

REVIEW ARTICLE

CURRENT CONCEPTS

Amebiasis

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DIARRHEAL DISEASES CONTINUE TO BE MAJOR CAUSES OF MORBIDITY and mortality in children in developing countries. For example, in Bangladesh 1 in 30 children dies of diarrhea or dysentery by his or her fifth birthday.¹ In developed countries the microorganisms that cause diarrheal disease remain of concern because of their potential use as bioterrorist agents. Bacillary dysentery is most commonly caused by microorganisms belonging to the genus shigella, whereas amebic dysentery is caused by the protozoan parasite *Entamoeba histolytica*. The annual number of shigella infections throughout the world is believed to be approximately 164 million.² Estimates of *E. histolytica* infections have primarily been based on examinations of stool for ova and parasites, but these tests are insensitive and cannot differentiate *E. histolytica* from morphologically identical species that are nonpathogenic, such as *E. dispar* and *E. moshkovskii*.^{3,4}

Specific and sensitive means to detect *E. histolytica* in stool are now available and include antigen detection and the polymerase chain reaction (PCR).⁵ Two recent studies in developing countries used these modern diagnostic tests. A three-year study in Dhaka, Bangladesh, showed that preschool children had a 2.2 percent frequency of amebic dysentery, as compared with a 5.3 percent frequency of shigella dysentery⁶ (and unpublished data). The annual incidence of amebic liver abscess was reported to be 21 cases per 100,000 inhabitants in Hue City, Vietnam.⁷ In the United States, where fecal-oral transmission is unusual, amebiasis is most commonly seen in immigrants from and travelers to developing countries. The disease is more severe in the very young and old and in patients receiving corticosteroids.

ENTAMOEBIA HISTOLYTICA

Molecular phylogeny places *entamoeba* on one of the lowermost branches of the eukaryotic tree, closest to dictyostelium. Although the organism was originally thought to lack mitochondria, nuclear-encoded mitochondrial genes and a remnant organelle have now been identified.^{8,9} Unusual features of *entamoeba* include polyploid chromosomes that vary in length; multiple origins of DNA replication; abundant, repetitive DNA; closely spaced genes that largely lack introns; a novel GAAC element controlling the expression of messenger RNA; and unique endocytic pathways.¹⁰⁻¹³

PATHOGENESIS

Ingestion of the quadrinucleate cyst of *E. histolytica* from fecally contaminated food or water initiates infection (Fig. 1). This is a daily occurrence among the poor in developing countries and is a threat to inhabitants of developed countries, as the epidemic linked to contaminated municipal water supplies in Tbilisi, Republic of Georgia, demonstrates.¹⁴ Excystation in the intestinal lumen produces trophozoites that use the galactose and

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N-acetyl-D-galactosamine (Gal/GalNAc)-specific lectin to adhere to colonic mucins and thereby colonize the large intestine.¹⁵ The reproduction of trophozoites has no sexual cycle, and the overall population of *E. histolytica* appears to be clonal.¹⁶ Aggregation of amebae in the mucin layer most likely triggers encystation by means of the Gal/GalNAc-specific lectin.¹⁷ Cysts excreted in stool perpetuate the life cycle by further fecal-oral spread.

Colitis results when the trophozoite penetrates the intestinal mucous layer, which otherwise acts as a barrier to invasion by inhibiting amebic adherence to the underlying epithelium and by slowing trophozoite motility.¹⁸ Invasion is mediated by the killing of epithelial cells, neutrophils, and lymphocytes by trophozoites, which occurs only after the parasite lectin engages host N-acetyl-D-galactosamine on O-linked cell-surface oligosaccharides.¹⁵ The interaction of the lectin with glycoconjugates is stereospecific and multivalent.¹⁹ The identity of the high-affinity intestinal epithelial-cell receptor is unknown. Secretion by the ameba of amoebapore, a 5-kD pore-forming protein, may contribute to killing.²⁰ Activation of human caspase 3, a distal effector molecule in the apoptotic pathway, occurs rapidly after amebic contact, and caspases are required for cell killing in vitro and for the formation of amebic liver abscesses in vivo.^{21,22}

Interaction of the parasite with the intestinal epithelium causes an inflammatory response marked by the activation of nuclear factor κ B and the secretion of lymphokines.^{23,24} The development of this epithelial response may depend on trophozoite virulence factors such as cysteine proteinase and leads to intestinal abnormalities through neutrophil-mediated damage. Neutrophils can also be protective, however, in that activation of neutrophils or macrophages by tumor necrosis factor α or interferon γ kills amebae in vitro and limits the size of amebic liver abscesses.²⁵ In contrast to the intense inflammatory response typical of early invasive amebiasis, inflammation surrounding well-established colonic ulcers and liver abscesses is minimal, given the degree of tissue damage.²⁶

During chronic infection, *E. histolytica* evades the host immune response in several ways. The Gal/GalNAc-specific lectin has sequence similarity and antigenic cross-reactivity to CD59, a human leukocyte antigen that prevents the assembly of the complement C5b-C9 membrane attack complex.²⁷ Amebic cysteine proteinases rapidly degrade the complement anaphylatoxins C3a and C5a.²⁸ The

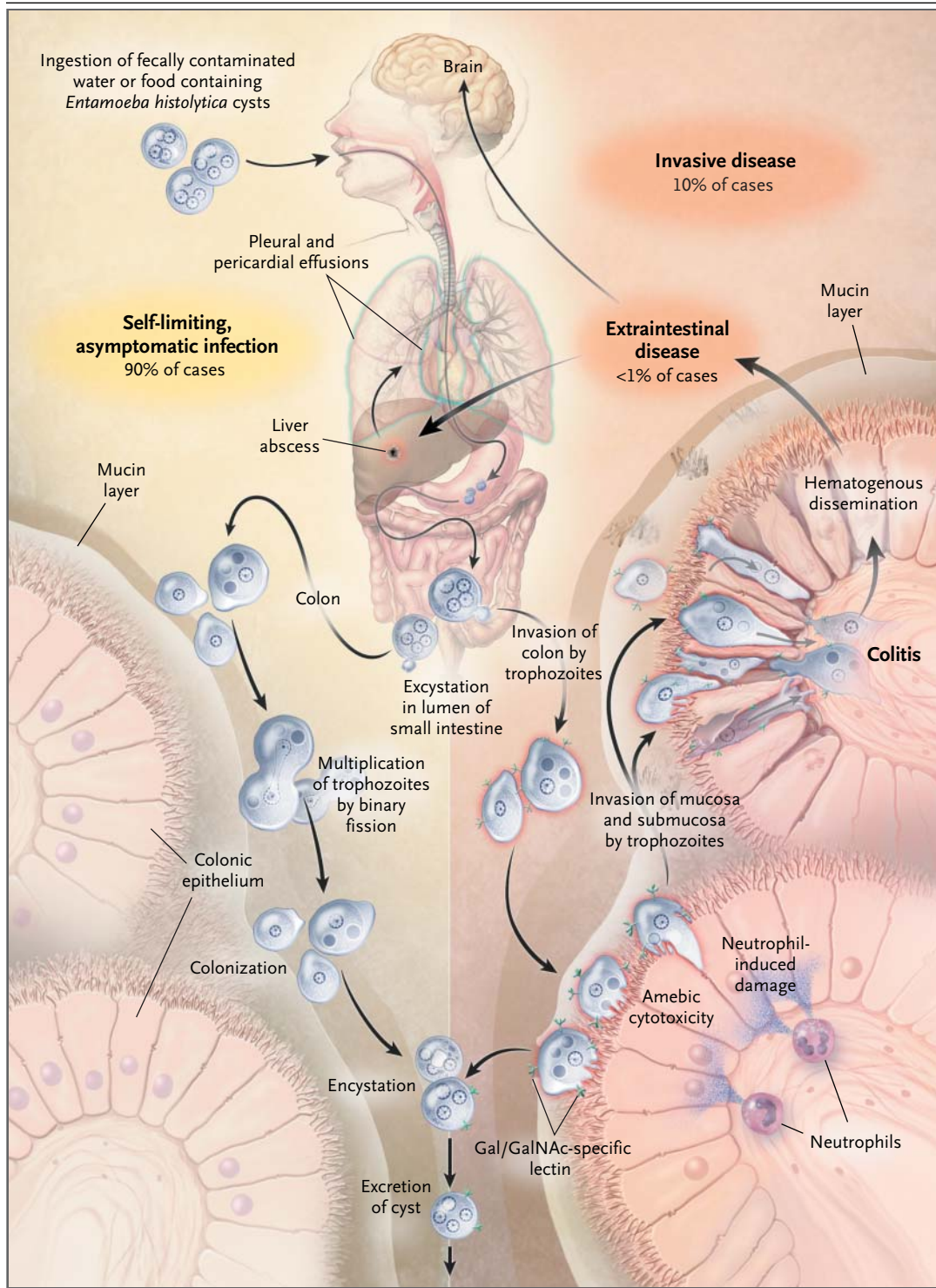
cysteine proteinases also degrade secretory IgA and serum IgG, possibly protecting amebae from opsonization. Finally, amebae appear to suppress both the macrophage respiratory burst and antigen presentation by class II major-histocompatibility-complex (MHC) molecules.

IMMUNITY

Immunity to infection with *E. histolytica* is associated with a mucosal IgA response against the carbohydrate-recognition domain of the Gal/GalNAc lectin. Over a one-year period, children with this response had 86 percent fewer new infections than children without this response.⁶ Cell-mediated responses have been described in patients with amebic liver abscess, characterized by lymphocyte proliferation and lymphokine secretion that is amebicidal in vitro.²⁹ One study found that in patients with liver abscess, the prevalence of the class II MHC haplotype HLA-DR3 is increased by a factor of more than three, suggesting a role of CD4+ T-cell function in the outcome of the disease.³⁰ It is noteworthy, however, that the acquired immunodeficiency syndrome pandemic has not led to increases in invasive amebiasis, although asymptomatic intestinal colonization is undoubtedly common.³¹ In fact, in the murine model of amebic colitis, the depletion of CD4+ T cells decreases the severity of the disease.³²

Figure 1 (facing page). Life Cycle of *Entamoeba histolytica*.

Infection is normally initiated by the ingestion of fecally contaminated water or food containing *E. histolytica* cysts. The infective cyst form of the parasite survives passage through the stomach and small intestine. Excystation occurs in the bowel lumen, where motile and potentially invasive trophozoites are formed. In most infections the trophozoites aggregate in the intestinal mucin layer and form new cysts, resulting in a self-limited and asymptomatic infection. In some cases, however, adherence to and lysis of the colonic epithelium, mediated by the galactose and N-acetyl-D-galactosamine (Gal/GalNAc)-specific lectin, initiates invasion of the colon by trophozoites. Neutrophils responding to the invasion contribute to cellular damage at the site of invasion. Once the intestinal epithelium is invaded, extraintestinal spread to the peritoneum, liver, and other sites may follow. Factors controlling invasion, as opposed to encystation, most likely include parasite "quorum sensing" signaled by the Gal/GalNAc-specific lectin, interactions of amebae with the bacterial flora of the intestine, and innate and acquired immune responses of the host.



INTESTINAL AMEBIASIS

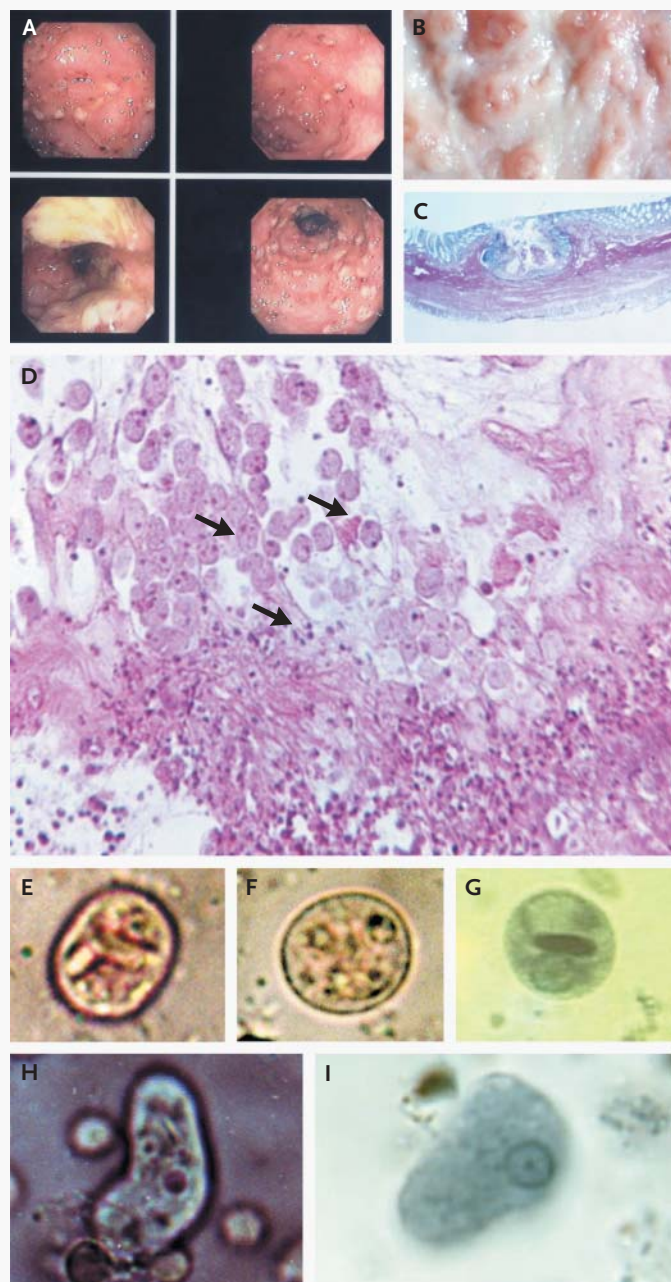


Figure 2. Endoscopic and Pathological Features of Intestinal Amebiasis.

Panel A shows the appearance of intestinal amebiasis on colonoscopy. Panel B shows colonic ulcers averaging 1 to 2 mm in diameter on gross pathological examination. Panel C shows a cross-section of a flasked-shaped colonic ulcer (hematoxylin and eosin, $\times 20$). Panel D shows an inflammatory response to intestinal invasion by *Entamoeba histolytica* (hematoxylin and eosin, $\times 100$). Arrows indicate *E. histolytica* trophozoites. Panels E and F show *E. histolytica* cysts in a saline preparation ($\times 1000$), and Panel G shows an iodine-stained cyst from stool ($\times 1000$). Panel H shows an *E. histolytica* trophozoite with an ingested erythrocyte in a saline preparation from stool ($\times 1000$), and Panel I shows a trophozoite from stool stained with trichrome ($\times 1000$). (Panels B, C, and D are from the slide collection of the late Dr. Harrison Juniper.)

Infection with *E. histolytica* may be asymptomatic or may cause dysentery or extraintestinal disease (Fig. 2 and 3). Asymptomatic infection should be treated because of its potential to progress to invasive disease. Patients with amebic colitis typically present with a several-week history of cramping abdominal pain, weight loss, and watery or bloody diarrhea. The insidious onset and variable signs and symptoms make diagnosis difficult, with fever and grossly bloody stool absent in most cases.³³⁻³⁵ The differential diagnosis of a diarrheal illness with occult or grossly bloody stools should include infection with shigella, salmonella, campylobacter, and enteroinvasive and enterohemorrhagic *Escherichia coli*. Noninfectious causes include inflammatory bowel disease, ischemic colitis, diverticulitis, and arteriovenous malformation.

Unusual manifestations of amebic colitis include acute necrotizing colitis, toxic megacolon, ameboma (Fig. 3B), and perianal ulceration with potential formation of a fistula. Acute necrotizing colitis is rare (occurring in less than 0.5 percent of cases) and is associated with a mortality rate of more than 40 percent.³⁵ Patients with acute necrotizing colitis typically appear very ill, with fever, bloody mucoid diarrhea, abdominal pain with rebound tenderness, and signs of peritoneal irritation. Surgical intervention is indicated if there is bowel perforation or if the patient has no response to antiamebic therapy. Toxic megacolon is rare (occurring in approximately 0.5 percent of cases) and is typically associated with the use of corticosteroids. Early recognition and surgical intervention are important, since patients with toxic megacolon usually have no response to antiamebic therapy alone. Ameboma results from the formation of annular colonic granulation tissue at a single site or multiple sites, usually in the cecum or ascending colon. An ameboma may mimic carcinoma of the colon (Fig. 3B).

In developing countries, intestinal amebiasis is most commonly diagnosed by identifying cysts or motile trophozoites on a saline wet mount of a stool specimen (Fig. 2E, 2F, and 2H). The drawbacks of this method include its low sensitivity and false positive results owing to the presence of *E. dispar* or *E. moshkovskii* infection. The diagnosis should ideally be based on the detection in stool of *E. histolytica*-specific antigen or DNA and by the presence of antiamebic antibodies in serum (Table 1). Field studies that directly compared PCR with stool culture or antigen-detection tests for the diagnosis of

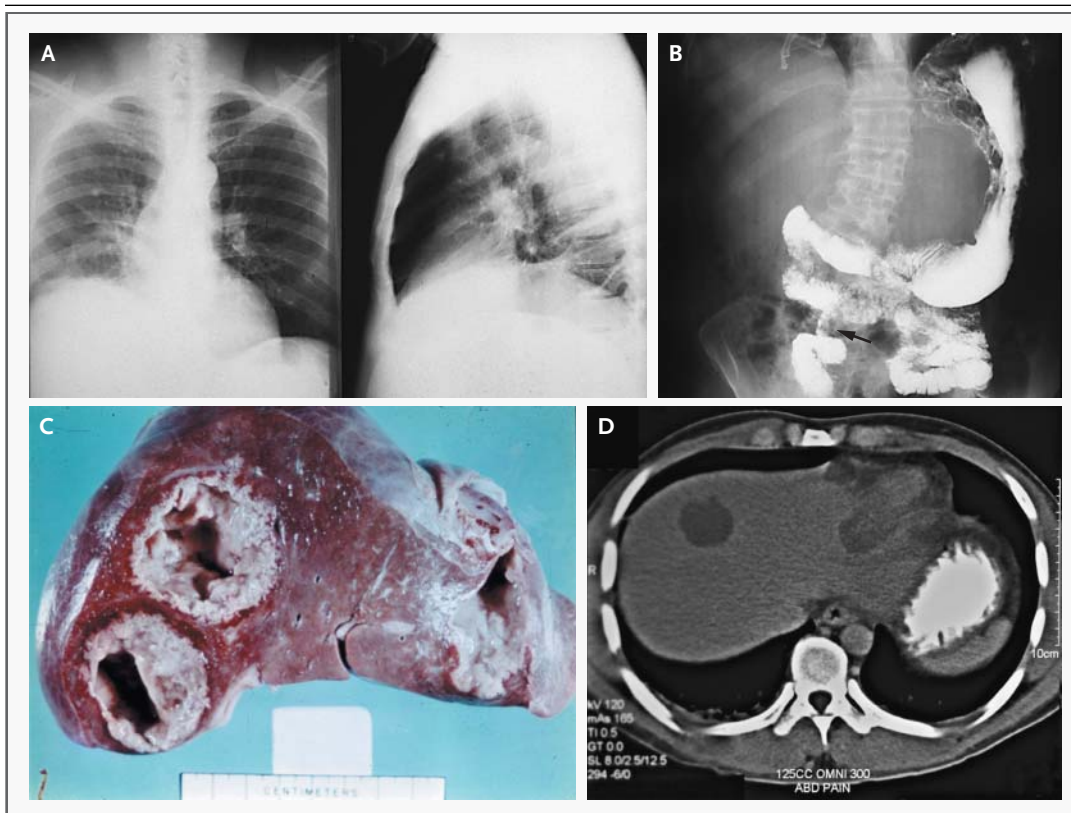


Figure 3. Radiographic and Pathological Features of Extraintestinal Amebiasis.

Panel A shows a posteroanterior (left-hand side) and lateral (right-hand side) chest radiograph in a patient with amebic liver abscess. The findings include elevated right hemidiaphragm and evidence of atelectasis. Panel B shows luminal narrowing (arrow) on a barium-enema examination in a patient with ameboma. Panel C shows two abscesses in the right lobe and one abscess in the left lobe in a patient with amebic liver abscess. In Panel D, abdominal computed tomography in a patient with amebic liver abscess shows one abscess in the right lobe and one abscess in the left lobe.

E. histolytica infection suggest that these three methods perform equally well.^{5,36} An important aid to antigen-detection and PCR-based tests is the detection of serum antibodies against amebae, which are present in 70 to more than 90 percent of patients with symptomatic *E. histolytica* infection.³⁷⁻⁴⁰ A drawback of current serologic tests is that patients remain positive for years after infection, making it difficult to distinguish new from past infection in regions of the world where the seroprevalence is high. Examination of colonic mucosal biopsy specimens and exudates can reveal a wide range of histopathological findings associated with amebic colitis, including diffuse, nonspecific mucosal thickening with or without ulceration and, in rare cases, the presence of amebae in the mucinous exudate; focal ulcerations (Fig. 2B) with or without amebae in a diffusely inflamed mucosal layer; classic flask-

shaped lesions (Fig. 2C) with ulceration extending through the mucosa and muscularis mucosa into the submucosa; and necrosis and perforation of the intestinal wall.⁴¹ Staining with periodic acid-Schiff or immunoperoxidase and antilectin antibodies aids in the visualization of amebae.⁴²

AMEBIC LIVER ABSCESS

Amebic liver abscess is 10 times as common in men as in women and is a rare disease in children.^{37,43,44} Approximately 80 percent of patients with amebic liver abscess present with symptoms that develop relatively quickly (typically within two to four weeks), including fever, cough, and a constant, dull, aching abdominal pain in the right upper quadrant or epigastrium. Involvement of the diaphragmatic surface of the liver may lead to right-sided pleural pain or

Table 1. Sensitivity of Tests for the Diagnosis of Amebiasis.*

Test	Colitis	Liver Abscess
		percent
Microscopy		
Stool	25–60	10–40
Abscess fluid	NA	≤20
Antigen detection		
Stool	90	~40
Serum	65 (early)	~100
Abscess fluid	NA	(before treatment) ~40
Indirect hemagglutination (antibody)		
Serum obtained during acute illness	70	70–80
Serum obtained during convalescence	>90	>90

* NA denotes not applicable.

referred shoulder pain. Associated gastrointestinal symptoms, which occur in 10 to 35 percent of patients, include nausea, vomiting, abdominal cramping, abdominal distention, diarrhea, and constipation. Hepatomegaly with point tenderness over the liver, below the ribs, or in the intercostal spaces is a typical finding.^{43,44}

Laboratory studies may reveal a mild-to-moderate leukocytosis and anemia. Patients with acute amebic liver abscess tend to have a normal alkaline phosphatase level and an elevated alanine aminotransferase level; the opposite is true of patients with chronic disease.⁴⁴ Ultrasonography, abdominal computed tomography, and magnetic resonance imaging are all excellent for detecting liver lesions (usually single lesions in the right lobe) but are not specific for amebic liver abscess (Fig. 3).

The differential diagnosis of a liver mass should include pyogenic liver abscess, necrotic hepatoma, and echinococcal cyst (usually an incidental finding that is not the cause of fever and abdominal pain). Patients with amebic liver abscess are more likely than patients with pyogenic liver abscess to be male, to be younger than 50 years of age, to have immigrated from or traveled to a country where the disease is endemic, and not to have jaundice, biliary disease, or diabetes mellitus. Less than half of patients with amebic liver abscess have parasites detected in their stool by antigen detection.

Helpful clues to the diagnosis include the presence of epidemiologic risk factors for amebiasis and the presence of serum antiamebic antibodies (present in 70 to 80 percent of patients at the time

of presentation) (Table 1). Preliminary studies indicate that the detection of serum amebic antigens is a sensitive, noninvasive means of diagnosis.⁵ Occasionally, aspiration of the abscess is required to rule out a pyogenic abscess. Amebae are visualized in the abscess fluid in a minority of patients with amebic liver abscess.

Complications of amebic liver abscess may arise from rupture of the abscess with extension into the peritoneum, pleural cavity, or pericardium. Extrahepatic amebic abscesses have occasionally been described in the lung, brain, and skin and presumably result from hematogenous spread.

THERAPY

Therapy for invasive infection differs from therapy for noninvasive infection. Noninvasive infections may be treated with paromomycin. Nitroimidazoles, particularly metronidazole, are the mainstay of therapy for invasive amebiasis⁴⁵ (Table 2). Nitroimidazoles with longer half-lives (namely, tinidazole, secnidazole, and ornidazole) are better tolerated and allow shorter periods of treatment but are not available in the United States. Approximately 90 percent of patients who present with mild-to-moderate amebic dysentery have a response to nitroimidazole therapy. In the rare case of fulminant amebic colitis, it is prudent to add broad-spectrum antibiotics to treat intestinal bacteria that may spill into the peritoneum; surgical intervention is occasionally required for acute abdomen, gastrointestinal bleeding, or toxic megacolon. Parasites persist in the intestine in as many as 40 to 60 percent of patients who receive nitroimidazole. Therefore, nitroimidazole treatment should be followed with paromomycin or the second-line agent diloxanide furoate to cure luminal infection. Metronidazole and paromomycin should not be given at the same time, since the diarrhea that is a common side effect of paromomycin may make it difficult to assess the patient's response to therapy.⁴⁶⁻⁴⁸

Therapeutic aspiration of an amebic liver abscess is occasionally required as an adjunct to antiparasitic therapy. Drainage of the abscess should be considered in patients who have no clinical response to drug therapy within five to seven days or those with a high risk of abscess rupture, as defined by a cavity with a diameter of more than 5 cm or by the presence of lesions in the left lobe.⁴⁹ Bacterial coinfection of amebic liver abscess has occasionally been observed (both before and as a complication of

Table 2. Drug Therapy for the Treatment of Amebiasis.*

Drug	Adult Dosage	Pediatric Dosage	Side Effects
Amebic liver abscess			
give			
Metronidazole	750 mg orally 3 times a day for 7–10 days	35–50 mg/kg of body weight/day in 3 divided doses for 7–10 days	Primarily gastrointestinal: anorexia, nausea, vomiting, diarrhea, abdominal discomfort, or unpleasant metallic taste; disulfuram-like intolerance reaction with alcohol; rarely, neurotoxicity, including seizures, peripheral neuropathy, dizziness, confusion, irritability
or			
Tinidazole†	800 mg orally 3 times a day for 5 days	60 mg/kg/day (maximum, 2 g) for 5 days	Primarily gastrointestinal and disulfuram-like intolerance reaction as for metronidazole
followed by a luminal agent			
Paromomycin	25–35 mg/kg/day in 3 divided doses for 7 days	25–35 mg/kg/day in 3 divided doses for 7 days	Primarily gastrointestinal: diarrhea, gastrointestinal upset
or second-line agent			
Diloxanide furoate‡	500 mg orally 3 times a day for 10 days	20 mg/kg/day in 3 divided doses for 10 days	Primarily gastrointestinal: flatulence, nausea, vomiting, pruritus, urticaria
Amebic colitis			
give			
Metronidazole	750 mg orally 3 times a day for 7–10 days	35–50 mg/kg/day in 3 divided doses for 7–10 days	As for amebic liver abscess
followed by a luminal agent (as for amebic liver abscess)			
Asymptomatic intestinal colonization			
give			
Paromomycin	25–35 mg/kg/day in 3 divided doses for 7 days	25–35 mg/kg/day in 3 divided doses for 7 days	Primarily gastrointestinal: diarrhea, gastrointestinal upset
or second-line agent			
Diloxanide furoate‡	500 mg orally 3 times a day for 10 days	20 mg/kg/day in 3 divided doses for 10 days	Primarily gastrointestinal: flatulence, nausea, vomiting, pruritus, urticaria

* The information is updated annually by the *Medical Letter on Drugs and Therapeutics* at <http://www.medletter.com/html/prm.htm#Parasitic>.

† This drug is not yet available in the United States.

‡ This drug is not available in the United States.

drainage), and it is reasonable to add antibiotics, drainage, or both to the treatment regimen in the absence of a prompt response to nitroimidazole therapy. Imaging-guided percutaneous treatment (needle aspiration or catheter drainage) has replaced surgical intervention as the procedure of choice for reducing the size of an abscess.⁴⁹

THE NEED FOR A VACCINE

In a perfect world amebiasis would be prevented by eradicating fecal contamination of food and water. However, providing safe food and water for all children in developing countries would require massive societal changes and monetary investments. An ef-

fective vaccine would be much less costly, and there are several reasons to indicate that a vaccine is a desirable and feasible goal. The high incidence of amebiasis in recent community-based studies suggests that an effective vaccine would improve child health in developing countries. That humans naturally acquire partial immunity against intestinal infection indicates that there should not be insurmountable barriers to stimulating an effective acquired immune response. Aiding vaccine design is the demonstration that several recombinant antigens, including the Gal/GalNAc-specific lectin, provide protection in animal models of amebiasis and that human immunity is linked to intestinal IgA against the lectin. The clonal-population structure of *E. histolytica* and, specifically, the high degree of sequence conservation of the Gal/GalNAc-specific lectin suggest that

a vaccine could be broadly protective.⁵⁰ Finally, the absence of epidemiologically significant animal reservoirs suggests that herd immunity could interrupt fecal-oral transmission in humans. The challenges will be to design vaccines capable of eliciting durable mucosal immunity, to understand the correlates of acquired immunity, and most important, to enlist the continued support of industrialized nations to combat diarrheal diseases of children in developing countries.

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Dr. Petri has reported receiving royalties from a patent license agreement with TechLab for a diagnostic test for amebiasis; these royalties accrue to the American Society of Tropical Medicine and Hygiene without benefit to Dr. Petri.

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