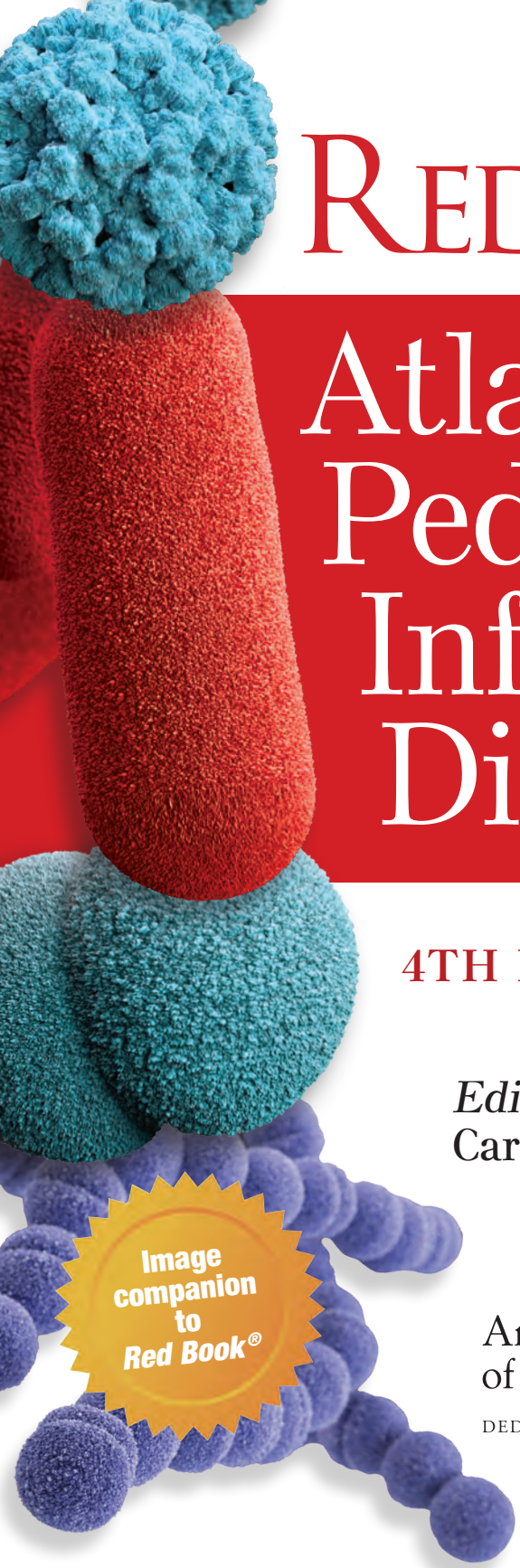

RED BOOK®

Atlas of Pediatric Infectious Diseases

4TH EDITION

Editor
Carol J. Baker, MD, FAAP

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN®

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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.

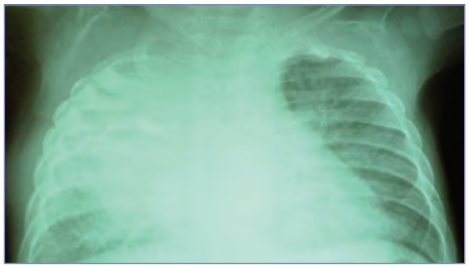

Image 1.1
An 8-month-old boy with pulmonary actinomycosis, an uncommon infection in infancy that may follow aspiration. As in this infant, most cases of actinomycosis are caused by *Actinomyces israelii.*

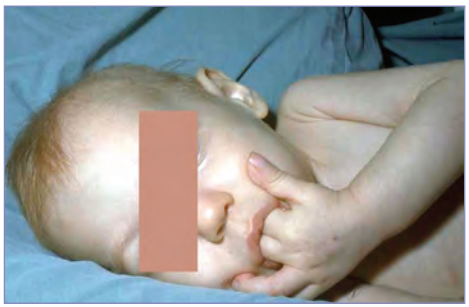

Image 1.3
Clubbing of the thumb and fingers of the 8-month-old boy in Images 1.1 and 1.2 with chronic pulmonary actinomycosis. Blood cultures were repeatedly negative without clinical signs of endocarditis. Courtesy of Edgar O. Ledbetter, MD, FAAP.

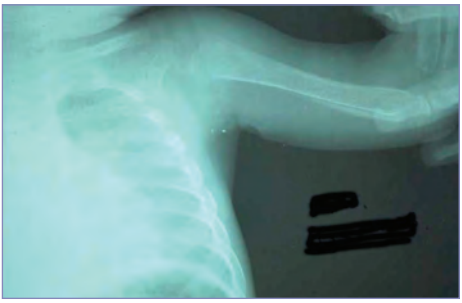

Image 1.2
Periosteal reaction along the left humeral shaft (diaphysis) in the 8-month-old boy in Image 1.1, with pulmonary actinomycosis. The presence of clubbing with this chronic suppurative pulmonary infection and absence of heart disease suggests pulmonary fibrosis contributed to this infant's pulmonary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

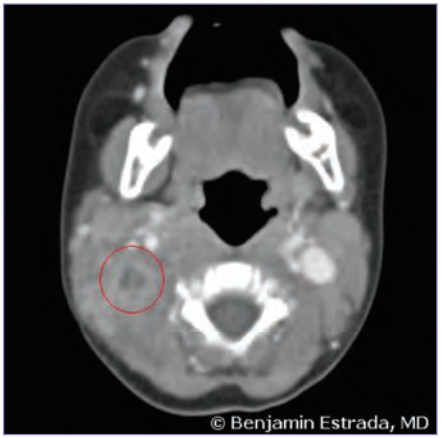

Image 1.4
Actinomyces cervical abscess in a 6-month-old girl. Courtesy of Benjamin Estrada, MD.

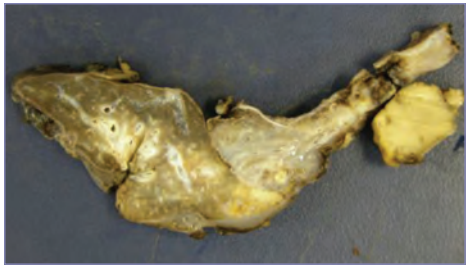

Image 1.5
The resected right lower lobe, diaphragm, and portion of the liver in a 3-year-old previously healthy girl with an unknown source for her pulmonary actinomycosis. Courtesy of Carol J. Baker, MD, FAAP.

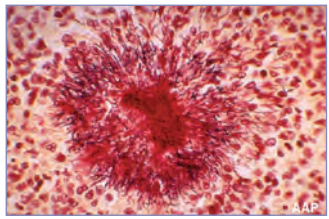

Image 1.7
Tissue showing filamentous branching rods of *Actinomyces israelii* (Brown and Brenn stain). *Actinomyces* species have fastidious growth requirements. Staining of a crushed sulfur granule reveals branching bacilli.

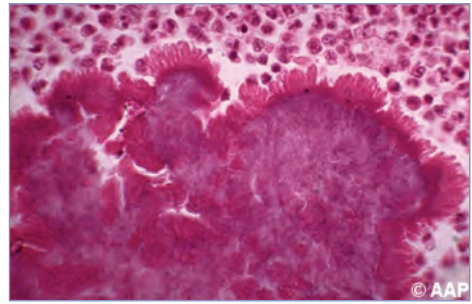

Image 1.6
A sulfur granule from an actinomycotic abscess (hematoxylin-eosin stain). While pathognomonic of actinomycosis, granules are not always present. A Gram stain of sulfur granules shows a dense reticulum of filaments.

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.

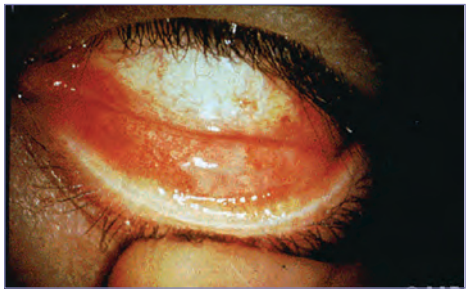

Image 2.1
Acute follicular adenovirus conjunctivitis. Adenoviruses are resistant to alcohol, detergents, and chlorhexidine and may contaminate ophthalmologic solutions and equipment. Instruments can be disinfected by steam autoclaving or immersion in 1% sodium hypochlorite for 10 minutes.

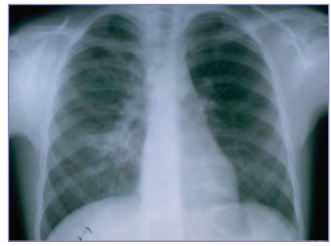

Image 2.2
Adenoviral pneumonia in an 8-year-old girl with diffuse pulmonary infiltrate bilaterally. Most adenoviral infections in the normal host are self-limited and require no specific treatment. Lobar consolidation is unusual.

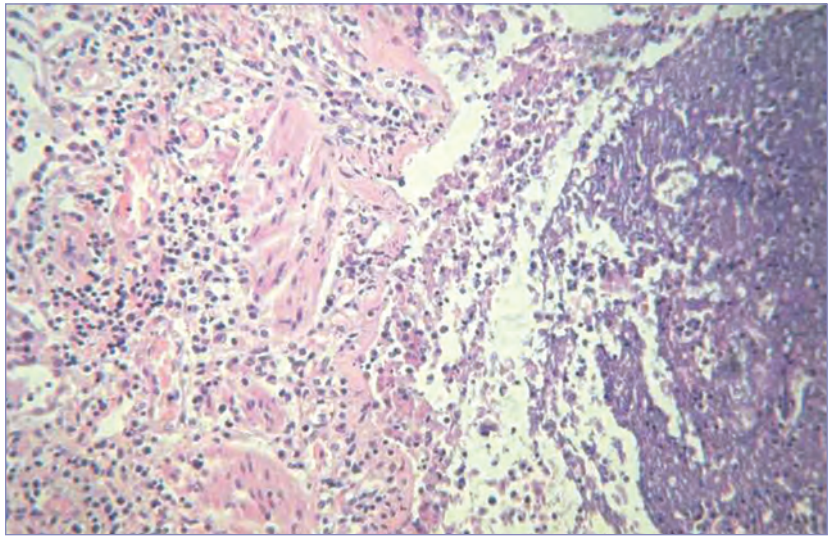

Image 2.3
Histopathology of the lung with bronchiolar occlusion in an immunocompromised child who died with adenoviral pneumonia. Note interstitial mononuclear cell infiltration and hyaline membranes. Adenoviruses types 3 and 7 can cause necrotizing bronchitis and bronchiolitis. Courtesy of Edgar O.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

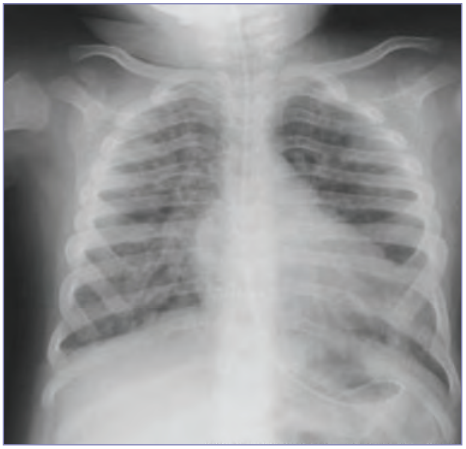

Image 2.4
Adenovirus pneumonia in a 4-year-old boy. Courtesy of Benjamin Estrada, MD.

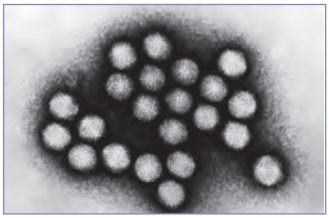

Image 2.6
Transmission electron micrograph of adenovirus. Adenoviruses have a characteristic icosahedral structure. Courtesy of Centers for Disease Control and Prevention.

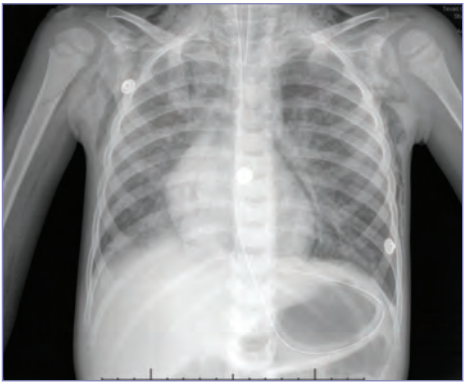

Image 2.5
This previously healthy 3-year-old boy presented with respiratory failure requiring intensive care for adenovirus type 7 pneumonia. He eventually recovered with some mild impairment in pulmonary function studies. Note the pneumomediastinum. Courtesy of Carol J. Baker, MD, FAAP.

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.

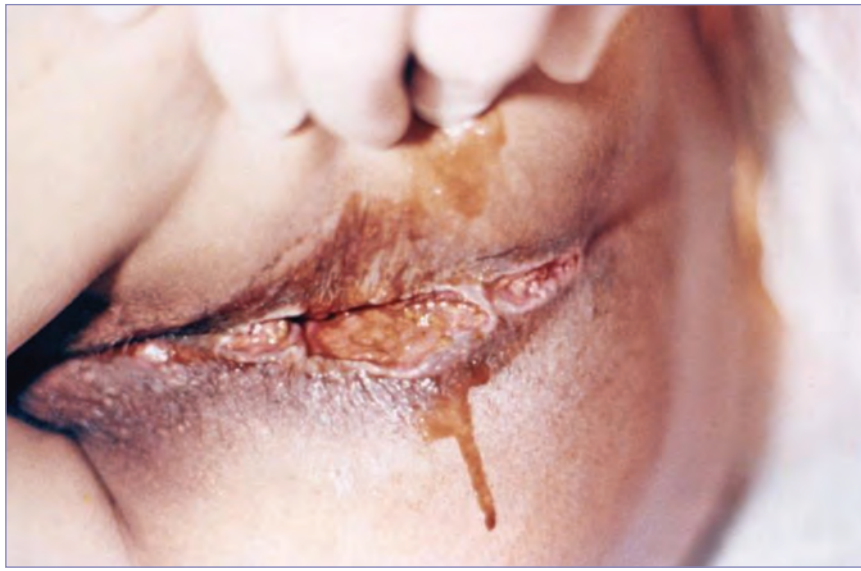

Image 3.1
This patient with amebiasis presented with tissue destruction and granulation of the anoperineal region caused by an *Entamoeba histolytica* infection. Courtesy of Centers for Disease Control and Prevention.

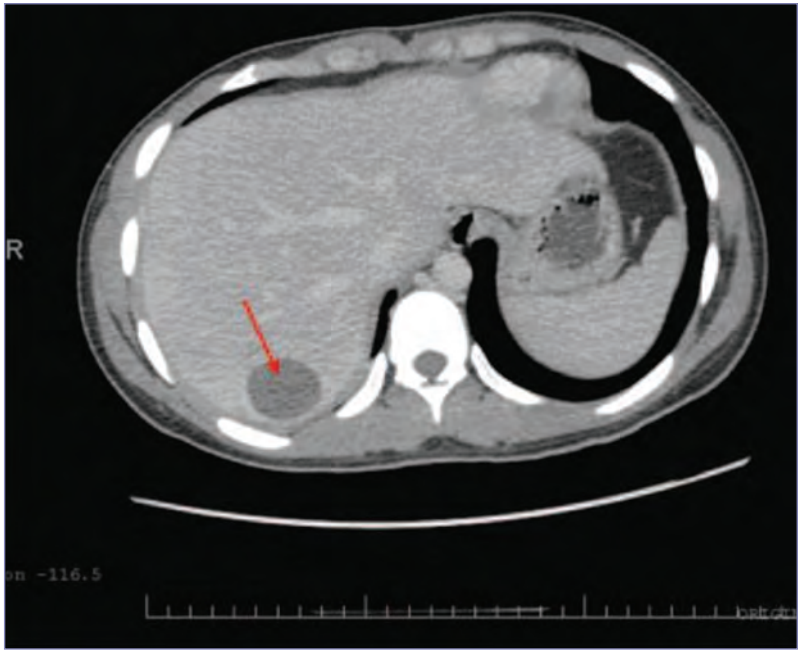

Image 3.2
Computed tomography scan of the abdomen showing a peripherally enhancing low-density lesion in the posterior aspect of the right hepatic lobe. Amebic liver abscess amebiasis, caused by the intestinal protozoal parasite *Entamoeba histolytica,* remains a global health problem, infecting about 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.*

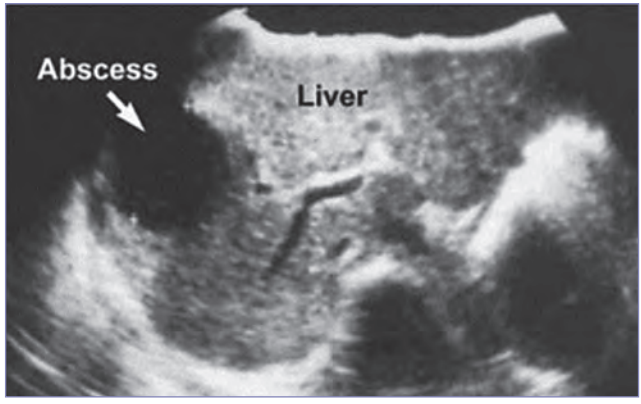

Image 3.3
Abdominal ultrasound showing a liver abscess caused by *Entamoeba histolytica*.

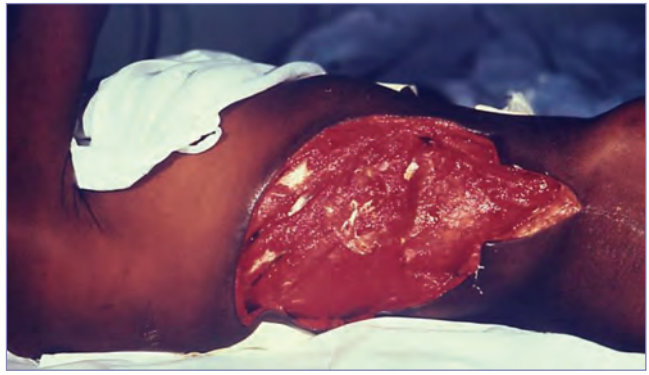

Image 3.4
This patient presented with a case of invasive extraintestinal amebiasis affecting the cutaneous region of the right flank. Courtesy of Centers for Disease Control and Prevention.

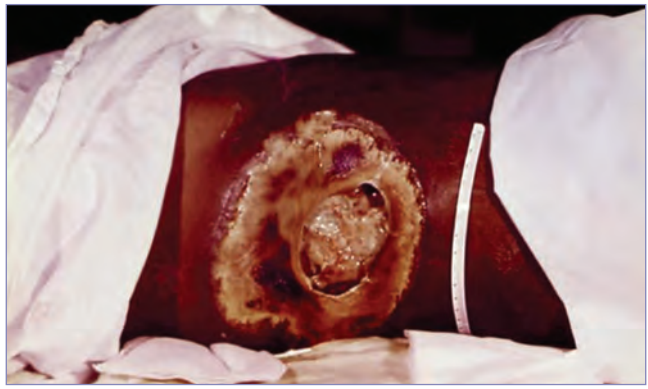

Image 3.5
This patient, also shown in Image 3.4, presented with a case of invasive extraintestinal amebiasis affecting the cutaneous region of the right flank causing severe tissue necrosis. Here we see the site of tissue destruction, pre-debridement. Courtesy of Centers for Disease Control and Prevention/Kerrison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

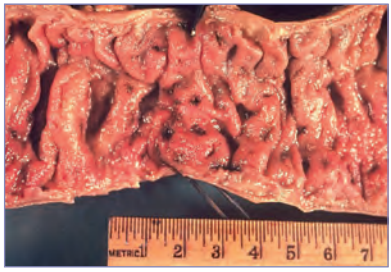

Image 3.6
Gross pathology of intestinal ulcers due to amebiasis. Courtesy of Centers for Disease Control and Prevention.

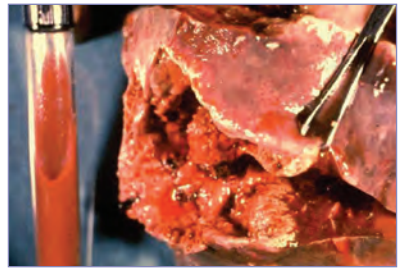

Image 3.7
Gross pathology of amebic (*Entamoeba histolytica*) abscess of liver; tube of "chocolate-like" pus from abscess. Amebic liver abscesses are usually singular and large and in the right lobe of the liver. Bacterial hepatic abscesses are more likely to be multiple. Courtesy of Centers for Disease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

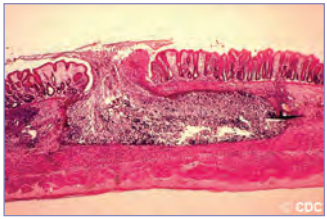

Image 3.8
Histopathologic features of a typical flask-shaped ulcer of intestinal amebiasis in a kitten. Courtesy of Centers for Disease Control and Prevention.

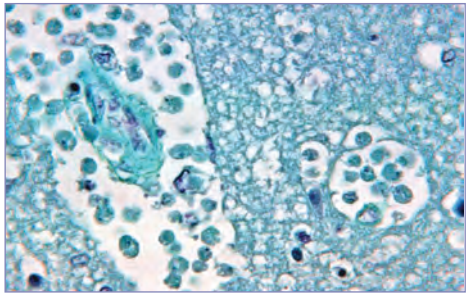

Image 3.9
This micrograph of a brain tissue specimen reveals the presence of *Entamoeba histolytica* amoebae (magnification ×500). In more serious cases of amebiasis, amoebae can cause an infection of tissue outside of the intestinal tract. Courtesy of Centers for Disease Control and Prevention.

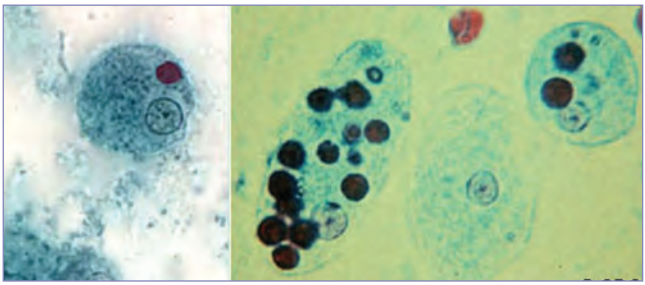

Image 3.10
Trophozoites of *Entamoeba histolytica* with ingested erythrocytes (trichrome stain). The ingested erythrocytes appear as dark inclusions. Erythrophagocytosis is the only characteristic that can be used to differentiate morphologically *E histolytica* from the nonpathogenic *Entamoeba dispar*. 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.

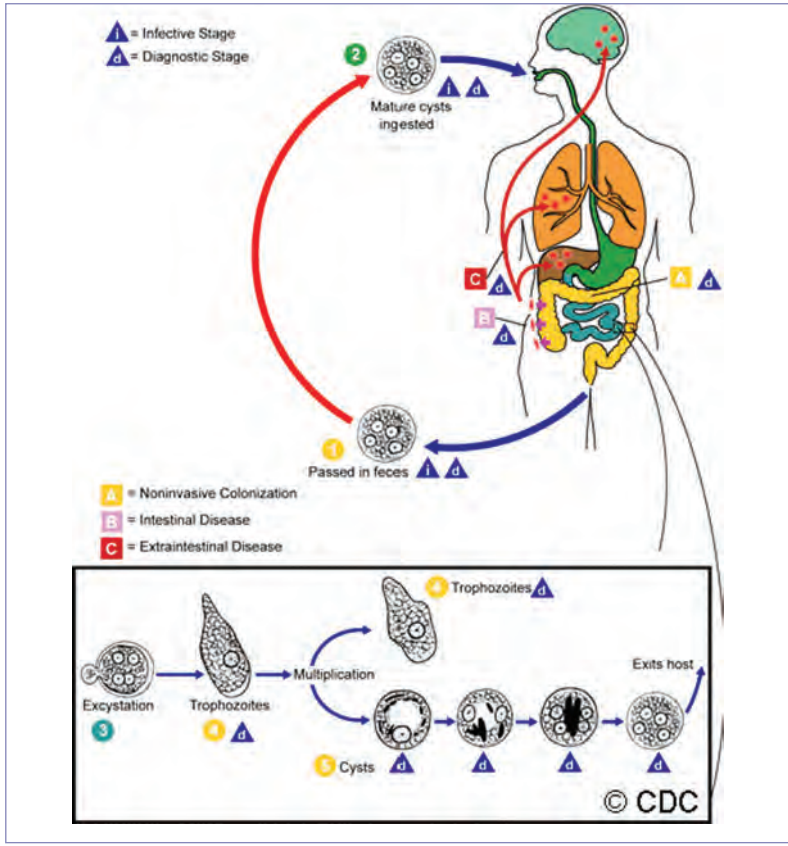

Image 3.11

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.

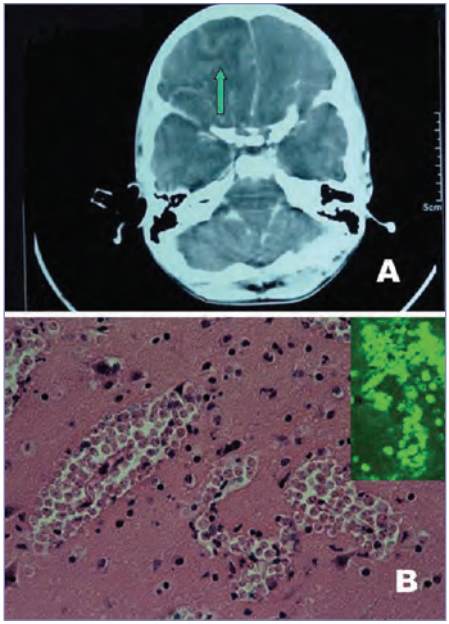

Image 4.1
A, Computed tomographic scan; note the right frontobasal collection (arrow) with a midline shift right to left. B, Brain histology; 3 large clusters of amebic vegetative forms are seen (hematoxylin-eosin stain, magnification ×250). Inset: positive indirect immunofluorescent analysis on tissue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

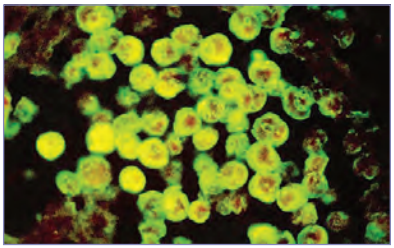

Image 4.3
Histopathologic features of amebic meningoencephalitis due to *Naegleria fowleri* (direct fluorescent antibody stain). Courtesy of Centers for Disease Control and Prevention

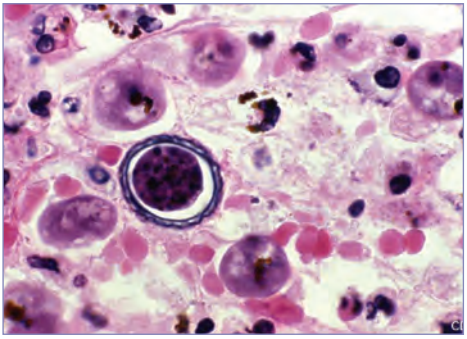

Image 4.2
This photomicrograph of brain tissue reveals free-living amoebas. Courtesy of Centers for Disease Control and Prevention.

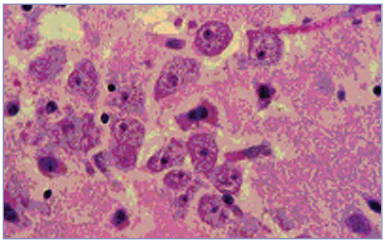

Image 4.4
Balamuthia mandrillaris trophozoites in brain tissue. Courtesy of Centers for Disease Control and Prevention.

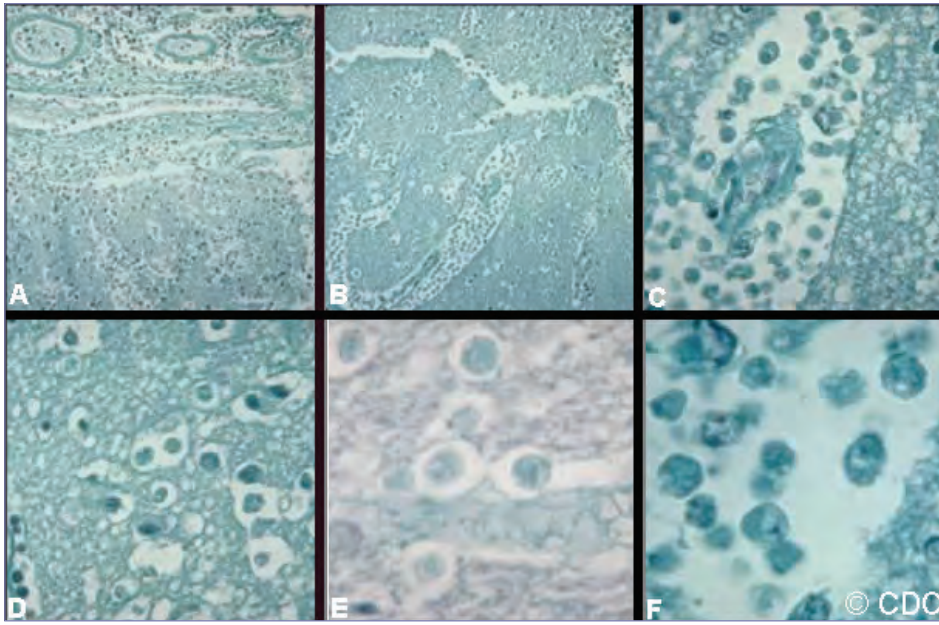

Image 4.5
A–F, *Naegleria fowleri* in brain tissue (trichrome stain). Courtesy of Centers for Disease Control and Prevention.

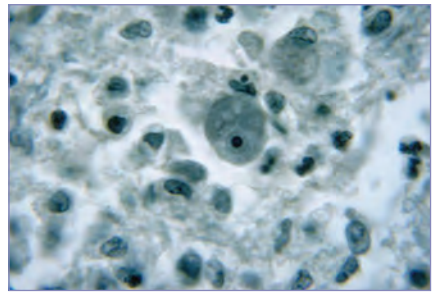

Image 4.6
This photomicrograph of a brain tissue specimen depicts the cytoarchitectural changes associated with a free-living amebic infection, which may have been caused by either *Naegleria fowleri*, or *Acanthamoeba* sp. The organisms were found in the brain of a Japanese prisoner of war in the 1950s, 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.