

125 - 230 Amebiasis and Infection with Free-Living Amebae

230 Amebiasis and Infection with Free-Living Amebae

serum levels of theophylline should be monitored closely in this situation. Tinidazole This nitroimidazole is effective for the treatment of amebiasis, giardiasis, and trichomoniasis. Like metronidazole, tinidazole must undergo reductive activation by the parasite's metabolic system before it can act on protozoal targets. Tinidazole inhibits the synthesis of new DNA in the parasite and causes degradation of existing DNA. The reduced free-radical derivatives alkylate DNA, with consequent cytotoxic damage to the parasite. This damage appears to be produced by short-lived reduction intermediates, resulting in helix destabilization and strand breakage of DNA. The mechanism of action and side effects of tinidazole are similar to those of metronidazole, but adverse events appear to be less frequent and severe with tinidazole. In addition, the significantly longer half-life of tinidazole (>12 h) offers potential cure with a single dose. Tribendimidine Tribendimidine, a diamidine derivative of aminophenylamidate, is a cholinergic agonist that is selective for the nicotinic acetylcholine receptors of nematode muscle. This novel agent has a broad spectrum of activity against a wide variety of helminths and is highly effective against food-borne trematodes, with a similar cure rate to praziquantel. Clinical trials have demonstrated efficacy of a single dose alone or in combination with other helminthics against soil-transmitted helminth infections. The drug is an L-type nicotinic acetylcholine receptor agonist and exhibits the same method of action as levamisole and pyrantel; therefore, it may not be effective in regions where resistance to these agents is widespread. It is not available in the United States. Triclabendazole In contrast to other benzimidazoles, the antihelminthic activity of triclabendazole is highly specific for *Fasciola* and *Paragonimus* species, with little activity against nematodes, cestodes, and other trematodes. Triclabendazole is effective against all stages of *Fasciola* species. The active sulfoxide metabolite of triclabendazole binds to fluke tubulin by assuming a unique nonplanar configuration and disrupts microtubule-based processes. Resistance to triclabendazole in veterinary use has been reported in Australia and Europe; however, no resistance has been documented in humans. Triclabendazole is rapidly absorbed after oral ingestion; administration with food enhances its absorption and shortens the elimination half-life of the active metabolite. Both the sulfoxide and the sulfone metabolites are highly protein bound (>99%). Treatment with

tricala bendazole is typically given in one or two doses. No clinical data are available regarding dose adjustment in renal or hepatic insufficiency; however, given the short course of therapy and extensive hepatic metabolism of triclabendazole, dose adjustment is unlikely to be necessary. No information exists on drug interactions. Trimethoprim-Sulfamethoxazole See Table 229-1 and Chap. 149. ■ ■FURTHER READING Dziduch K et al: The current directions of searching for antiparasitic drugs. *Molecules* 27:1534, 2022. Fehintola FA et al: Drug interactions in the treatment and chemoprophylaxis of malaria in HIV infected individuals in sub-Saharan Africa. *Curr Drug Metab* 12:51, 2011. Keiser J, Häberli C: Evaluation of commercially available anthelmintics in laboratory models of human intestinal nematode infections. *ACS Infect Dis* 7:1177, 2021. Keiser J et al: Antiparasitic drugs for paediatrics: Systematic review, formulations, pharmacokinetics, safety, efficacy, and implications for control. *Parasitology* 138:1620, 2011. Kelesidis T, Falagas ME: Substandard/counterfeit antimicrobial drugs. *Clin Microbiol Rev* 28:443, 2015. Pink R et al: Opportunities and challenges in antiparasitic drug discovery. *Nat Rev Drug Discov* 4:727, 2005.

Section 18 Protozoal Infections Rosa M. Andrade, Sharon L. Reed

Amebiasis and Infection

with Free-Living

Amebae AMEBIASIS ■ ■DEFINITION Amebiasis is an infection caused by *Entamoeba histolytica*, an intestinal protozoan. Its spectrum of clinical syndromes ranges from asymptomatic colonization (90% of cases) to invasive amebiasis, which accounts for 10% of affected individuals. Invasive amebiasis frequently presents as intestinal colitis (dysentery or diarrhea) or as extraintestinal amebiasis, in which abscesses of the liver are more commonly found than involvement of the lungs or brain. ■ ■LIFE CYCLE AND TRANSMISSION *E. histolytica* is acquired by ingestion of viable cysts from fecally contaminated water, food, or hands (Fig. 230-1). Food-borne exposure is the most prevalent form of transmission. It occurs when food handlers are shedding cysts or food is being grown with feces-contaminated soil, fertilizer, or water. Less common means of transmission include oral and anal sexual practices and, in rare instances, direct rectal inoculation through colonic irrigation devices. Motile trophozoites are released from cysts in the small intestine and, in most patients, remain as harmless commensals in the large bowel. After encystation, infectious cysts are shed in the stool and can survive for several weeks in a moist environment. In some patients, the trophozoites invade either the bowel mucosa, causing symptomatic colitis, or the bloodstream, causing distant abscesses of the liver, lungs, or brain. The trophozoites may not encyst in patients with active dysentery, and motile hematophagous trophozoites are frequently present in fresh stools. Trophozoites are rapidly killed by exposure to air or stomach acid and therefore can not transmit infection. CHAPTER 230 Amebiasis and Infection with Free-Living Amebae

■ ■EPIDEMIOLOGY *E. histolytica* infection typically affects underdeveloped tropical regions with poor sanitation systems and hygiene, occurring often in children <5 years of age. This infection is widespread in the Indian subcontinent and Africa, parts of East Asia (Thailand), and Central and South America (Mexico and Colombia). According to the Global Burden of Disease 2016 study, amebiasis accounts for 26,748 all-age deaths, including 4567 children <5 years old. In contrast, returning travelers, recent immigrants, men who have sex with men (MSM), military personnel, and inmates of institutions are the main groups at risk for amebiasis in developed countries. The

GeoSentinel Surveillance Network, which encompasses information from tropical medicine clinics on six continents, showed that, among long-term travelers (trip duration, >6 months), diarrhea due to *E. histolytica* was among the most common diagnoses. In countries like Japan and Spain, amebiasis is emerging as a sexually transmitted disease, first reported in HIV-positive MSM. However, in Japan, *E. histolytica* infections, symptomatic or asymptomatic, seem to be steadily spreading among non-HIV men and women. Worldwide, *E. histolytica* is the second most common cause of death related to parasitic infection (after malaria). Invasive colitis and liver abscesses are tenfold more common among men than among women; this difference has been attributed to a disparity in complement-mediated killing and effects of testosterone on the secretion of interferon γ . The wide spectrum of clinical disease caused by *Entamoeba* is due in part to the differences between the two major infecting species,

Necrotic abscess Following GI infection (usually asymptomatic), trophozoites may invade through the blood stream, causing necrotic abscesses, particularly of the liver. Encystation occurs in the large intestines. Trophozoites can invade the large bowel, causing flask-shaped ulcers and bloody diarrhea.

90% of patients are asymptomatically colonized but can still pass infectious cysts. **PART 5 Infectious Diseases Trophozoite** **FIGURE 230-1 Life cycle of *Entamoeba histolytica*.** GI, gastrointestinal; RBCs, red blood cells. *E. histolytica* and *E. dispar*. *E. histolytica* has unique surface antigens, is genetically distinct, and possesses virulence properties that distinguish it from the morphologically identical *E. dispar*. Most asymptomatic carriers, including MSM and patients with AIDS, harbor *E. dispar* and have self-limited infections. In this respect, *E. dispar* is dissimilar to other enteric pathogens such as *Cryptosporidium* and *Cystoisospora belli*, which can cause self-limited illnesses in immunocompetent hosts but devastating diarrhea in patients with AIDS. These observations indicate that *E. dispar* is incapable of causing invasive disease. Through genomic sequencing, new species of *Entamoeba* have been identified: *E. moshkovskii* and *E. bangladeshi*. These new species are microscopically indistinguishable from *E. histolytica*. Although *E. moshkovskii* causes diarrhea, weight loss, and colitis in mice, a prospective evaluation of children from the Mirpur community of Dhaka, Bangladesh, found that most children who had diarrheal diseases associated with *E. moshkovskii* were simultaneously infected with at least one other enteric pathogen. *E. bangladeshi* nov. sp., Bangladesh was first reported in 2012 in this Bangladeshi community; however, it has been isolated in South African subjects of all ages in recent years. Additional clinical and epidemiologic studies are needed to discern the true role of *E. bangladeshi* in the human host. ■ ■ **PATHOGENESIS AND PATHOLOGY** Both trophozoites and cysts are found in the intestinal lumen, but only trophozoites of *E. histolytica* invade tissue. The trophozoite is 20–60 μm in diameter and contains vacuoles and a nucleus with a characteristic central nucleolus. Trophozoites attach to colonic mucus and epithelial cells by Gal/GalNAc adherence lectin and release glycosidases and

Cysts and trophozoites are passed into soil or water. Cyst

Cysts are ingested in contaminated food or water. Stool Small intestines Large intestines

Excystation occurs in the small intestines, releasing a single motile trophozoite that colonizes the large bowel. RBCs proteases that cause degradation of mucus polymers. Extracellular cysteine

proteinases degrade collagen, elastin, IgA, IgG, and the anaphylatoxins C3a and C5a. After disruption of the mucous layer, trophozoites damage the mucosa by contact-dependent and contact-independent cytotoxicity. The contact-dependent cytotoxicity is attributable to induction of apoptotic cell death; trophocytosis-mediated cell death (ingestion of fragments of living cells); and lysis of inflammatory cells (neutrophils, monocytes, and lymphocytes), colonic cells, and hepatic cells through release of phospholipase A and pore-forming peptides. Contact-independent cytotoxicity follows production of inflammatory mediators, such as prostaglandin E₂, by trophozoites, ultimately leading to increased ion permeability of intercellular tight junctions. *E. histolytica* trophozoites are constantly exposed to reactive oxygen and nitrogen species arising from their own metabolism and from the host during tissue invasion. The ability to resist reactive oxygen species or reactive nitrogen species such as nitric oxide or S-nitrosothiols (e.g., S-nitrosoglutathione [GSNO] and S-nitrosocysteine [CySNO]) is also a virulence factor. Since *E. histolytica* lacks glutathione and glutathione reductase, it relies on its thioredoxin-thioredoxin reductase system to prevent, regulate, and repair the damage caused by oxidative stress. This antioxidant system is versatile: it has the ability to reduce reactive nitrogen species and use an alternative electron donor, such as nicotinamide adenine dinucleotide. In addition, trophozoites preincubated with *E. coli* 055 are more resistant to hydrogen peroxide-mediated killing by using bacterially produced malate dehydrogenase and oxaloacetate for protection from oxidative stress. Metronidazole, the current standard of therapy for amebiasis, seems to exert its antiparasitic effect through inhibition of this antioxidant system.

Phagocytosis is a virulence factor that leads to a defective proliferation of *E. histolytica* if inhibited. Trophozoites use membrane-associated carbohydrate-binding proteins to phagocytose intestinal bacteria, especially gram-negative Enterobacteriaceae, for their nutrients. Interactions with commensal bacteria, such as *Escherichia coli*, can attenuate the virulence of *E. histolytica* by decreasing the expression of Gal/GalNAc lectin. In contrast, ingestion of enteropathogenic bacteria, such as enteropathogenic *E. coli* and *Shigella dysenteriae*, increases expression of the Gal/GalNAc lectin and enhances *E. histolytica* cysteine protease activity. The interactions between *E. histolytica* and the gut microbiome can determine the severity of disease. During the first 2 years of life, the gut immune system and the microbiome mature rapidly. In one study, ~80% of children from the Bangladeshi community of Dhaka were found to be infected with *E. histolytica* by 2 years of age. Fecal anti-Gal/GalNAc lectin IgA was associated with protection from reinfection, while a high parasite burden in the first year of life was associated with the expansion of *Prevotella copri* in their gut microbiome and presence of diarrhea. In adults, the diversity of the gut microbiome can determine the pathogenesis of disease. As shown in a Japanese cohort through next-generation sequencing analysis, the gut microbiome in asymptomatic *E. histolytica* carriers was more homogeneous, with high abundance of Ruminococcaceae, Coriobacteriaceae, and Clostridiaceae, while these bacteria were absent or in low abundance in patients with invasive disease (symptomatic). These observations suggest the protective role of these bacteria. Antimicrobial peptides, such as cathelicidins, are an important component of innate immunity and are induced by *E. histolytica* upon intestinal invasion in a mouse model. In this model, cecal cathelicidin-related antimicrobial peptide mRNA increased by >4-fold at 3 days and >100-fold at 7 days. However, *E. histolytica* remained resistant to cathelicidin-mediated killing, probably because the antimicrobial peptide was digested by amebic cysteine proteinases. Other in vitro studies have shown that α - and β -defensins may damage *E. histolytica* membrane integrity. IgA plays a critical role in acquired immunity to *E. histolytica*. A study in Bangladeshi schoolchildren revealed that an intestinal IgA

response to Gal/GalNAc reduced the risk of new *E. histolytica* infection by 64%. Serum IgG antibody is not protective; titers correlate with the duration of illness rather than with the severity of disease. Indeed, Bangladeshi children with a serum IgG response were more likely than those without such a response to develop new *E. histolytica* infection. In infants from this same Bangladeshi community, passive immunity conferred by maternal parasite-specific IgA via breastfeeding resulted in a 39% reduced risk of infection and a 64% reduced risk of diarrheal disease from *E. histolytica* during the first year of life. However, this protection appeared to be species-specific, with little or no protection conferred from infections with other species such as *E. dispar* or *E. bangladeshi*. This Bangladeshi cohort has furthered our understanding of the genetic susceptibility factors associated with *E. histolytica* disease. Heterozygosity of the major histocompatibility complex (MHC) class II allele DQB1*0601 was found to protect against amebic intestinal disease, which supports the role of antigen processing and CD4+ T cells in resistance to amebiasis. Adipocyte leptin receptors (LEPRs) are expressed on intestinal epithelial cells, prevent apoptosis, promote tissue repair, and may decrease neutrophil infiltration. In this cohort, a single amino acid substitution (Q223R) in LEPRs nearly quadrupled the risk for amebic intestinal disease in children and increased the risk for amebic liver abscesses in adults. Similarly, variations in the locus of cAMP-responsive element modulator/cullin 2 (CREM/CUL2) may increase the risk for diarrhea in children who acquired *E. histolytica* within their first year of life. Interestingly, both genetic variations, Q223R and CREM, are overrepresented in this geographical region. The earliest intestinal lesions are microulcerations of the mucosa of the cecum, sigmoid colon, or rectum that release erythrocytes, inflammatory cells, and epithelial cells. A colonoscopy reveals small ulcers with heaped-up margins and normal intervening mucosa (Fig. 230-2A). Submucosal extension of ulcerations under viable-appearing surface

A CHAPTER 230 Amebiasis and Infection with Free-Living Amebae

B FIGURE 230-2 Endoscopic and histopathologic features of intestinal amebiasis. A. Appearance of ulcers on colonoscopy (arrows). B. Inflammatory infiltrate and *Entamoeba histolytica* trophozoites (arrows) in invasive amebic colitis (hematoxylin and eosin). (Courtesy of the Department of Pathology and Gastroenterology, San Diego VA Medical Center.) mucosa causes the classic “flask-shaped” ulcer containing trophozoites at the margins of dead and viable tissues. Although neutrophilic infiltrates may accompany early lesions in animals, human intestinal infection is marked by a paucity of inflammatory cells, probably in part because of the killing of neutrophils by trophozoites (Fig. 230-2B). Treated ulcers characteristically heal with little or no scarring. Occasionally, however, full-thickness necrosis and perforation occur. Rarely, intestinal infection results in the formation of a mass lesion, or ameboma, in the bowel lumen. The overlying mucosa is usually thin and ulcerated, while other layers of the wall are thickened, edematous, and hemorrhagic; this condition results in exuberant formation of granulation tissue with little fibrous-tissue response. Amebic liver abscesses are age- and gender-dependent. Men 30–60 years of age are most commonly infected at a rate 10–12 times higher than women in the same age group. Studies in animal models have demonstrated that testosterone may increase susceptibility to amebic liver abscess by modulating the secretion of interferon γ by natural killer T cells, which are activated through *E. histolytica* lipopeptidophosphoglycan present on the surface of ameba trophozoites. Liver

abscesses are always preceded by intestinal colonization, which may be asymptomatic. Blood vessels may be compromised early by wall lysis and thrombus formation. Trophozoites invade

veins to reach the liver through the portal venous system. *E. histolytica* is resistant to complement-mediated lysis—a property critical to survival in the bloodstream. Inoculation of amebae into the portal system of hamsters results in an acute cellular infiltrate consisting predominantly of neutrophils. Later, the neutrophils are lysed by contact with amebae, and the release of neutrophil toxins may contribute to necrosis of hepatocytes. The liver parenchyma is replaced by necrotic material that is surrounded by a thin rim of congested liver tissue. Although the necrotic contents of a liver abscess are classically described as “anchovy paste,” the fluid is variable in color; it is composed of bacteriologically sterile granular debris with few or no cells. Amebae, if seen, tend to be found near the capsule of the abscess.

■ ■ **CLINICAL SYNDROMES** **Intestinal Amebiasis** The most common type of amebic infection is asymptomatic cyst passage (90% of patients). Even in highly endemic areas, most patients harbor *E. dispar*. Symptomatic amebic colitis develops 2–6 weeks after the ingestion of infectious cysts. A gradual onset of lower abdominal pain and mild diarrhea is followed by malaise, weight loss, and diffuse lower abdominal or back pain. Cecal involvement may mimic acute appendicitis. Patients with full-blown dysentery may pass 10–12 stools per day. The stools contain little fecal material and consist mainly of blood and mucus. In contrast to those with bacterial diarrhea, fewer than 40% of patients with amebic dysentery are febrile. Virtually all patients have heme-positive stools.

PART 5 Infectious Diseases More fulminant intestinal infection, with severe abdominal pain, high fever, and profuse diarrhea, is rare and occurs predominantly in children. Patients may develop toxic megacolon, in which there is severe bowel dilation with intramural air. Patients receiving glucocorticoids are at risk for severe amebiasis. The association between severe amebiasis complications and glucocorticoid therapy emphasizes the importance of excluding amebiasis when inflammatory bowel disease is suspected. An occasional patient presents with only an asymptomatic or tender abdominal mass caused by an ameboma, which is easily confused with cancer on barium studies. A positive serologic test or biopsy can prevent unnecessary surgery in this setting. Environmental enteropathy (“impoverished gut”; blunted small intestinal villi with lamina propria inflammation) is observed in tropical developing areas with endemic enteric infections, such as amebiasis. It is associated with functional gastrointestinal impairment causing malnutrition and stunted growth in children within the first 2 years of life. Bangladeshi children with symptomatic *E. histolytica* infections were 2.9 times more likely to be malnourished and 4.7 times more likely to be short for their age than were children without symptomatic infections. These factors affect their cognitive development and may be linked to loss of productivity in adulthood.

Amebic Liver Abscess Extraintestinal infection by *E. histolytica* most often involves the liver. Of travelers who develop an amebic liver abscess after leaving an endemic area, 95% do so within 5 months. Young patients with an amebic liver abscess are more likely than older patients to present in the acute phase with prominent symptoms of <10 days’ duration. Most patients are febrile and have right-upper quadrant pain, which may be dull or pleuritic in nature and may radiate to the shoulder. Point tenderness over the liver and right-sided pleural effusion are common. Jaundice is rare. Although the initial site of infection is the colon, fewer than one-third of patients with an amebic abscess have active diarrhea. Older patients from endemic areas are more likely to have a subacute course lasting 6 months, with weight loss and hepatomegaly. About one-third of patients with chronic presentations are febrile. Thus, the clinical diagnosis of an amebic liver abscess may be difficult to establish because the symptoms and signs are often nonspecific. Since 10–15% of patients present only with fever, amebic liver abscess must be considered in the differential diagnosis of fever of unknown origin (Chap. 22).

Complications of Amebic Liver Abscess Pleuropulmonary involvement, which is reported in 20–30% of patients, is the most frequent complication of amebic liver abscess. Manifestations include sterile effusions, contiguous spread from the liver, and rupture into the pleural space. Sterile effusions and contiguous spread usually resolve with medical therapy, but frank rupture into the pleural space requires drainage. A hepatobronchial fistula may cause cough productive of large amounts of necrotic material that may contain amebae. This dramatic complication carries a good prognosis. Abscesses that rupture into the peritoneum may present as an indolent leak or an acute abdomen and require both percutaneous catheter drainage and medical therapy. Rupture into the pericardium, usually from abscesses of the left lobe of the liver, carries the gravest prognosis; it can occur during medical therapy and requires surgical drainage. Involvement of Other

Extraintestinal Sites The genitourinary tract may become involved by direct extension of amebiasis from the colon or by hematogenous spread of the infection. Painful genital ulcers, characterized by a punched-out appearance and profuse discharge, may develop secondary to extension from either the intestine or the liver. Both of these conditions respond well to medical therapy. Cerebral involvement has been reported in fewer than 0.1% of patients in large clinical series. Symptoms and prognosis depend on the size and location of the lesion. ■ ■

DIAGNOSTIC TESTS Laboratory Diagnosis Stool examinations, serologic tests, and noninvasive imaging of the liver remain the most important procedures in the diagnosis of amebiasis in most parts of the world. Fecal findings suggestive of amebic colitis include a positive test for heme, a paucity of neutrophils, and amebic cysts or trophozoites. The definitive diagnosis of amebic colitis is made by the demonstration of hematophagous trophozoites of *E. histolytica*. Because trophozoites are killed rapidly by water, drying, or barium, it is important to examine at least three fresh stool specimens. Examination of a combination of wet mounts, iodine-stained concentrates, and trichrome-stained preparations of fresh stool and concentrates for cysts or trophozoites confirms the diagnosis in 75–95% of cases. Cultures of amebae are more sensitive but are not routinely available. If stool examinations are negative, sigmoidoscopy with biopsy of the edge of ulcers may increase the yield, but this procedure is dangerous during fulminant colitis because of the risk of perforation. Trophozoites in a biopsy specimen from a colonic mass confirm the diagnosis of ameboma, but trophozoites are rare in liver aspirates because they are found in the abscess capsule and not in the readily aspirated necrotic center. Accurate diagnosis requires experience, since the trophozoites may be confused with neutrophils and the cysts must be differentiated morphologically from those of *Entamoeba hartmanni*, *Entamoeba coli*, and *Endolimax nana*, which do not cause clinical disease and do not warrant therapy. Unfortunately, the cysts of *E. histolytica* cannot be distinguished microscopically from those of *E. dispar*, *E. moshkovskii*, or *E. bangladeshi*. Therefore, the microscopic diagnosis of *E. histolytica* can be made only by the detection of *Entamoeba* trophozoites that have ingested erythrocytes. Serology is an important addition to the methods used for parasitologic diagnosis of invasive amebiasis. Enzyme-linked immunosorbent assays are positive in >90% of cases with colitis, ameboma, or liver abscess. Positive results in conjunction with the appropriate clinical syndrome suggest active disease because serologic findings usually revert to negative within 6–12 months. Even in highly endemic areas such as South Africa, fewer than 10% of asymptomatic individuals have a positive amebic serology. The interpretation of the indirect hemagglutination test is difficult because titers may remain positive for as long as 10 years. Early in infection, up to 10% of patients with acute amebic liver abscess may have negative serologic findings, which usually become positive within a week. In contrast to carriers of *E. dispar*, most asymptomatic carriers of *E. histolytica* develop antibodies. Thus, serologic tests are helpful in assessing the risk of invasive amebiasis in asymptomatic, cyst-passing individuals in nonendemic areas. Serologic tests

should also be performed in patients with ulcerative colitis before the institution of glucocorticoid therapy to prevent the development of severe colitis or toxic megacolon owing to unsuspected amebiasis. More sensitive, specific, and rapid tests in stool are now in use in most developed countries. Enzyme immunoassays using monoclonal antibodies for the Gal/GalNAc lectin allow specific detection of

E. histolytica in 96-well plates or a single cassette for rapid detection. Sensitivity is 87% and specificity >90% in stool and can also be used in liver abscess aspirates. The number of commercially available PCR tests has significantly expanded. Most are multiplex for GI protozoa alone or include major bacterial and viral pathogens, as well. The sensitivity and specificity approaches 100%, and results can be available in as little as an hour. Their cost precludes use in most developing countries. Other amplification tests such as a loop-mediated isothermal amplification (LAMP) assay may be a potential alternative for direct detection of *E. histolytica* DNA in pus samples from amebic liver abscesses. LAMP is a relatively simple, rapid, and low-cost method of DNA amplification that could be a better alternative for diagnosis in developing countries. Routine hematology and chemistry tests usually are not very helpful in the diagnosis of invasive amebiasis. About three-fourths of patients with an amebic liver abscess have leukocytosis (>10,000 cells/ μ L); this condition is particularly likely if symptoms are acute or complications have developed. Invasive amebiasis does not elicit eosinophilia. Anemia, if present, is usually multifactorial. Even with large liver abscesses, liver enzyme levels are normal or minimally elevated. The alkaline phosphatase level is most often elevated and may remain so for months. Aminotransferase elevations suggest acute disease or a complication. Radiographic Studies Radiographic barium studies are potentially dangerous in acute amebic colitis. Amebomas are usually identified first by a barium enema, but biopsy is necessary for differentiation from carcinoma. Radiographic techniques such as ultrasonography, CT, and MRI are all useful for detection of the round or oval hypoechoic cyst. More than 80% of patients who have had symptoms for >10 days have a single abscess of the right lobe of the liver (Fig. 230-3). Approximately 50% of patients who have had symptoms for <10 days have multiple abscesses. Findings associated with complications include large abscesses (>10 cm)

in the superior part of the right lobe, which may rupture into the pleural space; multiple lesions, which must be differentiated from pyogenic abscesses; and lesions of the left lobe, which may rupture into the pericardium. Because abscesses resolve slowly and may increase in size despite a clinical response to therapy, frequent follow-up ultrasonography may prove confusing. Complete resolution of a liver abscess FIGURE 230-3 Abdominal CT scan of a large amebic abscess of the right lobe of the liver. (Courtesy of the Department of Radiology, UCSD Medical Center, San Diego; with permission.)

within 6 months can be anticipated in two-thirds of patients, but 10% may have persistent abnormalities for a year.

Differential Diagnosis The differential diagnosis of intestinal amebiasis includes bacterial diarrheas (Chap. 138) caused by *Campylobacter* (Chap. 169); enteroinvasive *Escherichia coli* (Chap. 166); and species of *Shigella* (Chap. 172), *Salmonella* (Chap. 171), and *Vibrio* (Chap. 173). Because the typical patient with amebic colitis has less prominent fever than in these other conditions as well as heme-positive stools with few neutrophils, correct diagnosis requires bacterial cultures,

microscopic examination of stools, amebic serologic testing, and stool specific antigens or PCR. As has been mentioned, amebiasis must be ruled out in any patient thought to have inflammatory bowel disease. Because of the variety of presenting signs and symptoms, amebic liver abscess can easily be confused with pulmonary or gallbladder disease or with any febrile illness with few localizing signs, such as malaria (Chap. 231) or typhoid fever (Chap. 171). The diagnosis should be considered in members of high-risk groups who have recently traveled outside the United States (Chap. 130) and in inmates of institutions. Once radiographic studies have identified an abscess in the liver, the most important differential diagnosis is between amebic and pyogenic abscess. Patients with pyogenic abscess typically are older and have a history of underlying bowel disease or recent surgery. Amebic serology is helpful, but aspiration of the abscess, with Gram's staining and culture of the material, may be required for differentiation of the two diseases.

CHAPTER 230 TREATMENT Amebiasis

INTESTINAL DISEASE (TABLE 230-1) The drugs used to treat amebiasis can be classified according to their primary site of action. Luminal amebicides are poorly absorbed and reach high concentrations in the bowel, but their activity is limited to cysts and trophozoites close to the mucosa. Only two luminal drugs are available in the United States: iodoquinol and paromomycin. Indications for the use of luminal agents include eradication of cysts in patients with colitis or a liver abscess and treatment of asymptomatic carriers. The majority of asymptomatic individuals who pass cysts are colonized with *E. dispar*, which does not warrant specific therapy. However, it is prudent to treat asymptomatic individuals who pass cysts unless *E. dispar* colonization can be definitively demonstrated by specific antigen-detection tests.

Amebiasis and Infection with Free-Living Amebae

Tissue amebicides reach high concentrations in the blood and tissue after oral or parenteral administration. The development of nitroimidazole compounds, especially metronidazole, was a major advance in the treatment of invasive amebiasis. Patients with amebic colitis should be treated with IV or oral metronidazole. Side effects include nausea, vomiting, abdominal discomfort, and a disulfiram-like reaction. Another, longer-acting imidazole compound, tinidazole, is likewise effective and is available in the United States. All patients should also receive a full course of therapy with

TABLE 230-1 Drug Therapy for Amebiasis

INDICATION THERAPY

Asymptomatic carriage Luminal agent: iodoquinol (650-mg tablets), 650 mg tid for 20 days; or paromomycin (250-mg tablets), 500 mg tid for 10 days

Acute colitis Metronidazole (250- or 500-mg tablets), 750 mg PO or IV tid for 5–10 days; or tinidazole, 2 g/d PO for 3 days plus Luminal agent as above

Amebic liver abscess Metronidazole, 750 mg PO or IV for 5–10 days; or tinidazole, 2 g PO once; or ornidazole, 2 g PO once plus Luminal agent as above

aNot available in the United States.

a luminal agent, since metronidazole does not eradicate cysts. Resistance to metronidazole has been selected in the laboratory but has not been found in clinical isolates. Relapses are not uncommon and probably represent reinfection or failure to eradicate amebae from the bowel because of an inadequate dosage or duration of therapy.

AMEBIC LIVER ABSCESS Metronidazole is the drug of choice for amebic liver abscess. Longer-acting nitroimidazoles (tinidazole and ornidazole) have been effective as single-dose therapy in developing countries. With early diagnosis and therapy, mortality rates from uncomplicated amebic liver abscess are <1%. There is no evidence that combined therapy with two drugs is more effective than the single-drug regimen. Studies of South Africans with liver abscesses demonstrated that 72% of patients without intestinal symptoms had bowel infection with *E. histolytica*; thus, all treatment regimens should include a luminal agent to eradicate cysts and prevent further transmission. Amebic liver abscess recurs rarely.

More than 90% of patients respond dramatically to metronidazole therapy with decreases in both pain and fever within 72 h. Indications for aspiration of liver abscesses are (1) the need to rule out a pyogenic abscess, particularly in patients with multiple lesions; (2) the lack of a clinical response in 3–5 days; (3) the threat of imminent rupture; and (4) the need to prevent rupture of left-lobe abscesses into the pericardium. There is no evidence that aspiration, even of large abscesses (up to 10 cm), accelerates healing. Percutaneous drainage may be successful even if the liver abscess has already ruptured. Surgery should be reserved for instances of bowel perforation and rupture into the pericardium.

PART 5 Infectious Diseases ■ ■ PREVENTION Amebic infection is spread by ingestion of food or water contaminated with cysts. Since an asymptomatic carrier may excrete up to 15 million cysts per day, prevention of infection requires adequate sanitation and eradication of cyst carriage. In high-risk areas, infection can be minimized by the avoidance of unpeeled fruits and vegetables and the use of bottled water. Because cysts are resistant to readily attainable levels of chlorine, disinfection by iodination (tetraglycine hydroperiodide) is recommended. There is no effective prophylaxis.

INFECTION WITH FREE-LIVING AMEBAE ■ ■ EPIDEMIOLOGY There are multiple genera of free-living amebae, but the major human pathogens are *Acanthamoeba*, *Naegleria*, and *Balamuthia*. All of these parasites can cause serious central nervous system (CNS) infections, which are almost always fatal. *Acanthamoeba* and *Naegleria* are distributed throughout the world and have been isolated from a wide variety of fresh and brackish water, including water from taps, lakes, hot springs, swimming pools, heating and air-conditioning units, and hospital water networks, and even from the nasal passages of healthy children. Encystation may protect these protozoa from desiccation and food deprivation. The persistence of *Legionella pneumophila* in water supplies is attributable in part to chronic infection of free-living amebae, particularly *Acanthamoeba*. In vitro studies have suggested that several pathogens that can resist phagosome-mediated killing may be able to survive within water systems in free-living amebae. These pathogens include *Pseudomonas aeruginosa*, nontuberculous *Mycobacteria* (both slow-growing species—e.g., those in the *Mycobacterium avium* complex, *M. kansasii*, and *M. goodii*—and rapid-growing species—e.g., *M. chelonae* and *M. abscessus*), and viruses such as adenoviruses and echoviruses. In contrast, the environmental niche of free-living amebae of the genus *Balamuthia* appears to be soil. A soil sample from a flowerpot was linked to a fatal infection in a child. Cases have been reported from all continents except Africa, but the majority of cases are from warm, dry areas of the southwestern United States and Latin America. With better recognition of these pathogens, additional risk factors have been identified. Since 2010, five cases of *Naegleria fowleri*

infection have been reported in northern U.S. states and have been associated with exposure to piped water, which represents a new ecological niche. Since 2009, three clusters of *Balamuthia mandrillaris* infections have been associated with organ transplantation. *Acanthamoeba* species have caused large outbreaks of microbial keratitis associated with contact lens wear. ■

■ **NAEGLERIA INFECTIONS** Primary amebic meningoencephalitis (PAM) is a fulminant CNS infection caused by the free-living amoeba *Naegleria fowleri*, which thrives in warm freshwater of lakes and rivers. In the United States, 157 cases of PAM were reported from 1962 through 2022 for a total of 381 cases worldwide. Historically in southern states and more frequently during the summer, the number of infections reported annually has remained stable (0–8). However, cases in northern states have been on the rise. In 2010, a PAM case was reported for the first time from Minnesota; this case was followed by additional cases from Minnesota, Indiana, and Kansas in 2011 and 2012. With climate change, other areas may be at risk because of higher temperatures. It commonly affects healthy, male individuals (75%) with a median age of 14 years (range, 1 month–

85 years). Most patients (91%) were exposed to recreational freshwater from lakes, reservoirs, rivers, streams, or ditches. The remaining cases were due to tap-water exposure through nasal irrigation with a neti pot, playing on a backyard waterslide, and swimming in a poorly maintained pool. Despite evidence of extra-CNS dissemination of *N. fowleri* in PAM patients post-mortem, transplantation of their solid organs have not been associated with PAM in transplant recipients. The risk of PAM in transplant recipients needs to be carefully considered in individual cases. PAM occurs after *N. fowleri* trophozoites enter the CNS through the olfactory neuroepithelium following inhalation of water or dust contaminated with trophozoites or cysts. Trophozoites then migrate to the brain, avoiding the protective blood-brain barrier and invoking a neutrophilic response. After an incubation period of 2–15 days, severe headache, high fever, nausea, vomiting, and meningismus develop. Photophobia and palsies of the third, fourth, and sixth cranial nerves are common. Rapid progression to seizures and coma may follow. The prognosis is uniformly poor: most patients die within a week. The diagnosis of *Naegleria* infection should be considered in any patient who has purulent meningitis without evidence of bacteria on Gram's staining, antigen detection assay, and culture. Other laboratory findings resemble those for fulminant bacterial meningitis, with elevated intracranial pressure, high white blood cell counts (up to 20,000/ μ L), and elevated protein concentrations and low glucose levels in cerebrospinal fluid (CSF). Diagnosis depends on the detection of motile trophozoites in wet mounts of fresh spinal fluid. Antibodies to *Naegleria* species have been detected in healthy adults; thus, serologic testing is not useful in the diagnosis of acute infection. Diagnostic PCR and histochemical staining of biopsies are available through the CDC. A number of antimicrobial agents have in vitro activity against *N. fowleri*, but the prognosis remains poor. The few survivors have been treated with different combinations of amphotericin B, fluconazole, azithromycin, rifampin, and dexamethasone. The new antiparasitic agent miltefosine—an alkylphosphocholine compound used to treat breast cancer and visceral leishmaniasis—is active in vitro against *Naegleria*, *Acanthamoeba*, and *Balamuthia* and is now commercially available (impavido.com). All seven survivors among reported worldwide cases (381) included miltefosine as well as the five drugs above. Early diagnosis, prompt combination therapy including miltefosine, and aggressive management of neurologic complications, including therapeutic hypothermia, are important factors in better outcomes. A clinician whose patient may have PAM should contact the CDC Emergency Operations Center at (770) 488-7100 for assistance in diagnosis by PCR and treatment recommendations (which should include miltefosine). ■

■ **ACANTHAMOEBA INFECTIONS** Granulomatous Amebic Encephalitis Infection with at least eight different *Acanthamoeba* species follows a more indolent course

than *Naegleria* infection and typically occurs in chronically ill or debilitated patients. Risk factors include lymphoproliferative disorders, chemotherapy, glucocorticoid therapy, lupus erythematosus, post-transplant, and AIDS. Infection usually reaches the CNS hematogenously from a primary focus in the sinuses, skin, or lungs. In the CNS, the onset is insidious, and the syndrome often mimics a spaceoccupying lesion. Altered mental status, headache, and stiff neck may be accompanied by focal findings such as cranial nerve palsies, ataxia, and hemiparesis. Cutaneous ulcers or hard nodules containing amebae are frequently detected in AIDS patients with disseminated *Acanthamoeba* infection. Examination of the CSF for trophozoites may be diagnostically helpful, but lumbar puncture may be contraindicated because of increased intracerebral pressure. CT frequently reveals cortical and subcortical lesions of decreased density consistent with embolic infarcts. In other patients, multiple enhancing lesions with edema may mimic the CT appearance of toxoplasmosis (Chap. 235). Demonstration of the trophozoites and

cysts of *Acanthamoeba* on wet mounts or in biopsy specimens establishes the diagnosis. Culture on nonnutrient agar plates seeded with *Escherichia coli* also may be helpful. A real-time PCR assay to detect *Acanthamoeba*, *Naegleria*, and *Balamuthia* as well as a fluo rescein-labeled antiserum for the detection of protozoa in biopsy specimens are available from the CDC. Granulomatous amebic encephalitis in patients with AIDS or transplant recipients may have an accelerated course (with survival for only 3–40 days) because of the difficulty these individuals have in forming granulomas. Various antimicrobial agents have been used to treat *Acanthamoeba* infection, but miltefosine should be included in combination therapy. Keratitis The incidence of keratitis caused by *Acanthamoeba* has increased in the past 20 years, in part as a result of improved diagnosis. Earlier infections were associated with trauma to the eye and exposure to contaminated water. At present, most infections are linked to extended-wear contact lenses, and rare cases are associated with laser-assisted in situ keratomileusis (LASIK). Risk factors include the use of homemade saline, the wearing of lenses while swimming, and inadequate disinfection. Since contact lenses presumably cause microscopic trauma, early corneal findings may be nonspecific. The first symptoms usually include tearing and the painful sensation of a foreign body. Once infection is established, progression is rapid. The characteristic clinical sign is an annular, paracentral corneal ring representing a corneal abscess. Deeper corneal invasion and loss of vision may follow. The differential diagnosis includes bacterial, mycobacterial, and herpetic infection. The irregular polygonal cysts of *Acanthamoeba* (Fig. 230-4) may be identified in corneal scrapings or biopsy material, and trophozoites can be grown on special media. Cysts are resistant to available drugs, and the results of medical therapy have been disappointing. Some reports have suggested partial responses

FIGURE 230-4 Double-walled cyst of *Acanthamoeba castellanii*, as seen by phase-contrast microscopy. (From DJ Krogstad et al, in A Balows et al [eds]: *Manual of Clinical Microbiology*, 5th ed. Washington, DC, American Society for Microbiology, 1991.)

to polyhexamethylene biguanide (0.2%) or propamidine isethionate (0.1%) eyedrops. Severe infections usually require keratoplasty.

■ ■ **BALAMUTHIA INFECTIONS** *Balamuthia mandrillaris* is a free-living amoeba that was first identified in 1986 as the cause of a fatal infection in a mandrill baboon at the Wild Animal Park in San Diego, California. Since then more than 100 cases have been reported in the United States and 200 worldwide. The parasite has been isolated from soil and dust and is probably widespread in the environment. It is an important etiologic agent of granulomatous amebic encephalitis, cutaneous lesions, and sinus infections in humans. The potential risk factors for granulomatous amebic encephalitis identified by the California Encephalitis Project include young age, immunocompromising conditions, and Hispanic ethnicity. The infection likely starts with percutaneous or mucous membrane exposure and then spreads hematogenously to the brain and other organs—a pattern that explains the risk for transmission through organ transplantation. In 2009–2012, three clusters of organ transplant-transmitted *B. mandrillaris* infections were detected by recognition of severe unexpected illness in multiple recipients from the same donor after an incubation period of 17–24 days. Frequently, *Balamuthia* affects immunocompetent individuals, in whom the course is typically subacute, with focal neurologic signs, fever, seizures, and headaches leading to death within 1 week to several months after onset. Skin lesions may occur on the face, trunk, or extremities. In addition to dust inhalation, inoculation of trophozoites or cysts from stagnant water may occur through open wounds or mucous membranes. Diagnosis relies on examination of CSF, which reveals mononuclear or neutrophilic pleocytosis, elevated protein levels, and normal to low glucose concentrations. Amoebae are rarely isolated from CSF and require culture in the presence of

cell monolayers. Multiple hypodense lesions are usually detected with imaging studies (Fig. 230-5). The differential diagnosis includes tuberculomas (Chap. 183) and neurocysticercosis (Chap. 242). Testing for Balamuthia is part of the multiplex PCR test from the CDC. Fluorescent antibodies for serology and immunohistochemistry also are available. CHAPTER 230 Amebiasis and Infection with Free-Living Amebae

The nine surviving patients in the United States have been treated with a variety of drugs, including pentamidine, flucytosine, FIGURE 230-5 Brain MRI of amebic meningoencephalitis due to Balamuthia mandrillaris. A large lesion in the parieto-occipital lobe and other smaller lesions are seen. (Courtesy of the Department of Radiology, UCSD Medical Center, San Diego.)

Revision #1

Created 2026-01-06 16:32:46 UTC by Omar Ayman

Updated 2026-01-06 16:32:46 UTC by Omar Ayman