Amebic Liver Abscess

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Opinion statement

Amebic liver abscess should be suspected in travelers returning from endemic areas or in immunocompromised patients who present with fever, right upper quadrant pain, hepatomegaly, and a liver lesion on an imaging study. Rapid initiation of therapy without serologic confirmation of infection, if necessary, is important to minimize complications. Metronidazole is given orally or intravenously for 14 days. The drug is generally well tolerated and leads to resolution of symptoms in most patients within 2 to 3 days. It is effective against luminal cysts in only 50% of patients and, therefore, must be followed by a course of treatment with paromomycin (Humatin; Parke-Davis, Morris Plains, NJ) or another luminal antiamebic agent to eradicate the parasite. Image-guided drainage of an amebic liver abscess is indicated in patients who do not respond to antimicrobial therapy or who are at risk of abscess rupture. Surgery is reserved for patients with a ruptured abscess. Although medical therapy is generally successful in the treatment of infection caused by *Entamoeba histolytica*, the development of potent vaccines will be needed for worldwide eradication of disease attributable to *E. histolytica*.

Introduction

Amebiasis occurs predominantly in developing countries, with high endemic prevalence in Mexico, Central and South America, India, and eastern and southern Africa. However, an increase in international travel and immigration from endemic areas has also increased the incidence in industrialized countries [1]. Although approximately 10% of the world's population is thought to be infected with *Entamoeba* species, approximately 90% of these cases are probably due to the recently recognized nonpathogenic form *Entamoeba dispar*, which morphologically resembles *Entamoeba histolytica* and, therefore, was not recognized in earlier studies. Worldwide, approximately 40 to 50 million cases of amebic colitis and amebic liver abscess occur annually. An estimated 40,000 to 100,000 deaths per year are due to this parasitic infection, making this the third most deadly parasitic disease after malaria and schistosomiasis [2].

Humans are the main host for *E. histolytica* [3•]. Infection occurs by ingestion of the infective cyst form of *E. histolytica* from food and water contaminated with feces, from infected food handlers, and from produce fertilized with human feces. The cysts are resistant to stomach acid, and in the more basic environment of the small bowel, the mobile trophozoites develop and pass to the colon, where they invade the mucosa and cause amebic colitis. Liver abscesses develop from passage of the trophozoites through the enteric mucosa to the portal vein and liver. In the liver, the parasite causes acute inflammation, followed by granuloma formation and necrosis, resulting in abscess formation. Rarely, abscesses may form in the spleen, brain, or other organs.

Amebic liver abscess (ALA) is nearly 10 times more common in men than in women [4]. Although the exact basis for this discrepancy is unknown, it has been suggested that higher consumption of alcohol, which may damage Kupffer's cells, could be an important factor in the higher incidence in men [5••]. ALA affects predominantly younger patients between the ages of 20 and 40 years but is rarely found in children. It typically occurs in patients who have immigrated from or traveled to endemic areas. In the United States, it also affects patients who are immunocompromised or institutionalized.

Patients typically present with symptoms a few days to several weeks in duration. Fever, right upper quadrant

pain, and tender hepatomegaly are nearly universal reports [5••,6•,7••,8]. Patients may also report nausea and weight loss; only one third of patients with ALA have concomitant diarrhea, and jaundice is rare. Occasionally, patients may have decreased breath sounds at the right lung base or a pleural rub. On laboratory examination, there is mild leukocytosis (rarely with eosinophilia), anemia, and elevated serum aminotransferase and alkaline phosphatase levels. The serum albumin level and the prothrombin time may be abnormal, but serum bilirubin levels are typically normal.

When it is recognized and treated appropriately, ALA most often has an uncomplicated clinical course. Several risk factors have been associated with a poor outcome [9]. These include alcohol consumption of more than 80 g/d, the presence of jaundice (total bilirubin > 3.5 mg/dL), hypoalbuminemia (< 2 g/dL), anemia (Hb <8 g/dL), encephalopathy, a large abscess (> 5 cm or 500 mL), and multiple abscesses. Most of the morbidity and mortality from ALA is related to abscess rupture into the peritoneum, pleura, or pericardium in patients who are untreated or treated too late.

More than two thirds of patients with ALA do not have detectable cysts or *Entamoeba* antigen in their stool. Diagnosis is made by detecting circulating antibodies to *E. histolytica* antigens. A second-generation enzyme immunoassay is 99% sensitive and 90% specific [10–12]. Diagnosis by a polymerase chain reaction (PCR) test for amebic DNA in aspirates from ALA [13] as well as from feces has also been reported [14].

A chest roentgenogram may reveal an elevated right hemidiaphragm in approximately one half of the patients [5••]. Abdominal ultrasound, CT, or MRI will demonstrate the hepatic abscess. However, these imaging modalities cannot differentiate an ALA from a pyogenic hepatic abscess. Although ultrasound is slightly less sensitive than CT, it is generally more readily available and less costly, and often shows a round, hypoechoic and homogenous lesion [15]. Abscesses are single and involve the right lobe of the liver in about three quarters of patients [5••].

Treatment

- Treatment options include the prevention of infection by avoidance or cleaning of contaminated food and drug treatment with a nitroimidazole, which is generally followed by a luminal agent. Drug treatment in general is inexpensive and readily available in the United States and endemic areas. In high-risk patients or those refractory to antibiotic therapy alone, percutaneous aspiration or drainage of the abscess may be useful.

Diet and lifestyle

- In endemic areas, infection is often spread by food or water contaminated by feces or by handling of food by infected people. Travelers to these areas should avoid contaminated food and drinking water. Vegetables should be cooked or washed with a detergent and then soaked in vinegar for 10 to 15 minutes to eliminate cysts. Bottled water from a known source is preferable; otherwise, water should be boiled to kill the cysts before use. Commonly used concentrations of iodine or chloride are not sufficient to kill infectious cysts.
- As a public health measure, improvement in sanitation and waste disposal, as well as avoidance of human feces as fertilizer, will aid in the eradication of *Entamoeba* organisms.
- Avoidance of oral-anal sexual contact decreases the risk of infection.

Pharmacologic treatment

Metronidazole

Metronidazole (Flagyl; Searle, IL) is the standard treatment in the United States for both symptomatic amebic colitis and extraintestinal disease, mainly ALA. Several studies report a cure rate of greater than 90% in patients with ALA, and most patients improve clinically within 3 days [8,16]. When ALA is suspected, especially in persons with risk factors for a poor outcome, treatment should be

	initiated before confirmation of the diagnosis by serology. Primary resistance to metronidazole is rare. Tinidazole and ornidazole are similar nitroimidazoles that are available outside the United States and may be given for a shorter course.
Standard dosage	750 mg three times orally (or IV, if necessary) daily × 10 days.
Contraindications	Metronidazole should not be used during the first trimester of pregnancy or in patients with known hypersensitivity to imidazoles. Relative contraindications include the second and third trimesters of pregnancy, and pre-existing central nervous system disease (owing to the enhanced risk of seizures and peripheral neuropathy). Dose reduction is required in patients with end-stage liver disease or severe renal failure (glomerular filtration rate < 10 mL/min), in which case the recommended dose reduction is 50%.
Main drug interactions	Metronidazole decreases warfarin (Coumadin; DuPont Pharma, Wilmington, DE) metabolism, resulting in an increase in the prothrombin time and risk of bleeding. Metronidazole also inhibits metabolism of carbamazepine, thereby increasing the seizure threshold when both medications are given. Phenobarbital and phenytoin enhance the metabolism of metronidazole, resulting in decreased efficacy, whereas cimetidine decreases its metabolism, enhancing the risk of potential side effects. Metronidazole is a cytochrome P450 3A4 (CYP3A4) inhibitor and may decrease the metabolism of tacrolimus and cyclosporine, resulting in higher blood levels. A significant interaction with oral contraceptives has not been reported.
Main side effects	Nausea, metallic taste, anorexia, abdominal pain, and headaches are common. Less commonly, confusion, ataxia, and peripheral neuropathy with paresthesias may occur with long-term treatment. High-dose treatment can also cause seizures. Pancreatitis has been reported and improved after the drug was discontinued. In patients with hypersensitivity, metronidazole can produce urticaria and rash. Leukopenia occurs in approximately 1% of patients. Reversible thrombocytopenia and aplastic anemia are extremely rare.
Special points	If used in conjunction with ethanol, metronidazole exhibits a disulfiram-like effect, and patients should be advised to abstain from alcohol. Metronidazole is effective both in the bowel lumen as well as in tissues. However, luminal infection is eradicated in only 50% to 90% of patients, and therefore, treatment should be completed with diloxanide furoate, paromomycin, or iodoquinol (see later) [17].

Dehydroemetine

	Dehydroemetine (Mebedin) is available in the United States directly from the Centers for Disease Control and Prevention (CDC). It is reserved, often in combination with chloroquine, for patients with severe invasive amebiasis who do not respond to metronidazole therapy and are not amenable to percutaneous drainage.
Standard dosage	Dehydroemetine 1 to 1.5 mg/kg/d IM × 5 days (maximum dose, 90 mg/d); emetine 1 mg/kg/d (maximum dose, 60 mg/d).
Contraindications	Pregnancy and severe renal, cardiac, or neuromuscular disease.
Main drug interactions	None known.
Main side effects	Dehydroemetine is better tolerated than emetine. In its oral form, it may cause severe nausea. It also may cause muscle weakness and cardiac arrhythmias, requiring inpatient treatment with cardiac monitoring.
Special points	Emetine, the older form of this drug, is an alkaloid of ipecac and is generally associated with more severe side effects. Historically, it has been used against dysentery and was the first drug that was shown to have antiprotozoal properties in 1912. There are no data on the effectiveness of combined therapy with metronidazole; however, the combination has been used for the treatment of very severe cases of ALA.

Chloroquine

	Chloroquine is used mainly as an antimalarial agent, but it is also active against *E. histolytica* trophozoites and often given in conjunction with dehydroemetine.
Standard dosage	600 mg orally daily × 2 days, followed by 300 mg daily for 2 weeks; dose is calculated as chloroquine base.

Contraindications	Known retinal disease or visual field defects, known hypersensitivity to chloroquine.
Main drug interactions	Cimetidine decreases the metabolism of chloroquine, resulting in a longer half-life. Chloroquine may increase cyclosporine and penicillamine levels, and decrease the effect of levothyroxine.
Main side effects	Nausea, vomiting, anorexia, and diarrhea have been reported frequently. Ocular toxicity is generally observed in patients on long-term therapy. Chloroquine can cause methemoglobinemia, cardiomyopathy, and atrioventriular block. Neuropsychiatric symptoms include muscle weakness, ataxia, and psychosis.

Iodoquinol

	Iodoquinol (Yodoxin; Glenwood, S Hackensack, NJ) is active against *E. histolytica* trophozoites and cysts in the bowel lumen; however, its mechanism of action is poorly understood. It is given to patients with ALA after initial therapy with metronidazole. It is also used for asymptomatic patients in nonendemic areas who pass cysts in their stool in order to prevent invasive amebiasis. However, in endemic areas, treatment of asymptomatic patients is not recommended owing to the high rate of reinfection and the predominance of nonpathogenic *E. dispar*.
Standard dosage	650 mg orally three times daily for 20 days.
Contraindications	Hypersensitivity to iodine and 8-hydroxyquinolones, chronic diarrhea, and severe renal and hepatic dysfunction. Thyroid disease is a relative contraindication because of the high concentration (64%) of organically bound iodine in the drug.
Main drug interactions	No major interactions are reported, but iodoquinol interferes with the urine ferric chloride test used in children to diagnose phenylketonuria, giving false-positive results.
Main side effects	Neurotoxicity, especially in children, after long-term use, resulting in optic neuritis, optic atrophy, peripheral neuropathy, seizures, headaches, and vertigo. Owing to its iodine content, it may cause thyroid enlargement. In addition, patients may experience nausea, abdominal cramps and diarrhea.
Special points	Some authors suggest the use of other luminal agents because of the neurotoxicity of iodoquinol.

Paromomycin

	Paromomycin (Humatin; Parke-Davis, Morris Plains, NJ) is an aminoglycoside antibiotic that is used as a luminal antiamebic agent. It has been shown to eliminate intestinal infections in more than 90% of patients. It is used for the same indications as iodoquinol.
Standard dosage	30 mg/kg/day orally, divided in three doses × 7 days.
Contraindications	Paromomycin is contraindicated in patients with known hypersensitivity, as well as in patients with intestinal obstruction.
Main drug interactions	Concurrent use of digoxin and paromomycin may decrease the bioavailability of digoxin. Close monitoring is recommended.
Main side effects	Primarily gastrointestinal, mainly diarrhea; as a nonabsorbed aminoglycoside, paromycin is similar in its side effect profile to neomycin. Pancreatitis has been reported.
Special points	Paromomycin is not systemically absorbed.

Diloxanide furoate

	Diloxanide furoate (Furamide; Abbott Laboratories, North Chicago, IL) is also an effective luminal agent used after metronidazole to eradicate luminal cysts. It is hydrolyzed in the intestinal lumen and readily absorbed.
Standard dosage	500 mg orally three times daily × 10 days.
Contraindications	Diloxanide furoate should not be given to patients with known hypersensitivity to the drug or in pregnancy and during lactation.
Main drug interactions	No drug interactions have been reported.
Main side effects	Flatulence is reported most commonly; other side effects include nausea and vomiting, pruritus, and urticaria. Neurologic effects are headache, lethargy, vertigo, or dizziness and paresthesias.
Special points	This drug is available in the United States only through the CDC.

Therapeutic interventions

- Image-guided drainage has replaced surgery as the initial invasive therapeutic intervention in ALA. It is aimed at reducing abscess size and thereby decreasing the risk of rupture. Although uncomplicated patients with ALA can generally be treated medically, radiologic drainage is indicated in patients with a high risk of abscess rupture due to the size of the abscess (> 5 cm), location in the left lobe of the liver, or superficial location with minimal surrounding tissue. Patients who do not respond to medical therapy after 3 to 5 days should also be considered for such treatment. Drainage may also be used to diagnose amebic infection in patients without positive serology or stool examination in whom the history and presentation suggest ALA.
- In patients with uncomplicated ALA, the combination of needle aspiration of the abscess with metronidazole improved symptoms more rapidly and decreased the length of hospital stay than medical therapy alone. However, another study found no differences in relief of symptoms at 10 days and cavity healing after 1 year between these two treatment approaches [18]. With large abscesses, placement of a percutaneous drainage catheter is advantageous when compared with needle aspiration, which may have to be repeated several times [19–21].

Image-guided drainage

Standard procedure Under ultrasound or CT guidance and with sterile technique, a catheter is placed into the abscess cavity. Abscess fluid can be analyzed microscopically and by PCR for the presence of *E. histolytica* and cultured for secondary bacterial superinfection. The catheter is irrigated daily with normal saline and kept in place until the patient is afebrile and asymptomatic with resolution of the abscess. If needle aspiration is used, several procedures may be necessary to resolve symptoms [22].

Contraindications Difficult anatomic location of the abscess; inability of the patient to tolerate procedure. Although percutaneous drainage is not generally recommended for ruptured abscesses, it has been used successfully to circumvent the need for surgery in these patients [23,24].

Complications Bleeding, secondary bacterial infection, or occlusion or movement of catheter.

Cost/cost effectiveness Procedure requires imaging and radiologic staff. A drainage procedure is likely more cost effective than aspiration owing to improved healing and lack of the need for repeated aspirations with the drainage procedure, even though equipment and catheter maintenance are more expensive.

Surgery

- With the advent of image-guided drainage, the need for surgery in the management of ALA has become very rare. However, surgery is still indicated in patients who develop life-threatening complications, especially rupture of an abscess, or if abscess drainage is required but image-guided techniques are not available or applicable [25].

Open laparotomy

Standard procedure For suspected or documented intraperitoneal rupture, open laparotomy is performed. Wider surgical exploration of the thoracic cavity is required with intrapleural or intrapericardial rupture of the abscess.

Complications As with any surgical procedure, bleeding, infection, and anesthetic-associated complications are the main adverse events.

Cost/cost effectiveness This procedure is much more expensive than interventional radiology but may be the only life-saving intervention in selected cases.

Emerging therapies

Vaccine development

- Patients with prior intestinal amebiasis have a lower incidence of ALA in historical controlled studies, suggesting that mucosal immunity develops. Indeed, IgA antiamebic antibodies have been detected in the saliva of previously infected persons. These findings suggest that humans mount an immunologic response to amebic exposure, a prerequisite for vaccine development. These antibodies have been shown to prevent amebic infections when injected into severe combined immunodeficient mice. Thus far, vaccine strategies have been directed to trophozoite antigens because trophozoites can be kept in culture and the antigens are easier to obtain. Three proteins have been used as the basis for parenteral recombinant antigen vaccines: the serine-rich *E. histolytica* protein (SREHP), the Gal/GalNAc-binding lectin, and a 29-kDa cysteine-rich *E. histolytica* antigen. They have been studied in the gerbil model of ALA using direct trophozoite injection into the liver and have resulted in protection from abscess formation.
- Another approach has been the development of an oral vaccine, because stimulation of mucosal IgA may block the initial amebic adherence to intestinal epithelial cells, thereby preventing both colonization and invasive disease. Cholera toxin or its B subunit in conjunction with SREHP (as a fusion protein) or concomitant application of a Gal/GalNAc subunit have been given orally to mice and shown to elicit a protective mucosal immunologic response. Another approach is the use of attenuated *Salmonella* species as an oral delivery system for recombinant SREHP molecules. A major challenge will be to document protection against amebiasis with either parenteral or oral vaccine approaches in human studies [7••,26].

Molecular approaches

- With the sequencing of the *E. histolytica* genome, more structural and functional information will become available about this parasite. Antisense RNA techniques are already being used to define the functions of previously uncharacterized proteins [27]. As with other diseases, this approach may also prove to be useful in the treatment of amebiasis.

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