

# A Review of the Global Burden, New Diagnostics, and Current Therapeutics for Amebiasis

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Amebiasis, due to the pathogenic parasite *Entamoeba histolytica*, is a leading cause of diarrhea globally. Largely an infection of impoverished communities in developing countries, amebiasis has emerged as an important infection among returning travelers, immigrants, and men who have sex with men residing in developed countries. Severe cases can be associated with high case fatality. Polymerase chain reaction–based diagnosis is increasingly available but remains underutilized. Nitroimidazoles are currently recommended for treatment, but new drug development to treat parasitic agents is a high priority. Amebiasis should be considered before corticosteroid therapy to decrease complications. There is no effective vaccine, so prevention focuses on sanitation and access to clean water. Further understanding of parasite biology and pathogenesis will advance future targeted therapeutic and preventative strategies.

**Keywords.** amebiasis; diarrhea; colitis; burden; PCR; HIV; MSM.

Amebiasis is caused by infection with the pseudopod-forming, nonflagellated protozoan parasite *Entamoeba histolytica*. Amebiasis can be asymptomatic or can lead to the development of severe infection with amebic colitis and amebic liver abscess. The significance of amebiasis is exemplified in several ways. Amebic colitis is a leading cause of severe diarrhea worldwide and is listed among the top 15 causes of diarrhea in the first 2 years of life in children living in the developing world, where diarrhea remains the third leading cause of death, accounting for 9% of all deaths in children under the age of 5 years [1–3]. Fulminant amebic colitis is an uncommon complication of amebiasis but is associated with high mortality, and on average more than 50% with severe colitis die [4]. *E. histolytica* is classified as a category B priority biodefense pathogen by the National Institute of Allergy and Infectious Diseases (NIAID) because of its low infectious dose, chlorine resistance, and environmental stability, properties that can pose a threat of easy dissemination through contamination of food and water supplies. Even in low-incidence settings, these properties of the parasite lead to outbreaks among military and general populations [5–7]. In addition, *E. histolytica* is one of

the most common causes of infectious diarrhea among travelers returning from endemic areas [8].

Advances in molecular diagnostic methodologies have improved our understanding and led to the recognition and separation of *E. histolytica* from nonpathogenic species of *Entamoeba*. Of the many *Entamoeba* species that infect humans, 3 species are morphologically indistinguishable from *E. histolytica*. Of these 3, *E. moshkovskii* may cause diarrhea, whereas *E. dispar* and the newly described *E. bangladeshi* are considered nonpathogenic [9]. Earlier descriptions of amebiasis relying solely on microscopy may have been obscured by these nonpathogenic strains. There is no vaccine to prevent amebiasis. Nitroimidazoles are the mainstay treatment for invasive amebiasis. Given the toxicity that can be associated with this class and potential concerns for development of resistance, as has already been reported for some anaerobic pathogens, new therapies are needed [10]. In addition, the NIAID has set priorities for drug development for treatment of category B pathogens. For these reasons, improved understanding of amebiasis pathogenesis is needed as a way forward toward enhanced treatment and prevention. This report reviews recent literature expanding our knowledge of the epidemiology, clinical presentation, and management of amebiasis, while providing important new insights into diagnostic evaluation and prevention.

## EPIDEMIOLOGY

### Global Burden

The global significance of amebiasis is widespread, with the highest burden of amebiasis borne by those residing in developing countries, particularly the tropics and subtropics, where there is inadequate hygiene and access to sanitation. Millions

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of people are infected with *E. histolytica*, making amebic colitis a leading cause of diarrhea, estimated to kill more than 55 000 people each year [1]. Amebiasis is endemic in developing parts of Central and South America, Africa, and Asia. In the United States, the incidence of amebiasis is low, though amebiasis-related deaths still routinely occur, accounting for at least 5 deaths per year [11]. Amebiasis in the United States is seen mostly in returning travelers or immigrants from endemic countries [12]. Data from the GeoSentinel Surveillance Network, a large international surveillance and monitoring system, have shown that *E. histolytica* is the third most frequently isolated pathogen among returning travelers with infectious gastrointestinal disease. Amebiasis accounts for 12.5% of all microbiologically confirmed cases, with an estimated incidence of 14 in every 1000 returning travelers [8]. Travelers to South Asia, the Middle East, and South America appear to have the highest risk, in particular those volunteering as missionary workers or doing other volunteering work. Even travel of household or sexual contacts to an endemic area may pose a risk of infection [13]. Other industrialized countries including parts of Asia, Europe, North America, and Australia have highlighted gay men, bisexual men, and other men who have sex with men (MSM) as a population at higher risk of acquiring amebiasis than the general population. Recent reports from Taiwan and Japan, for example, have shown high rates of invasive amebiasis in HIV-infected MSM [14, 15].

In developing countries, the exact burden of amebiasis is difficult to quantify, and reports can be affected by geographic region, study design, sample size, incubation, symptom severity, and the sensitivity of the diagnostic modality used (Table 1). In addition, diagnostic capacities and surveillance are often limited in areas where *E. histolytica* is endemic. Recent reports, however, have shown that the seroprevalence of *E. histolytica* in some rural communities of Mexico remains as high as 42% [16]. In an urban slum of Dhaka, Bangladesh, 11% of children had an episode of amebic diarrhea in the first year of life [17]. By cross-sectional survey, *E. histolytica* was detected using polymerase chain reaction (PCR) in 13.7% of fecal samples in northeast states of India [18]. *E. histolytica* seropositivity was found to be 11% among 7 provinces of China and was as high as 41% among MSM in the provinces of Beijing and Tianjin [19, 20]. A re-emergence of *E. histolytica* infection was described in Jeddah, Saudi Arabia, among children under the age of 16 years presenting to the hospital with acute gastroenteritis. Using fecal antigen detection, *E. histolytica* was found to be the most prevalent enteropathogen associated with diarrhea, with a prevalence of 20% [21]. The epidemiology on the incidence and prevalence of amebiasis in Africa is particularly limited, but it appears widespread, as exemplified in a cross-sectional study of patients attending gastroenterology clinics in South Africa, where *E. histolytica* was detected by PCR in 8.5% of fecal samples [22]. In the large Global Enteric Multi-Center Study

**Table 1. Recent Prevalence Estimates of *Entamoeba histolytica* Infection by World Regions**

Country	f, %	Method	Study Characteristics	Ref.
<b>Latin America and Caribbean</b>				
Durango, Mexico	42	AB	Cross-sectional serosurvey among rural communities	[16, 48]
<b>Asia Pacific</b>				
Beijing and Tianjin, China	41	AB	Cross-sectional serosurvey of men who have sex with men	[20]
CCDC, China	11	AB	Cross-sectional serosurvey of the general population	[19]
Lahore, Pakistan	17	AG	Cross-sectional survey among 3 different socioeconomic strata	[49]
Northeast, India	14	PCR	Cross-sectional survey	[18]
Dhaka, Bangladesh	11	PCR	Prospective birth cohort study of infants followed for 1 year	[17]
Selangor, Malaysia	8	PCR	Cross-sectional survey of selected ethnic groups	[50]
Sydney, Australia	5	AB	Retrospective study of HIV-infected men who have sex with men	[51]
Mirzapur, Bangladesh	3	AG	Multinational case-control study of children <5 years with MSD	[23]
Vellore, India, and Naushahro Feroze, Pakistan	1 <sup>a</sup>	AG	Multinational prospective birth cohort study of children followed for 2 years to determine the adjusted attributable fraction of diarrhea	[52]
<b>Europe</b>				
Turkey	32	AG	Prevalence study among patients presenting with ulcerative colitis	[53]
<b>Middle East</b>				
Jeddah, Saudi Arabia	20	AG	Cross-sectional study of children hospitalized with acute diarrhea	[21]
Yemen	20	PCR	Community-based cross-sectional survey	[54]
<b>Africa</b>				
Cairo, Egypt	38	AG	Case-control study of patients presenting with acute diarrhea	[55]
Vhembe, South Africa	34	AB	Cross-sectional serosurvey	[56]
Giyani and Soshanguve, South Africa	9	PCR	Cross-sectional study of patients attending gastroenterology clinic	[22]

Abbreviations: AB, serology; AG, stool antigen detection; CCDC, Chinese Center of Disease Control and Prevention (7 provinces of China including Guangxi, Qinghai, Guizhou, Shanghai, Sichuan, Sinkiang, and Beijing); f, frequency; MSD, moderate to severe diarrhea; PCR, stool detection by polymerase chain reaction.

<sup>a</sup>In year 2 of life.

(GEMS), *E. histolytica* was 1 of the top 10 causative agents of moderate to severe diarrhea in children under the age of five years in 2 of their 7 study sites across sub-Saharan Africa and South Asia. In addition, *E. histolytica* diarrhea was associated with a relatively greater risk of death across all GEMS sites and was the enteric pathogen with the highest hazard ratio for death in the second year of life [23]. Recent re-analysis of specimens from GEMS, to reassess estimates of pathogen-specific diarrhea exclusively using PCR diagnostics, showed that *E. histolytica* was 1 of the top 7 pathogens causing dysentery, with the most frequent cause of dysentery led by the combined group of *Shigella* species and enteroinvasive *Escherichia coli* [2]. In summary, the global impact of amebic infection remains significant, though challenging to quantify with precision given several methodologic and epidemiologic complexities, but prevalence estimates remain as high as 40% in some populations (Table 1).

### Transmission

The life cycle of *E. histolytica* is simple, with only 2 stages, existing as either an infectious cyst or invasive trophozoite (Figure 1). Transmission occurs after the ingestion of the infectious cyst. This most commonly arises from fecally contaminated hands, food, or water, but there is a new appreciation that exposure to fecal matter may occur during sexual contact, in particular among MSM groups [24]. Following ingestion, excystation to trophozoites occurs, and the released trophozoites migrate to the large intestine, multiplying by binary fission to produce

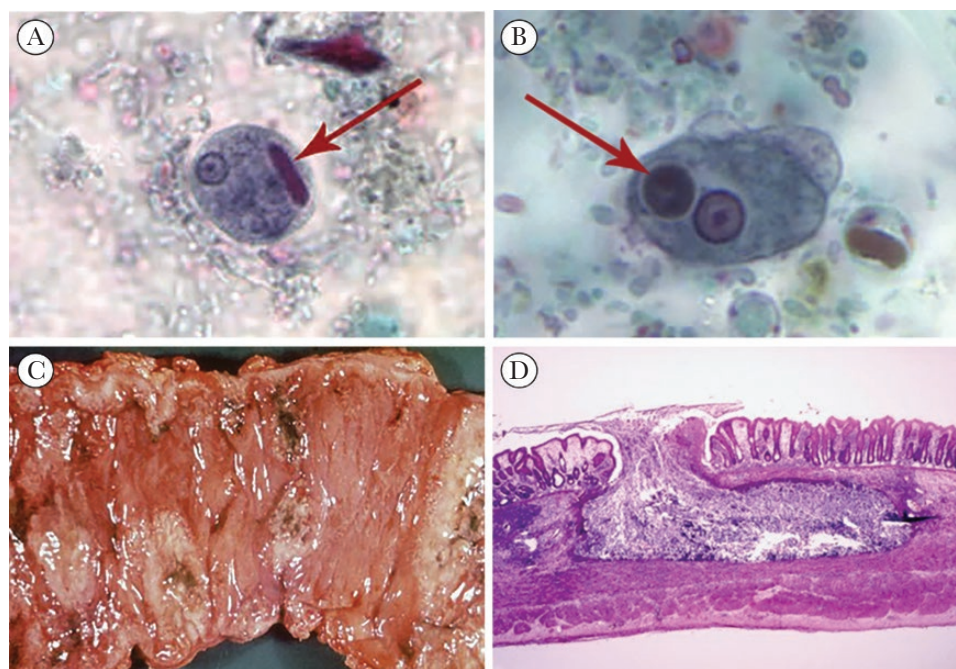
more cysts. The trophozoite may invade the intestinal epithelium and even pass to extra-intestinal sites such as the liver via hepatic portal circulation or disseminate further to distant sites such as the brain and lungs hematogenously. Symptoms may occur within weeks after ingestion but may also develop years after infection.

Cysts and trophozoites are passed in stools. Several properties of the cyst help it to remain hardy in the environment for weeks, whereas trophozoites do not survive. For example, cysts are resistant to gastric acidity and are also relatively resistant to chlorine. The low infectious dose and environmental stability can predispose to the development of outbreaks [5, 6]. Cysts can be killed by boiling.

### PATHOGENESIS

*E. histolytica* pathogenesis can be characterized by 3 events: host cell death, inflammation, and parasite invasion. Contact with host cells is required for parasite-induced death. Adherence is mediated through the parasite Gal/GalNAc lectin adhesion molecule. Trophozoites are able to kill host cells by several different mechanisms, which include inducing programmed cell death, phagocytosis, and trogocytosis [25].

*E. histolytica* causes inflammation of the colon, termed amebic colitis. The intestinal epithelium is the point of first contact for *E. histolytica*. Before cell adherence, trophozoites secrete immune modulators that stimulate epithelial cells, resulting in



**Figure 1.** *Entamoeba histolytica* in stool and pathological features of intestinal amebiasis. A, Cyst of *E. histolytica*/*E. dispar* stained with trichrome. Note the chromatoid body with blunt ends (red arrow). B, Trophozoite of *E. histolytica* with ingested erythrocytes stained with trichrome. The ingested erythrocytes appear as dark inclusions (red arrow). The parasite shows nuclei that have the typical small, centrally located karyosome and thin, uniform peripheral chromatin. C, Intestinal tissue from a patient with amebic colitis showing multiple ulcers. D, Classic flask-shaped ulcer of amebiasis (courtesy of the Centers for Disease Control and Prevention).

cytokine production and subsequent mucosal inflammatory cell infiltration [26, 27]. *E. histolytica*, like several pathogenic protozoa, secretes a protein homolog of the proinflammatory cytokine macrophage migration inhibitory factor (*EhMIF*). A positive correlation was recently found between *EhMIF* levels and intestinal inflammation in persons with amebic colitis [28]. It would seem counterintuitive for parasites to produce a molecule like *EhMIF*; however, *E. histolytica* has developed a number of mechanisms to evade the immune response and persist in the host [27]. Also, *E. histolytica* exploits the inflammatory response to promote its own invasion. *EhMIF*-induced inflammation results in increased production in matrix metalloproteinases (MMPs) [28]. MMPs break down the extracellular matrix in the gut to promote cell migration and are overexpressed in all infections with protozoan parasites, including amebiasis [29, 30]. In a recent study, MMPs were shown to be necessary for *E. histolytica* tissue invasion [31]. It appears that *EhMIF* is a parasite virulence factor that triggers inflammation, resulting in increased expression of MMPs, which promotes invasion of the host.

## IMMUNE RESPONSE

Various host immune mechanisms are elicited in response to amebiasis in an attempt to clear or prevent infection. Interferon gamma (IFN- $\gamma$ ) appears to provide protection from amebiasis, as children with higher IFN- $\gamma$  had a significantly lower incidence of future *E. histolytica* diarrhea [32]. Also, protection from amebiasis includes acquired immunity from antibodies against the amebic antigens Gal/GalNAc lectin and *EhMIF*. Infected children develop antibodies against *EhMIF*, which are associated with protection from reinfection [28, 33]. Although the immune response is normally protective, it can also produce undesirable effects when the response is excessive. For example, higher TNF- $\alpha$  production was shown to correlate with *E. histolytica* diarrhea in children. Another cytokine produced during infection is interleukin-8 (IL-8), a potent neutrophil chemoattractant. In response to IL-8, neutrophils infiltrate the intestinal tract as the first cells of an innate immune response to amebic invasion [27, 30]. Patients with severe amebic colitis have higher colonic tissue levels of IL-8 and neutrophils, suggesting that neutrophils might be responsible for collateral tissue damage during inflammation at the site of invasion [34–36].

## CLINICAL MANIFESTATIONS

The majority of *E. histolytica* infections are asymptomatic; only about 10%–20% progress to develop symptomatic infection. The reasons for this are poorly understood but result from an interplay of several factors related to parasite, host, and environment. Recently, it was found that the gut microbiome is enriched in *Prevotella copri* in people with amebic diarrhea, indicating that dysbiosis may in part contribute to susceptibility to the development of colitis [22].

## Intraluminal Amebiasis

Asymptomatic infection is referred to as luminal amebiasis. Screening for asymptomatic infection should be considered in those with a personal history of travel to/immigration from an endemic area or a history of this in either a household or sexual contact. A gender difference in amebiasis is not seen in children, but interestingly, in the adult population, invasive disease is more common in males than females, particularly for amebic liver abscess [12].

## Amebic Colitis

Symptomatic intestinal infection can have a wide spectrum of manifestations (Table 2). One hallmark of amebic colitis is diarrhea, which may be watery or bloody and present with abdominal cramps, pain/tenderness, and weight loss. Presentation may be acute or more gradual, and amebic colitis may also present similarly to inflammatory bowel disease (IBD). It may not be possible to distinguish amebic colitis from IBD even by imaging, inflammatory markers, or endoscopy, and the colon may appear friable, with diffuse ulceration by gross examination (Figure 1) [4]. Disease may be limited to the ascending colon or cecum. Life-threatening manifestations of amebic colitis include fulminant infection, which can result in massive areas of colonic involvement with perforation and peritonitis, bowel necrosis, or toxic megacolon [4]. Corticosteroid use has been described as a risk factor for the development of fulminant forms of amebic colitis [4]. Patients may be toxic in appearance, febrile, and hypotensive, with profuse bloody diarrhea, abdominal pain, distension, and signs of peritonism. The case fatality of fulminant amebic colitis ranges from 40% to 89%. Toxic

**Table 2. Clinical Findings in Amebic Colitis and Amebic Liver Abscess**

Characteristic	Amebic Colitis	Amebic Liver Abscess
Migration from or travel to an endemic area	++++	++++
Diarrhea	++++	++
Heme-positive stools	+++	-
Abdominal pain	++++	++++ <sup>a</sup>
Hepatomegaly	-	++
Weight loss	++	++
Fever >38°C	+	++++
Cough	-	++
Leukocytosis	+/-	++++ <sup>b</sup>
Elevated alkaline phosphatase	-	++++ <sup>c</sup>
Sigmoidoscopy/colonoscopy	Friable colonic mucosa with discrete ulcers	-
Abdominal imaging (ultrasound, CT, or MRI)	Colonic inflammation and bowel wall thickening	Intrahepatic lesion typically right lobe, often solitary

++++,  $\geq 75\%$ ; +++, 50–74%; ++, 25–49%; +, <25%; +/- variable.

Abbreviations: CT, computed tomography; MRI, magnetic resonance imaging.

<sup>a</sup>Pain is located in the right upper quadrant in amebic liver abscess.

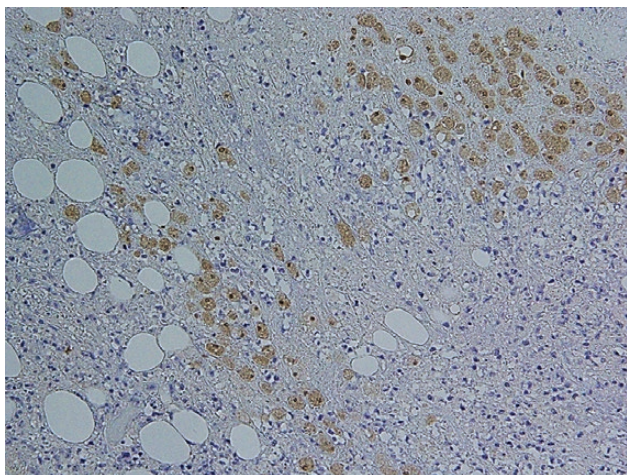
<sup>b</sup>Typically without eosinophilia.

<sup>c</sup>Transaminase enzymes may also be elevated in amebic liver abscess.

megacolon has been described in a patient with amebic colitis and heavy use of the antimotility agent loperamide [37]. Other implicated risk factors for fulminant disease include diabetes mellitus, alcoholism, malignancy/chemotherapy, and pregnancy [4]. Amebic colitis may also present as acute appendicitis (Figure 2). Appendicitis was noted in up to 15% of Japanese HIV-infected patients presenting with appendicitis and undergoing appendectomy [38]. The only distinguishing feature was a higher median neutrophil count in those with amebic infection compared with those without in this series [38]. Ameboma, the development of tumor-like granulation tissue in the colonic lumen, can mimic colonic cancer. The differential diagnosis of amebic colitis includes bacterial enteric infection, such as *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., enterohemorrhagic *E. coli*, enteroinvasive *E. coli*, *Clostridium difficile* infection, IBD, and other noninfectious causes of colitis. The aid of stool PCR and culture can help to distinguish several of these differentials.

#### Disseminated Amebic Disease

Amebic liver abscess, which is the most common extra-intestinal manifestation, develops when trophozoites disseminate to the liver. For poorly understood reasons, amebic liver abscesses are 10 times more common in men than women, often presenting between the ages of 20 and 40 years. Onset can be acute, subacute, or subtle. Hepatic amebiasis has been reported over 20 years after the last visit to an endemic area, so any travel history may be important in this diagnosis. The majority will present with fever and right upper quadrant pain, typically without concurrent dysentery or gastrointestinal symptoms (Table 2) [12]. Hepatomegaly with point tenderness over the liver can often be detected. Cough and respiratory symptoms, including pleuritic right-sided chest pain, may occur, or even referred pain to the shoulder. Elevated alkaline phosphatase and



**Figure 2.** Amebic colitis. Immunohistochemical staining of trophozoites (brown) using specific anti-*Entamoeba histolytica* macrophage migration inhibitory factor antibodies in a patient with amebic appendicitis.

peripheral leukocytosis, usually in the range of 12 000–20 000/ $\text{mm}^3$ , is seen, though typically without eosinophilia. Imaging more often reveals right lobe lesions, usually solitary, but left lobe or multiple lesions may be less commonly seen (Table 2) [12]. Amebic liver abscess may be difficult to clinically distinguish from pyogenic liver abscess. Echinococcal cysts of the liver are another important differential, but they tend to appear as multiple clustered fluid collections without surrounding enhancement on imaging. Peripheral eosinophilia is rare with amebic liver abscess and is more commonly associated with echinococcosis and hepatic fascioliasis (liver fluke). Detection of bacteremia by blood culture, stool studies, and serology will also help to narrow the differential. Occasionally, diagnostic or therapeutic aspiration is required. Aspiration of the amebic liver abscess reveals “anchovy paste,” chocolate-colored fluid consisting of necrotic hepatocytes.

Pleuropulmonary amebiasis can occur as a complication of ruptured amebic liver abscess, presenting with pneumonitis or lung abscess. Intraperitoneal rupture is rare but can be life-threatening if there is pericardial involvement. Trophozoites may also on occasion disseminate hematogenously to the central nervous system and other extra-intestinal sites [39].

#### LABORATORY DIAGNOSIS

A number of diagnostic modalities are available to assist with diagnosis, including microscopy, antigen detection, molecular tests, and serology (Table 3). Often a combination of tests is required to establish diagnosis. Traditionally, microscopy has been the most widely used but has limited diagnostic utility and is no longer recommended as a reliable way to diagnose amebiasis. Most cases of extra-intestinal abscess occur without concurrent intestinal infection, resulting in lower sensitivity of stool studies for the diagnosis of amebic liver abscess.

##### Stool Microscopy

Cysts and trophozoites can be visualized by an experienced eye, sometimes with evidence of hemophagocytosis. Fresh stools increase the recovery of both trophozoites and cysts and can be prepared as either wet mounts or stained preparations. Mature cysts have 4 nuclei measuring about 12–15  $\mu\text{m}$  in diameter. Trophozoites have a single nucleus and are slightly larger, measuring about 15–20  $\mu\text{m}$ . Microscopy should not be used when other modalities are accessible.

##### Stool Antigen Detection

Antigen detection tests have helped to overcome some of the limitations of stool microscopy and are easy to use, but in practice have variable sensitivity and specificity, particularly in low-endemic areas [40]. Although several EIA kits are commercially available, they are not as widely available in resource-limited settings. The Techlab *E. histolytica* II test (Blacksburg, VA), which detects *E. histolytica*-derived Gal/GalNAc-specific lectin, can exclude nonpathogenic *E. dispar*, as can the Cellabs CELISA Path

**Table 3. Comparison of Laboratory Diagnostic Tests for Amebiasis**

Method	Sensitivity, % [Reference]	Specificity, % [Reference]	Advantages	Disadvantages
Microscopy	<60% [4]	-	Widely available	Poor sensitivity and specificity; cannot differentiate from other <i>Entamoeba</i> spp.
			Screens for other parasites	Multiple stools need to be submitted
			Minimal equipment and reagents required	Skilled observer required; time-consuming
Serology	65%–92% [16]	>90% [16]	High sensitivity and specificity, useful adjunct to stool studies	Serology remains positive for years after resolution of infection, so less helpful in endemic areas; more useful in travelers
			Rapid turnaround	Antibody response is often detectable by the time of presentation but may need to be repeated in 7–10 days if initially negative
Stool antigen detection	0%–88% [42]	>80% [42]	May have high sensitivity in endemic areas but reduced sensitivity in nonendemic areas	Poor sensitivity for amebic liver abscess
			Simple to perform, rapid turnaround time, and commercially available combined tests exist to detect several enteroparasites	Requires fresh, not fixative preserved stool for analysis
PCR	92%–100% [42]	89%–100% [42]	Gold standard; high sensitivity and specificity for colitis and liver abscess with increasing availability	More expensive; cost may limit use in resource-limited settings
			Rapid turnaround; automated systems reduce technician time and risk of contamination	Requires analysis instruments, kits, and skilled technician
			Can be combined with multiplex panels to detect multiple enteric pathogens at a time	

Abbreviation: PCR, polymerase chain reaction.

(Brookvale, Australia). A false-negative EIA test was reported from Spain, possibly from interference, as the result turned positive with subsequent testing [41]. Recently, an E. HISTOLYTICA QUIK CHEK immunochromatographic (IC) assay, which is simple to perform and has a quick turnaround time, was approved by the US Food and Drug Administration (FDA).

#### Stool Molecular Studies

Stool PCR is extremely sensitive. It is considered the gold standard for diagnosis of amebiasis and is becoming readily available through FDA-cleared gastrointestinal panels that simultaneously detect multiple enteropathogens, such as the BD Max Enteric Parasite Panel (Becton, Dickinson and Company, Sparks, MD), the Luminex xTAG Gastrointestinal Pathogen Panel (Luminex Corporation, Toronto, Canada), and the Biofire FilmArray Gastrointestinal Panel (BioFire Diagnostics, Salt Lake City, UT) [42]. The use of PCR is also endorsed by the World Health Organization, but the expense and requirement for technical expertise may limit use in resource-limited settings [43]. Purulent fluid aspirated from liver abscess can also be tested.

#### Serology

Serology is a useful adjunct to stool studies. Several EIA kits for antibody detection are commercially available, including indirect fluorescence, immunoelectrophoresis, and immunosorbent assays, but the indirect hemagglutination test has been replaced by EIA. Antibody detection is particularly helpful in the diagnosis of extra-intestinal disease, when stool studies may be negative. False-positive results have been reported [12].

Antibodies remain detectable for years after successful treatment, so it is difficult to reliably distinguish between active and past infection.

#### Other Diagnostic Methods

Amebic ulcers most often develop in the cecum. Histology obtained by diagnostic endoscopic biopsy or surgical resection may show the characteristic flask-shaped ulcer (Figure 1). Trophozoites may be identified at the edge of the ulcer or within the tissue, using periodic acid-Schiff staining or immunoperoxidase staining with specific anti-*E. histolytica* antibodies (Figure 2).

#### Imaging

Ultrasonography, abdominal computed tomography (CT), and magnetic resonance imaging are all good modalities to detect liver abscess. By ultrasound, a cystic intrahepatic hypoechoic lesion can be found. By CT, an abscess with a nonenhancing center surrounded by a rim of inflammation can be seen following contrast administration. The detection of a space-occupying lesion in the liver and positive amebic serology supports the diagnosis of amebic liver abscess.

#### THERAPY

All patients with amebiasis should be treated (Table 4). Patients with clinical disease require treatment with 2 drugs: an amebicidal tissue-active agent and a luminal cysticidal agent. Those with asymptomatic amebiasis need only be treated with a luminal cysticidal agent to prevent invasion and transmission.

**Table 4. Antiparasitic Therapy for *Entamoeba histolytica* Infection**

	Drug of Choice	Daily Dose	Duration, d	Alternatives
<b>Tissue-active agent</b>				
Amebic colitis <sup>a</sup>	Metronidazole or Tinidazole	750 mg po TID (35–50 mg/kg/d divided TID) 2 g po once daily (50 mg/kg once daily)	5–10 3–5	Nitazoxanide <sup>b</sup>
Amebic liver abscess and disseminated amebic disease <sup>a</sup>	Metronidazole or Tinidazole	750 mg po TID (35–50 mg/kg/d divided TID) 2 g po once daily (50 mg/kg once daily)	10 5	-
<b>Luminal agent</b>				
Asymptomatic carriage or following tissue-active agent	Paromomycin	25–35 mg/kg/d by mouth divided TID	7	Iodoquinol/diiodohydroxyquin diloxanide furoate <sup>c</sup>

Abbreviations: BID, twice daily; IV, intravenous; po, by mouth; TID, three times daily.

<sup>a</sup>Severe disease or unable to tolerate oral therapy, use metronidazole 1500 mg IV divided TID (7.5–30 mg/kg/d divided TID) [46].

<sup>b</sup>Limited data, 500 mg po BID (≥12 years), 200 mg BID (age 4–11 years), or 100 mg BID (age 1–3 years) for 3 days.

<sup>c</sup>Iodoquinol 650 mg po TID (30–40 mg/kg/d po divided TID for children) for 20 days after meals (optic neuritis and peripheral neuropathy have been reported), diloxanide furoate 500 mg po TID (20 mg/kg/d po divided TID for children) for 10 days [57].

The amebicidal agents include metronidazole and tinidazole, which are both nitroimidazole agents. They are highly effective at eliminating invading trophozoites and remain the recommended therapy for amebic colitis and amebic liver disease. Tinidazole has a longer half-life and is better tolerated, but metronidazole is as effective at clearing parasites [44]. Side effects of metronidazole include nausea, headache, anorexia, metallic taste, peripheral neuropathy, and disulfiram-like reaction with alcohol. The nitroimidazoles do not effectively eradicate luminal cysts and must be followed by a luminal agent. The thiazolidine agent nitazoxanide, with reputed broad-spectrum antimicrobial properties, was shown in a small single-center trial from Egypt to have clinical and microbiologic response in patients treated for hepatic and intestinal amebiasis of >90%. However, the unexpectedly high response rate in the placebo group of 40%–50% raises methodologic concerns [45].

The aminoglycoside paromomycin is a luminal cysticidal agent. As it may cause diarrhea, paromomycin should not be administered at the same time as the nitroimidazole agent. Diloxanide and iodoquinol are alternatives, but neither is available in the United States.

Patients with fulminant amebic colitis will additionally require fluid resuscitation, broad-spectrum antimicrobial therapy for peritonitis, intensive supportive care, and surgical intervention for bowel perforation and bowel necrosis. Occasionally, colectomy has been necessitated by the development of toxic megacolon or extensive bowel necrosis [4]. In patients who are unable to tolerate or absorb oral metronidazole, intravenous metronidazole should be used [46].

Drainage of liver abscess, either by image-guided or open aspiration, may occasionally be required in addition to antiparasitic therapy. Drainage is typically reserved for those who do not show prompt clinical response to antiparasitic therapy by

about 72 hours or those at high risk for impending abscess rupture, typically defined by a cavity with a diameter >5–10 cm or by left lobe abscess, which could rupture into the pericardium. Serial imaging may show that it takes months following appropriate therapy for the abscess cavity to resolve [12].

Auranofin, a gold compound that has been used to treat selective cases of rheumatoid arthritis, has entered into early clinical drug development as an antiparasitic agent, but further study is needed to determine if it will be an effective treatment of amebiasis and whether known safety concerns such as diarrhea, rash, and bone marrow suppression will limit its use [47].

## PREVENTION

There is no vaccine to prevent amebiasis. The focus of primary preventative efforts, therefore, remains food and water safety, attention to hand hygiene, and avoidance of fecal–oral exposure, including through sexual practices. Before travel to endemic areas such as Asia, Mexico, South America, and sub-Saharan Africa, patients should be advised on food safety to prevent enteric illness. Patients, especially MSM, should also be advised to avoid sexual practices that may lead to fecal–oral transmission. Patients should be asked about prior travel and screened appropriately for secondary prevention. Even a remote travel history is important, as amebic liver abscess and fulminant amebic colitis could occur years after travel. Household contacts of patients with amebiasis should be screened, as amebiasis may spread among family and household contacts [4]. Patients with a new diagnosis of IBD who have traveled to an endemic area should be screened as well, as fulminant amebic colitis may ensue if patients are administered corticosteroid or other immunosuppressive therapy with misdiagnosis [4]. Use of loperamide should be avoided in amebic colitis [37].

## CONCLUSION

Amebiasis remains one of the most significant enteropathogens worldwide. Advances in molecular epidemiology and pathogenesis have advanced our understanding of this parasite; however, many gaps in knowledge remain. In addition, although efforts are ongoing, there is no vaccine and only a single effective drug class. Prevention remains challenging, highlighting the need for improved awareness of this infection and novel therapeutic and preventative strategies.

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