Amebiasis

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On completion of this article, you should be able to: (1) request the appropriate tests for differentiating the morphologically identical Entamoeba *species* E histolytica, E dispar, *and* E moshkovskii *on the basis of initial laboratory reports; (2) recognize symptoms and complications of invasive amebiasis; and (3) apply the World Health Organization/Pan American Health Organization guidelines for diagnosis and treatment of amebiasis.*

Amebiasis is defined as infection with *Entamoeba histolytica*, regardless of associated symptomatology. In resource-rich nations, this parasitic protozoan is seen primarily in travelers to and emigrants from endemic areas. Infections range from asymptomatic colonization to amebic colitis and life-threatening abscesses. Importantly, disease may occur months to years after exposure. Although *E histolytica* was previously thought to infect 10% of the world's population, 2 morphologically identical but genetically distinct and apparently nonpathogenic *Entamoeba* species are now recognized as causing most asymptomatic cases. To avoid unnecessary and possibly harmful therapies, clinicians should follow the diagnostic and treatment guidelines of the World Health Organization.

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ALA = amebic liver abscess; PAHO = Pan American Health Organization; WHO = World Health Organization

Amebiasis is defined by the World Health Organization (WHO) and Pan American Health Organization (PAHO) as infection with *Entamoeba histolytica*, regardless of symptomatology.[1] This protozoan parasite has a global distribution and an especially high prevalence in countries where poor socioeconomic and sanitary conditions predominate.[2] In resource-rich nations, infections may be seen in travelers to and emigrants from endemic areas.[3] Most infections are asymptomatic, but tissue invasion may result in amebic colitis, life-threatening hepatic abscesses, and even hematogenous spread to distant organs.[3,4] Importantly, disease can occur months to years after exposure[5] and must remain in the differential diagnosis in at-risk populations.

Advances in molecular technologies have revolutionized our understanding of this organism.[3] Most notably, 2 additional *Entamoeba* species that are morphologically indistinguishable from *E histolytica* have been recognized in humans. As our knowledge of the global epidemiology and pathogenicity of *Entamoeba* spp increases, new clinical algorithms are developed.[1] The latest nomenclature and recommendations, although unfamiliar and confusing to many, are important for appropriate patient care. Our review discusses what is known about these 3 *Entamoeba* spp and clarifies the currently accepted recommendations for diagnosis and treatment.

THE "NEW" *ENTAMOEBA* SPECIES: *ENTAMOEBA DISPAR* AND *ENTAMOEBA MOSHKOVSKII*

It is a long-held misconception that 10% of the world's population is infected with *E histolytica*. In fact, most of these infections should be attributed to the morphologically identical but nonpathogenic *E dispar*. Emile Brumpt[6] first proposed the existence of 2 indistinguishable *Entamoeba* spp, one pathogenic and one nonpathogenic, in 1925. However, not until 1978 was evidence for the existence of 2 separate entities provided by new technology (isoenzyme analysis).[7] More recent studies using methodologies capable of distinguishing the 2 species suggest that *E dispar* is up to 10 times more prevalent in asymptomatic patients than *E histolytica* in endemic regions.[8-11] Little is currently known about their epidemiology in resource-rich nations, where the incidence of both is rare, but previous reports of infection with *E histolytica* based only on morphology likely represent *E dispar*.

The discovery of a third morphologically identical *Entamoeba* spp further complicated our understanding of the epidemiology of *E histolytica*. The new species, named *E moshkovskii*, was first recognized as a ubiquitous free-living organism in 1941[12]; it has been reported in humans from both resource-rich and resource-poor nations.[13,14] Although largely nonpathogenic, some recent evidence suggests that it may have a role in human intestinal disease. Much remains unknown regarding the pathogenicity and epidemiology of *E moshkovskii*.

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THE DEFINITIVE PATHOGEN: *E HISTOLYTICA*

E histolytica is the pathogenic species responsible for amebic colitis throughout the world. It infects people of both sexes and all ages; however, populations at risk may vary with geographic location, host susceptibility, and differences in organism virulence. People in highly endemic areas probably have recurrent asymptomatic infections, thus accounting for the high reported prevalence.[5,15] In developed countries, amebic colitis is most commonly found in travelers to or emigrants from endemic countries, institutionalized persons, and patients infected with human immunodeficiency virus.[16-18] Men who have sex with men were previously thought to have an increased incidence of infection, but this supposition was based on morphologic studies. New evidence suggests that these men were colonized primarily with *E dispar* rather than *E histolytica*.[19,20]

The simple life cycle of *E histolytica* begins when infectious cysts are ingested in fecally contaminated food or water.[21] This association with poor sanitation explains why resource-poor nations carry the bulk of the world's disease. After ingestion and passage through the stomach, the organism excysts and emerges in the large intestine as an active trophozoite. Trophozoites multiply by simple division and encyst as they move further down the large bowel. Cysts are then expelled with the feces and may remain viable in a moist environment for weeks to months.[18,21] Amebae typically subsist on a diet of intestinal bacteria and partially digested host food but are capable of tissue invasion and dissemination. Most infections (≥90%) remain asymptomatic,[5,15] suggesting that tissue invasion is an aberration rather than a typical behavior.

Invasive intestinal disease may occur days to years after initial infection and is characterized classically by abdominal pain and bloody diarrhea.[18] Watery or mucus-containing diarrhea, constipation, and tenesmus may also occur.[3] This clinical picture corresponds histologically with trophozoites invading and laterally undermining the intestinal surface to form the so-called flask-shaped ulcers (Figure 1). The right side of the colon is commonly involved.[4] Severe cases of amebic colitis are characterized by copious bloody diarrhea, diffuse abdominal pain, and (rarely) fever. Extensive fulminant necrotizing colitis, the most severe form of intestinal disease, is often fatal.[18] Patients at increased risk of severe disease include those who are very young, very old, malnourished, or pregnant and those who are receiving corticosteroids.[3] Some evidence suggests that patients infected with human immunodeficiency virus are at increased risk of severe disease,[22] but this is not universally accepted.[23] Complications of intestinal disease include stricture, rectovaginal fistulas, formation of an annular intraluminal mass (ameboma), bowel obstruction, perianal skin ulceration, toxic megacolon, perforation, peritonitis, shock, and death.[3,18] Chronic intestinal amebiasis is also well described; patients with this condition can have years of intermittent abdominal pain, diarrhea, and weight loss.[21]

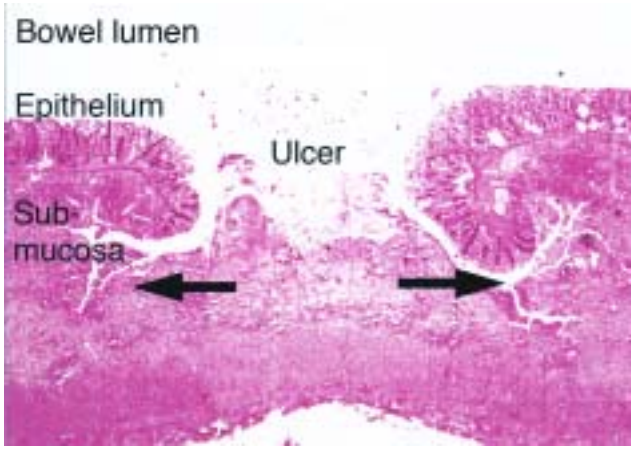

FIGURE 1. "Flask-shaped" ulcer of invasive intestinal amebiasis (hematoxylin-eosin, original magnification ×50). Note that the apex of the ulcer at the bowel lumen is narrower than the base, accounting for the flask shape. This is formed as trophozoites invade through the mucosa and move laterally into the submucosa (direction of ulcer expansion is marked by arrows). Microscopically, trophozoites are localized to the advancing edges of the submucosal ulcer. Image courtesy of John Williams, CBiol, MIBiol, London School of Hygiene and Tropical Medicine.

On rare occasions, *E histolytica* trophozoites enter the bloodstream and disseminate to other body sites, most commonly the liver via spread from the intestine through the portal vein. The right lobe is 4 times more likely to be involved than the left because it receives the bulk of the venous drainage from the right colon.[4] Adult men aged 20 to 40 years are most frequently affected, although people of both sexes and all ages may develop an amebic liver abscess (ALA).[17,18] Disease can occur years after exposure and may follow the onset of immunosuppression.[18]

Hepatic invasion by amebic trophozoites results in marked tissue destruction with neutrophil recruitment, cellular necrosis, and formation of microabscesses that gradually coalesce.[4] Most patients (65%-75%) present with a single abscess; however, multiple abscesses may also be formed.[18] Abscesses consist of soft, necrotic, acellular yellow-brown debris, described as "anchovy paste."[21] Amebae are seldom identified in aspirates because they are located at the periphery of the lesion.[18] White blood cells are also not usually seen, presumably because they have been destroyed by the amebic trophozoites.

Clinical presentation of ALA is highly variable and commonly includes tender hepatomegaly and pain in the

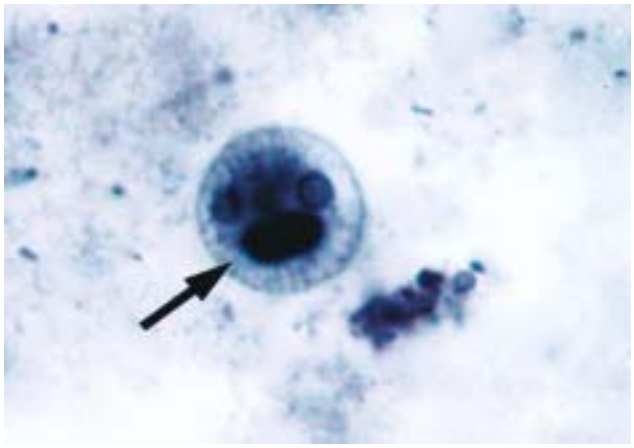

FIGURE 2. Classic cyst morphology of *Entamoeba histolytica/dispar/moshkovskii* (iron hematoxylin stain of fecal sample, original magnification ×1000). Cysts range from 10 to 16 μm in diameter (mean, 12.5 μm) and contain up to 4 nuclei, each with a central irregular dot and peripheral rim of chromatin. As seen above, all 4 nuclei are rarely visible in the same plane of focus. Chromatoid bodies (crystallized ribosomes) are also commonly seen (dark staining mass; arrow). Although this morphology allows for identification of these 3 organisms, exact speciation requires further testing. Image courtesy of Professor John Williams, London School of Hygiene and Tropical Medicine.

right upper quadrant.[18] Unlike amebic colitis, ALA is commonly accompanied by fever,[3] as well as by rigors, chills, and profuse sweating.[18] Most patients do not have concurrent colitis and cysts, and trophozoites are not always seen on fecal smears,[3] posing an important diagnostic challenge. Jaundice is not typically present; elevated bilirubin levels are seen in less than 50% of patients, but elevated alkaline phosphatase levels are common.[18] Complications include secondary bacterial infection; perforation into peritoneal, pleural, and pericardial cavities; septic shock; and death.[4,18]

Perhaps the most serious complication is amebic metastasis from the liver. Rarely, trophozoites end up in other regions of the body, such as the brain, spleen, lungs, and genitourinary tract, through hematogenous or direct spread.[3] Brain abscesses are extremely rare and are associated with high mortality rates.[2] Like patients with ALA, those with disseminated disease do not usually have concomitant amebic colitis.[3] Disseminated disease is not an adaptive mechanism for the parasite because its life cycle cannot be completed outside the intestine.

RADIOLOGIC AND ENDOSCOPIC FEATURES OF INTESTINAL AND EXTRAINTESTINAL DISEASE

When amebiasis is suspected, radiologic and endoscopic examination may lend further support for a diagnosis. Colonoscopy can provide a wide spectrum of findings, from rare large-bowel ulcers in mild disease to diffuse mucosal ulceration, hemorrhage, colonic stricture, and presence of an ameboma.[18] Grossly, these findings may resemble those seen with inflammatory bowel disease; therefore, correlation with histopathology and laboratory results is essential.[18,21] Endoscopy is contraindicated in patients with evidence of peritonitis, severe dehydration, or shock.[18]

Radiologic studies may also be helpful in evaluating a patient with possible ALA. Chest and abdominal radiography often reveal a pleural effusion and raised hemidiaphragm overlying the involved liver lobe.[18] Ultrasonography reveals lesions that are typically hypoechoic and well defined with rounded edges.[4] Computed tomography and magnetic resonance imaging can further characterize an abscess and allow for better detection of smaller lesions. All 3 techniques may facilitate guided needle biopsy and drainage if indicated.[4] An abscess can usually be distinguished from solid lesions and biliary tract disease, but the differentiation between bacterial and amebic abscesses is less clear. Gallium scans may have a role in this differential diagnosis because amebic abscesses are usually "cold" on scan because of the lack of white blood cells in the abscess, whereas bacterial abscesses are typically "hot."[21]

DEFINITIVE DIAGNOSIS OF *E HISTOLYTICA, E DISPAR,* AND *E MOSHKOVSKII* INFECTIONS

Clinically, it is desirable to definitively distinguish *E histolytica* from *E dispar* and *E moshkovskii* because, of the 3, it is the only proven human pathogen.[17] The diagnosis of invasive amebiasis is usually suggested by the patient's presenting symptoms, exposure history, and radiologic findings but should be confirmed with microbiological laboratory results. Many laboratory methods exist for identification of *E histolytica*, *E dispar*, and/or *E moshkovskii*, and the clinician should be aware that tests vary considerably in price, sensitivity, specificity, and the ability to definitively differentiate among the 3 species.

Light microscopic examination of fecal specimens (ie, "ova and parasite" examination) is often the first step in diagnosis[3]; the characteristic trophozoites and cysts can often be identified through direct, concentrated, and/or permanently stained smears (Figure 2). Because organisms may appear intermittently, current recommendations call for submission of 3 stool specimens on different days during a period of 10 days.[3] As mentioned previously, stool specimens from patients with disseminated disease may not contain cysts and trophozoites, despite repeated examinations.[3]

If stool cannot be examined in the fresh state (within 15 minutes) for motile trophozoites, then it should be placed

immediately in an appropriate fixative to prevent deterioration of organisms.[3] Unfortunately, microscopy alone cannot differentiate *E histolytica* from *E dispar* and *E moshkovskii;* additional tests are required for definitive speciation. The rare exception is when trophozoites containing ingested red blood cells are identified; they are strongly (but not definitively) indicative of invasive amebiasis.[1] Trophozoites may also be identified in intestinal biopsy specimens, scrapings, or aspirates,[21] allowing a diagnosis of amebiasis to be made if mucosal invasion and ulceration are also observed.

When only examination of stool specimens is available, the WHO/PAHO recommends that morphologically consistent cysts and trophozoites receive the nonspecific diagnosis *E histolytica/E dispar*,[1] which could now be augmented to include *E moshkovskii*. The clinician must then interpret this laboratory result in the context of the individual patient and determine whether treatment is warranted.

When possible, *E histolytica* should be definitively identified.[1] Identification methods include biopsy, serology, antigen detection, and molecular assays. Culture may be performed by some large specialty laboratories but is technically challenging and time-consuming. Furthermore, a negative culture result from intestinal samples does not exclude *E histolytica*[1] because sensitivity is less than 100%. Culture followed by isoenzyme analysis is the criterion standard in diagnosis; however, it will likely be replaced by molecular assays in the near future.[3,11]

Serologic tests detect the presence of species-specific antibodies in the patient's serum. They are particularly useful in nonendemic countries where prevalence is low and have a good sensitivity and specificity for detecting invasive intestinal disease. They are also the test of choice for ALA because titers are typically high and test sensitivities and specificities exceed 95% with most assays.[3,21] The primary disadvantage of serologic tests is that they cannot distinguish between past and current infection unless IgM is detected; IgM antibodies to *E histolytica* are short-lived and rarely detected. In contrast, IgG antibodies are long-lived but highly prevalent in endemic settings because of past exposure.[3] Serologic assays, which are also less sensitive in asymptomatic infection, take 7 to 10 days to appear in the bloodstream, resulting in possible false-negative results.[3] Enzyme-linked immunosorbent assay is the most popular test in the diagnostic setting because of its speed and ease of use.[3]

Fecal antigen detection tests use specific monoclonal or polyclonal antibodies to detect *E histolytica* antigens. They are rapid, highly sensitive, and widely used in the diagnostic laboratory.[11] Antigen tests are useful for confirming microscopic findings and providing a diagnosis in patients with negative fecal smear results. They are also helpful for interpreting positive results on amebic serology in patients from endemic countries because positive results on an antigen test indicate current rather than past infection.[11,21] Some antigen detection kits can also be used on serum and material obtained from aspirated abscesses, offering greater sensitivity than microscopy for extraintestinal disease.[18] Not all commercial kits are capable of speciation; some demonstrate cross-reactivity between *E histolytica* and *E dispar*. Antigen detection methods are also not as sensitive as polymerase chain reaction assays[3,11] and may have low specificity in nonendemic regions.[24] Clinicians should be familiar with the specifications of the kits used in their laboratory and confirm a suspected diagnosis if indicated.

The highest sensitivity and specificity for the diagnosis of *E histolytica* are offered by DNA-based tests. Many assays are available, including conventional and real-time polymerase chain reaction formats[3]; however, they are currently used primarily by research and reference laboratories. Like most molecular amplification assays, they remain impractical for resource-limited settings because of their equipment, personnel, and facility requirements.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of amebic colitis must include bacterial (eg, *Salmonella* and *Shigella* spp, *Mycobacterium tuberculosis*), parasitic (eg, *Schistosoma mansoni, Balantidium coli*), and noninfectious (eg, inflammatory bowel disease, carcinoma, ischemic colitis, diverticulitis) causes of dysentery.[3,18] When present, amebomas may mimic carcinoma, tuberculosis, or an appendiceal mass.[18] Diagnostic tests in the work-up of patients with dysentery might include stool cultures for bacteria, ova, and parasites (other than *E histolytica*) and assays for bacterial toxins.[3] Biopsy specimens of intestinal ulcers are useful for confirming the presence of trophozoites and for excluding other etiologies.

Given its varied clinical presentation and possible delay of onset, the diagnosis of ALA may not be straightforward. The differential diagnosis includes bacterial abscess, echinococcal cyst, tuberculosis, and primary or metastatic tumor,[18] all which would have vastly different treatments. Radiology can differentiate between many noninfectious and infectious etiologies; however, bacterial and amebic abscesses may appear remarkably similar. In comparison with bacterial abscesses, ALAs are more likely to be solitary, subcapsular, and located in the right lobe of the liver, but these findings are not always reliable.[4,18] Occasionally, ALA may cause a pneumonia-like presentation with pleuritic pain, cough, and dyspnea.[18] Radiologic imaging, clinical history, findings on physical examination, and serologic results are essential for including or excluding the diagnosis of ALA.

TREATMENT

The WHO/PAHO recommendations state that, when possible, *E histolytica* should be differentiated from morphologically similar species and treated appropriately. Given the small but substantial risk of invasive disease and the potential to transmit the infection to others, WHO/PAHO recommends treating all cases of proven *E histolytica*, regardless of symptoms.[1] If *E dispar* is the only species identified, then no treatment should be given and other causes should be sought as appropriate.[1,11]

In resource-poor countries, the standard but less optimal approach is to treat all patients with cysts and trophozoites identified on stool examination without additional testing for speciation.[3] This method results in vast overtreatment and may hasten the development of drug resistance in *E histolytica*.[3] Thus, WHO/PAHO recommends withholding treatment from asymptomatic patients when only a morphologic diagnosis by stool examination is available (ie, *E histolytica*/*E dispar*/*E moshkovskii*), unless another reason to suspect *E histolytica* infection exists.[1] Even if patients diagnosed as being infected with *E histolytica*/*E dispar*/*E moshkovskii* have symptoms, other causes of disease, such as bacterial colitis, should not be excluded until further testing is done.[1] Prophylaxis for *E histolytica* infection with amebicides is not recommended under any circumstances.[1]

The medications recommended to treat confirmed amebiasis vary with clinical manifestation. Asymptomatic intestinal infection with *E histolytica* should be treated with luminal amebicides, such as paromomycin and diloxanide furoate.[18] These medications will eradicate the luminal amebae and prevent subsequent tissue invasion and spread of the infection through cysts.[18,21] Paromomycin, more widely available in the United States, has the advantage of not being absorbed in the bowel.[21] Abdominal cramps and nausea are the most commonly reported adverse effects. A 10-day course at 30 mg/kg per day (divided into 3 daily doses) is typical. Some recommend follow-up stool examination to confirm eradication of cysts.[21]

Compared with asymptomatic infection, intestinal and extraintestinal invasive disease are aerobic processes and should be treated with tissue amebicides, such as 5-nitroimidazoles (eg, metronidazole), which are readily absorbed into the bloodstream.[1] Metronidazole (750 mg, 3 times a day, for 5-10 days) is the most commonly used drug in the United States for invasive amebiasis.[21] Because little metronidazole reaches the lumen of the colon, treatment should be followed by administration of a luminal agent to eradicate any potential intestinal reservoirs.[21] Most uncomplicated cases respond to a 5-day course of metronidazole; however, a 10-day course is useful in severe cases.[18] Metronidazole may also be given parenterally to critically ill patients and can be supplemented with an antibiotic to cover secondary sepsis with bowel flora. The most common adverse effects of metronidazole are abdominal discomfort and nausea; most patients, however, are able to complete a full 5- to 10-day course. Serious adverse drug reactions include confusion, ataxia, and seizures.[4]

A promising new regimen for invasive amebiasis is a 3-day course of nitazoxanide. This drug is effective against both luminal and invasive forms and has the added benefit of eliminating other intestinal parasites, including helminths.[21] Surgery may be necessary in cases of perforation, abscess, obstruction, stricture, or toxic megacolon. However, given the friable nature of the inflamed mucosa, bowel repair is risky and should be avoided when possible.[18,21]

Like amebic colitis, ALA typically responds well to a 5- to 10-day course of metronidazole, which should also be followed with a luminal amebicide.[21] Metronidazole is the drug of choice in this setting, given its fast intestinal absorption, excellent bioavailability in tissue, and good abscess penetration.[4] Surgical or percutaneous drainage of ALAs is generally not recommended because of the risk of content spillage and/or bacterial superinfection; exceptions are cases of imminent rupture, failure to respond to treatment after 4 to 5 days, and secondary bacterial infection.[4,21] After treatment, ultrasonography may be used to monitor abscess regression, which occurs slowly during a period of 3 to 12 months.[4] Small cystic defects may remain indefinitely.[18]

Amebae rarely disseminate beyond the portal circulation. Given the small number of cases, no definitive treatment guidelines are available for management of extraintestinal, extrahepatic disease. As mentioned previously, infections with *E dispar* do not require treatment. Less is known about *E moshkovskii*, but it is likely that this infection also would not require treatment in most cases.

CONCLUSION

Recent discoveries have revolutionized our understanding of the epidemiology of *Entamoeba* spp infections and have led to important treatment and diagnostic recommendations. To avoid unnecessary and possibly harmful therapies, clinicians should follow the precise guidelines promulgated by the WHO/PAHO in 1997, including definitive differentiation of *E histolytica* from morphologically identical nonpathogenic species. Such definite differentiation is especially important in countries with adequate sanitation measures, where the predominant organism identified from morphologic stool examination will be *E dispar*. Because they have the highest sensitivity and specificity, molecular technologies offer the greatest diagnostic potential for

laboratories in resource-rich countries at this juncture; however, some antigen detection tests can also provide reliable speciation. When speciation is impossible, we recommend using the phrase "*E histolytica/E dispar/E moshkovskii*" to describe the morphologically identical species seen on stool examination. Continued use of new technologies will be crucial in elucidating the true epidemiology and pathogenesis of *Entamoeba* spp, including the less well-studied *E moshkovskii*. Continued development of affordable, sensitive, and specific diagnostic tools will be required for use in resource-poor settings, where the incidence of disease is highest.

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CME Questions About Amebiasis

1. According to the World Health Organization (WHO)/Pan American Health Organization (PAHO), which <u>*one*</u> of the following describes the <u>*causative*</u> agent(s) of amebiasis?

   a. All intestinal amebae
   b. All intestinal and extraintestinal amebae
   c. *Entamoeba histolytica/dispar*
   d. Any *Entamoeba* species
   e. *E histolytica*

2. Which <u>*one*</u> of the following is <u>*true*</u> regarding *E histolytica*?

   a. It infects 10% of the world's population
   b. It commonly spreads to extraintestinal sites such as the liver
   c. Organisms can usually be identified from amebic liver abscesses (ALAs)
   d. The bulk of the world's disease is in developed nations
   e. It is indistinguishable from *E dispar* and *Entamoeba moshkovskii* by light microscopy

3. Which <u>*one*</u> of the following is the <u>*WHO-recommended*</u> treatment for a patient diagnosed as being infected specifically with *E dispar*?

   a. No therapy; additional laboratory tests should be performed as clinically indicated
   b. A 5-nitroimidazole compound, such as metronidazole
   c. A luminal agent, such as paromomycin
   d. A tissue amebicide followed by a luminal agent
   e. Diloxanide furoate

4. Which *one* of the following symptoms does *not* characterize amebiasis?

   a. Watery or mucus-containing stool
   b. Increased risk of mucosal dysplasia
   c. Blood-containing stool
   d. Risk of perforation and peritonitis
   e. Trophozoite invasion into the submucosa, laterally undermining the overlying mucosa

5. Which *one* of the following is the *best* reason for treating ALA with both a gut (luminal) and tissue amebicide?

   a. Prevention of drug resistance
   b. Synergistic dual action of the 2 medications
   c. Penetration of necrotic abscesses allowed by the combination of medications
   d. Liver abscess treated by the tissue amebicide; any bowel infection eliminated by the luminal amebicide
   e. Combination therapy is the only medication formulation available

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