum (sebaceous gland abscess) in an adolescent girl.

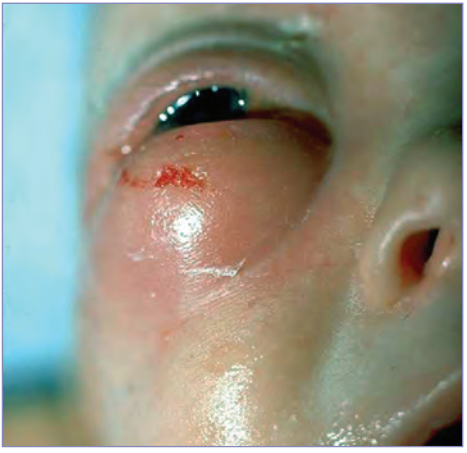


Image 133.5
An infant with orbital cellulitis and ethmoid sinusitis due to *Staphylococcus aureus*. Copyright Martin G. Myers, MD.

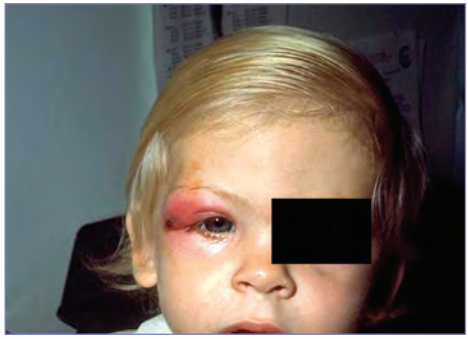


Image 133.6
Periorbital cellulitis due to *Staphylococcus aureus*–infected lesion adjacent to the orbit (most likely secondary to a recent insect bite). Courtesy of Edgar O. Ledbetter, MD, FAAP.

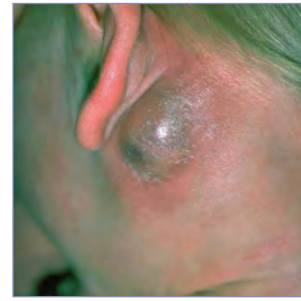


Image 133.7
A 1½-year-old boy, atopic, with subauricular lymphadenitis due to *Staphylococcus aureus*.

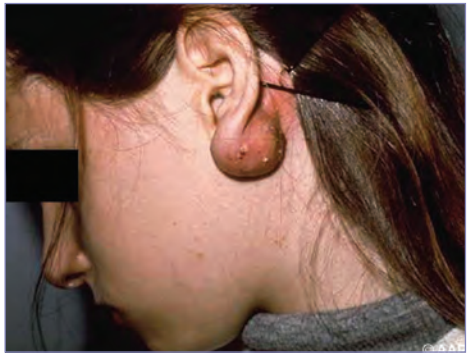


Image 133.8
Staphylococcus aureus abscess of the lobe of the left ear secondary to ear piercing in an adolescent girl. Courtesy of Edgar O. Ledbetter, MD, FAAP.

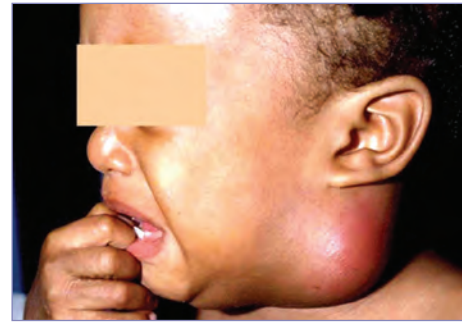


Image 133.9
Subauricular cervical adenitis *Staphylococcus aureus* in a 2-year-old boy.

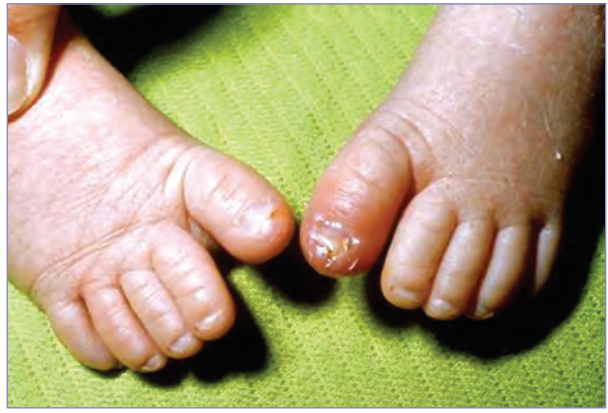


Image 133.10
Posttraumatic paronychia due to *Staphylococcus aureus* of the left great toe of an infant. Courtesy of Edgar O. Ledbetter, MD, FAAP.

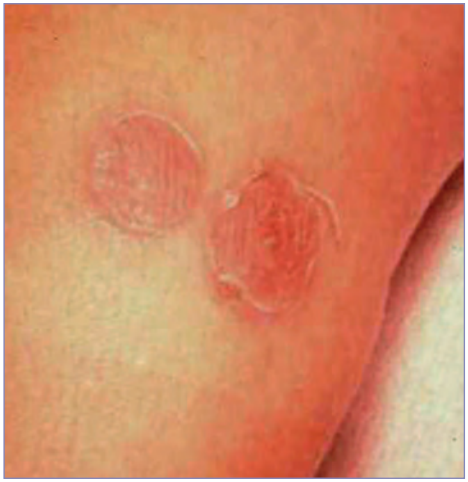


Image 133.11
Impetigo (bullous) due to *Staphylococcus aureus*.

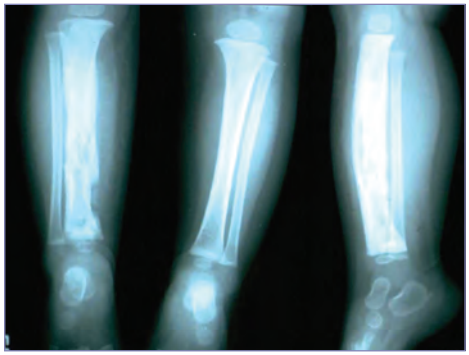


Image 133.13
Chronic osteomyelitis of the right tibia due to *Staphylococcus aureus*.

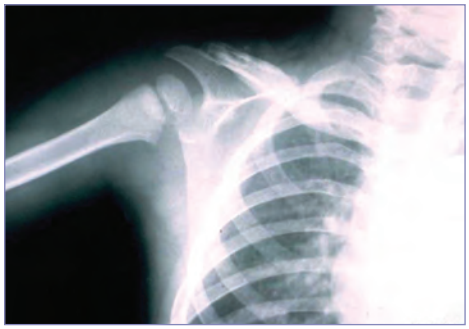


Image 133.15
Chronic osteomyelitis of the clavicle in a 12-year-old boy due to *Staphylococcus aureus*.

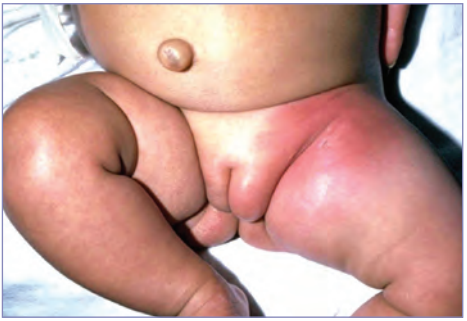


Image 133.12
Cellulitis (inguinal) due to *Staphylococcus aureus*. Copyright Neal Halsey, MD.

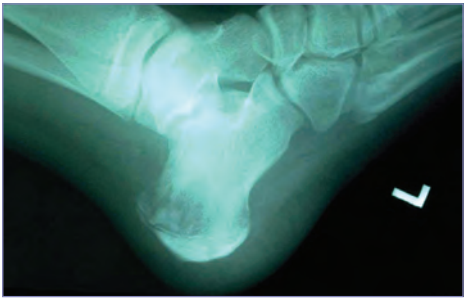


Image 133.14
Osteomyelitis of the calcaneus due to *Staphylococcus aureus* with no history of injury.

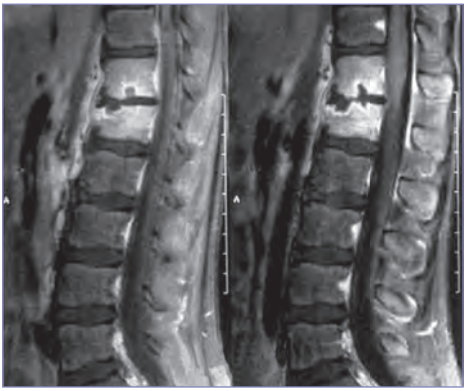


Image 133.16
Vertebral osteomyelitis in a 13-year-old with a 6-week history of back pain. Magnetic resonance imaging revealed osteolytic changes of the anterior segments of the first and second lumbar vertebrae. A culture of the biopsy specimen grew methicillin-resistant *Staphylococcus aureus*.

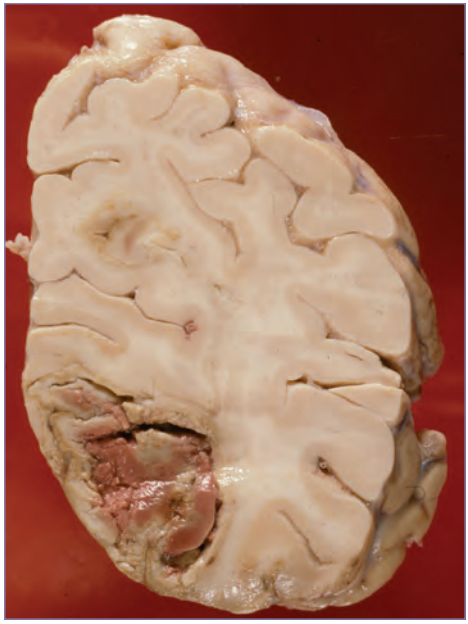


Image 133.17
Cerebral infarct in a patient with bacterial endocarditis. Courtesy of Dimitris P. Agamanolis, MD.

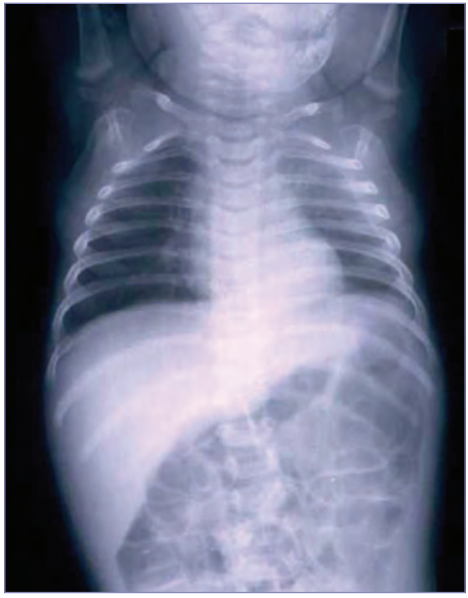


Image 133.19
Staphylococcal pneumonia, primary, with rapid progression and empyema. The infant had only mild respiratory distress and paralytic ileus without fever when first examined.

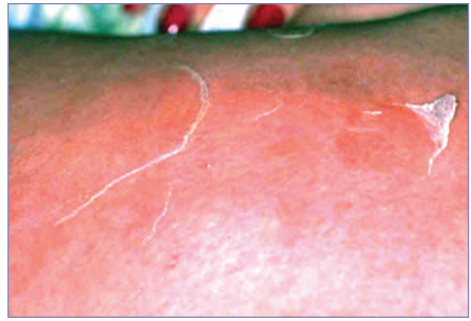


Image 133.18
Staphylococcal scalded skin syndrome with a positive Nikolsky sign.

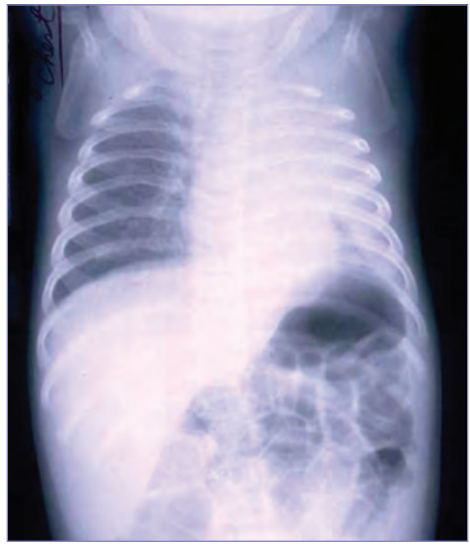


Image 133.20
Staphylococcal pneumonia, primary, with rapid progression with empyema. This is the same patient as in Image 133.19.

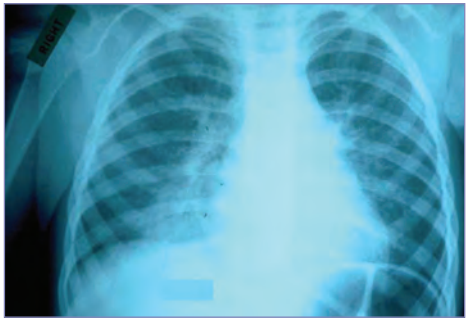


Image 133.21
Pneumonia due to *Staphylococcus aureus* with right lower lobe infiltrate in a preschool-aged child (day 1). Courtesy of Edgar O. Ledbetter, MD, FAAP.

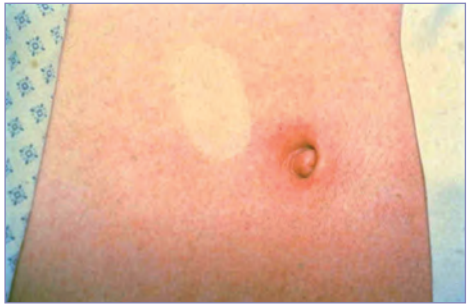


Image 133.23
Erythroderma that blanches on pressure in a patient with toxic shock syndrome. The mortality rate for staphylococcal toxic shock syndrome is lower than that of streptococcal toxic shock syndrome.

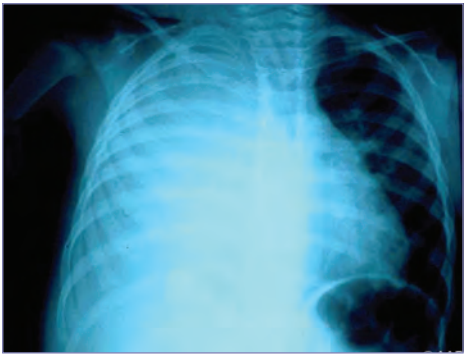


Image 133.22
Staphylococcal pneumonia with massive empyema demonstrating the rather rapid progression typical of staphylococcal infection. This is the same patient as in Image 133.21 (day 4). Courtesy of Edgar O. Ledbetter, MD, FAAP.

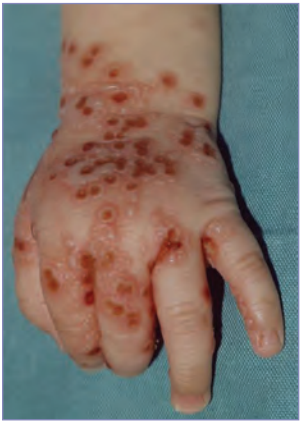


Image 133.24
Children who have atopic dermatitis are prone to recurrent skin infections, particularly with *Staphylococcus aureus* and herpes simplex, for several reasons. Exacerbations of eczema disrupt the skin's protective barrier. The failure to produce endogenous antimicrobial peptides has been offered as a reason.

Image 133.25
A *Staphylococcus aureus* isolate tested by the gradient diffusion method with vancomycin, daptomycin, and linezolid on Mueller-Hinton-IH agar. The minimum inhibitory concentration of each agent is determined by the intersection of the organism growth with the strip as measured using the scale inscribed on the strip. Used with permission from *Clinical Infectious Diseases.*

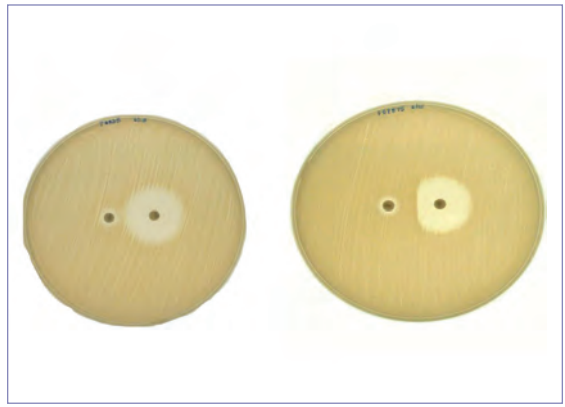


Image 133.26
D zone test for clindamycin-induced resistance by *Staphylococcus aureus*. The left shows a negative result and the right shows a positive one. Courtesy of Sarah Long, MD, FAAP.

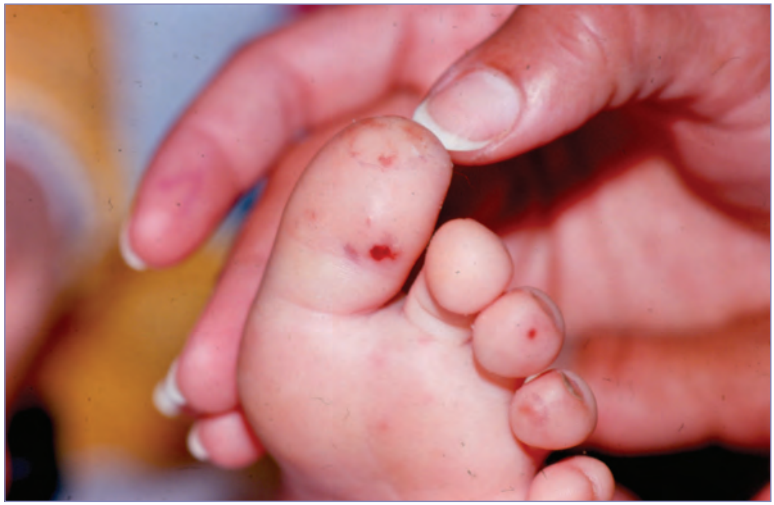


Image 133.27
Janeway lesions on the toes of a 4-year-old with subacute bacterial endocarditis caused by *Staphylococcus aureus.* Courtesy of Carol J. Baker, MD.

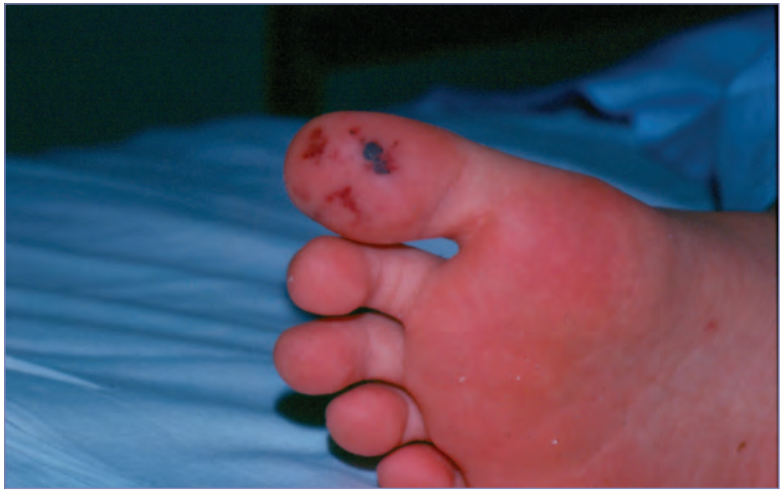


Image 133.28
Nontender, small erythematous or hemorrhagic macular or nodular lesions (Janeway lesions) of the toe in a 10-year-old boy who had acute *Staphylococcus aureus* bacterial endocarditis of the aortic valve. Courtesy of Carol J. Baker, MD.

CHAPTER 134

Coagulase-Negative Staphylococcal Infections

CLINICAL MANIFESTATIONS

Most coagulase-negative staphylococci (CoNS) isolates from patient specimens represent contamination of culture material. Of the isolates that do not represent contamination, most come from infections associated with health care, such as patients with obvious disruptions of host defenses caused by surgery, medical device insertion, immunosuppression, or immature host defense (eg, very low birth weight infants). CoNS are the most common cause of late-onset bacteremia among preterm infants, typically infants weighing less than 1,500 g at birth, and of episodes of health care-associated bacteremia in all age groups. CoNS are responsible for bacteremia in children with intravascular catheters, vascular grafts, intracardiac patches, prosthetic cardiac valves, or pacemaker wires. Infection also may occur associated with other indwelling foreign bodies, including cerebrospinal fluid shunts, peritoneal catheters, spinal instrumentation, baclofen pumps, pacemakers, or prosthetic joints. Mediastinitis after open-heart surgery, endophthalmitis after intraocular trauma, and omphalitis and scalp abscesses in preterm neonates have been described. CoNS also can enter the bloodstream from the respiratory tract of mechanically ventilated preterm infants or from the gastrointestinal tract of infants with necrotizing enterocolitis. Some species of CoNS are associated with urinary tract infection, including *Staphylococcus saprophyticus* in adolescent and young adult females, often after sexual intercourse, and *Staphylococcus epidermidis* and *Staphylococcus haemolyticus* in hospitalized patients with urinary tract catheters. *Staphylococcus lugdunensis* is of particular significance, because it may cause infections resembling *Staphylococcus aureus*, including skin and soft tissue infection and bacteremia with or without endocarditis.

ETIOLOGY

There are more than 40 named coagulase-negative *Staphylococcus* species; *Staphylococcus epidermidis*, *S haemolyticus*, *S saprophyticus*, *Staphylococcus schleiferi*, and *S lugdunensis* most often are associated with human infections. Many CoNS produce an exopolysaccharide slime biofilm that makes these organisms, as they bind to medical devices (eg, catheters), relatively inaccessible to host defenses and antimicrobial agents.

EPIDEMIOLOGY

CoNS are common inhabitants of the skin and mucous membranes. Virtually all infants have colonization at multiple sites by 2 to 4 days of age. The most frequently isolated CoNS organism is *S epidermidis*, which is found widely in most areas of skin. Different species colonize specific areas of the body. *S haemolyticus* is found on areas of skin with numerous apocrine glands, and *S auricularis* is found in the external ear canal. *S lugdunensis* has a predilection for colonization of the inguinal and groin areas. The frequency of health care-associated CoNS infections increased steadily until 2000, when these infections decreased because of rigorous infection control measures. Infants and children in intensive care units, including neonatal intensive care units, have the highest incidence of CoNS bloodstream infections. CoNS can be introduced at the time of medical device placement, through mucous membrane or skin breaks, through loss of bowel wall integrity (eg, necrotizing enterocolitis in very preterm neonates), or during catheter manipulation. Less often, health care professionals with environmental CoNS colonization on their hands transmit the organism.

The **incubation period** is unknown. A long delay can occur between acquisition of the organism and onset of disease.

DIAGNOSTICS TESTS

CoNS are nonfastidious organisms readily isolated in culture using the same media and incubation conditions as are used for *S aureus*. Tests for coagulase by traditional methods or by latex agglutination are the same as are used for *S aureus*. CoNS isolated from a single blood culture commonly are classified as skin contaminants introduced into the blood culture bottle during venipuncture, and full identification and antimicrobial susceptibility testing are not performed by most clinical laboratories. Rapid differentiation of CoNS and *S aureus* in

positive blood culture can be obtained by using fluorescent in situ hybridization (FISH) probes or multiplex PCR panel assays. In a very preterm neonate, an immunocompromised person, or a patient with an indwelling catheter or prosthetic device, repeated isolation of the same species of CoNS based on identification using biochemical test systems or MALDI-TOF mass spectroscopy from blood cultures or another normally sterile body fluid often indicates true infection. Genotyping of the isolates more strongly supports the diagnosis; however, fewer methods are available for the CoNS. For central line-associated bloodstream infection, quantitative blood cultures from the catheter generally will have 5 to 10 times more organisms than cultures from a peripheral blood vessel. This type of analysis requires that both a peripheral and line blood culture be performed at the same time.

Criteria that suggest CoNS as pathogens, rather than contaminants, include the following: 2 or more positive blood cultures from different collection sites; single positive culture from blood and another sterile site (eg, cerebrospinal fluid, joint) with identical antimicrobial susceptibility patterns for each isolate; growth in a continuously monitored blood culture system within 15 hours of incubation; an intravascular catheter that has been in place for 3 days or more; similar or identical genotypes among all isolates; and clinical findings (eg, abscess).

TREATMENT

More than 90% of health care-associated CoNS strains are methicillin resistant. Methicillin-resistant strains are resistant to all beta-lactam drugs, including cephalosporins (except ceftaroline), and usually several other drug classes. Intravenous vancomycin is recommended for treatment of serious infections caused by CoNS strains resistant to beta-lactam antimicrobial agents. An exception to this is *S lugdunensis*, which generally is oxacillin susceptible. Treatment of infected foreign bodies should be continued for 10 to 14 days parenterally. Antimicrobial lock therapy of tunneled central lines may result in a higher rate of catheter salvage in adults with CoNS infections, but experience with this approach is limited in children. If blood cultures remain positive for more than 3 to 5 days after initiation of appropriate antimicrobial therapy for CoNS or if the clinical illness fails to improve, the central line should be removed, parenteral therapy should be continued, and the patient should be evaluated for metastatic foci of infection. If a central line can be removed, there is no demonstrable thrombus, and bacteremia resolves promptly, a 5-day course of therapy is appropriate for CoNS (other than *S lugdunensis*, which should be managed similarly to *S aureus* catheter-related infections).

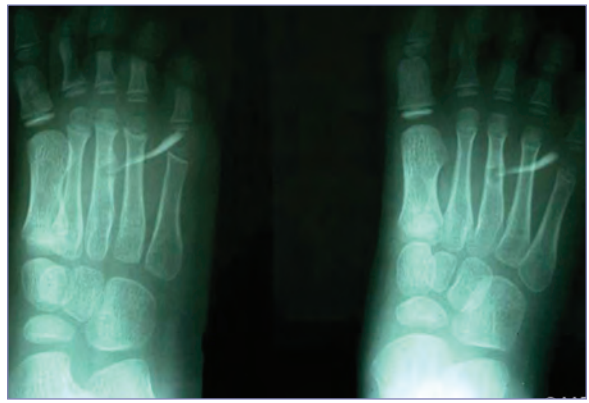


Image 134.1
Osteomyelitis due to *Staphylococcus epidermidis* secondary to foreign body penetration of third metatarsal of right foot in a 5-year-old boy. Coagulase-negative staphylococcal infections are often associated with disruption of normal defense mechanisms. Courtesy of Edgar O. Ledbetter, MD, FAAP.

CHAPTER 135

Group A Streptococcal Infections

CLINICAL MANIFESTATIONS

The most common group A streptococcal (GAS) infection is acute pharyngotonsillitis (pharyngitis), which is heralded by sore throat with tonsillar inflammation and often tender anterior cervical lymphadenopathy. Pharyngitis can be accompanied by palatal petechiae or a strawberry tongue. Purulent complications of pharyngitis usually occur in patients not treated with antimicrobial agents and include otitis media, sinusitis, peritonsillar or retropharyngeal abscesses, and suppurative cervical adenitis. Nonsuppurative complications include acute rheumatic fever (ARF) and acute glomerulonephritis. The goal of antimicrobial therapy for GAS pharyngitis is to reduce acute morbidity, suppurative and nonsuppurative (ARF) complications, and transmission to close contacts. Antimicrobial therapy for preventing acute poststreptococcal glomerulonephritis after pyoderma or pharyngitis is not effective.

Scarlet fever occurs most often in association with pharyngitis and, rarely, with pyoderma or an infected wound. Scarlet fever usually is a mild disease in the modern era and involves a characteristic confluent erythematous sandpaper-like rash that is caused by one or more of several erythrogenic exotoxins produced by group A streptococci. Other than occurrence of rash, the epidemiologic features, symptoms, signs, sequelae, and treatment of scarlet fever are the same as those of streptococcal pharyngitis.

Acute streptococcal pharyngitis is uncommon in children younger than 3 years. Instead, they may present with rhinitis and then develop a protracted illness with moderate fever, irritability, and anorexia (streptococcal fever or streptococcosis). The second most common site of GAS infection is skin. Streptococcal skin infections (eg, pyoderma or impetigo) can be followed by acute glomerulonephritis, which occasionally occurs in epidemics. ARF has not been proven to be a sequela of GAS skin infection.

Other manifestations of GAS infections include erysipelas, cellulitis (including perianal), vaginitis, bacteremia, sepsis, pneumonia, endocarditis, pericarditis, septic arthritis, necrotizing fasciitis, purpura fulminans, osteomyelitis, myositis, puerperal sepsis, surgical wound infection, mastoiditis, and neonatal omphalitis. Invasive GAS infections often are associated with bacteremia with or without a local focus of infection and can present as streptococcal toxic shock syndrome (STSS), overwhelming sepsis, or necrotizing fasciitis. Necrotizing fasciitis can follow minor or unrecognized trauma, often involves an extremity, and presents as pain out of proportion to examination findings.

STSS is caused by infection of normally sterile body sites (blood, pleura, cerebrospinal fluid) with toxin-producing GAS strains and typically manifests as a severe acute illness characterized by fever, generalized erythroderma, rapid-onset hypotension, and signs of multiorgan involvement, including rapidly progressive renal failure. Evidence of local soft tissue infection (eg, cellulitis, myositis, or necrotizing fasciitis) associated with severe, rapidly increasing pain is common, but STSS can occur without an identifiable focus of infection or with foci such as pneumonia with or without empyema, osteomyelitis, arthritis, or endocarditis.

Rheumatic fever is a nonsuppurative sequela of GAS pharyngitis and is endemic in Africa, Asia, and the Pacific, including the indigenous population in Australia. The United States and Europe are considered low-risk populations, but cases continue to occur sporadically.

An association between GAS infection and sudden onset of obsessive-compulsive behavior, tic disorders, or other unexplained acute neurologic changes—pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS), as a subset of pediatric acute-onset neuropsychiatric syndrome (PANS)—has been proposed. The data for an association with GAS and either PANDAS or PANS rely on small and as yet unduplicated studies. In the absence of acute clinical symptoms and signs of pharyngitis, GAS testing (by culture, antigen detection, or serology) is not recommended for such patients. There also is insufficient evidence to support antibiotic

treatment or prophylaxis, Immune Globulin Intravenous, or plasmapheresis for children with symptoms suggestive of PANDAS or PANS. Management is best directed by specialists who could include child psychiatrists, behavioral and developmental pediatricians, or child neurologists.

ETIOLOGY

More than 240 distinct serotypes or genotypes of group A streptococci (*Streptococcus pyogenes*) have been identified based on M-protein serotype or M-protein gene sequence (*emm* types). Because of a variety of factors, including M nontypability and *emm* sequence variation within given M types, *emm* typing generally is more discriminating than M-protein serotyping. Epidemiologic studies indicate an association between certain serotypes (eg, types 1, 3, 5, 6, 14, 18, 19, and 24) and rheumatic fever, but a specific rheumatogenic factor has not been identified. Several serotypes (eg, types 2, 49, 55, 57, 59, 60, and 61) more commonly are associated with pyoderma and acute glomerulonephritis. Other serotypes (eg, types 1, 6, and 12) are associated with pharyngitis and acute glomerulonephritis. Although many M types can cause STSS, most cases are caused by M types 1 and 3 strains producing at least 1 of several different pyrogenic exotoxins, most commonly streptococcal pyrogenic exotoxin A (SPE A). These toxins act as superantigens that stimulate production of tumor necrosis factor and other inflammatory mediators that cause capillary leak and other physiologic changes, leading to hypotension and multiorgan damage.

EPIDEMIOLOGY

Pharyngitis usually results from contact with the respiratory tract secretions of a person who has GAS pharyngitis. Fomites and household pets, such as dogs, are not vectors of GAS infection. Pharyngitis and impetigo (and their nonsuppurative complications) can be associated with crowding, which often is present in socioeconomically disadvantaged populations. The close contact that occurs in schools, child care centers, contact sports (eg, wrestling), boarding schools, and military installations facilitates transmission. Foodborne outbreaks of pharyngitis occur rarely and are a consequence of human contamination of food in conjunction with improper food preparation or refrigeration procedures.

GAS pharyngitis occurs at all ages but is most common among school-aged children and adolescents, peaking at 7 to 8 years of age. GAS pharyngitis and pyoderma are substantially less common in adults than in children.

Geographically, GAS pharyngitis and pyoderma are ubiquitous. Pyoderma is more common in tropical climates and warm seasons, at least in part because of antecedent insect bites and other minor skin trauma. Streptococcal pharyngitis is more common during late autumn, winter, and spring in temperate climates, in part because of close person-to-person contact in schools. Communicability of patients with streptococcal pharyngitis is highest during acute infection and, when untreated, gradually diminishes over a period of weeks.

Throat culture surveys of healthy asymptomatic children during the streptococcal season and during school outbreaks of pharyngitis have yielded GAS prevalence rates as high as 25%. These surveys identified children who were chronic pharyngeal carriers. Carriage of GAS can persist for many months, but risk of transmission from carriers to others is low.

In streptococcal impetigo, the organism usually is acquired by direct contact from another person. GAS colonization of healthy skin usually precedes development of impetigo, but group A streptococci do not penetrate intact skin. Impetiginous lesions occur at the site of breaks in skin (eg, insect bites, burns, traumatic wounds, varicella lesions). After development of impetiginous lesions, the upper respiratory tract often becomes colonized with GAS. Infection of surgical wounds and postpartum (puerperal) sepsis usually result from transmission through direct contact. Health care workers who are anal or vaginal carriers of GAS and people with skin infection or pharyngeal colonization can transmit GAS organisms to surgical and obstetrical patients, resulting in health care-associated outbreaks. Infections in neonates, uncommon in the United States but common in many developing countries, result from

intrapartum or contact transmission; in the latter situation, infection can begin as omphalitis, cellulitis, or necrotizing fasciitis.

In the United States, the incidence of invasive GAS infections is highest in infants and the elderly. Fatal cases in children are not common. Before use of varicella vaccine, varicella was the most commonly identified predisposing factor for invasive GAS infection in children. Other factors increasing risk include exposure to other children and household crowding. The portal of entry is unknown in most invasive GAS infections but is presumed to be skin or mucous membranes. Such infections rarely follow symptomatic GAS pharyngitis. An association between use of nonsteroidal anti-inflammatory drugs and invasive GAS infections in children with varicella has been described, but a causal relationship has not been established.

STSS can occur at any age. Fewer than 5% of cases of invasive streptococcal infections in children are associated with STSS. Among children, STSS has been reported with focal lesions (eg, varicella, cellulitis, trauma, osteomyelitis, pneumonia), and with bacteremia without a defined focus. Mortality rates are substantially lower for children than for adults with STSS.

During epidemics of GAS infections on military bases in the 1950s, rheumatic fever developed in 3% of untreated patients with acute GAS pharyngitis; rare cases have occurred in treated patients. The current incidence in the United States is not precisely known but is substantially less than 1%. The incidence of ARF in the United States decreased sharply during the 20th century, and rates of this nonsuppurative sequela are low, with rare exception. Focal outbreaks of ARF in school-aged children occurred in several areas in the 1990s, and small clusters continue to be reported periodically. The highest US rates of ARF are in Utah and Hawaii and are most likely related to circulation of particularly rheumatogenic strains. The occurrence of ARF reemphasizes the importance of diagnosing GAS pharyngitis accurately and treating with a recommended antimicrobial regimen.

The **incubation period** for streptococcal pharyngitis is 2 to 5 days. For impetigo, a 7- to 10-day period between acquisition of GAS on healthy skin and development of lesions has been demonstrated. The **incubation period** for STSS is not known.

DIAGNOSTIC TESTS

Children with pharyngitis and obvious viral symptoms (eg, rhinorrhea, cough, hoarseness, oral ulcers) should not be tested or treated for GAS infection; testing also generally is not recommended for children younger than 3 years. Laboratory confirmation before initiation of antimicrobial treatment is required for children with pharyngitis without viral symptoms, because many will not have GAS pharyngitis. A specimen should be obtained by vigorous swabbing using a pair of swabs on both tonsils and the posterior pharynx for rapid antigen testing. It is recommended that a throat swab from a child with a negative rapid antigen test result be submitted to the laboratory for isolation of GAS; the second swab can be used for this purpose. Culture on sheep blood agar can confirm GAS infection, with latex agglutination differentiating GAS from other beta-hemolytic streptococci (group C or G). False-negative culture results occur in fewer than 10% of symptomatic patients when an adequate throat swab specimen is obtained and cultured by trained personnel. Recovery of group A streptococci from the pharynx does not distinguish patients with true acute streptococcal infection from streptococcal carriers who have an intercurrent viral pharyngitis. The number of colonies of group A streptococci on a culture plate also does not reliably differentiate true infection from carriage. Cultures that are negative for group A streptococci after 18 to 24 hours of incubation should be incubated for a second day to optimize recovery of group A streptococci.

Several rapid diagnostic tests for GAS pharyngitis are available. Most are based on nitrous acid extraction of GAS carbohydrate antigen from organisms obtained by throat swab. Specificities of these tests generally are high (very few false-positive results), but the reported sensitivities vary considerably (ie, false-negative results occur). As with throat swab cultures, sensitivity of these tests is highly dependent on the quality of the throat swab specimen, the experience of the person performing the test, and the rigor of the culture method used for comparison. The US Food and

Drug Administration (FDA) has cleared a variety of rapid tests for use in home settings. Parents should be informed that home use is discouraged because of the risk of false-positive testing that represents colonization.

Because of the very high specificity of rapid tests, a positive test result does not require throat culture confirmation. Rapid diagnostic tests using techniques such as polymerase chain reaction (PCR), chemiluminescent DNA probes, and isothermal nucleic acid amplification tests have been developed. The FDA recently approved isothermal nucleic acid amplification tests for detection of group A streptococci from throat swab specimens. Some studies suggest that these tests may be as sensitive as standard throat cultures on sheep blood agar.

Indications for GAS Testing

Factors to be considered in the decision to obtain a throat swab specimen for testing children with pharyngitis are the patient's age, signs and symptoms, season, and family and community epidemiology, including contact with a person with GAS infection or presence in the family of a person with a history of ARF or of poststreptococcal glomerulonephritis.

- Children with manifestations highly suggestive of viral infection, such as coryza, conjunctivitis, hoarseness, cough, anterior stomatitis, discrete ulcerative oral lesions, or diarrhea, are very unlikely to have true GAS pharyngitis and should not be tested.
- Testing children younger than 3 years generally is not indicated.
- In contrast, children with acute onset of sore throat and clinical signs and symptoms such as pharyngeal exudate, pain on swallowing, fever, and enlarged tender anterior cervical lymph nodes, without concurrent viral symptoms and/or exposure to a person with GAS pharyngitis, are more likely to have GAS infection and should have a rapid antigen test and a throat culture if the rapid test result is negative.

Testing Contacts for GAS Infection

Indications for testing contacts for GAS infection vary according to circumstances. Testing asymptomatic household contacts for GAS infection is not recommended except when the contacts are at increased risk of developing sequelae of GAS infection, such as ARF or acute glomerulonephritis; if test results are positive, such contacts should be treated.

In schools, child care centers, or other environments in which large numbers of people are in close contact, the prevalence of GAS pharyngeal carriage in healthy children can be as high as 25% in the absence of an outbreak of streptococcal disease. Therefore, classroom or more widespread culture sampling generally is not indicated.

Follow-up Throat Cultures

Post-treatment throat swab cultures are indicated only for patients who are at particularly high risk of ARF (eg, those living in an area with endemic infection). Repeated courses of antimicrobial therapy are not indicated for asymptomatic patients with cultures positive for group A streptococci; the exceptions are people who have personally had or whose family members have had ARF or other uncommon epidemiologic circumstances, such as a community outbreak of ARF or acute poststreptococcal glomerulonephritis.

Patients who have repeated episodes of pharyngitis at short intervals and in whom GAS infection is documented by culture or antigen detection test present a special problem. Most often, these people are chronic GAS carriers who are experiencing frequent viral illnesses and for whom repeated testing and use of antimicrobial agents are unnecessary. In assessing such patients, inadequate adherence to oral treatment also should be considered. Testing asymptomatic household contacts usually is not helpful. However, if multiple household members have pharyngitis or other GAS infections, simultaneous cultures of all household members and treatment of all with positive cultures or rapid antigen test results may be of value.

Testing for Group A Streptococci in Non-pharyngitis Infections

Cultures of impetiginous lesions often yield both streptococci and staphylococci, and determination of the primary pathogen generally is not possible. Culture is performed when it is necessary to determine susceptibility of the *S aureus* organisms. In suspected invasive GAS infections, cultures of blood and of focal sites of possible infection are indicated. In necrotizing fasciitis, imaging studies may delay, rather than facilitate, establishing the diagnosis. Clinical suspicion of necrotizing fasciitis should prompt urgent surgical evaluation with intervention, including débridement of deep tissues with Gram stain and culture of surgical specimens. STSS is diagnosed on the basis of clinical and laboratory findings and isolation of group A streptococci. Blood culture results are positive for GAS in approximately 50% of patients with STSS. Culture results from a focal site of infection also usually are positive and can remain so for several days after appropriate antimicrobial agents have been initiated.

TREATMENT

S pyogenes uniformly is susceptible to beta-lactam antimicrobial agents (penicillins and cephalosporins), and susceptibility testing is needed only for non–beta-lactam agents, such as erythromycin, clindamycin, or a macrolide, to which *S pyogenes* can be resistant.

Pharyngitis

- Penicillin V is the drug of choice for treatment of GAS pharyngitis. A clinical GAS isolate resistant to penicillin or cephalosporin has never been documented. Prompt administration of penicillin shortens the clinical course, decreases risk of suppurative sequelae and transmission, and prevents ARF, even when administered up to 9 days after illness onset. For all patients with ARF, a complete course of penicillin or another appropriate antimicrobial agent for GAS pharyngitis should be administered, even if group A streptococci are not recovered in the initial throat culture.
- Amoxicillin administered orally as a single daily dose for 10 days is as effective as penicillin V or amoxicillin administered orally multiple times per day for 10 days, and is available as a more palatable suspension than penicillin V. This regimen has been endorsed by the American Heart Association and the Infectious Diseases Society of America in its guidelines for the treatment of GAS pharyngitis and the prevention of ARF.
- Treatment failures may occur more often with oral penicillin than with intramuscular penicillin G benzathine because of inadequate adherence to oral therapy. In addition, short-course treatment (less than 10 days) for GAS pharyngitis, particularly with penicillin V, is associated with inferior bacteriologic eradication rates.
- Intramuscular penicillin G benzathine is appropriate therapy. It ensures adequate blood concentrations and avoids the problem of adherence, but administration may be painful. Discomfort is decreased if the preparation of penicillin G benzathine is brought to room temperature before intramuscular injection. Mixtures containing shorter-acting penicillins (eg, penicillin G procaine) in addition to penicillin G benzathine have not been demonstrated to be more effective than penicillin G benzathine alone but are less painful when administered.
- For patients who have a history of nonanaphylactic allergy to penicillin, a 10-day course of a narrow-spectrum (first-generation) oral cephalosporin (ie, cephalexin) is indicated. Patients with immediate (anaphylactic) or type I hypersensitivity to penicillin should be treated with oral clindamycin (20 mg/kg per day in 3 divided doses; maximum, 900 mg/day for 10 days) rather than a cephalosporin.
- An oral macrolide or azalide (eg, erythromycin, clarithromycin, or azithromycin) also is acceptable for patients who are allergic to penicillins. Therapy for 10 days is indicated, except for azithromycin, which is indicated for 5 days. Erythromycin is associated with substantially higher rates of gastrointestinal tract adverse effects compared with clarithromycin or azithromycin. GAS strains resistant to macrolides or azalides have been

highly prevalent in some areas of the world and have resulted in treatment failures. In recent years, macrolide resistance rates in most areas of the United States have been 5% to 10%, but resistance rates up to 20% have been reported.

- Tetracyclines, sulfonamides (including trimethoprim-sulfamethoxazole), and fluoroquinolones should not be used for treating GAS pharyngitis.

Children who have a recurrence of GAS pharyngitis shortly after completing a full course of a recommended oral antimicrobial agent can be retreated with the same antimicrobial agent, an alternative oral drug, or an intramuscular dose of penicillin G benzathine, especially if inadequate adherence to oral therapy is suspected. Alternative drugs include a narrow-spectrum cephalosporin (ie, cephalexin), amoxicillin-clavulanate, clindamycin, a macrolide, or an azalide. Expert opinions differ about the most appropriate therapy in this circumstance.

Management of a patient who has repeated and frequent episodes of acute pharyngitis associated with repeatedly positive laboratory tests for group A streptococci is problematic. To determine whether the patient is a long-term streptococcal pharyngeal carrier who is experiencing repeated episodes of intercurrent viral pharyngitis (which is the situation in most cases), the following should be determined: (1) whether the clinical findings are more suggestive of group A streptococci or a viral infection; (2) whether epidemiologic factors in the household or community support group A streptococci or a virus as the cause; (3) the nature of the clinical response to the antimicrobial therapy (in true GAS pharyngitis, response to therapy usually is 24 hours or less); and (4) whether laboratory test results are positive for GAS infection at times between episodes of acute pharyngitis (suggesting that the patient is a carrier). Measurement of a serial serologic response to GAS extracellular antigens (eg, antistreptolysin O) should be discouraged, because interpretation can be very difficult.

Pharyngeal Carriers

Antimicrobial therapy is not indicated for most GAS pharyngeal carriers. The few specific situations in which eradication of carriage may be indicated include the following: (1) a local outbreak of ARF or poststreptococcal glomerulonephritis; (2) an outbreak of GAS pharyngitis in a closed or semiclosed community; (3) a family history of ARF; or (4) multiple ("ping-pong") episodes of documented symptomatic GAS pharyngitis occurring within a family for many weeks despite appropriate therapy.

GAS carriage can be difficult to eradicate with conventional antimicrobial therapy. A number of antimicrobial agents, including clindamycin, cephalosporins, amoxicillin-clavulanate, azithromycin, or a combination that includes either penicillin V or penicillin G benzathine with rifampin for the last 4 days of treatment have been demonstrated to be more effective than penicillin alone in terminating chronic streptococcal carriage. Of these drugs, oral clindamycin for 10 days has been reported to be most effective. Documented eradication of the carrier state is helpful in the evaluation of subsequent episodes of acute pharyngitis; however, carriage can recur after reacquisition of GAS infection, as some individuals appear to be "carrier prone."

Nonbullous Impetigo

Topical mupirocin or retapamulin ointment may be useful for limiting person-to-person spread of nonbullous impetigo and for eradicating localized disease. With multiple lesions or with nonbullous impetigo in multiple family members, child care groups, or athletic teams, impetigo should be treated with oral antimicrobial agents active against both group A streptococci and *S aureus.*

Toxic Shock Syndrome

As outlined in Tables 135.1 and 135.2, most aspects of management are the same for toxic shock syndrome caused by group A streptococci or by *S aureus.* Paramount are immediate aggressive fluid replacement, management of respiratory and cardiac failure, if present, and aggressive surgical débridement of any deep-seated infection. Because *S pyogenes* and

Table 135.1
Management of Streptococcal Toxic Shock Syndrome Without Necrotizing Fasciitis

- Fluid management to maintain adequate venous return and cardiac filling pressures to prevent end-organ damage
- Anticipatory management of multisystem organ failure
- Parenteral antimicrobial therapy at maximum doses with the capacity to
  - Kill organism with bactericidal cell wall inhibitor (eg, beta-lactamase–resistant antimicrobial agent)
  - Decrease enzyme, toxin, or cytokine production with protein synthesis inhibitor (eg, clindamycin)
- IGIV often is used as an adjunct, typically at 1 g/kg on day 1, followed by 0.5 g/kg on 1-2 subsequent days

IGIV indicates Immune Globulin Intravenous.

Table 135.2
Management of Streptococcal Toxic Shock Syndrome With Necrotizing Fasciitis

- Principles outlined in Table 135.1
- Immediate surgical evaluation
  - Exploration or incisional biopsy for diagnosis and culture
  - Resection of all necrotic tissue
- Repeated resection of tissue may be needed if infection persists or progresses

S aureus toxic shock syndrome are difficult to distinguish clinically, initial antimicrobial therapy should include an antistaphylococcal agent and a protein synthesis-inhibiting antimicrobial agent, such as clindamycin. The addition of clindamycin to penicillin is recommended for serious GAS infections, because the antimicrobial activity of clindamycin is not affected by inoculum size (does not have the Eagle effect that can be observed with the beta-lactam antibiotics), has a long postantimicrobial effect, and acts on bacteria by inhibiting protein synthesis. Inhibition of protein synthesis results in suppression of synthesis of the *S pyogenes* antiphagocytic M-protein and bacterial toxins. Clindamycin should not be used **alone** as initial antimicrobial therapy in life-threatening situations, because in the United States, 1% to 2% of GAS strains are resistant to clindamycin. Higher resistance rates have been reported for strains associated with invasive infection and may be as high as 10%.

Once GAS infection has been confirmed, antimicrobial therapy should be tailored to penicillin and clindamycin. Intravenous therapy should be continued at least until the patient is afebrile and stable hemodynamically and blood is sterile, as evidenced by negative culture results. The total duration of therapy is based on duration established for the primary site of infection.

Aggressive drainage and irrigation of accessible sites of infection should be performed as soon as possible. If necrotizing fasciitis is suspected, immediate surgical exploration or biopsy is crucial to identify and débride deep soft tissue infection.

Immune Globulin Intravenous (IGIV) may be considered as adjunctive therapy for STSS or necrotizing fasciitis if the patient is severely ill.

Other Infections

Parenteral antimicrobial therapy is required for severe infections, such as endocarditis, pneumonia, empyema, abscess, septicemia,

Table 135.3
Revised Jones Criteria (2015)

1. All patients require evidence of antecedent GAS infection for diagnosis of ARF (except in case of chorea, where evidence of antecedent GAS infection is not required).
2. To confirm an initial diagnosis of ARF, need 2 major OR 1 major and 2 minor criteria.
3. To confirm recurrent ARF diagnosis, need 2 major OR 1 major and 2 minor OR 3 minor criteria.
4. Criteria for diagnosis are dependent on whether patient is from a low-risk or a moderate-/high-risk population. Moderate- and high-risk populations include countries where ARF remains endemic (Africa, Asia-Pacific, indigenous population of Australia). The United States, Canada, and Europe are examples of a low-risk population.
5. Major and minor criteria are listed below, by risk categorization; differences for moderate-/high-risk populations are bolded.

Low-Risk Population	Moderate- and High-Risk Population
Major Criteria • Carditis (clinical or subclinical) • Arthritis (polyarthritis only) • Chorea • Subcutaneous nodules • Erythema marginatum	**Major Criteria** • Carditis (clinical or subclinical) • Arthritis (polyarthritis or monoarthritis, or polyarthralgia) • Chorea • Subcutaneous nodules • Erythema marginatum
Minor Criteria • Polyarthralgia • Fever ≥38.5°C • ESR ≥60 mm/h and/or CRP ≥3 mg/dL • Prolonged PR interval (in absence of carditis)	**Minor Criteria** • Monoarthralgia • Fever ≥38°C • ESR ≥30 mm/h and/or CRP ≥3 mg/dL • Prolonged PR interval (in absence of carditis)

Derived from Table 7 in Gewitz MH, Baltimore RS, Tani LY, et al. Revision of the Jones criteria for the diagnosis of acute rheumatic fever in the era of Doppler echocardiography: a scientific statement from the American Heart Association. *Circulation.* 2015;131(20):1806–1818.
ESR indicates erythrocyte sedimentation rate; CRP, C-reactive protein.

meningitis, arthritis, osteomyelitis, erysipelas, necrotizing fasciitis, and neonatal omphalitis. Treatment often is prolonged.

Acute Rheumatic Fever

Jones criteria for diagnosis of ARF were established in 1944, modified in 1992, and revised in 2015 as echocardiography has become more widely available globally and studies have confirmed the presence of echocardiographic mitral and aortic regurgitation in patients with ARF who have no auscultatory findings. The 2015 revision of the Jones criteria (Table 135.3) differentiates major and minor criteria based on whether the child is from a population at low risk for ARF (United States and Europe) or a population at moderate/high risk (Africa, Asia-Pacific, indigenous Australian population, any other populations not clearly low risk).

- Laboratory evidence of antecedent GAS infection should be confirmed in all cases of suspected ARF, and evidence includes an increased or rising ASO or anti-DNAase B titer, or a positive rapid antigen or streptococcal throat culture. Because of the long latency between GAS infection and presentation with chorea, such laboratory evidence may be lacking in cases where chorea is the major criteria.

- Major criteria continue to include carditis (clinical and subclinical), arthritis (highly responsive to aspirin or nonsteroidal anti-inflammatory agents), chorea, subcutaneous nodules, and erythema marginatum.
- Echocardiography/Doppler testing should be performed in all cases and specific echocardiographic criteria are available to define subclinical carditis (eg, rheumatic valvulitis). Both clinical and subclinical carditis are major criteria.
- In terms of the major criteria, in low-risk populations, the arthritis that is seen is a migratory polyarthritis usually involving large joints. In moderate/high-risk populations, joint involvement may be mono- or polyarthritis or include only polyarthralgia (assuming autoimmune, viral, and reactive arthropathies are excluded).
- Minor criteria in low-risk populations include fever ≥38.5°F, polyarthralgia, sedimentation rate ≥60 mm and/or C-reactive protein (CRP) ≥3.0 mg/dL, and prolonged PR interval (unless carditis is a major criterion). In moderate- to high-risk populations, a lower fever ≥38°F is accepted, monoarthralgia is a minor criterion, a lower sedimentation rate ≥30 mm and/or CRP ≥3.0 mg/dL is accepted, and prolonged PR interval (unless carditis is a major criterion) is included.

For a primary episode, 2 major criteria or 1 major and 2 minor criteria are required for diagnosis. Following a primary ARF episode, in patients with documentation of reinfection with group A streptococci, 2 major, 1 major and 2 minor, or 3 minor features are enough to confirm the diagnosis of ARF recurrence.

Treatment for ARF includes eradication of GAS with a standard pharyngitis regimen, treatment of acute manifestations (eg, arthritis or valvulitis associated heart failure), education for parents and patient, and initiation of secondary prophylaxis to prevent against future GAS infection.

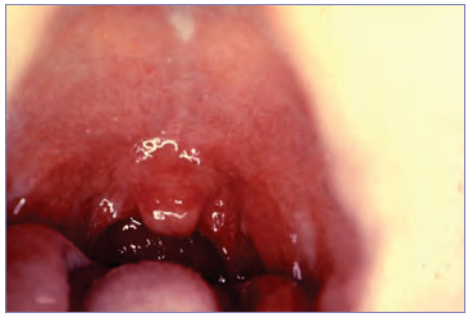


Image 135.1
Group A streptococcal pharyngitis with inflammation of the tonsils and uvula. Courtesy of Centers for Disease Control and Prevention.

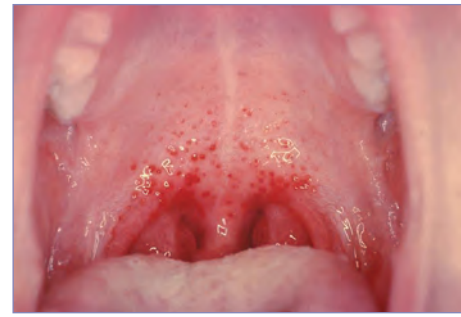


Image 135.2
Note inflammation of the oropharynx with petechiae on the soft palate, small red spots caused by group A streptococcal pharyngitis. Courtesy of Centers for Disease Control and Prevention.

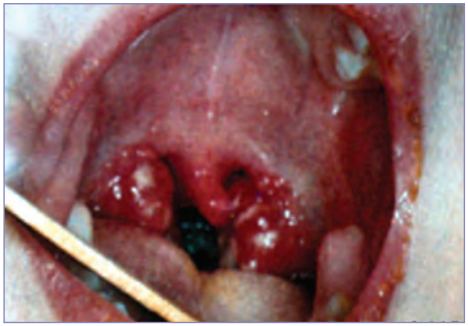


Image 135.3
Erythematous tonsils in a child with group A streptococcal pharyngitis.

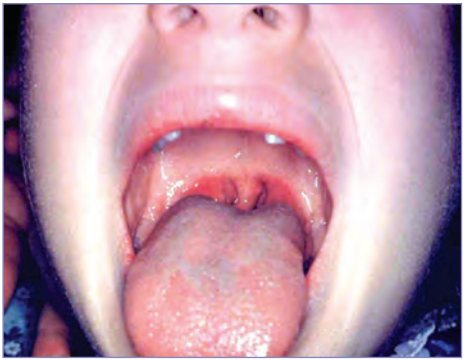


Image 135.4
Group A streptococcal pharyngitis with localized erythema and edema of the tonsils and soft palate.

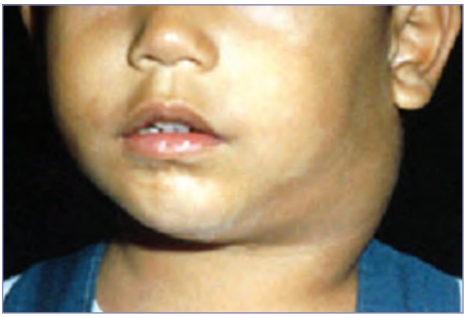


Image 135.5
Group A streptococcal nasopharyngitis in a toddler, which is often associated with tender anterior cervical lymphadenopathy. A throat culture result is not always positive when the infection has localized to the cervical lymph nodes.

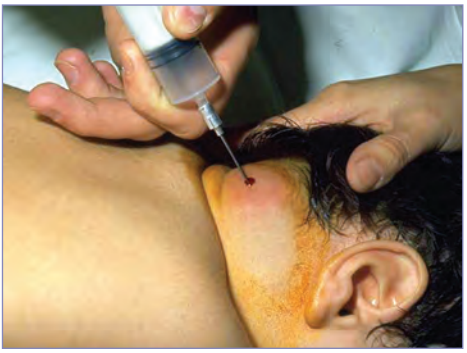


Image 135.6
Posterior cervical lymph node aspiration. Culture result was positive for group A streptococci. Courtesy of Edgar O. Ledbetter, MD, FAAP.

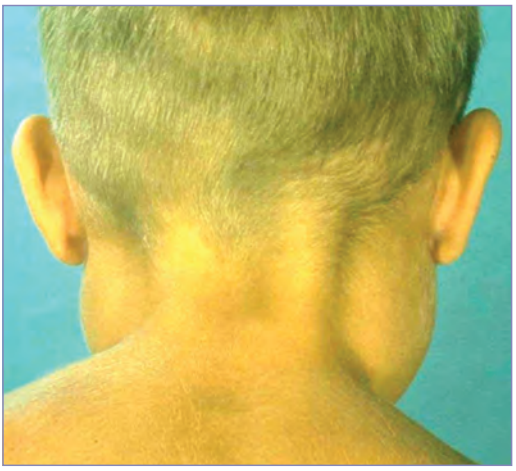


Image 135.7
Bilateral cervical lymphadenitis (posterior view).

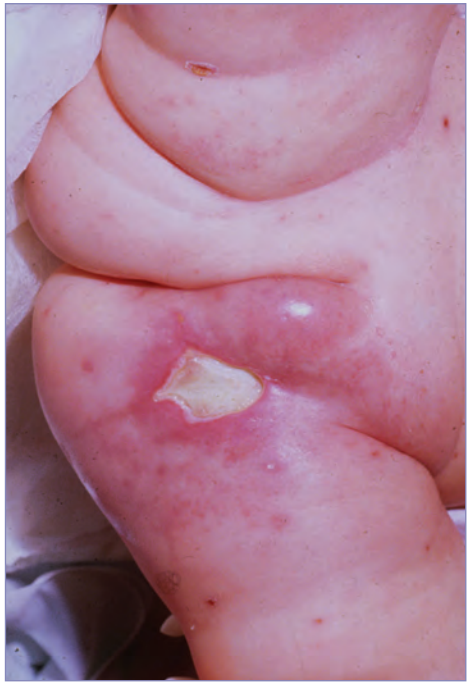


Image 135.8
Group A streptococcal cellulitis and necrotizing fasciitis in the perineal area of a 7-month-old girl, complicating varicella. Courtesy of George Nankervis, MD.

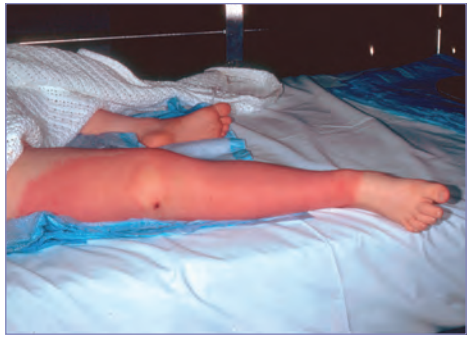


Image 135.10
Group A streptococcal cellulitis (erysipelas) of the right leg in a school-aged child secondary to impetigo. Courtesy of George Nankervis, MD.

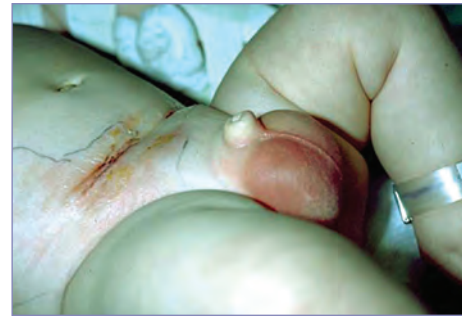


Image 135.9
A 5-month-old boy with group A streptococcal cellulitis 12 hours after herniorrhaphy. Copyright Martin G. Myers, MD.

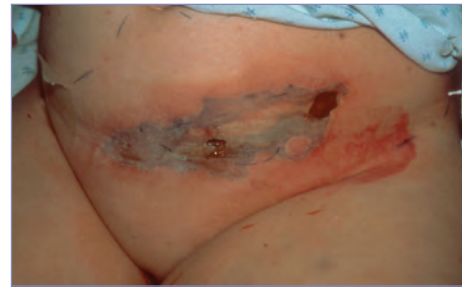


Image 135.11
Group A streptococcal necrotizing fasciitis complicating varicella in a 3-year-old girl. Courtesy of George Nankervis, MD.

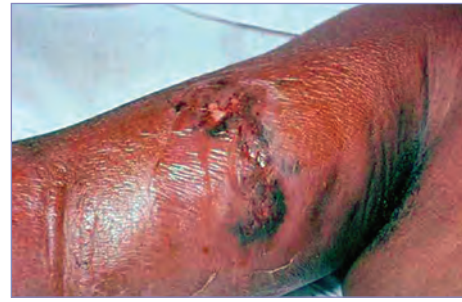


Image 135.12
Necrotizing fasciitis of the left upper arm and shoulder secondary to group A streptococcus.

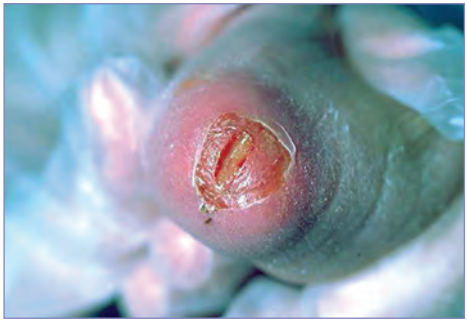


Image 135.13
An infant boy with group A streptococcal infection at a heel-stick site. Copyright Martin G. Myers, MD.

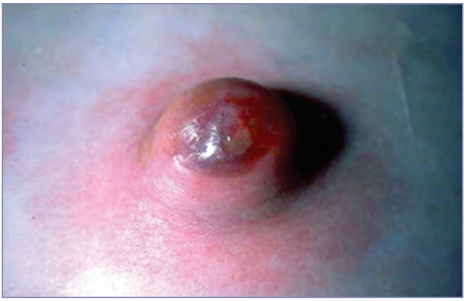


Image 135.14
A newborn with group A streptococcal omphalitis and peritonitis. Copyright Martin G. Myers, MD.

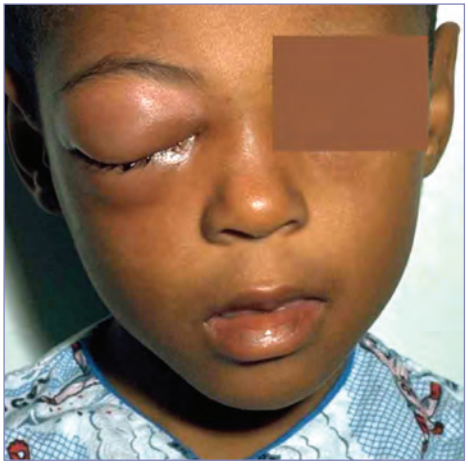


Image 135.15
Group A streptococcal ethmoid sinusitis with periorbital cellulitis.

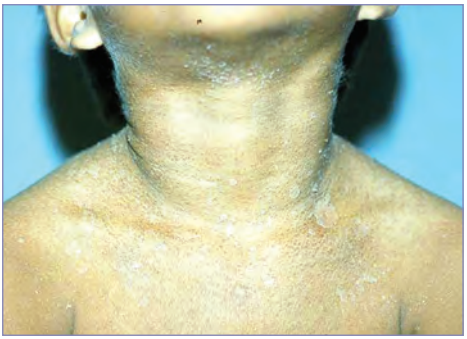


Image 135.16
Group A streptococcal scarlet fever with characteristic sandpaper-like rash with desquamation in a 6-year-old boy. Courtesy of Edgar O. Ledbetter, MD, FAAP.

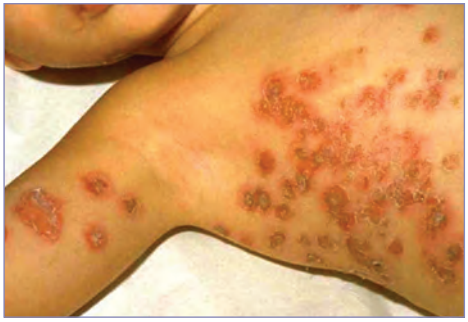


Image 135.18
Group A streptococcal impetigo.

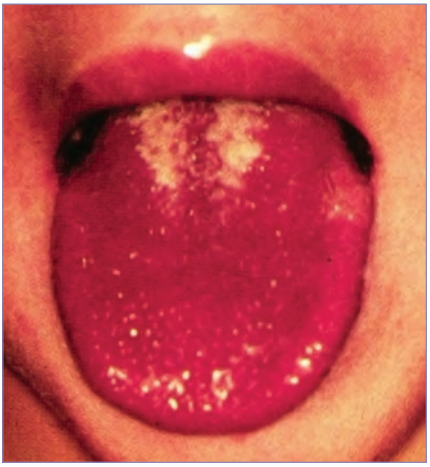


Image 135.17
The characteristic inflammatory changes in the tongue (ie, the strawberry tongue) of scarlet fever. Courtesy of Paul Wehrle, MD.

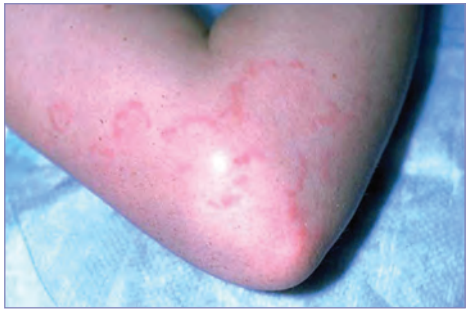


Image 135.19
Erythema marginatum in a 12-year-old girl. Although a characteristic rash of rheumatic fever, it is noted in fewer than 3% of cases. Its serpiginous border and evanescent nature serve to distinguish it from erythema migrans lesions of Lyme disease. Copyright Martin G. Myers, MD.

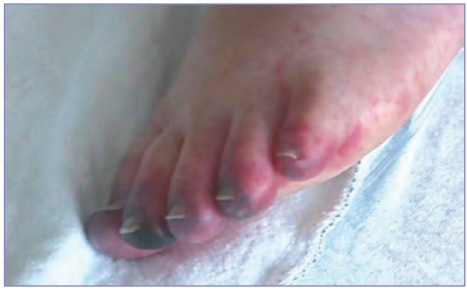


Image 135.21
Purpura fulminans in a 6-year-old girl with *Streptococcus pyogenes* septicemia. Courtesy of Benjamin Estrada, MD.

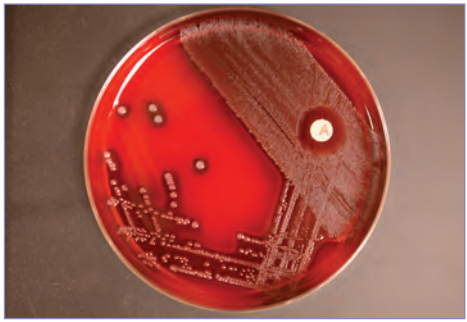


Image 135.24
Streptococcus pyogenes on blood agar. The bacitracin disc has been placed to help distinguish group A streptococci from other β-hemolytic streptococci. The formation of any zone of inhibition is considered a positive test result. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

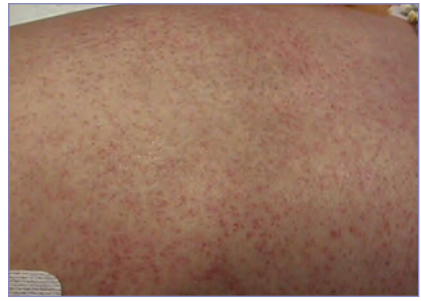


Image 135.20
Petechial rash in a 6-year-old girl with *Streptococcus pyogenes* septicemia. Courtesy of Benjamin Estrada, MD.

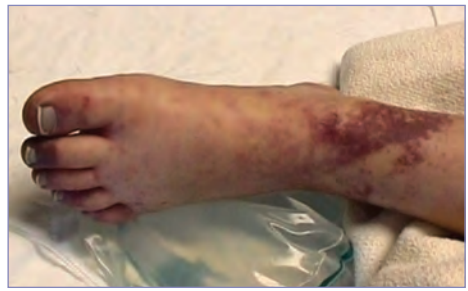


Image 135.22
Purpura fulminans in a 6-year-old girl with *Streptococcus pyogenes* septicemia. Courtesy of Benjamin Estrada, MD.

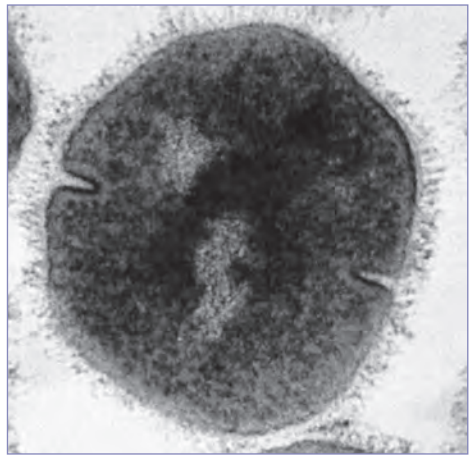


Image 135.23
Electron micrograph (magnification ×70,000) of an ultrathin section of *Streptococcus pyogenes*. Courtesy of Centers for Disease Control and Prevention/Dr Vincent A. Fischetti, Rockefeller University.

CHAPTER 136

Group B Streptococcal Infections

CLINICAL MANIFESTATIONS

Group B streptococci are a major cause of perinatal infections, including bacteremia, endometritis, intra-amniotic infection (formerly called chorioamnionitis), and urinary tract infections in women during pregnancy and immediately postpartum, and of systemic and focal infections in neonates and young infants. Invasive disease in infants is categorized by chronologic age at onset. Early-onset disease usually occurs within the first 24 hours of life (range, 0 through 6 days) and is characterized by signs of systemic infection, respiratory distress, apnea, shock, pneumonia, and less often, meningitis (5%–10% of cases). Late-onset disease, which typically occurs at 3 to 4 weeks of age (range, 7 through 89 days), commonly manifests as occult bacteremia or meningitis (approximately 30% of cases); other focal infections, such as adenitis, cellulitis, osteomyelitis, septic arthritis, pneumonia, and necrotizing fasciitis, occur less commonly. Nearly 50% of survivors of early- or late-onset meningitis have long-term neurologic sequelae (encephalomalacia, cortical blindness, cerebral palsy, visual impairment, hearing deficits, or learning disabilities). Late, late-onset disease occurs at 90 days of age and beyond, usually in very preterm infants requiring prolonged hospitalization. Group B streptococci also cause systemic infections in nonpregnant adults with underlying medical conditions, such as diabetes mellitus, obesity, chronic liver or renal disease, malignancy, or other immunocompromising conditions and in adults 65 years and older.

ETIOLOGY

Group B streptococci (*Streptococcus agalactiae*) are gram-positive, aerobic diplococci that typically produce a narrow zone of beta hemolysis on 5% sheep blood agar. These organisms are divided into 10 types by capsular polysaccharides (Ia, Ib, and II through IX). Types Ia, Ib, II, III, and V account for approximately 95% of cases in infants in the United States, with type IV emerging as an important cause of invasive infections in adults. Type III is the predominant cause of early- and late-onset meningitis and the majority of late-onset infections in infants. Capsular polysaccharides and pilus-like structures are important virulence factors and are potential vaccine candidates.

EPIDEMIOLOGY

Group B streptococci are common inhabitants of the human gastrointestinal and genitourinary tracts. Less commonly, they colonize the pharynx. The colonization rate in pregnant women ranges from 15% to 35%. Colonization during pregnancy can be constant or intermittent. Before recommendations were made for prevention of early-onset group B streptococcal (GBS) disease through maternal intrapartum antibiotic prophylaxis, the incidence was 1 to 4 cases per 1,000 live births; early-onset disease accounted for approximately 75% of cases in infants and occurred in approximately 1 to 2 infants per 100 colonized women. Following widespread implementation of maternal intrapartum antibiotic prophylaxis, the incidence of early-onset disease has decreased by more than 80% to an estimated 0.22 cases per 1,000 live births in 2016. The use of intrapartum chemoprophylaxis has had no measurable effect on late-onset GBS disease. In recent years, the incidence of late-onset disease has nearly equaled that of early-onset disease (0.25 cases per 1,000 live births in 2016). The case-fatality ratio in term infants ranges from 1% to 3% but is higher in preterm neonates (estimated to be 20% for early-onset disease and 5% for late-onset disease). Approximately 70% of early-onset and 50% of late-onset cases afflict term neonates.

Transmission from mother to infant occurs shortly before or during delivery. After delivery, person-to-person transmission can occur. Although rare, GBS infection can be acquired in the nursery from health care professionals (probably resulting from omissions in hand hygiene) or visitors and more commonly in the community (colonized family members or caregivers). The risk of early-onset disease is increased in preterm infants (less than 37 weeks' gestation), infants born after the amniotic membranes have been ruptured 18 hours or more, and infants born to women with high genital GBS inoculum, intrapartum fever (temperature 38°C [100.4°F] or greater),

intra-amniotic infection (formerly called chorioamnionitis), GBS bacteriuria during the current pregnancy, or a previous infant with invasive GBS disease. A low or an undetectable maternal concentration of capsular type-specific serum antibody to capsular polysaccharide of the infecting strain also is a predisposing factor for neonatal infection. Other risk factors are intrauterine fetal monitoring and maternal age younger than 20 years. Black race is an independent risk factor for both early-onset and late-onset disease. Although the incidence of early-onset disease has declined in all racial groups since the 1990s, rates consistently have been higher among black infants (0.51 cases per 1,000 live births in 2014) compared with white infants (0.17 cases per 1,000 live births), with the highest incidence observed among preterm black infants (0.96 per 1,000 live births in 2014). The reason for this racial/ethnic disparity is not known. The period of communicability is unknown but can extend throughout the duration of colonization or disease. Infants can remain colonized for several months after birth and after treatment for systemic infection. Recurrent GBS disease affects an estimated 1% to 3% of appropriately treated infants.

The **incubation period** of early-onset disease is fewer than 7 days. In late-onset and late, late-onset disease, the **incubation period** is unknown.

DIAGNOSTIC TESTS

Visualization of gram-positive cocci in pairs or short chains by Gram stain of body fluids that typically are sterile (eg, cerebrospinal fluid [CSF], abscess, or joint fluid) provides presumptive evidence of infection. Growth of the organism from cultures of blood, CSF, or if present, a suppurative focus is necessary to establish the diagnosis. A meningitis/encephalitis multiplex panel polymerase chain reaction assay is approved for direct testing of CSF and detection of GBS along with many other bacterial, viral, and fungal pathogens. Clinical experience with this multiplex assay is limited. For prenatal GBS screening, vaginal and rectal swab maternal specimens are collected and enriched in commercially available selective broth mediums for 18 to 24 hours at 35°C to 37°C in ambient air or 5% carbon dioxide and subsequently plated on tryptic soy blood agar or other selective agars for a further 24- to 48-hour incubation and isolation. Alternatively, DNA probe assays, latex agglutination assays, and nucleic acid amplification assays are available to detect GBS from enriched broth specimens. One is approved for intrapartum detection of GBS from vaginal/rectal swab specimens collected from pregnant women presenting in labor if GBS colonization is unknown.

TREATMENT

- Ampicillin plus an aminoglycoside administered intravenously (IV) is the initial treatment of choice for a newborn infant with presumptive early-onset GBS infection. For empirical therapy of late-onset meningitis, ampicillin and an aminoglycoside or a third-generation cephalosporin (eg, cefotaxime) are recommended. If the infant is 2 months or older, vancomycin and ceftriaxone are recommended to ensure that therapy would be appropriate for *Streptococcus pneumoniae* meningitis until results of cultures confirm GBS.

- Penicillin G alone administered IV is the drug of choice when GBS has been identified as the cause of the infection and when clinical and microbiologic responses have been documented. Ampicillin given IV is an acceptable alternative therapy.

- For infants with meningitis attributable to GBS, high doses of penicillin G intravenously, is recommended for 2 to 3 weeks. Some experts recommend a second lumbar puncture be performed approximately 24 to 48 hours after initiation of therapy to assist in management and prognosis. If CSF sterility is not achieved, a complicated course (eg, cerebral infarcts, cerebritis, ventriculitis) can be expected; an increasing protein concentration suggests an intracranial complication (eg, infarction, subdural empyema, ventricular obstruction). Failed hearing screen, abnormal neurologic examination, and certain cranial imaging abnormalities at discharge predict an adverse long-term outcome. Consultation with a specialist in pediatric infectious diseases can assist in treatment of all cases of neonatal meningitis including GBS. For infants with bacteremia

without a defined focus, treatment should be continued for 10 days exclusively by the parenteral route. Although one publication suggests completing treatment for less duration and/or with an oral antibiotic in uncomplicated cases, data demonstrating outcomes similar to those reported for 10 days of parenteral therapy are lacking.

- Because of the reported increased risk of infection, birth mates of a multiple birth index case with early- or late-onset disease should be observed carefully and evaluated and treated empirically for suspected systemic infection if signs of illness occur; treatment should be continued for a full course for those with confirmed infection.

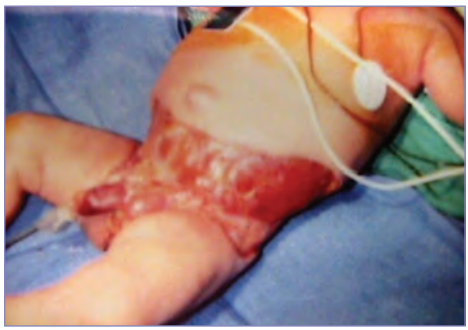


Image 136.1
Streptococcus agalactiae necrotizing fasciitis in a 3-month-old. Courtesy of Benjamin Estrada, MD.

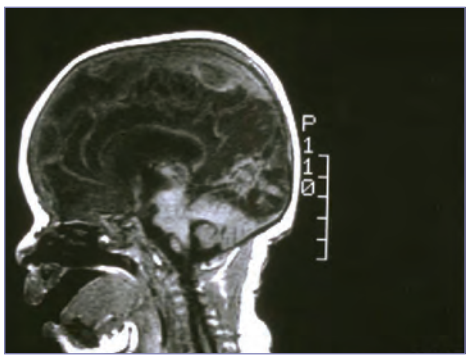


Image 136.3
Magnetic resonance imaging after group B streptococcal meningitis.

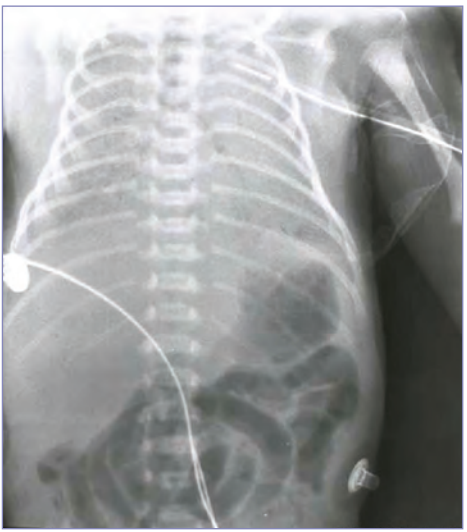


Image 136.2
Bilateral, severe group B streptococcal pneumonia in a neonate.

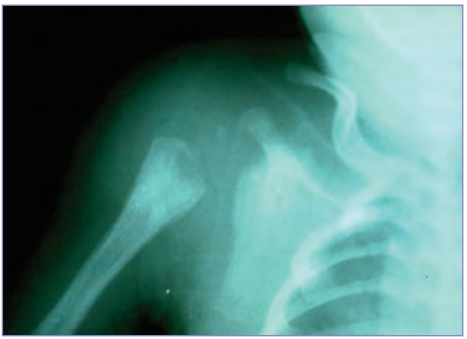


Image 136.4
Neonatal group B streptococcal septic arthritis of the right shoulder joint and osteomyelitis of the right proximal humerus.

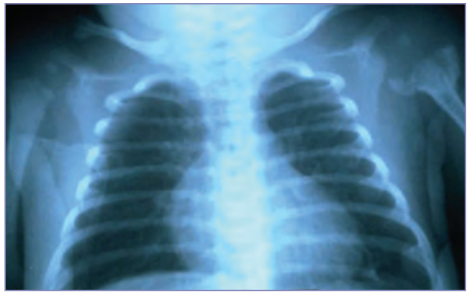


Image 136.5
Neonatal group B streptococcal septic arthritis (left shoulder joint) and osteomyelitis of the left proximal humerus. Courtesy of Edgar O. Ledbetter, MD, FAAP.

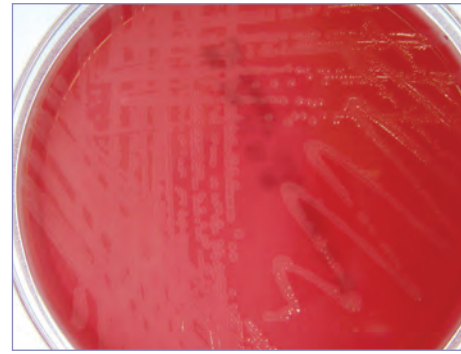


Image 136.6
Streptococcus agalactiae, 24-hour sheep blood agar plate, β-hemolysis, close-up view. Courtesy of Robert Jerris, MD.

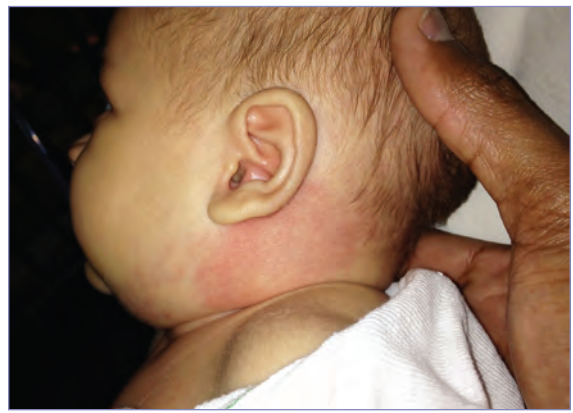


Image 136.7
A term 3-week-old who had poor feeding and irritability followed 2 hours later by fever to 38.1°C (100.6°F). On admission to the hospital 3 hours later, he required fluid resuscitation and intravenous antibiotic therapy. His spinal fluid was within reference range, but the blood culture grew group B streptococcus. At admission, the physical examination revealed the classic facial and submandibular erythema, tenderness, and swelling characteristic of group B streptococcal cellulitis. Courtesy of Nate Serazin, MD, and C. Mary Healy, MD.

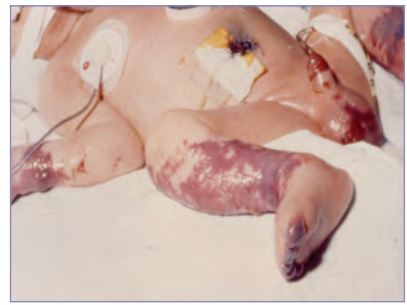


Image 136.8
A term 3-day-old with fatal group B streptococcus sepsis and peripheral gangrene. Courtesy of Carol J. Baker, MD, FAAP.

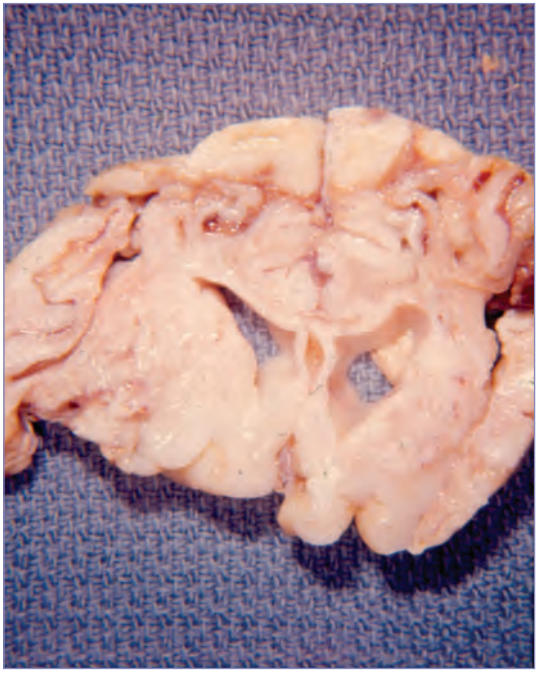


Image 136.9
The brain of a 3-week old term boy with late-onset group B streptococcal meningitis and fatal status epilepticus. Courtesy of Carol J. Baker, MD.

CHAPTER 137

Non-Group A or B Streptococcal and Enterococcal Infections

CLINICAL MANIFESTATIONS

Streptococci other than Lancefield groups A or B can be associated with invasive disease in infants, children, adolescents, and adults. The principal clinical syndromes of groups C and G streptococci (most belong to the *Streptococcus dysgalactiae* group) are bacteremia, septicemia, upper and lower respiratory tract infections (eg, pharyngitis, sinusitis, and pneumonia), skin and soft tissue infections, septic arthritis, osteomyelitis, meningitis with a parameningeal focus, brain abscess, toxic shock syndrome, pericarditis, and endocarditis with various clinical manifestations. Viridans streptococci are the most common cause of bacterial endocarditis in children, especially children with congenital or valvular heart disease, and these organisms are a common cause of bacteremia in neutropenic patients with cancer in the first 2 weeks after hematopoietic stem cell transplantation and as a cause of central line-associated bacteremia. Among the viridans streptococci, group F streptococci (most belong to the *Streptococcus anginosus* group) are implicated in complicated sinus infection but are an infrequent cause of invasive infection. More serious *S anginosus* group infections include brain or dental abscesses or abscesses in other sites, including lymph nodes, liver, pelvis, and lung. These organisms also may cause sinusitis and other head and neck infections, meningitis, spondylodiskitis, spinal epidural abscesses, subdural empyema, peritonitis, appendicitis, abdominal wound infections, and cholangitis. Enterococci are associated with bacteremia in neonates and bacteremia, device-associated infections, intra-abdominal abscesses, and urinary tract infections in those with abnormal anatomy and in older children and adults.

ETIOLOGY

Changes in taxonomy and nomenclature of the *Streptococcus* genus have evolved with advances in molecular technology (Table 137.1). Among gram-positive organisms that are catalase negative and display chains by Gram stain, the genera associated most often with human disease are *Streptococcus* and *Enterococcus*.

The genus *Streptococcus* has been subdivided into 6 species groups on the basis of 16S rRNA gene sequencing. Members of the genus that are beta-hemolytic on blood agar plates include *Streptococcus pyogenes*, *Streptococcus agalactiae*, and groups C and G streptococci; *S dysgalactiae* subspecies *equisimilis* is the group C subspecies most often associated with human infections. Streptococci that are non-beta–hemolytic (alpha-hemolytic or nonhemolytic) on blood agar plates include: (1) *Streptococcus pneumoniae;* (2) the *Streptococcus bovis* group; and (3) viridans streptococci clinically relevant in humans,

Table 137.1
Classification of Streptococci Most Commonly Associated With Disease, by Lancefield Group and by Hemolysis

Species	Lancefield Group	Hemolysis
Streptococcus pyogenes	A	β
Streptococcus agalactiae	B	β
Streptococcus dysgalactiae subspecies *equisimilis*, *Streptococcus equi* subspecies *zooepidemicus*	C	β
Enterococcus faecalis, Enterococcus faecium, Streptococcus bovis	D	β
Streptococcus canis	G	β
Streptococcus pneumoniae, viridans streptococci	Not groupable[a]	β

[a]Occasional viridans streptococci have variable hemolysis and can possess Lancefield group A, C, F, or G antigens.

which include 5 *Streptococcus* species groups (*S anginosus* group, *mitis* group, *sanguinis* group, *salivarius* group, and *mutans* group). The *anginosus* group (also known as the *Streptococcus milleri* group) includes *S anginosus*, *Streptococcus constellatus*, and *Streptococcus intermedius*. This group can have variable hemolysis, and approximately one third possess group A, C, F, or G antigens. Nutritionally variant streptococci, once thought to be viridans streptococci, now are classified in the genera *Abiotrophia* and *Granulicatella*.

The genus *Enterococcus* (previously included with Lancefield group D streptococci) contains at least 18 species, with *Enterococcus faecalis* and *Enterococcus faecium* accounting for most human enterococcal infections. Outbreaks and health care-associated spread in association with vancomycin-resistant enterococcal strains including *Enterococcus gallinarum*, *Enterococcus casseliflavus*, or *Enterococcus flavescens* also have occurred occasionally. Nonenterococcal group D streptococci include *S bovis* and *Streptococcus equinus*, both members of the *bovis* group.

EPIDEMIOLOGY

The habitats that non-group A and B streptococci and enterococci occupy in humans include the skin (groups C and G), oropharynx (groups C and G and the *mutans* group), gastrointestinal tract (groups C and G, *bovis* group, and *Enterococcus* species), and vagina (groups C, D, and G and *Enterococcus* species). Typical human habitats of species of viridans streptococci are the oropharynx, epithelial surfaces of the oral cavity, teeth, skin, and gastrointestinal and genitourinary tracts. Intrapartum transmission is responsible for most cases of early-onset neonatal infection caused by non-group A and B streptococci and enterococci. Environmental contamination or transmission via hands of health care professionals can lead to colonization of patients. Groups C and G streptococci can cause foodborne outbreaks of pharyngitis.

The **incubation period** and the period of communicability are unknown.

DIAGNOSTIC TESTS

Diagnosis is established by culture of usually sterile body sites or abscesses with appropriate biochemical testing and serologic analysis for definitive identification. Mass spectrometry is unreliable in differentiation of *S pneumoniae* from viridians streptococci. Antimicrobial susceptibility testing of isolates from usually sterile sites should be performed to guide treatment of infections caused by viridans streptococci or enterococci. The proportion of vancomycin-resistant enterococci (VRE) among hospitalized patients can be as high as 30%. Selective agars are available for screening of vancomycin-resistant enterococcus from stool specimens. A rapid automated, molecular assay currently is available for direct detection of *vanA* gene, which confers vancomycin resistance, from rectal swab specimens for screening of VRE.

TREATMENT

Penicillin G is the drug of choice for groups C and G streptococci. Other agents with good activity include ampicillin, third- and fourth-generation cephalosporins, vancomycin, and linezolid. The combination of gentamicin with a beta-lactam antimicrobial agent (eg, penicillin or ampicillin) or vancomycin may enhance bactericidal activity needed for treatment of life-threatening infections (eg, endocarditis or meningitis).

Many viridans streptococci remain susceptible to penicillin. Infections caused by strains susceptible to penicillin, including endocarditis, can be treated with penicillin or ceftriaxone. Strains considered relatively resistant to penicillin (minimum inhibitory concentration [MIC] $>0.12\ \mu g/mL$ and $<0.5\ \mu g/mL$) should be treated with penicillin, ampicillin, or ceftriaxone for 4 weeks, combined for the first 2 weeks with gentamicin, if the patient has endocarditis. Strains that are penicillin resistant (MIC $\geq 0.5\ \mu g/mL$) can be treated with cephalosporins (especially ceftriaxone), vancomycin, linezolid, or daptomycin. *Abiotrophia* and *Granulicatella* organisms can exhibit relative or high-level resistance to penicillin. The combination of high-dose penicillin or vancomycin and an aminoglycoside can enhance bactericidal activity.

Enterococci exhibit uniform resistance to cephalosporins and semisynthetic penicillins, and most are intrinsically resistant to clindamycin. The vast majority of *E faecalis* strains are susceptible to ampicillin. *E faecium* strains may be multidrug resistant. Systemic enterococcal infections, such as endocarditis or meningitis, should be treated with penicillin or ampicillin (if the isolate is susceptible) or vancomycin combined with gentamicin. Gentamicin should be discontinued if in vitro susceptibility testing demonstrates high-level resistance, in which case synergy cannot be achieved. In general, children with a central line-associated bloodstream infection caused by enterococci should have the device removed promptly. Linezolid is approved for use in children, including neonates. Isolates of VRE that also are resistant to linezolid have been described, and resistance can develop during prolonged linezolid treatment. Most vancomycin-resistant isolates of *E faecalis* and *E faecium* are daptomycin-susceptible. Daptomycin should not be used to treat pneumonia.

Endocarditis

Guidelines for treatment of infective endocarditis in children from the American Heart Association should be consulted for regimens that are appropriate for children and adolescents.

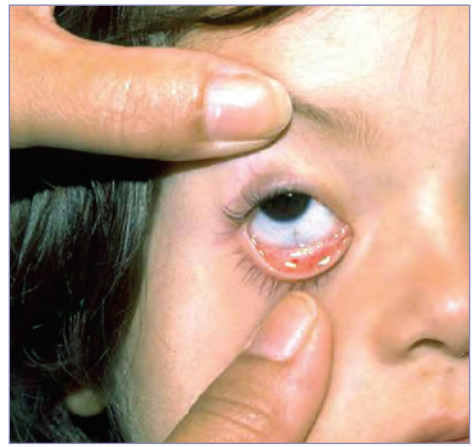


Image 137.1
Conjunctival (palpebral) petechiae in an adolescent girl with *Streptococcus viridans* subacute bacterial endocarditis.

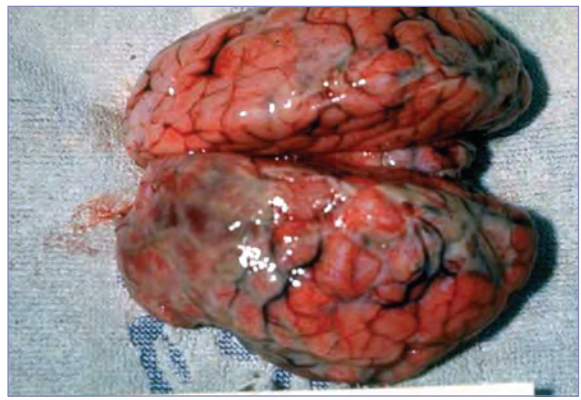


Image 137.2
Brain from a neonate with *Enterococcus faecalis* meningitis showing copious purulent exudate covering the meninges. Courtesy of Edgar O. Ledbetter MD, FAAP.

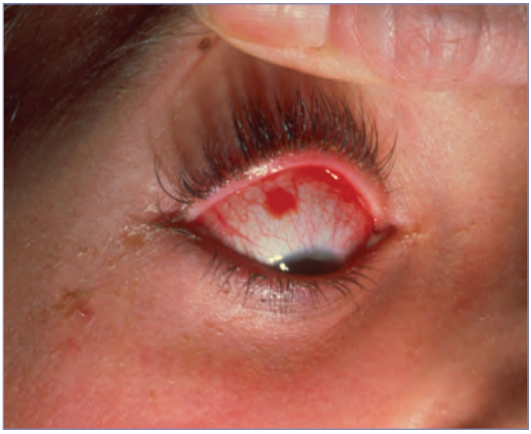


Image 137.3
A conjunctival hemorrhage in an adolescent girl with enterococcal endocarditis. Courtesy of George Nankervis, MD.

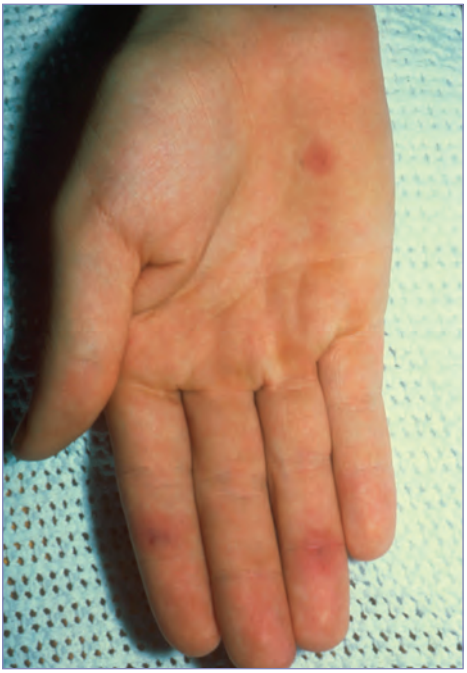


Image 137.4
Osler nodes on the fingers and a Janeway lesion in the palm of the same patient as in Image 137.3 with enterococcal endocarditis. Courtesy of George Nankervis, MD.

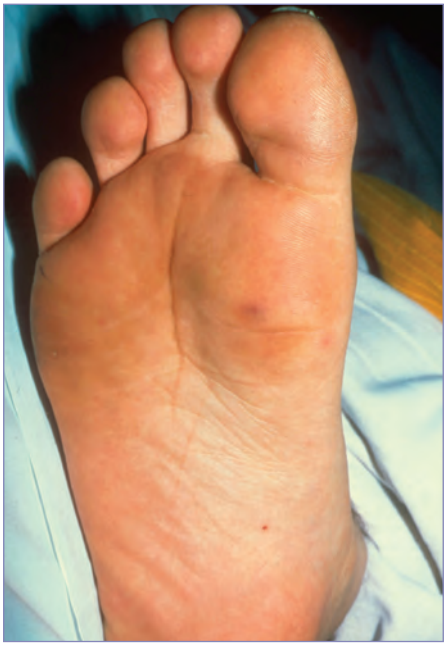


Image 137.5
A Janeway lesion on the sole of the same patient as in Images 137.3 and 137.4 with enterococcal endocarditis. Courtesy of George Nankervis, MD.

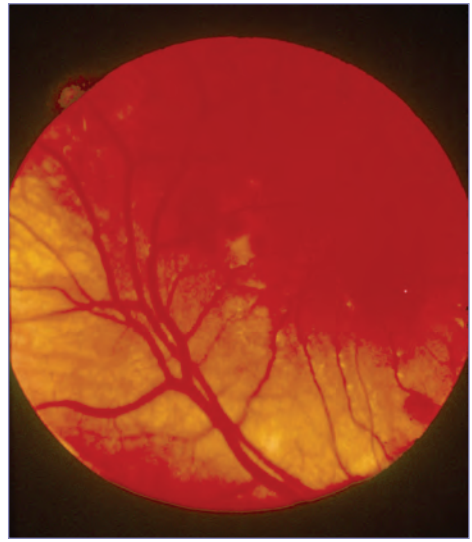


Image 137.6
Hemorrhagic retinitis with Roth spots in the adolescent girl in Images 137.3, 137.4, and 137.5 with enterococcal endocarditis. Courtesy of George Nankervis, MD.

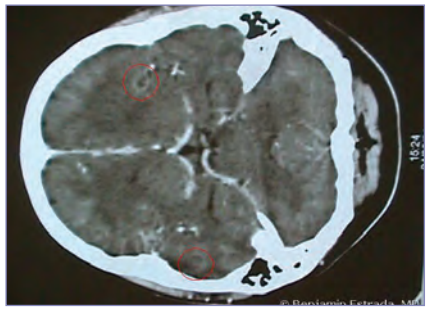


Image 137.7
Brain abscesses in a 13-year-old with *Streptococcus viridans* endocarditis. Courtesy of Benjamin Estrada, MD.

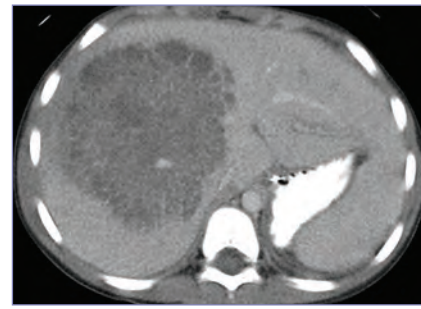


Image 137.8
Computed tomography scan showing a large liver abscess in a previously healthy 5-year-old girl with abdominal pain and nausea. Culture results were positive for *anginosus* (formerly *milleri*) group streptococci. Courtesy of Preeti Jaggi, MD.

CHAPTER 138

Strongyloidiasis

(*Strongyloides stercoralis*)

CLINICAL MANIFESTATIONS

Most infections with *Strongyloides stercoralis* are asymptomatic. When symptoms occur, they most often are related to larval skin invasion, tissue migration, or the presence of adult worms in the intestine. Infective (filariform) larvae are acquired from skin contact with contaminated soil, producing transient pruritic papules at the site of penetration. Larvae migrate to the lungs and can cause a transient pneumonitis or Löffler-like syndrome. After ascending the tracheobronchial tree, larvae are swallowed and mature into adults within the gastrointestinal tract. Symptoms of intestinal infection include nonspecific abdominal pain, malabsorption, vomiting, and diarrhea. Larval migration from defecated stool can result in migratory pruritic skin lesions in the perianal area, buttocks, and upper thighs, which may present as serpiginous, erythematous tracks called "larva currens." Immunocompromised people, most often those receiving glucocorticoids for underlying malignancy or autoimmune disease, solid organ or hematopoietic stem cell transplant recipients (through both reactivation of prior asymptomatic infection in the recipient, or to donor-derived infection), and people infected with human T-lymphotropic virus 1 (HTLV-1), are at risk of *Strongyloides* hyperinfection syndrome and disseminated disease, in which larvae migrate via the systemic circulation to distant organs, including the brain, liver, kidney, heart, and skin. This condition, which frequently is fatal, is characterized by fever, abdominal pain, diffuse pulmonary infiltrates, and septicemia or meningitis caused by enteric gram-negative bacilli.

ETIOLOGY

S stercoralis is a nematode (roundworm).

EPIDEMIOLOGY

Strongyloidiasis is endemic in the tropics and subtropics, including the southeastern United States, wherever suitable moist soil and improper disposal of human waste coexist. Because of the capacity for autoinfection, people can remain infected for decades even after leaving an area of endemic infection. Humans are the principal hosts, but dogs, cats, and other animals can serve as reservoirs. Transmission involves penetration of skin by filariform larvae from contact with contaminated soil. Infections rarely can be acquired from intimate skin contact or from inadvertent coprophagy, such as from ingestion of contaminated food or within institutional settings. Adult females release eggs in the small intestine, where they hatch as first-stage (rhabditiform) larvae that are excreted in feces. A small percentage of larvae molt to the infective (filariform) stage during intestinal transit, at which point they can penetrate the bowel mucosa or perianal skin, thus maintaining the life cycle within a single person (autoinfection).

The **incubation period** is unknown.

DIAGNOSTIC TESTS

Strongyloidiasis can be difficult to diagnose in immunocompetent people, because excretion of larvae in feces is highly variable and often of low intensity. At least 3 consecutive stool specimens should be examined microscopically for characteristic larvae (not eggs), but stool concentration techniques may be required to establish the diagnosis. The use of culture methods to visualize tracks of larval migration on agar media may have greater sensitivity than fecal microscopy, but these techniques are not available routinely; examination of duodenal contents obtained using the string test (Entero-Test) or a direct aspirate through a flexible endoscope also may demonstrate larvae. Eosinophilia (blood eosinophil count greater than 500/μL) is common in chronic infection, but its absence does not eliminate infection from consideration. When eosinophilia is absent in hyperinfection syndrome, it may predict poor outcome. Serodiagnosis by enzyme immunoassay is more sensitive, although variable among different commercial assays, and cross-reaction with other nematode species is possible; newer methods such as a luciferase immunoprecipitation system technique with recombinant antigen are even more sensitive and specific but currently only available in reference laboratories.

In disseminated strongyloidiasis, filariform larvae may be isolated from other specimens such as sputum or bronchoalveolar lavage fluid, spinal fluid, or in skin biopsies. Gram-negative bacillary meningitis and bacteremia are commonly associated findings in disseminated disease and carry a high mortality rate.

TREATMENT

Ivermectin is the treatment of choice for both chronic (asymptomatic) strongyloidiasis and hyperinfection with disseminated disease.

Ivermectin is the treatment of choice for intestinal strongyloidiasis. An alternative agent is albendazole, although it is associated with lower cure rates. Mebendazole is not recommended. Prolonged or repeated treatment may be necessary in people with hyperinfection and disseminated strongyloidiasis, and relapse can occur.

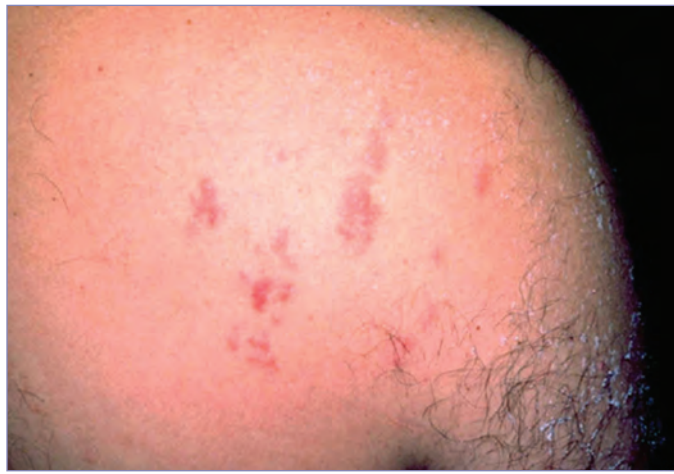


Image 138.1
Cutaneous migration sites of *Strongyloides stercoralis* over the left shoulder area.

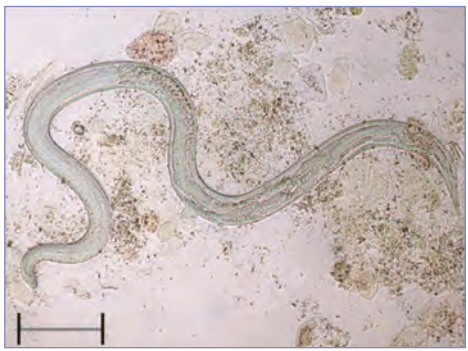


Image 138.2
Adult female of *Strongyloides stercoralis* collected in bronchial fluid of a patient with disseminated disease (scale bar = 400 µm). Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases.*

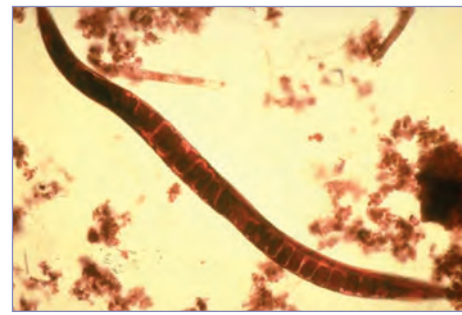


Image 138.3
Strongyloides stercoralis larvae (oil-immersion magnification).

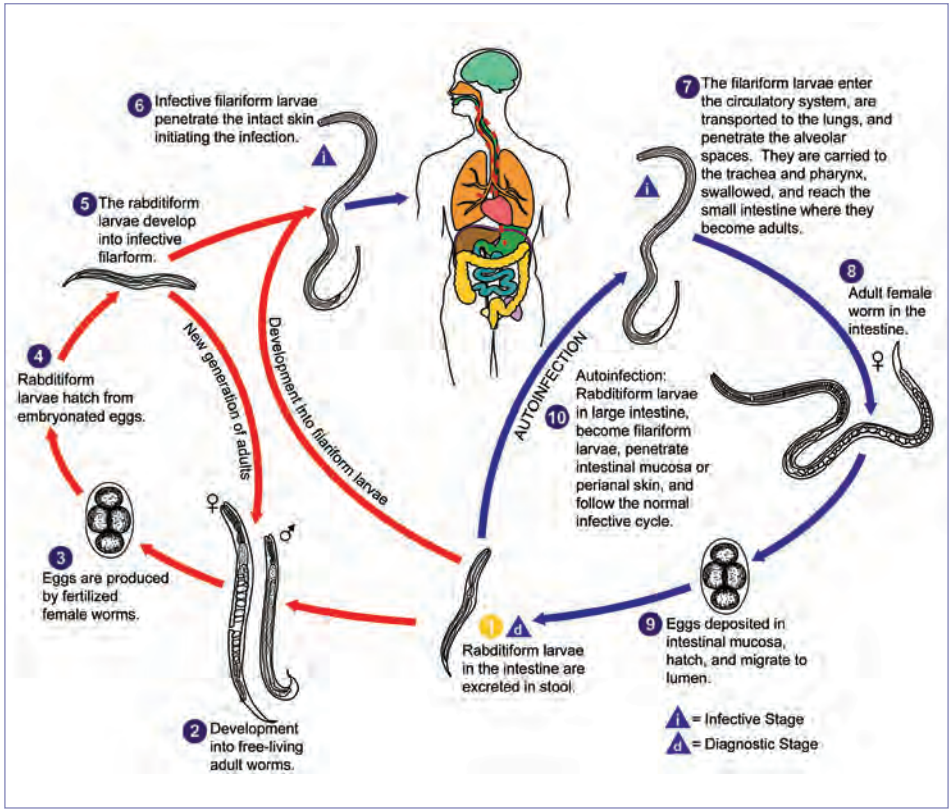


Image 138.4

The *Strongyloides* life cycle is complex among helminths with its alternation between free-living and parasitic cycles and its potential for autoinfection and multiplication within the host. Two types of cycles exist. Free-living cycle: The rhabditiform larvae passed in the stool (1) (see Parasitic cycle) can either molt twice and become infective filariform larvae (direct development) (6) or molt 4 times and become free-living adult males and females (2) that mate and produce eggs (3), from which rhabditiform larvae hatch (4). The latter, in turn, can develop (5) into either a new generation of free-living adults (as represented in 2) or infective filariform larvae (6). The filariform larvae penetrate the human host skin to initiate the parasitic cycle. Parasitic cycle: Filariform larvae in contaminated soil penetrate human skin (6) and are transported to the lungs, where they penetrate the alveolar spaces; they are carried through the bronchial tree to the pharynx, are swallowed, and then reach the small intestine (7). In the small intestine they molt twice and become adult female worms (8). The females live threaded in the epithelium of the small intestine and by parthenogenesis produce eggs (9), which yield rhabditiform larvae. The rhabditiform larvae can either be passed in the stool (1) (see Free-living cycle) or can cause autoinfection (10). In autoinfection, the rhabditiform larvae become infective filariform larvae, which can penetrate the intestinal mucosa (internal autoinfection) or the skin of the perianal area (external autoinfection); in either case, the filariform larvae may follow the previously described route, being carried successively to the lungs, bronchial tree, pharynx, and small intestine, where they mature into adults; or they may disseminate widely in the body. To date, occurrence of autoinfection in humans with helminthic infections is recognized only in *Strongyloides stercoralis* and *Capillaria philippinensis* infections. In the case of *Strongyloides*, autoinfection may explain the possibility of persistent infections for many years in persons who have not been in an endemic area and of hyperinfections in immunodepressed individuals.

CHAPTER 139

Syphilis

CLINICAL MANIFESTATIONS

Congenital Syphilis

Intrauterine infection with *Treponema pallidum* can result in stillbirth, hydrops fetalis, or preterm birth or may be clinically silent at birth. Infected infants can have hepatosplenomegaly; snuffles (copious nasal secretions); lymphadenopathy; mucocutaneous lesions; pneumonia; osteochondritis, periostitis, and pseudoparalysis; edema; rash (maculopapular consisting of small dark red-copper spots that is most severe on the hands and feet); hemolytic anemia; or thrombocytopenia at birth or within the first 4 to 8 weeks of age. Skin lesions or moist nasal secretions of congenital syphilis are highly infectious. However, organisms rarely are found in lesions more than 24 hours after treatment has begun. Untreated infants, regardless of whether they have manifestations in early infancy, may develop late manifestations, which usually appear after 2 years of age and involve the central nervous system (CNS), bones and joints, teeth, eyes, and skin. Some consequences of intrauterine infection may not become apparent until many years after birth, such as interstitial keratitis (5–20 years of age), eighth cranial nerve deafness (10–40 years of age), Hutchinson teeth (peg-shaped, notched central incisors), anterior bowing of the shins, frontal bossing, mulberry molars, saddle nose, rhagades (perioral fissures), and Clutton joints (symmetric, painless swelling of the knees). The first 3 manifestations are referred to as the Hutchinson triad. Late manifestations can be prevented by treatment of early infection.

Acquired Syphilis

Infection with *T pallidum* in children or adults can be divided into 3 stages. The **primary stage** (or "**primary syphilis**") appears as one or more painless indurated ulcers (chancres) of the skin or mucous membranes at the site of inoculation. Lesions most commonly appear on the genitalia but may appear elsewhere, depending on the type of sexual contact (eg, oral, anal). These lesions appear, on average, 3 weeks (10–90 days) after exposure and heal spontaneously in a few weeks. Adjacent lymph nodes frequently are enlarged but are nontender. Chancres sometimes are not recognized clinically and are present during the secondary stage of syphilis. The **secondary stage** (or "**secondary syphilis**"), beginning 1 to 2 months later, is characterized by fever, sore throat, muscle aches, rash, mucocutaneous lesions, and generalized lymphadenopathy. The polymorphic maculopapular rash is generalized and typically includes the palms and soles. In moist areas around the vulva or anus, hypertrophic papular lesions (condyloma lata) can occur and can be confused with condyloma acuminata secondary to human papillomavirus (HPV) infection. Malaise, splenomegaly, headache, alopecia, and arthralgia also can be present. Secondary syphilis can be mistaken for other conditions, because its signs and symptoms are nonspecific. This stage also resolves spontaneously without treatment in approximately 3 to 12 weeks. A variable latent period follows but sometimes is interrupted during the first few years by recurrences of symptoms of secondary syphilis. **Latent syphilis** is the period after infection when patients are seroreactive but demonstrate no clinical manifestations of disease. Latent syphilis acquired within the preceding year is referred to as **early latent syphilis;** all other cases of latent syphilis are **late latent syphilis** (>1 year). Patients who have latent syphilis of unknown duration should be managed clinically as if they have late latent syphilis. The **tertiary stage** of infection occurs 15 to 30 years after the initial infection and can include gumma formation (soft, noncancerous growths that can destroy tissue) or cardiovascular involvement (including aortitis). Neurosyphilis, defined as infection of the central nervous system (CNS) with *T pallidum*, can occur at any stage of infection, especially in people infected with human immunodeficiency virus (HIV) and neonates with congenital syphilis. Manifestations of neurosyphilis include syphilitic meningitis, uveitis, seizures, optic atrophy, and (typically years after infection) dementia and posterior spinal cord degeneration (tabes dorsalis).

ETIOLOGY

T pallidum subspecies *pallidum* (*T pallidum*) is a thin, motile spirochete that is extremely fastidious, surviving only briefly outside the host. The organism has not been cultivated successfully on artificial media.

EPIDEMIOLOGY

Syphilis, which is rare in much of the industrialized world, persists in the United States and in resource-limited countries. In 2000 and 2001, the rate of primary and secondary syphilis was the lowest since reporting began in 1941. This rate increased almost every year since then, although initially mostly among men who have sex with men. In 2014, the rate of primary and secondary syphilis increased in every region of the United States in both men and women, with a concomitant increase in cases of congenital syphilis. Primary and secondary rates of syphilis are highest in black, non-Hispanic people and in males compared with females.

Congenital syphilis is contracted from an infected mother via transplacental transmission of *T pallidum* during pregnancy, or rarely at birth from contact with maternal lesions. Among women with untreated early syphilis, as many as 40% of pregnancies result in spontaneous abortion, stillbirth, or perinatal death. Infection can be transmitted to the fetus at any stage of maternal disease. The rate of transmission is 60% to 100% during primary and secondary syphilis and slowly decreases with later stages of maternal infection (approximately 40% with early latent infection and 8% with late latent infection).

Acquired syphilis almost always is contracted through direct sexual contact with ulcerative lesions of the skin or mucous membranes of infected people. Open, moist lesions of the primary or secondary stages are highly infectious. Relapses of secondary syphilis with infectious mucocutaneous lesions have been observed 4 years after primary infection.

Syphilis acquired beyond the neonatal period should be considered highly suggestive of sexual abuse in infants and prepubertal children once vertical transmission is excluded. The possibility of nonvenereal endemic syphilis should also be considered in children who have recently emigrated from areas with endemic infection. Health care providers are required to report suspected sexual abuse to the state child protective services agency.

The **incubation period** for acquired primary syphilis typically is 3 weeks (10 to 90 days).

DIAGNOSTIC TESTS

Definitive diagnosis is made when spirochetes are identified by microscopic darkfield examination of lesion exudate, nasal discharge, or tissue, such as placenta, umbilical cord, or autopsy specimens. *T pallidum* can be detected by polymerase chain reaction (PCR) assay, but these are not yet available. Direct fluorescent antibody (DFA) tests no longer are available in the United States. Specimens should be scraped from moist mucocutaneous lesions or aspirated from a regional lymph node. Although such testing can provide a definitive diagnosis, serologic testing also is necessary.

Presumptive diagnosis requires both nontreponemal and treponemal serologic tests. Nontreponemal tests for syphilis include the Venereal Disease Research Laboratory (VDRL) slide test and the rapid plasma reagin (RPR) test. These tests are inexpensive, are performed rapidly, and provide semiquantitative results through serial twofold dilutions that can help define disease activity and monitor response to therapy. However, nontreponemal test results may be falsely negative (ie, nonreactive) in early primary syphilis, latent acquired syphilis of long duration, and late congenital syphilis. Occasionally, a nontreponemal test performed on serum samples containing high concentrations of antibody against *T pallidum* will be weakly reactive or falsely negative, a reaction termed the prozone phenomenon; diluting serum results in a positive test. RPR titers generally are higher than VDRL titers; thus, when nontreponemal tests are used to monitor treatment response, the same test must be used throughout the follow-up period to ensure comparability of results.

A reactive nontreponemal test result from a patient with typical lesions indicates a presumptive diagnosis of syphilis but must be confirmed by one of the specific treponemal tests to exclude a false-positive test result.

False-positive nontreponemal results can be caused by certain viral infections (eg, Epstein-Barr virus infection, hepatitis, varicella, measles), lymphoma, tuberculosis, malaria, endocarditis, connective tissue disease, pregnancy, abuse of injection drugs, laboratory or technical error, or Wharton jelly contamination when umbilical cord blood specimens are used. Treatment should not be delayed while awaiting the results of the treponemal test results if the patient is symptomatic or at high risk of infection. A sustained fourfold or greater decrease in titer, equivalent to a change of 2 dilutions (eg, from 1:32 to 1:8), of the nontreponemal test result after treatment usually demonstrates adequate therapy, whereas a sustained fourfold increase in titer (eg, from 1:8 to 1:32) after treatment suggests reinfection or relapse. The nontreponemal test titer usually decreases fourfold or greater within 6 to 12 months after therapy for primary or secondary syphilis and usually becomes nonreactive within 1 year after successful therapy if the infection was treated early. The patient usually becomes seronegative within 2 years even if the initial titer was high or the infection was congenital. Some people will continue to have low stable nontreponemal antibody titers (eg, VDRL titer 1:2 or less; RPR titer 1:4 or less) despite effective therapy.

Treponemal tests in use include the *T pallidum* particle agglutination (TP-PA) test, *T pallidum* enzyme immunoassay (TP-EIA), *T pallidum* chemiluminescent assay (TP-CIA), and fluorescent treponemal antibody absorption (FTA-ABS) test. Most people who have reactive treponemal test results remain reactive for life, even after successful therapy. However, 15% to 25% of patients treated during the primary stage revert to being serologically nonreactive on treponemal testing after 2 to 3 years. Treponemal tests also are not 100% specific for syphilis; positive reactions occur variably in patients with other spirochetal diseases, such as yaws, pinta, leptospirosis, rat-bite fever, relapsing fever, and Lyme disease. Nontreponemal tests can be used to differentiate Lyme disease from syphilis, because the VDRL test is nonreactive in Lyme disease.

In most cases, if a patient has a positive RPR or VDRL in low titer and has a negative treponemal test result, the nontreponemal antibody test result will be a false positive. However, in patients with early syphilis, the nontreponemal test may become positive before the treponemal test. Therefore, retesting in 2 to 4 weeks and again later if clinically indicated should be considered in persons at increased risk for syphilis, including pregnant women.

The Centers for Disease Control and Prevention (CDC) recommend syphilis serologic screening with a nontreponemal test to identify people with possible untreated infection; this screening is followed by confirmation using one of the several available treponemal tests ("conventional diagnostic" approach). However, because of cost issues, some clinical laboratories and blood banks have begun to screen samples using treponemal tests (eg, TP-EIA or TP-CIA) first rather than beginning with a nontreponemal test. This "reverse-sequence screening" approach can be associated with high rates of false-positive results, especially in low-prevalence populations. When the reverse-sequence algorithm is used, people with a positive TP-EIA/TP-CIA result and a negative nontreponemal test result (discordant result) should have a second treponemal test targeting a different *T pallidum* antigen performed to confirm the results of the original test. If the second treponemal test result is negative and the person is at low risk for syphilis, the original treponemal test result likely was a false positive. All patients who have syphilis should be tested for HIV infection and other sexually transmitted infections (STIs).

Cerebrospinal Fluid Tests

Cerebrospinal fluid (CSF) abnormalities in patients with neurosyphilis can include increased protein concentration, increased white blood cell (WBC) count, and/or a reactive CSF-VDRL test result. Outside the neonatal period, the CSF-VDRL is highly specific but is insensitive; thus, a negative CSF-VDRL result does not exclude a diagnosis of neurosyphilis. Conversely, a reactive CSF-VDRL test in a neonate can be the result of nontreponemal IgG antibodies that cross the blood-brain barrier.

The CSF leukocyte count usually is elevated in neurosyphilis (>5 WBCs/mm^3). CSF cell counts as high as 25 WBCs/mm^3 or protein concentration up to 150 mg/dL may occur among normal, noninfected term neonates and can be even higher in preterm neonates; however, lower values (ie, 5 WBCs/mm^3 and protein of 40 mg/dL) should be considered the upper limits of normal when assessing a term infant for congenital syphilis. A positive CSF FTA-ABS result can support the diagnosis of neurosyphilis but by itself cannot establish the diagnosis. The TP-PA or RPR test for CSF should not be used for CSF evaluation.

Testing During Pregnancy

Prevention of congenital syphilis depends on the identification and adequate treatment of pregnant women with syphilis. All women should be screened serologically for syphilis early in pregnancy. False-negative test results are possible in recent infection, and syphilis may be acquired later in pregnancy. In communities and populations in which the prevalence of syphilis is high, and for women at high risk for infection, serologic testing also should be performed at 28 to 32 weeks' gestation and again at delivery. A nontreponemal test (RPR or VDRL) is recommended for screening, followed by a treponemal test if the screening result is positive. In most cases, if the treponemal antibody test result is negative, the nontreponemal test result is falsely positive and no further evaluation is necessary. However, retesting in 2 to 4 weeks should be considered.

If the reverse-sequence screening algorithm is used, pregnant women with reactive treponemal EIA/CIA test should have a confirmatory quantitative nontreponemal test. If the nontreponemal test result is negative, a second treponemal test using a different *T pallidum* antigen should be obtained. If the second treponemal test is positive, it may be attributable to a prior infection adequately treated in the past or to untreated syphilis in a late stage.

For women treated for syphilis during pregnancy, follow-up nontreponemal serologic testing is necessary to assess the effectiveness of therapy. Treated pregnant women with syphilis should have quantitative nontreponemal serologic tests repeated at 28 to 32 weeks of gestation and at delivery. Serologic titers may be repeated monthly in women at high risk of reinfection or in geographic areas where the prevalence of syphilis is high.

Sonographic evaluation of the fetus should be performed when syphilis is diagnosed during the second half of pregnancy. Pathologic examination of the placenta or umbilical cord at delivery also should be performed. Any woman who delivers a stillborn infant after 20 weeks' gestation should be tested for syphilis.

Evaluation of Infants for Congenital Infection During the Newborn Period to 1 Month of Age

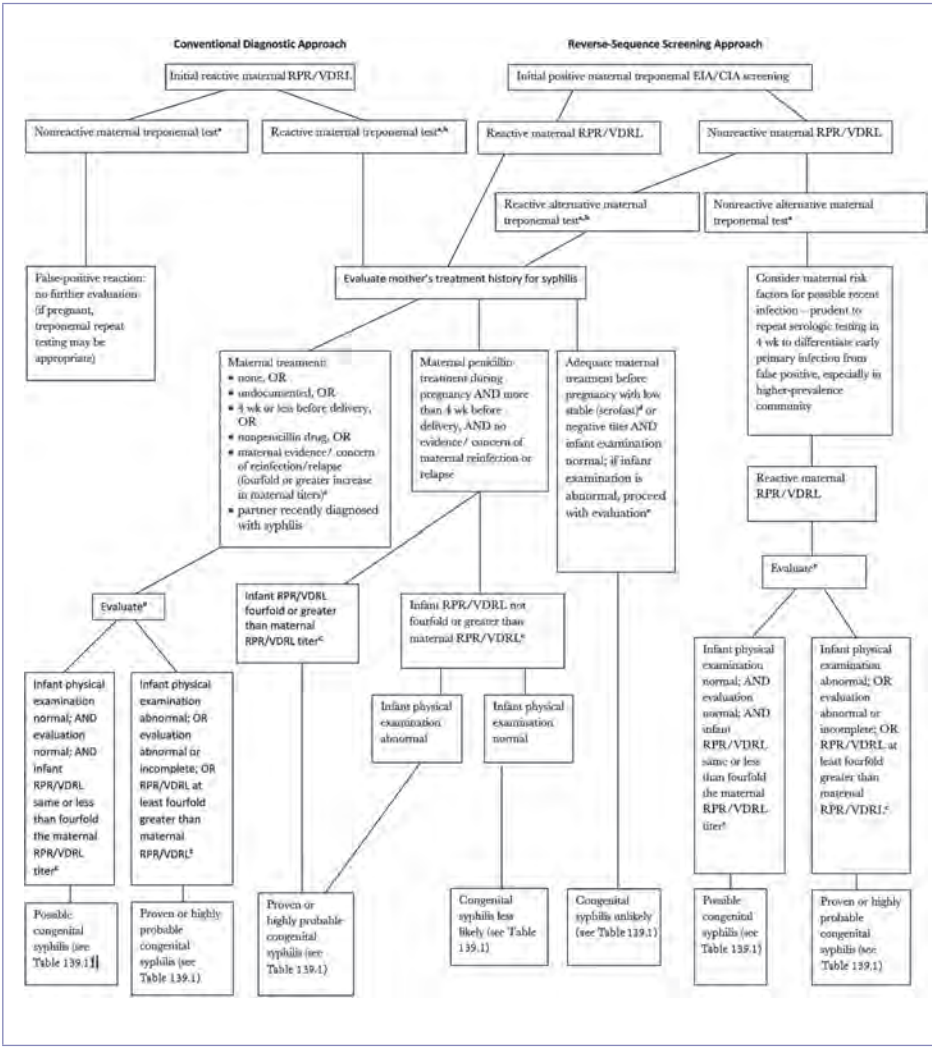
No newborn infant should be discharged from the hospital without determination of the mother's serologic status for syphilis. All infants born to seropositive mothers require a careful examination and a nontreponemal test obtained from the infant. The test performed on the infant should be the same as that performed on the mother to enable comparison of titer results. A negative maternal RPR or VDRL test result at delivery does not exclude congenital syphilis, although such a situation is rare. The diagnostic approach to infants being evaluated for congenital syphilis is presented in Figure 139.1, with treatment recommendations provided in Table 139.1. Other causes of elevated CSF laboratory values should be considered when an infant is being evaluated for congenital syphilis. Infants born to mothers who have syphilis and HIV infection do not require different evaluation, therapy, or follow-up for syphilis than is recommended for all infants.

Evaluation of Infants >1 Month of Age and Children

Infants and children identified as having reactive serologic tests for syphilis should have maternal serologic test results and records reviewed to assess whether they have congenital or acquired syphilis. The recommended evaluation for congenital syphilis includes a CSF examination plus other tests as clinically indicated (eg, long bone or chest radiography, complete blood cell count, differential and platelet count). CSF examination also should be performed in patients with neurologic or ophthalmic signs or symptoms (eg, iritis, uveitis), evidence of active tertiary syphilis (eg, aortitis,

Figure 139.1

Algorithm for diagnostic approach of infants born to mothers with reactive serologic tests for syphilis.



RPR indicates rapid plasma reagin; VDRL, Venereal Disease Research Laboratory.

[a] *Treponema pallidum* particle agglutination (TP-PA) (which is the preferred treponemal test), fluorescent treponemal antibody absorption (FTA-ABS), or microhemagglutination test for antibodies to *T pallidum* (MHA-TP).

[b] Test for human immunodeficiency virus (HIV) antibody. Infants of HIV-infected mothers do not require different evaluation or treatment for syphilis.

[c] A fourfold change in titer is the same as a change of 2 dilutions. For example, a titer of 1:64 is fourfold greater than a titer of 1:16, and a titer of 1:4 is fourfold lower than a titer of 1:16. When comparing titers, the same type of nontreponemal test should be used (eg, if the initial test was an RPR, the follow-up test should also be an RPR).

[d] Stable VDRL titers 1:2 or less or RPR 1:4 or less beyond 1 year after successful treatment are considered low serofast.

[e] Complete blood cell (CBC) and platelet count; cerebrospinal fluid (CSF) examination for cell count, protein, and quantitative VDRL; other tests as clinically indicated (eg, chest radiographs, long-bone radiographs, eye examination, liver function tests, neuroimaging, and auditory brainstem response).

Table 139.1

Evaluation and Treatment of Infants With Possible, Probable, or Confirmed Congenital Syphilis

Category	Findings	Recommended Evaluation	Treatment
Proven or highly probable congenital syphilis	Abnormal physical examination consistent with congenital syphilis OR A serum quantitative nontreponemal serologic titer that is fourfold or more higher than the mother's titer OR A positive result of darkfield test or PCR assay of lesions or body fluid(s)	CSF analysis (CSF VDRL, cell count, and protein) CBC with differential and platelet count Other tests (as clinically indicated): • Long-bone radiography • Chest radiography • Transaminases • Neuroimaging • Ophthalmologic examination • Auditory brain stem response	Aqueous crystalline penicillin G, 50,000 U/kg, IV, every 12 hours (1 wk or younger), then every 8 h for infants older than 1 wk, for a total of 10 days of therapy[a] (**preferred**) OR Procaine penicillin G, 50,000 U/kg, IM, as single daily dose for 10 days
Possible congenital syphilis	Normal infant examination AND A serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer AND ONE OF THE FOLLOWING: Mother was not treated, was inadequately treated, or had no documentation of receiving treatment; OR Mother was treated with erythromycin or a regimen other than those recommended in the guideline (ie, a nonpenicillin regimen) OR Mother received recommended treatment <4 wk before delivery	CSF analysis (CSF VDRL, cell count, and protein) CBC with differential and platelet count Long-bone radiography These evaluations may not be necessary if 10 days of parenteral therapy is administered	Same as above OR Benzathine penicillin G, 50 000 U/kg, IM, single dose (recommended by some experts, but only if all components of the evaluation are obtained and are normal, including normal CSF results[b] and follow-up is certain (some experts)

Table 139.1 (*continued*)

Category	Findings	Recommended Evaluation	Treatment
Congenital syphilis less likely	Normal infant examination AND A serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer AND Mother was treated during pregnancy, treatment was appropriate for stage of infection, and treatment was administered >4 wk before delivery AND Mother has no evidence of reinfection or relapse	Not recommended	

(*continued*)

Table 139.1 (*continued*)

Category	Findings	Recommended Evaluation	Treatment
Congenital syphilis is unlikely	Normal infant examination AND A serum quantitative nontreponemal serologic titer equal to or less than fourfold the maternal titer AND Mother was treated adequately before pregnancy AND Mother's nontreponemal serologic titer remained low and stable (ie, serofast) before and during pregnancy and at delivery (eg, VDRL ≤1:2; RPR ≤1:4)	Not recommended	No treatment required, but infants with reactive nontreponemal tests should be followed serologically to ensure test result returns to negative Benzathine penicillin G, 50,000 U/kg, IM, single dose can be considered if follow-up is uncertain and infant has a reactive test (some experts) Neonates with a negative nontreponemal test result at birth and whose mothers were seroreactive at delivery should be retested at 3 mo to rule out serologically negative incubating congenital syphilis at the time of birth

PCR indicates polymerase chain reaction; CSF, cerebrospinal fluid; CBC, complete blood cell count; VDRL, Venereal Disease Research Laboratory; IV, intravenously; IM, intramuscularly; RPR, rapid plasma reagin.

[a] If 24 hours or more of therapy is missed, the entire course must be restarted.

[b] If CSF is not obtained or uninterpretable (eg, bloody tap), a 10-day course is recommended.

gumma), or treatment failure. Some experts recommend performing a CSF examination on all patients who have latent syphilis and a nontreponemal serologic test result of 1:32 or greater or in patients who are HIV infected and have a serum CD4+ T-lymphocyte count of 350 or less, because the risk of asymptomatic neurosyphilis in these circumstances is increased approximately threefold.

TREATMENT

Parenteral penicillin G remains the preferred drug for treatment of syphilis at any stage. Recommendations for penicillin G use and duration of therapy vary, depending on the stage of disease and clinical manifestations. Parenteral penicillin G is the only documented effective therapy for patients who have neurosyphilis, congenital syphilis, or syphilis during pregnancy and is recommended for people with HIV infection. Infants and children with a history of penicillin allergy or who develop presumed penicillin allergy during treatment should be desensitized and then treated with penicillin whenever possible.

Congenital Syphilis: Newborn Period to 1 Month of Age

The management of congenital syphilis is based on whether the infant has proven or probable congenital syphilis, has possible congenital syphilis, or is considered less likely or unlikely to have syphilis. The treatment of infants with congenital syphilis is detailed in Table 139.1, with the diagnostic approach to such infants presented in Figure 139.1. If more than 1 day of therapy is missed, the entire course should be restarted. Data supporting use of other antimicrobial agents (eg, ampicillin) for treatment of congenital syphilis are not available. When possible, a full 10-day course of penicillin is preferred, even if ampicillin initially was provided for possible sepsis.

Congenital Syphilis: Infants ≥1 Month of Age and Children

Infants older than 1 month who possibly have congenital syphilis should be treated with intravenous aqueous crystalline penicillin intravenously every 4–6 hours for 10 days. This regimen also should be used to treat children older than 2 years who have late and previously untreated congenital syphilis. Some experts suggest giving such patients a single dose of penicillin G benzathine intramuscularly after the 10-day course of intravenous aqueous crystalline penicillin. If the patient has no clinical manifestations of disease, the CSF examination is normal, and the result of the CSF-VDRL test is negative, some experts would treat with 3 weekly doses of penicillin G benzathine intramuscularly.

Syphilis in Pregnancy

Regardless of stage of pregnancy, women should be treated with penicillin according to the dosage schedules appropriate for the stage of syphilis as recommended for nonpregnant patients (Table 139.2). For penicillin-allergic patients, no proven alternative therapy has been established. A pregnant woman with a history of penicillin allergy should have skin testing, if available, to evaluate for true allergy, and should be treated with penicillin if allergy is not confirmed; if allergy is confirmed, the woman should undergo desensitization followed by treatment with penicillin.

Early Acquired Syphilis (Primary, Secondary, Early Latent Syphilis)

A single intramuscular dose of penicillin G benzathine is the preferred treatment for children and adults (Table 139.2). For nonpregnant patients who are allergic to penicillin, doxycycline or (if ≥8 years of age) tetracycline should be given for 14 days. Clinical studies (along with biologic and pharmacologic considerations) suggest that ceftriaxone at 1 g, once daily, either intramuscularly or intravenously, for 10 to 14 days (for adolescents and adults) is effective for early-acquired syphilis. Azithromycin can be effective as a single oral dose of 2 g; however, azithromycin treatment failures have been reported. Close follow-up of people receiving any alternative therapy is essential. When follow-up cannot be ensured, especially for children younger than 8 years, consideration must be given to hospitalization and desensitization followed by administration of penicillin G.

Syphilis of More Than 1 Year's Duration (Late Latent Syphilis and Late Syphilis)

Penicillin G benzathine should be administered intramuscularly, weekly, for 3 successive weeks (Table 139.2). In patients who are allergic to penicillin, tetracycline or doxycycline (both if ≥8 years of age) for 4 weeks should be given only with close serologic and clinical follow-up. Limited clinical studies suggest that ceftriaxone might be effective, but the optimal dose and duration have not been defined.

Neurosyphilis

For children, intravenous aqueous crystalline penicillin G for 10 to 14 days is recommended. Some experts recommend additional subsequent therapy with intramuscular penicillin G benzathine for up to 3 single weekly doses (Table 139.2). A patient with a history of penicillin allergy should have skin testing to evaluate for true allergy and treated with penicillin if allergy is not confirmed; if allergy is confirmed, the patient should undergo desensitization followed by treatment with penicillin.

Other Considerations

Mothers of infants with congenital syphilis should be tested for other STIs, including *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, HIV, and hepatitis B. If injection drug use is suspected, the mother also may be at risk of hepatitis C virus infection. All patients with syphilis should be tested for other STIs, including *N gonorrhoeae*, *C trachomatis*, HIV, and hepatitis B. Patients who have primary syphilis should be retested for HIV after 3 months if the first HIV test result is negative. Immunization status for hepatitis B and human papillomavirus (HPV) should be reviewed and vaccines should be administered if not up to date. For people with HIV infection and syphilis, careful follow-up is essential. People with HIV infection who have early syphilis may be at increased risk of neurologic complications and higher rates of treatment failure with currently recommended regimens. Partners who were exposed within 90 days preceding the diagnosis of primary, secondary, or early latent syphilis in the index patient should be treated presumptively for syphilis, even if they are seronegative.

Children with acquired primary, secondary, or latent syphilis should be evaluated for possible sexual assault or abuse.

Follow-up and Management

Congenital Syphilis

All infants who have reactive serologic tests for syphilis or were born to mothers who were seroreactive at delivery should receive careful follow-up evaluations during regularly scheduled well-child care visits at 2, 4, 6, and 12 months of age. Serologic nontreponemal tests should be performed every 2 to 3 months until the nontreponemal test becomes nonreactive. Nontreponemal antibody titers should decrease by 3 months of age and should be nonreactive by 6 months of age, whether the infant was infected and adequately treated or was not infected and initially seropositive because of transplacentally acquired maternal antibody. The serologic response after therapy may be slower for infants treated after the neonatal period. Patients with increasing titers or with persistent stable titers 6 to 12 months after initial treatment should be reevaluated, including a CSF examination, and treated with a 10-day course of parenteral penicillin G, even if they were treated previously.

Treponemal tests should not be used to evaluate treatment response, because results for an infected child can remain positive despite effective therapy. Passively transferred maternal treponemal antibodies can persist in an infant until 15 months of age. A reactive treponemal test after 18 months of age is diagnostic of congenital syphilis. If the nontreponemal test is nonreactive at this time, no further evaluation or treatment is necessary. If the nontreponemal test is reactive at 18 months of age, the infant should be evaluated (or reevaluated) fully and treated for congenital syphilis.

Treated infants with congenital neurosyphilis should undergo repeated clinical evaluation and CSF examination at 6-month intervals until their CSF examination is normal. A reactive CSF VDRL test or abnormal CSF indices that cannot be attributed to another ongoing illness at the 6-month interval are indications for

Table 139.2
Recommended Treatment for Syphilis in People Older Than 1 Month

Status	Children	Adults
Primary, secondary, and early latent syphilis[a]	Penicillin G benzathine,[b] 50,000 U/kg, IM, up to the adult dose of 2.4 million U in a single dose	Penicillin G benzathine, 2.4 million U, IM, in a single dose **OR** *If allergic to penicillin and not pregnant,* Doxycycline, 100 mg, orally, twice a day for 14 days **OR** Tetracycline, 500 mg, orally, 4 times/day for 14 days (≥8 y only)
Late latent syphilis[c]	Penicillin G benzathine, 50,000 U/kg, IM, up to the adult dose of 2.4 million U, administered as 3 single doses at 1-wk intervals (total 150,000 U/kg, up to the adult dose of 7.2 million U)	Penicillin G benzathine, 7.2 million U total, administered as 3 doses of 2.4 million U, IM, each at 1-wk intervals **OR** *If allergic to penicillin and not pregnant,* Doxycycline, 100 mg, orally, twice a day for 4 wk (≥8 y only) **OR** Tetracycline, 500 mg, orally, 4 times/day for 4 wk (≥8 y only)
Tertiary	…	Penicillin G benzathine, 7.2 million U total, administered as 3 doses of 2.4 million U, IM, at 1-wk intervals *If allergic to penicillin and not pregnant, consult an infectious diseases expert*
Neurosyphilis[d]	Aqueous crystalline penicillin G, 200,000–300,000 U/kg/day, IV, administered as 50,000 U/kg every 4–6 h for 10–14 days, in doses not to exceed the adult dose	Aqueous crystalline penicillin G, 18–24 million U per day, administered as 3–4 million U, IV, every 4 h for 10–14 days[e] **OR** Penicillin G procaine,[c] 2.4 million U, IM, once daily **PLUS** probenecid, 500 mg, orally, 4 times/day, both for 10–14 days[e]

IV indicates intravenously; IM, intramuscularly.
[a]Early latent syphilis is defined as being acquired within the preceding year.
[b]Penicillin G benzathine and penicillin G procaine are approved for intramuscular administration only.
[c]Late latent syphilis is defined as syphilis beyond 1 year's duration.
[d]Patients who are allergic to penicillin should be desensitized.
[e]Some experts administer penicillin G benzathine, 2.4 million U, IM, once per week for up to 3 weeks after completion of these neurosyphilis treatment regimens.

retreatment. Neuroimaging studies, such as magnetic resonance imaging, should be considered in these children.

Acquired Syphilis

People with acquired syphilis should have clinical and serologic evaluations following treatment to evaluate for persistence or recurrence of symptoms or an inadequate serologic response following therapy. People with primary or secondary syphilis should have clinical and serologic evaluations performed at 6 and 12 months after treatment. If signs or symptoms persist or recur, or a fourfold or greater increase in nontreponemal titers occurs, treatment failure or reinfection may be responsible. CSF analysis, HIV testing, and retreatment based on CSF findings are indicated. Failure of nontreponemal titers to decline fourfold within 6 to 12 months may also indicate treatment failure.

Following treatment, people with latent syphilis should experience a fourfold or greater decline in nontreponemal titers within 12 to 24 months. If titers increase at least fourfold or initial high titers fail to fall fourfold, or symptoms of syphilis develop, reevaluation, including a CSF examination, is warranted.

Additional guidance can be found in the current CDC guidelines for the management of sexually transmitted diseases.

In all these instances, retreatment should be performed with 3 weekly injections of penicillin G benzathine intramuscularly unless CSF examination indicates that neurosyphilis is present, at which time treatment for neurosyphilis should be initiated. Retreated patients should be treated with the schedules recommended for patients with syphilis for more than 1 year, and only 1 retreatment course is indicated. The possibility of reinfection or concurrent HIV infection should always be considered when retreating patients with early syphilis, and repeat HIV testing should be performed in such cases.

Patients with neurosyphilis associated with acquired syphilis must have periodic serologic testing, clinical evaluation at 6-month intervals, and repeat CSF examinations. If the CSF white blood cell count has not decreased after 6 months or if the CSF white blood cell count or protein concentration is not normal after 2 years, retreatment should be considered. CSF abnormalities may persist for extended periods of time in people with HIV infection with neurosyphilis. Close follow-up is warranted.

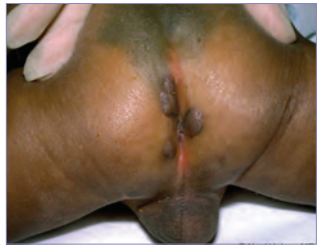


Image 139.1
Cutaneous syphilis in a 6-month-old. Courtesy of Neal Halsey, MD.

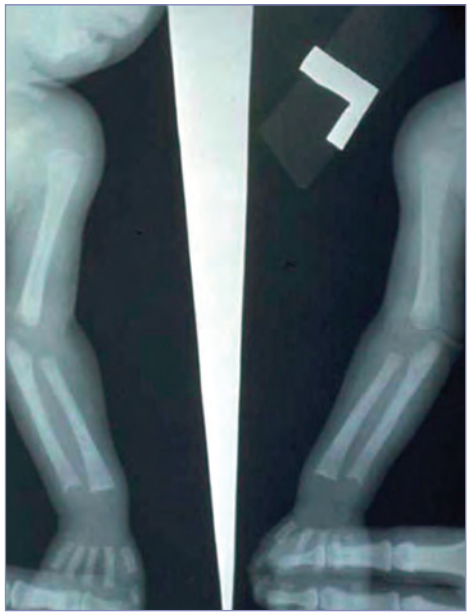


Image 139.3
Upper extremities of the patient in Image 139.2 with early periostitis and radiolucency of the distal radius and ulna bilaterally. Courtesy of Edgar O. Ledbetter, MD, FAAP.

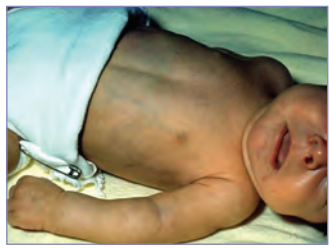


Image 139.5
A newborn with congenital syphilis with bleeding from the nares and tender swelling of the wrists and elbows secondary to luetic periostitis.

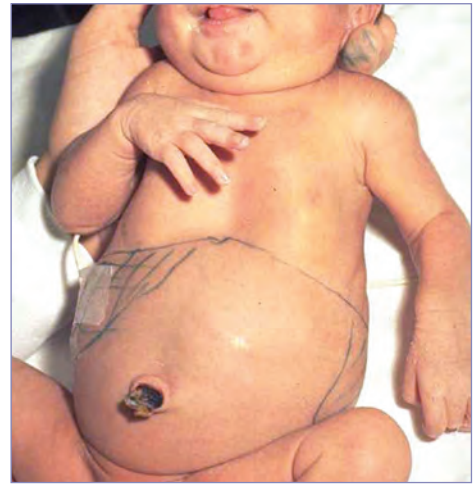


Image 139.2
Congenital syphilis in a 2-week-old boy with marked hepatosplenomegaly. The neonate kept his upper extremities in a flail-like position because of painful periostitis. Courtesy of Edgar O. Ledbetter, MD, FAAP.

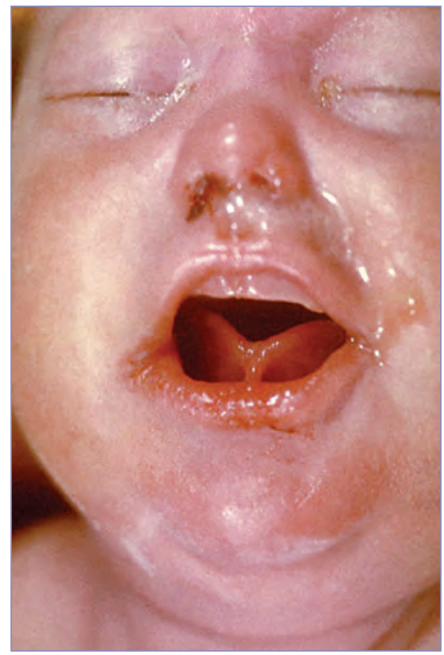


Image 139.4
The face of a newborn displaying pathologic morphology indicative of congenital syphilis with striking mucous membrane involvement. Courtesy of Centers for Disease Control and Prevention.

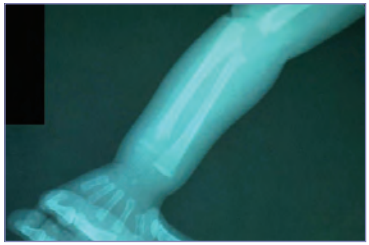


Image 139.6
Congenital syphilis with metaphyseal destruction of distal humerus, radius, and ulna.

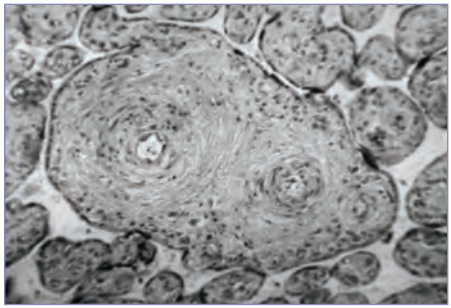


Image 139.8
A photomicrograph revealing cytoarchitectural changes of the placenta seen in congenital syphilis. The chorionic villi are enlarged and contain dense laminated connective tissue, and the capillaries distributed throughout the villi are compressed by this connective tissue proliferation (hematoxylin-eosin stain, magnification ×450). Courtesy of Centers for Disease Control and Prevention.

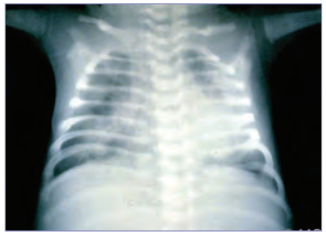


Image 139.10
A 3-day-old with severe pneumonia alba.

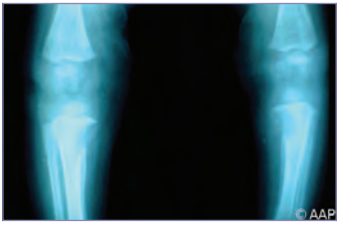


Image 139.7
Congenital syphilis with proximal tibial metaphysitis (Wimberger sign).

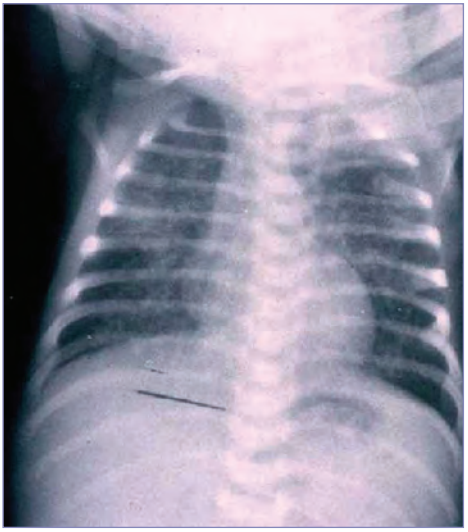


Image 139.9
Congenital syphilis with pneumonia alba. The infant survived with penicillin treatment.

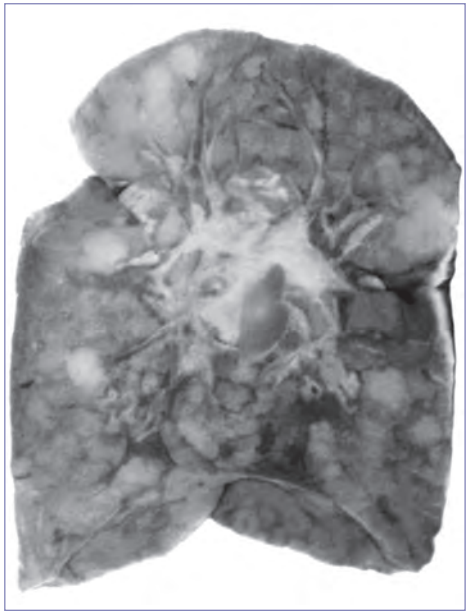


Image 139.11
This pathologic condition of the lungs, known as pneumonia alba, is caused by congenital syphilis. The lungs are enlarged, heavy, uniformly firm, and yellow-white in color. Seventy percent of all pregnant women with untreated primary syphilis may transmit the infection to their fetuses. Courtesy of Centers for Disease Control and Prevention.

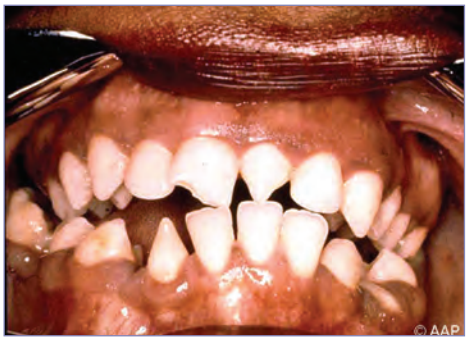


Image 139.13
Hutchinson teeth, a late manifestation of congenital syphilis. Changes occur in secondary dentition. The central incisors are smaller than normal and have sloping sides. Courtesy of Edgar O. Ledbetter, MD, FAAP.

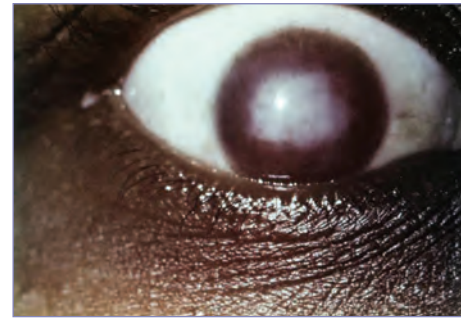


Image 139.12
This photograph depicts the presence of a diffuse stromal haze in the cornea of a female patient, known as interstitial keratitis, which was due to her late-staged congenital syphilitic condition. Interstitial keratitis, which is an inflammation of the cornea's connective tissue elements and usually affects both eyes, can occur as a complication brought on by congenital or acquired syphilis. Interstitial keratitis usually occurs in children older than 2 years. Courtesy of Centers for Disease Control and Prevention.

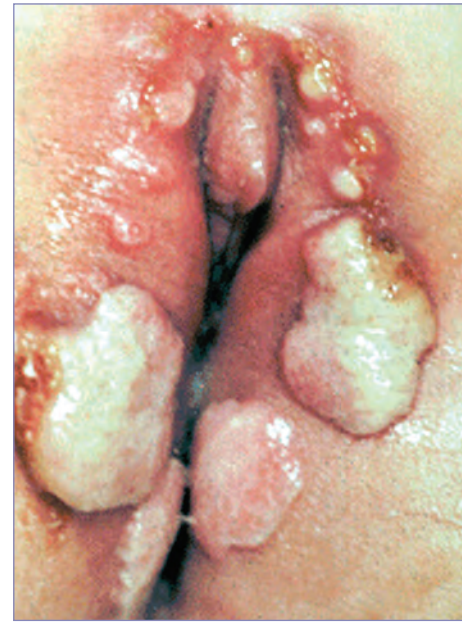


Image 139.14
Condyloma latum in a 7-year-old girl who had been sexually abused. These whitish gray, moist lesions are caused by *Treponema pallidum* and are highly contagious.

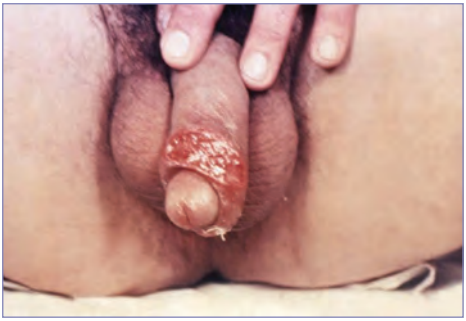


Image 139.15
This image shows an extensive chancre located on the penile shaft due to a primary syphilitic infection caused by *Treponema pallidum*. The primary stage of syphilis is usually marked by the appearance of a single lesion, called a *chancre*. The chancre is usually firm, round, small, and painless. It appears at the spot where *T pallidum* entered the body and lasts 3 to 6 weeks, healing on its own. Courtesy of Centers for Disease Control and Prevention.

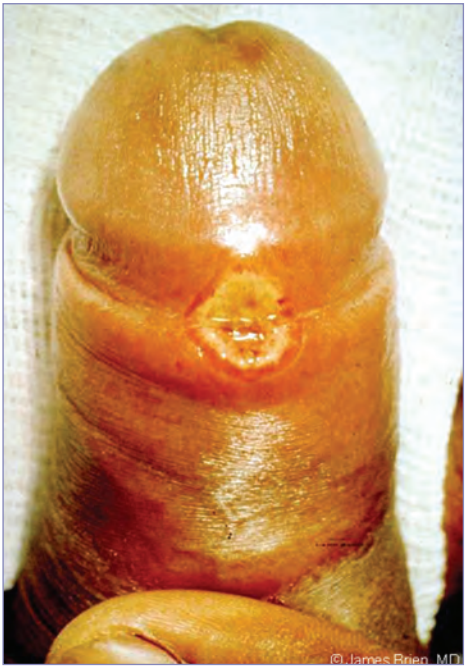


Image 139.16
Syphilis with penile chancre. Copyright James Brien, DO.

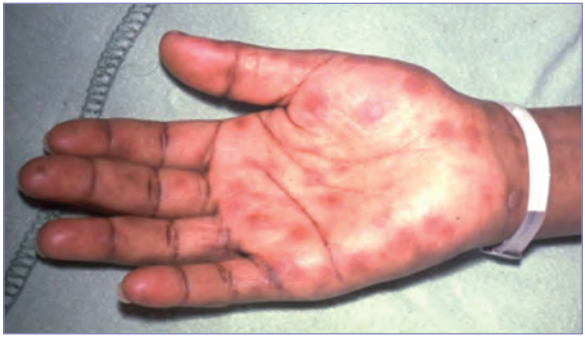


Image 139.17
A 16-year-old girl with rash of secondary syphilis noticed at 3 months' gestation of her pregnancy. The sign and symptoms of secondary syphilis generally occur 6 to 8 weeks after the primary infection when primary lesions have usually healed.

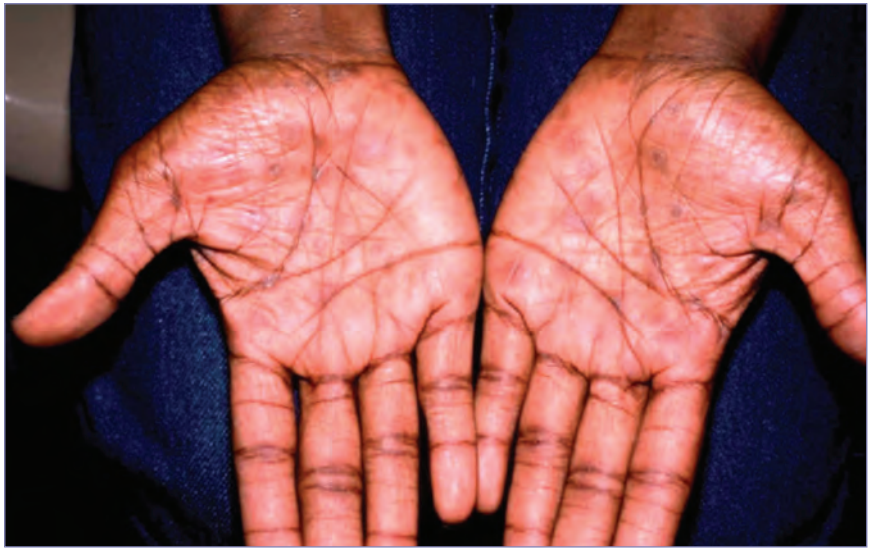


Image 139.18
Secondary syphilis in a different patient than Image 139.17 with discrete palmar lesions. The diagnosis was suspected because of the palmar lesions.

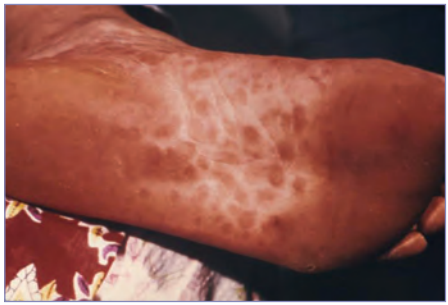


Image 139.19
This patient presented with a papular rash on the sole of the foot due to secondary syphilis. The second stage of syphilis starts when one or more areas of the skin break into a rash that appears as rough red or reddish-brown spots on the palms of the hands and the bottoms of the feet. Even without treatment, the rash clears up spontaneously. Courtesy of Centers for Disease Control and Prevention.

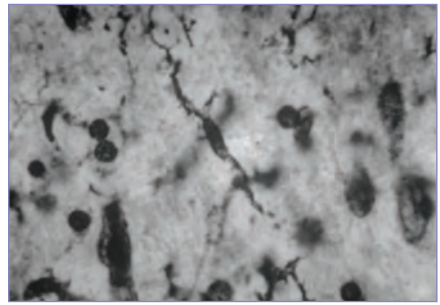


Image 139.20
Elongated microglia (rod cells) due to untreated syphilis, leading to general paresis known as *paretic neurosyphilis*. Neurosyphilis is a slowly progressive and destructive infection of the brain and spinal cord that occurs in untreated syphilis. This image shows bipolar, elongated microglia (rod cells) characteristic of paretic neurosyphilis (Hortega method, magnification ×950). Courtesy of Centers for Disease Control and Prevention.

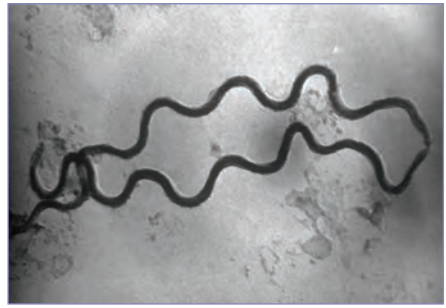


Image 139.21
An electron photomicrograph of 2 spiral-shaped *Treponema pallidum* bacteria (magnification ×36,000). Courtesy of Centers for Disease Control and Prevention.

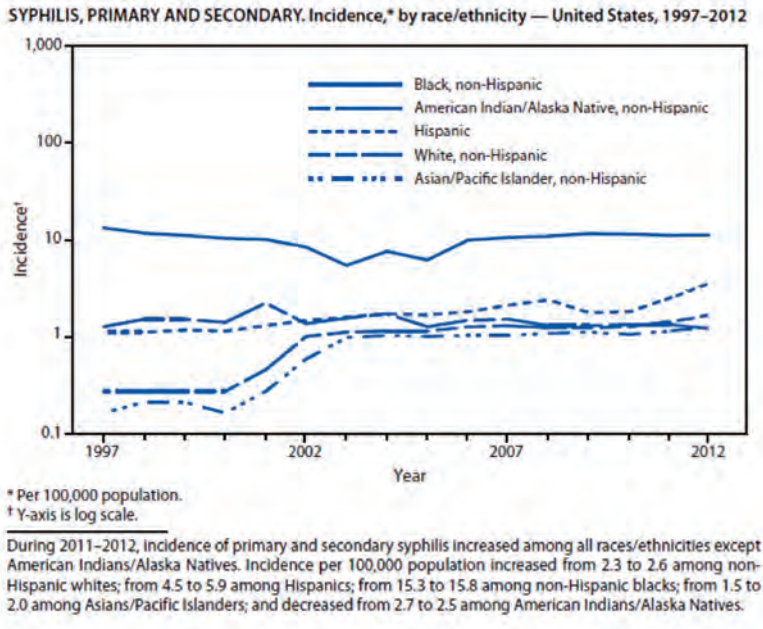


Image 139.22
Syphilis, primary and secondary. Incidence, by race/ethnicity—United States, 1997–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

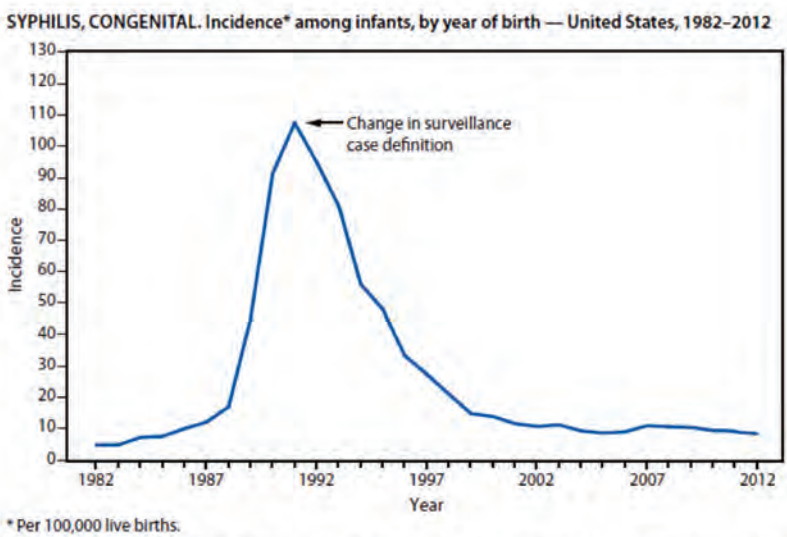


Image 139.23
Syphilis, congenital. Incidence among infants, by year of birth—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

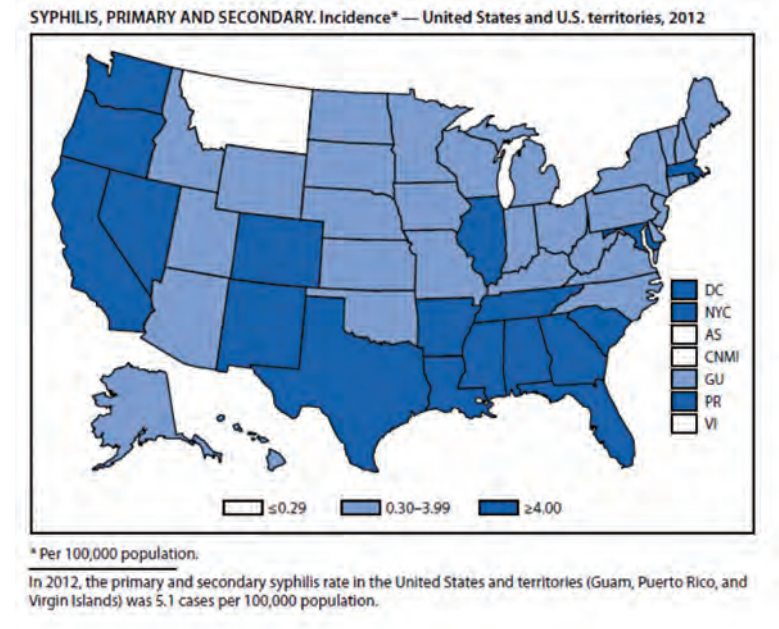


Image 139.24
Syphilis, primary and secondary. Incidence—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

Image 139.25
Mucocutaneous lesions of congenital syphilis in a term newborn. Courtesy of Carol J. Baker, MD, FAAP.

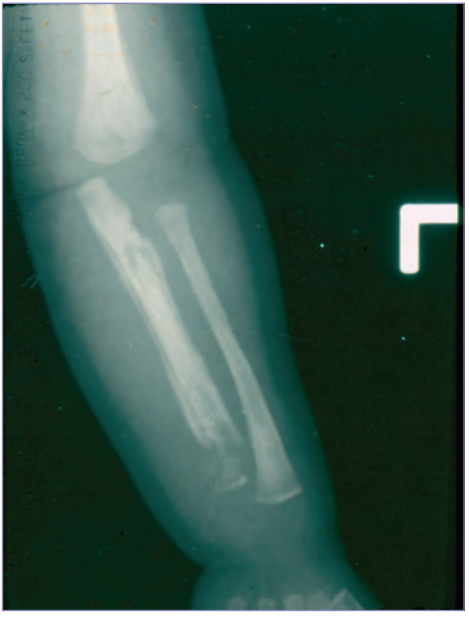


Image 139.27
Radiograph of the forearm of the newborn in Image 139.26 illustrating the periostitis of the radius and ulna. Courtesy of Carol J. Baker, MD, FAAP.

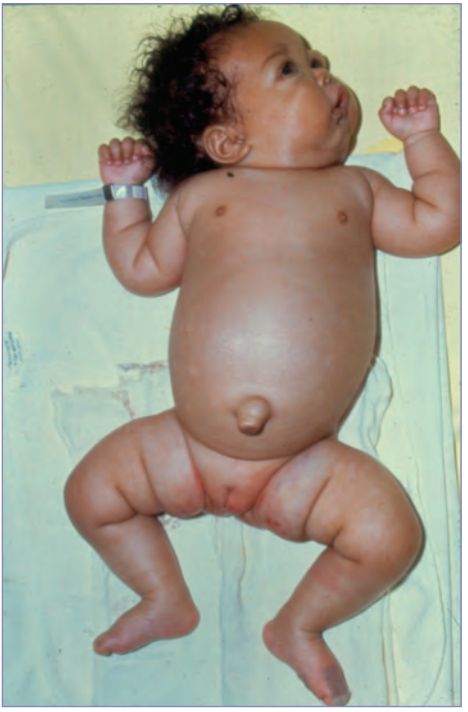


Image 139.26
A term newborn with ascites, hepatosplenomegaly, adenopathy, and periostitis caused by congenital syphilis. Although rare, nephrotic syndrome can result from congenital syphilis. Courtesy of Carol J. Baker, MD, FAAP.

CHAPTER 140

Tapeworm Diseases

(Taeniasis and Cysticercosis)

CLINICAL MANIFESTATIONS

Taeniasis

Infection with adult tapeworms often is asymptomatic; however, mild gastrointestinal tract symptoms, such as nausea, diarrhea, and pain, can occur. Tapeworm segments can be seen migrating from the anus or in feces.

Cysticercosis

In contrast, cysticercosis caused by larval pork tapeworm (*Taenia solium*) infection can have serious consequences. Manifestations depend on the location and number of pork tapeworm larval cysts (cysticerci) and on the host response. Cysticerci may be found anywhere in the body. The most common and serious manifestations are caused by cysticerci in the central nervous system. Larval cysts of *T solium* in the brain (neurocysticercosis) can cause seizures, obstructive hydrocephalus, and other neurologic signs and symptoms. Neurocysticercosis is the leading infectious cause of epilepsy in the developing world. The host reaction to degenerating cysticerci can produce signs and symptoms of meningitis or stroke. Cysts in the spinal column can cause gait disturbance, pain, or transverse myelitis. Subcutaneous cysticerci produce palpable nodules, and ocular involvement can cause visual impairment.

ETIOLOGY

Taeniasis is caused by intestinal infection by the adult tapeworm, *Taenia saginata* (beef tapeworm) or *T solium* (pork tapeworm). *Taenia asiatica* causes taeniasis in Asia. Human cysticercosis is caused only by the larvae of *T solium* (*Cysticercus cellulosae*).

EPIDEMIOLOGY

These tapeworm diseases have worldwide distribution. Prevalence is high in areas with poor sanitation and human fecal contamination in areas where cattle graze or swine are fed. Most cases of *T solium* infection in the United States are imported from Latin America or Asia, although the disease is prevalent in sub-Saharan Africa as well. High rates of *T saginata* infection occur in Mexico, parts of South America, East Africa, and central Europe. *T asiatica* is common in China, Taiwan, and Southeast Asia. Taeniasis is acquired by eating undercooked beef (*T saginata*), pork (*T solium*), or pig viscera (*T asiatica*) that contain encysted larvae.

Cysticercosis in humans is acquired by ingesting eggs of the pork tapeworm (*T solium*) through direct fecal-oral contact with a person harboring the adult tapeworm or through ingestion of fecally contaminated food. Autoinfection is possible. Eggs are found only in human feces, because humans are the obligate definitive host. Eggs liberate oncospheres in the intestine that migrate through the blood and lymphatics to tissues throughout the body, including the central nervous system, where the oncospheres develop into cysticerci. Although most cases of cysticercosis in the United States have been imported, cysticercosis can be acquired in the United States from tapeworm carriers who emigrated from an area with endemic infection and still have *T solium* intestinal-stage infection. *T saginata* and *T asiatica* do not cause cysticercosis.

The **incubation period** for taeniasis (the time from ingestion of the larvae until segments are passed in the feces) is 2 to 3 months; for cysticercosis, several years.

DIAGNOSIS

Diagnosis of taeniasis (adult tapeworm infection) is based on demonstration of the proglottids or ova in feces or the perianal region. However, these techniques are insensitive. Species identification of the parasite is based on the different structures of gravid proglottids and scolex.

Diagnosis of neurocysticercosis typically depends on clinical presentation and imaging of the central nervous system. Serologic testing also is helpful in certain cases. Computed tomography (CT) scanning or magnetic resonance imaging (MRI) of the brain or spinal cord are used to demonstrate lesions compatible with cysticerci. CT scans are helpful in identifying calcifications. MRI is better at identifying extraparenchymal cysts (eg, in ventricles or the subarachnoid space). Antibody assays that detect specific antibodies to larval *T solium* in serum and cerebrospinal fluid (CSF) are useful to

confirm the diagnosis and are required in the absence of the identification of a scolex on imaging. Antibody tests have limited sensitivity if only one cysticercus or only calcified cysticerci are present; tests are available through the Centers for Disease Control and Prevention and a few commercial laboratories. In general, antibody tests are more sensitive with serum specimens than with CSF specimens. Serum antibody assay results often are negative in children with solitary parenchymal lesions but usually are positive in patients with multiple lesions. A negative serologic test does not exclude the diagnosis of neurocysticercosis when the clinical suspicion is high.

TREATMENT

Taeniasis

Praziquantel is highly effective for eradicating infection with the adult tapeworm. Praziquantel is not approved for this indication, but dosing recommendations are available only for children 4 years and older. Niclosamide is not approved for treatment of *T solium* infection but is approved for treatment of *T saginata* infection. However, niclosamide is not available commercially in the United States.

Cysticercosis

Neurocysticercosis treatment should be individualized on the basis of the number, location, and viability of cysticerci as assessed by neuroimaging studies (MRI or CT scan) and the clinical manifestations. Management generally is aimed at symptoms and should include antiseizure medications for patients with seizures and surgery for patients with hydrocephalus. Two antiparasitic drugs—albendazole and praziquantel—are available. Although both drugs are cysticercidal and hasten radiologic resolution of cysts, symptoms result from the host inflammatory response and may be exacerbated by treatment. Although not all symptomatic patients with a single cyst within brain parenchyma require antiparasitic medication, controlled studies demonstrate that clinical resolution and seizure recurrence rates are improved with albendazole. Two studies have demonstrated that in those with more than 2 lesions, the response rate was better when albendazole was coadministered with praziquantel and corticosteroids. When a single agent is used, albendazole is preferred over praziquantel because it has fewer drug-drug interactions with anticonvulsants and steroids. Cyst stage is important when considering whether or not to treat with an antiparasitic medication. Patients with viable and colloidal (early degenerating/inflamed) cysts may benefit from an antiparasitic medication. Patients with granular and calcified cysts do not benefit from antiparasitic treatment. Duration of corticosteroid therapy is longer in patients with subarachnoid disease, vasculitis, or encephalitis. Arachnoiditis, vasculitis, or diffuse cerebral edema (cysticercal encephalitis) are treated with corticosteroid therapy until the cerebral edema is controlled. Corticosteroids can affect the tissue concentrations of albendazole. Patients requiring prolonged steroids may need to be screened for strongyloidiasis, latent tuberculosis, and vitamin D deficiency.

The medical and surgical management of cysticercosis can be highly complex and often needs to be conducted in consultation with a neurologist or neurosurgeon and an infectious diseases or tropical medicine expert with experience treating neurocysticercosis. Seizures may recur for months or years. Anticonvulsant therapy is recommended until there is neuroradiologic evidence of resolution and seizures have not occurred for 6 months (for a single lesion) or 1 to 2 years (for multiple lesions). Calcification of cysts may require prolonged or indefinite use of anticonvulsants. Subarachnoid cysticercosis does not respond well to the regimens used for parenchymal disease and generally should be treated with prolonged courses of corticosteroids and antiparasitic drugs. Intraventricular cysticerci and hydrocephalus usually require surgical therapy. Intraventricular cysticerci often can be removed by endoscopic surgery, which is the treatment of choice. If cysticerci cannot be removed easily, hydrocephalus should be corrected with placement of intraventricular shunts. Adjunctive chemotherapy with antiparasitic agents and corticosteroids may decrease the rate of subsequent shunt failure. Ocular cysticercosis is treated by surgical excision of the cysticerci. Ocular cysticercosis generally is not treated with anthelmintic drugs, which can exacerbate inflammation.

An ophthalmic examination should be performed before treatment to rule out intraocular cysticerci. Spinal cysticercosis may be treated with medical and/or surgical therapy. There is not adequate evidence to guide the choice of medical versus surgical therapy.

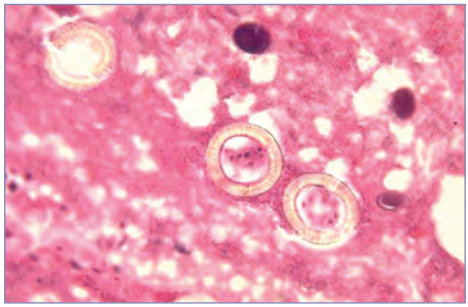


Image 140.1
Histopathologic features of *Taenia saginata* in the appendix.

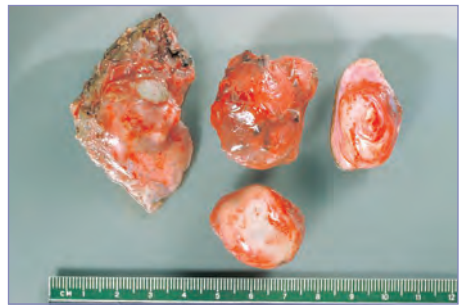


Image 140.2
Gross pathology photograph of the membrane and hydatid daughter cysts excised from a human lung. Hydatid disease is a parasitic infestation by a tapeworm of the genus *Echinococcus*. Endemic areas usually involve low-income countries. The liver is the most common organ involved, followed by the lungs. Courtesy of Centers for Disease Control and Prevention.

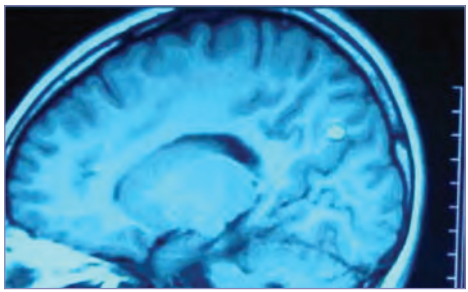


Image 140.3
Neurocysticercosis in an 11-year-old girl apparent on computed tomography scan. Courtesy of Benjamin Estrada, MD.

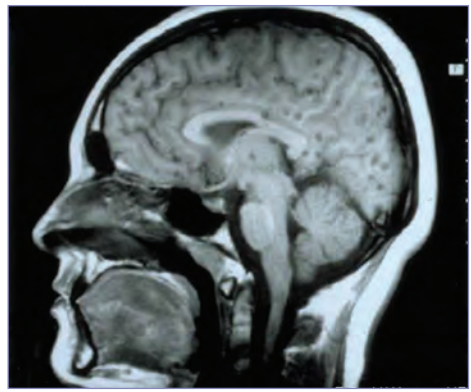


Image 140.4
Cerebral neurocysticercosis with diffuse, scattered, ring-enhancing lesions throughout the brain parenchyma with focal edema evident on computed tomography scan.

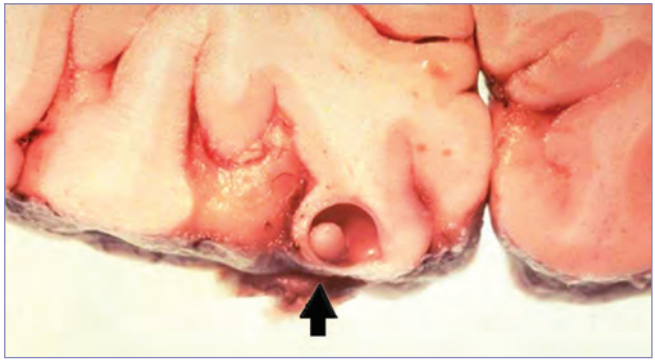


Image 140.5
Cross section showing cysticercosis of the brain at autopsy.

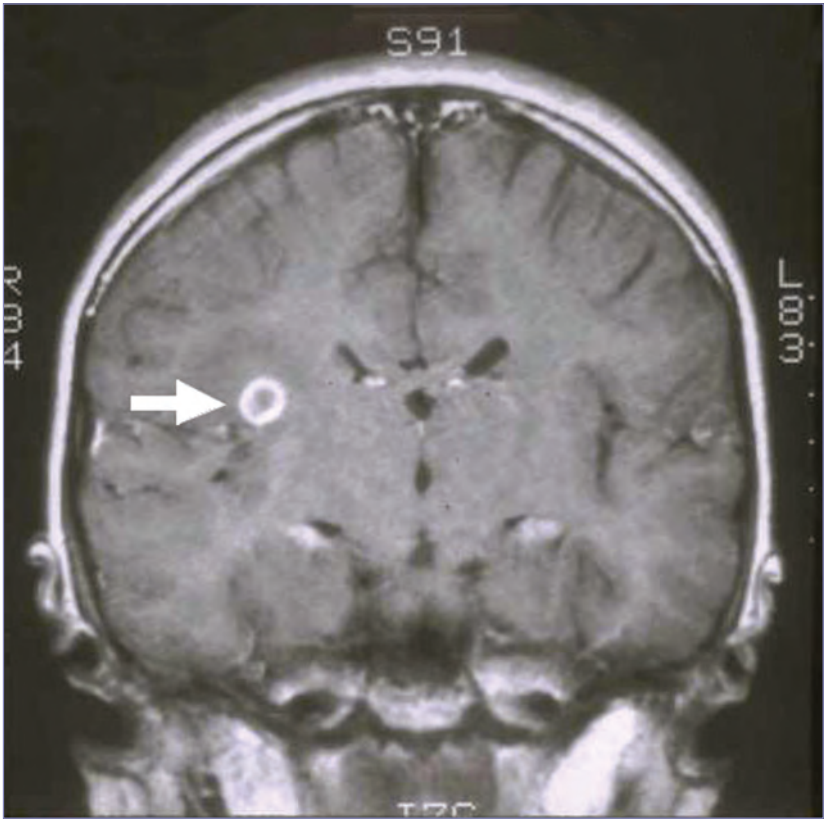


Image 140.6
A young boy with a seizure. Magnetic resonance imaging of the brain revealed a ringlike lesion characteristic of neurocysticercosis. Copyright Barbara Ann Jantausch, MD, FAAP.

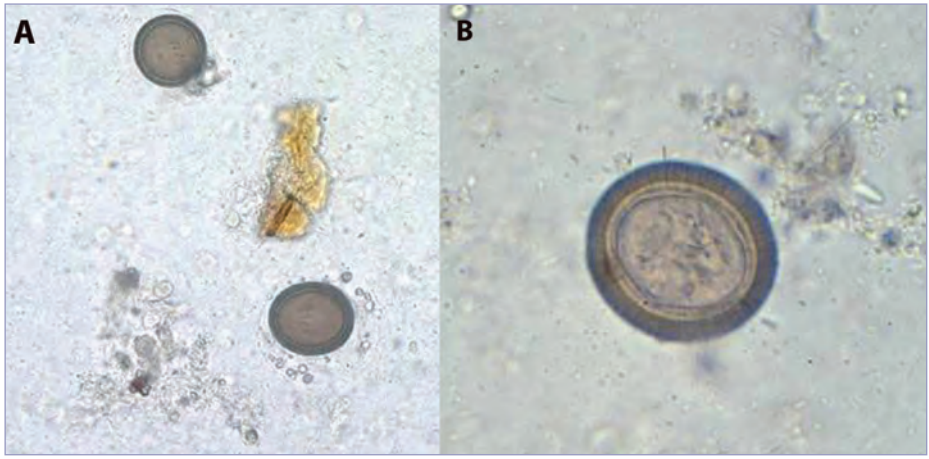


Image 140.7
The eggs of *Taenia solium* and *Taenia saginata* are indistinguishable from each other, as well as from other members of the *Taeniidae* family. The eggs measure 30 to 35 µm in diameter and are radially striated. The internal oncosphere contains 6 refractile hooks. *Taenia* species eggs in unstained wet mounts. Courtesy of Centers for Disease Control and Prevention.

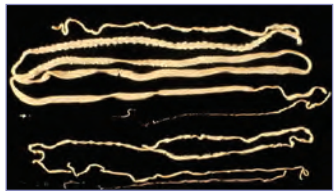


Image 140.8
Taenia saginata adult tapeworm.

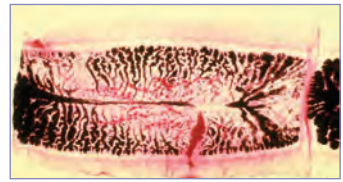


Image 140.9
Taenia saginata gravid proglottid. Courtesy of James Brien, MD.

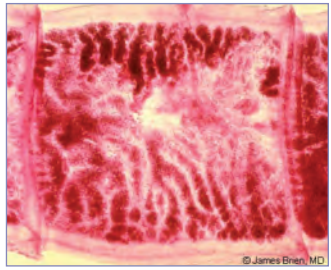


Image 140.10
Taenia solium gravid proglottid. Courtesy of James Brien, MD.

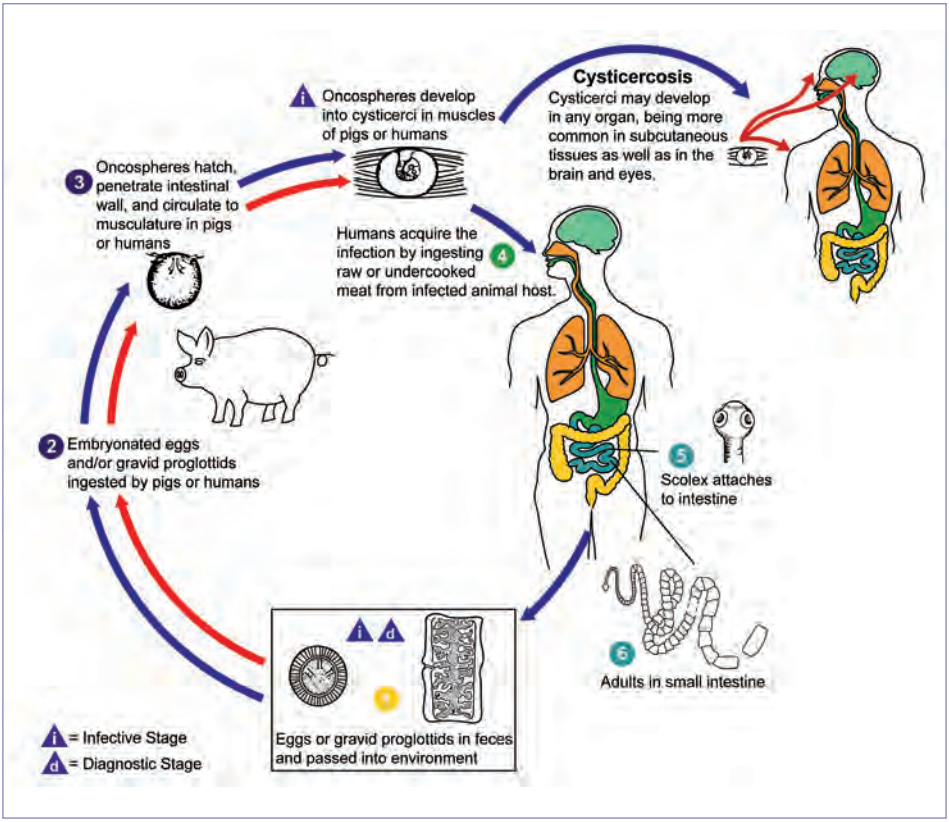


Image 140.11

Cysticercosis is an infection of humans and pigs with the larval stages of the parasitic cestode, *Taenia solium*. This infection is caused by ingestion of eggs shed in the feces of a human tapeworm carrier (1). Pigs and humans become infected by ingesting eggs or gravid proglottids (2). Humans are infected by ingestion of food contaminated with feces or by autoinfection. In the latter case, a human infected with adult *T solium* can ingest eggs produced by that tapeworm through fecal contamination or, possibly, from proglottids carried into the stomach by reverse peristalsis. Once eggs are ingested, oncospheres hatch in the intestine (3), invade the intestinal wall, and migrate to striated muscles, as well as the brain, liver, and other tissues, where they develop into cysticerci. In humans, cysts can cause serious sequelae if they localize in the brain, resulting in neurocysticercosis. The parasite life cycle is completed, resulting in human tapeworm infection when humans ingest undercooked pork containing cysticerci (4). Cysts evaginate and attach to the small intestine by their scolex (5). Adult tapeworms develop (up to 2–7 m in length and produce <1,000 proglottids, each with approximately 50,000 eggs) and reside in the small intestine for years (6). Courtesy of Centers for Disease Control and Prevention/Alexander J. da Silva, PhD/Melanie Moser.

CHAPTER 141

Other Tapeworm Infections

(Including Hydatid Disease)

Most tapeworm infections are asymptomatic, but nausea, abdominal pain, and diarrhea have been observed in people who are heavily infected.

ETIOLOGIES, DIAGNOSIS, AND TREATMENT

Hymenolepis nana

This tapeworm, also called the dwarf tapeworm because it is the smallest of the adult human tapeworms, can complete its entire life cycle within humans. New infection may be acquired by ingestion of eggs passed in feces of infected people or by ingestion of infected arthropods (fleas) that have gotten into food. More problematic is autoinfection, which perpetuates infection in the host, because eggs can hatch within the intestine and reinitiate the life cycle, leading to development of new worms and an increasing worm burden. Most infections are asymptomatic. With heavy infection, young children may develop abdominal cramps, diarrhea, and irritability. Anal pruritus and difficulty sleeping also have been reported. Diagnosis is made by recognition of the characteristic eggs passed in stool. Sometimes this infection is mistaken for pinworms. Praziquantel is the treatment of choice, with nitazoxanide as an alternative drug; niclosamide is an alternative therapeutic option but is not available in the United States. If infection persists after treatment, retreatment with praziquantel is indicated.

Dipylidium caninum

This is the most common tapeworm of dogs and cats and has a wide geographic distribution. Fleas, after a blood meal from an infected dog or cat, serve as intermediate host. Children, who inadvertently swallow a dog or cat flea during close contact with infected pets, then develop infection from *Dipylidium caninum*. Although often asymptomatic, some children have abdominal pain, diarrhea, and anal pruritus. Diagnosis is made by finding the characteristic eggs or motile proglottids in stool. Proglottids resemble rice kernels and may be mistaken for maggots or fly larvae. The infection is self-limiting in the human host and typically spontaneously clears by 6 weeks. Therapy with praziquantel is effective. Niclosamide is an alternative.

Diphyllobothrium latum (and Related Species)

These are the largest tapeworms that can infect humans. Fish are intermediate hosts of the *Diphyllobothrium latum* tapeworm, also called fish tapeworm. Consumption of infected, raw or undercooked (including trout and pike) or anadromous fish (salmon) leads to infection. Three to 6 weeks after ingestion, the adult tapeworm matures and begins to lay eggs. Abdominal pain and diarrhea may occur. The worm may cause mechanical obstruction of the bowel or gallbladder, diarrhea, abdominal pain, or rarely, megaloblastic anemia secondary to vitamin B_{12} deficiency. Diagnosis is made by recognition of the characteristic proglottids or eggs passed in stool. Therapy with praziquantel is effective; niclosamide is an alternative.

Echinococcus granulosus and *Echinococcus multilocularis*

The larval forms of these tapeworms cause human echinococcosis. *Echinococcus granulosus* causes the disease cystic echinococcosis, also known as hydatid disease. The distribution of *E granulosus* is related to sheep or cattle herding, although dogs are the definitive host. Areas of high prevalence include parts of Central and South America, East Africa, Eastern Europe, the Middle East, the Mediterranean region, China, and Central Asia. The parasite also is endemic in Australia and New Zealand. In the United States, small foci of endemic transmission have been reported in Arizona, California, New Mexico, and Utah, and a strain of the parasite is adapted to wolves, moose, and caribou in Alaska and Canada. Dogs, coyotes, wolves, dingoes, and jackals can become infected by swallowing protoscolices of the parasite within hydatid cysts in the organs of slaughtered sheep or other intermediate hosts. Dogs pass embryonated eggs in their stools, and intermediate hosts become infected by swallowing the eggs. If humans swallow *Echinococcus* eggs, they become inadvertent intermediate hosts,

and cysts can develop in various organs, such as the liver, lungs, kidneys, and spleen. Cysts caused by larvae of *E granulosus* usually grow slowly (1 cm in diameter per year) and eventually can contain several liters of fluid. If a cyst ruptures, anaphylaxis and multiple secondary cysts from seeding of protoscolices can result. Clinical diagnosis often is difficult. A history of contact with dogs in an area with endemic infection is helpful. Cystic lesions can be demonstrated by radiography, ultrasonography, or computed tomography of various organs. Serologic testing is helpful, but false-negative results occur. Treatment depends on ultrasonographic staging and may include antiparasitic therapy, PAIR (**p**uncture **a**spiration, **i**njection of protoscolicidal agents, and **r**easpiration), surgical excision, or no treatment but with watchful waiting. In uncomplicated cases, treatment of choice is PAIR. Contraindications to PAIR include communication of the cyst with the biliary tract (eg, bile staining after initial aspiration), superficial cysts, and heavily septated cysts. Surgical therapy is indicated for complicated cases and requires meticulous care to prevent spillage, including preparations such as soaking of surgical drapes in hypertonic saline. In general, the cyst should be removed intact, because leakage of contents is associated with a higher rate of complications. Patients are at risk of anaphylactic reactions to cyst contents. Treatment with albendazole generally should be initiated days to weeks before surgery or PAIR and continued for several weeks to months afterward.

Echinococcus multilocularis, the causative agent for alveolar echinococcosis, has definitive hosts (foxes, coyotes, other wild canines) and rodents as intermediate hosts. Alveolar echinococcosis is characterized by invasive growth of the larvae in the liver with occasional metastatic spread, most worrisome to the brain. Alveolar echinococcosis is limited to the northern hemisphere and usually is diagnosed in people 50 years or older. The disease has been reported frequently from Western China. Diagnosis can be confirmed by imaging and serologic testing. The preferred treatment is surgical removal of the entire larval mass. In nonresectable cases, continuous treatment with albendazole has been associated with clinical improvement.

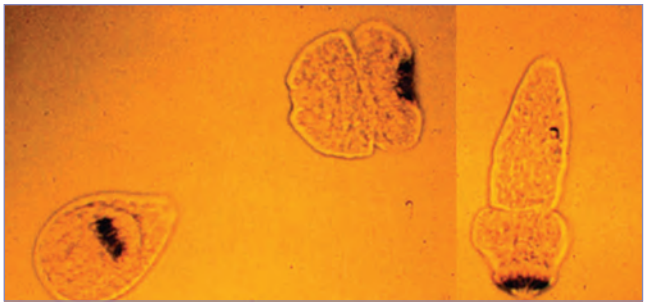


Image 141.1
Hydatid sand. Fluid aspirated from a hydatid cyst will show multiple protoscolices (size, approximately 100 µm), each of which has typical hooklets. The protoscolices, which are normally invaginated (left), evaginate (middle, then right) when put in saline.

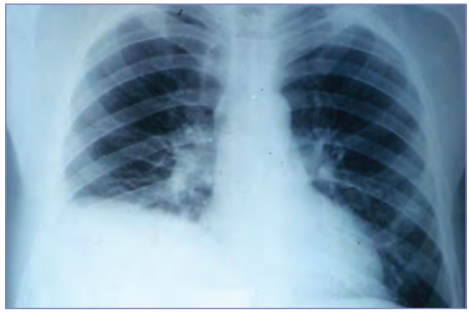


Image 141.2
Echinococcus cyst in the right lobe of the liver in a 27-year-old man. Note the striking elevation of the right hemidiaphragm. Courtesy of Edgar O. Ledbetter, MD, FAAP.

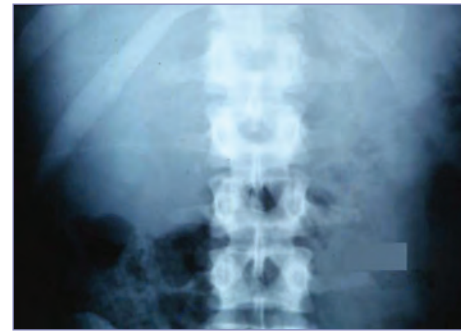


Image 141.3
Abdominal radiograph showing hepatic mass (echinococcus cyst). This is the same patient as in Image 141.2. Courtesy of Edgar O. Ledbetter, MD, FAAP.

Image 141.4
Proglottids of *Dipylidium caninum*. Such proglottids (average mature size, 12 × 3 mm) have 2 genital pores, one in the middle of each lateral margin. Proglottids may be passed singly or in chains and, occasionally, may be seen dangling from the anus. They are pumpkin seed–shaped when passed and often resemble rice grains when dried. Courtesy of Centers for Disease Control and Prevention.

Image 141.5
Adult tapeworm, *Dipylidium caninum*. The scolex of the worm is very narrow and the proglottids, as they mature, get larger.

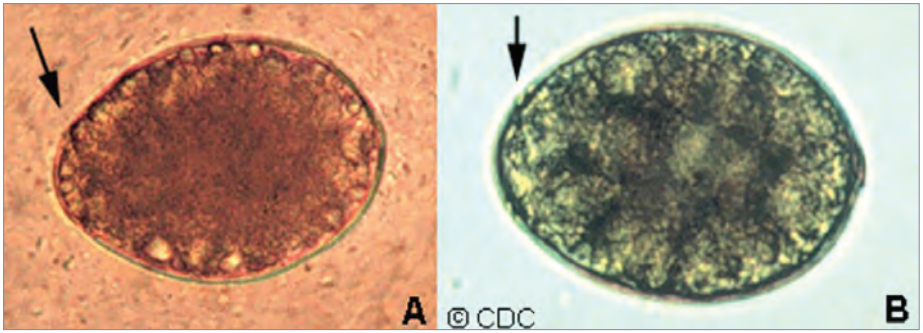


Image 141.6
Eggs of *Diphyllobothrium latum.* These eggs are oval or ellipsoidal, with an operculum (arrows) at one end that can be inconspicuous (A). At the opposite (abopercular) end is a small knob that can be barely discernible (B). The eggs are passed in the stool unembryonated. Size range, 58 to 76 µm by 40 to 51 µm. Courtesy of Centers for Disease Control and Prevention.

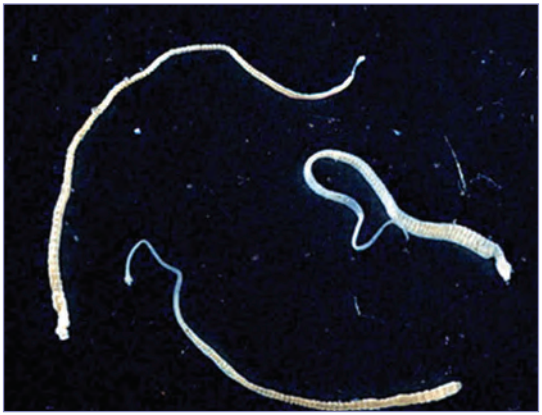


Image 141.7
Three adult *Hymenolepis nana* tapeworms. Each tapeworm (length, 15–40 mm) has a small, rounded scolex at the anterior end, and proglottids can be distinguished at the posterior, wider end. Courtesy of Centers for Disease Control and Prevention.

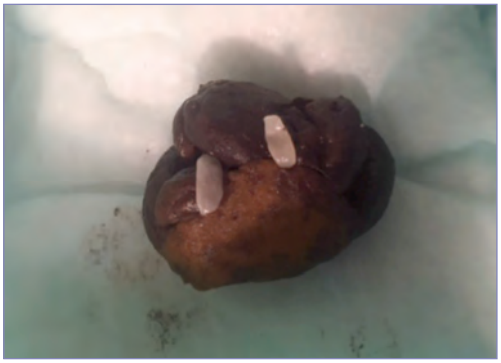


Image 141.8
Dog tapeworm, *Dipylidium caninum*, in the stool of a 7-month-old boy. Courtesy of Carol J. Baker, MD, FAAP.

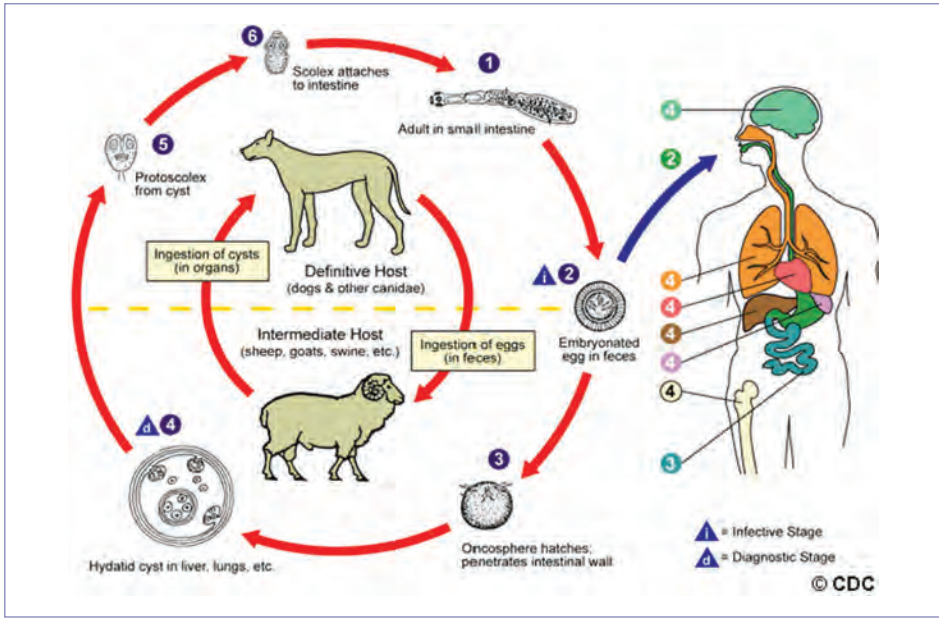


Image 141.9

The adult *Echinococcus granulosus* (3–6 mm long) (1) resides in the small bowel of the definitive hosts (dogs or other canids). Gravid proglottids release eggs (2) that are passed in the feces. After ingestion by a suitable intermediate host (under natural conditions, sheep, goat, swine, cattle, horses, camel), the egg hatches in the small bowel and releases an oncosphere (3) that penetrates the intestinal wall and migrates through the circulatory system into various organs, especially the liver and lungs. In these organs, the oncosphere develops into a cyst (4) that enlarges gradually, producing protoscolices and daughter cysts that fill the cyst interior. The definitive host becomes infected by ingesting the cyst-containing organs of the infected intermediate host. After ingestion, the protoscolices (1) evaginate, attach to the intestinal mucosa (6), and develop into adult stages (1) in 32 to 80 days. The same life cycle occurs with *Echinococcus multilocularis* (1.2–3.7 mm long), with the following differences: the definitive hosts are foxes and, to a lesser extent, dogs, cats, coyotes, and wolves; the intermediate host are small rodents; and larval growth (in the liver) remains indefinitely in the proliferative stage, resulting in invasion of the surrounding tissues. With *Echinococcus vogeli* (up to 5.6 mm long), the definitive hosts are bush dogs and dogs, the intermediate hosts are rodents, and the larval stage (in the liver, lungs, and other organs) develops externally and internally, resulting in multiple vesicles. *Echinococcus oligarthrus* (up to 2.9 mm long) has a life cycle that involves wild felids as definitive hosts and rodents as intermediate hosts. Humans become infected by ingesting eggs (2), with resulting release of oncospheres (3) in the intestine and the development of cysts (4) in various organs.

CHAPTER 142

Tetanus

(Lockjaw)

CLINICAL MANIFESTATIONS

Tetanus is caused by neurotoxin produced by the anaerobic bacterium *Clostridium tetani* in a contaminated wound and can manifest in 4 overlapping clinical forms: generalized, local, neonatal, and cephalic.

Generalized tetanus (lockjaw) is a neurologic disease manifesting as trismus and severe muscular spasms, including risus sardonicus. Onset is gradual, occurring over 1 to 7 days, and symptoms progress to severe painful generalized muscle spasms, which often are aggravated by any external stimulus. Autonomic dysfunction, manifesting as diaphoresis, tachycardia, labile blood pressure, and arrhythmias, often is present. Severe spasms persist for 1 week or more and subside over several weeks in people who recover. Neonatal tetanus is a form of generalized tetanus occurring in newborn infants lacking protective passive immunity because their mothers are not immune.

Local tetanus manifests as local muscle spasms in areas contiguous to a wound. **Cephalic tetanus** is a dysfunction of cranial nerves associated with infected wounds on the head and neck. Local and cephalic tetanus can precede generalized tetanus.

ETIOLOGY

C tetani is a spore-forming, obligate anaerobic, gram-positive bacillus. This organism is a wound contaminant that causes neither tissue destruction nor an inflammatory response. The vegetative form of *C tetani* produces a potent plasmid-encoded exotoxin (tetanospasmin). The heavy chain of tetanospasmin binds to the presynaptic motor neuron and facilitates entry of the light chain, a zinc-dependent protease, into the cytosol. After retrograde axonal transport to the spinal cord, the toxin enters central inhibitory neurons and cleaves synaptobrevin, which is integral to the binding of neurotransmitter containing vesicles to the cell membrane. As a result, gamma-aminobutyric acid- and glycine-containing vesicles are not released, and inhibitory action on motor and autonomic neurons is lost.

EPIDEMIOLOGY

Tetanus occurs worldwide and is more common in warmer climates and during warmer months, in part because of higher frequency of contaminated wounds associated with those locations and seasons. The organism, a normal inhabitant of soil and animal and human intestines, is ubiquitous in the environment, especially where contamination by excreta is common. Organisms multiply in wounds, recognized or unrecognized, and elaborate toxins in the presence of anaerobic conditions. Contaminated wounds, especially wounds with devitalized tissue and deep-puncture trauma, are at greatest risk. Neonatal tetanus is common in many resource-limited countries where pregnant women are not immunized appropriately against tetanus and nonsterile umbilical cord-care practices are followed. Globally, activities are ongoing to eliminate maternal and neonatal tetanus by improving vaccination coverage among pregnant women and promoting safe delivery practices. Although progress continues to be made, 21 countries had still not reached the maternal and neonatal tetanus elimination status by the end of 2015. The World Health Organization estimates that in 2015, 34,019 newborn infants died from neonatal tetanus, a 96% reduction from the late 1980s.

Widespread active immunization against tetanus has modified the epidemiology of disease in the United States, where 40 or fewer cases have been reported annually since 1999. Tetanus is not transmissible from person to person.

The **incubation period** ranges from 3 to 21 days, usually within 8 days. In neonatal tetanus, signs usually appear from 4 to 14 days after birth (mean 7 days).

DIAGNOSTIC TESTS

The diagnosis of tetanus is made clinically by excluding other causes of tetanic spasms, such as hypocalcemic tetany, phenothiazine reaction, strychnine poisoning, and conversion disorder. Attempts to culture *C tetani* are associated with poor yield, and a negative

culture does not rule out disease. A protective serum antitoxin concentration should not be used to exclude the diagnosis of tetanus.

TREATMENT

A single dose of human Tetanus Immune Globulin (TIG) is recommended for treatment. However, the optimal therapeutic dose has not been established. Available preparations must be administered intramuscularly. Infiltration of part of the dose locally around the wound is recommended, although the efficacy of this approach has not been proven. If TIG is not available (such as is the case in some countries), Immune Globulin Intravenous (IGIV) can be used. All wounds should be cleaned and débrided properly, especially if extensive necrosis is present. In neonatal tetanus, wide excision of the umbilical stump is not indicated.

Supportive care and pharmacotherapy to control tetanic spasms and autonomic instability are of major importance. Oral (or intravenous) metronidazole is effective in decreasing the number of vegetative forms of *C tetani* and is the antimicrobial agent of choice. Parenteral penicillin G is an alternative treatment. Therapy for 7 to 10 days is recommended. Active immunization against tetanus always should be undertaken during convalescence from tetanus. Because of the extreme potency of tiny amounts of toxin, tetanus disease may not result in immunity.

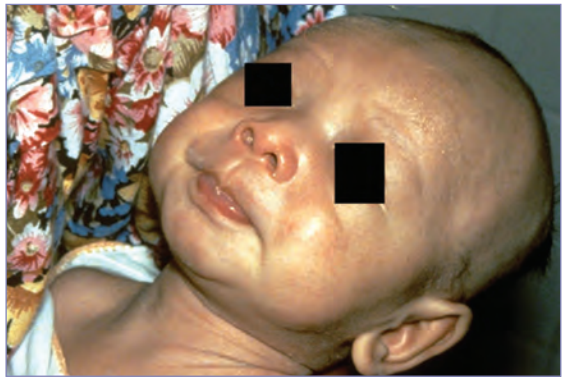


Image 142.1
This infant with tetanus has spasm of the facial muscles with trismus.

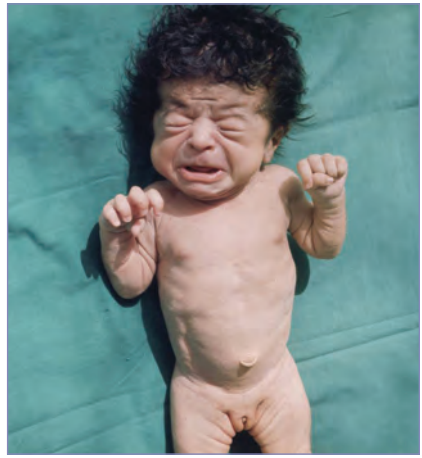


Image 142.2
Severe muscular spasms with trismus in a newborn who acquired neonatal tetanus from contamination of the umbilical stump. Courtesy of Ralph R. Salimpour, MD, DCH, FAAP.

Image 142.3
This neonate is displaying a body rigidity produced by *Clostridium tetani* exotoxin. Neonatal tetanus may occur in neonates born without protective passive immunity, when the mother is not immune. It usually occurs through infection of the unhealed umbilical stump, particularly when the stump is cut with an unsterile instrument. Courtesy of Centers for Disease Control and Prevention.

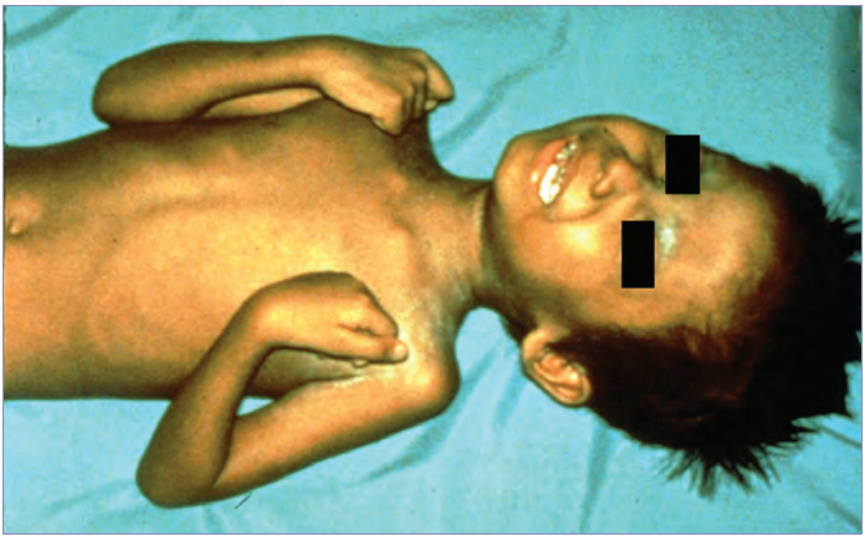


Image 142.4
A preschool-aged boy with tetanus with severe muscle contractions, generalized, caused by tetanospasmin action in the central nervous system. Courtesy of the Immunization Action Coalition.

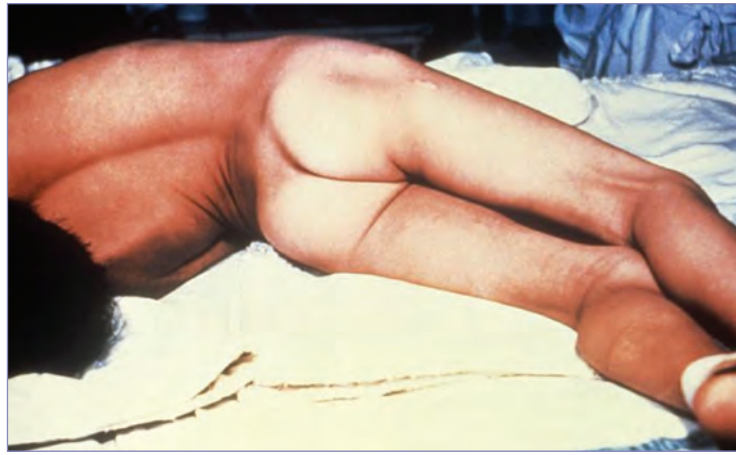


Image 142.5
This patient is displaying a bodily posture known as opisthotonos due to *Clostridium tetani* exotoxin. Generalized tetanus, the most common type (about 80%), usually presents with a descending pattern, starting with trismus or lockjaw, followed by stiffness of the neck, difficulty in swallowing, and rigidity of abdominal muscles. Courtesy of Centers for Disease Control and Prevention.

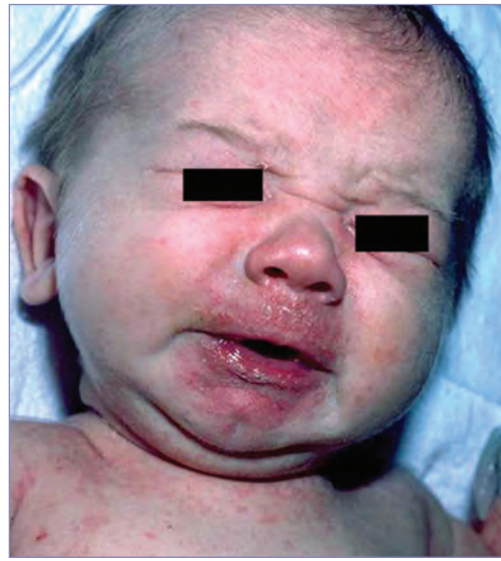


Image 142.6
The face of an infant with neonatal tetanus with risus sardonicus. Copyright Martin G. Myers, MD.

CHAPTER 143

Tinea Capitis

(Ringworm of the Scalp)

CLINICAL MANIFESTATIONS

Dermatophytic fungal infections of the scalp usually present with an area of localized alopecia and scaling. However, a spectrum can include subtle findings of mild hair loss with faint scaling or a large hairless, boggy erythematous area (kerion). Other manifestations include a common "black dot" pattern reflecting stubs of broken-off hairs at the scalp surface; a less common "grey patch" pattern with prominent, well-demarcated alopecic areas of scaling and erythema; or a vesiculopustular pattern resembling bacterial folliculitis. Regional lymphadenopathy may be present.

The differential diagnosis for tinea capitis depends on the clinical presentation. In the classic scaling presentation, clinicians should consider atopic dermatitis, seborrheic dermatitis, and psoriasis. Alopecia should raise the possibility of trichotillomania and alopecia areata, although these disorders usually are not associated with scaling. When vesiculopustular in nature, lice infestation and bacterial infection should be considered. A boggy fluctuant mass likely represents a kerion, but primary (or secondary) bacterial infection can be considered. Although scalp scarring can result from tinea, particularly when a kerion suppurates, the presence of scalp scarring should raise the possibility of an autoimmune disorder, such as discoid lupus.

An associated skin eruption, known as a dermatophytic or "id" reaction, can occur as a hypersensitivity reaction to the infecting fungus and can manifest as diffuse, pruritic, papular, vesicular, and/or eczematous lesions occurring at sites distant from the fungal infection. Id reactions may have onset following institution of therapy but do not represent a drug allergy.

ETIOLOGY

Tinea capitis develops when dermatophyte fungal elements invade the scalp hair follicle and shaft. The specific pathogen varies by geographic region and mode of transmission. The primary causes of the disease are fungi of the genus *Trichophyton*, including *Trichophyton tonsurans* and *Trichophyton violaceum*, as well as *Microsporum*, including *Microsporum canis* and *Microsporum audouinii*.

EPIDEMIOLOGY

In the United States, tinea capitis occurs predominantly in young black school-aged children who are infected with *T tonsurans*. However, tinea capitis occurs in all racial and ethnic groups as well as in infants and postmenopausal female caregivers. *T tonsurans* is transmitted person to person. *T violaceum* is more common in Europe and Africa and is seen more frequently in immigrant populations in the United States.

M canis is associated with less than 10% of infections but is more evenly distributed among racial/ethnic groups. *M canis* infection almost always results from contact with infected pets, particularly kittens or puppies. *M canis* outbreaks in schools and child care facilities have followed visits from infected animals.

The dermatophyte organism remains viable for prolonged periods on fomites (eg, brushes, combs, hats, towels), and the rate of asymptomatic carriage and infected individuals among family members of index cases is high. The role of asymptomatic carriers is unclear, but almost certainly carriers may serve as a reservoir of infection within families, schools, and communities.

Immunocompromised people and those with trisomy 21 have an increased susceptibility to dermatophyte infections. Accumulating data also implicate a genetic predisposition to tinea infections in certain individuals.

The **incubation period** is unknown but is thought to be 1 to 3 weeks.

DIAGNOSTIC TESTS

The presence of alopecia, pruritus, scale, and posterior cervical lymphadenopathy makes the diagnosis of tinea capitis almost certain, and most clinicians will choose to treat empirically. Diagnosis can be confirmed by dermatoscopy of the affected area or by microscopic evaluation of a potassium hydroxide wet mount of cutaneous scrapings. Dermatoscopic evaluation

of areas of alopecia with a lighted magnifier may show comma- or corkscrew-shaped hairs. Potassium hydroxide wet mount microscopy may be used to examine hairs and scale obtained by gentle scraping of a moistened area of the scalp with a blunt scalpel, toothbrush, brush, or plucking with tweezers. Arthroconidia can be visualized within the hair shaft in endothrix infections, such as *T tonsurans*, while ectothrix infections, such as *M canis*, exhibit conidia on the outside of the hair shaft. In both forms, septate hyphae may be visualized in scrapings from the scalp surface. Fungal culture can establish a diagnosis, in conjunction with or instead of microscopy. If fungal culture is desired, a cotton-tipped applicator can be used to gently swab an affected area. The sample is transported to a mycology laboratory for processing; 2 to 4 weeks of incubation on Sabouraud dextrose agar are required for results. Polymerase chain reaction and periodic acid-Schiff stain testing of specimens are available but are expensive and generally are unnecessary. Under Wood lamp, tinea lesions are not fluorescent unless the etiologic agent is of the *Microsporum* genus, in which blue-green fluorescence is noted.

TREATMENT

Tinea capitis always requires systemic medication, because the fungal infection is found at the root of the hair follicles, where topical agents do not reach. Optimal treatment of tinea capitis includes considerations of drug tolerability, availability, and cost. Experts generally use griseofulvin but at high doses. Griseofulvin is approved by the US Food and Drug Administration (FDA) for children 2 years or older, is available in either liquid or tablet form, can be administered on a daily basis, and should be taken with fatty foods. Terbinafine granules (contained in capsules) can be used in children 4 years and older for a duration of 6 weeks. To improve palatability, the capsules can be opened and the granules mixed in non-acidic food, such as pudding or peanut butter.

For *T tonsurans*, most experts consider terbinafine a better choice than griseofulvin because of the possibility of shorter duration of therapy and equal or superior effectiveness. The FDA recommends baseline and periodic assessment of serum hepatic enzymes when using terbinafine; some clinicians forego baseline screening in otherwise healthy children but perform follow-up testing 4 to 6 weeks later if therapy is ongoing. Fluconazole is the only oral antifungal agent approved by the FDA for children younger than 2 years.

For *M canis* infection, high-dose griseofulvin is recommended. Topical treatment, such as with selenium sulfide or ketoconazole or ciclopirox shampoos, may be useful as an adjunct to systemic therapy to decrease carriage of viable conidia. Shampoo can be applied 2 to 3 times per week and left in place for 5 to 10 minutes. Treatments should continue for at least 2 weeks.

Kerion is managed by systemic antifungal treatment as outlined above; combined antifungal and corticosteroid therapy (either oral or intralesional) has not been shown to be superior to antifungal therapy alone. Unless secondary bacterial infection has occurred, treatment with antimicrobial agents is unnecessary.

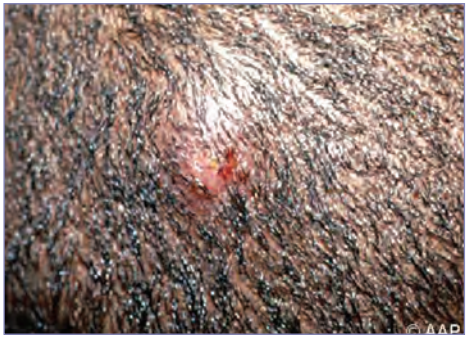


Image 143.1
Tinea capitis may cause hair loss. Remnants of infected hairs ("black dots") that have broken at the scalp line may be noted within areas of alopecia.

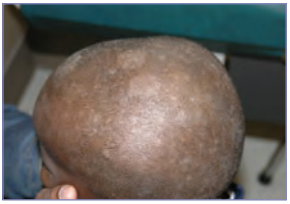


Image 143.2
A 4-year-old with multiple areas of alopecia and hair loss. This boy had a 3-week history of "dandruff." The scaling became more apparent following a shaved haircut. The barber saw areas of hair loss and was concerned about ringworm. He recommended medical evaluation. Physical examination indicated multiple patches of alopecia with a light appearance to the broken hair stubs in the areas of alopecia. Wood lamp examination indicated numerous patches of fluorescence. Culture result was positive for *Microsporum canis*. He was treated with griseofulvin for a total of 7 weeks. His hair has grown back without scarring. Follow-up examination result with Wood lamp was negative, although a sibling was noted to have a kerion and required treatment. Courtesy of Will Sorey, MD.

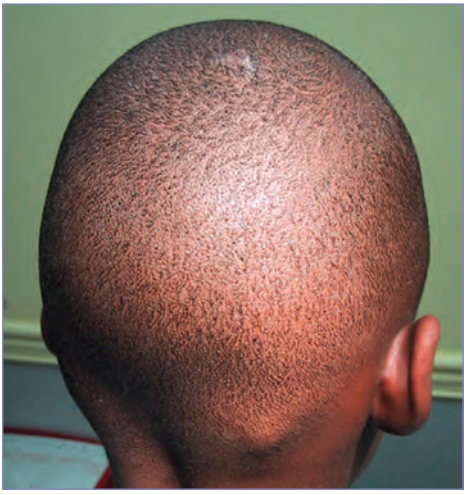


Image 143.3
An 8-year-old boy with a bald spot, hair loss, and enlarging posterior cervical lymph node for 2 weeks. The node was described as tender, not fluctuant, and without erythema of the overlying scalp. The area of hair loss was boggy and fluctuant. The patient responded well to treatment with griseofulvin. Copyright Stan Block, MD, FAAP.

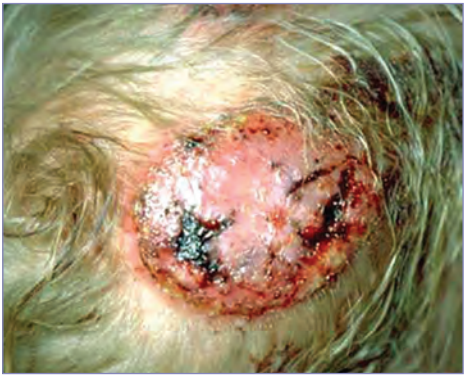


Image 143.4
A 2½-year-old boy with a kerion secondary to chronic, progressive tinea capitis. Copyright Martin G. Myers, MD.

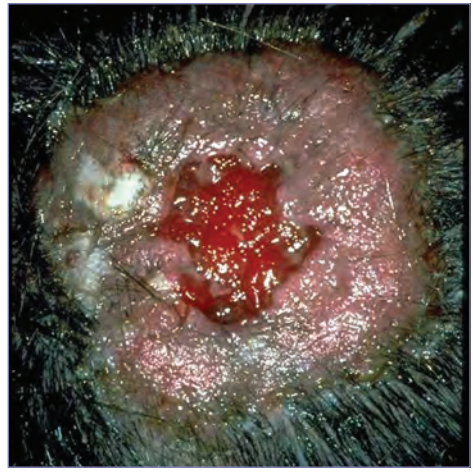


Image 143.5
Close-up of tinea capitis (*Microsporum audouinii*).

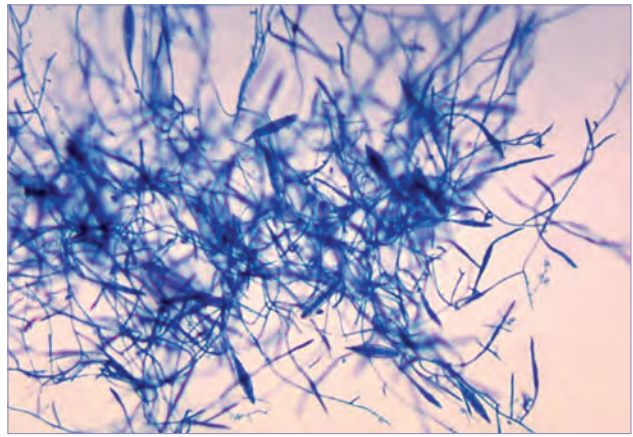


Image 143.6
Microsporum audouinii. *Microsporum canis*, a zoophilic dermatophyte often found in cats and dogs, is a common cause of tinea corporis and tinea capitis in humans. Other dermatophytes are included in the genera *Epidermophyton* and *Trichophyton*. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 144

Tinea Corporis

(Ringworm of the Body)

CLINICAL MANIFESTATIONS

Superficial tinea infections of the nonhairy (glabrous) skin, termed tinea corporis, involve the face, trunk, or limbs. The lesions often are ring-shaped or circular (hence, the lay term "ringworm") and are sharply marginated. The involved skin is slightly erythematous and scaly, with color variations from red to brown. The eruption can display a scaly, vesicular, or pustular border (often serpiginous) with central clearing. Small confluent plaques or papules as well as multiple lesions can occur, particularly in wrestlers (tinea gladiatorum).

The differential diagnosis for tinea corporis includes candidiasis, psoriasis, other dermatitides (seborrheic, atopic, irritant or allergic, generally caused by therapeutic agents applied to the area), pityriasis (tinea versicolor), nummular eczema, erythema annulare centrifugum, and erythrasma (an eruption of reddish brown patches resulting from superficial bacterial skin infection caused by *Corynebacterium minutissimum*).

The typical appearance of the lesions is altered in patients who have been treated erroneously with topical corticosteroids. Known as tinea incognito, this altered appearance includes diminished erythema and absence of typical scaling borders. Such patients also can develop Majocchi granuloma, a fungal invasion of the hair shaft and surrounding dermis, which causes a granulomatous dermal reaction that can extend into the surrounding subcutaneous fat. Majocchi granuloma also can occur without prior use of corticosteroids.

An associated dermatophytic or "id" reaction can be present as a hypersensitivity reaction to the infecting fungus, manifesting as diffuse, pruritic, papular, vesicular, or eczematous lesions, which can occur at sites distant from the fungal infection. Sometimes id reactions first appear following institution of therapy, but they do not represent a drug allergy.

In patients with diminished T-lymphocyte function (eg, human immunodeficiency virus infection), skin lesions can occur as grouped papules or pustules without erythema or scaling.

ETIOLOGY

Tinea corporis develops when dermatophytic fungi invade the outer skin layers at the affected body region. Primary etiologic agents are *Trichophyton* species, especially *Trichophyton tonsurans*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes; Microsporum* species, especially *Microsporum canis;* and *Epidermophyton floccosum*.

EPIDEMIOLOGY

Causative fungi occur worldwide and are transmissible by direct contact with infected humans, animals, soil, or fomites (eg, brushes, combs, hats, towels), where organisms can remain viable for prolonged periods.

Immunocompromised people and those with trisomy 21 have an increased susceptibility to dermatophyte infections. Accumulating data also implicate a genetic predisposition to tinea infections in certain individuals.

The **incubation period** is thought to be 1 to 3 weeks but can be shorter.

DIAGNOSTIC TESTS

Tinea corporis is diagnosed by clinical manifestations and can be confirmed by microscopic examination of a potassium hydroxide wet mount of skin scrapings or fungal culture. Skin scrapings are obtained by gentle scraping of a moistened area with a blunt scalpel, toothbrush, or brush or by plucking with tweezers. If fungal culture is desired, a cotton-tipped applicator can be used to gently swab an affected area and requires 2 to 4 weeks of incubation on Sabouraud dextrose agar for growth. Polymerase chain reaction and periodic acid-Schiff stain evaluation of specimens are available but are expensive and generally are not necessary. Under Wood lamp, tinea is not fluorescent unless the etiologic agent is of the genus *Microsporum*, in which case a blue-green fluorescence can be seen.

TREATMENT

A myriad of topical options are available for treatment. Some topical agents are approved by the US Food and Drug Administration (FDA) only for certain lesion locations and age groups and with applications specified as once or twice daily. Any of the following products (applied twice daily) are reasonable first-line therapies if appropriate for age: miconazole, clotrimazole, tolnaftate, or ciclopirox. Any of the following products also can be used (applied once daily) if appropriate for age: ketoconazole, econazole, naftifine, or luliconazole. Oxiconazole and sulconazole can be used (once or twice daily) if appropriate for age.

Although clinical resolution may be evident within 2 weeks of therapy, continuing therapy for another 2 to 4 weeks generally is recommended. If significant clinical improvement is not observed after 2 weeks of treatment, an alternate diagnosis and/or systemic therapy should be considered. Topical preparations of antifungal medication combined with a corticosteroid should not be used because of inferior effectiveness, the possibility of leading to Majocchi granuloma, and increase in the rate of relapse, higher cost, and potential for adverse corticosteroid effects.

If lesions are extensive or unresponsive to topical therapy, griseofulvin or terbinafine may be administered orally for 4 to 6 weeks. Oral fluconazole is approved for other indications in children 6 months and older. If a Majocchi granuloma is present, oral antifungal therapy is recommended because topical therapy is unlikely to penetrate adequately to eradicate infection.

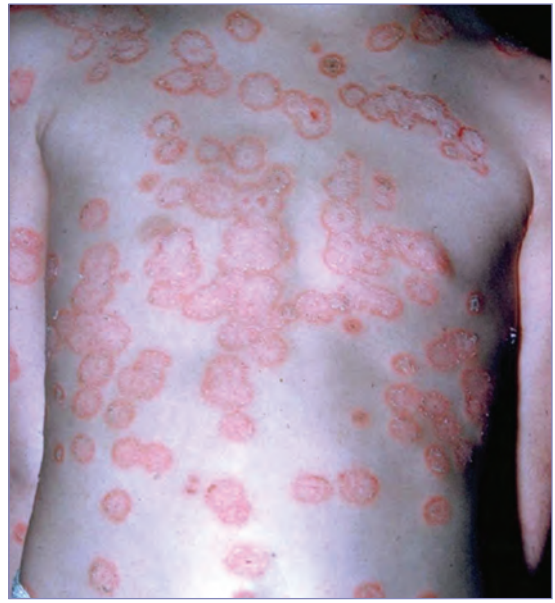


Image 144.1
Generalized tinea corporis in a 5-year-old girl.

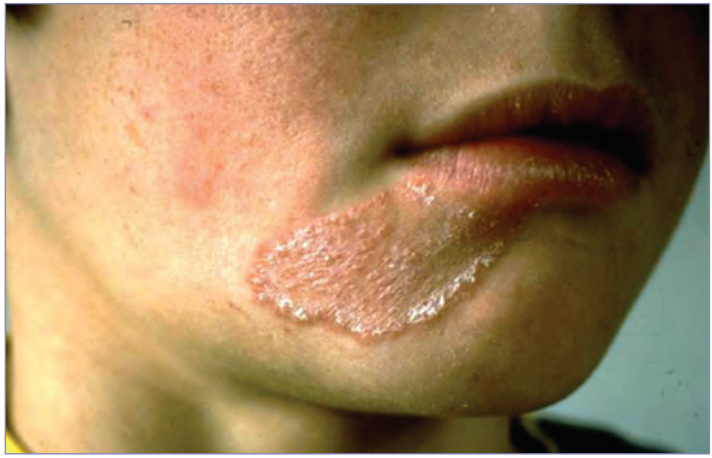


Image 144.2
Tinea corporis of the face. These annular erythematous lesions have a scaly center.

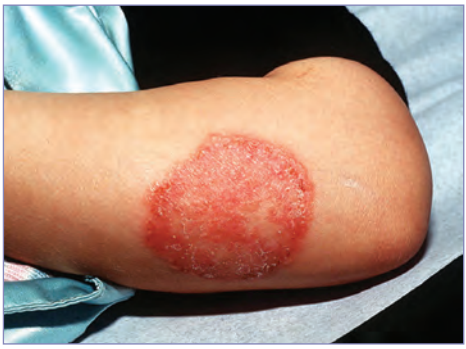


Image 144.3
Tinea corporis of the arm. This 6-year-old girl had enlarging skin lesion that had been present for 1 week. Copyright Larry I. Corman.

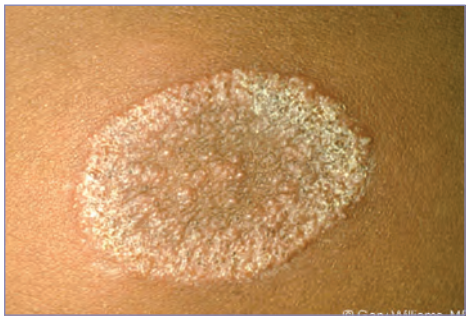


Image 144.4
Tinea corporis lesion in a 10-year-old girl.

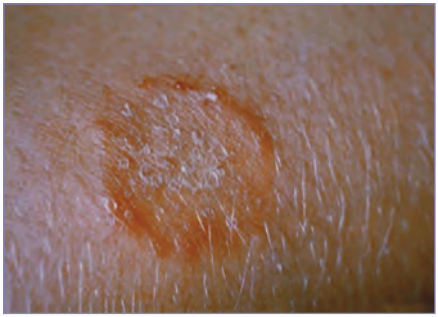


Image 144.5
This patient presented with ringworm on the arm, or tinea corporis, caused by *Trichophyton* mentagrophytes. The genus *Trichophyton* inhabits the soil, humans, or animals and is one of the leading causes of hair, skin, and nail infections, or dermatophytosis, in humans. Courtesy of Centers for Disease Control and Prevention.

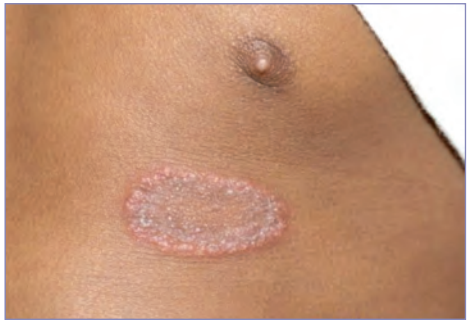


Image 144.6
A 16-month-old with a pruritic patch on his trunk. It had gotten larger over the past 3 days. He had a cat with dandruff and hair loss. The cat slept on his bed during the sunny part of the day. The child was treated with antifungal cream. The cat was evaluated by a veterinarian and cultured positive for *Microsporum canis*. This represents tinea corporis, commonly called ringworm. Courtesy of Will Sorey, MD.

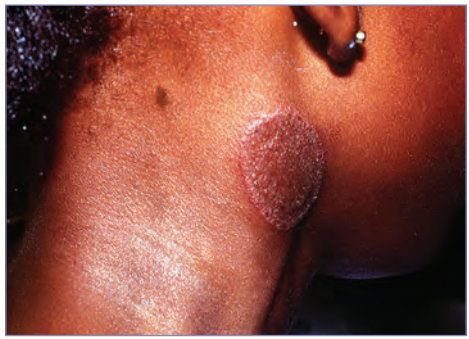


Image 144.8
Tinea corporis involving the neck of a 10-year-old girl with an enlarging lesion that had been present for 9 days. Courtesy of Larry I. Corman.

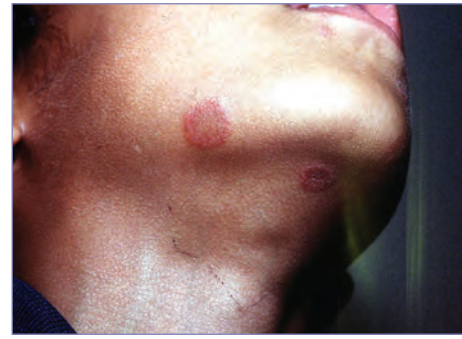


Image 144.7
Tinea corporis of the chin on a 6-year-old girl with enlarging lesions. The patient was successfully treated with clotrimazole. Copyright Larry I. Corman.

Image 144.9
This photomicrograph reveals a number of macroconidia of the dermatophytic fungus *Epidermophyton floccosum*, which is known to be a cause of dermatophytosis leading to tinea corporis (ringworm), tinea cruris (jock itch), tinea pedis (athlete's foot), and onychomycosis or tinea unguium, a fungal infection of the nail bed. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 145

Tinea Cruris

(Jock Itch)

CLINICAL MANIFESTATIONS

Tinea cruris is a common superficial fungal disorder of the groin, pubic/perianal area, and upper thighs in adults but is uncommon in children. The lesions often are ring-shaped or circular (hence, the lay term "ringworm"), are sharply marginated, and can be intensely pruritic (jock itch). The involved skin is slightly erythematous and scaly, with color variations from red to brown. Lesions can display a scaly, vesicular, or pustular border (often serpiginous) with central clearing. In chronic infections, the margins can be subtle, and lichenification may be present.

The differential diagnosis for tinea cruris includes intertrigo, candidiasis, psoriasis, other dermatitides (seborrheic, atopic, irritant or allergic, generally caused by therapeutic agents applied to the area), pityriasis (tinea versicolor), nummular eczema, erythema annulare centrifugum, and erythrasma (an eruption of reddish brown patches resulting from superficial bacterial skin infection caused by *Corynebacterium minutissimum*).

An altered appearance known as tinea incognito can occur in patients who have been treated erroneously with topical corticosteroids, which includes diminished erythema and absence of typical scaling borders. Such patients also can develop Majocchi granuloma when fungi invade the hair shaft and surrounding dermis, causing a granulomatous dermal reaction that can extend into the surrounding subcutaneous fat. Majocchi granuloma also can occur without prior use of topical corticosteroid.

An associated skin eruption, known as a dermatophytic or "id" reaction, can occur as a hypersensitivity reaction to the infecting fungus and manifests as diffuse, pruritic, papular, vesicular, or eczematous lesions at sites distant from the fungal infection. An id reaction can first occur following institution of therapy but does not represent a drug allergy.

Immunocompromised patients and those with trisomy 21 have increased susceptibility to dermatophyte infections. Accumulating data also implicate a genetic predisposition to tinea infections in certain individuals.

ETIOLOGY

Tinea cruris develops when dermatophyte fungi invade the outer skin layers of the affected body region. The fungi *Epidermophyton floccosum*, *Trichophyton rubrum*, and *Trichophyton mentagrophytes* are the most common causes. *Trichophyton tonsurans*, *Trichophyton verrucosum*, and *Trichophyton interdigitale* also have been identified as causes.

EPIDEMIOLOGY

Tinea cruris occurs predominantly in adolescent and adult males and is acquired principally through indirect contact with desquamated epithelium or hair. Direct person-to-person transmission also occurs. Moisture, close-fitting garments, friction, and obesity are predisposing factors. In patients with diminished T-lymphocyte function (eg, human immunodeficiency virus infection), skin lesions can appear as grouped papules or pustules unaccompanied by scaling or erythema.

The **incubation period** is unknown but is thought to be approximately 1 to 3 weeks.

DIAGNOSTIC TESTS

Confirmatory diagnostic modalities for tinea cruris are like that for tinea corporis.

TREATMENT

Treatment is like that for tinea corporis. Treatment of concurrent onychomycosis (tinea unguium) and tinea pedis may reduce recurrence. Recurrence is common, particularly if predisposing factors such as moisture and friction are not minimized. Loose-fitting clothing and the use of antifungal powders, such as tolnaftate and miconazole, should aid in recovery and prevent recurrence.

If lesions are unresponsive to topical therapy, griseofulvin, administered orally for 4 to 6 weeks, may be effective. Oral terbinafine,

itraconazole, and fluconazole also are options. If a Majocchi granuloma (deep folliculitis) is present, oral antifungal therapy is recommended. Dermatophyte infections in other locations, if present, should be treated concurrently.

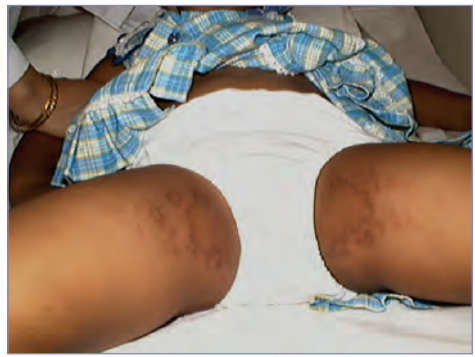


Image 145.1
Symmetrical, confluent, annular, scaly red, and hyperpigmented plaques. This 10-year-old girl developed a chronic itchy eruption on the groin that spread to the anterior thighs. A potassium hydroxide preparation showed hyphae, and she was treated successfully with topical antifungal cream.

CHAPTER 146

Tinea Pedis and Tinea Unguium (Onychomycosis)

(Athlete's Foot, Ringworm of the Feet)

CLINICAL MANIFESTATIONS

Tinea pedis can have a variety of clinical manifestations in children. Lesions can involve all areas of the foot but usually are patchy in distribution, with a predisposition to cause fissures, macerated areas, and scaling between toes, particularly in the third and fourth interdigital spaces. A pruritic, fine scaly, or vesiculopustular eruption is most common. "Moccasin foot" exhibits confluent, hyperkeratotic, dry scaling of the soles. Additionally, toenails can be infected (onychomycosis or tinea unguium) and become distorted, discolored, and thickened with accumulation of subungual debris. A superficial white form of foot and toenail fungal infection can occur in children. Toenails may be the source for recurrent tinea pedis.

Tinea pedis must be differentiated from dyshidrotic eczema, atopic dermatitis, contact dermatitis, juvenile plantar dermatosis, palmoplantar keratoderma, and erythrasma (an eruption of reddish brown patches resulting from superficial bacterial skin infection caused by *Corynebacterium minutissimum*).

An associated skin eruption, known as a dermatophytic or "id" reaction, can occur as a hypersensitivity reaction to the infecting fungus and manifests as diffuse, pruritic, papular, vesicular, or eczematous lesions at sites distant from the fungal infection. An id reaction can first occur following institution of therapy but does not represent a drug allergy.

In patients with diminished T-lymphocyte function (eg, human immunodeficiency virus infection), skin lesions may appear as grouped papules or pustules unaccompanied by erythema or scaling.

ETIOLOGY

Tinea pedis and unguium develop when dermatophytic fungi invade the skin layers and nails of the affected body region. The fungi *Trichophyton rubrum*, *Trichophyton mentagrophytes*, and *Epidermophyton floccosum* are the most common causes of tinea pedis.

EPIDEMIOLOGY

Tinea pedis is a common infection worldwide in adolescents and adults but is less common in young children. Fungi are acquired by contact with infected skin scales or organisms present in damp areas, such as swimming pools, locker rooms, and showers. Tinea pedis may spread among family members in the household; this may represent enhanced genetic susceptibility as well as increased exposure to the organism. The incidence of onychomycosis increases with age, with worldwide prevalence estimated to be from 0.1% to 0.87%. The increased use of occlusive footwear earlier in childhood and exposure to high-risk areas (eg, swimming pools, gyms) earlier in life may be associated with an increase of tinea pedis in children. Childhood onychomycosis is associated with a history of tinea pedis, a history of family member infection, increased number of siblings, and male sex. Immunocompromised people and those with trisomy 21 have increased susceptibility to dermatophyte infections. Accumulating data also implicate a genetic predisposition to tinea infections in certain individuals.

The **incubation period** is unknown, thought to be approximately 1 to 3 weeks but can be shorter.

DIAGNOSTIC TESTS

Confirmatory diagnostic tests for tinea pedis are similar to those for tinea corporis. Fungal infection of the nail (tinea unguium or onychomycosis) can be verified by direct microscopic examination with potassium hydroxide, fungal culture of desquamated subungual material, or fungal stain of a nail clippings fixed in formalin.

TREATMENT

A myriad of topical options are available for treatment of tinea pedis. Therapy duration of 2 weeks usually is sufficient for milder cases of tinea pedis in children. Acute vesicular lesions can be treated with intermittent use of open wet compresses (eg, with Burow solution, diluted 1:80). Tinea pedis that is severe,

chronic, or refractory to topical treatment can be treated with oral therapy like that for tinea corporis.

Recurrence of tinea pedis is prevented by proper foot hygiene, which includes keeping the feet dry and cool, cleaning gently, drying between the toes, use of absorbent antifungal foot powder, exposing affected areas to air frequently, and avoidance of occlusive footwear, nylon socks, and other fabrics that interfere with dissipation of moisture. Protective footwear should be worn in common areas such as pools, gyms, and other public facilities.

In the past, onychomycosis (tinea unguium) was believed to require oral therapy; however, topical antifungal lacquers and solutions have been developed that are effective for distal toenail infections that do not involve the nail matrix. Despite lower cure rates, topical agents are preferred because of substantially lower adverse effects, lack of drug-drug interactions, and avoidance of laboratory tests monitoring for toxicity. Topical ciclopirox 8% can be used in patients 12 years and older and can be applied to affected toenail(s) once daily for 4 to 8 weeks. Efinaconazole 10% solution and tavaborole 5% solution can be used for tinea unguium in adults. Topical therapies appear to show a higher cure rate in children than in adults, possibly because of thinner nail plates and faster nail growth rate in children.

Studies in adults have demonstrated the best cure rates for onychomycosis (tinea unguium) are with oral itraconazole or terbinafine. Although oral therapies are more likely to lead to cure, they also require laboratory monitoring and can induce drug–drug interactions. The duration of therapy is the same as for adults (6 weeks for fingernail infection, 12 weeks for toenail infection). Pediatric dosing of oral itraconazole is not established for superficial mycoses.

Factors that influence choice of therapy include the severity of the infection, the result of fungal culture or potassium hydroxide preparation (if performed), prior treatments, concomitant drug therapy for other illnesses, patient preference, and cost.

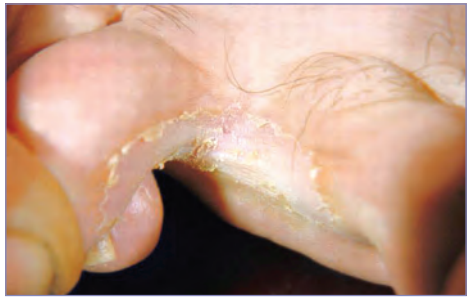


Image 146.1
This patient presented with ringworm or tinea pedis of the toes, which is also known as athlete's foot. Tinea pedis is a fungal infection of the feet, principally involving the toe webs and soles. Athlete's foot can be caused by the fungi *Epidermophyton floccosum* or by numerous members of the *Trichophyton* genus. Courtesy of Centers for Disease Control and Prevention.

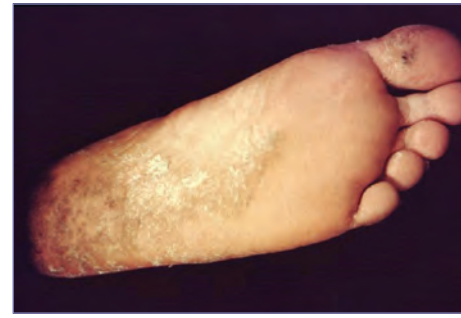


Image 146.2
This patient presented with ringworm of the foot (tinea pedis) due to the dermatophytic fungus *Trichophyton rubrum*. Individuals who practice generally poor hygiene, wear enclosed footwear such as tennis shoes, endure prolonged wetting of the skin (ie, sweating during exercise), and experience minor skin or nail injuries are more prone to experience tinea infections. Courtesy of Centers for Disease Control and Prevention.

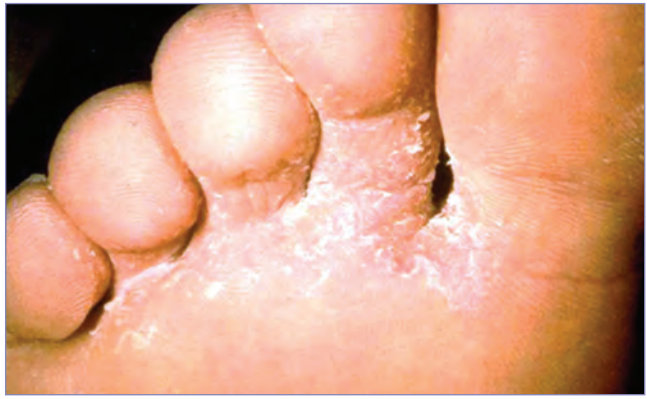


Image 146.3
Tinea pedis and tinea unguium.

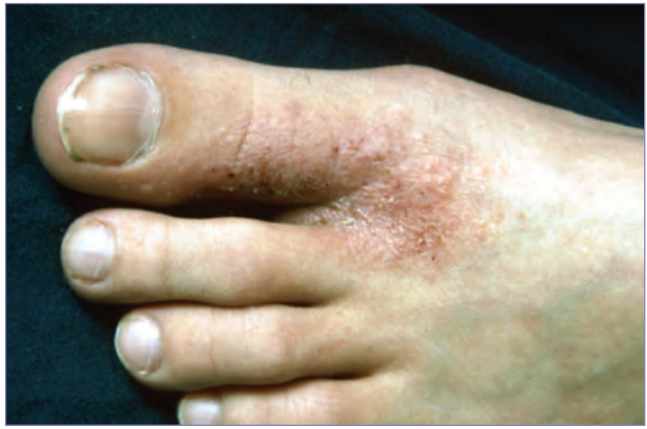


Image 146.4
Tinea pedis and tinea unguium.

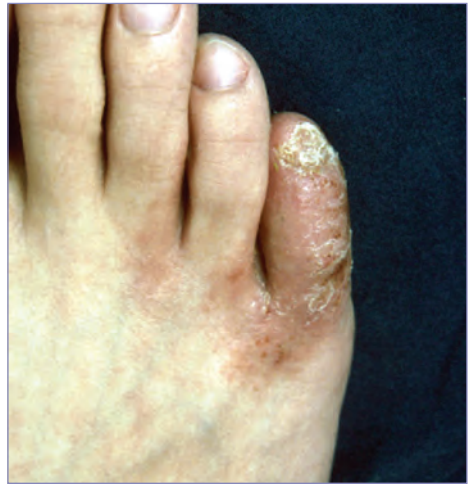


Image 146.5
Tinea pedis and tinea unguium infection. This is the same patient as in Image 146.4.

CHAPTER 147

Toxocariasis

(Visceral Toxocariasis [a Form of Visceral Larva Migrans]; Ocular Toxocariasis [a Form of Ocular Larva Migrans])

CLINICAL MANIFESTATIONS

The severity of symptoms associated with toxocariasis correlates roughly with the number of infective eggs ingested and the degree of the host inflammatory response. Although most infected children are asymptomatic, symptoms of visceral toxocariasis include fever, cough, wheezing, abdominal pain, and malaise. Laboratory abnormalities include leukocytosis, eosinophilia, and hypergammaglobulinemia. Ocular invasion (resulting in uveitis, endophthalmitis, or retinal granulomas) most often manifests as unilateral vision loss, often without other systemic signs of infection. Atypical manifestations include myocarditis, seizures and other signs of encephalitis, and hemorrhagic rash.

ETIOLOGY

Toxocariasis is caused by *Toxocara* species, which are nematode parasites (roundworms) of dogs and cats (especially puppies or kittens), specifically *Toxocara canis* and *Toxocara cati* in the United States; most cases are caused by *T canis*.

EPIDEMIOLOGY

On the basis of a nationally representative survey, 14% of the US population older than 5 years has serologic evidence of *Toxocara* infection. Visceral toxocariasis typically occurs in children 2 to 7 years of age but can occur in older children and adults. Ocular toxocariasis usually occurs in older children and adolescents. The highest seroprevalence is found among African American children, children in the southern United States, and some indigenous communities in Canada, as well as populations with low education levels and those living in areas where dog feces are found. Humans are infected by ingestion of soil containing infective eggs of the parasite. Eggs may be found wherever dogs and cats defecate, often in sandboxes and playgrounds. Eggs become infective after 2 to 4 weeks in the environment and may persist long-term in the soil. Direct contact with dogs is not necessary, because eggs are not infective immediately when shed in the feces. Infection risk is highest in hot, humid regions where eggs remain viable in soil.

The **incubation period** is not known.

DIAGNOSTIC TESTS

Laboratory findings include marked leukocytosis with eosinophilia, and occasionally anemia and hypergammaglobulinemia. Patients with visceral disease frequently have increased titers of isohemagglutinin to the A and B blood group antigens. An enzyme-linked immunosorbent assay for *Toxocara* antibodies in serum or vitreous fluid is available through the Centers for Disease Control and Prevention as well as commercial laboratories. However, a positive antibody test result does not distinguish between past and current infection, and the test is less sensitive for diagnosis of ocular toxocariasis. For visceral disease, imaging of the liver using ultrasonography, computed tomography, or magnetic resonance imaging may reveal diffuse parenchymal lesions measuring less than 2 cm in diameter. Microscopic identification of larvae in a liver biopsy specimen is diagnostic, but this test is not sensitive or specific and therefore rarely indicated.

TREATMENT

Albendazole is recommended for treatment of visceral toxocariasis. Mebendazole is an alternative. In severe cases with myocarditis or involvement of the central nervous system, corticosteroid therapy should be considered.

The benefits of anthelmintic treatment for ocular toxocariasis are not well defined, although positive outcomes have been reported with a 2-week course of albendazole and prednisone. Inflammation may be decreased by topical or systemic corticosteroids, and secondary damage may be decreased with ophthalmologic surgery.

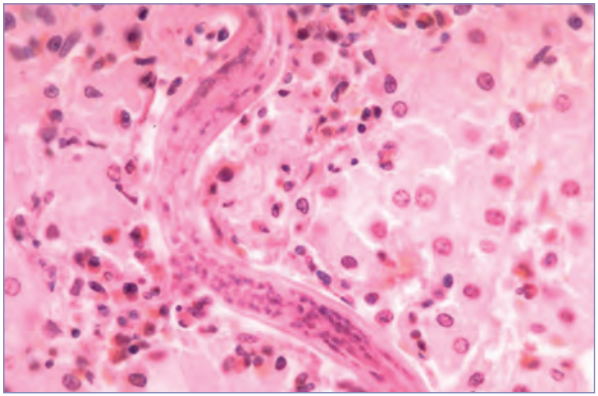


Image 147.1
Visceral toxocariasis (previously visceral larva migrans) with *Toxocara canis* larvae on liver biopsy.

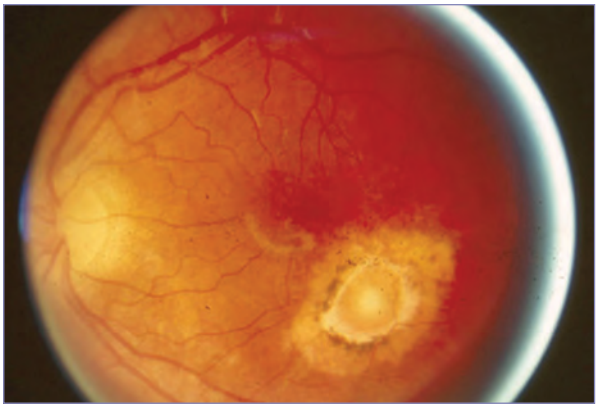


Image 147.2
Toxocara canis. Fundus damage from larval invasion. Courtesy of Hugh Moffet, MD.

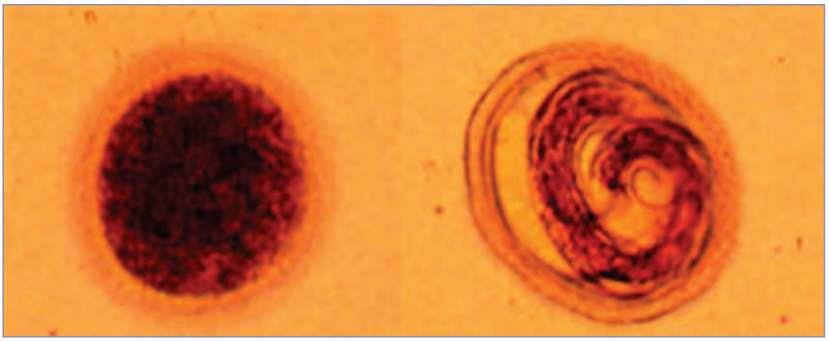


Image 147.3
Eggs of *Toxocara canis*. These eggs are passed in dog feces, especially puppy feces. Humans do not produce or excrete eggs; therefore, eggs are not a diagnostic finding in human toxocariasis. The egg to the left is fertilized but not yet embryonated, while the egg to the right contains a well-developed larva. The latter egg would be infective if ingested by a human (frequently, a child).

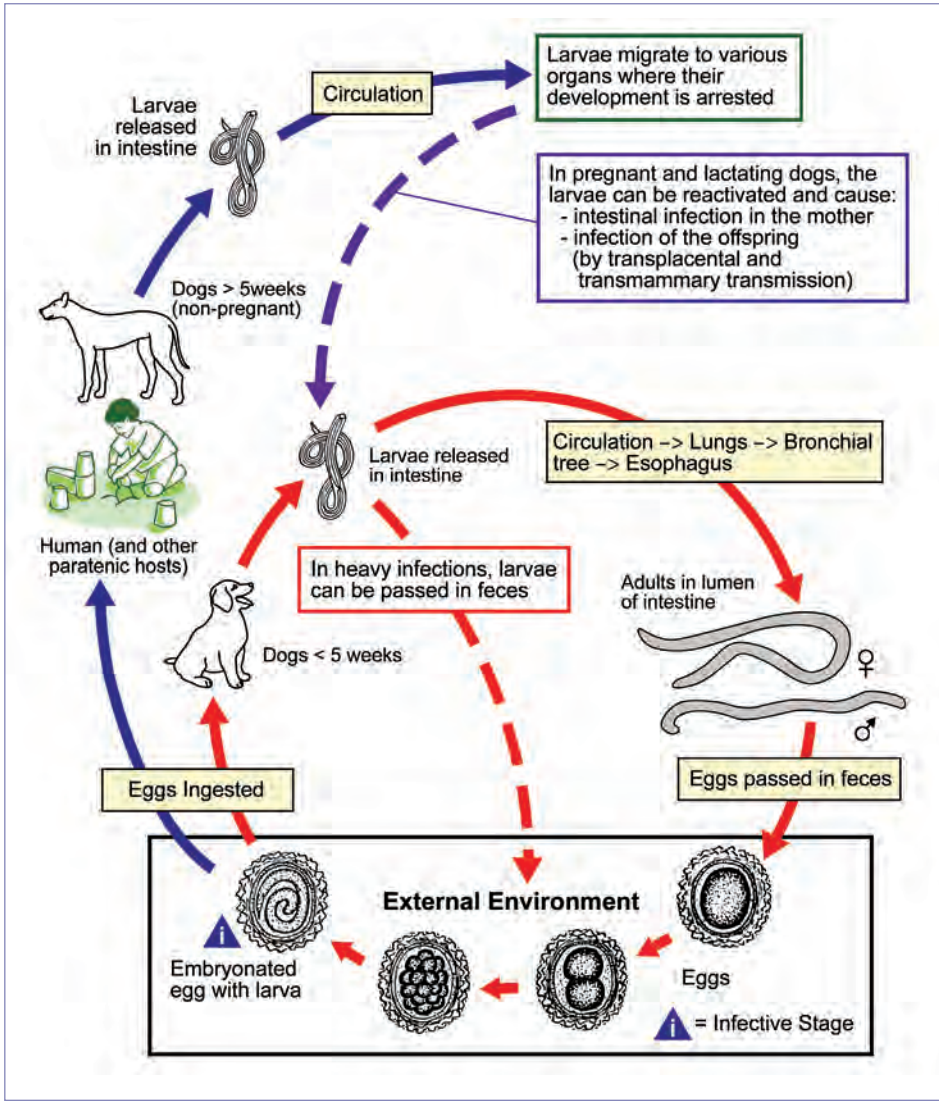


Image 147.4

Toxocara canis accomplishes its life cycle in dogs, with humans acquiring the infection as accidental hosts. Following ingestion by dogs, the infective eggs yield larvae that penetrate the gut wall and migrate into various tissues, where they encyst if the dog is older than 5 weeks. In younger dogs, the larvae migrate through the lungs, bronchial tree, and esophagus; adult worms develop and oviposit in the small intestine. In the older dogs, the encysted stages are reactivated during pregnancy and infect by the transplacental and transmammary routes of the puppies, in whose small intestine adult worms become established. Thus, infective eggs are excreted by lactating adult female dogs and puppies. Humans are paratenic hosts who become infected by ingesting infective eggs in contaminated soil. After ingestion, the eggs yield larvae that penetrate the intestinal wall and are carried by the circulation to a wide variety of tissues (liver, heart, lungs, brain, muscle, eyes). While the larvae do not undergo any further development in these sites, they can cause severe local reactions that are the basis of toxocariasis. Courtesy of Centers for Disease Control and Prevention/Alexander J. da Silva, PhD/Melanie Moser.

CHAPTER 148

Toxoplasma gondii Infections

(Toxoplasmosis)

Common syndromes associated with acute infection or reactivation of chronic infection with *Toxoplasma gondii* in immunocompetent or, more often, immunocompromised patients include lymphadenopathy with atypical lymphocytosis and hepatic dysfunction, fever, meningoencephalitis, chorioretinitis, myocarditis, pneumonitis, myositis, and myelitis. *Toxoplasma* infection should be considered in the differential diagnosis of any person presenting with visual symptoms compatible with chorioretinitis, especially a pregnant woman or newborn infant, and regardless of lack of prior symptoms compatible with a primary infection.

CLINICAL MANIFESTATIONS

Asymptomatic Infection

Up to 50% of all age groups patients infected have no recognized risk factors and are asymptomatic.

Congenital Infection

In the United States, mothers are not screened routinely for toxoplasmosis. It is estimated that approximately 12% of infants with congenital infection are born without clinical manifestations at birth; however, visual or hearing impairment, learning disabilities, or mental retardation later will become apparent in a large proportion of these children. Chorioretinitis occurs in 72% of the offspring whose infected mothers were not treated during pregnancy and in up to 25% in those whose mothers were treated. In France, where mothers are screened systematically and treated during pregnancy for toxoplasmosis, 88% of infants with congenital infection appear healthy at birth, 9% have mild-moderate sequelae, and 3% have severe sequelae on follow-up.

The classic triad of chorioretinitis, cerebral calcifications, and hydrocephalus is highly suggestive of congenital toxoplasmosis. However, most cases do not present with this triad. Additional findings of congenital toxoplasmosis at birth include microcephaly, seizures, hearing loss, strabismus, a maculopapular rash, generalized lymphadenopathy, hepatomegaly, splenomegaly, jaundice, pneumonia, diarrhea, anemia, petechiae, and thrombocytopenia. Chorioretinitis often reactivates later in life and results in vision loss symptoms. Meningoencephalitis with cerebrospinal fluid (CSF) abnormalities can be present at birth, often with extremely high protein concentrations (eg, >500 mg/dL) and eosinophilia. Some severely affected fetuses or neonates die in utero or within a few days of birth. Cerebral calcifications can be demonstrated by plain radiography, ultrasonography, computed tomography (CT), or magnetic resonance imaging (MRI) of the head. CT is the radiologic technique of choice, because it is the most sensitive for detection of calcifications and can reveal brain abnormalities when plain radiographic and ultrasonographic studies are normal.

Postnatally Acquired Primary Infection

T gondii infection acquired after birth is asymptomatic in almost all immunocompetent patients. When symptoms develop, they may be nonspecific and can include malaise, fever, headache, sore throat, arthralgia, and myalgia. Lymphadenopathy, frequently cervical, is the most common sign. Patients occasionally have a mononucleosis-like illness associated with a macular rash, hepatosplenomegaly, hepatic dysfunction, and atypical lymphocytosis. The clinical course usually is benign and self-limited. In a subset of immunocompetent individuals and in immunocompromised patients, primary infection may present with persistent fever, myocarditis, myositis, hepatitis, pericarditis, pneumonia, encephalitis with and without brain abscesses, and skin lesions. These syndromes and a more aggressive clinical course, including life-threatening pneumonia, are especially common in patients who acquired primary toxoplasmosis in certain tropical countries in South America, such as French Guiana, Brazil, and Colombia. Toxoplasmosis should be included in the differential diagnosis of ill travelers who return home with these unexplained syndromes. Occasionally, this more aggressive clinical presentation has been

observed in immunocompetent individuals infected in the United States, likely from acute infections associated with high parasite load or highly virulent strains.

Toxoplasmic chorioretinitis can occur in the setting of postnatally acquired infection. Most commonly, acute onset of blurred vision, eye pain, decreased visual acuity, floaters, scotoma, photophobia, or epiphora are noted. Ocular disease can reactivate years after the initial infection in healthy and immunocompromised individuals. The morphology of the retinal lesions with postnatally acquired infection is like that of in utero infection. A focal necrotizing retinitis with vitritis, occasionally with anterior uveitis, most commonly is described. Often, an atrophic retinochoroidal scar is seen. Complications can include chronic iridocyclitis, cataract formation, secondary glaucoma, band keratopathy, cystoid macular edema, retinal detachment, and if the optic nerve is involved, optic atrophy.

Reactivation of Chronic Infection in Immunocompromised Patients

Reactivation of latent infection may occur in an immunocompromised patient (eg, organ transplant recipient who is receiving certain monoclonal antibodies, such as alemtuzumab). Reactivation of latent disease can result in life-threatening encephalitis, brain abscesses, seizures, pneumonia, posterior or panuveitis (always with chorioretinitis), fever of unknown origin, disseminated disease, myocarditis, or skin lesions. Toxoplasmic encephalitis (TE) can present as a single brain lesion on MRI or as a diffuse and rapidly progressive process in the setting of apparently normal brain imaging. MRI is superior to CT for the diagnosis of TE and can detect lesions not revealed by CT. In patients with acquired immunodeficiency syndrome (AIDS), TE is the most common cause of space-occupying brain lesions and typically presents with acute to subacute neurologic or psychiatric symptoms and multiple ring-enhancing brain lesions. In these patients, a clear improvement in their neurologic examination within 7 to 10 days of beginning empirical anti-*Toxoplasma* therapy is considered diagnostic of TE.

In immunosuppressed patients without human immunodeficiency virus (HIV) infection who present with multiple ring-enhancing brain lesions, brain biopsy should be pursued to establish a tissue diagnosis rather than initiating empirical anti-*Toxoplasma* treatment, because the differential diagnosis is broad and includes a variety of pathogens, such as fungal, mycobacterial, and *Nocardia* infections, as well as neoplasms.

Seropositive hematopoietic stem cell and solid organ transplant recipients are at risk for reactivation of primary infection. In these patients, toxoplasmosis can manifest as pneumonia, unexplained fever or seizures, myocarditis, hepatosplenomegaly, lymphadenopathy, or skin lesions in addition to brain abscesses and diffuse encephalitis. *T gondii*-seropositive solid organ donors (D+) can transmit the parasite, via the allograft, to seronegative recipients (R–). Thirty percent of D+/R– heart transplant recipients not receiving prophylaxis for *T gondii* develop clinical toxoplasmosis.

ETIOLOGY

T gondii is a protozoan and obligate intracellular parasite that exists in nature in relatively few clonal lineages (types I, II, and III, and other lineages including atypical strains). The infectious forms include tachyzoites, tissue cysts containing bradyzoites, and oocysts containing sporozoites. The tachyzoite and the corresponding host immune reaction are responsible for symptoms observed during acute infection or during reactivation of a latent infection. The tissue cyst is responsible for latent infection and usually is present in brain, eye, cardiac tissue, and skeletal muscle of humans and other warm-blooded animals.

EPIDEMIOLOGY

The seroprevalence of *T gondii* infection varies by geographic locale and socioeconomic strata of the population. The age-adjusted seroprevalence of infection in the United States has been estimated at 9% among women 15 to 44 years of age. *T gondii* is distributed worldwide and can infect most species of warm-blooded animals. Members of the feline family are the definitive host; they generally acquire the infection by ingestion of tissue cysts present in infected animals (eg, mice) or uncooked

household meats or by ingestion of oocysts present in soil organic matter, water, or food. Millions of oocysts are excreted in feline stools 3 to 30 days after primary infection and continue to be shed for 7 to 14 days. After excretion, oocysts require a maturation phase (sporulation) of 1 to 5 days in temperate climates before they are infective by the oral route. Sporulated oocysts can survive for years under most environmental conditions. Intermediate hosts (including sheep, pigs, mice, and cattle) can have tissue cysts in the brain, myocardium, skeletal muscle, and other organs. These cysts remain viable for the lifetime of the host. Humans usually become infected by consumption of raw or undercooked meat that contains cysts or by accidental ingestion of sporulated oocysts from soil or from contaminated food or water. Large outbreaks linked epidemiologically to contamination of municipal drinking water supplies have been reported. The main risk factors associated with acute infection in the United States include eating raw ground beef; eating rare lamb; eating locally produced cured, dried, or smoked meat; working with meat; drinking unpasteurized goat milk; and owning 3 or more kittens. Eating raw oysters, clams, or mussels also has been identified as a novel risk factor. Increased risk of acute infection in those who drink untreated water has been reported in the United States. There is no evidence of human-to-human transmission except through vertical transmission, blood products, or organ transplantation. Up to 50% of acutely infected people are asymptomatic.

In most cases, congenital transmission occurs from primary maternal infection during pregnancy. In utero infection rarely occurs from reactivated parasitemia in chronically infected immunocompromised pregnant women. In the United States, the incidence of acute primary *T gondii* infection during pregnancy has been estimated to be between 0.2/1,000 and 1.1/1,000 pregnant women; the incidence of congenital toxoplasmosis has been estimated to be between 0.5 cases and 0.82 cases per 10,000 live births. Infection rarely has occurred following a laboratory accident or from blood or blood product transfusion.

The **incubation period** of postnatally acquired infection is approximately 7 days (range, 4–21 days).

DIAGNOSTIC TESTS

Serologic tests are the primary means of diagnosing primary and latent infection. Initial serologic testing for *Toxoplasma* immunoglobulin (Ig) G and IgM can be performed by nonreference laboratories. However, positive *Toxoplasma* IgM test results can be falsely positive, so an additional sample should be submitted to reference laboratories with special expertise in *Toxoplasma* serologic assays and their interpretation (Palo Alto Medical Foundation Toxoplasma Serology Laboratory [PAMF-TSL]; Palo Alto, CA; **www.pamf.org/serology**; telephone: 650/853-4828; email: toxolab@pamf.org) and for additional confirmatory testing (eg, IgM testing by the double-sandwich enzyme-linked immunosorbent assay [ELISA] using antigen obtained from live parasites, IgA, IgE, avidity, and differential agglutination). Moreover, testing of neonates or young infants with congenital toxoplasmosis and of pregnant women with suspected acute primary infection during gestation should be confirmed routinely at the PAMF-TSL reference laboratory, where specific panels of tests with high diagnostic accuracy will be performed.

IgG-specific antibodies achieve a peak concentration 3 to 5 months after infection and remain positive indefinitely. Most patients will have low-positive IgG antibody titers 6 months after the acute infection. IgM-specific antibodies can be detected 2 weeks after infection, achieve peak concentrations in 1 month, decrease thereafter, and usually become undetectable within 6 to 9 months. However, a positive IgM test result may persist for years without apparent clinical significance. To determine the approximate time of infection in IgG-positive adults, specific IgM antibody determinations should be performed. The lack of *T gondii*-specific IgM antibodies in a person with low-positive titers of IgG antibodies (eg, a dye test at PAMF-TSL ≤512) indicates infection of at least 6 months' duration. In contrast, detectable *T gondii*-specific IgM antibodies can indicate recent infection, chronic infection, or a false-positive reaction. If the timing of infection is clinically important (eg, in a pregnant

woman), sera with positive *T gondii*-specific IgM test results should be sent to PAMF-TSL to establish acute versus chronic infection. If acute infection is confirmed at PAMF-TSL, further testing can be performed to estimate the timing of the infection. Laboratory tests that have been found to be helpful in determining timing of infection in patients with positive IgM test results include an IgG avidity test, the differential agglutination (AC/HS) test, and IgA- and IgE-specific antibody tests. The presence of high-avidity IgG antibodies indicates that infection occurred at least 12 to 16 weeks previously. However, the presence of low-avidity antibodies is not a reliable indication of more recent infection, and treatment may affect the maturation of IgG avidity and prolong the presence of low-avidity antibodies. A nonacute pattern in the AC/HS test is essentially indicative of an infection that was acquired at least 12 months before the serum was obtained. However, like low-avidity IgG test results, an acute AC/HS pattern can last for several months and does not necessarily establish the diagnosis of acute infection. Tests to detect IgA and IgE antibodies, which decrease to undetectable concentrations sooner than do IgM antibodies, also are useful for diagnosis of congenital infections and infections in pregnant women, for whom more precise information about the timing of infection is needed. *T gondii*-specific IgA and IgE antibody tests are available in *Toxoplasma* reference laboratories but generally not in other laboratories. Their presence, particularly at high titers, is indicative of an infection acquired within the past 3 months.

Maternal test results help in the interpretation of test results for a newborn infant. If the mother was not tested during pregnancy, a maternal serum sample should be tested for IgG and IgM, and AC/HS and avidity tests should be performed as soon as possible. Only 2 states (Massachusetts and New Hampshire) routinely screen all newborn infants for antibody to *T gondii*.

Polymerase chain reaction (PCR) detection has been applied to virtually any body fluid or tissue, and *T gondii*-specific immunoperoxidase staining in any tissue, depending on the clinical scenario. Specimens in which PCR assay can be performed include amniotic fluid, CSF, whole blood, bronchoalveolar lavage fluid, vitreous fluid, aqueous humor, peritoneal fluid, ascitic fluid, pleural fluid, bone marrow, and urine. Essentially any tissue can be stained with *T gondii*-specific immunoperoxidase; the presence of extracellular antigens and a surrounding inflammatory response also are diagnostic of toxoplasmosis. A positive PCR test result in tissue must be interpreted with caution, because it may amplify tachyzoite or bradyzoite DNA and, therefore, cannot distinguish between the presence of tachyzoites with acute infection or reactivation or bradyzoites with chronic latent infection.

Congenital Toxoplasmosis

When a neonate is suspected of being congenitally infected with *T gondii*, neonatal peripheral blood for *Toxoplasma* IgG (in parallel with maternal blood for *Toxoplasma* IgG), IgM ISAGA, and IgA ELISA should be sent to a toxoplasmosis reference laboratory (eg, PAMF-TSL). A complete blood cell count and transaminase tests should be performed. Peripheral blood *Toxoplasma* PCR, urine *Toxoplasma* PCR, and CSF *Toxoplasma* PCR should be performed as soon as possible after birth when there is strong suspicion of congenital toxoplasmosis; CSF *Toxoplasma* PCR can be deferred in infants with low suspicion of congenital toxoplasmosis. When CSF is obtained, it should be sent for CSF cell count, differential, protein, and glucose determinations. If there is concern for false-positive *Toxoplasma* IgM or IgA results because of possible contamination of infant's blood with maternal blood during labor, the infant's serologic tests should be repeated at least 10 days after birth (half-life of *Toxoplasma* IgM antibodies is approximately 5 days, and for IgA antibodies is approximately 10 days).

The diagnosis of congenital toxoplasmosis can be confirmed by detection of

- *T gondii* in umbilical cord blood or in urine, peripheral blood, or CSF of newborn infant, by mouse inoculation;
- *T gondii* DNA by PCR in amniotic fluid or in peripheral blood, urine, or CSF of newborn infant (no US Food and Drug Administration [FDA]-approved tests);

- IgA and/or IgM antibody to *T gondii* in fetal or newborn blood;
- IgG and/or IgM antibody to *T gondii* in the CSF of the newborn infant;
- Fetal or newborn *T gondii*-specific IgG 4 times greater than maternal *T gondii*-specific IgG; or
- IgG antibody to *T gondii* that increases or remains positive after 12 months of life in an infant with clinical manifestations consistent with congenital toxoplasmosis but not explained by another diagnosis (eg, Chagas disease, syphilis, rubella, cytomegalovirus, HIV, HTLV, Zika virus, hepatitis B and C).

Evaluation of the infant with congenital toxoplasmosis should include ophthalmologic, auditory, and neurologic examinations; lumbar puncture; and CT of the head. Follow-up ophthalmologic evaluations are necessary, even if initial evaluation was normal. In a French cohort of children with congenital toxoplasmosis, initial retinal lesions were first detected after 7 months of age in 75% of the cases, after 3 years in 50%, and after 8 years in 25%. Long-term neurodevelopmental evaluations are required.

Infants born to women who are infected simultaneously with HIV and *T gondii* and who are not receiving anti-*Toxoplasma* prophylaxis should be evaluated for congenital toxoplasmosis because of an increased likelihood of maternal reactivation and congenital transmission in this setting. Expert advice is available at PAMF-TSL and Toxoplasmosis Research Institute and Center; Chicago, IL; **www.toxoplasmosis.org;** telephone 773/834-4131; email rmcleod@midway.uchicago.edu.

Immunocompromised Patients

Immunocompromised patients (eg, people with AIDS, hematopoietic stem cell or solid organ transplant recipients, people with cancer, or people taking immunosuppressive drugs) who are infected latently with *T gondii* have variable titers of IgG antibody to *T gondii* but rarely have IgM antibody. Immunocompromised patients should be tested for *T gondii*-specific IgG before commencing immunosuppressive therapy or as soon as possible after their status of immunosuppression is diagnosed to determine whether they are chronically infected with *T gondii* and at risk of reactivation of latent infection. Active disease in immunosuppressed patients may or may not result in seroconversion and a fourfold increase in IgG antibody titers; consequently, serologic diagnosis in these patients often is difficult.

In HIV-infected patients who are seropositive for *T gondii* IgG, reactivation of their latent infection usually is manifested by toxoplasmic encephalitis (TE). TE can be diagnosed presumptively by characteristic clinical and radiographic findings (MRI typically shows multiple ring-enhancing brain lesions). If there is no clinical response to an empirical trial of anti-*T gondii* therapy within 10 days, demonstration of *T gondii* organisms, antigen, or DNA in specimens such as blood, CSF, or bronchoalveolar fluid may be necessary to confirm the diagnosis, and alternative etiologies (eg, chronic Chagas disease) should be considered as the evaluation continues. TE also can present as diffuse encephalitis without space-occupying lesions on brain MRI.

Ocular Toxoplasmosis

Toxoplasmic chorioretinitis usually is diagnosed based on characteristic retinal lesions in conjunction with a positive serum *T gondii*-specific IgG test result. All patients with eye disease also should have an IgM test performed; if a positive IgM test result is confirmed at a reference laboratory and eye lesions are consistent with toxoplasma chorioretinitis, ocular disease is the result of an acute *T gondii* infection rather than reactivation of a chronic infection. Patients who have atypical retinal lesions or who fail to respond to anti-*T gondii* therapy should undergo examination of vitreous fluid or aqueous humor by PCR, and antibody testing (using the Goldmann-Witmer coefficient, which compares the proportion of *Toxoplasma*-specific IgG in the intraocular sample with that in serum, as measured by ELISA or radioimmunoassay) should be considered. A Goldmann-Witmer coefficient greater than 2 or 3 is considered diagnostic of ocular toxoplasmosis.

TREATMENT

Most cases of acquired infection in an immunocompetent host do not require specific antimicrobial therapy unless infection occurs during pregnancy or symptoms are severe or persistent. Treatment of primary *T gondii* infection in **pregnant women,** including women with HIV infection who reactivate their chronic *Toxoplasma* infection, is recommended. Spiramycin treatment of primary infection during gestation is used to prevent transmission of *T gondii* from mother to fetus in cases in which there is no evidence yet of fetal infection. Spiramycin does not reliably treat the fetus because it does not readily cross the placenta. Spiramycin is available only as an investigational drug in the United States if recommended by PAMF-TSL or the Toxoplasmosis Research Institute and Center and with authorization from the FDA (telephone: 301/796-1400; fax: 301/796-9883). If fetal infection is confirmed at or after 18 weeks of gestation or if the mother acquires infection during the third trimester, pyrimethamine plus sulfadiazine and leucovorin should be used, because they cross the placenta.

Infants with symptomatic congenital toxoplasmosis should receive oral therapy with pyrimethamine plus sulfadiazine and folinic acid (leucovorin) for 12 months; folinic acid is used to minimize pyrimethamine toxicity. If CSF protein is ≥1 g/dL or patient has severe chorioretinitis, prednisone is administered twice daily until CSF protein <1 g/dL or resolution of severe chorioretinitis; steroids are initiated after 72 hours of anti-*Toxoplasma* therapy. Infants with asymptomatic congenital toxoplasmosis, the same regimen used for symptomatic infants (pyrimethamine, sulfadiazine, and folinic acid), should be used but for 3 months.

Older children with toxoplasmic chorioretinitis should receive oral therapy with pyrimethamine, sulfadiazine, and folinic acid for 1 to 2 weeks beyond resolution of clinical manifestations or approximately 4 to 6 weeks.

Immunocompetent and immunocompromised children with severe primary toxoplasmosis and **immunocompromised children with reactivation of toxoplasmosis** should receive oral therapy with pyrimethamine, sulfadiazine, and folinic acid; for **HIV-infected children and adolescents,** treatment guidelines are found at **https://aidsinfo.nih.gov/guidelines.**

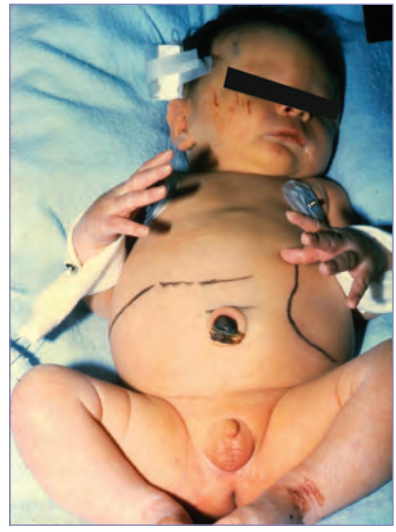


Image 148.1
A 12-day-old boy with congenital toxoplasmosis with marked hepatosplenomegaly. Courtesy of George Nankervis, MD.

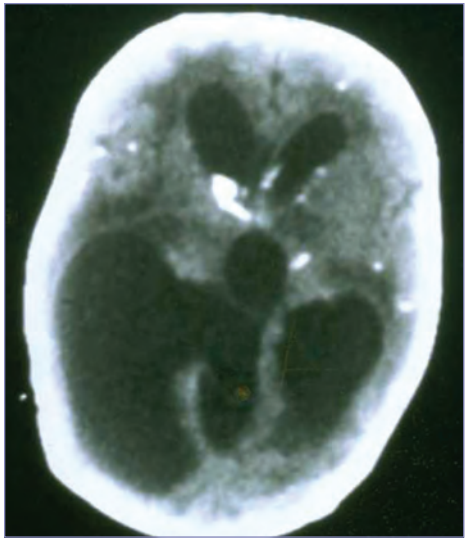


Image 148.2
Congenital infection evident on a computed tomography scan of the head that shows diffuse calcifications and hydrocephaly.

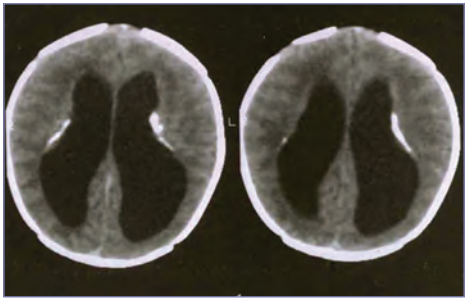


Image 148.3
A 3-day-old boy presented with a seizure. His computed tomography scan demonstrated hydrocephalus and periventricular calcification, suggestive of congenital infection, such as toxoplasmosis, rubella, cytomegalovirus, or herpes simplex. *Toxoplasma* serology was positive, and the neonate was treated for congenital toxoplasmosis with pyrimethamine, sulfadiazine, and folinic acid. Copyright Barbara Jantausch, MD, FAAP, MD.

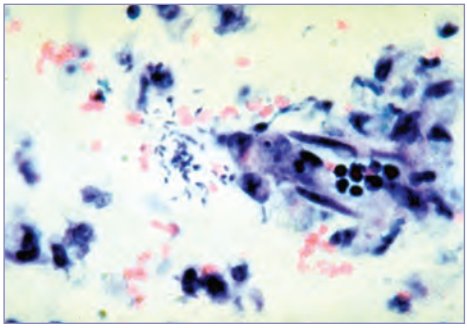


Image 148.4
Brain biopsy shows multiple *Toxoplasma gondii* organisms (Giemsa stain, original magnification ×400). Copyright Jerri Ann Jenista, MD, MD.

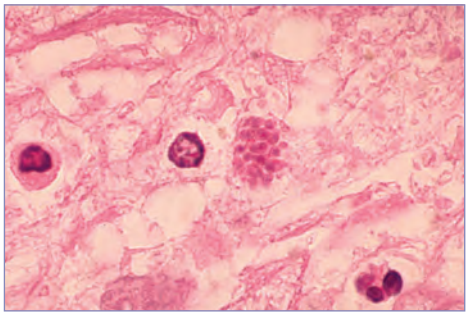


Image 148.5
Histopathology of toxoplasmosis of the brain in fatal AIDS. Pseudocyst contains numerous tachyzoites of *Toxoplasma gondii*. Courtesy of Centers for Disease Control and Prevention.

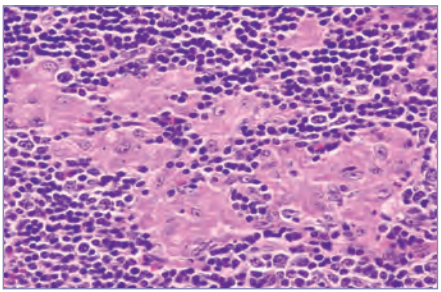


Image 148.6
Toxoplasma lymphadenitis. Noncaseating epithelioid cell granulomas in lymph node. Courtesy of Dimitris P. Agamanolis, MD.

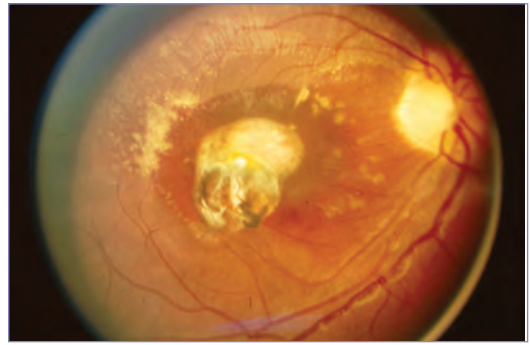


Image 148.7
Toxoplasma gondii retinitis. Note well-defined areas of chorioretinitis with pigmentation and irregular scarring.

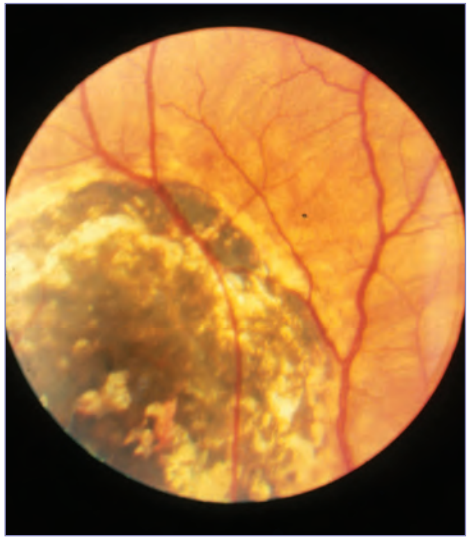


Image 148.8
Extensive chorioretinitis in an infant with congenital toxoplasmosis. Courtesy of George Nankervis, MD.

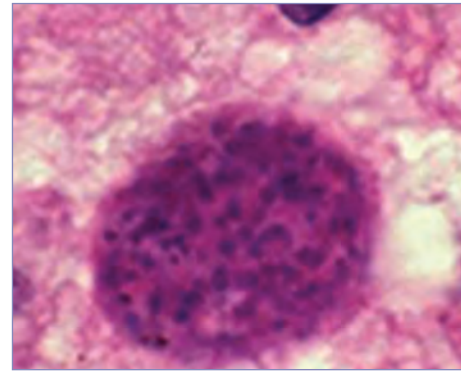


Image 148.10
Cysts of *Toxoplasma gondii* usually range in size from 5 to 50 µm in diameter. Cysts are usually spherical in the brain but more elongated in cardiac and skeletal muscles. They may be found in various sites throughout the body of the host but are most common in the brain and skeletal and cardiac muscles. *T gondii* cyst in brain tissue (hematoxylin-eosin stain). Courtesy of Centers for Disease Control and Prevention.

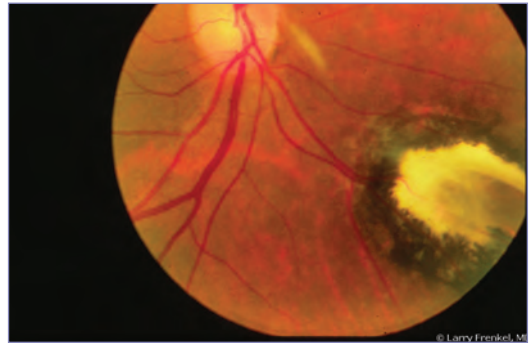


Image 148.9
A neonate with congenital toxoplasmosis with chorioretinitis. Courtesy of Larry Frenkel, MD.

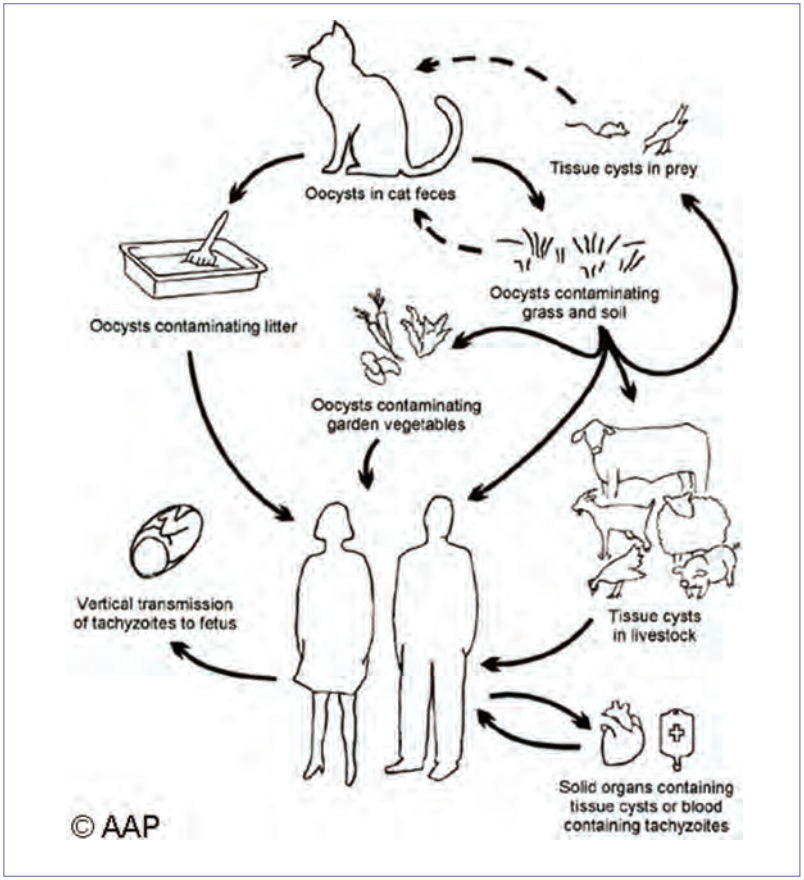


Image 148.11

Pathways for infection with *Toxoplasma gondii*. The only source for the production of *T gondii* oocysts is the feline intestinal tract. Humans usually acquire the disease by direct ingestion of oocysts from contaminated sources (eg, soil, cat litter, garden vegetables) or the ingestion of tissue cysts present in undercooked tissues from infected animals. Fetal infection occurs most commonly following acute maternal infection in pregnancy, but it also can occur following reactivation of latent infection in immunocompromised women. Pathways leading to human disease (solid arrow); pathways leading to feline infection (dashed arrow).

CHAPTER 149

Trichinellosis

(*Trichinella spiralis* and Other Species)

CLINICAL MANIFESTATIONS

The clinical spectrum of *Trichinella* infection ranges from inapparent to fulminant and fatal illness, although most infections are asymptomatic. The severity of disease is proportional to the infective dose. During the first week after ingesting infected meat, a person may experience abdominal discomfort, nausea, vomiting, and/or diarrhea as excysted larvae penetrate the intestinal mucosa. Two to 8 weeks later, as progeny larvae migrate into tissues, fever, myalgia, periorbital edema, urticarial rash, and conjunctival and subungual hemorrhages may develop. In severe infections, myocarditis, neurologic involvement, and pneumonitis can occur in 1 or 2 months. Larvae may remain viable in tissues for years; calcification of some larvae in skeletal muscle usually occurs within 6 to 24 months and may be detected using various imaging modalities.

ETIOLOGY

Infection is caused by nematodes (roundworms) of the genus *Trichinella.* Seven species have been implicated in human disease; worldwide, *Trichinella spiralis* is the most common cause of human infection.

EPIDEMIOLOGY

Infection is enzootic worldwide in carnivores and omnivores, especially scavengers. Infection occurs as a result of ingestion of raw or insufficiently cooked meat containing encysted larvae of *Trichinella* species. Commercial and home-raised pork remain a source of human infections, but meats other than pork, such as venison, horse meat, and particularly meats from wild carnivorous or omnivorous game (especially bear, boar, seal, and walrus), now are the most common sources of infection. The disease is not transmitted from person to person.

The **incubation period** usually is less than 1 month.

DIAGNOSTIC TESTS

Eosinophilia of up to 70%, in conjunction with compatible symptoms and dietary history, suggests the diagnosis. Increases in concentrations of muscle enzymes, such as creatinine phosphokinase and lactic dehydrogenase, occur. Identification of larvae in suspect meat can be the most rapid source of diagnostic information. Encapsulated larvae in a skeletal muscle biopsy specimen (particularly deltoid and gastrocnemius) can be visualized under light microscopy beginning 2 weeks after infection by examining hematoxylin-eosin stained slides or sediment from digested muscle tissue. Serologic tests are available through the Centers for Disease Control and Prevention. Serum antibody titers generally take 3 or more weeks to become positive and may remain positive for years. Testing paired acute and convalescent serum specimens usually is diagnostic.

TREATMENT

Albendazole and mebendazole both are recommended for treatment of acute trichinellosis, although anthelmintics typically do not kill larvae that have already encysted within muscles. Coadministration of corticosteroids with anthelmintics is recommended when systemic symptoms are severe. Corticosteroids can be lifesaving when the central nervous system or heart is involved.

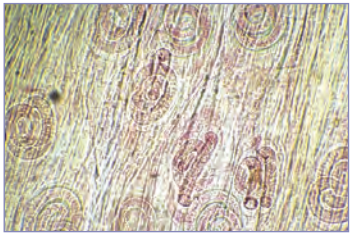


Image 149.1
Larvae of *Trichinella spiralis* in skeletal muscle biopsy. This disease is acquired by eating undercooked meat, usually pork, containing encysted *Trichinella* larvae.

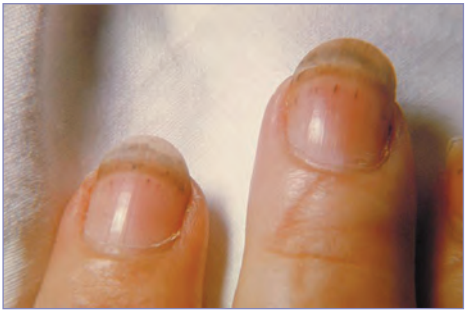


Image 149.3
Here the parasitic disease trichinosis is manifested by splinter hemorrhages under the fingernails. Trichinosis, or trichinellosis, is caused by eating raw or undercooked pork infected with the larvae of a species of worm called *Trichinella*. Initial symptoms include nausea, diarrhea, vomiting, fatigue, fever, and abdominal discomfort. Courtesy of Centers for Disease Control and Prevention/Dr Thomas F. Sellers, Emory University.

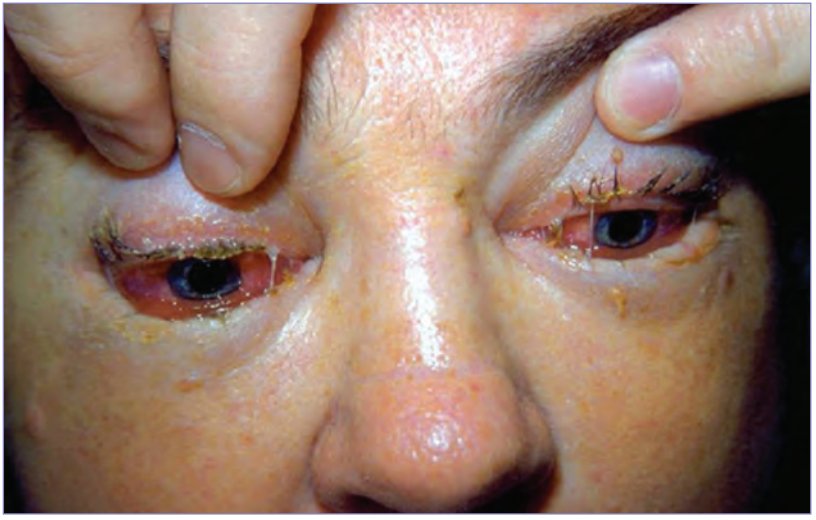


Image 149.2
This patient with trichinosis had periorbital swelling, muscle pain, diarrhea, and 28% (0.28) eosinophils. Courtesy of Centers for Disease Control and Prevention/Dr Thomas F. Sellers, Emory University.

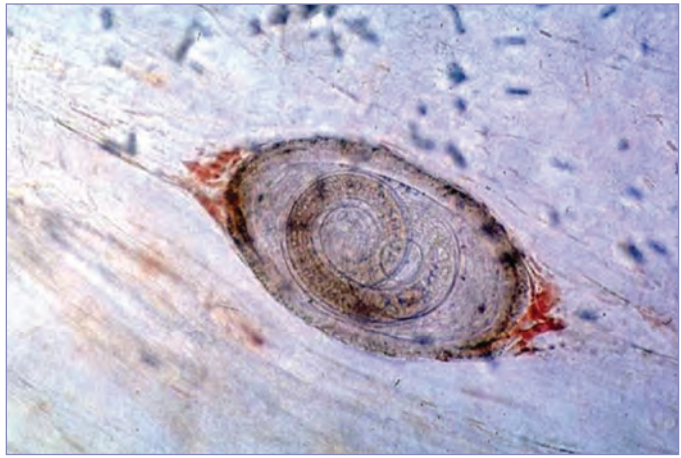


Image 149.4
Trichinella larvae in a sample of infected meat (light microscopy, magnification ×100). Courtesy of *Emerging Infectious Diseases.*

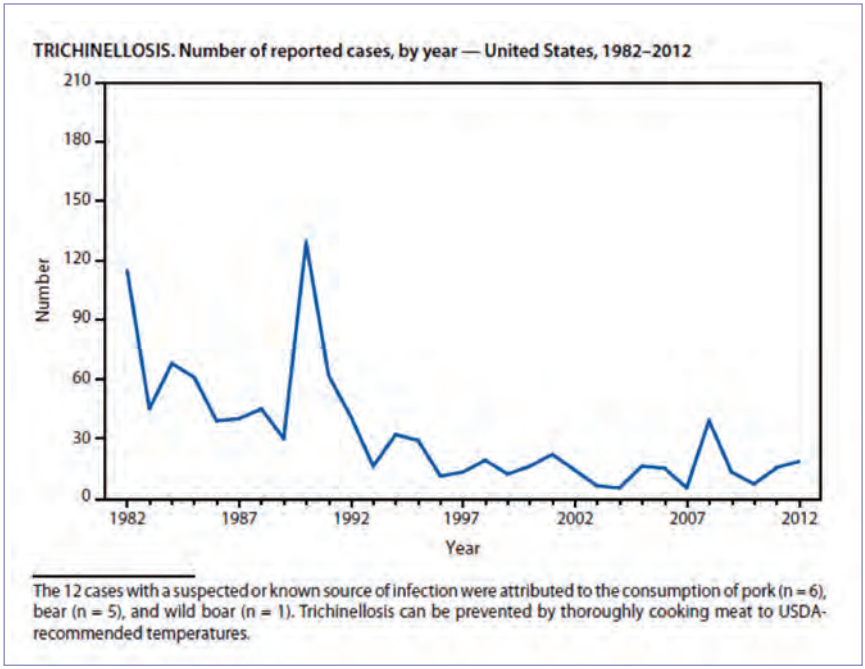


Image 149.5
Trichinellosis. Number of reported cases, by year—United States, 1982–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

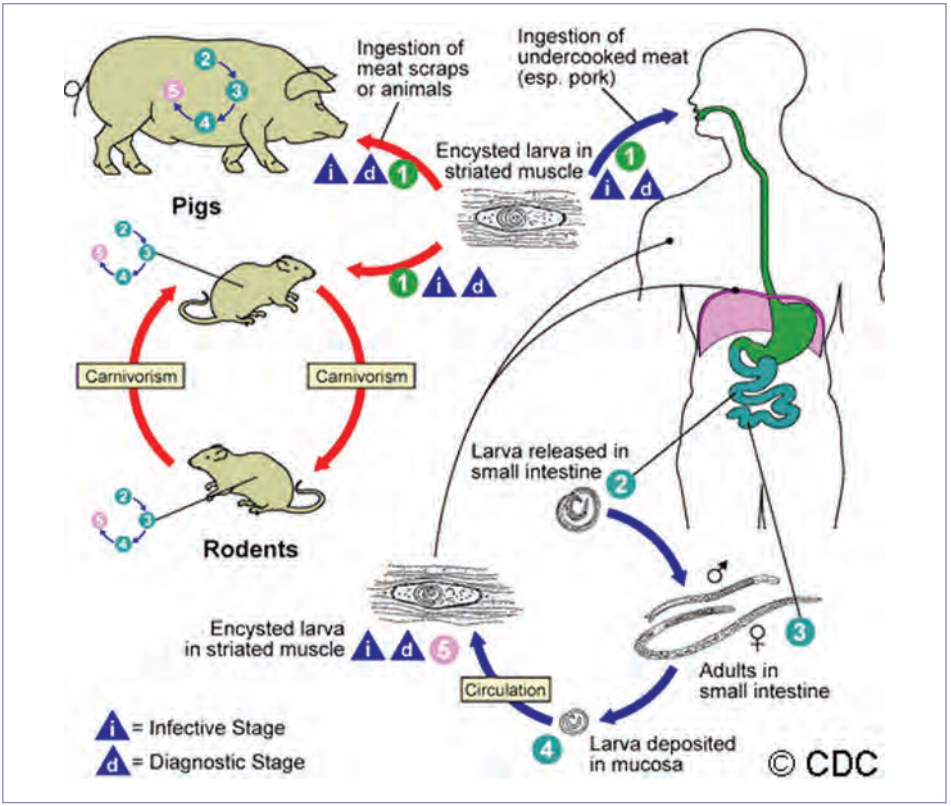


Image 149.6

Life cycle. Trichinosis is acquired by ingesting meat containing cysts (encysted larvae) (1) of *Trichinella*. After exposure to gastric acid and pepsin, the larvae are released (2) from the cysts and invade the small bowel mucosa, where they develop into adult worms (3) (female, 2.2 mm in length; males, 1.2 mm in length; life span in the small bowel, 4 weeks). After 1 week, the females release larvae (4) that migrate to the striated muscles, where they encyst (5). *Trichinella pseudospiralis,* however, do not encyst. Encystment is completed in 4 to 5 weeks and the encysted larvae may remain viable for several years. Ingestion of the encysted larvae perpetuates the cycle. Rats and rodents are primarily responsible for maintaining the endemicity of this infection. Carnivorous or omnivorous animals, such as pigs or bears, feed on infected rodents or meat from other animals. Different animal hosts are implicated in the life cycle of the different species of *Trichinella*. Humans are accidentally infected when eating improperly processed meat of these carnivorous animals (or eating food contaminated with such meat). Courtesy of Centers for Disease Control and Prevention.

CHAPTER 150

Trichomonas vaginalis Infections

(Trichomoniasis)

CLINICAL MANIFESTATIONS

Trichomonas vaginalis infection is asymptomatic in 70% to 85% of infected people. Untreated infections may persist for months to years. Clinical manifestations in symptomatic pubertal or postpubertal females may include a diffuse vaginal discharge, odor, and vulvovaginal pruritus and irritation. Dysuria and, less often, lower abdominal pain can occur. Vaginal discharge may be any color but classically is yellow-green, frothy, and malodorous. The vulva and vaginal mucosa can be erythematous and edematous. The cervix can be inflamed and sometimes is covered with numerous punctate cervical hemorrhages and swollen papillae, referred to as "strawberry" cervix. This finding occurs in less than 5% of infected females. Clinical manifestations in symptomatic men include urethritis and, rarely, epididymitis or prostatitis. Reinfection is common, and resistance to treatment is uncommon but increasing. Rectal infections are uncommon, and oral infections have not been described.

T vaginalis infections in pregnant females have been associated with premature rupture of the membranes and preterm delivery. Perinatal infection may occur in up to 5% of neonates of infected mothers. *T vaginalis* in female newborn infants may cause vaginal discharge during the first weeks of life but usually is self-limited, resolving as maternal hormones are metabolized. Respiratory infections in newborn infants may occur as well.

ETIOLOGY

T vaginalis is a flagellated protozoan approximately the size of a leukocyte. It requires adherence to host cells for survival.

EPIDEMIOLOGY

Although formal surveillance programs are not in place, several studies suggest that *T vaginalis* infection is the most common nonviral sexually transmitted infection (STI) in the United States and globally. Prevalence in a nationally representative sample of sexually experienced 14- to 19-year-old females in the United States was 2.1% in the early 2000s. It commonly coexists with other conditions, particularly with *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections and with bacterial vaginosis. Transmission results almost exclusively from sexual contact, and the presence of *T vaginalis* in a child or preadolescent beyond the perinatal period is considered highly suspicious for sexual abuse. *T vaginalis* infection can increase both the acquisition and transmission of human immunodeficiency virus (HIV).

The **incubation period** averages 1 week (range, 5 to 28 days).

DIAGNOSTIC TESTS

The use of highly sensitive and specific tests is recommended for detecting *T vaginalis*. The nucleic acid amplification test (NAAT) is the most sensitive means of diagnosing *T vaginalis* infection. The APTIMA *T vaginalis* assay (Hologic Gen-Probe, San Diego, CA), Quidel Amplivue Trich assay (Quidel, San Diego, CA), Xpert TV (Cepheid, Sunnyvale, CA), and BD Probe Tec TV Qx Amplified DNA Assay (Becton Dickinson, Franklin Lakes, NJ) are commercially available assays for testing vaginal swab, endocervical swab, and urine specimens of females. Analyst-specific *Trichomonas* reagents can be used with urine or urethral swab specimens in laboratories that have met Clinical Laboratory Improvement Amendments (CLIA) requirements and validated their *T vaginalis* NAAT performance on male specimens. Because the duration of persistence of *T vaginalis* nucleic acids in genital specimens is not established, NAAT diagnostic tests within the first few weeks after treatment should not be used routinely to assess therapeutic success or failure.

Culture of *T vaginalis* in Diamond media or other trichomoniasis-specific culture systems (eg, InPouch, BioMed Diagnostics, White City, OR) is a sensitive and specific method of diagnosis in females with a sensitivity of 75% to 96% but has lower sensitivity in males. The most common method for *T vaginalis* diagnosis in a symptomatic female typically is examination of a wet-mount preparation of vaginal discharge. Microscopy sensitivity is only 51% to

65% for *T vaginalis* diagnosis in female vaginal specimens and is less sensitive for male urethral, urine sediment, and semen specimens; test sensitivity declines even further if the microscopic evaluation is delayed.

Two other FDA-cleared tests are available for testing vaginal swab specimens that are more sensitive than microscopy. The OSOM *Trichomonas* Rapid Test (OSOM, Sekisui Diagnostics, Framingham, MA) is a CLIA-waived, antigen-detection, rapid point-of-care test that uses immunochromatographic capillary flow dipstick technology. Results are available within 10 minutes, with a sensitivity of 82% to 95%. The Affirm VPIII (Becton Dickinson, Sparks, MD) is a DNA hybridization probe test for *T vaginalis*, *Gardnerella vaginalis*, and *Candida albicans*. Results are available in 45 minutes, with a sensitivity of 63% for *T vaginalis* detection. Vaginal swab specimens can be tested as a point-of-care test or sent to a clinical laboratory.

TREATMENT

Treatment of adolescents and young adults with metronidazole in a single dose results in cure rates of approximately 84% to 98%. Treatment with tinidazole in a single dose has resulted in cure rates of approximately 92% to 100%. Both drugs are approved for this indication in adolescents and young adults, and metronidazole is approved in children. Tinidazole generally is more expensive and has fewer gastrointestinal adverse effects. Topical vaginal preparations should not be used. Sexual partners should be treated, even if asymptomatic, because reinfection can occur.

Although most recurrent *T vaginalis* infections result from reinfection, some recurrent infections might be attributed to antimicrobial resistance. Metronidazole resistance occurs in 4% to 10% and tinidazole resistance in 1% of cases. If treatment failure occurs, the same drugs for 7 days should be used. If treatment failure occurs again, higher doses for 7 days may be used. If several 1-week regimens have failed in a person who is unlikely to have nonadherence or reinfection, testing of the organism for metronidazole and tinidazole susceptibility is recommended.

Alternative regimens for *T vaginalis* treatment might be effective but have not been evaluated systematically. Metronidazole and tinidazole both are nitroimidazoles. Patients with an immunoglobulin (Ig) E mediated-type allergy to a nitroimidazole can be managed by metronidazole desensitization according to a published regimen in consultation with a specialist.

Pregnancy

T vaginalis infection in pregnant females is associated with adverse pregnancy outcomes, particularly premature rupture of membranes, preterm delivery, and delivery of an infant with low birth weight. Although metronidazole treatment produces parasitologic cure, trials have shown no significant difference in perinatal morbidity following metronidazole treatment. Symptomatic pregnant females, regardless of pregnancy stage, should be tested and consideration should be given to treatment with metronidazole. In lactating females to whom metronidazole is administered, some clinicians advise deferring breastfeeding for 12 to 24 hours following maternal treatment using tinidazole; interruption of breastfeeding is recommended during treatment and for 3 days after a single 2-g dose.

People infected with *T vaginalis* should be evaluated for other STIs, including syphilis, gonorrhea, chlamydia, HIV, human papillomavirus (HPV), and hepatitis B infections. HPV and hepatitis B vaccines should be administered if the person's immunization status for these is not completed. For newborn infants, infection with *T vaginalis* acquired maternally is self-limited, and treatment is not recommended.

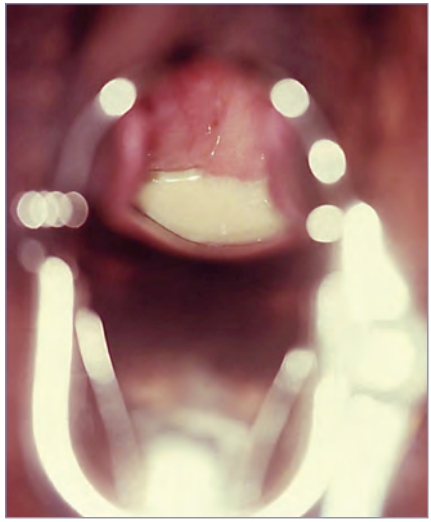


Image 150.1
This was a case of *Trichomonas* vaginitis revealing a copious purulent discharge emanating from the cervical os. *Trichomonas vaginalis*, a flagellate, is the most common pathogenic protozoan of humans in industrialized countries. This protozoan resides in the female lower genital tract and the male urethra and prostate, where it replicates by binary fission. Courtesy of Centers for Disease Control and Prevention.

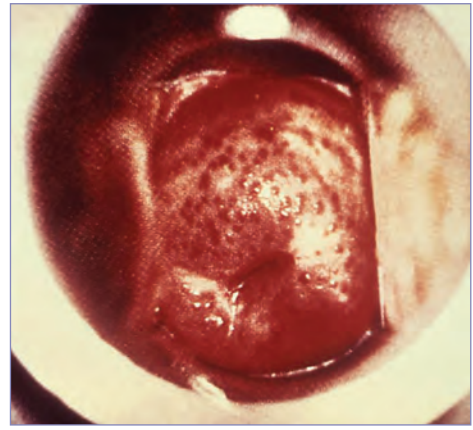


Image 150.2
This patient presented with a strawberry cervix (colpitis macularis) due to a *Trichomonas vaginalis* infection, or trichomoniasis. The term *strawberry cervix* is used to describe the appearance of the cervix due to the presence of *T vaginalis* protozoa. The cervical mucosa reveals punctate hemorrhages along with accompanying vesicles or papules. Courtesy of Centers for Disease Control and Prevention.

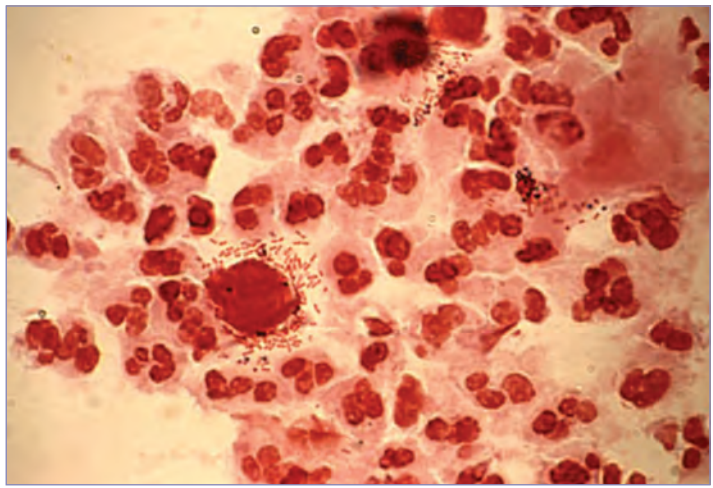


Image 150.3
This Gram-stained micrograph of a urethral discharge revealed the presence of trichomonads and gram-negative rods. *Trichomonas vaginalis*, a flagellate, is the most common pathogenic protozoan of humans in industrialized countries. This protozoan resides in the female lower genital tract and the male urethra and prostate, where it replicates by binary fission. Courtesy of Centers for Disease Control and Prevention.

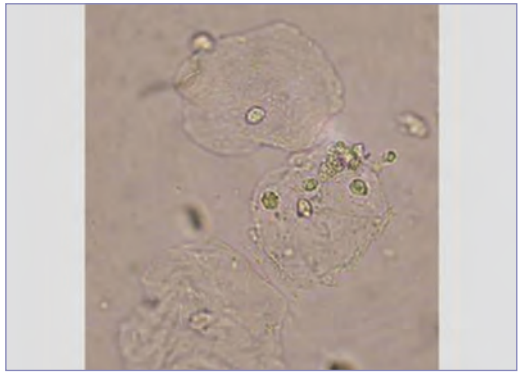


Image 150.4
An asymptomatic vaginal discharge in a premenarcheal girl who has other signs of the effects of estrogen is most likely is due to physiological leukorrhea. The discharge is caused by the desquamation of vaginal epithelial cells in response to the effect of estrogen on the vaginal mucosa. Prior to puberty, the vaginal mucosa is atrophic, the pH of vaginal secretions is 6.5 to 7.5, and the bacterial flora are mixed. Following the onset of puberty, *Lactobacillus* becomes the predominant organism in the vagina. These gram-positive bacilli metabolize sloughed epithelial cells, producing lactic acid and decreasing the pH level of the vagina to less than 4.5. Courtesy of H. Cody Meissner, MD, FAAP.

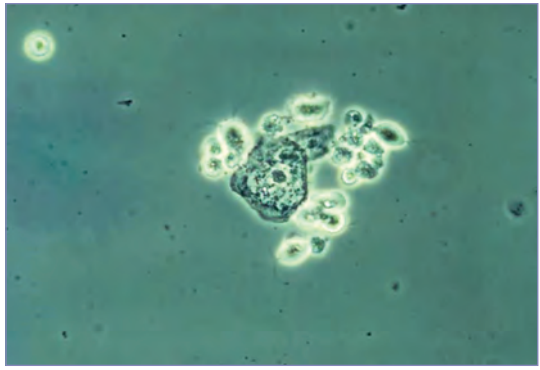


Image 150.5
This phase contrast wet mount micrograph of a vaginal discharge revealed the presence of *Trichomonas vaginalis* protozoa. *T vaginalis*, a flagellate, is the most common pathogenic protozoan of humans in industrialized countries. This protozoan resides in the female lower genital tract and the male urethra and prostate, where it replicates by binary fission. Courtesy of Centers for Disease Control and Prevention.

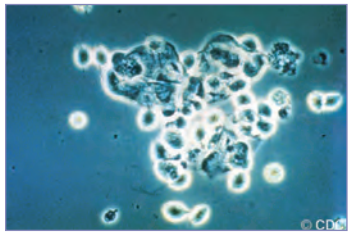


Image 150.6
Wet mount showing the presence of motile trichomonads in vaginal secretions. This indicates an infection caused by *Trichomonas vaginalis*. Courtesy of Centers for Disease Control and Prevention.

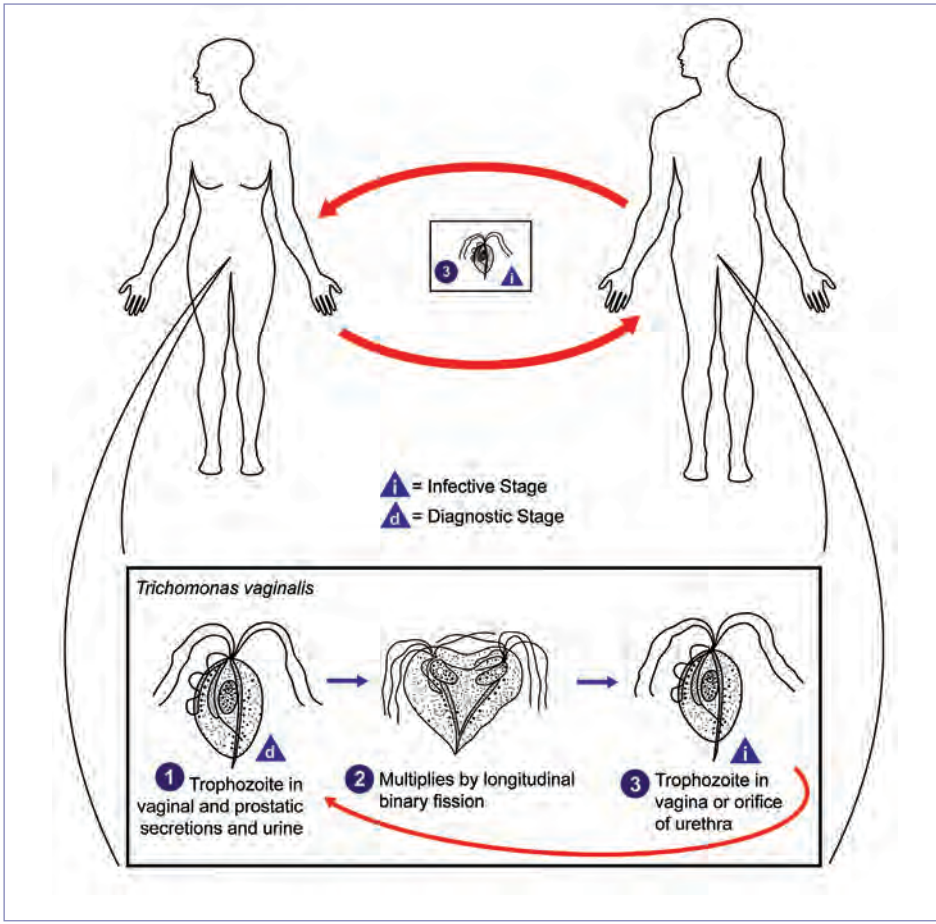


Image 150.7

Trichomonas vaginalis resides in the female lower genital tract and the male urethra and prostate (1), where it replicates by binary fission (2). The parasite does not appear to have a cyst form and does not survive well in the external environment. *T vaginalis* is transmitted among humans, its only known host, primarily by sexual intercourse (3). Courtesy of Centers for Disease Control and Prevention/Alexander J. da Silva, PhD/ Melanie Moser.

CHAPTER 151

Trichuriasis

(Whipworm Infection)

CLINICAL MANIFESTATIONS

Disease caused by the whipworm *Trichuris trichiura* generally is proportional to the intensity of the infection. Although most infected children are asymptomatic, those with heavy infestations can develop a colitis that mimics inflammatory bowel disease and can lead to anemia, physical growth restriction, and clubbing. More serious is the condition called *Trichuris* dysentery syndrome, which is characterized by severe abdominal pain, tenesmus, bloody diarrhea, and occasionally rectal prolapse.

ETIOLOGY

T trichiura, the human whipworm, is the causative agent of trichuriasis. Adult worms are 30 to 50 mm long with a large, thread-like anterior end that embeds in the mucosa of the large intestine.

EPIDEMIOLOGY

T trichiura is the second most prevalent soil-transmitted helminth in the world, occurring mainly in tropical regions with poor sanitation. It is coendemic with *Ascaris* and hookworm species. Humans are the natural reservoir. Eggs excreted in moist soil require a minimum of 10 days of incubation before they are infectious. Children become infected by accidental ingestion of infective eggs in food or on hands contaminated with soil. The disease is not directly communicable from person to person.

The time between infection and appearance of eggs in the stool (**incubation period**) is approximately 12 weeks.

DIAGNOSTIC TESTS

Eggs may be found on direct examination of stool by the use of the Kato-Katz thick smear method or the McMaster method, although diagnosis of light to moderate infections may require concentration techniques.

TREATMENT

Mebendazole, albendazole, or ivermectin administered for 3 days are recommended for the treatment of whipworm infection, although the cure rate for any single drug is low. Reexamination of stool specimens 2 to 4 weeks after therapy to document cure is recommended, and those who fail therapy should be retreated. Combination therapy with 2 anthelmintics (eg, albendazole or mebendazole with ivermectin) may result in higher cure rates and should be considered in patients who persistently test positive following single-agent treatment. A combination of albendazole and oxantel pamoate recently was noted to have the best efficacy, but oxantel pamoate is not available in the United States.

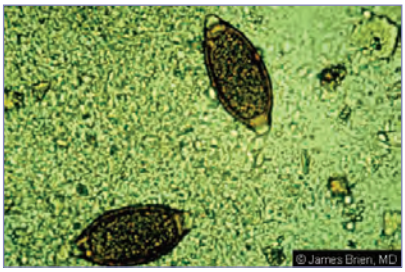


Image 151.1
Trichuris trichiura ova.

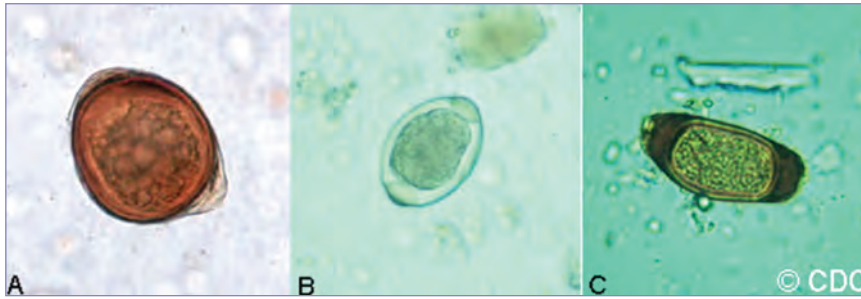


Image 151.2
Trichuris trichiura ova. A–C, Atypical *Trichuris* species eggs. Courtesy of Centers for Disease Control and Prevention.

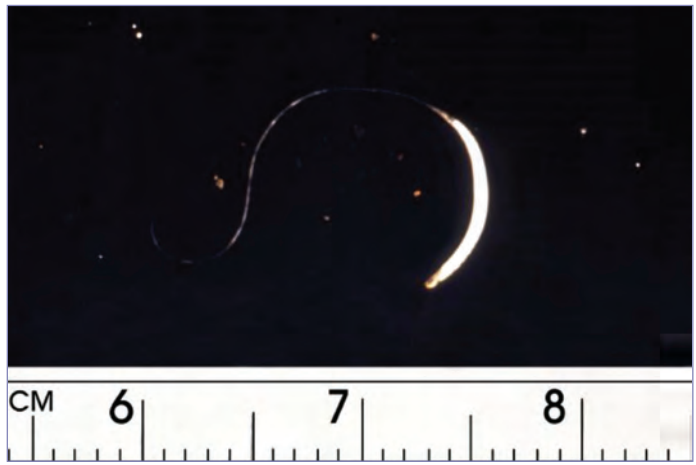


Image 151.3
This micrograph of an adult *Trichuris* female human whipworm reveals its size as approximately 4 cm. The female *Trichuris trichiura* worms begin to oviposit in the cecum and ascending colon 60 to 70 days after infection. Female worms in the cecum shed between 3,000 and 20,000 eggs per day. The life span of the adults is about 1 year. Courtesy of Centers for Disease Control and Prevention.

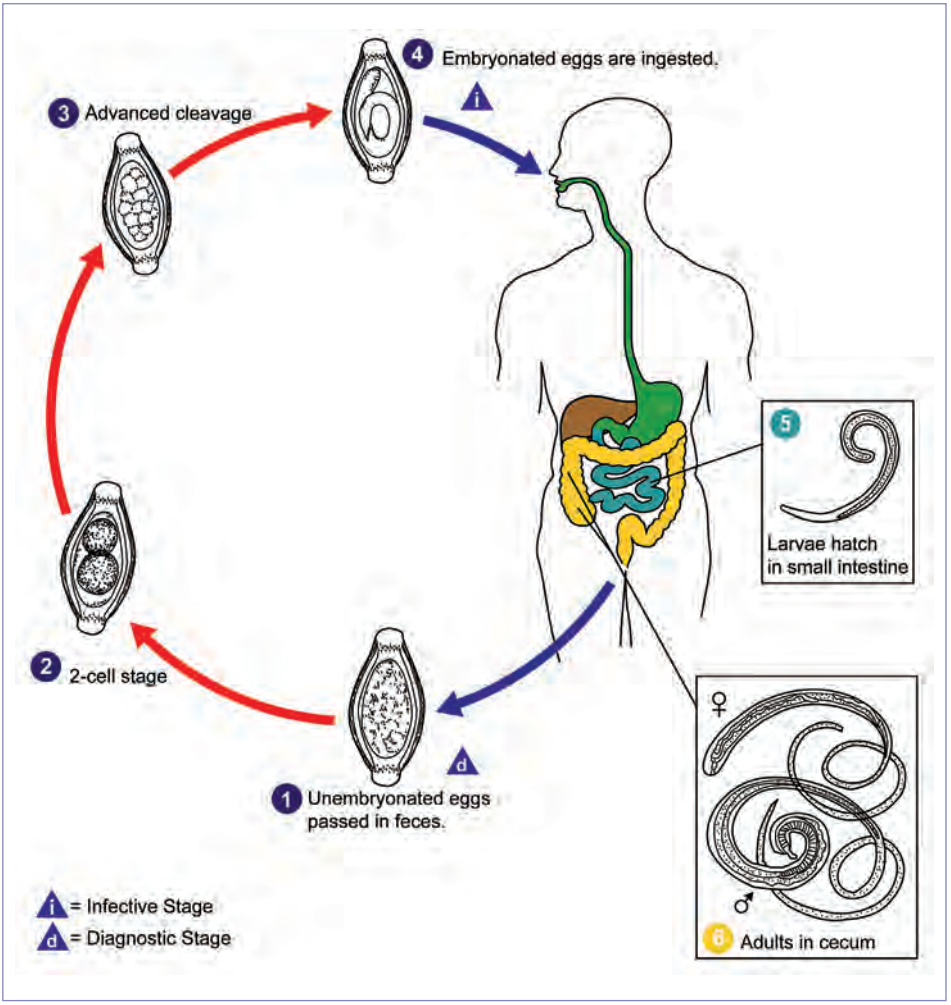


Image 151.4

Trichuris trichiura life cycle. The unembryonated eggs are passed with the stool (1). In the soil, the eggs develop into a 2-cell stage (2) and an advanced cleavage stage (3) and then they embryonate (4); eggs become infective in 15 to 30 days. After ingestion (soil-contaminated hands or food), the eggs hatch in the small intestine and release larvae (5) that mature and establish themselves as adults in the colon (6). The adult worms (approximately 4 cm in length) live in the cecum and ascending colon. The adult worms are fixed in that location, with the anterior portions threaded into the mucosa. The females begin to oviposit 60 to 70 days after infection. Female worms in the cecum shed between 3,000 and 20,000 eggs per day. The life span of the adults is about 1 year. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 152

African Trypanosomiasis

(African Sleeping Sickness)

CLINICAL MANIFESTATIONS

The clinical course of human African trypanosomiasis has 2 stages: the first is the hemolymphatic stage, in which the parasite multiplies in subcutaneous tissues, lymph, and blood. Once the parasite crosses the blood-brain barrier and infects the central nervous system (CNS), the disease enters the second stage, known as the neurologic stage. The rapidity of disease progression and clinical manifestations vary with the infecting subspecies. With *Trypanosoma brucei gambiense* infection (West African sleeping sickness), initial symptoms may be mild and include fever, muscle aches, and malaise. Pruritus, rash, weight loss, and generalized lymphadenopathy can occur. Posterior cervical lymphadenopathy, known as Winterbottom sign, may be present. CNS involvement typically develops after 1 to 2 years with development of behavioral changes, cachexia, headache, hallucinations, delusions, and daytime somnolence followed by nighttime insomnia. In contrast, *Trypanosoma brucei rhodesiense* infection (East African sleeping sickness) is an acute, generalized illness that develops days to weeks after parasite inoculation, with manifestations including high fever, lymphadenopathy, rash, muscle and joint aches, thrombocytopenia, hepatitis, anemia, myocarditis, and rarely, laboratory evidence of disseminated intravascular coagulopathy. A chancre may develop at the site of the tsetse fly bite. Clinical meningoencephalitis can develop after onset of the untreated systemic illness. Both forms of African trypanosomiasis have high fatality rates; without treatment, infected patients usually die within weeks to months after clinical onset of disease caused by *T brucei rhodesiense* and within a few years from disease caused by *T brucei gambiense*.

ETIOLOGY

Human African trypanosomiasis (sleeping sickness) occurs in sub-Saharan Africa. It is caused by *Trypanosoma brucei* subspecies, which are protozoan parasites transmitted by blood-feeding tsetse flies. The west and central African (Gambian) form progresses more slowly and is caused by *T brucei gambiense*. The east and southern African (Rhodesian) form is more acute and is caused by *T brucei rhodesiense*. Both are extracellular protozoan hemoflagellates that live in blood and tissue of the human host.

EPIDEMIOLOGY

Worldwide, 7,106 human cases of African trypanosomiasis were reported annually to the World Health Organization in 2012, with 3,796 cases reported in 2014. Whereas more than 98% of the total reported cases have been caused by *T brucei gambiense*, the occasional reported cases of African trypanosomiasis in the United States typically have been in returning travelers who became infected with *T brucei rhodesiense* while on safari in East Africa. Transmission of *T brucei* subspecies is confined to an area in Africa between the latitudes of 15° north and 20° south, corresponding precisely with the distribution of the tsetse fly vector (*Glossina* species). In West and Central Africa, humans are the main reservoir of *T brucei gambiense*, although the parasite sometimes can be found in domestic animals, such as dogs and pigs. In East Africa, wild animals, such as antelope, bush buck, and hartebeest, constitute the major reservoirs for sporadic infections with *T brucei rhodesiense*, although cattle serve as reservoir hosts in local outbreaks. In addition to the bite of the tsetse fly, *T brucei* subspecies can also be transmitted congenitally and through blood transfusions or organ transplantation, although these modes are uncommon.

The **incubation period** for *T brucei rhodesiense* infection is 3 to 21 days, and for most cases is 5 to 14 days; for *T brucei gambiense* infection, the incubation period usually is longer.

DIAGNOSTIC TESTS

Diagnosis is made by identification of trypanosomes in specimens of blood, cerebrospinal fluid (CSF), or fluid aspirated from a chancre or lymph node or by inoculation of susceptible laboratory animals (mice) with heparinized blood in the case of *T brucei rhodesiense* infection. Examination of CSF is critical to management, and all patients should undergo

lumbar puncture; concentration methods (such as the double-centrifugation technique) typically should be used. Concentration and Giemsa staining of the buffy coat layer of peripheral blood also can be helpful and is easier for *T brucei rhodesiense*, because the density of organisms in circulating blood is higher than for *T brucei gambiense. T brucei gambiense* is more likely to be found in lymph node aspirates than in blood. The most widely used criteria for CNS involvement include the identification of trypanosomes in CSF or a CSF white blood cell count of 6 or higher; elevated protein and an increase in immunoglobulin M also may suggest second-stage disease. Serologic testing for antibodies to *T brucei gambiense* is available outside the United States and typically is used only for screening purposes to help identify suspect cases; there is no comparable serologic screening test for *T brucei rhodesiense.*

TREATMENT

The choice of drug(s) used for treatment depends on the type and stage of African trypanosomiasis (**www.cdc.gov/parasites/sleepingsickness/health_professionals/index.html#tx**). When no evidence of CNS involvement is present, the drug of choice for the acute hemolymphatic stage of infection is pentamidine for *T brucei gambiense* infection and suramin for *T brucei rhodesiense* infection. For treatment of CNS infection, the drug of choice is eflornithine for *T brucei gambiense* infection and melarsoprol for *T brucei rhodesiense* infection (eflornithine is not effective for CNS treatment of *T brucei rhodesiense*). Melarsoprol encephalopathy may be reduced in severity by concomitant administration of corticosteroids. In certain cases, nifurtimox is added to eflornithine or melarsoprol. Consultation with a specialist familiar with the disease and its treatment is recommended. Because of the risk of relapse, patients who have had CNS involvement should undergo repeated CSF examinations every 6 months for 2 years.

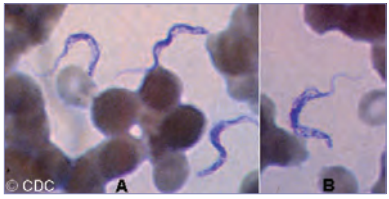


Image 152.1
A–B, Two areas from a thin blood smear (Giemsa stain) from a patient with African trypanosomiasis. Typical trypomastigote stages (the only stages found in patients) are a posterior kinetoplast, a centrally located nucleus, an undulating membrane, and an anterior flagellum. The 2 *Trypanosoma brucei* species that cause human trypanosomiasis, *T brucei gambiense* and *T brucei rhodesiense,* are indistinguishable morphologically. The trypanosomes length range is 14 to 33 µm. Courtesy of Centers for Disease Control and Prevention.

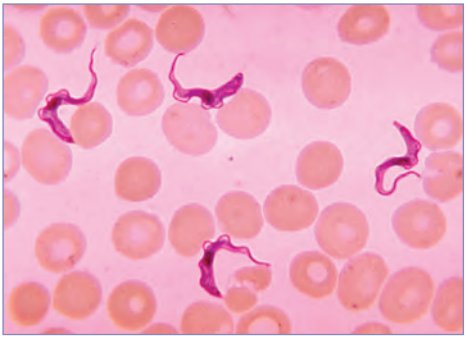


Image 152.2
Trypanosoma forms in blood smear from a patient with African trypanosomiasis (hematoxylin-eosin stain).

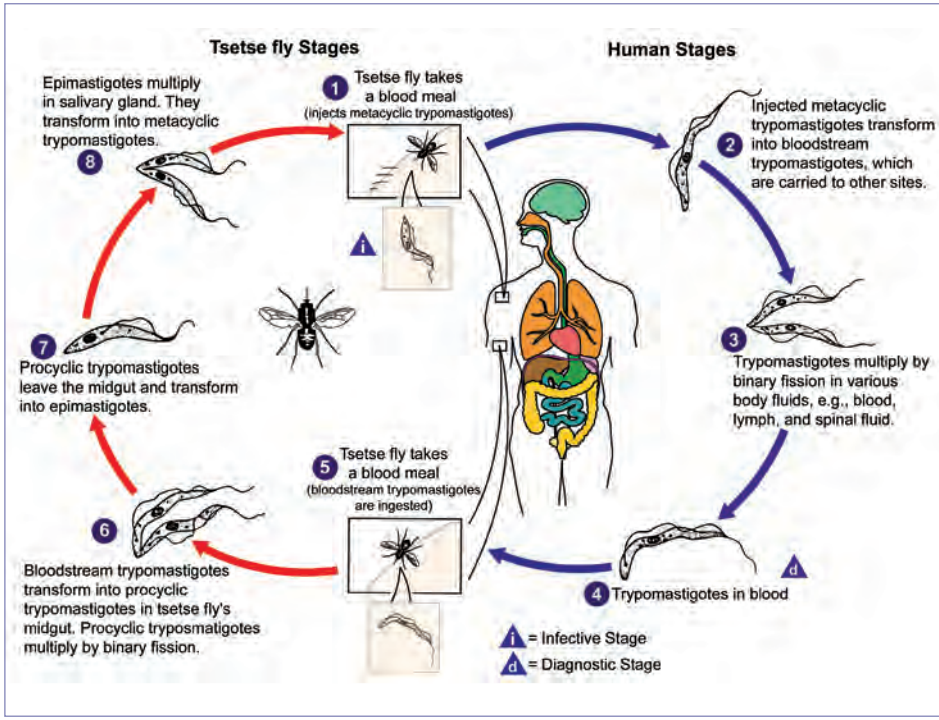


Image 152.3

Life cycle. During a blood meal on the mammalian host, an infected tsetse fly (genus *Glossina*) injects metacyclic trypomastigotes into skin tissue. The parasites enter the lymphatic system and pass into the bloodstream (1). Inside the host, they transform into bloodstream trypomastigotes (2), are carried to other sites throughout the body, reach other body fluids (eg, lymph, spinal fluid), and continue the replication by binary fission (3). The entire life cycle of African trypanosomes is represented by extracellular stages. The tsetse fly becomes infected with bloodstream trypomastigotes when taking a blood meal on an infected mammalian host (4, 5). In the fly's midgut, the parasites transform into procyclic trypomastigotes, multiply by binary fission (6), leave the midgut, and transform into epimastigotes (7). The epimastigotes reach the fly's salivary glands and continue multiplication by binary fission (8). The cycle in the fly takes approximately 3 weeks. Humans are the main reservoir for *Trypanosoma brucei gambiense,* but this species can also be found in animals. Wild game animals are the main reservoir of *Trypanosoma brucei rhodesiense.* Courtesy of Centers for Disease Control and Prevention.

CHAPTER 153

American Trypanosomiasis

(Chagas Disease)

CLINICAL MANIFESTATIONS

The acute phase of *Trypanosoma cruzi* infection lasts 2 to 3 months, followed by the chronic phase that, in the absence of successful antiparasitic treatment, is lifelong. The acute phase commonly is asymptomatic or characterized by mild, nonspecific symptoms. Young children are more likely to exhibit symptoms than are adults. Fever, edema, malaise, lymphadenopathy, and hepatosplenomegaly may develop. Meningoencephalitis and/or acute myocarditis rarely occur. Unilateral edema of the eyelids, known as the Romaña sign, may occur if the portal of entry is the conjunctiva, but it is usually not present. The edematous skin may be violaceous and associated with conjunctivitis and enlargement of the ipsilateral preauricular lymph node. In some patients, a red, indurated nodule known as a chagoma develops at the site of the original inoculation, usually on the face or arms. The symptoms of acute Chagas disease can resolve without treatment within 3 months, and patients pass into the chronic phase of the infection.

Most people with chronic *T cruzi* infection have no signs or symptoms and have the indeterminate form of chronic Chagas disease. In 20% to 30% of cases, serious progressive sequelae affecting the heart and/or gastrointestinal tract develop years to decades after the initial infection (called determinate forms of chronic Chagas disease). Chagas cardiomyopathy is characterized by conduction system abnormalities, especially right bundle branch block and ventricular arrhythmias, and may progress to dilated cardiomyopathy and congestive heart failure. Patients with Chagas cardiomyopathy may die suddenly from ventricular arrhythmias, complete heart block, or embolic phenomena; death also may occur from intractable congestive heart failure. Less commonly, patients with chronic Chagas disease may develop digestive disease with dilatation of the colon and/or esophagus with swallowing difficulties accompanied by severe weight loss.

Congenital Chagas disease occurs in 1% to 10% of infants born to infected mothers. This may be characterized by low birth weight, hepatosplenomegaly, myocarditis, and/or meningoencephalitis with seizures and tremors, but most infants with congenital *T cruzi* infection have no signs of disease. Reactivation of chronic *T cruzi* infection with parasitemia may be life threatening and may occur in immunocompromised people, including people infected with human immunodeficiency virus and those who are immunosuppressed after transplantation.

ETIOLOGY

T cruzi, a protozoan hemoflagellate, causes American trypanosomiasis (Chagas disease).

EPIDEMIOLOGY

Parasites are transmitted in feces of infected triatomine insects (sometimes called "kissing bugs," a type of reduviid; local Spanish/Portuguese names include vinchuca, chinche picuda, or barbeiro). When found indoors, they tend to be found in pet areas, under bedding, and in areas of rodent infestation. The bugs defecate during or after taking a blood meal. The bitten person is inoculated through inadvertent rubbing of insect feces containing the parasite into the site of the bite through the harmed skin or mucous membranes of the eye. The parasite also can be transmitted congenitally, during solid organ transplantation, through blood transfusion, and by ingestion of food or drink contaminated by the vector's excreta. Accidental laboratory infections can result from handling parasite cultures or blood from infected people or laboratory animals, usually through needlestick injuries. Vectorborne transmission of the disease, for the most part, is limited to the Western hemisphere, predominantly Mexico and Central and South America. In the United States, 10 species of kissing bugs are known to exist; this results in a distribution of parasites into the southern states from California to Florida and in the East northward to Maryland. Significant numbers of wild animals are infected, including opossums, armadillos, wood rats, and squirrels. Animals usually acquire the parasite by eating the bugs. Rare vectorborne cases of Chagas disease have been noted in the United States. Nevertheless, most *T cruzi*-infected

individuals in the United States are immigrants from areas of Latin America with endemic infection.

There are an estimated 300,000 individuals with *T cruzi* infection in the United States. Assuming a 1% to 5% risk of congenital transmission, based on estimates of maternal infection, approximately 63 to 315 infants are born with Chagas disease in the United States every year. Several transfusion- and transplantation-associated cases have been documented in the United States.

The disease is an important cause of morbidity and death in Latin America, where an estimated 8 million people are infected, of whom approximately 30% to 40% either have or will develop cardiomyopathy and/or gastrointestinal tract disorders.

The **incubation period** for the acute phase of disease is 1 to 2 weeks or longer. Chronic manifestations do not appear for years to decades.

DIAGNOSTIC TESTS

During the acute phase of disease, the parasite is demonstrable in blood specimens by Giemsa staining after a concentration technique or in direct wet-mount or buffy coat preparations. Molecular detection techniques (available at the Centers for Disease Control and Prevention [CDC]) also have high sensitivity in the acute phase. The chronic phase of *T cruzi* infection is characterized by low-level parasitemia; the sensitivity of polymerase chain reaction (PCR) assay is less than 50%. Diagnosis in the chronic phase relies on serologic tests to demonstrate immunoglobulin (Ig) G antibodies against *T cruzi*. Serologic tests include indirect immunofluorescent and enzyme immunosorbent assays; no single serologic test is sufficiently sensitive or specific to confirm a diagnosis of chronic *T cruzi* infection.

The diagnosis of congenital Chagas disease can be made during the first 3 months of life by identification of motile trypomastigotes by direct microscopy of fresh anticoagulated blood specimens or by PCR testing, which is a useful tool in infants and has higher sensitivity than serologic testing. If not diagnosed earlier, serologic testing should be performed after 9 months of age, once serum immunoglobulin (Ig) G measurements are expected to reflect infant response rather than maternal antibody. Some countries have congenital Chagas disease screening programs, which combine maternal screening with microscopic examination of cord blood from infants of seropositive mothers.

TREATMENT

The only drugs with proven efficacy are benznidazole and nifurtimox. Benznidazole is US Food and Drug Administration-approved for use in children 2 to 12 years of age for the treatment of Chagas disease. Nifurtimox is not approved but can be obtained from the CDC for treatment of patients.

Antitrypanosomal treatment is recommended for all cases of acute and congenital Chagas disease, reactivated infection attributable to immunosuppression, and chronic *T cruzi* infection in children younger than 18 years. Treatment of chronic *T cruzi* infection in adults without advanced cardiomyopathy generally is recommended.

Trypanocidal therapy with benznidazole in patients with established Chagas cardiomyopathy significantly reduces serum parasite detection but does not significantly reduce cardiac clinical deterioration or death through 5 years of follow-up and is, therefore, not recommended. Both drugs have significant adverse effect profiles. The recommended treatment courses are at least 60 days.

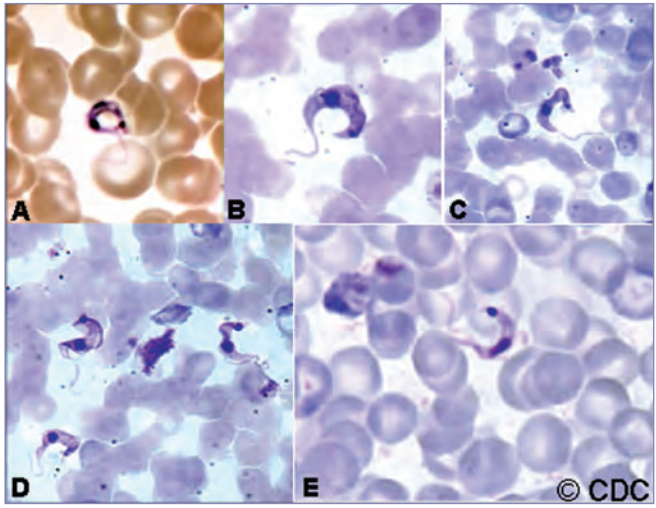


Image 153.1
A–E, *Trypanosoma cruzi* in blood smears (Giemsa stain). Courtesy of Centers for Disease Control and Prevention.

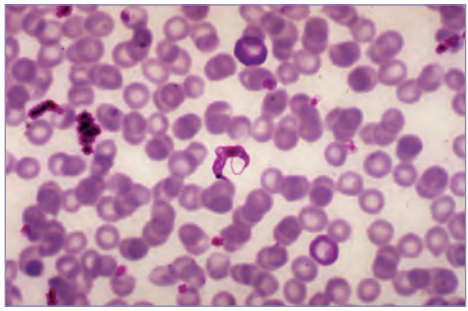


Image 153.2
This is a photomicrograph of *Trypanosoma cruzi* in a blood smear using Giemsa staining technique. This protozoan parasite, *T cruzi*, is the causative agent for Chagas disease, also known as American trypanosomiasis. It is estimated that 16 to 18 million people are infected with Chagas disease and, of those infected, 50,000 will die each year. Courtesy of Centers for Disease Control and Prevention.

Image 153.3
Adult female "kissing bug" of the species *Triatoma rubida*, the most abundant triatomine species in southern Arizona (scale bar = 1 cm). Chagas disease is endemic throughout Mexico and Central and South America, with 7.7 million persons infected, 108.6 million persons considered at risk, 33.3 million symptomatic cases, an annual incidence of 42,500 cases (through vectorial transmission), and 21,000 deaths every year. This disease is caused by the protozoan parasite *Trypanosoma cruzi*, which is transmitted to humans by bloodsucking insects of the family *Reduviidae* (*Triatominae*). Although mainly a vectorborne disease, Chagas disease also can be acquired by humans through blood transfusions and organ transplantation, congenitally (from a pregnant woman to her baby), and through oral contamination (eg, foodborne).

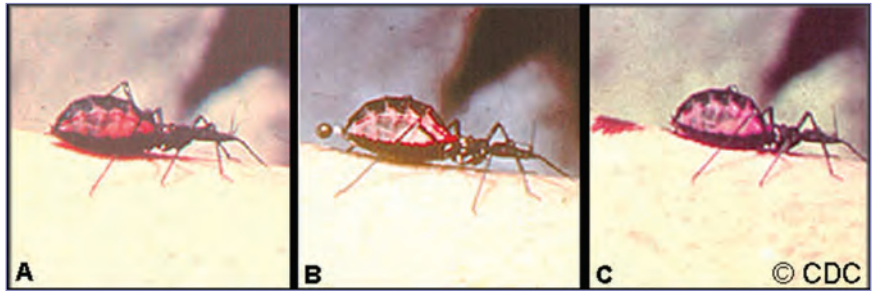


Image 153.4
A–C, Triatomine bug, *Trypanosoma cruzi* vector, defecating on the wound after taking a blood meal. Courtesy of the Centers for Disease Control and Prevention.

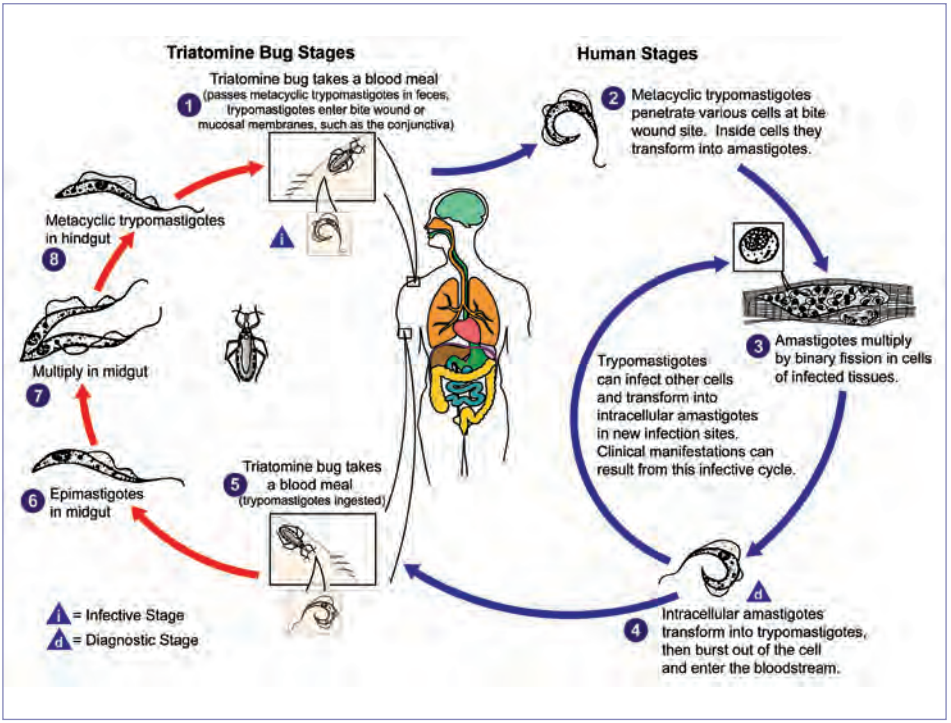


Image 153.5

Life cycle. An infected triatomine insect vector (or "kissing bug") takes a blood meal and releases trypomastigotes in its feces near the site of the bite wound. Trypomastigotes enter the host through the wound or through intact mucosal membranes, such as the conjunctiva (1). Common triatomine vector species for trypanosomiasis belong to the genera *Triatoma*, *Rhodnius*, and *Panstrongylus*. Inside the host, the trypomastigotes invade cells, where they differentiate into intracellular amastigotes (2). The amastigotes multiply by binary fission (3), differentiate into trypomastigotes, and then are released into the circulation as bloodstream trypomastigotes (4). Trypomastigotes infect cells from a variety of tissues and transform into intracellular amastigotes in new infection sites. Clinical manifestations can result from this infective cycle. The bloodstream trypomastigotes do not replicate (different from African trypanosomes). Replication resumes only when the parasites enter human or animal blood that contains circulating parasites (5). The ingested trypomastigotes transform into epimastigotes in the vector's midgut (6). The parasites multiply and differentiate in the midgut (7) and differentiate into infective metacyclic trypomastigotes in the hindgut (8). *Trypanosoma cruzi* can also be transmitted through blood transfusions, organ transplantation, transplacentally, and in laboratory accidents. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 154

Tuberculosis

CLINICAL MANIFESTATIONS

Tuberculosis disease is caused by infection with organisms of the *Mycobacterium tuberculosis* complex. Most infections caused by *M tuberculosis* complex in children and adolescents are asymptomatic. When pulmonary tuberculosis occurs, clinical manifestations most often appear 1 to 6 months after infection and include fever, weight loss or poor weight gain, growth delay, cough, night sweats, and chills. Chest radiographic findings rarely are specific for tuberculosis and include lymphadenopathy of the hilar, subcarinal, paratracheal, or mediastinal nodes; atelectasis or infiltrate of a segment or lobe; pleural effusion that can conceal small interstitial lesions; interstitial cavities; or miliary-pattern infiltrates. In selected instances, computed tomography or magnetic resonance imaging of the chest can clarify indistinct radiographic findings, but these methods are not necessary for routine diagnosis. Although cavitation is common in reactivation "adult" tuberculosis, cavitation is uncommon in childhood tuberculosis. Necrosis and cavitation can result from a progressive primary focus in very young or immunocompromised patients and in the setting of lymphobronchial disease. Extrapulmonary manifestations include meningitis and granulomatous inflammation of the lymph nodes, bones, joints, skin, and middle ear and mastoid. Gastrointestinal tract tuberculosis can mimic inflammatory bowel disease. Renal tuberculosis and progression to disease from latent *M tuberculosis* infection ("adult-type pulmonary tuberculosis") are unusual in younger children but can occur in adolescents. In addition, chronic abdominal pain with peritonitis and intermittent partial intestinal obstruction can be present in disease caused by *Mycobacterium bovis.* Congenital tuberculosis can mimic neonatal sepsis, or the infant may come to medical attention in the first 90 days of life with bronchopneumonia and hepatosplenomegaly. Clinical findings in patients with drug-resistant tuberculosis disease are indistinguishable from manifestations in patients with drug-susceptible disease.

ETIOLOGY

The causative agent is *M tuberculosis* complex, a group of closely related acid-fast bacilli, which routinely includes the human pathogens *M tuberculosis*, *M bovis*, *Mycobacterium africanum*, and a few additional species infrequently associated with human infection. *M africanum* is rare in the United States, so clinical laboratories do not distinguish it routinely, and treatment recommendations are the same as for *M tuberculosis. M bovis* can be distinguished from *M tuberculosis* in reference laboratories, and although the spectrum of illness caused by *M bovis* is similar to that of *M tuberculosis*, the epidemiology, treatment, and prevention are different.

Definitions

- **Positive tuberculin skin test (TST).** A positive TST result (Table 154.1) indicates possible infection with *M tuberculosis* complex. Tuberculin reactivity appears 2 to 10 weeks after initial infection; the median interval is 3 to 4 weeks. Bacille Calmette-Guérin (BCG) immunization can produce a positive TST result.

- **Positive interferon-gamma release assay (IGRA).** A positive IGRA result indicates probable infection with *M tuberculosis* complex. IGRAs measure ex vivo interferon-gamma production from T lymphocytes in response to stimulation with antigens specific to *M tuberculosis* complex, including *M tuberculosis* and *M bovis.*

- **Exposed person** is a person who has had recent (eg, within 3 months) contact with another person with suspected or confirmed contagious tuberculosis disease (ie, pulmonary, laryngeal, tracheal, or endobronchial disease) and who has a negative TST or IGRA result, normal physical examination findings, and chest radiographic findings that are normal or not compatible with tuberculosis. Some exposed people are or become infected (and subsequently develop a positive TST or IGRA result), and others do not become infected after exposure; the 2 groups cannot be distinguished initially.

Table 154.1
Definitions of Positive Tuberculin Skin Test (TST) Results in Infants, Children, and Adolescents[a]

Induration 5 mm or greater

Children in close contact with known or suspected contagious people with tuberculosis disease

Children suspected to have tuberculosis disease:

- Findings on chest radiograph consistent with active or previous tuberculosis disease
- Clinical evidence of tuberculosis disease[b]

Children receiving immunosuppressive therapy[c] or with immunosuppressive conditions, including HIV infection

Induration 10 mm or greater

Children at increased risk of disseminated tuberculosis disease:

- Children younger than 4 y
- Children with other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition

Children with likelihood of increased exposure to tuberculosis disease:

- Children born in high-prevalence regions of the world
- Children who travel to high-prevalence regions of the world
- Children frequently exposed to adults who are HIV infected, homeless, or incarcerated; users of illicit drugs; or residents of nursing homes

Induration 15 mm or greater

Children 4 y or older without any risk factors

[a] These definitions apply regardless of previous bacille Calmette-Guérin (BCG) immunization; erythema alone at TST site does not indicate a positive test result. Tests should be read at 48 to 72 hours after placement.
[b] Evidence by physical examination or laboratory assessment that would include tuberculosis in the working differential diagnosis (eg, meningitis).
[c] Including immunosuppressive doses of corticosteroids or tumor necrosis factor-alpha antagonists or blockers.

- **Source case** is the person who has transmitted infection with *M tuberculosis* complex to another person who subsequently develops infection not yet clinically apparent (especially a young child) or develops established latent *M tuberculosis* infection (LTBI) or tuberculosis disease.
- **LTBI** is *M tuberculosis* complex infection in a person who has a positive TST or IGRA result, no physical findings of disease, and chest radiograph findings that are normal or reveal evidence of healed infection (eg, calcification in the lung, the hilar lymph nodes, or both). Hilar adenopathy is evidence of tuberculous disease, not LTBI.
- **Tuberculosis disease** is an illness in a person with infection in whom symptoms, signs, or radiographic manifestations caused by *M tuberculosis* complex are apparent; disease can be pulmonary, extrapulmonary, or both.
- **Directly observed therapy (DOT)** is an intervention by which medications are administered directly to the patient by a health care professional or trained third party (not a relative or friend) who observes and documents that the patient ingests each dose of medication and assesses for possible adverse drug effects.
- **Multidrug-resistant tuberculosis** is an infection or disease caused by a strain of *M tuberculosis* complex that is resistant to at least isoniazid and rifampin.
- **Extensively drug-resistant tuberculosis** is an infection or disease caused by a strain of *M tuberculosis* complex that is resistant to isoniazid and rifampin, at least 1 fluoroquinolone, and at least 1 of the following parenteral drugs: amikacin, kanamycin, or capreomycin.

- **Bacille Calmette-Guérin (BCG)** is a live attenuated vaccine strain of *M bovis*. BCG vaccine rarely is administered to children in the United States but is one of the most widely used vaccines in the world. An isolate of BCG can be distinguished from wild-type *M bovis* only in a reference laboratory.

EPIDEMIOLOGY

Case rates of tuberculosis in all ages are higher in urban, low-income areas and in nonwhite racial and ethnic groups; more than 80% of reported cases in the United States occur in Hispanic and nonwhite people. In recent years, more than 65% of all US cases have been in people born outside the United States. Almost 80% of childhood TB disease is associated with some form of foreign contact of the child, parent, or a household member. Specific groups with greater LTBI and disease rates include immigrants, international adoptees, refugees from or travelers to high-prevalence regions (eg, Asia, Africa, Latin America, and countries of the former Soviet Union), homeless people, people who use alcohol excessively or illicit drugs, and residents of certain correctional facilities and other congregate settings. Secondhand smoke exposure increases the risk of TB disease in infected children.

Infants and postpubertal adolescents are at increased risk of progression of LTBI to tuberculosis disease. Other predictive factors for development of disease include recent infection (within the past 2 years); immunodeficiency, especially from HIV infection; use of immunosuppressive drugs, such as prolonged or high-dose corticosteroid therapy or chemotherapy; intravenous drug use; and certain diseases or medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, and malnutrition. Tuberculosis disease has occurred in adolescents and adults being treated with tumor necrosis factor-alpha (TNF-alpha) antagonists or blocking agents, such as infliximab. A positive TST or IGRA result should be accepted as indicative of infection in individuals receiving or soon to receive these medications, and the patient should be evaluated and treated accordingly.

A diagnosis of LTBI or tuberculosis disease in a young child is a public health sentinel event often representing recent transmission. Transmission of *M tuberculosis* complex is airborne, with inhalation of droplet nuclei usually produced by an adult or adolescent with contagious pulmonary, endobronchial, or laryngeal tuberculosis disease. Although contagiousness usually lasts only a few days to weeks after initiation of effective drug therapy, it can last longer, especially when the adult patient has a positive acid-fast sputum smear, significant productive cough, pulmonary cavities, does not adhere to medical therapy, or is infected with a drug-resistant strain. If the sputum smear becomes negative for acid-fast bacilli (AFB) on 3 separate specimens at least 8 hours apart after treatment is started and the patient has improved clinically with resolution of cough, the treated person can be considered at low risk of transmitting *M tuberculosis*. Children younger than 10 years with only adenopathy in the chest or small pulmonary lesions (paucibacillary disease) and nonproductive cough rarely are contagious. Unusual cases of adult-form pulmonary disease in young children, particularly with lung cavities and positive sputum-smear microscopy for AFB, and cases of congenital tuberculosis can be contagious.

M bovis is transmitted most often by unpasteurized dairy products, but airborne human-to-human transmission can occur.

The **incubation period** from infection to development of a positive TST or IGRA result is 2 to 10 weeks. Many years can elapse between initial *M tuberculosis* infection and subsequent disease.

DIAGNOSTIC TESTS

Testing for *M tuberculosis* Infection

The Tuberculin Skin Test (TST)

The TST is an indirect method for detecting *M tuberculosis* infection. It is one of 2 methods for diagnosing LTBI, the other method being IGRA. Both methods rely on specific cellular sensitization after infection. Conditions that decrease lymphocyte numbers or function can reduce the sensitivity of these tests. The routine (ie, Mantoux) technique of administering the skin test consists of 5 tuberculin units of purified protein derivative (PPD; 0.1 mL)

injected intradermally using a 27-gauge needle and a 1.0-mL syringe into the volar aspect of the forearm. Creation of a palpable wheal 6 to 10 mm in diameter is crucial to accurate testing.

Administration of TSTs and interpretation of results should be performed by trained and experienced health care personnel, because administration and interpretation by unskilled people and family members are unreliable. The standardized time for assessing the TST result is 48 to 72 hours after administration. The diameter of **induration,** in millimeters, is measured transversely to the long axis of the forearm and should be recorded as the result. Positive TST results, as defined in Table 154.1, can persist for several weeks. Lack of reaction to a TST does not exclude LTBI or tuberculosis disease. Approximately 10% to 40% of immunocompetent children with culture-documented tuberculosis disease do not react initially to a TST. Host factors, such as young age, poor nutrition, immunosuppression, viral infections (especially measles, varicella, and influenza), recent *M tuberculosis* infection, and disseminated tuberculosis disease, can decrease TST reactivity.

Classification of TST results is based on epidemiologic and clinical factors. Interpretation of the size of induration (mm) as a positive result varies with the person's risk of LTBI and likelihood of progression to tuberculosis disease. Current guidelines from the Centers for Disease Control and Prevention (CDC) and the American Academy of Pediatrics (AAP) recommend interpretation of TST findings on the basis of an individual's risk stratification. Prompt clinical and radiographic evaluation of all children and adolescents with a positive TST result is recommended.

Generally, interpretation of TST results in BCG recipients who are known contacts of a person with tuberculosis disease or who are at high risk of tuberculosis disease is the same as for people who have not received BCG vaccine. After BCG immunization, distinguishing between a positive TST result caused by *M tuberculosis* complex infection and that caused by BCG is difficult. Reactivity of the TST after receipt of BCG vaccine does not occur in some patients. The size of the TST reaction (ie, mm of induration) attributable to BCG immunization depends on many factors, including age at BCG immunization, quality and strain of BCG vaccine used, number of doses of BCG vaccine received, nutritional and immunologic status of the vaccine recipient, frequency of TST administration, and time lapse between immunization and TST. Evidence that increases the probability that a positive TST result is attributable to LTBI includes known contact with a person with contagious tuberculosis, a family history of tuberculosis disease, more than 5 years since neonatal BCG immunization, and a TST reaction 15 mm or greater.

Blood-Based Testing With Interferon-Gamma Release Assays (IGRAs)

QuantiFERON-TB Gold In-Tube (QIAGEN, Germantown, MD) and T-SPOT.*TB* (Oxford Immunotec Inc, Marlborough, MA) are blood tests that measure ex vivo interferon-gamma production from T lymphocytes in response to stimulation with antigens specific to *M tuberculosis* complex, which includes *M tuberculosis* and *M bovis.* However, the IGRA antigens used are not found in BCG. As with TSTs, IGRAs cannot distinguish between latent infection and disease, and a negative result from these tests cannot exclude the possibility of tuberculosis disease in a patient with suggestive clinical findings (Table 154.2). The sensitivity of IGRA tests is similar to that of TSTs for detecting infection in adults and children who have untreated culture-confirmed tuberculosis. In many clinical settings, the specificity of IGRAs is higher than that for the TST, because the antigens used are not found in BCG or most pathogenic nontuberculous mycobacteria (eg, are not found in *M avium* complex, but are found in *M kansasii*, *M szulgai*, and *M marinum*). IGRAs consistently perform well in children 2 years and older, and some data support their use for even younger children. The negative predictive value of IGRAs is not clear, but in general, if the IGRA result is negative and the TST result is positive in an asymptomatic, unexposed child, the diagnosis of LTBI is unlikely, especially if the child has received a BCG vaccine. A negative result for either a TST or an IGRA should be considered as especially unreliable in infants younger than 3 months.

Table 154.2
Tuberculin Skin Test (TST) and IGRA Recommendations for Infants, Children, and Adolescents[a]

Children for whom immediate TST or IGRA is indicated[b]:
- Contacts of people with confirmed or suspected contagious tuberculosis (contact investigation)
- Children with radiographic or clinical findings suggesting tuberculosis disease
- Children immigrating from countries with endemic infection (eg, Asia, Middle East, Africa, Latin America, countries of the former Soviet Union), including international adoptees
- Children with history of significant travel to countries with endemic infection who have substantial contact with the resident population[c]

Children who should have annual TST or IGRA:
- Children with HIV infection

Children at increased risk of progression of LTBI to tuberculosis disease: Children with other medical conditions, including diabetes mellitus, chronic renal failure, malnutrition, congenital or acquired immunodeficiencies, and children receiving tumor necrosis factor (TNF) antagonists, deserve special consideration. Initial histories of potential exposure to tuberculosis should be included for all these patients. If these histories or local epidemiologic factors suggest a possibility of exposure, immediate and periodic TST or IGRA should be considered. **A TST or IGRA should be performed before initiation of immunosuppressive therapy, including prolonged systemic corticosteroid administration, organ transplantation, use of TNF-alpha antagonists or blockers, or other immunosuppressive therapy in any child requiring these treatments.**

IGRA indicates interferon-gamma release assay; HIV, human immunodeficiency virus; LTBI, latent *M tuberculosis* infection.
[a]Bacille Calmette-Guérin immunization is not a contraindication to a TST.
[b]Beginning as early as 3 months of age for TST and 2 years of age for IGRAs, for LTBI and disease.
[c]If the child is well and has no history of exposure, the TST or IGRA should be delayed for up to 10 weeks after return.

TST Versus IGRA

For children younger than 2 years, TST is the preferred method for detection of *M tuberculosis* infection. For children 2 years and older, either TST or IGRA can be used, but in people previously vaccinated with BCG IGRA is preferred to avoid a false-positive TST result. If a BCG-vaccinated child who is 2 years and older has a positive TST, IGRA can be performed to help determine whether it is attributable to LTBI or to the previous BCG vaccine. Low-grade, false-positive IGRA results occur in some individuals. However,

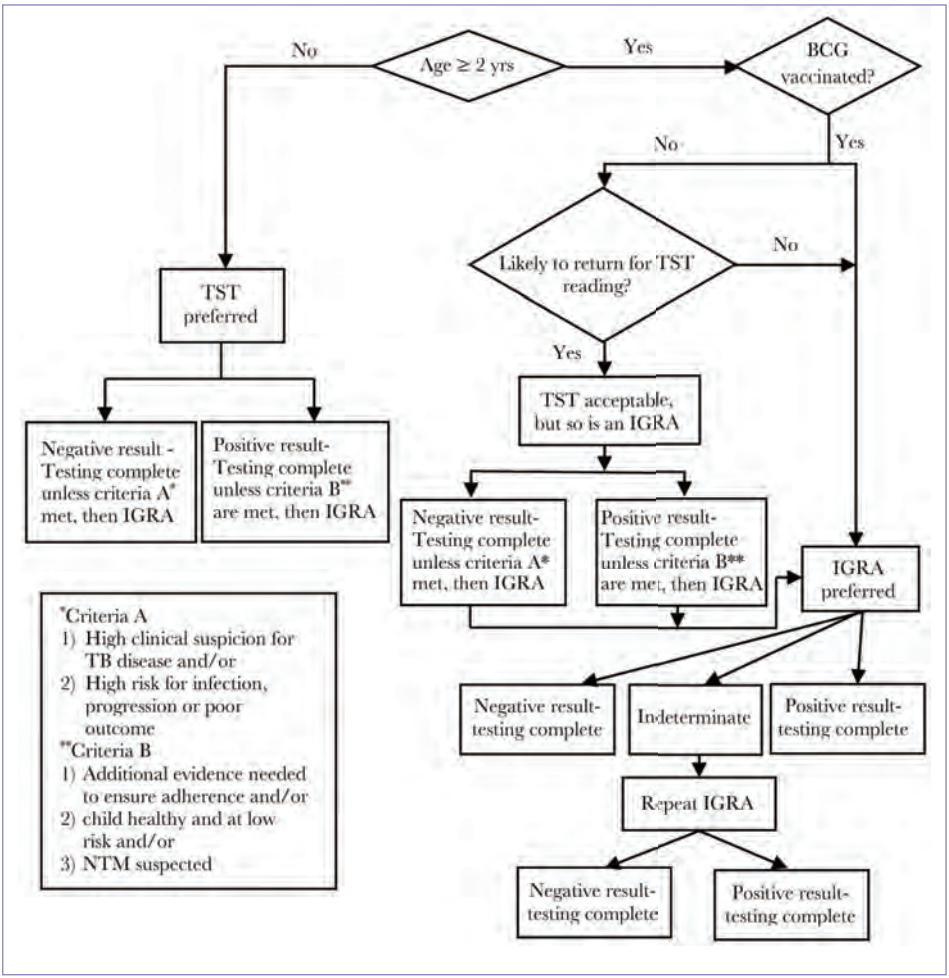
- Children with a positive IGRA should be considered infected with *M tuberculosis* complex. However, a negative IGRA result cannot absolutely exclude infection.
- Indeterminate or invalid IGRA results have several possible causes that could be related to the patient, the assay, or the assay's performance. These results do not exclude *M tuberculosis* infection and may necessitate repeat testing, possibly with a different test.

Specific recommendations for TST and IGRA use are provided in Figure 154.1.

Use of Tests for *M tuberculosis* Infection

The most reliable strategies for identifying LTBI and preventing tuberculosis disease in children are based on thorough and expedient contact investigations. Contact investigations are public health interventions that should be coordinated through the local public health department. Universal testing with TST or IGRA, including programs based at schools, child care centers, and camps that include populations at low risk, is discouraged because it results in either a low yield of positive results or a large proportion of false-positive results. However, using a questionnaire to determine risk factors for LTBI can be effective in health

Figure 154.1
Guidance on strategy for use of TST and IGRA for diagnosis of LTBI by age and BCG immunization status



care settings. Simple questionnaires can identify children with risk factors for LTBI (Table 154.3) who then should have a TST or IGRA performed. Risk assessment for tuberculosis should be performed at the first encounter of a child with a health care provider, and then annually if possible. Household investigation of children for tuberculosis is indicated whenever a TST or IGRA result of a household member converts from a negative to positive result (indicating recent infection).

HIV Infection

Children with HIV infection are considered at high risk for tuberculosis and should be tested annually beginning at 3 through 12 months of age if perinatally infected or at the time of HIV diagnosis in older children or adolescents. Conversely, children who have tuberculosis disease should be tested for HIV infection. The clinical manifestations and radiographic appearance of tuberculosis disease in children with HIV infection tend to be similar to those in immunocompetent children, but manifestations in these children can be more severe and unusual and more often include extrapulmonary involvement. In HIV-infected patients, a TST induration of ≥5 mm is considered a positive result (see Table 154.1); however, a false-negative TST or IGRA result attributable to HIV-related immunosuppression also can

Table 154.3
Validated Questions for Determining Risk of LTBI in Children in the United States

• Has a family member or contact had tuberculosis disease? • Has a family member had a positive tuberculin skin test result? • Was your child born in a high-risk country (countries other than the United States, Canada, Australia, New Zealand, or Western and Northern European countries)? • Has your child traveled to a high-risk country? How much contact did your child have with the resident population?

LTBI indicates latent *M tuberculosis* infection.

occur. Specimens for culture and, if available, PCR should be obtained from all HIV-infected children with suspected tuberculosis.

Organ Transplant Patients

The risk of tuberculosis in organ transplant patients is several-fold greater than in the general population. A careful history of previous exposure to tuberculosis should be taken from all transplant candidates, including details about previous TST results and exposure to individuals with active TB. All transplant candidates should undergo evaluation by TST or IGRA for LTBI before the initiation of immunosuppressive therapy. A positive result of either test should be taken as evidence of *M tuberculosis* infection.

Patients Receiving Immunosuppressive Therapies Including Biologic Response Modifiers

Patients should be questioned for risk factors for *M tuberculosis* complex infection. In the presence or absence of tuberculosis risk factors, a TST or IGRA should be performed before the initiation of therapy with high-dose systemic corticosteroids, antimetabolite agents, and tumor necrosis factor antagonists or blockers (eg, infliximab and etanercept).

Other Considerations

Testing for tuberculosis at any age is not required before administration of live-virus vaccines. Measles vaccine temporarily can suppress tuberculin reactivity for at least 4 to 6 weeks, but the effect of varicella, yellow fever, and live attenuated influenza vaccines on TST reactivity and IGRA results is not known. If indicated, a TST can be applied or blood drawn for an IGRA at the same visit during which these vaccines are administered. The effects of live-virus vaccination on IGRA characteristics have not been determined; the same precautions as for TST should be followed. There is no evidence that inactivated vaccines, polysaccharide vaccines, or recombinant or subunit vaccines or toxoids interfere with clinical interpretation of TST or IGRAs.

Sensitivity to PPD tuberculin antigen persists for years in most instances, even after effective treatment. The durability of positive IGRA results has not been determined. Repeat testing with either TST or IGRA has no known clinical utility for assessing the effectiveness of treatment or for diagnosing newly acquired infection in patients who previously were infected with *M tuberculosis*.

Assessing for *M tuberculosis* Disease

Although both IGRA and TST testing provide evidence for infection with *M tuberculosis*, they cannot distinguish active infection from LTBI. Patients with positive IGRA or TST results should be evaluated for tuberculous disease before initiating any therapeutic intervention. This assessment should include: (1) query for symptoms of active tuberculosis disease, (2) physical examination for signs of active disease, and (3) chest radiograph. If radiographic signs of active tuberculosis (eg, airspace opacities, pleural effusions, cavities, or changes on serial radiographs) are found, sputum or gastric aspirate samples should be obtained. Children younger than 12 months who are suspected of having pulmonary or extrapulmonary tuberculosis disease (eg, have a positive TST and clinical or physical examination signs, or chest radiograph abnormalities consistent with

tuberculosis disease), with or without neurologic symptoms, should have a lumbar puncture. Some experts also recommend performing a lumbar puncture in children 12 through 23 months of age with tuberculosis disease, with or without neurologic symptoms or signs. Children 24 months of age and older with tuberculosis disease require a lumbar puncture only if they have neurologic symptoms or signs.

Laboratory isolation of *M tuberculosis* complex by culture from a specimen of sputum, gastric aspirate, bronchial washing, pleural fluid, cerebrospinal fluid (CSF), urine, or other body fluid or a tissue biopsy specimen confirms the diagnosis of tuberculosis disease. Children older than 2 years and adolescents frequently can produce sputum spontaneously or by induction with aerosolized hypertonic saline. Studies have demonstrated successful collections of induced sputum from infants with pulmonary tuberculosis, but this requires special expertise. The best specimen for diagnosis of pulmonary tuberculosis in any child or adolescent in whom cough is absent or nonproductive and sputum cannot be induced is an early-morning gastric aspirate. Gastric aspirate specimens should be obtained with a nasogastric tube on awakening the child and before ambulation or feeding. Aspirates collected on 3 separate mornings should be submitted for testing by staining and culture.

Fluorescent staining methods for specimen smears are more sensitive than the traditional Kinyoun acid fast smears and are preferred. The overall diagnostic yield of microscopy of gastric aspirates and induced sputum is low in children with clinically suspected pulmonary tuberculosis, and false-positive smear results caused by the presence of nontuberculous mycobacteria occur rarely. Histologic examination for and demonstration of AFB and granulomas in biopsy specimens from lymph node, pleura, mesentery, liver, bone marrow, or other tissues can be useful, but *M tuberculosis* complex organisms cannot be distinguished reliably from other mycobacteria in stained specimens. Regardless of results of the AFB smears, each specimen should be cultured.

Because *M tuberculosis* complex organisms are slow growing, detection of these organisms may take as long as 10 weeks using solid media; use of liquid media and continuous monitoring systems allows detection within 1 to 6 weeks, usually within 3 weeks. Even with optimal culture techniques, *M tuberculosis* complex organisms are isolated from fewer than 75% of infants and 50% of children with pulmonary tuberculosis diagnosed by clinical criteria. Current methods for species identification of isolates from culture include molecular probes, nucleic acid amplification tests (NAATs), genetic sequencing, mass spectrometry, and biochemical tests. *M bovis* usually is suspected because of pyrazinamide resistance, which is characteristic of almost all *M bovis* isolates, but further biochemical or molecular testing is required to distinguish *M bovis* from *M tuberculosis*.

For a child with clinically suspected tuberculosis disease, finding the source case supports the child's presumptive diagnosis and provides the likely drug susceptibility of the child's organism. Culture material should be collected from children with evidence of tuberculosis disease, especially when (1) an isolate from a source case is not available; (2) the presumed source case has drug-resistant tuberculosis; (3) the child is immunocompromised or ill enough to require hospital admission; or (4) the child has extrapulmonary disease. Traditional methods of determining drug susceptibility require bacterial isolation. Several new molecular methods of rapidly determining drug resistance directly from clinical samples now are available.

Two NAATs are available for detection of *M tuberculosis* complex organisms from smear-positive and smear-negative sputum specimens. One system, Xpert MTB-RIF (Cepheid, Sunnyvale, CA), also can detect the genetic marker for rifampin resistance in specimens within 2 hours. For children, Xpert MTB-RIF is more sensitive than microscopy but is not as sensitive as, and does not replace, culture. It is widely available in countries with a high prevalence of tuberculosis and is increasingly available in the United States. The CDC recommends NAAT testing on at least 1 respiratory tract specimen in the patient with suspected tuberculosis.

TREATMENT (TABLE 154.4)

Specific Drugs

Antituberculosis drugs kill or inhibit multiplication of *M tuberculosis* complex organisms, thereby arresting progression of infection and preventing most complications. Chemotherapy does not cause rapid disappearance of already caseous or granulomatous lesions (eg, mediastinal lymphadenitis). For treatment of tuberculosis disease, these drugs always must be used in recommended combination and dosage to minimize emergence of drug-resistant strains. Use of nonstandard regimens for any reason (eg, drug allergy, drug resistance) should be undertaken only by an expert in treating tuberculosis.

Isoniazid is bactericidal, rapidly absorbed, and well tolerated and penetrates into body fluids, including CSF. Isoniazid is metabolized in the liver and excreted primarily through the kidneys. Hepatotoxic effects are rare in children but can be life threatening. In children and adolescents who receive recommended doses, peripheral neuritis or seizures caused by inhibition of pyridoxine metabolism are rare, and most do not need pyridoxine supplements. Pyridoxine supplementation is recommended for exclusively breastfed infants and for children and adolescents who have meat- and milk-deficient diets; children with nutritional deficiencies, including all symptomatic HIV-infected children; and pregnant adolescents and women. For infants and young children, isoniazid tablets can be pulverized or compounded by some pharmacies.

Rifampin is a bactericidal agent in the rifamycin class of drugs that is absorbed rapidly and penetrates into body fluids, including CSF. Other drugs in the rifamycin class approved for treating tuberculosis are rifabutin and rifapentine. Rifampin is metabolized by the liver and can alter the pharmacokinetics and serum concentrations of many other drugs. Rare adverse effects include hepatotoxicity, influenza-like symptoms, pruritus, and thrombocytopenia. Rifampin is excreted in bile and urine and can cause orange urine, sweat, and tears, with discoloration of soft contact lenses. Rifampin can make oral contraceptives ineffective, so nonhormonal birth-control methods should be adopted when rifampin is administered to sexually active female adolescents and adults. For infants and young children, the contents of the capsules can be suspended in flavored syrup or sprinkled on semisoft foods (eg, pudding).

Rifabutin is a suitable alternative to rifampin in HIV-infected children receiving antiretroviral therapy that restricts the use of rifampin because of drug interactions; however, experience in children is limited, and there is no commercially available pediatric formulation.

Rifapentine is a long-acting rifamycin that permits weekly dosing in selected adults and adolescents with tuberculosis disease and is used for short-course multidrug treatment for LTBI.

Pyrazinamide attains therapeutic CSF concentrations, is detectable in macrophages, is administered orally, and is metabolized by the liver. Administration of pyrazinamide for the first 2 months with isoniazid and rifampin allows for 6-month regimens in immunocompetent patients with drug-susceptible tuberculosis. Almost all isolates of *M bovis* are resistant to pyrazinamide.

Ethambutol is well absorbed after oral administration, diffuses well into tissues, and is excreted in urine. Ethambutol is bacteriostatic, and its primary therapeutic role is to prevent emergence of drug resistance. Ethambutol can cause reversible or irreversible optic neuritis but reports in children with normal renal function are rare.

Occasionally, a patient cannot tolerate oral medications. Isoniazid, rifampin, kanamycin and related drugs, linezolid, and fluoroquinolones can be administered parenterally.

Treatment Regimens for LTBI

Several regimens are available. Any of these options is considered adequate, depending on the circumstances for individual patients. When indicated for LTBI, doses are the same as for treatment of tuberculosis.

Isoniazid-Rifapentine Therapy for LTBI

Based on a large clinical trial (which included children 2–11 years of age), the CDC recommended in 2011 a 12-week, once-weekly dose of

Table 154.4
Recommended Usual Treatment Regimens for Drug-Susceptible Tuberculosis in Infants, Children, and Adolescents

Infection or Disease Category	Regimen	Remarks
Latent *M tuberculosis* infection (positive TST or IGRA result, no disease)[a]		
• Isoniazid susceptible	12 weeks of isoniazid plus rifapentine, once a week OR 4 mo of rifampin, once a day OR 9 mo of isoniazid, once a day	Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended. If daily therapy is not possible, DOT twice a week can be used for 9 mo.
• Isoniazid resistant	4 mo of rifampin, once a day	Continuous daily therapy is required. Intermittent therapy even by DOT is not recommended.
• Isoniazid-rifampin resistant	Consult a tuberculosis specialist	Moxifloxacin or levofloxacin with or without ethambutol or pyrazinamide.
Pulmonary and extrapulmonary (except meningitis)[b]	2 mo of isoniazid, rifampin, pyrazinamide, and ethambutol daily or twice weekly, followed by 4 mo of isoniazid and rifampin[c] by DOT[d] for drug-susceptible *Mycobacterium tuberculosis* 9 to 12 mo of isoniazid and rifampin for drug-susceptible *Mycobacterium bovis*	Some experts recommend a 3-drug initial regimen (isoniazid, rifampin, and pyrazinamide) if the risk of drug resistance is low. DOT is highly desirable. If hilar adenopathy only and the risk of drug resistance is low, a 6-mo course of isoniazid and rifampin is sufficient. Drugs can be given 2 or 3 times/week under DOT.

(*continued*)

Table 154.4 (*continued*)

Infection or Disease Category	Regimen	Remarks
Meningitis	2 mo of isoniazid, rifampin, pyrazinamide, and an aminoglycoside[e] or ethionamide, once a day, followed by 7–10 mo of isoniazid and rifampin, once a day or twice a week (9–12 mo total) for drug-susceptible *M tuberculosis* At least 12 mo of therapy without pyrazinamide for drug-susceptible *M bovis*	For patients who may have acquired tuberculosis in geographic areas where resistance to streptomycin is common, kanamycin, amikacin, or capreomycin can be used instead of streptomycin.

TST indicates tuberculin skin test; IGRA, interferon-gamma release assay; DOT, directly observed therapy.
[a] See text for comments and additional acceptable/alternative regimens.
[b] Duration of therapy may be longer for human immunodeficiency virus (HIV)-infected people, and additional drugs and dosing intervals may be indicated (see Tuberculosis Disease and HIV Infection section).
[c] Medications should be administered daily for the first 2 weeks to 2 months of treatment and then can be administered 2 to 3 times per week by DOT. (Twice-weekly therapy is not recommended for HIV-infected people.)
[d] If initial chest radiograph shows pulmonary cavities and sputum culture after 2 months of therapy remains positive, the continuation phase is extended to 7 months, for a total treatment duration of 9 months.
[e] Streptomycin, kanamycin, amikacin, or capreomycin.

isoniazid and rifapentine for treatment of LTBI. This regimen was shown to be safe, well tolerated, and at least as efficacious as 9 months of isoniazid given daily by self-supervision. Most experts consider isoniazid-rifapentine to be the preferred regimen for treatment of LTBI for children 5 years and older, and some experts prefer isoniazid-rifapentine therapy for LTBI in children 2 years and older. Isoniazid-rifapentine should not be used in children younger than 2 years because of a lack of pharmacokinetic data.

Rifampin Therapy for LTBI

Rifampin given daily for 4 months also is an acceptable regimen for the treatment of LTBI. Most of the data supporting the efficacy of this regimen come from case control studies in adults and a few trials that included children. The regimen has been as effective as 9 months of daily isoniazid, rates of adverse effects have been low, and therapy completion rates have been much higher than for 9 months of isoniazid.

Isoniazid Therapy for LTBI

A 9-month course of daily isoniazid therapy in children has an efficacy that approaches 100% if adherence to therapy is high. Unfortunately, many studies have shown the adherence and completion rates to be 50% to 75% over 9 months when families administer isoniazid on their own. Isoniazid should not be used if the child received antituberculosis therapy previously or if resistance to isoniazid is suspected or proven in the source case. Additionally, immigrants who received isoniazid in countries with high rates of isoniazid-resistant tuberculosis may not have been treated adequately.

For infants, children, and adolescents, including those with HIV infection or other immunocompromising conditions, the recommended duration of isoniazid therapy in the United States is 9 months. The World Health Organization recommends a 6-month course of isoniazid, but modeling studies have shown that the efficacy of 6 months of treatment is approximately 30% less than that of a 9-month course. Many experts accept 6 months of uninterrupted treatment as adequate. When adherence with daily therapy with isoniazid cannot be ensured, twice-a-week DOT can be considered, but each dose must be observed directly. Determination of serum transaminase concentrations before or during therapy is not indicated except in patients with underlying liver or biliary disease or during pregnancy or the first 12 weeks

postpartum, with concurrent use of other potentially hepatotoxic drugs (eg, anticonvulsant or HIV agents).

Additional Regimens for Treatment of LTBI

Additional possible regime for treatment of LTBI are: (1) 3 months of daily isoniazid and rifampin; or (2) 2 months of daily rifampin and pyrazinamide when given as part of RIPE (*r*ifampin, *i*soniazid, *p*yrazinamide, and *e*thambutol) therapy for suspected tuberculosis disease that subsequently is determined to be *M tuberculosis* infection only.

Therapy for LTBI and Contacts of Patients With Isoniazid-Resistant M tuberculosis *and When Isoniazid Cannot Be Administered*

The incidence of isoniazid resistance among *M tuberculosis* complex isolates from US patients is approximately 9%. Risk factors for drug resistance are listed in Table 154.5. If the source case is found to have isoniazid-resistant, rifampin-susceptible organisms, isoniazid should be discontinued and rifampin should be administered daily to contacts for a total course of 4 months. Optimal therapy for children with LTBI caused by organisms with resistance to isoniazid and rifampin (ie, multidrug resistance) is not known. In these circumstances, a fluoroquinolone alone and multidrug regimens have been used, but the safety and the efficacy of these empiric regimens have not been assessed in clinical trials. Drugs to consider include levofloxacin, with or without the addition of pyrazinamide or ethambutol, depending on susceptibility of the isolate. Consultation with a tuberculosis specialist is indicated.

Treatment of Tuberculosis Disease

The goal of treatment is to achieve killing of replicating organisms in the tuberculous lesion in the shortest possible time. Achievement of this goal minimizes the possibility of development of resistant organisms. The major problem limiting successful treatment is poor adherence to prescribed treatment regimens. The use of DOT decreases the rates of relapse, treatment failures, and drug resistance; therefore, DOT is recommended strongly for treatment of all children and adolescents with tuberculosis disease in the United States.

Therapy for Presumed or Known Drug-Susceptible Pulmonary Tuberculosis

A 6-month, 4-drug regimen consisting initially of RIPE for the first 2 months and isoniazid and rifampin for the remaining 4 months is recommended for treatment of pulmonary disease, pulmonary disease with hilar adenopathy, and hilar adenopathy disease in infants, children, and adolescents when a multidrug-resistant case is not suspected as the source of infection or when favorable drug-susceptibility results are available from the patient or the likely source case. Some experts administer 3 drugs (isoniazid, rifampin, and pyrazinamide) as the initial regimen if a presumed source case has been identified with known susceptible *M tuberculosis* or has no risk factors for drug-resistant *M tuberculosis.* For children with hilar adenopathy in whom drug resistance is not a consideration, a 6-month regimen of only isoniazid and rifampin is considered adequate by some experts. If the chest radiograph shows one or more pulmonary cavities and sputum culture remains positive after 2 months of therapy, the duration of therapy should be extended to 9 months.

In the 6-month regimen with 4-drug RIPE therapy, drugs are administered once a day for at least the first 2 weeks by DOT at least 5 days per week. An alternative to daily dosing between 2 weeks and 2 months of treatment is to administer these drugs 2 or 3 times a week by DOT (except in HIV-infected people, in whom intermittent dosing is not recommended). After the initial 2-month period, a DOT regimen of isoniazid and rifampin given 2 or 3 times a week is acceptable.

Therapy for Drug-Resistant Pulmonary Tuberculosis Disease

Drug resistance is more common in certain groups (see Table 154.5). When **resistance to drugs other than isoniazid** is likely, initial therapy should be adjusted by adding at least 2 drugs to match the presumed drug susceptibility pattern until drug susceptibility results are available. If an isolate from the pediatric case under treatment is not available, drug susceptibilities can be inferred by the drug susceptibility pattern of isolates from the source case. Data for guiding drug selection

Table 154.5
People at Increased Risk of Drug-Resistant Tuberculosis Infection or Disease

- People with a history of treatment for tuberculosis disease (or whose source case for the contact received such treatment)
- Contacts of a patient with drug-resistant contagious tuberculosis disease
- People from countries with high prevalence of drug-resistant tuberculosis, such as Russia and certain nations of the former Soviet Union, Asia, Africa, and Latin America
- Infected people whose source case has positive smears for acid-fast bacilli or cultures after 2 months of appropriate antituberculosis therapy and patients who do not respond to a standard treatment regimen
- Residence in geographic area with a high percentage of drug-resistant isolates

Source: **wwwnc.cdc.gov/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/tuberculosis.**

may not be available for foreign-born children or in circumstances of international travel or adoption. If this information is not available, a 4- or 5-drug initial regimen should be strongly considered with close monitoring for clinical response.

Most cases of pulmonary tuberculosis in children that are caused by an isoniazid-resistant but rifampin- and pyrazinamide-susceptible strain of *M tuberculosis* complex can be treated with a 6-month regimen of rifampin, pyrazinamide, and ethambutol. For cases of multidrug-resistant tuberculosis disease, the treatment regimen needed is complex and expert consultation is recommended. Therapy for multidrug-resistant tuberculosis is administered for 12 to 24 months from the time of culture conversion to negativity. An injectable drug, initially administered 5 days per week, such as amikacin, kanamycin, or capreomycin, often is used for the first 4 to 6 months of treatment, as tolerated. Regimens in which drugs are administered intermittently are not recommended for drug-resistant disease; daily DOT is critical to prevent emergence of additional resistance. An expert in drug-resistant tuberculosis should be consulted for all drug-resistant cases.

Extrapulmonary Tuberculosis Disease

In general, extrapulmonary tuberculosis—with the exception of meningitis—can be treated with the same regimens as used for pulmonary tuberculosis. For suspected drug-susceptible tuberculous meningitis, daily treatment with isoniazid, rifampin, pyrazinamide, and ethionamide, if possible, or an aminoglycoside (parenteral streptomycin, kanamycin, amikacin, or capreomycin) should be initiated. When susceptibility to first-line drugs is established, the ethionamide or aminoglycoside can be discontinued. Pyrazinamide is given for a total of 2 months, and isoniazid and rifampin are given for a total of 9 to 12 months. Isoniazid and rifampin can be given daily or 2 or 3 times per week after the first 2 months of treatment if the child has responded well.

Evaluation and Monitoring of Therapy in Children and Adolescents

Careful monthly monitoring of clinical and bacteriologic responses to therapy is important. With DOT, clinical evaluation is an integral component of each visit for drug administration. For patients with pulmonary tuberculosis, chest radiographs often are obtained after 2 months of therapy to evaluate response. Even with successful 6-month regimens, hilar adenopathy can persist for 2 to 3 years; normal radiographic findings are not necessary to discontinue therapy. Follow-up chest radiography beyond termination of successful therapy usually is not necessary unless clinical deterioration occurs.

If therapy has been interrupted, the date of completion should be extended. Although guidelines cannot be provided for every situation, factors to consider when establishing the date of completion include the following:

(1) length of interruption of therapy; (2) time during therapy (early or late) when interruption occurred; and (3) the patient's clinical, radiographic, and bacteriologic status before, during, and after interruption of therapy. The total doses administered by DOT should be calculated to guide the duration of therapy. Consultation with a specialist in tuberculosis is advised.

Untoward effects of isoniazid therapy, including severe hepatitis in otherwise healthy infants, children, and adolescents, are rare. Routine determination of serum transaminase concentrations is not recommended. In most other circumstances, monthly clinical evaluations to observe for signs or symptoms of hepatitis and other adverse effects of drug therapy without routine monitoring of transaminase concentrations is appropriate follow-up. Regular physician-patient contact to assess drug adherence, efficacy, and adverse effects is an important aspect of management. Patients should be provided with written instructions and advised to call a physician immediately if symptoms of adverse events, in particular hepatotoxicity (ie, nausea, vomiting, abdominal pain, jaundice), develop.

Other Treatment Considerations

Corticosteroids

The evidence supporting adjuvant treatment with corticosteroids for children with tuberculosis disease is incomplete. Corticosteroids are definitely indicated for children with tuberculous meningitis, because corticosteroids decrease rates of mortality and long-term neurologic impairment. Corticosteroids can be considered for children with pleural and pericardial effusions (to hasten reabsorption of fluid), severe miliary disease (to mitigate alveolocapillary block), endobronchial disease (to relieve obstruction and atelectasis), and abdominal tuberculosis (to decrease the risk of strictures).

Tuberculosis Disease and HIV Infection

Most HIV-infected adults with drug-susceptible tuberculosis respond well to standard treatment regimens. However, optimal therapy for tuberculosis in children with HIV infection has not been established. Treating tuberculosis in an HIV-infected child is complicated by antiretroviral drug interactions with the rifamycins and overlapping toxicities. Therapy always should include at least 4 drugs initially, should be administered daily via DOT, and should be continued for at least 6 months. Isoniazid, rifampin, and pyrazinamide, usually with ethambutol, should be administered for at least the first 2 months. Ethambutol can be discontinued once drug-resistant tuberculosis disease is excluded. Rifampin may be contraindicated in people who are receiving antiretroviral therapy. Rifabutin is substituted for rifampin in some circumstances.

Immunizations

Patients who are receiving treatment for tuberculosis can receive measles and other age-appropriate attenuated live-virus vaccines unless they are receiving high-dose systemic corticosteroids, are severely ill, or have other specific contraindications to immunization.

Tuberculosis During Pregnancy and Breastfeeding

Pregnant women who have a positive TST or IGRA result, are asymptomatic, have a normal chest radiograph, and had recent contact with a contagious person should be considered for isoniazid therapy. Therapy in these circumstances should begin after the first trimester and the recommended duration is 9 months. If there has been no recent contact with a contagious case, therapy can be delayed until after delivery. Pyridoxine supplementation is indicated for all pregnant and breastfeeding women receiving isoniazid.

If tuberculosis disease is diagnosed during pregnancy, a regimen of isoniazid, rifampin, and ethambutol is recommended. Pyrazinamide commonly is used in a 3- or 4-drug regimen, but safety during pregnancy has not been established. At least 6 months of therapy is indicated for drug-susceptible tuberculosis disease if pyrazinamide is used; at least 9 months of therapy is indicated if pyrazinamide is not used. Prompt initiation of therapy is mandatory to protect mother and fetus.

Isoniazid, ethambutol, and rifampin are relatively safe for the fetus. The benefit of ethambutol and rifampin for therapy of tuberculosis disease in the mother outweighs the risk to the infant. Because aminoglycosides (streptomycin, kanamycin, amikacin, or capreomycin) can cause ototoxic effects in the fetus, they should not be used unless administration is essential for effective treatment. Ethionamide has been demonstrated to be teratogenic, so its use during pregnancy is contraindicated.

Although isoniazid is secreted in human milk, no adverse effects of isoniazid on nursing infants have been demonstrated. Breastfed infants do not require pyridoxine supplementation unless they are receiving isoniazid. The isoniazid dosage of a breastfed infant whose mother is taking isoniazid does not require adjustment for the small amount of drug in the milk.

Congenital Tuberculosis

Congenital tuberculosis is rare, but in utero infections can occur after maternal bacillemia and have been reported following in vitro fertilization of women from countries with endemic disease in whom infertility likely was related to subclinical maternal genitourinary tract tuberculosis.

If a newborn infant is suspected of having congenital tuberculosis, a TST and IGRA test, chest radiography, lumbar puncture, and appropriate cultures and radiography should be performed promptly. The TST result usually is negative in newborn infants with congenital or perinatally acquired infection. Hence, regardless of the TST or IGRA results, treatment of the infant should be initiated promptly with rifampin, isoniazid, pyrazinamide, and either ethambutol (RIPE) or an aminoglycoside (streptomycin, kanamycin, amikacin, or capreomycin). The placenta should be examined histologically for granulomata and AFB, and a specimen should be cultured for *M tuberculosis* complex. The mother should be evaluated for presence of pulmonary or extrapulmonary disease, including genitourinary tuberculosis. If the physical examination and chest radiographic findings support the diagnosis of tuberculosis disease, the newborn infant should be treated with a regimen recommended for tuberculosis disease. If meningitis is confirmed, corticosteroids should be added. Drug susceptibility testing of the organism recovered from the mother, infant, or both should be performed. HIV testing of the mother is essential.

Management of the Newborn Infant Whose Mother Has LTBI or Tuberculosis Disease

Management of the newborn infant is based on categorization of the maternal infection. Although protection of the infant from exposure and infection is of paramount importance, contact between infant and mother should be allowed when possible. Differing circumstances and resulting recommendations are as follows:

- **Mother has a positive TST or IGRA result and normal chest radiographic findings.** If the mother is asymptomatic, no separation is required. The mother usually is a candidate for treatment of LTBI after the initial postpartum period. The newborn infant needs no special evaluation or therapy. Because of the young infant's exquisite susceptibility and because the mother's positive TST or IGRA result could be a marker of an unrecognized case of contagious tuberculosis within the household, other household members should have a TST or IGRA and further evaluation; this should not delay the infant's discharge from the hospital. These mothers can breastfeed their infants.
- **Mother has clinical signs and symptoms or abnormal findings on chest radiograph consistent with tuberculosis disease.** Cases of suspected or proven tuberculosis disease in mothers should be reported immediately to the local health department, and investigation of all household members started as soon as possible. If the mother has tuberculosis disease, the infant should be evaluated for congenital tuberculosis, and the mother should be tested for HIV infection. The mother and the infant should be separated until the mother has been evaluated and, if tuberculosis disease is suspected, until the mother and infant are receiving appropriate antituberculosis therapy, the mother wears a mask, and the mother understands and is willing to adhere to infection-control measures. During separation, expressed human milk can be fed to

the infant unless mother has signs of tuberculous mastitis, which is rare. Once the infant is receiving isoniazid, separation is not necessary unless the mother has possible multidrug-resistant tuberculosis disease or has poor adherence to treatment and DOT is not possible. If the mother is suspected of having multidrug-resistant tuberculosis disease, an expert in tuberculosis disease treatment should be consulted. Women with drug-susceptible tuberculosis disease who have been treated appropriately for 2 or more weeks and who are not considered contagious can breastfeed.

If congenital tuberculosis is excluded, isoniazid is administered until the infant is 3 or 4 months of age, when a TST should be performed. If the TST result is negative at 3 to 4 months of age and the mother has good adherence and response to treatment and no longer is contagious, isoniazid should be discontinued. If the TST result is positive, the infant should be reassessed for tuberculosis disease. If tuberculosis disease is excluded, isoniazid alone should be continued for a total of 9 months. The infant should be evaluated monthly during treatment for signs of illness or poor growth.

- **Mother has a positive TST or IGRA and abnormal findings on chest radiography but no evidence of tuberculosis disease.** If the chest radiograph of the mother appears abnormal but is not suggestive of tuberculosis disease and the history, physical examination, and sputum smear indicate no evidence of tuberculosis disease, the infant can be assumed to be at low risk of *M tuberculosis* infection and need not be separated from the mother. The mother and her infant should receive follow-up care and the mother should be treated for LTBI. Other household members should have a TST or IGRA and further evaluation.

ISOLATION OF THE HOSPITALIZED PATIENT

Most children with tuberculosis disease, especially children younger than 10 years, are not contagious. Exceptions are the following: (1) children with pulmonary cavities; (2) children with positive sputum AFB smears; (3) children with laryngeal involvement; (4) children with extensive pulmonary infection; or (5) neonates or infants with congenital tuberculosis undergoing procedures that involve the oropharyngeal airway (eg, endotracheal intubation). In these instances, airborne infection isolation precautions for tuberculosis are indicated until effective therapy has been initiated, sputum smears are negative, and coughing has abated. Additional criteria apply to multidrug-resistant tuberculosis. Children with no cough and negative sputum AFB smears can be hospitalized in an open ward. Infection-control measures for hospital personnel and visitors exposed to contagious patients should include the use of personally "fit tested" and "sealed" N-95 particulate respirators for all patient contacts.

The major concern in infection control relates to adult household members and contacts that can be the source of infection. Visitation should be limited to people who have been evaluated and do not have tuberculosis. Household members and contacts should be managed with tuberculosis precautions when visiting until they are demonstrated not to have contagious tuberculosis.

Tuberculosis Caused by *M bovis*

Infections with *M bovis* account for approximately 1% to 2% of tuberculosis cases in the United States and higher along the border with Mexico. Children who come from countries where *M bovis* is prevalent in cattle or whose parents come from those countries are more likely to be infected. Most infections in humans are transmitted from cattle by unpasteurized milk and its products, such as fresh cheese, although human-to-human transmission by the airborne route has been documented. In children, *M bovis* more commonly causes cervical lymphadenitis, intestinal tuberculosis disease and peritonitis, and meningitis. In adults, latent *M bovis* infection can progress to advanced pulmonary disease, with a risk of transmission to others.

The TST result typically is positive in a person infected with *M bovis;* IGRAs have not been studied systematically for diagnosing *M bovis* infection in particular, but theoretically they should have acceptable test characteristics. The definitive diagnosis of *M bovis* infection requires a culture isolate. The commonly used

methods for identifying a microbial isolate as *M tuberculosis* complex do not distinguish *M bovis* from *M tuberculosis*, *M africanum*, and BCG; *M bovis* is suspected in clinical laboratories by its typical resistance to pyrazinamide. This approach can be unreliable, and species confirmation at a reference laboratory should be requested when *M bovis* is suspected. Molecular genotyping through the state health department may assist in identifying *M bovis*. Resistance to first-line drugs in addition to pyrazinamide has been reported but is uncommon. BCG rarely is isolated from pediatric clinical specimens in the United States; however, it should be suspected from localized BCG suppuration or draining lymphadenitis in children who recently (within several months) have received BCG vaccine. Only a reference laboratory can distinguish an isolate of BCG from an isolate of *M bovis*.

Therapy for *M bovis* Disease

Treatment recommendations for *M bovis* disease in children and adults are based on results from treatment trials for *M tuberculosis* disease. Although most strains of *M bovis* are pyrazinamide-resistant and resistance to other first-line drugs has been reported, multidrug-resistant strains are rare. Initial therapy for disease caused by *M bovis* should include 3 or 4 drugs, excluding pyrazinamide, that would be used to treat disease attributable to *M tuberculosis*. For isoniazid- and rifampin-susceptible strains, a total treatment course of at least 9 months is recommended.

Parents should be counseled about the many infectious diseases transmitted by unpasteurized milk and its products, and parents who might import traditional dairy products from countries where *M bovis* infection is prevalent in cattle should be advised against giving those products to their children. When people are exposed to an adult who has pulmonary disease caused by *M bovis* infection, they should be evaluated by the same methods as for *M tuberculosis*.

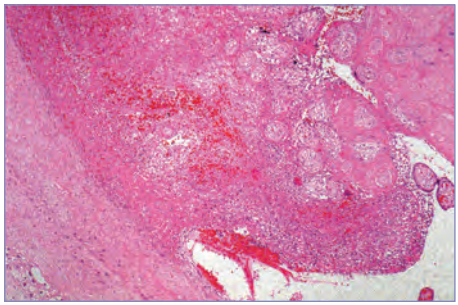


Image 154.1
A photomicrograph showing tuberculosis of the placenta. Although a rare circumstance, mother-to-child transmission of *Mycobacterium tuberculosis* can take place through the blood from different regions of the mother's body or originate from lesions within the placenta, as is the case here. Courtesy of Centers for Disease Control and Prevention.

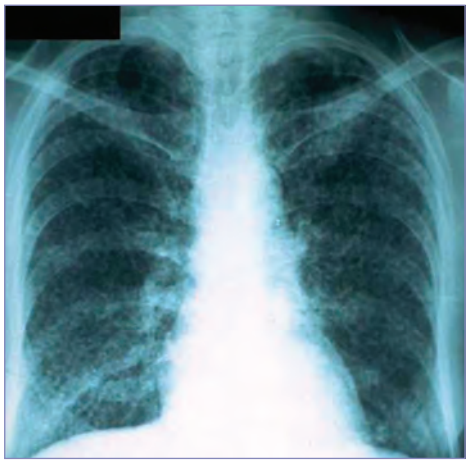


Image 154.3
Tuberculosis, miliary, in a 29-year-old woman 4 months after delivery. Tuberculosis may exacerbate during pregnancy.

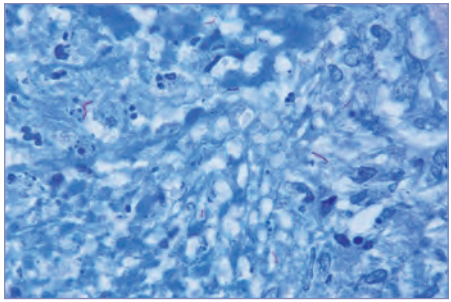


Image 154.2
Histopathology of placenta thrombus with inflammatory cells and acid-fast bacilli of *Mycobacterium tuberculosis* (Ziehl-Neelsen stain). Courtesy of Centers for Disease Control and Prevention.

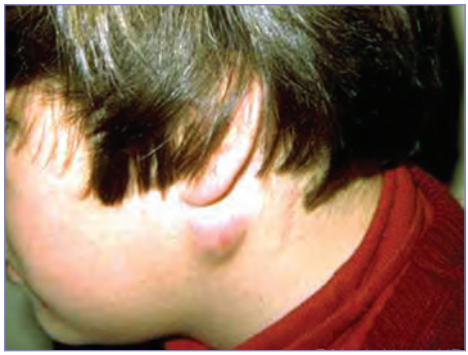


Image 154.4
Young man with *Mycobacterium tuberculosis* cervical lymphadenitis. Copyright Martin G. Myers, MD.

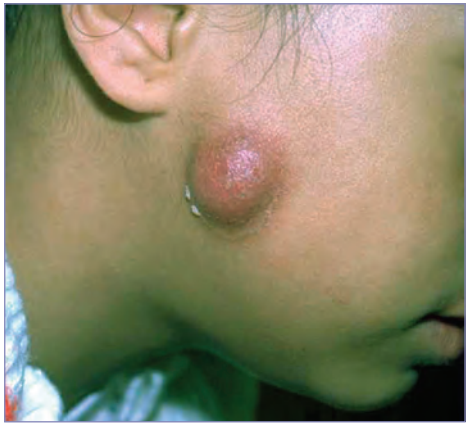


Image 154.5
Young woman with *Mycobacterium tuberculosis* cervical lymphadenitis. Copyright Martin G. Myers, MD.

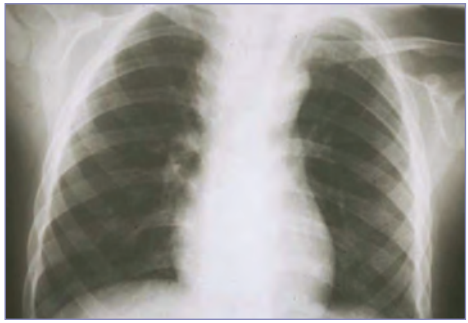


Image 154.6
Mycobacterium tuberculosis infection with paratracheal lymph nodes.

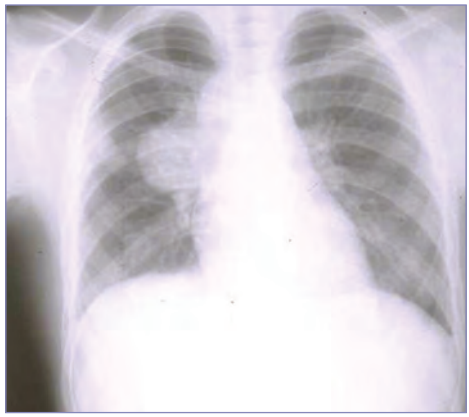


Image 154.8
A 13-year-old boy with tuberculosis. The patient had a 1-week history of shortness of breath and sharp pain on his right side while riding his bicycle. A purified protein derivative revealed 20 by 25 mm of induration at 72 hours. The chest computed tomography scan revealed right hilar adenopathy and a primary complex in the right peripheral lung field. Copyright Barbara Jantausch, MD, FAAP.

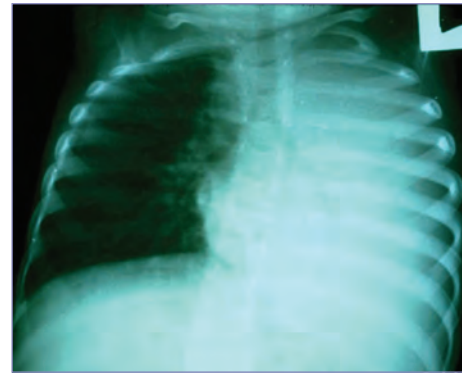


Image 154.7
A 1-year-old with endobronchial tuberculosis with pulmonary consolidation.

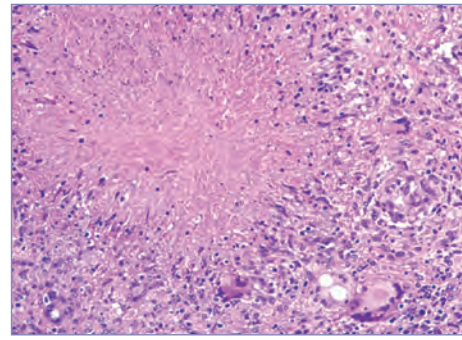


Image 154.9
Tuberculosis. Caseation and Langhans giant cells in a lymph node. Courtesy of Dimitris P. Agamanolis, MD.

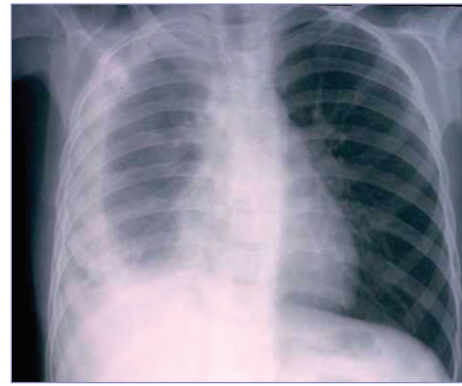


Image 154.10
Pulmonary tuberculosis with right pleural effusion.

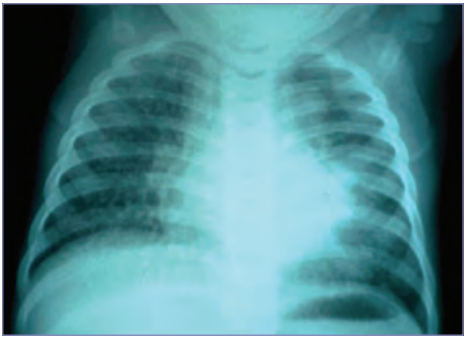


Image 154.11
A 10-month-old with radiographic changes of miliary tuberculosis.

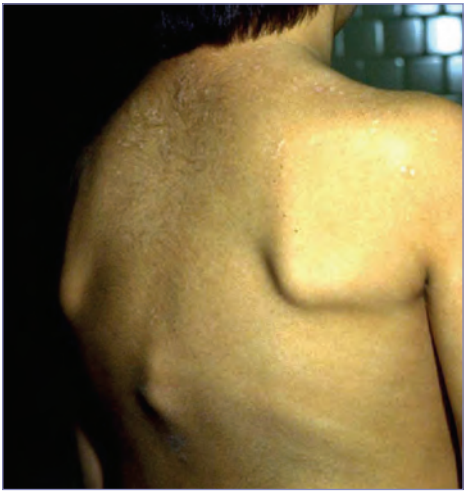


Image 154.13
Tuberculosis of the spine with paravertebral abscess (Pott disease).

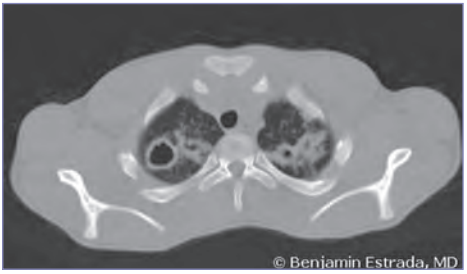


Image 154.16
Cavitary tuberculosis in a 15-year-old boy delineated by computed tomography scan. Courtesy of Benjamin Estrada, MD.

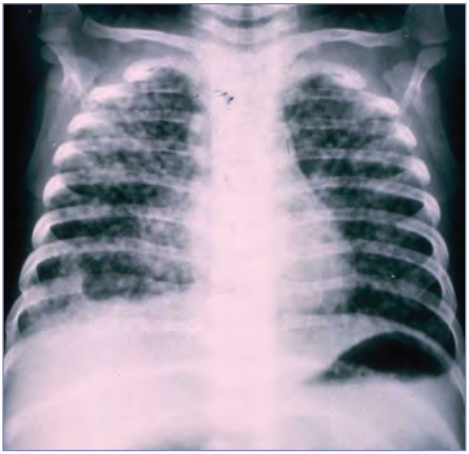


Image 154.12
Miliary tuberculosis with pulmonary cavitation (right lung).

Image 154.14
A 15-year-old boy with tuberculous epididymitis. Copyright Martin G. Myers, MD.

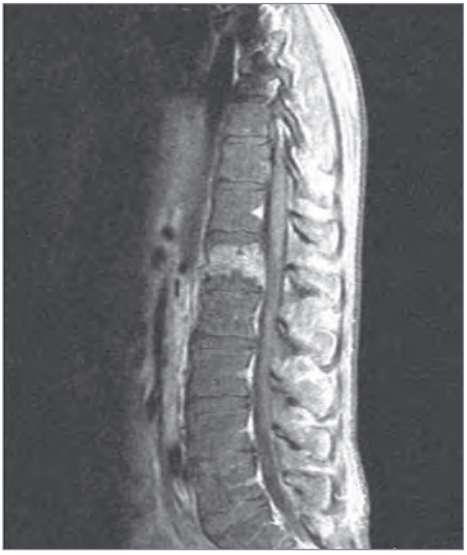


Image 154.15
Tuberculous spondylitis in a 14-year-old boy demonstrated by magnetic resonance imaging. Courtesy of Benjamin Estrada, MD.

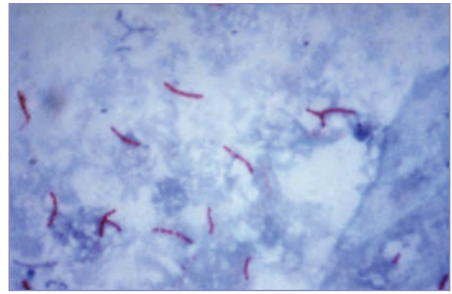


Image 154.17
This photomicrograph reveals *Mycobacterium tuberculosis* bacteria by using acid-fast Ziehl-Neelsen stain (magnification ×1,000). The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution, such as the Ziehl-Neelsen or Kinyoun stains that are carbolfuchsin methods specific for *M tuberculosis*. Courtesy of Centers for Disease Control and Prevention.

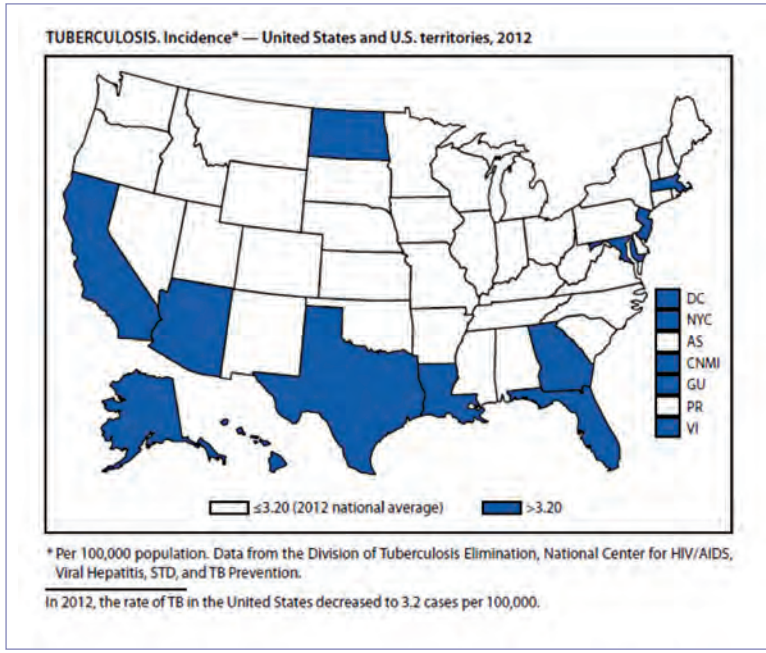


Image 154.18
Tuberculosis. Incidence—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

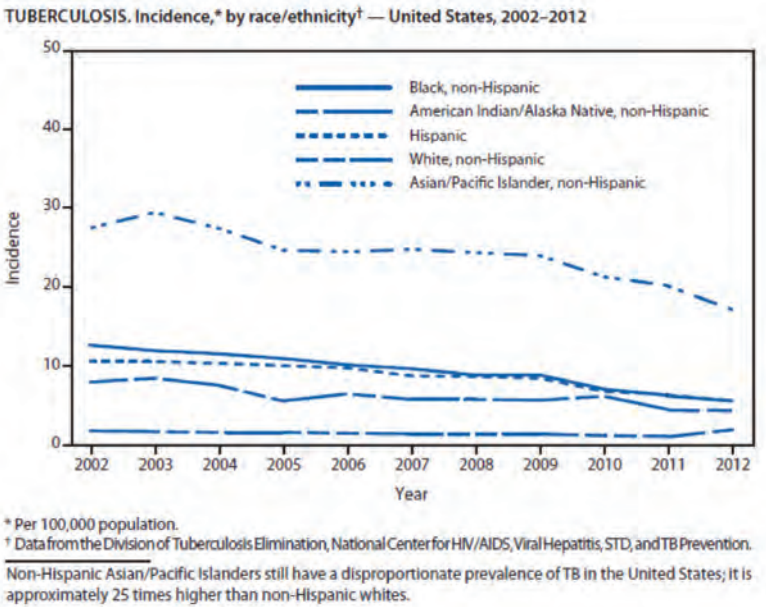


Image 154.19
Tuberculosis. Incidence, by race/ethnicity—United States, 2002–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

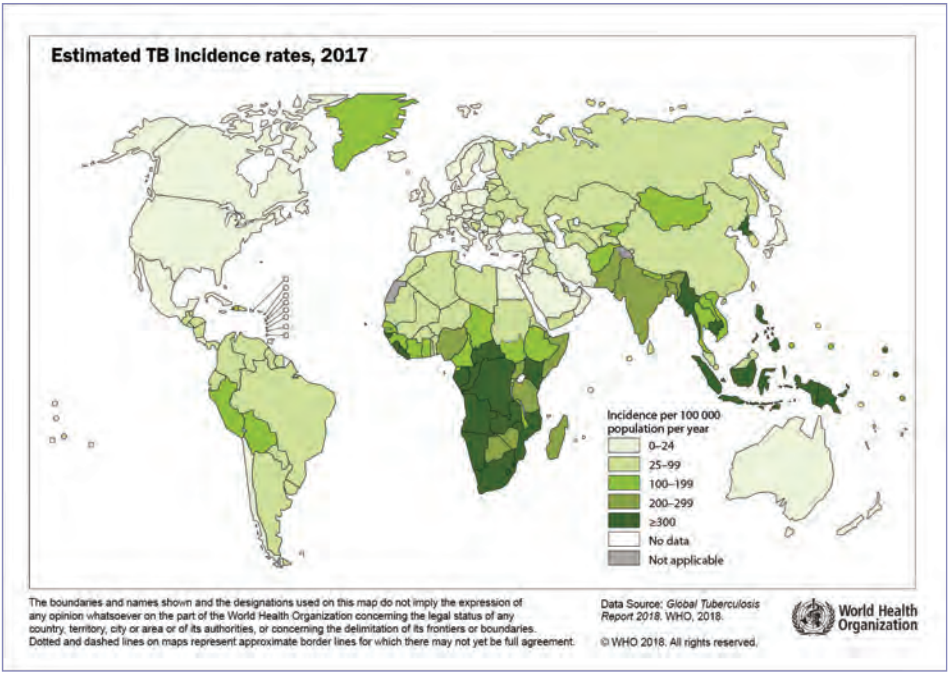


Image 154.20
Estimated tuberculosis incidence rates, 2017. Courtesy of World Health Organization. **http://gamapserver.who.int/mapLibrary/Files/Maps/Global_TB_incidence_2017.png.**

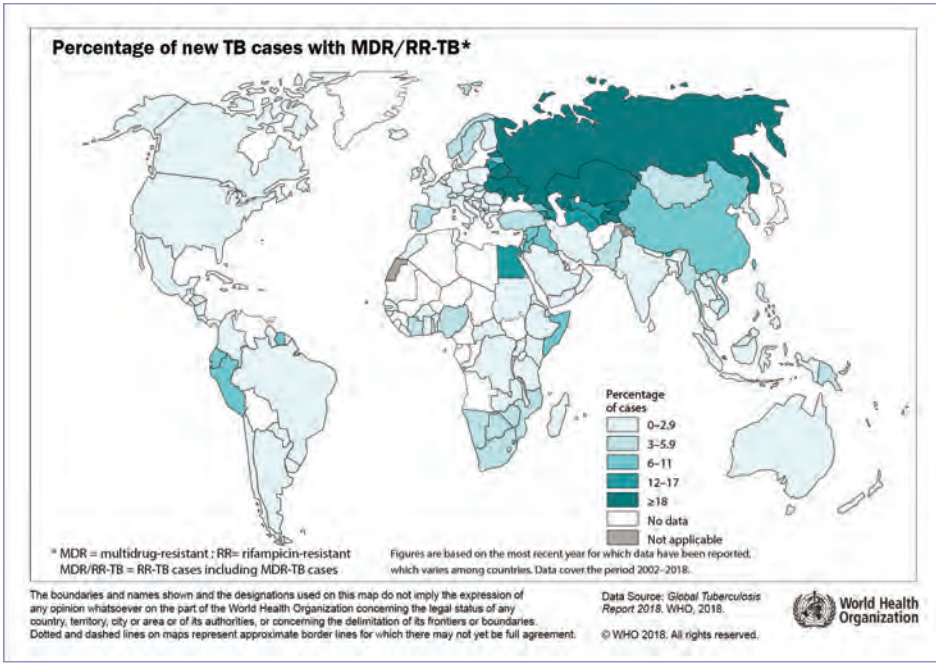


Image 154.21
Percentage of new tuberculosis cases with multidrug-resistant/rifampicin-resistant disease. Courtesy of the World Health Organization. **http://gamapserver.who.int/mapLibrary/Files/Maps/Global_TB_cases_new_mdr_rr_2017.png.**

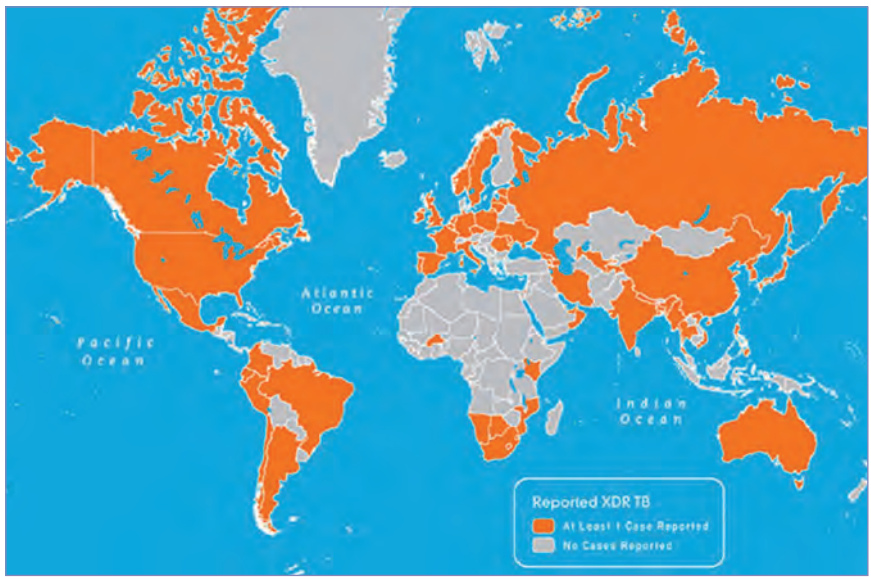


Image 154.22
Distribution of countries and territories reporting at least 1 case of extensively drug-resistant tuberculosis as of 2010. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 155

Nontuberculous Mycobacteria

(Environmental Mycobacteria, Mycobacteria Other Than *Mycobacterium tuberculosis*)

CLINICAL MANIFESTATIONS

Several syndromes are caused by nontuberculous mycobacteria (NTM). In children, the most common of these syndromes is cervical lymphadenitis. Cutaneous infection may follow soil- or water-contaminated traumatic wounds, surgeries, or cosmetic procedures (eg, tattoos, pedicures, body piercings). Less common syndromes include soft tissue infection, osteomyelitis, otitis media, central catheter-associated bloodstream infections, and pulmonary infections, especially in adolescents with cystic fibrosis. NTM, especially *Mycobacterium avium* complex (MAC [including *M avium* and *Mycobacterium avium-intracellulare*]) and *Mycobacterium abscessus*, can be recovered from sputum in 10% to 20% of adolescents and young adults with cystic fibrosis and can be associated with fever and declining clinical status. Disseminated infections almost always are associated with impaired cell-mediated immunity, as found in children with congenital immune defects (eg, interleukin-12 deficiency, NF-kappa-β essential modulator [NEMO] mutation and related disorders, and interferon-gamma receptor defects), hematopoietic stem cell transplants, or advanced human immunodeficiency virus (HIV) infection. Disseminated NTM infection, most commonly MAC, is rare in HIV-infected children during the first year of life. The frequency of disseminated MAC increases with increasing age and declining CD4+ T-lymphocyte counts, typically less than 50 cells/μL, in children older than 6 years. Manifestations of disseminated NTM infections depend on the species and route of infection but include fever, night sweats, weight loss, abdominal pain, fatigue, diarrhea, and anemia. These signs and symptoms also are found in advanced immunosuppressed HIV-infected children without disseminated MAC. For HIV-infected children who have disseminated MAC, respiratory symptoms and isolated pulmonary disease are uncommon. In HIV-infected patients developing immune restoration with initiation of combination antiretroviral therapy (cART), local NTM symptoms can worsen temporarily. This immune reconstitution syndrome usually occurs 2 to 4 weeks after initiation of cART. Symptoms can include worsening fever, swollen lymph nodes, local pain, and laboratory abnormalities.

In 2015, an outbreak in Switzerland occurred in which cases of *Mycobacterium chimaera* infection were associated with heater-cooler units (Stöckert 3T, manufactured by Sorin Group Deutschland, now LivaNova) used in open heart surgery and were believed to be caused by aerosolization of contaminated water in the units. Presentation was indolent in all cases, and diagnosis occurred years after exposure. Fever, myalgia, arthralgia, fatigue, and weight loss were initial manifestations. Prosthetic valve endocarditis or vascular graft infection was most commonly identified, but other manifestations have included osteomyelitis, hepatitis, pancytopenia, renal insufficiency, and splenomegaly. Subsequently, patients have been identified internationally and in the United States. It has determined that all heater-cooler units have common design features that could lead to aerosol formation.

ETIOLOGY

Of the more than 130 species of NTM that have been identified, only a few cause most human infections. The species most commonly infecting children in the United States are MAC, *Mycobacterium fortuitum*, *M abscessus*, and *Mycobacterium marinum* (Table 155.1). Several new species, which can be detected by nucleic acid amplification testing but cannot be grown by routine culture methods, have been identified in lymph nodes of children with cervical adenitis. NTM disease in patients with HIV infection usually is caused by MAC. *M fortuitum*, *Mycobacterium chelonae*, *Mycobacterium smegmatis*, and *M abscessus* commonly are referred to as "rapidly growing" mycobacteria, because sufficient growth and identification can be achieved in the laboratory within 3 to 7 days, whereas MAC, *M marinum*, *Mycobacterium szulgai*, and most other NTM usually require several weeks before sufficient growth occurs for identification and are referred to as "slow growing" mycobacteria. Rapidly growing mycobacteria have been

Table 155.1
Diseases Caused by Nontuberculous *Mycobacterium* Species

Clinical Disease	Common Species	Less Common Species in the United States
Cutaneous infection	*M marinum, M chelonae, M fortuitum, M abscessus*	*M ulcerans*[a]
Lymphadenitis	MAC; *M haemophilum; M lentiflavum*	*M kansasii, M fortuitum, M malmoense*[b]
Otologic infection	*M abscessus*	*M fortuitum*
Pulmonary infection	MAC, *M kansasii, M abscessus*	*M xenopi, M malmoense,*[b] *M szulgai, M fortuitum, M simiae*
Catheter-associated infection	*M chelonae, M fortuitum*	*M abscessus*
Prosthetic valve endocarditis	*M chelonae, M fortuitum*	*M chimaera*
Skeletal infection	MAC, *M kansasii, M fortuitum*	*M chelonae, M marinum, M abscessus, M ulcerans*[a]
Disseminated	MAC	*M kansasii, M genavense, M haemophilum, M chelonae*

MAC indicates *Mycobacterium avium* complex.
[a]Not endemic in the United States.
[b]Found primarily in Northern Europe.

implicated in wound, soft tissue, bone, pulmonary, central venous catheter, and middle-ear infections. Other mycobacterial species that usually are not pathogenic have caused infections in immunocompromised hosts or have been associated with the presence of a foreign body.

EPIDEMIOLOGY

Many NTM species are ubiquitous in nature, being found in soil, food, water, and animals. Tap water is the major reservoir for *Mycobacterium kansasii*, *Mycobacterium lentiflavum*, *Mycobacterium xenopi*, *Mycobacterium simiae*, and health care-associated infections attributable to *M abscessus* and *M fortuitum.* Outbreaks have been associated with contaminated water used for acupuncture, pedicures, inks used for tattooing and in children undergoing pulpotomy, which has been associated with improperly maintained dental unit water lines. For *M marinum*, water in a fish tank or aquarium or an injury in a salt-water environment are the major sources of infection. The environmental reservoir for *M abscessus* and MAC causing pulmonary infection is unknown. Although many people are exposed to NTM, it is unknown why some exposures result in acute or chronic infection. Usual portals of entry for NTM infection are believed to be abrasions in the skin, such as cutaneous lesions caused by *M marinum;* penetrating trauma, such as needles and organic material most often associated with *M abscessus* and *M fortuitum;* surgical sites, especially for central vascular catheters; oropharyngeal mucosa, which is the presumed portal of entry for cervical lymphadenitis; tooth eruption, which is the presumed portal of entry for submandibular lymphadenitis; gastrointestinal or respiratory tract, for disseminated MAC; and respiratory tract, including tympanostomy tubes for otitis media. Pulmonary disease and rare cases of mediastinal adenitis and endobronchial disease occur. NTM can be important emerging pathogens in patients with cystic fibrosis and are emerging pathogens in individuals receiving biologic response modifiers, such as antitumor necrosis factor-alpha agents. Most infections remain localized at the portal of entry or in regional lymph nodes. Dissemination to distal sites primarily occurs in immunocompromised hosts, except in the

case of *M chimaera* infections in those exposed during open-heart surgery, most of whom are immunocompetent. No definitive evidence of person-to-person transmission of NTM exists. Outbreaks of otitis media caused by *M abscessus* have been associated with polyethylene ear tubes and use of contaminated equipment or water. Large clusters of dental infections caused by *M abscessus* have been associated with use of tap water for rinsing and irrigation during procedures. A waterborne route of transmission has been implicated for MAC infection in some immunodeficient hosts. Buruli ulcer disease is a skin and bone infection caused by *Mycobacterium ulcerans*, an emerging disease causing significant morbidity and disability in tropical areas such as Africa, Asia, South America, Australia, and the western Pacific.

The **incubation periods** are variable.

DIAGNOSTIC TESTS

Routine screening of respiratory or gastrointestinal tract specimens for MAC microorganisms is not recommended. Definitive diagnosis of NTM disease requires isolation of the organism. Consultation with the laboratory should occur to ensure that culture specimens are handled correctly. Because NTM commonly are found in the environment, contamination of cultures or transient colonization can occur. Caution must be exercised in interpretation of cultures obtained from nonsterile sites, such as gastric washing specimens, endoscopy material, a single expectorated sputum sample, or urine specimens, and also when the species cultured usually is nonpathogenic (eg, *Mycobacterium terrae* complex or *Mycobacterium gordonae*). An acid-fast bacilli smear-positive sample and repeated isolation on culture media of a single species from any site are more likely to indicate disease than culture contamination or transient colonization. Diagnostic criteria for NTM lung disease in adults include 2 or more separate sputum samples or 1 bronchial alveolar lavage specimen that grows NTM. These criteria have not been validated in children and apply best to MAC, *M kansasii*, and *M abscessus*. NTM isolates from draining sinus tracts or wounds almost always are significant clinically. Recovery of NTM from sites that usually are sterile, such as cerebrospinal fluid, pleural fluid, bone marrow, blood, lymph node aspirates, middle ear or mastoid aspirates, or surgically excised tissue, are very likely to be significant. However, rare instances of sample or laboratory contamination leading to a false-positive culture result have been reported. With radiometric or nonradiometric broth techniques, blood cultures are highly sensitive in recovery of MAC and other bloodborne NTM species. If disseminated MAC disease is confirmed, the patient should be evaluated to identify an underlying immunodeficiency condition (eg, HIV, gamma interferon receptor deficiency). Polymerase chain reaction-based assays for some NTM have been developed but are not yet widely available in commercial diagnostic laboratories.

Patients with NTM infection such as *M marinum*, *M kansasii*, or MAC cervical lymphadenitis can have a positive tuberculin skin test (TST) result, because the purified protein derivative preparation, derived from *M tuberculosis*, shares a number of antigens with these NTM species. These TST reactions usually measure less than 10 mm of induration but can measure more than 15 mm. The interferon-gamma release assays (IGRAs) use 2 or 3 antigens to detect infection with *M tuberculosis*. Although these antigens are not found on *M avium-intracellulare* and most other NTM species, cross reactions can occur with infection caused by *M kansasii*, *M marinum*, and *M szulgai*.

TREATMENT

Many NTM are relatively resistant in vitro to antituberculosis drugs. In vitro resistance to these agents, however, does not necessarily correlate with clinical response, especially with MAC infections. Only limited controlled trials of drug treatment have been performed in patients with NTM infections. The approach to initial therapy should be directed by the following: (1) the species causing the infection; (2) the results of drug-susceptibility testing; (3) the site(s) of infection; (4) the patient's immune status; and (5) the need to treat a patient presumptively for tuberculosis while awaiting culture reports that subsequently reveal NTM.

For NTM lymphadenitis in otherwise healthy children, especially when the disease is caused by MAC, complete surgical excision is curative and limits scar formation. Therapy with clarithromycin or azithromycin combined with ethambutol and/or rifampin or rifabutin may be beneficial for children in whom surgical excision is not possible or is incomplete and for children with recurrent disease, although published reports of antimicrobial therapy without surgical incision have had variable success rates. The natural history of NTM lymphadenitis without curative surgical excision is slow resolution but with a high risk of spontaneous drainage through the skin and resulting scarring, even when antimicrobial management is used. Joint decision making with the parent(s) and possibly the child, depending on age, is important in developing the best treatment plan for each patient.

The choice of drugs, dosages, and duration should be reviewed with a consultant experienced in the management of NTM infections (Table 155.2). Indwelling foreign bodies should be removed, and surgical débridement for serious localized disease is optimal. Clinical isolates of MAC usually are resistant to many of the approved antituberculosis drugs, including isoniazid, but generally are susceptible to clarithromycin and azithromycin and often are susceptible to combinations of ethambutol, rifabutin or rifampin, and amikacin or streptomycin. Susceptibility testing to these other agents has not been standardized and, thus, is not recommended routinely. Isolates of rapidly growing mycobacteria (*M fortuitum*, *M abscessus*, and *M chelonae*) should be tested in vitro against drugs to which they commonly are susceptible and that have been used with some therapeutic success (eg, amikacin, imipenem, sulfamethoxazole or trimethoprim-sulfamethoxazole, cefoxitin, ciprofloxacin, clarithromycin, linezolid, clofazimine, doxycycline, and tigecycline).

The duration of therapy for NTM infections will depend on host status, site(s) of involvement, and severity. Patients receiving therapy should be monitored. Patients receiving clarithromycin plus rifabutin or high-dose rifabutin (with another drug) should be observed for the rifabutin-related development of leukopenia, uveitis, polyarthralgia, and pseudojaundice. Most patients who respond ultimately show substantial clinical improvement in the first 4 to 6 weeks of therapy. Most experts recommend a minimum of 3 to 6 months or longer.

For patients with cystic fibrosis and isolation of MAC species, treatment is suggested only for those with clinical symptoms not attributable to other causes, worsening lung function, and chest radiographic progression. The decision to embark on therapy should take into consideration susceptibility testing results and should involve consultation with an expert in cystic fibrosis care.

In patients with acquired immunodeficiency syndrome (AIDS) and in other immunocompromised people with disseminated MAC infection, multidrug therapy is recommended. Treatment of disseminated MAC infection should be undertaken in consultation with an expert. The optimal time to initiate ART in a child in whom HIV and disseminated MAC are newly diagnosed is not established. Many experts treat disseminated MAC for 2 weeks before initiating ART to minimize occurrence of the immune reconstitution syndrome and minimize confusion relating to the cause of drug-associated toxicity.

Table 155.2
Treatment of Nontuberculous Mycobacteria Infections in Children

Organism	Disease	Initial Treatment
Slowly Growing Species		
Mycobacterium avium complex (MAC); *Mycobacterium haemophilum; Mycobacterium lentiflavum*	Lymphadenitis	Complete excision of lymph nodes; if excision incomplete or disease recurs, clarithromycin or azithromycin plus ethambutol and/or rifampin (or rifabutin).
	Pulmonary infection	Clarithromycin or azithromycin plus ethambutol with rifampin or rifabutin (pulmonary resection in some patients who fail to respond to drug therapy). For severe disease, an initial course of amikacin or streptomycin often is included. Clinical data in adults with mild to moderate disease support that 3-times-weekly therapy is as effective as daily therapy, with less toxicity. For patients with advanced or cavitary disease, drugs should be given daily.
Mycobacterium chimaera	Prosthetic valve endocarditis	Valve removal, prolonged antimicrobial therapy based on susceptibility testing.
	Disseminated	See text.
Mycobacterium kansasii	Pulmonary infection	Rifampin plus ethambutol with isoniazid daily. If rifampin resistance is detected, a 3-drug regimen based on drug susceptibility testing should be used.
	Osteomyelitis	Surgical débridement and prolonged antimicrobial therapy using rifampin plus ethambutol with isoniazid.
Mycobacterium marinum	Cutaneous infection	None, if minor; rifampin, trimethoprim-sulfamethoxazole, clarithromycin, or doxycycline[a] for moderate disease; extensive lesions may require surgical débridement. Susceptibility testing not routinely required.
Mycobacterium ulcerans	Cutaneous and bone infections	Daily intramuscular streptomycin and oral rifampin for 8 weeks; excision to remove necrotic tissue, if present.
Rapidly Growing Species		
Mycobacterium fortuitum group	Cutaneous infection	Initial therapy for serious disease is amikacin plus meropenem, IV, followed by clarithromycin, doxycycline[a] or trimethoprim-sulfamethoxazole, or ciprofloxacin, orally, on the basis of susceptibility testing; may require surgical excision. Up to 50% of isolates are resistant to cefoxitin.

Table 155.2 (*continued*)

Organism	Disease	Initial Treatment
Rapidly Growing Species (*continued*)		
Mycobacterium fortuitum group (*continued*)	Catheter infection	Catheter removal and amikacin plus meropenem, IV; clarithromycin, trimethoprim-sulfamethoxazole, or ciprofloxacin, orally, on the basis of susceptibility testing.
Mycobacterium abscessus	Otitis media; cutaneous infection	There is no reliable antimicrobial regimen because of variability in drug susceptibility. Clarithromycin plus initial course of amikacin plus cefoxitin or imipenem/meropenem; may require surgical débridement on the basis of susceptibility testing (50% are amikacin resistant).
	Pulmonary infection (in cystic fibrosis)	Serious disease, clarithromycin, amikacin, and cefoxitin or imipenem/meropenem on the basis of susceptibility testing; most isolates have very low MICs to tigecycline; may require surgical resection.
Mycobacterium chelonae	Catheter infection, prosthetic valve endocarditis	Catheter removal; débridement, removal of foreign material; valve replacement; and tobramycin (initially) plus clarithromycin, meropenem, and linezolid.
	Disseminated cutaneous infection	Tobramycin and meropenem or linezolid (initially) plus clarithromycin.

IV indicates intravenously; MIC, minimum inhibitory concentration.
[a] Doxycycline can be used for short durations (ie, 21 days or less) without regard to patient age, but for longer treatment durations is not recommended for children younger than 8 years. Only 50% of isolates of *M marinum* are susceptible to doxycycline.

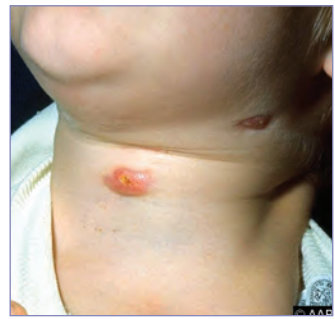


Image 155.1
Atypical mycobacterial tuberculous infection (lymphadenitis) with ulceration.

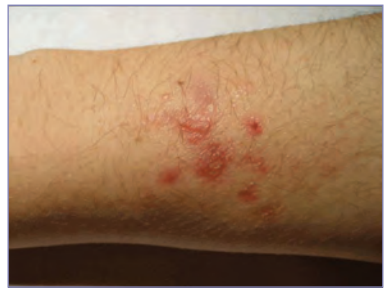


Image 155.2
Skin and soft-tissue infections caused by nontuberculous mycobacteria (NTM) usually occur after traumatic injury, surgery, or cosmetic procedures, which may expose a wound to soil, water, or medical devices occasionally contaminated with environmental mycobacteria. Although the epidemiology and clinical presentations of NTM responsible for skin and soft tissue infections differ, some species (*Mycobacterium avium* complex, *Mycobacterium kansasii*, *Mycobacterium xenopi*, and *Mycobacterium marinum*) have been reported worldwide, whereas others (*Mycobacterium ulcerans*) have limited geographic distribution. This figure shows *M marinum* infection of the arm of a fish-tank worker. *M marinum* causes diseases in many fish species and is distributed worldwide. It is an opportunistic pathogen of humans, in whom infection is infrequent and occurs by direct injury from fish fins or bites or after cutaneous trauma and subsequent exposure to contaminated water or other sources of infection (shrimp, shellfish, frogs, turtles, dolphin, eels, and oysters). Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases*.

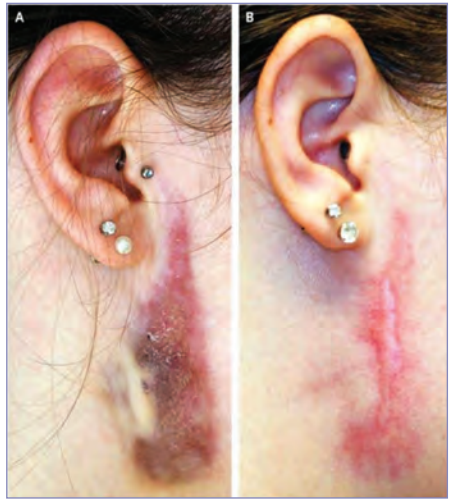


Image 155.3
An 18-year-old woman presented with a large, fluctuant, violaceous plaque on her right cheek (A). Her right tragus had been professionally pierced 6 months earlier, and streaking had developed along the angle of her jaw 1 month after the piercing. A biopsy specimen showed granulomatous inflammation. The tissue culture grew *Mycobacterium fortuitum*. Copyright *New England Journal of Medicine*.

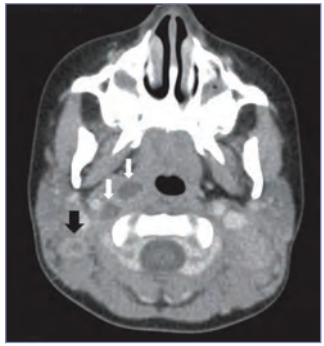


Image 155.4
Computed tomography scan of the neck of a 3-year-old girl showing right lateral retropharyngeal abscess (white arrows) and enlarged bilateral posterior cervical lymph nodes with low attenuation of a right cervical lymph node (black arrow), consistent with atypical mycobacterium adenitis. Courtesy of *Emerging Infectious Diseases.*

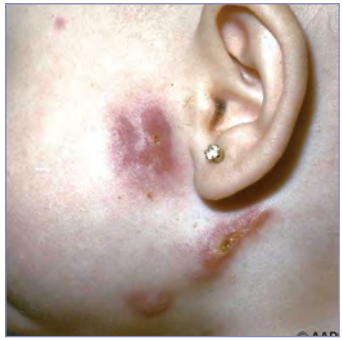


Image 155.6
Atypical mycobacterial lymphadenitis.

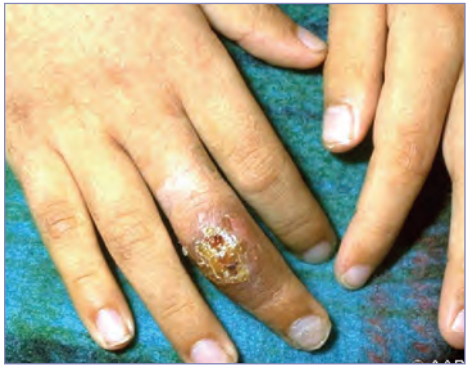


Image 155.8
The same patient as in Image 155.7 with atypical mycobacterial tuberculosis osteomyelitis of the right middle finger.

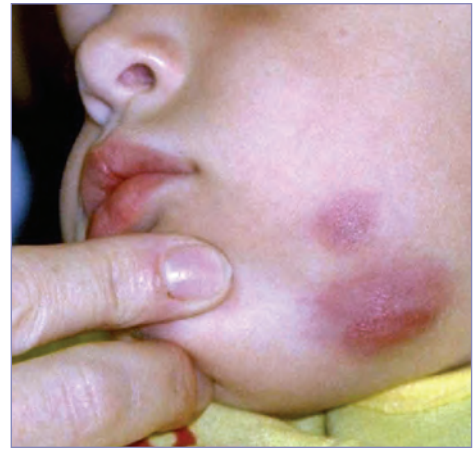


Image 155.5
Atypical mycobacterial tuberculosis (lymphadenitis) with ulceration.

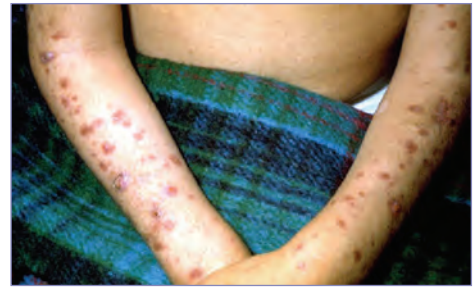


Image 155.7
Disseminated atypical mycobacterial tuberculosis with generalized cutaneous lesions in a boy with acute lymphoblastic leukemia in remission.

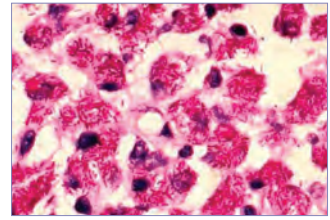


Image 155.9
Mycobacterium avium intracellulare infection of the lymph node in a patient with AIDS (Ziehl-Neelsen stain).

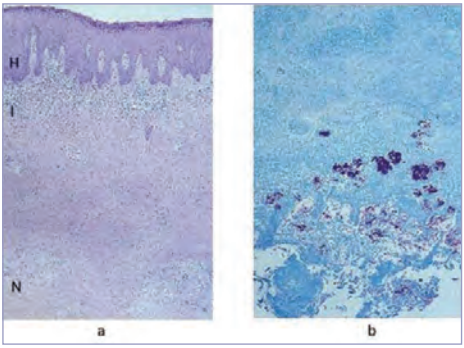


Image 155.10
A, Hematoxylin-eosin stain of a lesion specimen showing definitive Buruli ulcer disease in the pre-ulcerative stage (original magnification ×50). Notice the psoriasiform epidermal hyperplasia (H), superficial dermal lichenoid inflammatory infiltrate (I), and necrosis of subcutaneous tissues (N). B, Ziehl-Neelsen stain of the same nodule, showing abundant colonies of acid-fast bacilli in the necrotic subcutaneous tissues (original magnification ×100). Courtesy of *Emerging Infectious Diseases.*

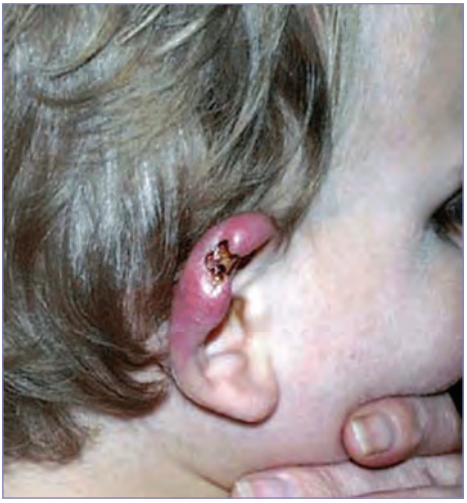


Image 155.11
An 18-month-old with culture- and polymerase chain reaction–confirmed Buruli ulcer of the right ear. She had briefly visited St Leonards, Australia. The initial lesion resembled a mosquito or other insect bite. Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases* and Paul D. R. Johnson.

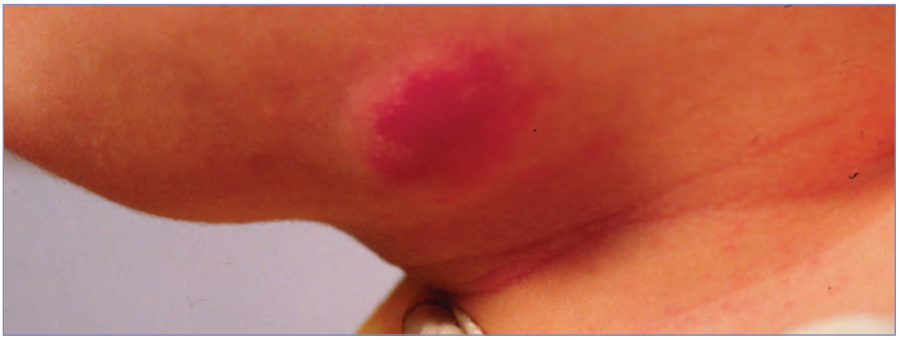


Image 155.12
A 2-year-old boy with a *Mycobacterium marinum* infection of submandibular lymphoid tissue. Courtesy of Larry Frenkel, MD.

CHAPTER 156

Tularemia

CLINICAL MANIFESTATIONS

There are several common presentations of tularemia in children, with ulceroglandular disease being the most frequently identified. Characterized by a maculopapular lesion at the entry site with subsequent ulceration and slow healing, the ulceroglandular variant is associated with tender regional lymphadenopathy that can drain spontaneously. The glandular variant (regional lymphadenopathy with no ulcer) also is common. Less common disease variants include oculoglandular (severe conjunctivitis and preauricular lymphadenopathy), oropharyngeal (severe exudative stomatitis, pharyngitis, or tonsillitis with cervical lymphadenopathy), vesicular skin lesions that can be mistaken for herpes simplex virus or varicella zoster virus cutaneous infections, typhoidal (high fever, hepatomegaly, splenomegaly, systemic infection including septicemia; pneumonia and or meningitis may be seen as complications), and intestinal (intestinal pain, vomiting, and diarrhea). Pneumonic tularemia, characterized by flu-like symptoms often without chest radiograph abnormalities, presents with fever, dry cough, chest pain, and hilar adenopathy and normally is associated with farming or, infrequently, lawn maintenance activities that create aerosols and dust. This would also be the anticipated variant after intentional aerosol release of organisms.

ETIOLOGY

Francisella tularensis is a small, weakly staining, Gram-negative pleomorphic coccobacillus. Two subspecies cause human infection in North America: *F tularensis* subspecies *tularensis* (type A), and *F tularensis* subspecies *holarctica* (type B). Type A can be further subdivided into 4 distinct genotypes (A1a, A1b, A2a, A2b), with A1b appearing to produce more serious disease in humans. Type A generally is considered more virulent, although either can be lethal, especially if inhaled.

EPIDEMIOLOGY

F tularensis can infect more than 100 animal species; the vertebrate species considered most important in enzootic cycles are rabbits, hares, and rodents, especially muskrats, voles, beavers, and prairie dogs. Domestic cats are an additional but rare source of infection. In the United States, a majority of human cases are attributed to tick bites but may also result from bites of other arthropod vectors, such as deer flies, or direct from contact with any of the aforementioned animal species. Infections attributable to tick and deer fly bites usually take the form of ulceroglandular or glandular tularemia. *F tularensis* bacteria can be transmitted to humans via the skin when handling infected animal tissue, as can occur when hunting or skinning infected rabbits, muskrats, prairie dogs, and other rodents. Infection has been reported in commercially traded hamsters and prairie dogs. Infection also can be acquired following ingestion of contaminated water or inadequately cooked meat, inhalation of contaminated aerosols generated during lawn mowing, brush cutting, or certain farming activities (eg, baling contaminated hay). At-risk people have occupational or recreational exposure to infected animals or their habitats; this includes rabbit hunters and trappers, people exposed to certain ticks or biting insects, and laboratory technicians working with *F tularensis*, which is highly infectious and may be aerosolized when grown in culture. In the United States, most cases occur during May through September. Approximately two thirds of cases occur in males, and one quarter of cases occur in children 1 to 14 years of age.

Tularemia has been reported in all US states except Hawaii. During 2005–2014, 1,424 cases were reported (median: 143 cases per year; range: 93–180). Seven states accounted for 66% of reported cases: Missouri (16%), Arkansas (15%), Oklahoma (9%), Kansas (9%), Massachusetts (6%), Nebraska (5%), and South Dakota (5%). Notably, during 2015, sharp increases occurred in the number of cases recorded in Colorado, Nebraska, South Dakota, and Wyoming. Of the 10 states with the highest incidence of tularemia, all but Massachusetts were located in the central or western United States.

Organisms can be present in blood during the first 2 weeks of disease and in cutaneous lesions for as long as 1 month if untreated. Person-to-person transmission has not been reported.

The **incubation period** usually is 3 to 5 days (range, 1–21 days).

DIAGNOSTIC TESTS

Diagnosis is established most often by serologic testing. Patients do not develop antibodies until the second week of illness. A single serum antibody titer of 1:128 or greater determined by microagglutination (MA) or of 1:160 or greater determined by tube agglutination (TA) is consistent with recent or past infection and constitutes a presumptive diagnosis. In acute infection, an antibody titer of >1:1,024 commonly is found. For those with suspected disease and an initial nondiagnostic titer, a repeat titer should be obtained in 2 to 4 weeks. Confirmation by serologic testing requires a fourfold or greater titer change between serum samples obtained at least 2 weeks apart, with 1 of the specimens having a minimum titer of 1:128 or greater by MA or 1:160 or greater by TA. Nonspecific cross-reactions can occur with specimens containing heterophile antibodies, or antibodies to *Brucella* species, *Legionella* species, or other Gram-negative bacteria. However, cross-reactions rarely result in MA or TA titers that are diagnostic. Because of its propensity for causing laboratory-acquired infections, laboratory personnel should be alerted when *F tularensis* infection is suspected.

F tularensis in ulcer exudate or aspirate material can be identified by laboratory developed polymerase chain reaction (PCR) assay or direct fluorescent antibody assay.

Immunohistochemical staining is specific for detection of *F tularensis* in fixed tissues; however, this method is not available in most clinical laboratories. Isolation of *F tularensis* from specimens of blood, skin, ulcers, lymph node drainage, gastric washings, or respiratory tract secretions is best achieved by inoculation of cysteine-enriched media, such as that used for clinical isolation of *Legionella* species. *F tularensis* often is isolated on chocolate agar. Because *F tularensis* is a biosafety level 3 agent, if suspected based on clinical and epidemiological history or Gram stain identification of tiny, gram-negative coccobacillus, further work should only be performed in a certified Class II Biosafety Cabinet.

TREATMENT

Gentamicin intramuscularly or intravenously is the drug of choice for the treatment of tularemia in children. Duration of therapy usually is 10 days. A 5- to 7-day course may be sufficient in mild disease, but a longer course is required for more severe illness (eg, meningitis). Ciprofloxacin is an alternative for mild disease. Doxycycline is associated with a higher rate of relapse compared with other therapies and, therefore, is not recommended for definitive treatment. Suppuration of lymph nodes can occur despite antimicrobial therapy. *F tularensis* is not susceptible to beta-lactams and carbapenems. Because of the difficulty in achieving good cerebrospinal fluid levels of gentamicin, combination therapy with doxycycline or ciprofloxacin plus gentamicin may be considered for patients with tularemic meningitis. Because treatment delay is associated with therapeutic failure, treatment should be initiated as soon as tularemia is suspected.

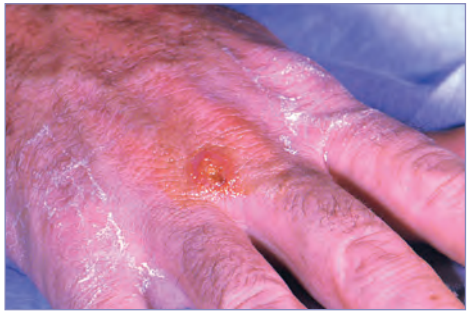


Image 156.1
A tularemic lesion on the dorsal skin of the right hand. Tularemia is caused by the bacterium *Francisella tularensis*. Symptoms vary depending on how the person was exposed to the disease; as shown here, they can include skin ulcers.

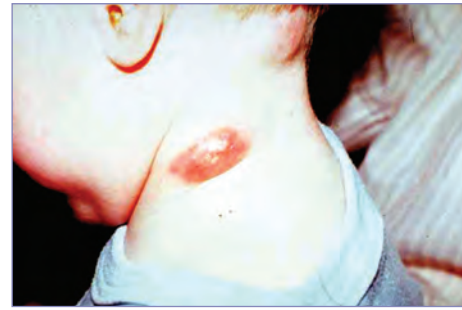


Image 156.2
An 8-year-old boy with 7 days of fever unresponsive to ceftriaxone was examined because of occipital and posterior cervical lymphadenitis. The cervical lymph node had spontaneously drained purulent material. A culture of the node aspirate was positive for *Francisella tularensis*. Courtesy of Richard Jacobs, MD.

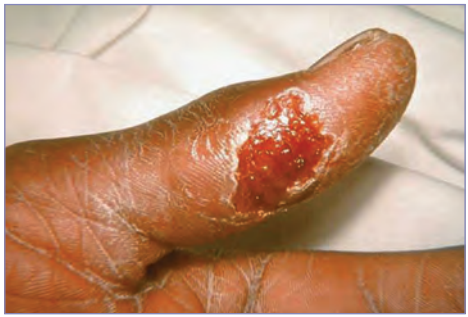


Image 156.3
Tularemic ulcer on the thumb. Irregular ulceration occurred at the site of entry of *Francisella tularensis*. Courtesy of the Centers for Disease Control and Prevention/Emory University, Dr Sellers.

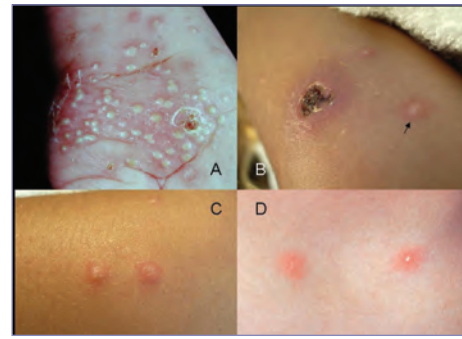


Image 156.4
A, A 6-week-old patient with vesicular tularemia initially diagnosed with herpes simplex infection. Complete herpes evaluation was negative. B–C, A 10-year-old with vesicular lesions on arms and legs thought to be varicella. Arrow (B) shows a vesicle near the primary eschar. Evaluation was negative for varicella and herpes. Culture results of the eschar and vesicles confirmed tularemia. D, Varicella lesions shown for comparison. Courtesy of Centers for Disease Control and Prevention/Heinz F. Eichenwald, MD.

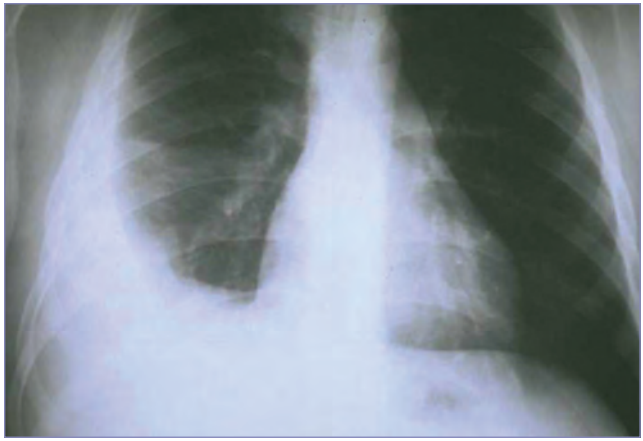


Image 156.5
Tularemia pneumonia. Posteroanterior chest radiograph showing pneumonia and pleural effusion in the lower lobe of the right lung; the pneumonia was unresponsive to ceftriaxone, azithromycin, and nafcillin. The patient had a history of tick bite and a high fever for 8 days, and his tularemia agglutinin titer was 1:2,048. An outbreak of pneumonic tularemia should prompt consideration of bioterrorism.

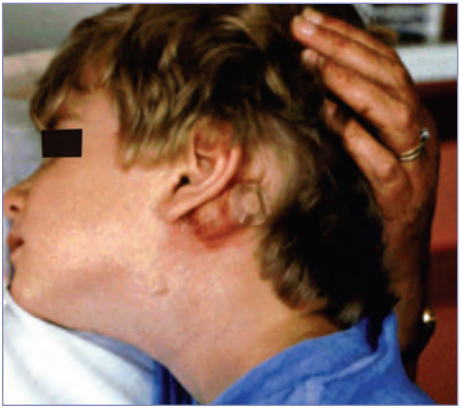


Image 156.6
Tularemia is a relatively rare infection that can manifest with painful cervical adenitis. This boy had a tick bite on his scalp that developed an ulcer followed by a large postauricular node. His tularemia titers were positive, and he responded to treatment with gentamycin.

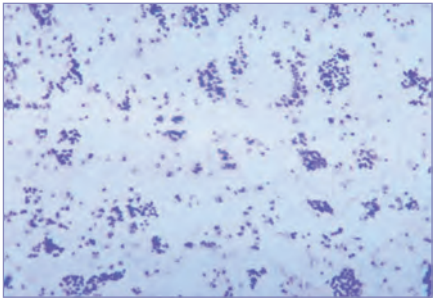


Image 156.7
This is a photomicrograph of *Francisella tularensis* bacteria with a methylene blue stain. *F tularensis* is considered to be a potential biological weapon because of its extreme infectivity, ease of dissemination, and substantial capacity to cause illness and death. Courtesy of Centers for Disease Control and Prevention.

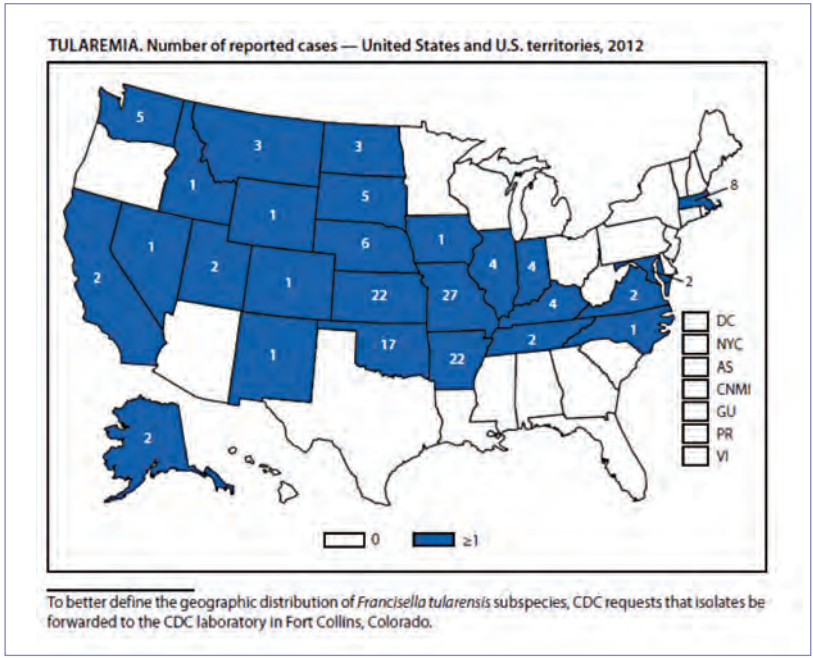


Image 156.8

Tularemia. Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

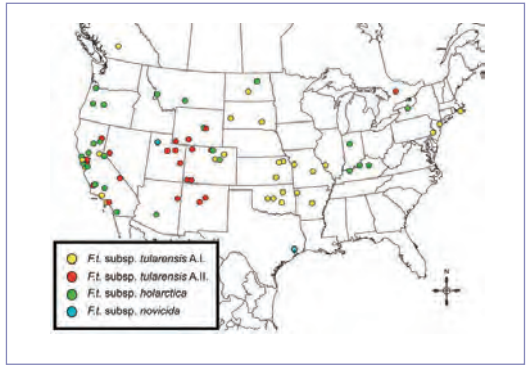


Image 156.9

Spatial distribution of 125 *Francisella tularensis* isolates for which information on originating county was available. Locations (colored circles) correspond to county centroids. More than 1 subspecies was isolated from some counties in California (Alameda, Contra Costa, Los Angeles, San Luis Obispo, and Santa Cruz) and Wyoming (Natrona). In some cases, a single circle may represent instances where more than 1 sample of a given subspecies or genotypic group was isolated from a single county. Two isolates with county information, 1 from northern British Columbia and 1 from Alaska, are not shown. Courtesy of *Emerging Infectious Diseases.*

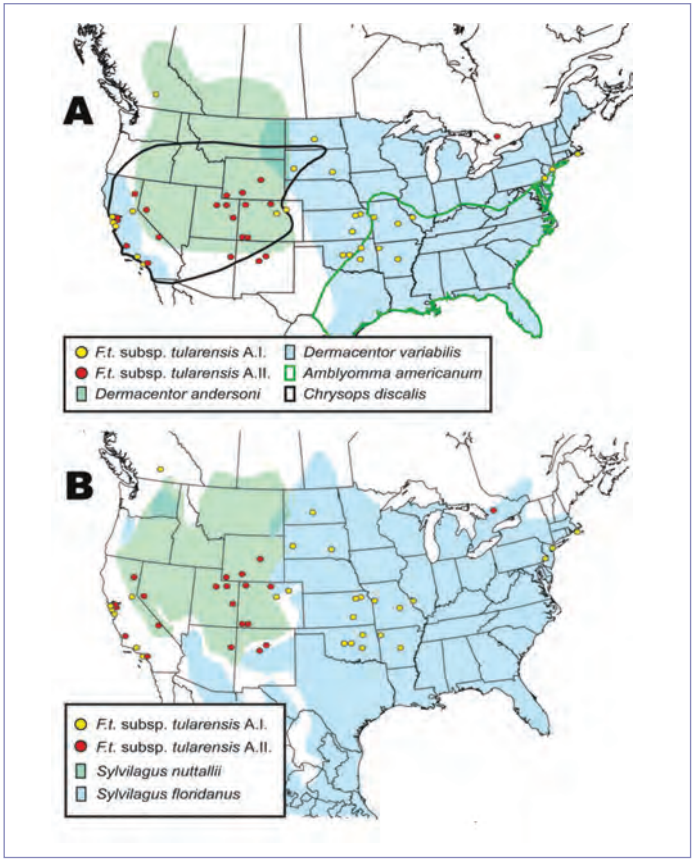


Image 156.10
Spatial distributions of isolates from the A1 and A2 subpopulations of *Francisella tularensis* subsp *tularensis* relative to (A) distribution of tularemia vectors *Dermacentor variabilis*, *Dermacentor andersoni*, *Amblyomma americanum*, and *Chrysops discalis* and (B) distribution of tularemia hosts *Sylvilagus nuttallii* and *Sylvilagus floridanus* species of rabbits. Courtesy of *Emerging Infectious Diseases*.

Image 156.11
This is a typical muskrat "house" camouflaged by reeds in Little Otter Creek, VT. The muskrat is a carrier of the bacterium *Francisella tularensis*, which is considered to be a dangerous potential biological weapon because of its extreme infectivity, ease of dissemination, and substantial capacity to cause illness and death. Courtesy of Centers for Disease Control and Prevention.

Image 156.12
This image depicts a male brown dog tick, *Rhipicephalus sanguineus*, from a superior, or dorsal, view looking down on this hard tick's scutum, or keratinized shield, which entirely covers its back, identifying it as a male. In the female, the dorsal abdomen is only partially covered, thereby offering room for abdominal expansion when she becomes engorged with blood while ingesting her blood meal obtained from her host. Courtesy of Centers for Disease Control and Prevention/James Gathany/William Nicholson.

CHAPTER 157

Endemic Typhus

(Murine Typhus)

CLINICAL MANIFESTATIONS

Endemic typhus resembles epidemic (louseborne) typhus but usually has a less abrupt onset with less severe systemic symptoms. In young children, the disease can be mild. Fever, present in almost all patients, can be accompanied by a persistent, usually severe, headache and myalgia. Nausea and vomiting also develop in approximately half of patients. A rash appears in approximately 50% of patients on day 4 to 7 of illness, is macular or maculopapular, lasts 4 to 8 days, and tends to remain discrete, with sparse lesions and no hemorrhage. Illness seldom lasts longer than 2 weeks; visceral involvement is uncommon. Laboratory findings include thrombocytopenia, elevated liver transaminases, and hyponatremia. Fatal outcome is rare except in untreated severe disease.

ETIOLOGY

Endemic typhus is caused by *Rickettsia typhi* and *Rickettsia felis*, which are gram-negative obligate intracellular bacteria.

EPIDEMIOLOGY

Rats, in which infection is unapparent, are the natural reservoirs for *Rickettsia typhi.* Outside the United States, the primary vector for transmission among rats and transmission to humans is the rat flea, *Xenopsylla cheopis*, although other fleas and mites have been implicated. In southern California and Texas, a suburban cycle involving cat fleas (*Ctenocephalides felis*) and opossums (*Didelphis virginiana*) has emerged as an important cause of endemic typhus. Infection occurs when infected flea feces are rubbed into broken skin or mucous membranes or are inhaled. The disease is worldwide in distribution and tends to occur most commonly in adults, in males, and during the months of April to October in the United States; in children, males and females are affected equally. Worldwide, exposure to rats and their fleas is the major risk factor for infection, although a history of such exposure often is absent. Endemic typhus is no longer rare in the United States, and it is likely underdiagnosed, with most cases occurring in southern California, southern Texas, the southeastern Gulf Coast, and Hawaii.

The **incubation period** is 6 to 14 days.

DIAGNOSTIC TESTS

Antibody titers determined with *R typhi* antigen by an indirect fluorescent antibody (IFA) assay are most commonly measured. Enzyme immunoassay or latex agglutination tests also are available. Antibody levels peak at around 4 weeks after infection, but results of these tests may be negative early in the course of illness. A fourfold increase in immunoglobulin (Ig) G titer between acute and convalescent serum specimens taken 2 to 3 weeks apart is diagnostic. Although more prone to false-positive results, immunoassays demonstrating increases in specific IgM antibody can aid in distinguishing clinical illness from previous exposure if interpreted with a concurrent IgG test result; use of IgM assays alone is not recommended. Serologic tests may not differentiate murine typhus caused by *R typhi* or *R felis* from epidemic (louseborne) typhus or from infection with spotted fever rickettsiae, such as *R rickettsii*, without antibody cross-absorption for IFA or western blotting analyses, which are not available routinely. Isolation of the organism in cell culture potentially is hazardous and is best performed by specialized laboratories. Routine hospital blood cultures are not suitable for culture of *R typhi.* Molecular diagnostic assays on infected whole blood and skin biopsies can distinguish endemic and epidemic typhus and other rickettsioses and along with immunohistochemical procedures on biopsy tissues can be performed at the Centers for Disease Control and Prevention.

TREATMENT

Doxycycline is the treatment of choice for endemic typhus, regardless of patient age. Early diagnosis should be based on clinical suspicion and epidemiology. In a patient with disease that is clinically compatible with endemic typhus, treatment should not be withheld because of a negative laboratory result or while awaiting laboratory confirmation, because severe or fatal infection can develop when treatment is delayed. Treatment should be continued for at least 3 days after defervescence

and evidence of clinical improvement is documented, and the total treatment course usually is 7 to 14 days. Fluoroquinolones or chloramphenicol are alternative medications but may not be as effective.

Image 157.1
A Norway rat, *Rattus norvegicus,* in a Kansas City, MO, corn storage bin. *R norvegicus* is known to be a reservoir of bubonic plague (transmitted to people by the bite of a flea or other insect), endemic typhus fever, rat-bite fever, and a few other dreaded diseases. Courtesy of Centers for Disease Control and Prevention.

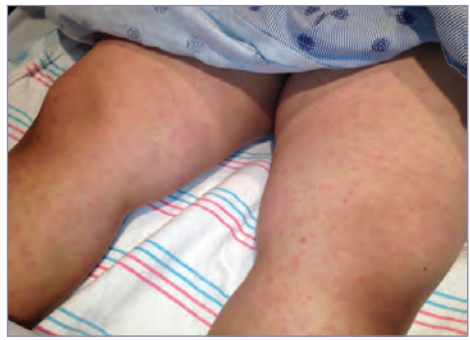


Image 157.2
A healthy 8-year-old boy had 5 days of fever, severe headache, and malaise before this rash began. He had been exposed to numerous cats with fleas before the onset of illness. Courtesy of Carol J. Baker, MD, FAAP.

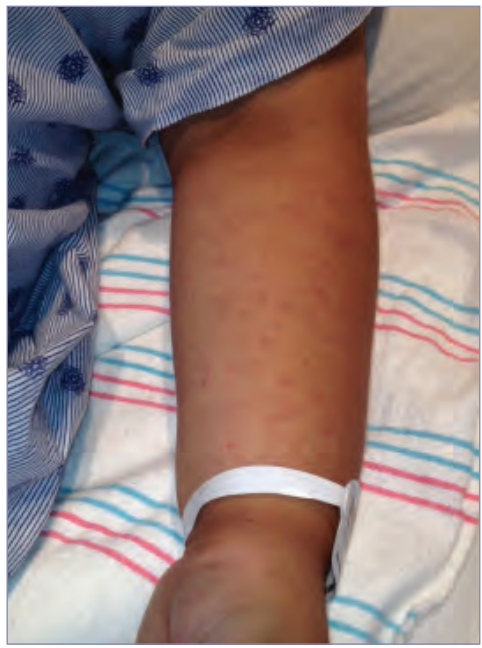


Image 157.3
The same boy as in Image 157.2 who had rash involving palms and soles as well as pancytopenia. He recovered completely with doxycycline therapy. Courtesy of Carol J. Baker, MD, FAAP.

CHAPTER 158

Epidemic Typhus

(Louseborne or Sylvatic Typhus)

CLINICAL MANIFESTATIONS

Clinically, epidemic typhus should be considered when people in crowded conditions or people with exposure to flying squirrels develop abrupt onset of high fever, chills, and myalgia accompanied by severe headache and malaise. Although patients with epidemic typhus often develop a rash by day 4 to 7 after the start of illness, rash may not always be present and should not be relied on for diagnosis. When present, the rash usually begins on the trunk and axilla, spreads centrifugally to the limbs, and generally spares the face, palms, and soles. The rash typically is macular to maculopapular, but in advanced stages can become petechial or hemorrhagic. There is no eschar, as might be present in many other rickettsial diseases. Abdominal complaints (stomach pain, nausea) and changes in mental status are common, including delirium, seizures, and coma. Myocardial and renal failure can occur when the disease is severe. The fatality rate in untreated people is as high as 30%. Mortality is less common in children, and the rate increases with advancing age. Untreated patients who recover typically have an illness lasting 2 weeks. Brill-Zinsser disease is a relapse of epidemic typhus that can occur years after the initial episode and is generally milder in nature. Factors that reactivate the rickettsiae are unknown, but relapse often is milder and of shorter duration. Laboratory abnormalities in epidemic typhus may include thrombocytopenia, increased hepatic enzymes, hyperbilirubinemia, and elevated blood urea nitrogen.

ETIOLOGY

Epidemic typhus is caused by *Rickettsia prowazekii.*

EPIDEMIOLOGY

Humans are the primary reservoir of the organism, which is transmitted from person to person by the human body louse, *Pediculus humanus humanus.* Infected louse feces are rubbed into broken skin or mucous membranes or are inhaled. All ages are affected. Poverty, crowding, and poor sanitary conditions contribute to the spread of body lice and, hence, the disease. Cases of epidemic typhus are rare in the United States; however, there is no formal system for epidemic typhus surveillance. The last known epidemic in the United States occurred in 1921. Cases have occurred throughout the world, including the colder, mountainous areas of Asia, Africa, some parts of Europe, and Central and South America, particularly in refugee camps and jails of resource-limited countries. Epidemic typhus is most common during winter, when conditions favor person-to-person transmission of the vector. Rickettsiae are present in the blood and tissues of patients during the early febrile phase but are not found in secretions. Direct person-to-person spread of the disease does not occur in the absence of the louse vector.

In the United States, sporadic human cases associated with close contact with infected flying squirrels (*Glaucomys volans*), their nests, or their ectoparasites occasionally are reported in the eastern United States. Cases have been reported in people who reside or work in flying squirrel-infested dwellings, even when direct contact is not reported. Flying squirrel-associated disease, called sylvatic typhus, typically presents with a similar but generally milder illness to that observed with body louse-transmitted infection. Untreated illness can be severe, although no fatal cases of sylvatic typhus have been reported; the later development of Brill Zinsser disease has been confirmed in at least 1 case of untreated sylvatic typhus. *Amblyomma* ticks in the Americas and in Ethiopia have been shown to carry *R prowazekii*, but their vector potential is unknown.

The **incubation period** is 1 to 2 weeks.

DIAGNOSTIC TESTS

Epidemic typhus may be diagnosed by the detection of *R prowazekii* DNA in acute blood and serum specimens by polymerase chain reaction (PCR) assay. The specimen should preferably be obtained within the first week of symptoms and before (or within 24 hours of) doxycycline administration, and a negative result does not rule out *R prowazekii* infection. Diagnosis may also be attained by the

detection of rickettsial DNA in biopsy or autopsy specimens by PCR assay or immunohistochemical (IHC) visualization of rickettsiae in tissues. The gold standard for serologic diagnosis of epidemic typhus is a fourfold increase in immunoglobulin (Ig) G antibody titer by the indirect fluorescent antibody (IFA) test. A negative acute serologic test result does not rule out a diagnosis of epidemic typhus. Both IgG and IgM antibodies begin to increase around day 7 to 10 after onset of symptoms; therefore, an elevated acute titer may represent past infection rather than acute infection. Low-level elevated antibody titers can be an incidental finding in a significant proportion of the general population in some regions. IgM antibodies may remain elevated for months and are not highly specific for acute epidemic typhus. A confirmed case, therefore, is one that shows a fourfold or greater increase in antigen-specific IgG between acute and convalescent sera obtained 2 to 6 weeks apart. Cross-reactivity may be observed to antibodies to *R typhi* (the agent of endemic typhus), *R rickettsii* (the agent of Rocky Mountain spotted fever), and other spotted fever group rickettsiae. Testing of acute and convalescent sera by enzyme immunoassays or dot blot immunoassay tests also can be used for assessing presence of antibody but are less useful for quantifying changes in titer.

TREATMENT

Doxycycline intravenously or orally is the drug of choice to treat epidemic typhus, regardless of patient age. Treatment should be continued for at least 3 days after defervescence and evidence of clinical improvement is documented, and the total treatment course is usually for 5 to 10 days. Other broad-spectrum antimicrobial agents, including ciprofloxacin, are not recommended. In epidemic situations in which antimicrobial agents may be limited eg, refugee camps), a single dose of doxycycline may provide treatment and facilitate outbreak control.

Image 158.1
Pediculus humanus humanus, the human body louse, viewed with electron microscope (magnification ×120). Courtesy of Centers for Disease Control and Prevention/*Emerging Infectious Diseases* and Cédric Foucault.

Image 158.2
Human body lice in clothes. Courtesy of Centers for Disease Control and Prevention/ *Emerging Infectious Diseases* and Cédric Foucault.

Image 158.3
This image depicts an adult female body louse, *Pediculus humanus*, and 2 larval young, which serve as the vector of epidemic typhus. Courtesy of Centers for Disease Control and Prevention.

CHAPTER 159

Ureaplasma urealyticum and *Ureaplasma parvum* Infections

CLINICAL MANIFESTATIONS

The role of *Ureaplasma* species in human disease is controversial. There has been an inconsistent association with *Ureaplasma urealyticum* infections and nongonococcal urethritis (NGU). Although 15% to 40% of cases of NGU are caused by *Chlamydia trachomatis* and an additional 15% to 25% by *Mycoplasma genitalium*, *U urealyticum*, but not *Ureaplasma parvum*, has been implicated as an etiologic agent in some cases in the United States. Without treatment, the infection usually resolves within 1 to 6 months, although asymptomatic infection may persist. There also has been an inconsistent relationship of infection by *Ureaplasma* species with prostatitis and epididymitis in men and salpingitis and endometritis in women. *Ureaplasma* organisms commonly are detected in placentas with histologic chorioamnionitis (now known as intra-amniotic infection). Some reports also describe an association between *Ureaplasma* infection with recurrent pregnancy loss and preterm birth.

Although *U urealyticum* and *U parvum* have been isolated from the lower respiratory tract and from lung biopsy specimens of preterm infants, their contribution to intrauterine pneumonia and chronic lung disease of prematurity remains controversial. These organisms also have been recovered from respiratory tract secretions of infants 3 months or younger with pneumonia, but their role in development of lower respiratory tract disease in otherwise healthy young infants is unclear. *Ureaplasma* species have been isolated from the bloodstream of newborn infants with bacteremia and from cerebrospinal fluid of infants with meningitis, intraventricular hemorrhage, and hydrocephalus. The contribution of *U urealyticum* to the outcome of infants with infections of the central nervous system is unclear given the confounding effects of preterm birth and intraventricular hemorrhage. Numerous cases of *U urealyticum* or *U parvum* arthritis, osteomyelitis, pneumonia, pericarditis, meningitis, and progressive sinopulmonary disease, mainly in immunocompromised patients, have been reported.

ETIOLOGY

Ureaplasma organisms are small pleomorphic bacteria that lack a cell wall. The genus contains 2 species capable of causing human infection, *U urealyticum* and *U parvum*.

EPIDEMIOLOGY

The principal reservoir of human *Ureaplasma* species is the genital tract of sexually active adults. Colonization occurs in approximately half of sexually active women; the incidence in sexually active men is lower. Colonization is uncommon in prepubertal children and adolescents who are not sexually active, but a positive genital tract culture is not a definitive cause of sexual abuse. Transmission during delivery is likely from an asymptomatic colonized mother to her newborn infant, and infection also may occur in utero. *Ureaplasma* species may colonize the throat, eyes, umbilicus, and perineum of newborn infants and may persist for several months after birth. *U parvum* generally is more common than *U urealyticum* as a colonizer in pregnant women and their offspring.

Because *Ureaplasma* species commonly are isolated from the female lower genital tract and neonatal respiratory tract in the absence of disease, a positive culture does not establish its causative role in acute infection. However, recovery of these organisms from an upper genital tract or lower respiratory tract specimen is much more indicative of true infection.

The **incubation period** after sexual transmission is 10 to 20 days.

DIAGNOSTIC TESTS

Specimens for culture require specific *Ureaplasma* transport media with refrigeration at 4°C (39°F). Dacron or calcium alginate swabs should be used; cotton swabs should be avoided. Several rapid, sensitive real-time polymerase chain reaction assays for detection of *U urealyticum* and *U parvum* have been developed. Many of these assays have greater sensitivity than culture, but they are only

available in reference laboratories. *Ureaplasma* species can be cultured in urea-containing broth and agar in 2 to 4 days.

TREATMENT

A positive *Ureaplasma* culture does not indicate need for therapy if the patient is asymptomatic. *Ureaplasma* species generally are susceptible to macrolides, tetracyclines, and quinolones, but because they lack a cell wall, they are not susceptible to penicillins or cephalosporins. They also are not susceptible to trimethoprim-sulfamethoxazole or clindamycin. For symptomatic children, adolescents, and adults, doxycycline can be used for treatment. Persistent urethritis after doxycycline treatment can be attributable to doxycycline-resistant *U urealyticum* or *M genitalium*. Recurrences are common. Azithromycin is the preferred antimicrobial agent for children younger than 8 years, people who are allergic to tetracyclines, and people with infections caused by tetracycline-resistant strains. A quinolone would be another option if azithromycin resistance is possible (eg, detection of *Ureaplasma* in a patient who has received azithromycin for prolonged periods).

Antimicrobial treatment with erythromycin has failed to prevent preterm delivery and in preterm infants has failed to prevent pulmonary disease. Although in vitro efficacy against *Ureaplasma* species is observed with clarithromycin, azithromycin, and fluoroquinolones, lack of evidence of benefit precludes recommendations on treatment for preterm infants. Definitive evidence of efficacy of antimicrobial agents in the treatment of central nervous system infections caused by *Ureaplasma* species in infants and children is lacking.

CHAPTER 160

Varicella-Zoster Virus Infections

CLINICAL MANIFESTATIONS

Primary infection results in varicella (chickenpox), manifesting in unvaccinated people as a generalized, pruritic, vesicular rash typically consisting of 250 to 500 lesions in varying stages of development (papules, vesicles) and resolution (crusting), low-grade fever, and other systemic symptoms. Complications include bacterial superinfection of skin lesions with or without bacterial sepsis, pneumonia, central nervous system involvement (acute cerebellar ataxia, encephalitis, stroke/vasculopathy), thrombocytopenia, and rarer complications such as glomerulonephritis, arthritis, and hepatitis. Primary viral pneumonia is not common among immunocompetent children but is the most common complication in adults. Varicella tends to be more severe in adults and in infants and adolescents than in other children. Before the introduction of routine immunization against varicella, an average of 100 to 125 people died of chickenpox in the United States each year. Breakthrough varicella cases can occur in immunized children but usually are mild and clinically modified. Reye syndrome may follow varicella, although this outcome has become very rare with the recommendation not to use salicylate-containing compounds (eg, aspirin, bismuth-subsalicylate) for children with chickenpox. In immunocompromised children, progressive, severe varicella may occur with continuing eruption of lesions (sometimes including hemorrhagic skin lesions) along with high fever persisting into the second week of illness and visceral dissemination (ie, encephalitis, hepatitis, and pneumonia). Severe and even fatal varicella has been reported in otherwise healthy children on high-dose corticosteroids for treatment of asthma and other illnesses. The risk is especially high when cortico-steroids are administered during the varicella incubation period.

Varicella-zoster virus (VZV) establishes latency in sensory (dorsal root, cranial nerve, and autonomic including enteric) ganglia during primary VZV infection. This latency occurs with wild-type VZV or with the vaccine strain. Reactivation results in herpes zoster (shingles), characterized by grouped vesicular skin lesions in the distribution of 1 to 3 sensory dermatomes, frequently accompanied by pain and/or itching localized to the area. *Postherpetic neuralgia*, pain that persists after resolution of the zoster rash, may last for weeks to months but is very unusual in children. Zoster occasionally becomes disseminated in immunocompromised patients, with lesions appearing outside the primary dermatomes and/or visceral complications. VZV reactivation less frequently occurs in the absence of skin rash (zoster sine herpete); these patients may present with aseptic meningitis, encephalitis, stroke, or gastrointestinal tract involvement (visceral zoster).

Fetal infection after maternal varicella during the first or early second trimester of pregnancy occasionally results in fetal death or varicella embryopathy, characterized by limb hypoplasia, cutaneous scarring, eye abnormalities, and damage to the central nervous system (congenital varicella syndrome). The incidence of the congenital varicella syndrome among infants born to mothers who experience gestational varicella is approximately 2% when infection occurs between 8 and 20 weeks of gestation. Rarely, cases of congenital varicella syndrome have been reported in infants of women infected after 20 weeks of pregnancy, the latest occurring at 28 weeks' gestation. Children infected with VZV in utero may develop zoster early in life without having had extrauterine varicella.

Varicella infection has a higher case-fatality rate in infants when the mother develops varicella from 5 days before to 2 days after delivery, because there is little opportunity for development and transfer of maternal antibody across the placenta prior to delivery and the infant's cellular immune system is immature. When varicella develops in a mother more than 5 days before delivery and gestational age is 28 weeks or more, the severity of disease in the newborn infant is modified by transplacental transfer of VZV-specific maternal immunoglobulin (Ig) G antibody. Neither wild-type VZV nor Oka vaccine strain virus have been shown to be transmitted by human milk; expressed/pumped

milk from a mother with varicella or zoster can be given to the infant, provided no lesions are on the breast.

ETIOLOGY

VZV (also known as human herpesvirus 3) is a member of the *Herpesviridae* family, the subfamily *Alphaherpesvirinae*, and the genus *Varicellovirus*.

EPIDEMIOLOGY

Humans are the only source of infection for this highly contagious virus. Infection occurs when the virus comes in contact with the mucosa of the upper respiratory tract or the conjunctiva of a susceptible person. Person-to-person transmission occurs either from direct contact with VZV lesions from varicella or herpes zoster or from airborne spread. Varicella is much more contagious than is herpes zoster. Skin lesions appear to be the major source of transmissible VZV; transmission from infected respiratory tract secretions is possible but probably less common. There is no evidence of VZV spread from fomites; the virus is extremely labile and is unable to survive for long in the environment. In utero infection occurs as a result of transplacental passage of virus during viremic maternal varicella infection. VZV infection in a household member usually results in infection of almost all susceptible people in that household. Children who acquire their infection at home (secondary family cases) often have more skin lesions than the index case. Health care-associated transmission is well documented in pediatric units.

In temperate climates in the prevaccine era, varicella was a childhood disease with a marked seasonal distribution, with peak incidence during late winter and early spring and among children younger than 10 years. High rates of vaccine coverage in the United States have effectively eliminated discernible seasonality of varicella. In tropical climates, acquisition of varicella often occurs later in childhood, resulting in a significant proportion of susceptible adults. Following implementation of universal immunization in the United States in 1995, varicella incidence declined in all age groups as a result of individual and herd immunity. In areas with active surveillance and high 1-dose vaccine coverage, the rate of varicella disease decreased by approximately 90% between 1995 and 2005. Since routine recommendation for 2 doses of vaccine in 2006, varicella outpatient visits have declined by an additional 60%, and varicella hospitalizations have declined by an additional 40%. The age of peak varicella incidence is shifting from children younger than 10 years to children 10 through 14 years of age, although the incidence in all age groups is lower than in the prevaccine era. Immunity to varicella generally is lifelong. Cellular immunity is more important than humoral immunity for limiting the extent of primary infection with VZV and for preventing reactivation of virus with herpes zoster. Symptomatic reinfection is uncommon in immunocompetent people. Asymptomatic primary infection is unusual.

Since 2007, coverage with 1 or more doses of varicella vaccine among 19- through 35-month-old children in the United States has been >90%. As most children are vaccinated against varicella and the incidence of wild-type varicella decreases, a greater proportion of varicella cases are occurring in immunized people as breakthrough disease.

Immunocompromised people with primary (varicella) or recurrent (herpes zoster) infection are at increased risk of severe disease. Severe varicella and disseminated zoster are more likely to develop in children with congenital T-lymphocyte defects or acquired immunodeficiency syndrome than in people with B-lymphocyte abnormalities. Other groups of pediatric patients who may experience more severe or complicated varicella include infants, adolescents, patients with chronic cutaneous or pulmonary disorders, and patients receiving systemic corticosteroids, other immunosuppressive therapy, or long-term salicylate therapy.

Patients are contagious from 1 to 2 days before onset of the rash until all lesions have crusted.

The **incubation period** usually is 14 to 16 days (range, 10–21 days) after exposure. The incubation period may be prolonged for as long as 28 days after receipt of Varicella-Zoster Immune Globulin (VariZIG) or Immune Globulin Intravenous (IGIV) and can be shortened in immunocompromised patients. Varicella can

develop between 2 and 16 days after birth in infants born to mothers with active varicella around the time of delivery.

DIAGNOSTIC TESTS

Diagnostic tests for VZV are summarized in Table 160.1. Vesicular fluid or a scab can be used to identify VZV using a polymerase chain reaction (PCR) test, which currently is the diagnostic method of choice. During the acute phase of illness, VZV also can be identified by PCR assay of saliva or buccal swabs, although VZV is more likely to be detected in vesicular fluid or scabs. VZV can be demonstrated by direct fluorescent antibody (DFA) assay, using scrapings of a vesicle base early in the eruption or by viral isolation in cell culture from vesicular fluid. Viral culture and DFA assay both are less sensitive than PCR assay, and neither method is capable of distinguishing vaccine-strain from wild-type viruses. PCR testing that discriminates between vaccine and wild-type VZV is available free of charge through the specialized reference laboratory at the Centers for Disease Control and Prevention.

A significant increase (4-fold increase in titer) in serum varicella immunoglobulin (Ig) G antibody between acute and convalescent samples by any standard serologic assay can confirm a diagnosis retrospectively, but this may not reliably occur in immunocompromised people. However, diagnosis of VZV infection by serologic testing seldom is indicated. Commercially available enzyme immunoassay (EIA) tests usually are not sufficiently sensitive to demonstrate reliably a vaccine-induced antibody response, and therefore, routine postvaccination serologic testing is not recommended. IgM tests are not reliable for routine confirmation or ruling out of acute infection. All VZV IgM assays are prone to false-negative and false-positive results.

TREATMENT

Nonspecific therapies for varicella include keeping fingernails short to prevent trauma and secondary bacterial infection from scratching, frequent bathing, application of calamine lotion to reduce pruritus, and acetaminophen for fever. Children with varicella should not receive

Table 160.1
Diagnostic Tests for Varicella-Zoster Virus (VZV) Infection

Test	Specimen	Comments
PCR	Vesicular swabs or scrapings, scabs from crusted lesions, biopsy tissue, CSF	Very sensitive method. Specific for VZV. Methods have been designed that distinguish vaccine strain from wild-type (see text).
DFA	Vesicle scraping, swab of lesion base (must include cells)	Specific for VZV. More rapid and more sensitive than culture, less sensitive than PCR.
Viral culture	Vesicular fluid, CSF, biopsy tissue	Distinguishes VZV from HSV. High cost, limited availability, requires up to a week for result. Least sensitive method.
Serology (IgG)	Acute and convalescent serum specimens for IgG	Specific for VZV. Commercial assays generally have low sensitivity to reliably detect vaccine-induced immunity. gpELISA and FAMA are the only IgG methods that can readily detect vaccine seroconversion, but these tests are not commercially available.
Capture IgM	Acute serum specimens for IgM	Specific for VZV. IgM inconsistently detected. Not reliable method for routine confirmation. Requires special equipment.

salicylates or salicylate-containing products (eg, aspirin, bismuth-subsalicylate), because these products increase the risk of Reye syndrome. Salicylate therapy should be stopped in an unimmunized child who is exposed to varicella. Treatment with ibuprofen is controversial and should be avoided if possible.

The decision to use antiviral therapy and the route and duration of therapy should be determined by host factors and extent of infection. Antiviral drugs have a limited window of opportunity to affect the outcome of VZV infection. In immunocompetent hosts, most virus replication has stopped by 72 hours after onset of rash; the duration of replication may be extended in immunocompromised hosts. Oral acyclovir and valacyclovir are not recommended for routine use in otherwise healthy younger children with varicella, because their use results in only a modest decrease in symptoms. Antiviral therapy should be considered for otherwise healthy people at increased risk of moderate to severe varicella, such as unvaccinated people older than 12 years, and those with chronic cutaneous or pulmonary disorders, those receiving long-term salicylate therapy, or those receiving short or intermittent courses of corticosteroids. Some experts also recommend use of oral acyclovir or valacyclovir for secondary household cases in which the disease usually is more severe than in the primary case.

Some experts recommend oral acyclovir or valacyclovir for pregnant women with varicella, especially during the second and third trimesters. Intravenous acyclovir is recommended for pregnant patients with serious complications of varicella. Intravenous acyclovir therapy is recommended for immunocompromised patients, including patients being treated with high-dose corticosteroid therapy for more than 14 days. Therapy initiated early in the course of the illness, especially within 24 hours of rash onset, maximizes benefit. Oral acyclovir should not be used to treat immunocompromised children with varicella because of poor oral bioavailability. Valacyclovir administered orally 3 times daily for 5 days is licensed for treatment of varicella in children 2 through 17 years of age. Some experts have used valacyclovir, with its improved bioavailability compared with oral acyclovir, in selected immunocompromised patients perceived to be at low to moderate risk of developing severe varicella, such as human immunodeficiency virus (HIV)-infected patients with relatively normal concentrations of CD4+ T-lymphocytes and children with leukemia in whom careful follow-up is ensured. Famciclovir is available for treatment of VZV infections in adults, but its efficacy and safety have not been established for children. Although VariZIG or, if not available, IGIV, administered shortly after exposure, can prevent or modify the course of disease, Immune Globulin preparations are not effective treatment once disease is established.

Infections caused by acyclovir-resistant VZV strains, which generally are rare and limited to immunocompromised hosts, should be treated with parenteral foscarnet.

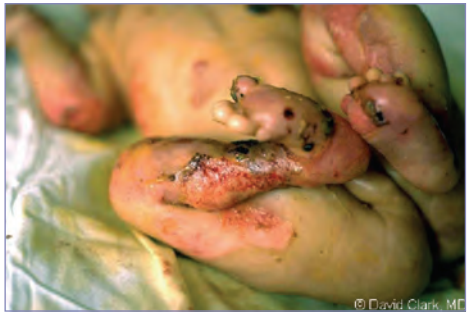


Image 160.1
Congenital varicella with short-limb syndrome and scarring of the skin. The mother had varicella during the first trimester of pregnancy. Courtesy of David Clark, MD.

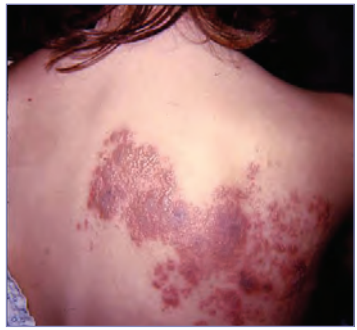


Image 160.3
Herpes zoster in an 18-year-old woman, a known illicit drug user, who also had an anaerobic lung abscess. Courtesy of Larry Frenkel, MD.

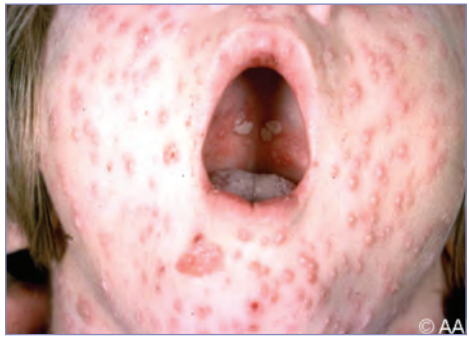


Image 160.5
This child acquired her infection from a younger sibling. Varicella lesions are apparent on the palate. This is the same child as in Image 160.4.

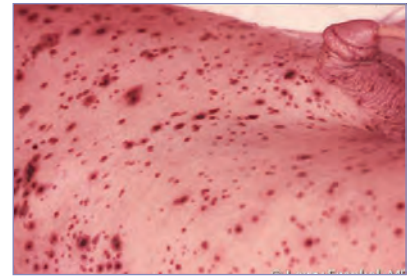


Image 160.2
A male toddler with hemorrhagic varicella complicating acute lymphocytic leukemia. Courtesy of Larry Frenkel, MD.

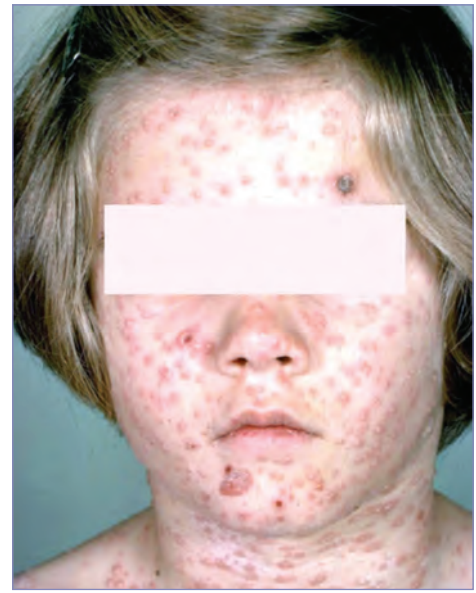


Image 160.4
School-aged girl with varicella who acquired it from a younger sibling, who had a milder clinical course with fewer lesions.

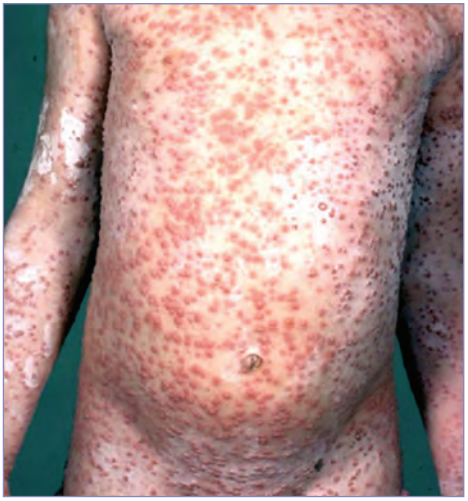


Image 160.6
School-aged child with varicella who acquired it from a younger sibling. This is the same child as in Images 160.4 and 160.5 who had calamine lotion applied by the parents for itching. She recovered without incident.

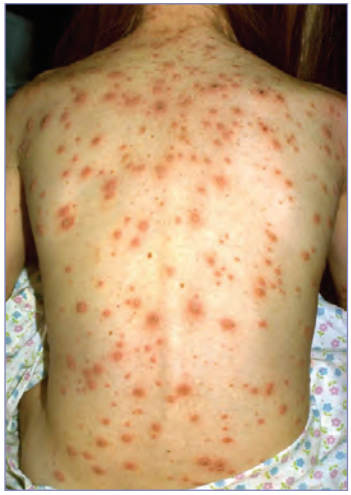


Image 160.9
An adolescent girl with varicella lesions in various stages. This is the same patient as in Images 160.7 and 160.8.

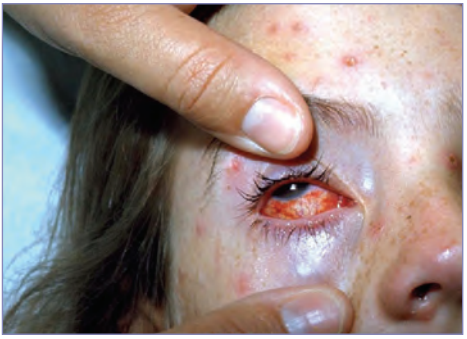


Image 160.7
Varicella with scleral lesions and bulbar conjunctivitis.

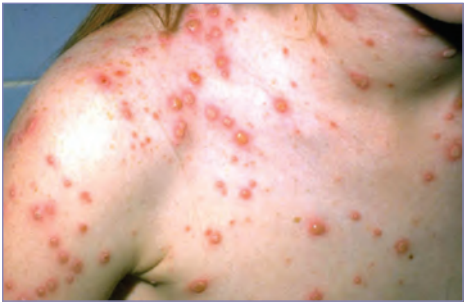


Image 160.8
An adolescent girl with varicella lesions in various stages. This is the same patient as in Image 160.7.

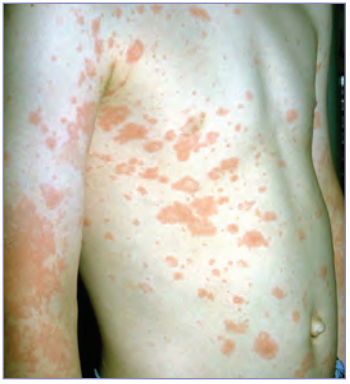


Image 160.10
Varicella with erythema multiforme.

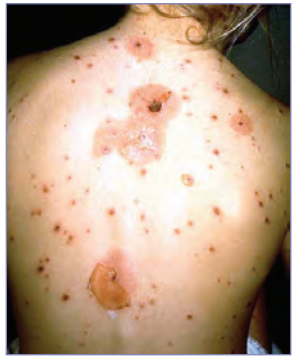


Image 160.11
Varicella with bullous lesions. Blood culture results were negative for bacteria. Cellulitis at sites of bullous lesions resolved while receiving oral dicloxacillin sodium. The child did not appear to be very ill.

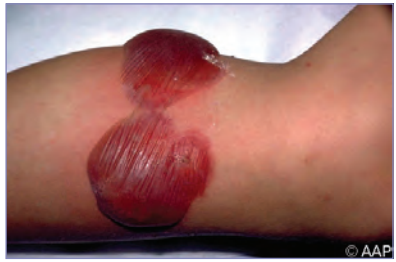


Image 160.13
Bullous varicella. *Staphylococcus aureus* organisms may be present in these large bullae.

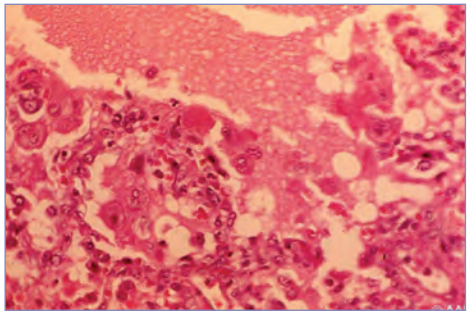


Image 160.15
Varicella (interstitial) pneumonia. Although rare in otherwise healthy children, this complication of varicella-zoster virus infection in adults accounts for much of the morbidity and mortality caused by the infection. Courtesy of Edgar O. Ledbetter, MD, FAAP.

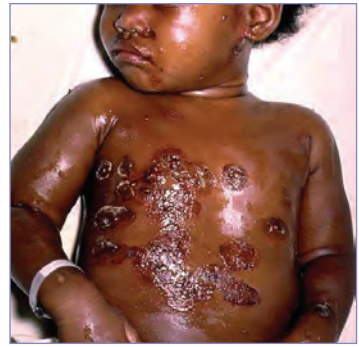


Image 160.12
Varicella with bullous lesions. Results of cultures of vesicle fluid were negative for bacteria.

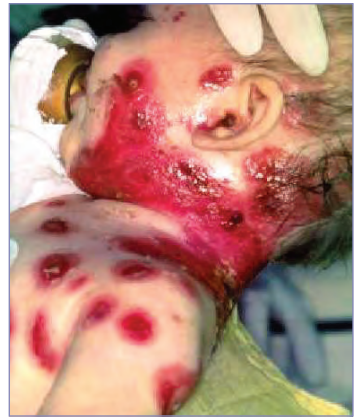


Image 160.14
A neonate with hemorrhagic varicella with cellulitis. This newborn contracted varicella at birth from his mother, who was infected.

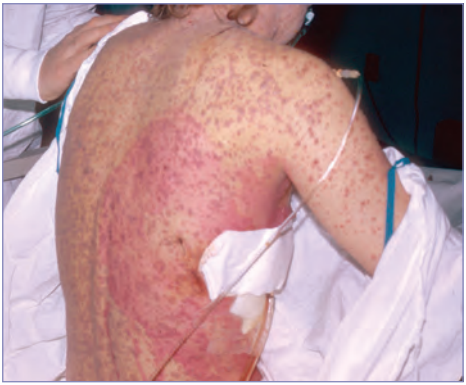


Image 160.16
Disseminated varicella in a 17-year-old girl with Hodgkin disease and failure to respond to intravenous acyclovir. Courtesy of George Nankervis, MD.

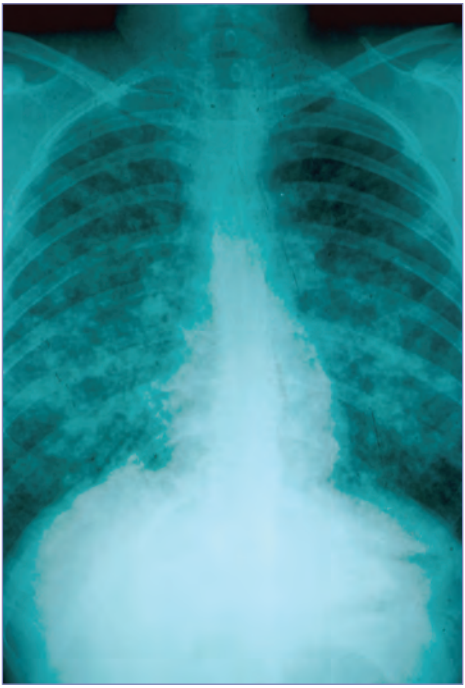


Image 160.17
Diffuse varicella pneumonia bilaterally shown in the chest radiograph of the patient in Image 160.16 with Hodgkin disease. Courtesy of George Nankervis, MD.

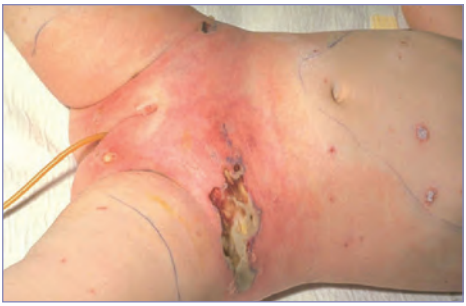


Image 160.18
Varicella complicated by necrotizing fasciitis. A blood culture result was positive for group A streptococcus. The disease responded to antibiotics and surgical debridement followed by primary surgical closure.

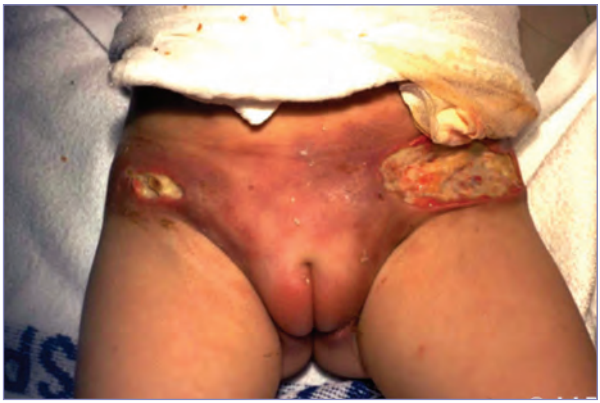


Image 160.19
Varicella and necrotizing fasciitis in the same patient as in Image 160.18 shortly after surgical debridement.

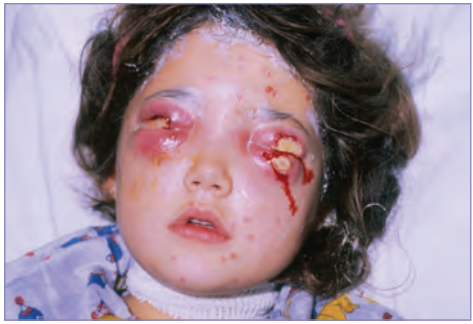


Image 160.20
A school-aged girl with bilateral periorbital cellulitis and necrotizing fasciitis caused by a group A β-hemolytic streptococcal infection complicating varicella. Courtesy of George Nankervis, MD.

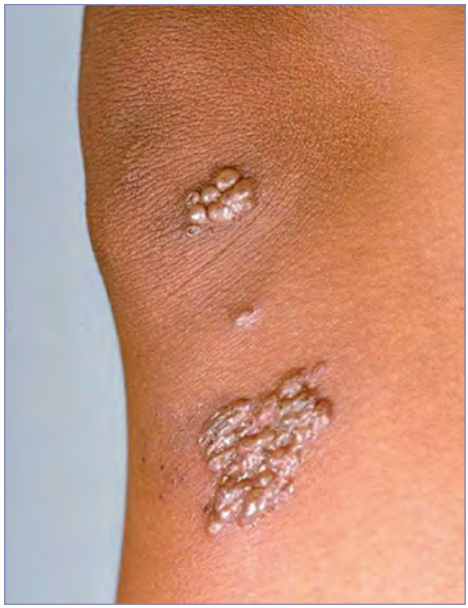


Image 160.22
Herpes zoster in an otherwise healthy child.

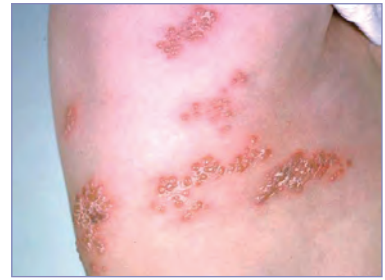


Image 160.21
Herpes zoster in an otherwise healthy child. Multiple dermatomes are involved.

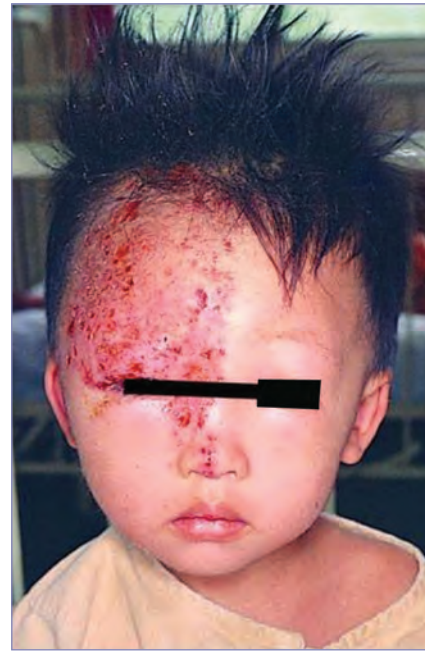


Image 160.23
Herpes zoster (shingles). Courtesy of C. W. Leung.

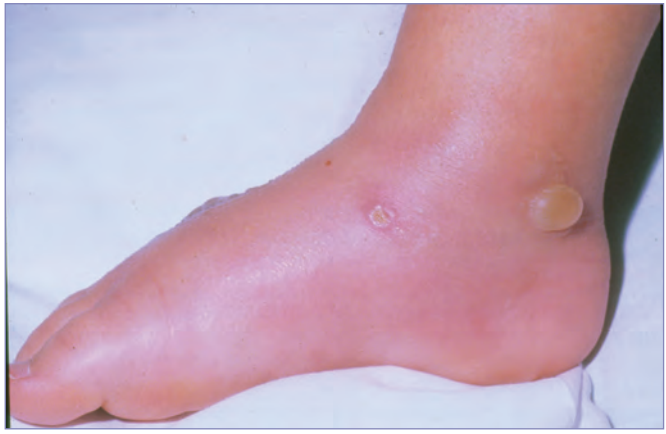


Image 160.24
Bullous varicella (uncomplicated) in a 1-year-old. Courtesy of George Nankervis, MD.

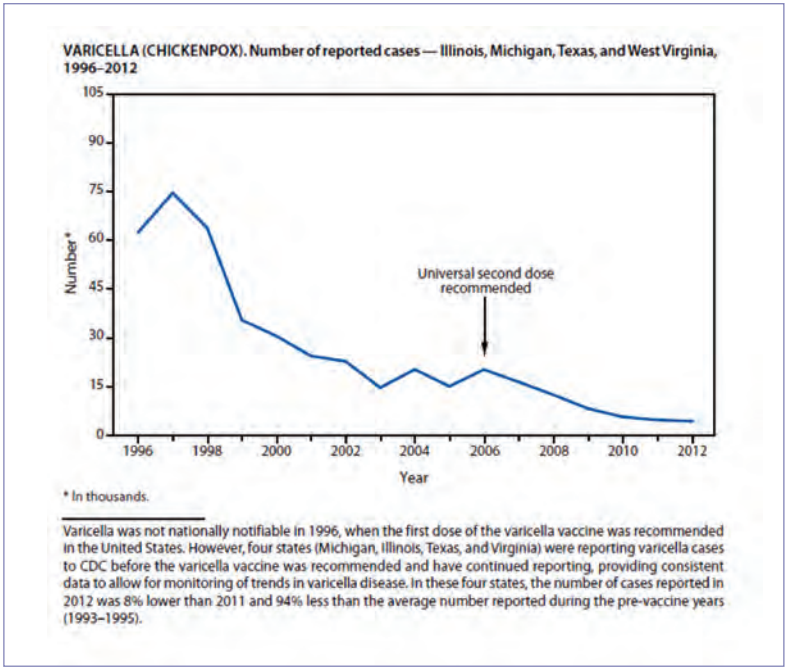


Image 160.25
Varicella (chickenpox). Number of reported cases—Illinois, Michigan, Texas, and West Virginia, 1996–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 161

Cholera

(*Vibrio cholerae*)

CLINICAL MANIFESTATIONS

Cholera is characterized by voluminous watery diarrhea and rapid onset of life-threatening dehydration. Hypovolemic shock may occur within hours of the onset of diarrhea. Stools have a characteristic rice-water appearance, are white-tinged and contain small flecks of mucus, and contain high concentrations of sodium, potassium, chloride, and bicarbonate. Vomiting is a common feature of cholera. Fever and abdominal cramps usually are absent. In addition to dehydration and hypovolemia, common complications of cholera include hypokalemia, metabolic acidosis, and hypoglycemia, particularly in children. Although severe cholera is a distinctive illness characterized by profuse diarrhea and rapid dehydration, people infected with toxigenic *Vibrio cholerae* O1 may have either no symptoms or mild to moderate diarrhea lasting 3 to 7 days.

ETIOLOGY

V cholerae is a curved or comma-shaped motile gram-negative rod. There are more than 200 *V cholerae* serogroups, some of which carry the cholera toxin (CT) gene. Although those serogroups with the CT gene and others without the CT gene can cause acute watery diarrhea, only toxin-producing serogroups O1 and O139 cause epidemic cholera, with O1 causing the vast majority of cases of cholera. *V cholerae* O1 is classified into 2 biotypes, classical and El Tor, and 2 major serotypes, Ogawa and Inaba. Since 1992, toxigenic *V cholerae* serogroup O139 has been recognized as a cause of epidemic cholera in Asia. Aside from the substitution of the O139 for the O1 antigen, the organism is almost identical to *V cholerae* O1 El Tor. All other serogroups of *V cholerae* are known collectively as *V cholerae* non-O1/non-O139. Toxin-producing strains of *V cholerae* non-O1/non-O139 can cause sporadic cases of severe dehydrating diarrheal illness but have not caused large outbreaks of cholera. Non–toxin-producing strains of *V cholerae* non-O1/non-O139 are associated with sporadic cases of gastroenteritis, sepsis, and rare cases of wound infection.

EPIDEMIOLOGY

Since the early 1800s, there have been 7 cholera pandemics. The current pandemic began in 1961 and is caused by *V cholerae* O1 El Tor. Molecular epidemiology shows that this pandemic has occurred in 3 successive waves, with each one spreading from South Asia to other regions in Asia, Africa, and the Western Pacific Islands (Oceania). In 1991, epidemic cholera caused by toxigenic *V cholerae* O1 El Tor appeared in Peru and spread to most countries in South, Central, and North America, causing more than 1 million cases of cholera before subsiding. In 2010, *V cholerae* O1 El Tor was introduced into Haiti, on the island of Hispaniola, initiating a massive epidemic of cholera. In the United States, sporadic cases resulting from travel to or ingestion of contaminated food transported from regions with endemic cholera are reported, including several cases imported from Hispaniola since 2010. Domestically acquired cases in the United States have been reported from eating Gulf coast seafood.

Humans are the only documented natural host, but free-living *V cholerae* organisms can persist in the aquatic environment. Infection primarily is acquired by ingestion of large numbers of organisms from contaminated water or food (particularly raw or undercooked shellfish, raw or partially dried fish, or moist grains or vegetables held at ambient temperature). People with low gastric acidity and with blood group O are at increased risk of severe cholera infection.

The **incubation period** usually is 1 to 3 days (range, few hours to 5 days).

DIAGNOSTIC TESTS

V cholerae can be cultured from fecal specimens (preferred) or vomitus plated on thiosulfate citrate bile salts sucrose agar. Because most laboratories in the United States do not culture routinely for *V cholerae* or other *Vibrio* organisms, clinicians should request appropriate cultures for clinically suspected cases.

Isolates of *V cholerae* should be sent to a state health department laboratory for confirmation and then forwarded to the Centers for Disease Control and Prevention (CDC) for confirmation, serogrouping, and detection of the cholera toxin gene. Several commercial tests for rapid antigen detection of *V cholerae* O1 and O139 in stool specimens have been developed. These *V cholerae* O1 and O139 rapid diagnostic tests (RDTs) have sensitivities ranging from approximately 80% to 97% and specificities of approximately 70% to 90% compared with culture on thiosulfate citrate bile salts sucrose agar. These tests are not a substitute for stool culture but potentially provide a rapid presumptive indication of a suspect cholera outbreak in regions where stool culture is not immediately available. Multiplex PCR assays for detection of various bacteria, parasites, and viruses associated with gastrointestinal tract infections can specifically detect *V cholera* directly from stool specimens.

TREATMENT

Timely and appropriate rehydration therapy is the cornerstone of management of cholera and reduces the mortality of severe cholera to less than 0.5%. Rehydration therapy should be based on World Health Organization (WHO) standards, with the goal of replacing the estimated fluid deficit within 3 to 4 hours of initial presentation. In patients with severe dehydration, isotonic intravenous fluids should be used, and lactated Ringer solution is the preferred commercially available option. For patients without severe dehydration, oral rehydration therapy using the WHO's reduced-osmolality oral rehydration solution (ORS) has been the standard, but data suggest that rice-based ORS or amylase-resistant starch ORS are more effective.

Prompt initiation of antimicrobial therapy decreases the duration and volume of diarrhea and decreases the shedding of viable bacteria. Antimicrobial therapy should be considered for people who are moderately to severely ill. The choice of antimicrobial therapy should be made based on age of the patient as well as prevailing patterns of antimicrobial resistance. Doxycycline and azithromycin are often used. In cases in which prevailing patterns of resistance are unknown, antimicrobial susceptibility testing should be performed and monitored. Zinc supplementation should be considered as an adjunct to rehydration in children.

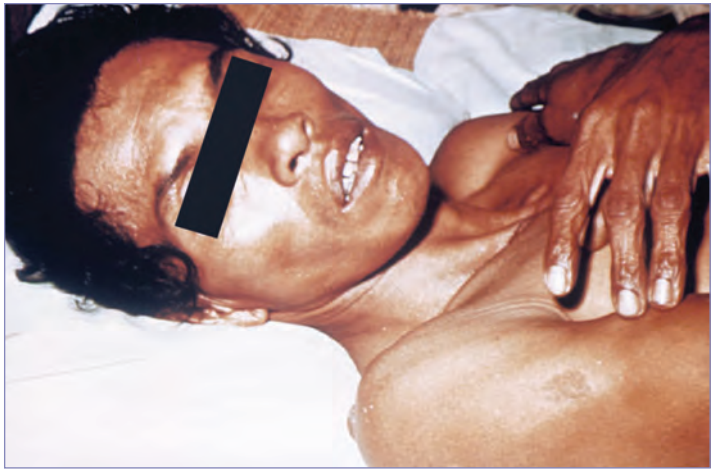


Image 161.1
An adult cholera patient with "washerwoman's hand" sign. Due to severe dehydration, cholera manifests itself in decreased skin turgor, which produces the so-called washerwoman's hand sign. Courtesy of Centers for Disease Control and Prevention.

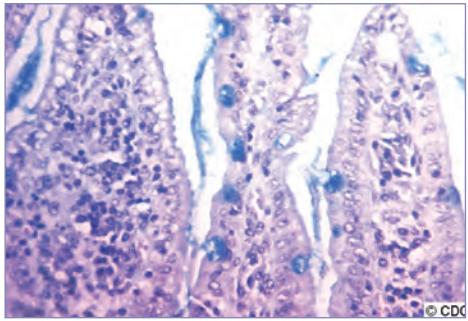


Image 161.2
Intestinal biopsy showing *Vibrio cholerae* causing increased mucus production. *V cholerae* is transmitted to humans through the ingestion of contaminated food or water and produces a cholera toxin that acts on the intestinal mucosa and causes severe diarrhea. Courtesy of Centers for Disease Control and Prevention.

Image 161.3
Here, a cup of typical rice-water stool from a cholera patient shows flecks of mucus that have settled to the bottom. These stools are inoffensive, with a faint fishy odor. They are isotonic with plasma and contain high levels of sodium, potassium, and bicarbonate. They also contain extraordinary quantities of *Vibrio cholerae* bacterial organisms. Courtesy of Centers for Disease Control and Prevention.

Image 161.4
Crabs have been a repeated source of cholera in the United States and elsewhere, even though they are rarely eaten raw. Crabs artificially inoculated with *Vibrio cholerae* O1 that have been boiled for less than 10 minutes or steamed for less than 30 minutes may still harbor viable vibrios, which can then multiply to high counts if the crabs are left at room temperature for several hours. Courtesy of Centers for Disease Control and Prevention.

Image 161.5
Typical *Vibrio cholerae*–contaminated water supply. Ingestion of *V cholerae*–contaminated water is a typical mode of pathogen transmission. Courtesy of Centers for Disease Control and Prevention.

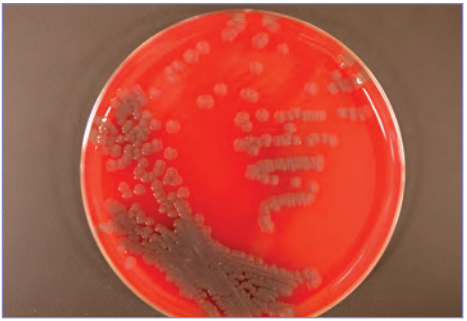


Image 161.7
Vibrio cholerae on blood agar. Colonies are nonhemolytic and opaque with a greenish cast. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

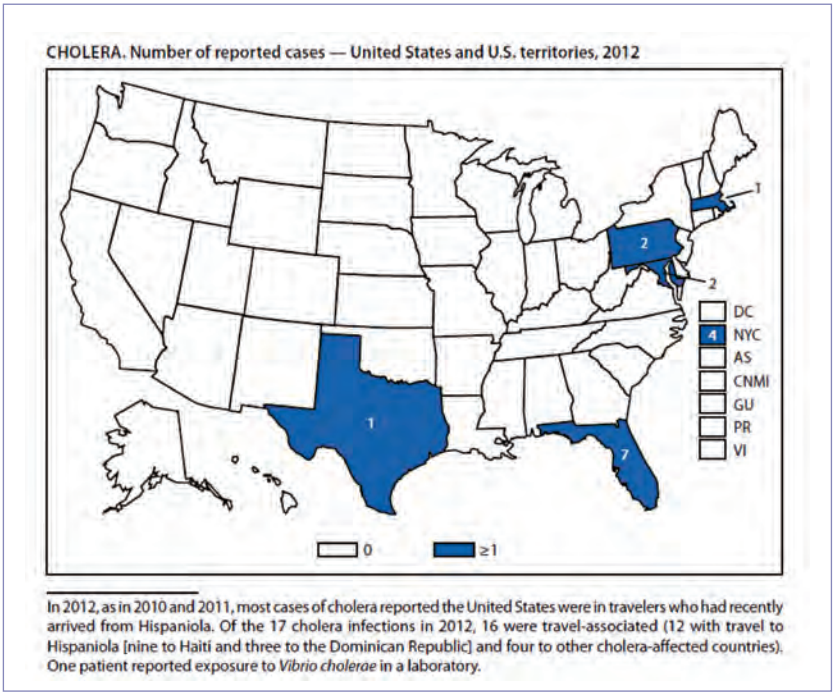


Image 161.6
Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 162

Other *Vibrio* Infections

CLINICAL MANIFESTATIONS

Illness attributable to the following (mostly nontoxigenic species) of the *Vibrionaceae* family is known as vibriosis: (1) *Vibrio parahaemolyticus*, *Vibrio vulnificus*, and other *Vibrio* species; (2) nontoxigenic *Vibrio cholerae;* (3) toxigenic *V cholerae* O75 and O141; and (4) members of the *Vibrionaceae* family that are not in the genus *Vibrio* (eg, *Grimontia hollisae*). Associated clinical syndromes include gastroenteritis, wound infection, and septicemia. Gastroenteritis is the most common syndrome and is characterized by acute onset of watery nonbloody stools and crampy abdominal pain. Approximately half of affected people will have low-grade fever, headache, and chills; approximately 30% will have vomiting. Spontaneous recovery follows in 2 to 5 days. Wound infections typically start as cellulitis with vesicles and can progress to hemorrhagic bullae, necrosis, and/or necrotizing fasciitis. Septicemia can be primary or follow gastroenteritis or wound infection and often is fulminant and accompanied by development of metastatic skin lesions within 36 hours. Risk factors for severe wound infections and for septicemia include liver disease, iron overload, hemolytic anemia, chronic renal failure, diabetes mellitus, low gastric acidity, and immunosuppression.

ETIOLOGY

Vibrio organisms are facultatively anaerobic, motile, gram-negative bacilli that are tolerant of salt. The most commonly reported nontoxigenic *Vibrio* species associated with diarrhea are *V parahaemolyticus* and *V cholerae* non-O1/non-O139. *V vulnificus* typically causes primary septicemia and severe wound infections, but the other species also can cause these syndromes. *V alginolyticus* typically causes wound infections.

EPIDEMIOLOGY

Vibrio species are natural inhabitants of marine and estuarine environments. In temperate climates, most noncholera *Vibrio* infections occur during summer and autumn months, when *Vibrio* populations in seawater are highest. Gastroenteritis usually follows ingestion of raw or undercooked seafood, especially oysters, clams, crabs, and shrimp. Wound infections usually are attributable to *V vulnificus* and can result from exposure of a preexisting wound to contaminated seawater or from punctures resulting from handling of contaminated fish or shellfish. Exposure to contaminated water during natural disasters, such as hurricanes, has resulted in wound infections. Person-to-person transmission has not been reported. Infections associated with noncholera *Vibrio* organisms became nationally notifiable in January 2007.

The **incubation period** for gastroenteritis is typically 24 hours (range, 5–92 hours); for wound infections and septicemia, the incubation period is 1 to 7 days.

DIAGNOSTIC TESTS

Depending on the clinical syndrome, *Vibrio* organisms can be isolated from stool, wound exudates, or blood. Because identification of the organism requires special techniques, laboratory personnel should be notified when infection with *Vibrio* species is suspected. Molecular diagnostics are useful if available.

TREATMENT

Diarrhea typically is mild and self-limited and requires only oral rehydration. Wound infections require surgical débridement of necrotic tissue, if present. Antimicrobial therapy is indicated for severe diarrhea, wound infection, and septicemia. Septicemia with or without hemorrhagic bullae and wound infections should be treated with a third-generation cephalosporin plus either doxycycline or ciprofloxacin. Severe diarrhea should be treated with doxycycline or ciprofloxacin. Doxycycline can be used for short durations (ie, 21 days or less) without regard to patient age. A combination of trimethoprim-sulfamethoxazole and an aminoglycoside is an alternative regimen.

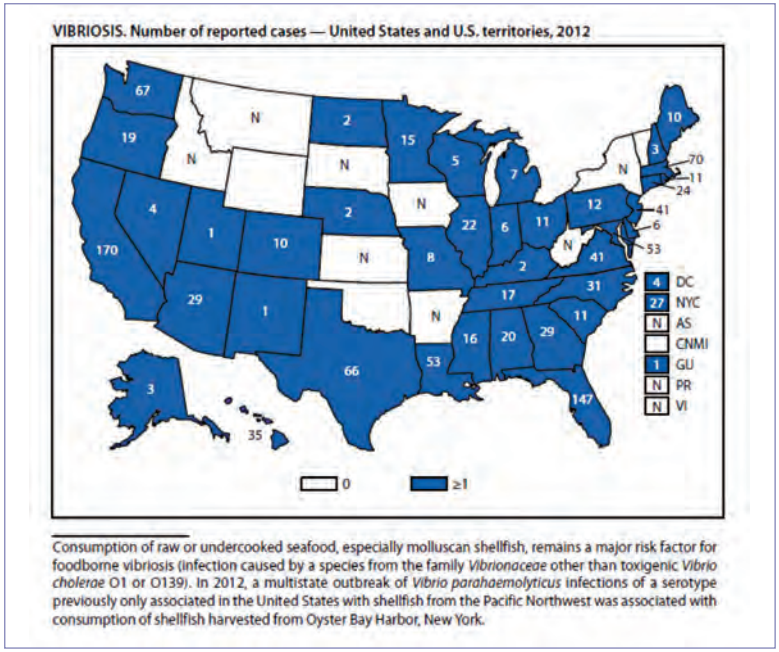


Image 162.1

Vibriosis. Number of reported cases—United States and US territories, 2012. Courtesy of *Morbidity and Mortality Weekly Report*.

CHAPTER 163

West Nile Virus

CLINICAL MANIFESTATIONS

An estimated 70% to 80% of people infected with West Nile virus (WNV) are asymptomatic. Most symptomatic people experience an acute systemic febrile illness that often includes headache, myalgia, arthralgia, vomiting, diarrhea, or a transient maculopapular rash. Less than 1% of infected people develop neuroinvasive disease, which typically manifests as meningitis, encephalitis, or acute flaccid myelitis. WNV meningitis is indistinguishable clinically from aseptic meningitis caused by other viruses. Patients with WNV encephalitis usually present with fever, headache, seizures, mental status changes, focal neurologic deficits, or movement disorders. WNV acute flaccid myelitis often is clinically and pathologically identical to poliovirus-associated poliomyelitis, with damage of anterior horn cells, and may progress to respiratory paralysis requiring mechanical ventilation. WNV-associated Guillain-Barré syndrome also has been reported and can be distinguished from WNV acute flaccid myelitis by clinical manifestations, findings on cerebrospinal fluid analysis, and electrophysiologic testing. Cardiac dysrhythmias, myocarditis, rhabdomyolysis, optic neuritis, uveitis, chorioretinitis, orchitis, pancreatitis, and hepatitis have been described rarely after WNV infection.

Routine clinical laboratory results generally are nonspecific in WNV infections. In patients with neuroinvasive disease, cerebrospinal fluid (CSF) examination generally shows lymphocytic pleocytosis, but neutrophils may predominate early in the illness. Brain magnetic resonance imaging frequently is normal, but signal abnormalities may be seen in the basal ganglia, thalamus, and brainstem with WNV encephalitis and in the spinal cord with WNV acute flaccid myelitis.

Most patients with WNV nonneuroinvasive disease or meningitis recover completely, but fatigue, malaise, and weakness can linger for weeks or months. Recovery from WNV encephalitis or acute flaccid myelitis often takes weeks to months, and patients often have residual neurologic deficits. Among patients with neuroinvasive disease, overall case-fatality rate is approximately 10% but is significantly higher in WNV encephalitis and myelitis than in WNV meningitis.

Most women known to have been infected with WNV during pregnancy have delivered infants without evidence of infection or clinical abnormalities; only a few cases of WNV in newborn infants have been confirmed. In the best-documented case of confirmed congenital WNV infection, the mother developed WNV encephalitis during week 27 of gestation, and the infant was born with cystic lesions of cerebral tissue and chorioretinitis. In a case of likely early human milk-transmitted infection, a woman developed encephalitis following postpartum transfusion, and 3 weeks later her breastfed infant had documented infection, although the infant remained healthy. If WNV disease is diagnosed during pregnancy, a detailed examination of the fetus and of the newborn infant should be performed.

ETIOLOGY

WNV is an RNA virus of the *Flaviviridae* family (genus *Flavivirus*) that is related antigenically to St Louis encephalitis and Japanese encephalitis viruses.

EPIDEMIOLOGY

WNV is an arthropodborne virus (arbovirus) that is transmitted in an enzootic cycle between mosquitoes and amplifying vertebrate hosts, primarily birds. WNV is transmitted to humans primarily through bites of infected *Culex* mosquitoes. Humans usually do not develop a level or duration of viremia sufficient to infect mosquitoes, and therefore are dead-end hosts. However, person-to-person WNV transmission can occur through blood transfusion and solid organ transplantation. Intrauterine and probable breastfeeding transmission have been described rarely. Transmission through percutaneous and mucosal exposure has occurred in laboratory workers and occupational settings.

WNV transmission has been documented on every continent except Antarctica. Since the 1990s, the largest outbreaks of WNV neuroinvasive disease have occurred in the Middle East, Europe, and North America. WNV first was detected in the Western Hemisphere in New York City in 1999 and subsequently spread

across the continental United States and Canada. From 1999 through 2015, a total of 20,265 cases of WNV neuroinvasive disease were reported in the United States. The national incidence of WNV neuroinvasive disease peaked in 2002 (2,946 cases and 278 deaths; 1.02 cases per 100,000 persons per year) and 2003 (2,866 cases and 232 deaths; 0.98 cases per 100,000), and again in 2012 (2,873 cases, 270 deaths; 0.92 cases per 100,000). Although incidence has declined, WNV remains the leading cause of neuroinvasive arboviral disease in the United States. In 2015, a total of 1,455 WNV neuroinvasive disease cases were reported—more than 10 times the number of neuroinvasive disease cases reported for all other domestic arboviruses combined. California (1.5 per 100,000), North Dakota (1.3 per 100,000), South Dakota (1.3 per 100,000), Oklahoma (1.3 per 100,000), Colorado (1.0 per 100,000), and Nebraska (1.0 per 100,000) had the highest incidence of reported neuroinvasive disease in 2015. Alaska and Hawaii are the only states that have not reported local transmission of WNV.

In temperate and subtropical regions, most human WNV infections occur in summer or early autumn. Although all age groups and both genders are susceptible to WNV infection, the incidence of severe disease (eg, encephalitis and death) is highest among older adults. In 2015, the incidence of neuroinvasive disease was 1.71 per 100,000 in adults 70 years or older compared with 0.03 per 100,000 in children younger than 10 years. Chronic renal failure and history of cancer, alcohol abuse, diabetes, or hypertension have been associated with developing severe WNV disease.

The **incubation period** usually is 2 to 6 days (range, 2–14 days) but can be up to 21 days in immunocompromised people.

DIAGNOSTIC TESTS

Detection of anti-WNV immunoglobulin (Ig) M antibodies in serum or CSF is the most common way to diagnose WNV infection. The presence of anti-WNV IgM usually is good evidence of recent WNV infection but may indicate infection with another closely related *Flavivirus*. Because anti-WNV IgM can persist in the serum of some patients for longer than 1 year, a positive test result occasionally may reflect past infection. Detection of WNV IgM in CSF generally is indicative of recent neuroinvasive infection. WNV IgM antibodies are detectable in most WNV-infected patients 3 to 8 days after symptom onset and remain detectible for 30 to 90 days, although it may persist for longer than 1 year. For patients in whom serum collected within 8 days of illness lacks detectable IgM, testing should be repeated on a convalescent sample. IgG antibody generally is detectable shortly after IgM and can persist for years. Plaque-reduction neutralization tests can be performed to measure virus-specific neutralizing antibodies and to discriminate between cross-reacting antibodies from closely related flaviviruses. A fourfold or greater increase in virus-specific neutralizing antibodies between acute- and convalescent-phase serum specimens collected 2 to 3 weeks apart may be used to confirm recent WNV infection.

Viral culture and WNV nucleic acid amplification tests (including reverse transcriptase-polymerase chain reaction) can be performed on acute-phase serum, CSF, or tissue specimens. However, by the time most immunocompetent patients present with clinical symptoms, WNV RNA usually no longer is detectable; polymerase chain reaction assay is not recommended for immunocompetent hosts. Immunohistochemical staining can detect WNV antigens in fixed tissue, but negative results are not definitive.

WNV disease should be considered in the differential diagnosis of febrile or acute neurologic illnesses associated with recent exposure to mosquitoes, blood transfusion, or solid organ transplantation and of illnesses in neonates whose mothers were infected with WNV during pregnancy or while breastfeeding. In addition to other more common causes of aseptic meningitis and encephalitis (eg, herpes simplex virus and enteroviruses), WNV and other arboviruses should also be considered in the differential diagnosis.

TREATMENT

Management of WNV disease is supportive. Although various therapies have been evaluated or used for WNV disease, none has shown specific benefit.

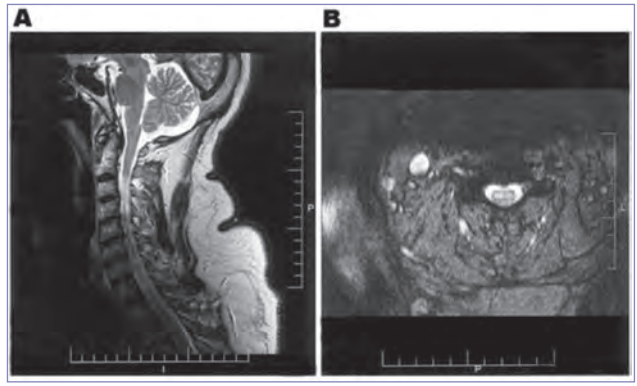


Image 163.1
West Nile virus–associated flaccid paralysis. Sagittal (A) and axial (B) T2-weighted magnetic resonance images of the cervical spinal cord in a patient with acute asymmetrical upper extremity weakness and subjective dyspnea. A, Diffuse cervical cord signal abnormality. B, Abnormal signal in the anterior horn region. Courtesy of *Emerging Infectious Diseases.*

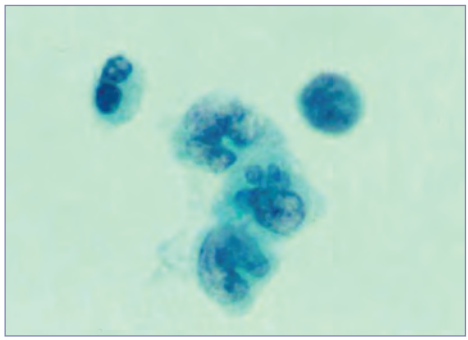


Image 163.2
Three Mollaret-like cells are present (center), with a neutrophil (upper left) and a lymphocyte (upper right) in cerebrospinal fluid from a patient with West Nile virus encephalitis, confirmed by reverse transcriptase-polymerase chain reaction and serologic testing (Papanicolaou stain, magnification ×500). Courtesy of Centers for Disease Control and Prevention.

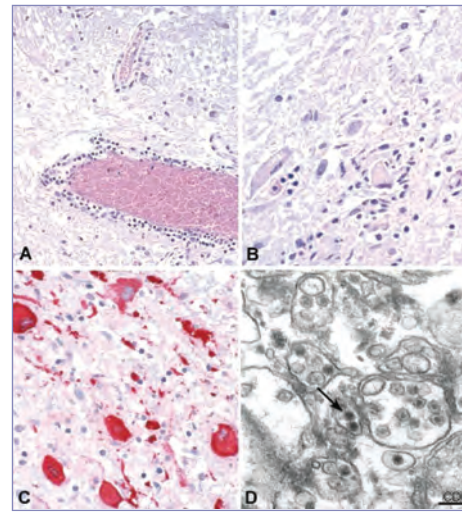


Image 163.3
Histopathologic features of West Nile virus (WNV) in human tissues. A–B, Inflammation, microglial nodules, and variable necrosis that occur during WNV encephalitis. C, WNV antigen (red) in neurons and neuronal processes using an immunohistochemical stain. D, Electron micrograph of WNV in the endoplasmic reticulum of a nerve cell (arrow) (bar = 100 nm). These 4 images are from a fatal case of WNV infection in a 39-year-old woman. Courtesy of *Emerging Infectious Diseases.*

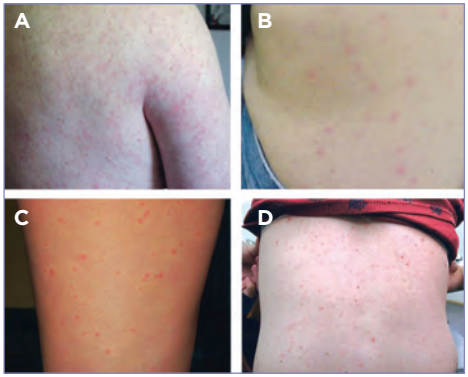


Image 163.4
Four patients with West Nile virus fever and erythematous, maculopapular rashes on the back (A), flank (B), posterior thigh (C), and back (D). Copyright *Clinical Infectious Diseases*.

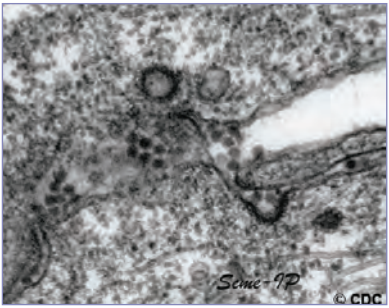


Image 163.5
Transmission electron micrograph of West Nile virus. This virus is transmitted between culicine mosquitoes and birds. Humans, horses, and other mammals are infected incidentally. Courtesy of Centers for Disease Control and Prevention.

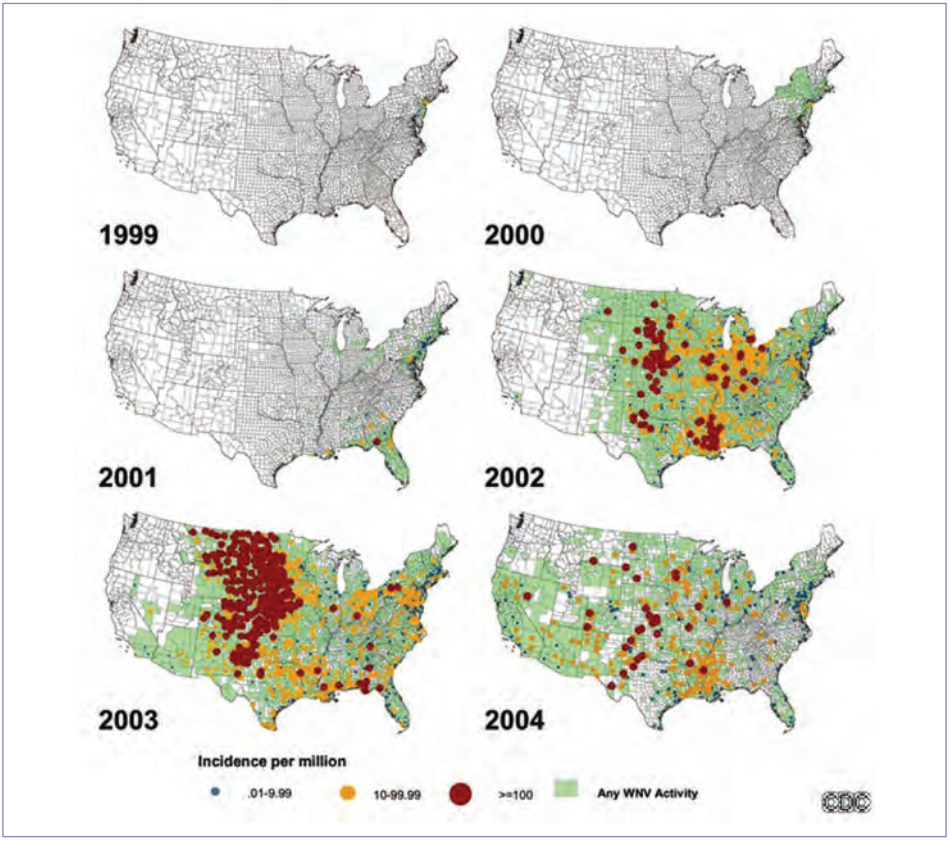


Image 163.6
Reported incidence of neuroinvasive West Nile virus disease by county in the United States, 1999–2004. Reported to Centers for Disease Control and Prevention by states through April 21, 2005. Courtesy of *Emerging Infectious Diseases*.

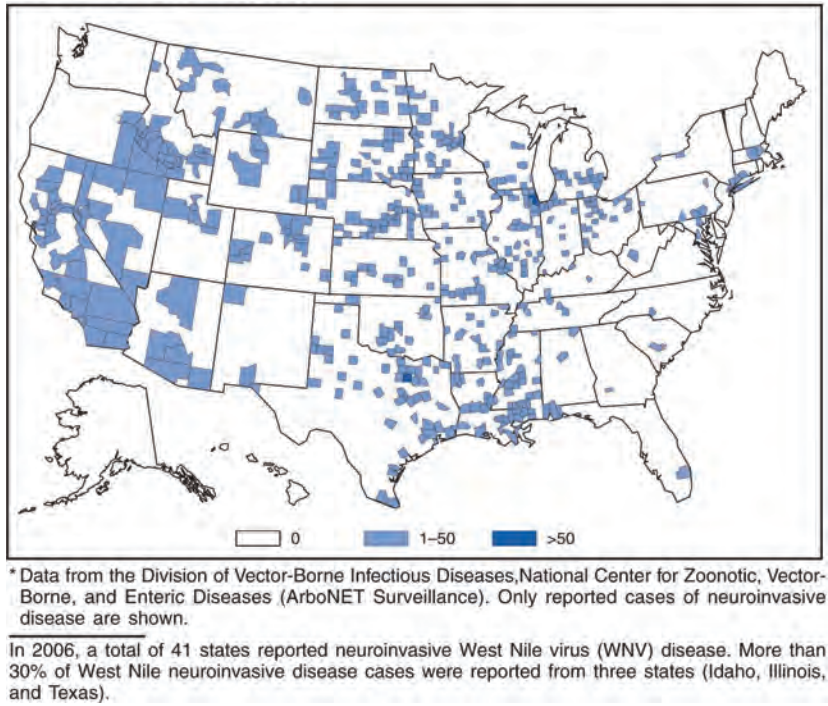


Image 163.7

West Nile encephalitis/meningitis reported by county—United States, 2006. Courtesy of *Morbidity and Mortality Weekly Report.*

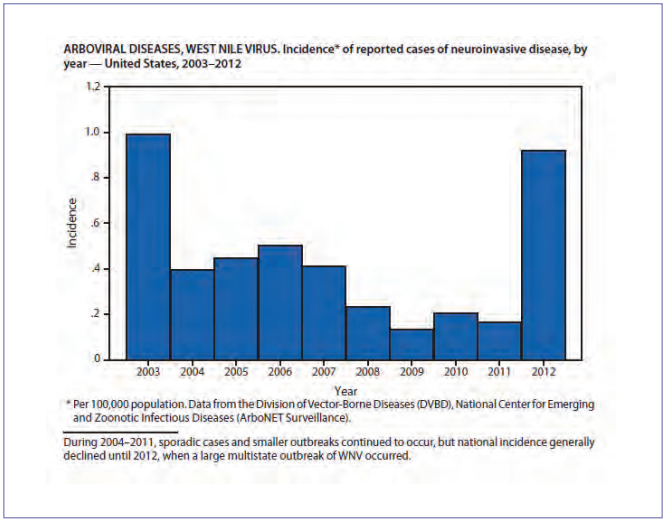


Image 163.8

Arboviral diseases, West Nile virus. Incidence of reported cases of neuroinvasive disease, by year—United States, 2003–2012. Courtesy of *Morbidity and Mortality Weekly Report.*

CHAPTER 164

Yersinia enterocolitica and *Yersinia pseudotuberculosis* Infections

(Enteritis and Other Illnesses)

CLINICAL MANIFESTATIONS

Yersinia enterocolitica causes several age-specific syndromes and a variety of other less commonly reported clinical illnesses. Infection with *Y enterocolitica* typically manifests as fever, diarrhea, and abdominal pain in children younger than 5 years; stool often contains leukocytes, blood, and mucus. Diarrhea commonly persists for more than 2 weeks. Relapsing disease and, rarely, necrotizing enterocolitis also have been described. In older children and adults, a pseudoappendicitis syndrome attributable to mesenteric lymphadenitis (fever, abdominal pain, tenderness in the right lower quadrant of the abdomen, and leukocytosis) predominates. Bacteremia is the major complication of *Y enterocolitica*-associated enteric infection occurring mostly in children younger than 1 year and in older children with predisposing conditions, such as excessive iron storage (eg, deferoxamine use, sickle cell disease, and beta-thalassemia) and immunosuppressive states. Extraintestinal manifestations of *Y enterocolitica* are uncommon and include pharyngitis, meningitis, osteomyelitis, pyomyositis, conjunctivitis, pneumonia, empyema, endocarditis, acute peritonitis, abscesses of the liver and spleen, urinary tract infection, and primary cutaneous infection. Postinfectious sequelae with *Y enterocolitica* infection include erythema nodosum, reactive arthritis, and proliferative glomerulonephritis. These sequelae occur most often in older children and adults, particularly people with HLA-B27 antigen.

Major manifestations of *Yersinia pseudotuberculosis* infection include fever, scarlatiniform rash, acute gastroenteritis, and abdominal symptoms. Acute pseudoappendiceal abdominal pain is common, resulting from ileocecal mesenteric adenitis or terminal ileitis. Other uncommon findings reported have been intestinal intussusception, erythema nodosum, septicemia mainly among individuals with underlying conditions, acute renal failure with nephritis, and sterile pleural and joint effusions. Clinical features can mimic those of Kawasaki disease; in Hiroshima, Japan, nearly 10% of children with a diagnosis of Kawasaki disease have serologic or culture evidence of *Y pseudotuberculosis* infection.

ETIOLOGY

The genus *Yersinia* consists of 17 species of gram-negative bacilli belonging to the family *Enterobacteriaceae. Y enterocolitica*, *Y pseudotuberculosis*, and *Yersinia pestis* are the 3 most recognized human pathogens; however, other *Yersinia* species also have been isolated from clinical specimens. *Y enterocolitica* bioserotypes most often associated with human illness are 1B/O:8, 2/O:5,27, 2/O:9, 3/O:3, and 4/O:3, with bioserotype 4/O:3 now predominating as the most common type in the United States. The 3 *Yersinia* species have in common a tropism for lymphoid tissue and share factors that promote serum resistance, coordinate gene expression, and facilitate iron acquisition. Virulence can be attributed to adhesion/invasion genes, enterotoxins, iron-scavenging genomic islands, and secretion systems. Highly pathogenic *Yersinia* are known to carry a 70 kb pYV virulence plasmid, which encodes a type III secretion system that is activated at human body temperatures and promotes entry into lymph tissues and subsequent evasion of host defense mechanisms.

EPIDEMIOLOGY

Yersinia infections are reported uncommonly in the United States. *Y enterocolitica* and *Y pseudotuberculosis* are isolated most often during the cool months of temperate climates. The Foodborne Disease Active Surveillance Network (FoodNet) conducts active surveillance for infections caused by 9 pathogens, including *Yersinia.* During FoodNet surveillance from 1996–2009, the average annual incidence of *Y enterocolitica* was 0.5 per 100,000 people and was highest in black people (0.9 per 100,000); there is a clear declining trend over the years from 3.9 to 0.4 per 100,000; 47% of infections were in children younger than 5 years; 28% were hospitalized, and 1% died. Most isolates were recovered from stool. In contrast, the average annual incidence of

Y pseudotuberculosis was 0.04 cases per 1 million people; the median age was 47 years, 72% were hospitalized, and 11% died. Two-thirds of *Y pseudotuberculosis* isolates were recovered from blood.

The principal reservoir of *Y enterocolitica* is swine, although it can be isolated from a variety of domestic and wildlife animals; *Y pseudotuberculosis* has been isolated from ungulates (deer, elk, goats, sheep, cattle), rodents (rats, squirrels, beaver), rabbits, and many bird species. Infection with *Y enterocolitica* is believed to be transmitted by ingestion of contaminated food (raw or incompletely cooked pork products, tofu, and unpasteurized or inadequately pasteurized milk), by contaminated surface or well water, by direct or indirect contact with animals, and rarely by transfusion with contaminated packed red blood cells and by person-to-person transmission. Cross-contamination has been documented to lead to infection in infants if their caregivers handle raw pork intestines (ie, chitterlings) and do not cleanse their hands adequately before handling the infant or the infant's toys, bottles, or pacifiers. *Y pseudotuberculosis* can follow exposure to well and mountain waters contaminated with animal feces. Household pets can be source of infection for children.

The **incubation period** typically is 4 to 6 days (range, 1–14 days). Organisms typically are excreted for 2 to 3 weeks in treated and up to 2 to 3 months in untreated cases.

DIAGNOSTIC TESTS

Y enterocolitica and *Y pseudotuberculosis* can be recovered from stool, throat swab specimens, mesenteric lymph nodes, peritoneal fluid, and blood. *Y enterocolitica* also has been isolated from synovial fluid, bile, urine, cerebrospinal fluid, sputum, pleural fluid, and wounds. Stool cultures generally yield bacteria during the first 2 weeks of illness, regardless of the nature of gastrointestinal tract manifestations. *Yersinia* organisms are not sought routinely in stool specimens by most laboratories in the United States. Laboratory personnel should be notified when *Yersinia* infection is suspected so that stool can be cultured on suitable media (eg, CIN agar); however, strains of *Y enterocolitica* 3/O:3 and *Y pseudotuberculosis* may be inhibited on CIN agar, and MacConkey is preferred. Results from nonsterile sites should be interpreted with caution. DNA-based gastrointestinal syndrome panels that can reliably detect *Yersinia* are commercially available. Biotyping and serotyping for further identification of pathogenic strains is available through public health reference laboratories. Infection also can be confirmed by demonstrating increases in serum antibody titer after infection, but these tests generally are available only in reference or research laboratories. Characteristic ultrasonographic features demonstrating edema of the wall of the terminal ileum and cecum with normal appendix help to distinguish pseudoappendicitis from appendicitis and can help avoid exploratory surgery.

TREATMENT

Neonates, immunocompromised hosts, and all patients with septicemia or extraintestinal disease require treatment for *Yersinia* infection. Parenteral therapy with a third-generation cephalosporin is appropriate, and evaluation of cerebrospinal fluid should be performed for infected neonates. Otherwise healthy infants with enterocolitis can be treated symptomatically. Antimicrobial therapy decreases the duration of fecal excretion of *Y enterocolitica* and *Y pseudotuberculosis*. Although a clinical benefit of antimicrobial therapy for immunocompetent patients with enterocolitis, pseudoappendicitis syndrome, or mesenteric adenitis has not been established, treatment also is unlikely to cause any detrimental clinical effects and can be considered because of its favorable effect on shedding of the organism. In addition to third-generation cephalosporins, *Y enterocolitica* and *Y pseudotuberculosis* usually are susceptible to trimethoprim-sulfamethoxazole, aminoglycosides, fluoroquinolones, or doxycycline.

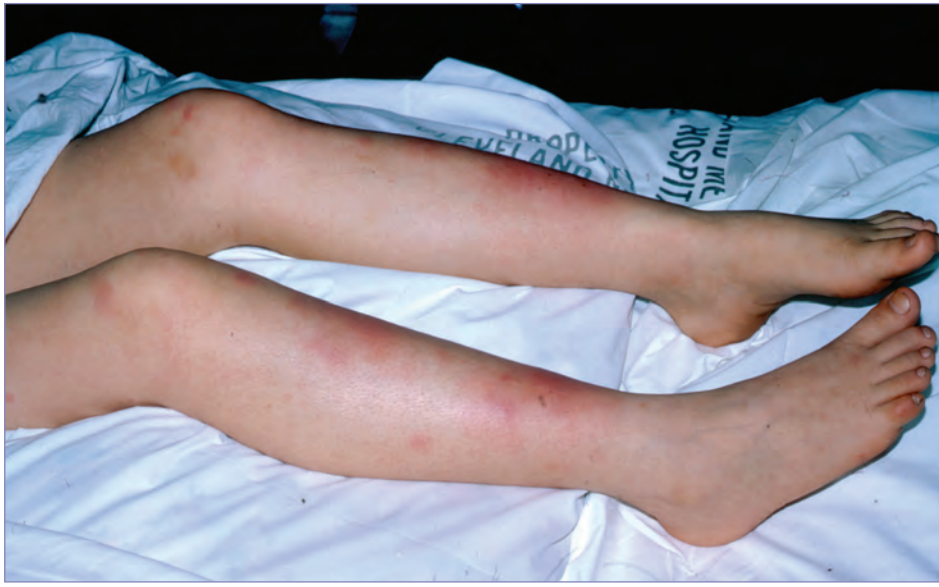


Image 164.1
Multiple erythema nodosum lesions over both lower extremities of a 10-year-old girl following a *Yersinia enterocolitica* infection. This immunoreactive complication may also occur in association with *Campylobacter jejuni* infections, tuberculosis, leprosy, coccidioidomycosis, histoplasmosis, and other infectious diseases. Courtesy of George Nankervis, MD.

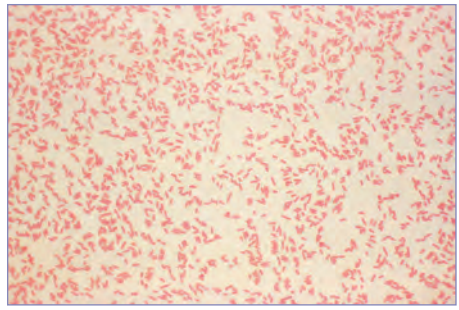


Image 164.2
A photomicrograph of *Yersinia enterocolitica* using Gram stain technique. Courtesy of Centers for Disease Control and Prevention.

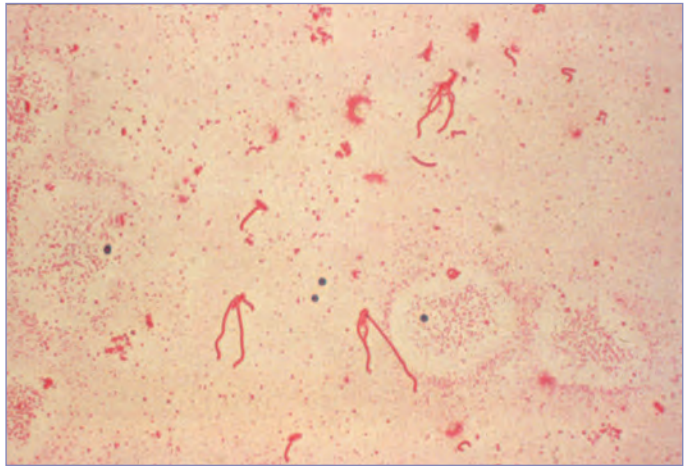


Image 164.3
A photomicrograph of *Yersinia enterocolitica* by using flagella staining technique. Symptoms of yersiniosis are fever, abdominal pain, and diarrhea (often bloody), and *Y enterocolitica* is the cause of most *Yersinia*-related illnesses in the United States (mostly in children). Courtesy of Centers for Disease Control and Prevention.

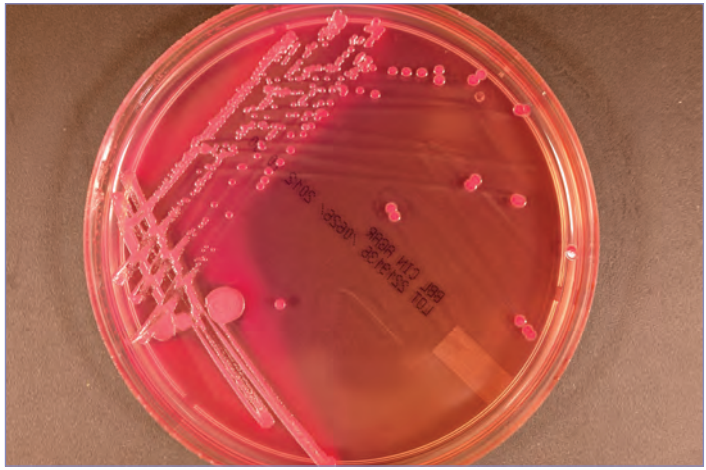


Image 164.4
Yersinia kristensenii on cefsulodin-irgasan-novobiocin agar. Colonies appear light rose in color with a darker, reddish center. Courtesy of Julia Rosebush, DO; Robert Jerris, PhD; and Theresa Stanley, M(ASCP).

CHAPTER 165

Zika Virus

CLINICAL MANIFESTATIONS

Most Zika virus infections are asymptomatic. In situations in which infection is symptomatic, the clinical disease usually is mild and symptoms last for a few days to a week. Commonly reported signs and symptoms include fever, pruritic maculopapular rash, arthralgia, and conjunctival hyperemia. Other findings include myalgia, headache, edema of the extremities, vomiting, retroorbital pain, and lymphadenopathy. Clinical laboratory abnormalities are observed uncommonly in symptomatic patients but can include thrombocytopenia, leukopenia, and increased liver transaminase concentrations. Severe disease requiring hospitalization and deaths are rare. However, Guillain-Barré syndrome and rare reports of other neurologic complications (eg, meningoencephalitis, myelitis, and uveitis) have been associated with Zika virus infection.

Congenital Zika virus infection can cause fetal loss as well as microcephaly and other serious neurologic anomalies. Clinical findings reported in infants with confirmed congenital Zika virus infection include brain anomalies (eg, subcortical calcifications, ventriculomegaly, abnormal gyral patterns, corpus callosum agenesis, and cerebellar hypoplasia), ocular anomalies (eg, microphthalmia, cataracts, chorioretinal atrophy, and optic nerve hypoplasia), congenital contractures (eg, clubfoot and arthrogryposis), and neurologic sequelae (eg, hypertonia, hypotonia, irritability, tremors, swallowing dysfunction, hearing loss, and visual impairment).

At least 2 cases of perinatal transmission from mothers who were viremic at delivery have been reported. One infant was asymptomatic; the other infant developed mild thrombocytopenia and a transient diffuse rash 4 days after delivery.

ETIOLOGY

Zika virus is a single-stranded, RNA virus in the genus *Flavivirus* that is related antigenically to dengue, yellow fever, West Nile, St. Louis encephalitis, and Japanese encephalitis viruses. Two major lineages, African and Asian, have been identified through phylogenetic analyses.

EPIDEMIOLOGY

Zika virus is transmitted to humans primarily by *Aedes aegypti* mosquitoes and less commonly by other *Aedes* (*Stegomyia*) species (eg, *Aedes albopictus*, *Aedes polynesiensis*, and *Aedes hensilli*). In the United States, *Ae aegypti* mosquitoes are found primarily in southern states. *Ae albopictus* mosquitoes have a wider distribution, including not only the southern United States but also extending north into the Ohio Valley and west to several plains states. *Ae aegypti* and *Ae albopictus* mosquitoes can be found in small areas of the southwest and parts of California. Both *Aedes* species of mosquitoes bite humans during the daytime. These are the same vectors that transmit dengue, chikungunya, and yellow fever viruses. Human and nonhuman primates are the main reservoirs of the virus, with humans acting as the primary host in which the virus multiplies, allowing spread to additional mosquitoes and then other humans. Additional modes of transmission have been identified, including perinatal, in utero, sexual, blood transfusion, and laboratory exposure. Although Zika virus has been detected in human milk, transmission through breastfeeding has not yet been demonstrated.

Zika virus first was identified in the Zika forest of Uganda in 1947. Prior to 2007, only sporadic human disease cases were reported from countries in Africa and Asia. In 2007, the first documented Zika virus disease outbreak was reported in the Federated States of Micronesia. In subsequent years, outbreaks of Zika virus disease were identified in countries in Southeast Asia and the Western Pacific. In 2015, Zika virus was identified for the first time in the Western hemisphere, with large outbreaks reported in Brazil. Since then, the virus has spread throughout much of the Americas, with 48 countries and territories in the Americas reporting local transmission. During 2016 in the United States, large outbreaks occurred in Puerto Rico and the US Virgin Islands, and limited local transmission was identified in parts of Florida and Texas.

The **incubation period** is 3 to 14 days after the bite; 50% of cases develop symptoms 7 days after exposure.

DIAGNOSTIC TESTS

Zika virus infection should be considered in patients with acute onset of fever, maculopapular rash, arthralgia, or conjunctivitis who live in or have traveled to an area with ongoing transmission in the 2 weeks preceding illness onset. Because dengue and chikungunya virus infections share a similar geographic distribution and symptomology with Zika virus infection, patients with suspected Zika virus infection also should be evaluated and managed for possible dengue or chikungunya virus infection. Other considerations in the differential diagnosis include malaria, rubella, measles, parvovirus, adenovirus, enterovirus, leptospirosis, rickettsiosis, and group A streptococcal infections.

Laboratory testing for Zika virus has a number of limitations. Zika virus RNA is only transiently present in body fluids; thus, a negative real-time reverse transcriptase-polymerase chain reaction (RT-PCR) result does not exclude infection. Likewise, a negative immunoglobulin (Ig) M serologic test result does not exclude infection because the serum specimen might have been collected before the development or after waning of IgM antibodies. Alternatively, IgM antibodies might be detectable for months after the initial infection, making it difficult to distinguish the timing of Zika acquisition. Cross-reactivity of the Zika virus IgM antibody tests with other flaviviruses can result in a false-positive test result.

Zika Laboratory Testing in Nonpregnant Symptomatic Individuals

For people with suspected Zika virus disease, Zika virus RT-PCR assay should be performed on serum and urine specimens collected <14 days after onset of symptoms. Serum immunoglobulin (Ig) M antibody testing should be performed if the RT-PCR result is negative or when ≥14 days have passed since illness onset.

Zika Laboratory Testing in Pregnant Women

Current recommendations from the Centers for Disease Control and Prevention (CDC) account for the decreasing prevalence of Zika virus disease cases in the Americas that occurred in 2017. Zika virus RT-PCR testing was offered as part of routine obstetric care to asymptomatic pregnant women with ongoing possible Zika virus exposure; however, because of the potential for persistence of IgM antibodies over several months, serologic testing is no longer recommended to screen asymptomatic women.

Zika Laboratory Testing for Congenital Infection

Zika virus testing is recommended for infants with clinical findings consistent with congenital Zika syndrome and possible maternal Zika virus exposure during pregnancy, regardless of maternal testing results, and for infants without clinical findings consistent with congenital Zika syndrome who are born to women with laboratory evidence of possible infection during pregnancy. Recommended laboratory testing for possible congenital Zika virus infection includes evaluation for Zika virus RNA in infant serum and urine and Zika virus IgM antibodies in serum. In addition, if cerebrospinal fluid (CSF) is obtained for other purposes, RT-PCR and IgM antibody testing should be performed on CSF, because CSF was the only sample that tested positive in a limited number of infants with congenital Zika virus infection.

Laboratory testing of infants should be performed as soon as possible after birth, although testing specimens within the first few weeks to months after birth might still be useful. If CSF was not collected for other reasons, testing CSF for Zika virus RNA and Zika virus IgM should be considered to improve the likelihood of diagnosis, especially if serum and urine testing are negative and another etiology has not been identified. Diagnosis of congenital Zika virus infection is confirmed by a positive Zika virus RT-PCR, or by a positive Zika virus IgM and neutralizing antibody result. If neither Zika virus RNA nor Zika IgM antibodies are detected, congenital Zika virus infection is unlikely.

The plaque reduction neutralization test (PRNT), which measures virus-specific neutralizing antibodies, can be used to help identify false-positive results. If the infant's initial sample is IgM nonnegative (nonnegative serology terminology varies by assay and might include "positive," "equivocal," "presumptive positive," or "possible positive") and RT-PCR negative,

and PRNT was not performed on the mother's sample, PRNT for Zika and dengue viruses should be performed on the infant's initial sample. If the Zika virus PRNT result is negative, this suggests that the infant's Zika virus IgM test result is a false positive. For infants with clinical findings consistent with congenital Zika syndrome or maternal evidence of possible Zika virus infection during pregnancy who were not tested near birth, PRNT at age ≥18 months (after maternal antibodies have dissipated from the infant's system) might help confirm or rule out congenital Zika virus infection. If the PRNT result is negative at age ≥18 months, congenital Zika virus infection is unlikely.

TREATMENT

No specific antiviral treatment currently is available for Zika virus disease. Only supportive care is indicated, including rest, fluids, and symptomatic treatment (acetaminophen to relieve fever and antihistamines to treat pruritus). Aspirin and nonsteroidal anti-inflammatory drugs should be avoided until dengue can be ruled out to reduce the risk of hemorrhagic complications. Figure 165.1 outlines the current recommended evaluation of infants with possible maternal and congenital Zika virus exposure during pregnancy.

Management of Infants With Clinical Findings Consistent With Congenital Zika Infection

Zika virus testing is recommended, ultrasonography of the head should be performed, and a comprehensive ophthalmologic examination should be performed by age 1 month by an ophthalmologist experienced in assessment of infants. Referrals to a developmental specialist and early intervention are recommended. Additional consultation should be considered by infectious disease (for evaluation of other congenital infections and assistance with Zika virus diagnosis and testing), clinical genetics (for evaluation for other causes of microcephaly or congenital anomalies), and neurology by age 1 month (for comprehensive neurologic examination and consideration for other evaluations, such as advanced neuroimaging and electroencephalography [EEG]). The initial clinical evaluation, including subspecialty consultations, can be performed before hospital discharge or as an outpatient. Infants should be referred for automated brainstem response (ABR) testing by age 1 month if the newborn hearing screen was passed using only otoacoustic emissions (OAE) methodology.

Clinical Management of Infants Without Clinical Findings Consistent With Congenital Zika Infection but Maternal Laboratory Evidence of Possible Zika Virus Infection During Pregnancy

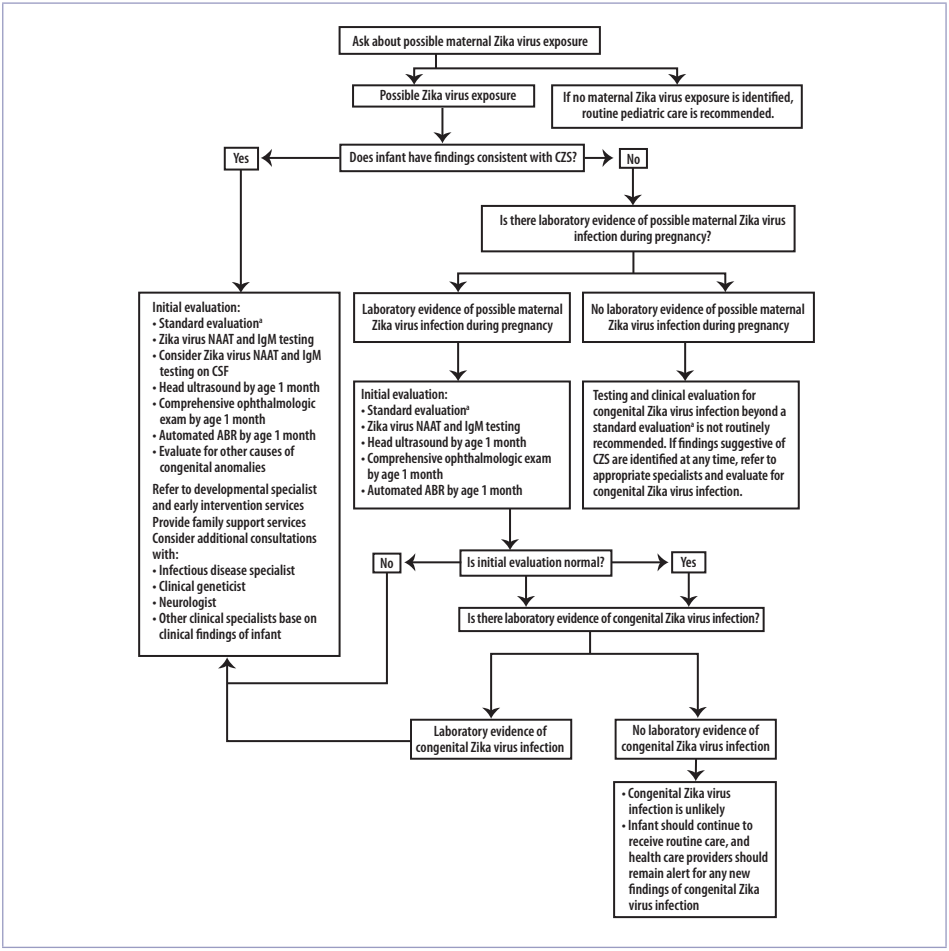
Zika virus testing is recommended, and ultrasonography of the head should be performed by age 1 month to detect subclinical brain findings. All infants should have a comprehensive ophthalmologic examination by age 1 month to detect subclinical eye findings; further follow-up visits with an ophthalmologist after the initial examination should be based on ophthalmology recommendations. Infants should be referred for automated ABR testing by 1 month of age if newborn screen was passed using only OAE methodology. Infants should be monitored for findings consistent with congenital Zika syndrome that could develop over time (eg, impaired visual acuity/function, hearing problems, developmental delay, delay in head growth).

Clinical Management of Infants Without Clinical Findings Consistent With Congenital Zika Infection Born to Mothers With Possible Zika Virus Infection During Pregnancy but Without Laboratory Evidence of Zika Virus During Pregnancy

Zika virus testing is not routinely recommended, and specialized clinical evaluation or follow-up is not routinely indicated. If findings suggestive of congenital Zika syndrome are identified at any time, referrals to the appropriate specialists should be made.

Figure 165.1

Recommendations for the evaluation of infants with possible congenital Zika virus infection based on infant clinical findings,[a,b] maternal testing results,[c,d] and infant testing results[e,f]—United States, October 2017



CZS indicates congenital Zika syndrome; NAAT, nucleic acid amplification test; IgM, immunoglobulin M; CSF, cerebrospinal fluid; ABR, auditory brainstem response; PRNT, plaque reduction neutralization test.

[a] All infants should receive a standard evaluation at birth and at each subsequent well-child visit by their health care providers, including (1) comprehensive physical examination, including growth parameters; and 2) age-appropriate vision screening and developmental monitoring and screening using validated tools. Infants should receive a standard newborn hearing screen at birth, preferably using auditory brainstem response.

[b] Automated ABR by age 1 month if newborn hearing screen passed but performed with otoacoustic emission methodology.

[c] Laboratory evidence of possible Zika virus infection during pregnancy is defined as (1) Zika virus infection detected by a Zika virus RNA NAAT such as RT-PCR on any maternal, placental, or fetal specimen (referred to as NAAT-confirmed), or (2) diagnosis of Zika virus infection, timing of infection cannot be determined or unspecified *Flavivirus* infection, timing of infection cannot be determined by serologic tests on a maternal specimen (ie, positive/equivocal Zika virus IgM and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT value; or negative Zika virus IgM, and positive or equivocal dengue virus IgM, and Zika virus PRNT titer ≥10, regardless of dengue virus PRNT titer). The use of PRNT for confirmation of Zika virus infection, including in pregnant women, is not routinely recommended in Puerto Rico (**www.cdc.gov/zika/laboratories/lab-guidance.html**).

[d] This group includes women who were never tested during pregnancy as well as those whose test result was negative because of issues related to timing or sensitivity and specificity of the test. Because the latter issues are not easily discerned, all mothers with possible exposure to Zika virus during pregnancy who do not have laboratory evidence of possible Zika virus infection, including those who tested negative with currently available technology, should be considered in this group.

[e] Laboratory testing of infants for Zika virus should be performed as early as possible, preferably within the first few days after birth, and includes concurrent Zika virus NAAT in infant serum and urine, and Zika virus IgM testing in serum. If CSF is obtained for other purposes, Zika virus NAAT and Zika virus IgM testing should be performed on CSF.

[f] Laboratory evidence of congenital Zika virus infection includes a positive Zika virus NAAT or a nonnegative Zika virus IgM with confirmatory neutralizing antibody testing, if PRNT confirmation is performed.

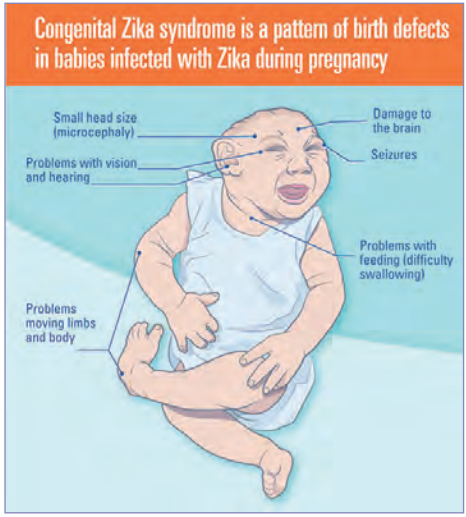


Image 165.1
Congenital Zika syndrome is a pattern of birth defects in babies infected with Zika virus during pregnancy. Courtesy of Centers for Disease Control and Prevention.

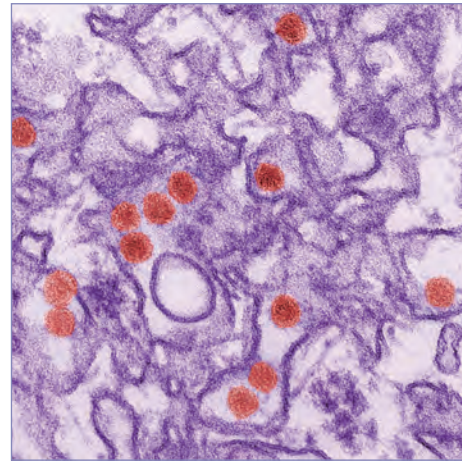


Image 165.2
Transmission electron micrograph of Zika virus, a member of the *Flaviviridae* family.

Image 165.3
A female *Aedes aegypti* mosquito takes flight as she leaves her host's skin surface. Courtesy of Centers for Disease Control and Prevention/James Gathany.

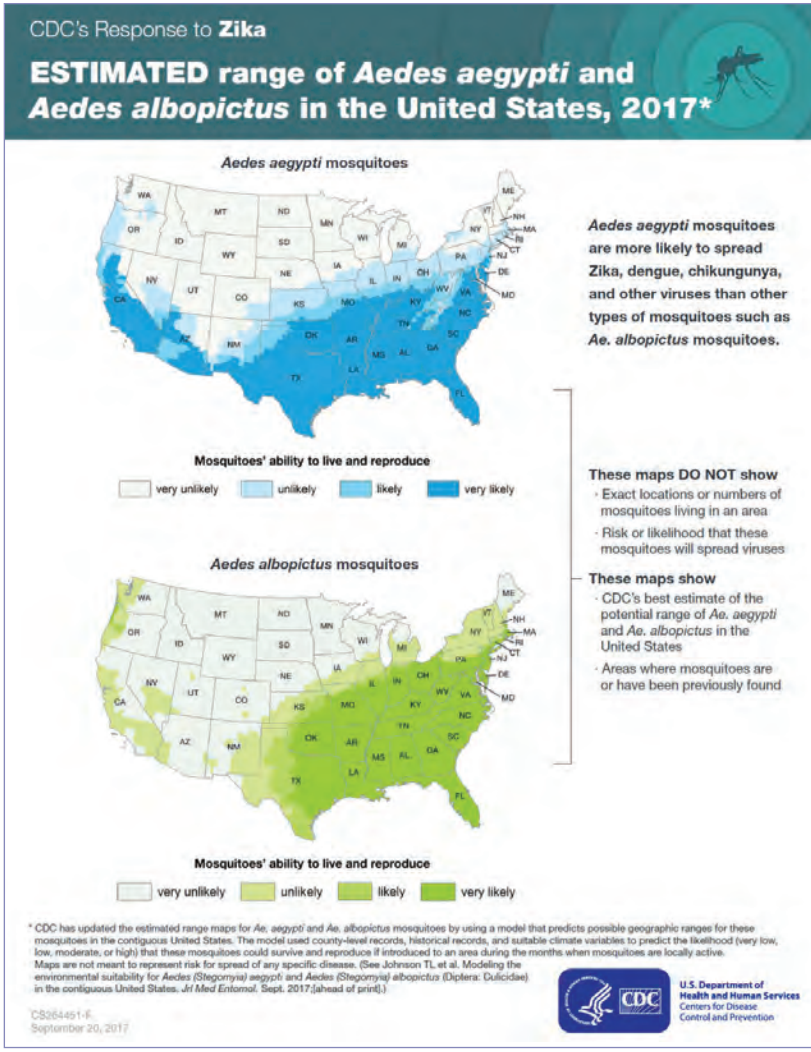


Image 165.4
Estimated range of *Aedes aegypti* and *Aedes albopictus* in the United States, 2017. Courtesy of Centers for Disease Control and Prevention.

Image 165.5
Baby with microcephaly. Courtesy of Pan American Health Organization and World Health Organization.

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