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Review

Recent advances in the diagnosis and management of amoebiasis

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ABSTRACT

With increasing international travel and migration, tropical and infectious diseases once largely confined to specialist institutes now present more widely. Amoebiasis is a potentially dangerous example since it may closely mimic the presentation of inflammatory bowel disease. Misdiagnosis and treatment with immunosuppressants can result in fulminant amoebiasis and death. This review considers the epidemiology, pathogenesis, clinical features, diagnosis and treatment of intestinal and extraintestinal amoebiasis. It is written primarily for gastroenterologists, surgeons and acute physicians.

BACKGROUND

Entamoeba histolytica is the only species of the protozoal genus *Entamoeba* known to cause the disease known as amoebiasis.¹ An estimated 50 million people worldwide are reported to be infected every year with *E. histolytica* and while approximately 90% may remain asymptomatic,² those that do develop symptoms will most commonly suffer bloody diarrhoea (amoebic colitis) and/or liver abscess,³ causing significant morbidity and mortality globally, with 2.2 million disability-adjusted life-years (DALYs) lost and 55 000 deaths per year.^{4–8} The majority of infections occur in low-income countries (LICs), in areas of contaminated water supply and poor sanitation, however, imported cases are increasingly identified in non-endemic regions such as the UK.⁹ Furthermore, symptoms and clinical features may mimic other conditions, such as inflammatory bowel disease (IBD), and in non-endemic regions particularly, misdiagnosis may lead to significant morbidity and in the worst-case scenario, mortality.

At least seven other species of the genus *Entamoeba* have been described: *Entamoeba gingivalis* in the buccal cavity, and six others in the intestine: *Entamoeba coli*, *Entamoeba hartmanni*, *Entamoeba polecki*, *Entamoeba dispar*, *Entamoeba moshkovskii* and *Entamoeba bangladeshi*. The latter three are morphologically indistinguishable from *E. histolytica* by light microscopy.¹⁰ Brumpt first described the existence of both pathogenic and non-pathogenic species of *Entamoeba*, the most prevalent being *E. dispar*.¹ Now molecular diagnostics can distinguish between *E. histolytica* and non-pathogenic amoebae, allowing precise diagnosis and are considered alongside other contemporary approaches to diagnosis and management of amoebiasis in this review.^{11–13}

Entamoeba coli: life cycle and pathophysiology

E. histolytica is a single-celled anaerobic eukaryote with a two-phase life cycle: infective cyst and invasive trophozoite. Infection begins by ingestion of cysts in food or water contaminated by human faeces. Transmission from animals to humans is thought to be rare.¹⁴ Cysts resist host defences by various mechanisms^{4 15 16} and on reaching the terminal ileum they release four trophozoites by the process of excystation.⁴ The galactose/N-acetylgalactosamine (Gal/GalNAc) specific lectin^{17–19} allows trophozoites to adhere to the colonic epithelium and cause tissue injury by the formation of amoebapores that rupture the host cell; release of cysteine proteases and induction of an interleukin-1 and interleukin-8-mediated inflammatory response, leading to trophozoite invasion and the formation of pathognomonic flask shaped ulceration in the submucosa.^{4 15 16} Access to the portal circulation via the

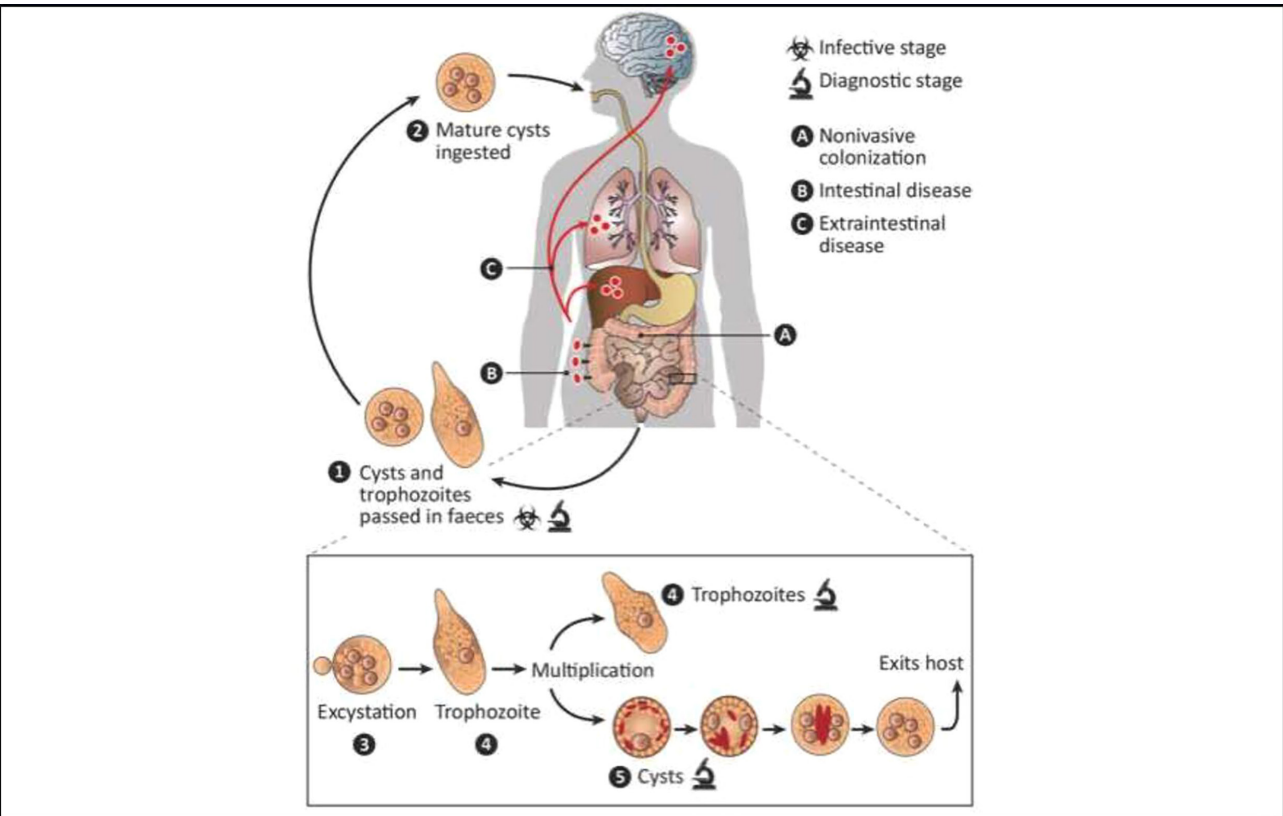


Figure 1 *Entamoeba histolytica* life cycle. Cysts and trophozoites are passed in faeces **1**. Cysts are typically found in formed stool, whereas trophozoites are typically found in diarrhoeal stool. Infection with *Entamoeba histolytica* (and *E. dispar*) occurs via ingestion of mature cysts **2** from faecally contaminated food, water, or hands. Exposure to infectious cysts and trophozoites in faecal matter during sexual contact may also occur. Excystation **3** occurs in the small intestine and trophozoites **4** are released, which migrate to the large intestine. Trophozoites may remain confined to the intestinal lumen (A): non-invasive infection) with individuals continuing to pass cysts in their stool (asymptomatic carriers). Trophozoites can invade the intestinal mucosa (B): intestinal disease), or blood vessels, reaching extraintestinal sites such as the liver, brain, and lungs (C): extraintestinal disease). Trophozoites multiply by binary fission and produce cysts **5**, and both stages are passed in the faeces **1**. Cysts can survive days to weeks in the external environment and remain infectious in the environment due to the protection conferred by their walls. Trophozoites passed in the stool are rapidly destroyed once outside the body, and if ingested would not survive exposure to the gastric environment. Adapted from source: CDC (Centers for Disease Control and Prevention, Atlanta, Georgia, USA): <https://www.cdc.gov/dpdx/amebiasis/>

gastrointestinal tract permits extraintestinal dissemination, most commonly leading to liver abscess formation. Trophozoites multiply by binary fission and those in the intestinal lumen encyst again prior to excretion, after which they can survive for up to 90 days.²⁰ It is not known why only a minority develop invasive disease but there is emerging evidence for host genetic susceptibility.^{15, 21} Figure 1, provided by CDC (Centers for Disease Control and Prevention, Atlanta, Georgia, USA), outlines the life cycle of *E. histolytica*.²²

Epidemiology and travel

The global prevalence of *E. histolytica* infection^{23, 24} is likely an overestimate due to regional endemicity, populations studied and the diagnostic capability to differentiate between non-pathogenic species.³ Nonetheless, amoebiasis is a significant global health burden, responsible for 55 000 deaths per year,⁵ predominantly in LICs, and particularly in children under 5 years⁹, where it is a major contributor to parasitic infection-related death and morbidity.^{5, 7} Tropical

and subtropical regions of Central and South America, Asia and Africa are the most widely affected and amoebiasis is most prevalent in Bangladesh, India, Brazil, Colombia, Mexico and China and accounts for up to 20%–40% of reported cases of infectious diarrhoea in some areas of Mexico, Turkey, China, Saudi Arabia, Yemen, Egypt and South Africa.^{5, 6, 23}

Globally, morbidity due to amoebiasis, measured by DALY, has decreased over the past 30 years due to improved sanitation and medication. However, there has been an interesting trend in high-income countries (HICs), such as North America and Australia, where DALY lost to amoebiasis have increased. This rise is attributed to factors like migration and travel, which have introduced the disease into regions where it was previously uncommon.⁹ In the UK, *E. histolytica* infection is notifiable by laboratories under the Health Protection Regulations (2010),²⁵ and approximately 100 infections are reported every year which likely underrepresents the true prevalence.²⁶ The GeoSentinel

Surveillance Network data indicate that *E. histolytica* is the third most commonly isolated infection globally among returning tourists who suffer from gastrointestinal disorders, responsible for between 0.3% and 10% of cases of diarrhoea experienced by visitors.²⁷

Travel to an endemic area most often precedes infection, with 50% of infections in the USA occurring in migrants from Mexico, Central and South America, India and Pakistan.^{28–30} Similarly in Spain, 46% of infections occurred in migrants and 56% had travelled to an endemic area, most often the Indian subcontinent, South or Central America and sub-Saharan Africa, with travel durations ranging from under 15 days to over 90 days, and symptoms commonly developing after, and not during, the travel period, sometimes developing months or years after exposure.³¹ Amoebic liver abscess (ALA) cases have been reported over 20 years after the last visit to an endemic area, suggesting chronic asymptomatic carriage of *E. histolytica* or possibly acquisition in a non-endemic country.³²

Risk factors for *Entamoeba histolytica* infection

Acquisition in non-endemic countries is well recognised, with an Australian study finding that approximately 8% of infected individuals had no prior travel history.³³ Other means of transmission are rare but include transmission following abdominal surgery,³⁴ and after use of contaminated colonic irrigation equipment.^{35,36} Sexual transmission can also occur. Epidemiological studies from HIC, including the USA, Japan, Taiwan, Korea and Australia have shown increased prevalence of *Entamoeba* carriage among men who have sex with men (MSM).^{37–44} The effect of co-existent HIV infection has also been studied showing higher rates of *E. histolytica* infection in HIV positive MSM, but clinical outcomes appear similar, irrespective of CD4 count.^{4,29,45–48} Importantly, carriage may occur via a sexual contact who has travelled to an endemic region, and not necessarily via travel by the symptomatic patient.

E. histolytica infection affects children and adults equally and can spread within families.⁴ Studies in adults show a male predominance, especially for ALA, up to 72%–76% of adult cases.^{4,6,29,31,47,49} The reason for this is not known; it may be due to higher alcohol consumption among males, with liver injury increasing susceptibility to abscess formation. Postmenopausal women are also at increased risk of liver abscesses; it is speculated hormonal factors in this group may be relevant.^{4,29} The Monthly Infectious Diseases Surveillance Report produced by Public Health Ontario, Canada, found a peak incidence in men aged 40–49 years and a Japanese review reported a median age of infection of 61 years.^{29,47} In the USA, amoebiasis-related deaths were found to be most prevalent for men over the age of 75 years.²⁹

Immunosuppressive medication, particularly corticosteroids, has been shown to cause increased severity

of infection.^{50–52} This is particularly concerning since amoebic colitis may mimic the appearances of IBD, both symptomatically and endoscopically. A systematic review of 24 cases of amoebic colitis reported that corticosteroid use resulted in rapid progression of disease; with increased rates of colonic perforation, amoeboma formation, rectovaginal fistula and extraintestinal dissemination, requiring more than half to undergo emergency surgery and a quarter resulting in death.⁵² Two-thirds of patients in this case series also received other immunosuppressive medication including azathioprine, methotrexate, tacrolimus and ciclosporin. Case reports also suggest that antitumour necrosis factor-alpha (anti TNF- α) treatment may lead to an increased risk of severe complications.⁵¹

Clinical features

90% of patients with *E. histolytica* infection are asymptomatic, and this is likely due to a combination of factors, such as differences in microbiome profile, proinflammatory cytokine responses and formation of antibodies to the parasite's Gal/GalNAc attachment lectin that influence the host response and clinical disease manifestations.⁶ 10% of pathogenic cyst carriers develop invasive amoebiasis within 1 year⁵³ and symptoms of infection will depend on the organ involved, of which the colon and liver are the most commonly affected. Patients with amoebic colitis typically present with a several week history of gradually worsening cramping abdominal pain, weight loss and watery, mucoid or bloody diarrhoea, making the distinction from IBD especially challenging.^{4,54} Other infectious colitides, such as *Shigella*, *Salmonella*, *Campylobacter* and diarrhoeagenic *E. coli* usually, have a shorter duration of illness. In a case series from the USA, the median duration of symptoms prediagnosis was 14 days and up to 6 months.⁴⁶ Table 1 describes the symptoms of amoebic colitis.

Physical examination may be unremarkable or may include abdominal tenderness (67%), distension (33%) and very rarely a palpable abdominal mass known as an amoeboma. This is a fibroinflammatory mass

Table 1 Symptoms of amoebic colitis²⁹

Symptoms	Prevalence
Diarrhoea – watery or bloody <small>4 28 31 32 46 54 81 86 116–122</small>	Very common >90%
Abdominal pain <small>4 28 31 46 54 75 81 116 118 121 123–125</small>	Common >60%
Fever <small>4 46 116 119 122 126</small>	Less common <40%
Weight loss <small>4 31 54 118</small>	Uncommon <25%
Rectal bleeding without diarrhoea <small>46 55 56 74 81 82 126–129</small>	Rare
Abdominal mass (amoeboma) <small>29 87</small>	Rare

representing chronic infection, typically in the caecum or ascending colon and palpated in the right iliac fossa and can resemble a phlegmon occurring in Crohn's disease.⁴⁶ Progression of dysentery to a necrotising or fulminant colitis occurs in 0.5%.^{45 55–65} These patients are typically very unwell with fever, bloody diarrhoea, vomiting and abdominal pain with rebound tenderness.^{54 66} Three-quarters of patients with fulminant amoebic colitis will develop toxic megacolon or perforation,⁴ with a mortality rate of 40%,⁵⁴ and the risk is greatest in immunocompromised, alcoholic, diabetic or pregnant patients.⁶⁶

There are over 50 case reports published in the last 10 years of atypical colonic presentations, which despite being extremely rare warrant awareness. These include amoebic appendicitis,^{67–73} peristomal ulceration,⁷⁴ large bowel obstruction,^{33 75} gallbladder infiltration,⁷⁶ perianal ulceration/fistulation,^{30 77 78} enteric fistulae,^{77 79 80} and infection residing within^{69 81–85} or appearances mimicking colorectal adenocarcinoma.^{33 86–95}

Amoebic liver abscess

ALA formation is the most common extraintestinal manifestation of amoebiasis, affecting 1% of infected individuals.⁴ On reaching the liver, *E. histolytica* generates an inflammatory reaction which causes hepatocyte necrosis, characteristically leading to the formation of a single, well-circumscribed abscess with a rim of connective tissue and containing brown so-called 'anchovy sauce' pus of dead hepatocytes, a few trophozoites and inflammatory cells.⁹⁶

There is significant variability in the onset of symptoms, which usually occur within 8–20 weeks (median 12 weeks) after travel to an endemic region,^{6 96 97} although there have been case reports of ALA development after more than 20 years,^{98–100} highlighting the importance of a obtaining a detailed travel history. Symptoms include fever and a dull or aching right upper quadrant pain, which may radiate to the epigastrium, chest or shoulder.⁹⁶ Cough and right sided pleural pain may be present when the abscess abuts the diaphragm; jaundice is uncommon and should raise suspicion of an alternative aetiology, particularly if multiple abscesses are present. Only 38% of patients report concomitant diarrhoea,⁹⁶ and others may report a resolved dysenteric syndrome, but the majority will not have concurrent amoebic colitis with their ALA.¹⁰¹ Physical examination usually demonstrates tenderness over the liver and hepatomegaly in about 50% of cases.^{4 6 29 102} A more chronic, subtle presentation has also been reported with symptoms of fever, weight loss and abdominal pain developing over months⁹⁶ and recurrence of the disease over many years, despite appropriate treatment, may rarely occur.¹⁰³

ALA was once a uniformly progressive and fatal disease, but the introduction of effective medical treatment has reduced its mortality rate to 1%–3% in uncomplicated cases.⁴ Prognostic markers for increased mortality include the presence of encephalopathy, hyperbilirubinaemia, hypoalbuminaemia and increased abscess size.¹⁰⁴ Other rare extraintestinal manifestations may occur, as described in [table 2](#).

Laboratory diagnosis

Diagnostic methods comprise faecal microscopy, microscopy of rectal scrapes, serology, histopathology and nucleic acid detection, in support of clinical history, endoscopic and radiological findings. Differentiating *E. histolytica* from the non-pathogenic *E. dispar* is essential for accurate diagnosis and initiation of appropriate treatment. See [table 3](#) for summary of diagnostic approaches.

Light microscopy of a fresh stool is widely available, inexpensive, quick, can visualise both cysts and trophozoites and is in common use in LIC. While cysts may be seen in both solid and loose stool, trophozoites will usually only be seen in a loose 'hot stool' (a stool which is examined as soon as it is produced, ideally within 20 min). Staining of a fixed faecal smear, for example, with iron haematoxylin, will enable more detailed demonstration of morphology, especially the nucleus. Microscopy may identify ingested erythrocytes within the trophozoite, confirming infection by *E. histolytica*. However, it is impossible for morphology to distinguish *E. histolytica* cysts from those of non-pathogenic species like *E. dispar* or *E. moskovskii*.¹⁰¹

Differentiation between *E. histolytica* and *E. dispar* can be made by isoenzyme analysis by starch gel electrophoresis of cultured amoebic trophozoites. However, culture is time consuming, requiring up to 10 days' incubation, and only successful 50%–70% of the time, so these techniques are not used in routine clinical practice.¹⁰¹

Antigen detection using ELISA is a simple and readily available technique, using a monoclonal antibody to *E. histolytica* Gal/GalNAc lectin in stool samples and liver abscess aspirate. There are several commercially available laboratory kits available, with reported sensitivities and specificities of over 80%.¹⁰⁵

Molecular approaches are now at the forefront in diagnosis and include DNA amplification tests, using PCR and loop-mediated isothermal amplification techniques. These are performed on stool samples or liver abscess aspirate and can accurately differentiate *E. histolytica* from non-pathogenic species. Available PCR techniques include conventional, nested, multiplex and real-time and target a range of specific genes, such as haemolysin gene (HLY6), which has up to 100% sensitivity and specificity on stool samples. Real-time multiplex stool

Table 2 Rare extraintestinal manifestations of *Entamoeba histolytica* infection

Site	Risk	Clinical features	Prognosis
Pulmonary 130–133	<ul style="list-style-type: none"> ▶ Accounts for 2%–3% of extraintestinal manifestations ▶ More common when ALA, especially if ruptured ▶ Occurs by haematogenous or lymphatic spread 	<ul style="list-style-type: none"> ▶ Cough ▶ 'Anchovy paste' sputum ▶ Haemoptysis ▶ Dyspnoea ▶ Pleuritic chest pain 	<ul style="list-style-type: none"> ▶ Radiology may show elevated right hemidiaphragm and consolidation. ▶ Mortality of >16% ▶ Most respond rapidly to treatment as per ALA
Pericardial 134 135	<ul style="list-style-type: none"> ▶ Very rare ▶ More common when ALA in left hepatic lobe that ruptures 	<ul style="list-style-type: none"> ▶ Chest pain ▶ Pericardial effusion ▶ Acute/constrictive pericarditis ▶ Cardiac tamponade ▶ Congestive cardiac failure 	<ul style="list-style-type: none"> ▶ Left sided ALA drainage is recommended ▶ Pericardiocentesis is recommended
Neurological 136–138	<ul style="list-style-type: none"> ▶ Very rare ▶ Always concomitant ALA ▶ Brain abscesses may be single or multiple 	<ul style="list-style-type: none"> ▶ Brain abscess ▶ Meningoencephalitis ▶ Headache ▶ Vomiting ▶ Impaired mental status ▶ Focal neurological signs 	<ul style="list-style-type: none"> ▶ Fatal if not diagnosed early ▶ CT findings non-specific ▶ Longer treatment durations required, up to 8 weeks ▶ Surgical evacuation may be required
Cutaneous 30 139	<ul style="list-style-type: none"> ▶ Very rare ▶ May occur in isolation or with other organ ▶ Risk from poor perianal hygiene and sexual transmission 	<ul style="list-style-type: none"> ▶ Painful perianal ulceration ▶ Single or multiple erythematous ulcers with well-demarcated elevated edges 	<ul style="list-style-type: none"> ▶ Trophozoites may be isolated from ulcer exudate or by scraping ulcer edge ▶ Extensive spread may require reconstructive surgery
Genital 37 42 43 140–143	<ul style="list-style-type: none"> ▶ Very rare ▶ risk factor anal sex 	<ul style="list-style-type: none"> ▶ Penile, vaginal and cervical ulcers ▶ Foul smelling vaginal discharge 	<ul style="list-style-type: none"> ▶ Treatment as per other forms ▶ Trace and treat sexual partner

ALA, amoebic liver abscess.

PCR is now commonplace in HIC and although costly, has the major advantage of being able to detect a wide panel of intestinal pathogens. In the UK, stool PCR enteric panels do not always include *E. histolytica*, and therefore, may require a specific request to use a dedicated *E. histolytica* stool PCR assay, which is not widely available in all labs and may need samples to be forwarded to regional laboratories.

Point-of-care stool testing potentially allows for rapid diagnosis and does not involve expensive laboratory equipment, so may be an option in LIC. There is a range of commercially available kits available, however, they have lower sensitivity and specificity and cannot reliably differentiate *Entamoeba* species.

Antibody detection tests measure IgG antibody levels in response to trophozoite antigen and may yield positive results within 7–14 days of symptom onset for both intestinal disease and liver abscess. Various methods are employed, of which ELISA is most commonly available with sensitivity and specificity of over 95% for liver abscess and is useful in non-endemic regions where prior exposure is unlikely. Where available, the amoebic fluorescent antibody test (IFAT) with the cellulose acetate precipitin test as a confirmatory assay, is an alternative. Importantly for gastroenterology practice, sensitivity of antibody detection is only around

60% in invasive intestinal amoebiasis. Amoebic serology can remain positive for several years after infection and thus is not suitable for use in endemic regions. Microscopy of liver abscess pus is unhelpful, showing cellular debris, and it is not a sensitive method for diagnosis since trophozoites are seen in less than 20% of cases. Molecular techniques such as PCR can also be performed on aspirated pus.

It is very important to rule out *E. histolytica* infection in all patients with a new or suspected diagnosis of IBD prior to starting immunosuppressive therapies. Where immunosuppression for IBD has to commence urgently and cannot be delayed, testing of a stool by amoebic PCR should be prioritised and treatment reviewed in the light of the result. The most reliable diagnostic test to rule out active infection is to test a single stool for *E. histolytica* using PCR, either as a standalone test or in a pan-enteric panel. Furthermore, a careful travel history should be obtained since development of disease may post-date initial infection by years. Additional confirmation of the diagnosis can be done by examining the histology of intestinal biopsies (see section on Histopathology) in cases where PCR is not available.

Where available, a full exposure history (travel, sexual contact, clinical reason to suspect amoebic

Table 3 Laboratory testing for *Entamoeba histolytica*

	Specimen	Details	Sensitivity	Specificity	Pros	Cons
Light microscopy	Stool	Can visualise cysts but cannot differentiate <i>E. histolytica</i> from non-pathogenic cysts. May visualise trophozoites in 'hot stool' (stool examined as soon as it is produced)	<60% ⁶	95% ¹⁴⁴	Cheap Widely available Can screen for other parasites	Low sensitivity and specificity Stool tests cannot diagnose extraintestinal infection
Antigen testing ELISA	Stool or liver abscess aspirate	Test for <i>E. histolytica</i> -specific antigens	Up to 88% ⁶	>80% ⁶	Can differentiate <i>Entamoeba</i> species Widely available	Need fresh (not preserved) stool Reduced sensitivity and specificity once therapy started and for carriers
PCR*	Stool and liver abscess aspirate	Test for <i>E. histolytica</i> -specific genes Gold standard for intestinal amoebiasis	92%–100% ⁶	89%–100% ⁶	Can differentiate <i>Entamoeba</i> species	Expensive Requires laboratory skill <i>E. histolytica</i> may not feature in routinely tested pathogen panels
Serology/antibody testing	Serum	Detects IgG to <i>E. histolytica</i> -specific antigen	65%–92% ⁶	>90% ⁶	Useful for both intestinal and extraintestinal infection	Lower sensitivity for intestinal amoebiasis (~60%) than ALA (~95%). Suitable for use in non-endemic regions False positives in endemic countries Positive within 7–14 days of symptoms Can remain positive for years after resolution of infection
Point-of-care antigen detection	Stool	Monoclonal antibody based	28%–100% ¹⁰¹	80%–100% ¹⁰¹	Cheap Quick	Cannot differentiate <i>Entamoeba</i> species Low sensitivity
Histopathology	Tissue	Light microscopy of formalin-fixed paraffin wax embedded histology specimens, such as colonic biopsies. Trophozoites visible on H&E staining, highlighted by staining with Periodic Acid Schiff	Insufficient data	Operator-dependent	Cheap Routine practice—no requirement for pretest suspicion Can be used on tissue from any site, both biopsies and surgical resections can be reported urgently within 24 hours	Tissue reaction pattern is not specific and can mimic Crohn's disease. Trophozoites may be missed or misdiagnosed and identification is operator-dependent

*UK Health Security Agency recommend PCR as the method of choice for diagnosis of *E. histolytica* in symptomatic and asymptomatic patients.^{2,6} ALA, amoebic liver abscess.

Table 4 Endoscopic features of amoebic colitis

Feature	Site	Prevalence
Erythema/inflammation 28 32 46 47 86 106 107 118 120 122 124 129 145	Patchy and variable distribution—may be pan-colonic with predominance in caecum and ascending colon	Common (>50%)
Exudate 32 106 107 146		Common (>25%)
Ulceration 32 46 47 74 85–87 106 107 117 119–124 126 145–152		Very common (>75%)
Nodule ('bump') 32 47 107 118 145		Rare (5%)
Mass (amoeboma) 85–87 107 115 125	Most commonly caecum	Very rare (<5%)
Active bleeding 126	At site of inflammation/ulceration	Very rare (<1%)
Stricture 75 149	Very rare—case reports of transverse colon	Stricture (<1%)
Coexistent adenocarcinoma 82 85 129	Very rare	Very rare (<5%)

colitis or new diagnosis of IBD) should be provided with the faecal sample, which may otherwise risk rejection by the laboratory, and contact with the microbiology team is recommended to arrange a 'hot stool' examination if there is a strong index of suspicion.

Colonoscopy

Although colonoscopy is not mandated for the diagnosis of amoebic colitis, patients with gastrointestinal symptoms, particularly if they are severe or chronic, are often evaluated endoscopically. Both symptoms and endoscopic appearances of amoebic colitis can mimic those seen in IBD in other forms of infectious colitis including intestinal tuberculosis.^{4 21 47 106} While endoscopic features may be indistinguishable between these conditions; characteristic features of amoebic colitis have been described.⁴⁷ Amoebic colitis often causes patchy inflammation with or without pale exudate and ulceration, with a predominance in the caecum and ascending colon since this is likely the site of excystation and trophozoite release, and next most commonly in the rectum, likely due to stasis of stool.^{47 106 107} Ulcers can range in size and character, from tiny erosions to larger ulcers (>2 cm) and are most often multiple and discrete. Surrounding mucosa can appear normal or inflamed. A mucosal 'bump' sign has been proposed as a pathognomonic endoscopic feature, consisting of a <1 cm inflammatory nodule infiltrated by trophozoites.⁴⁷ Table 4 and figure 2 describe the endoscopic features and appearances of amoebic colitis.

There are case reports describing the simultaneous diagnosis of colorectal adenocarcinoma with *E.*

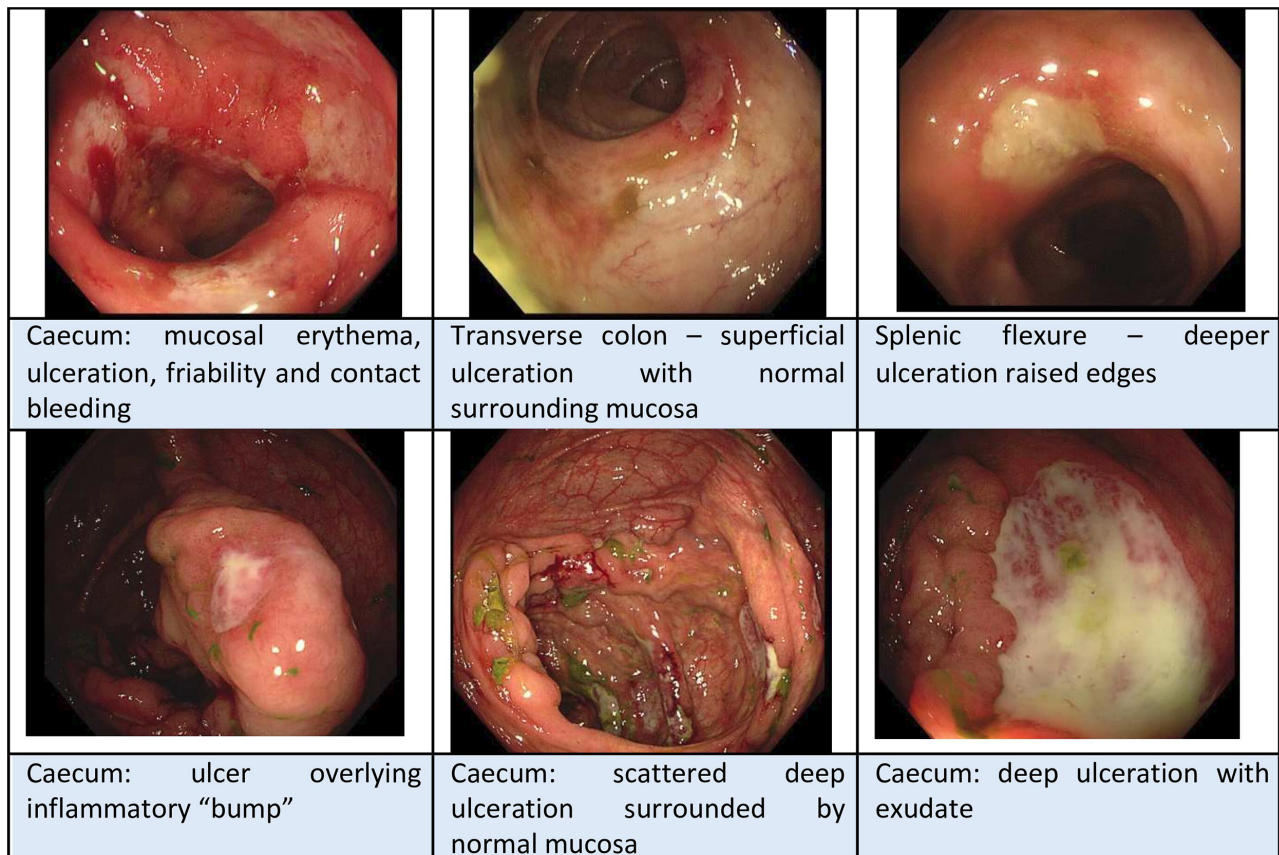


Figure 2 Endoscopic appearances of amoebic colitis.

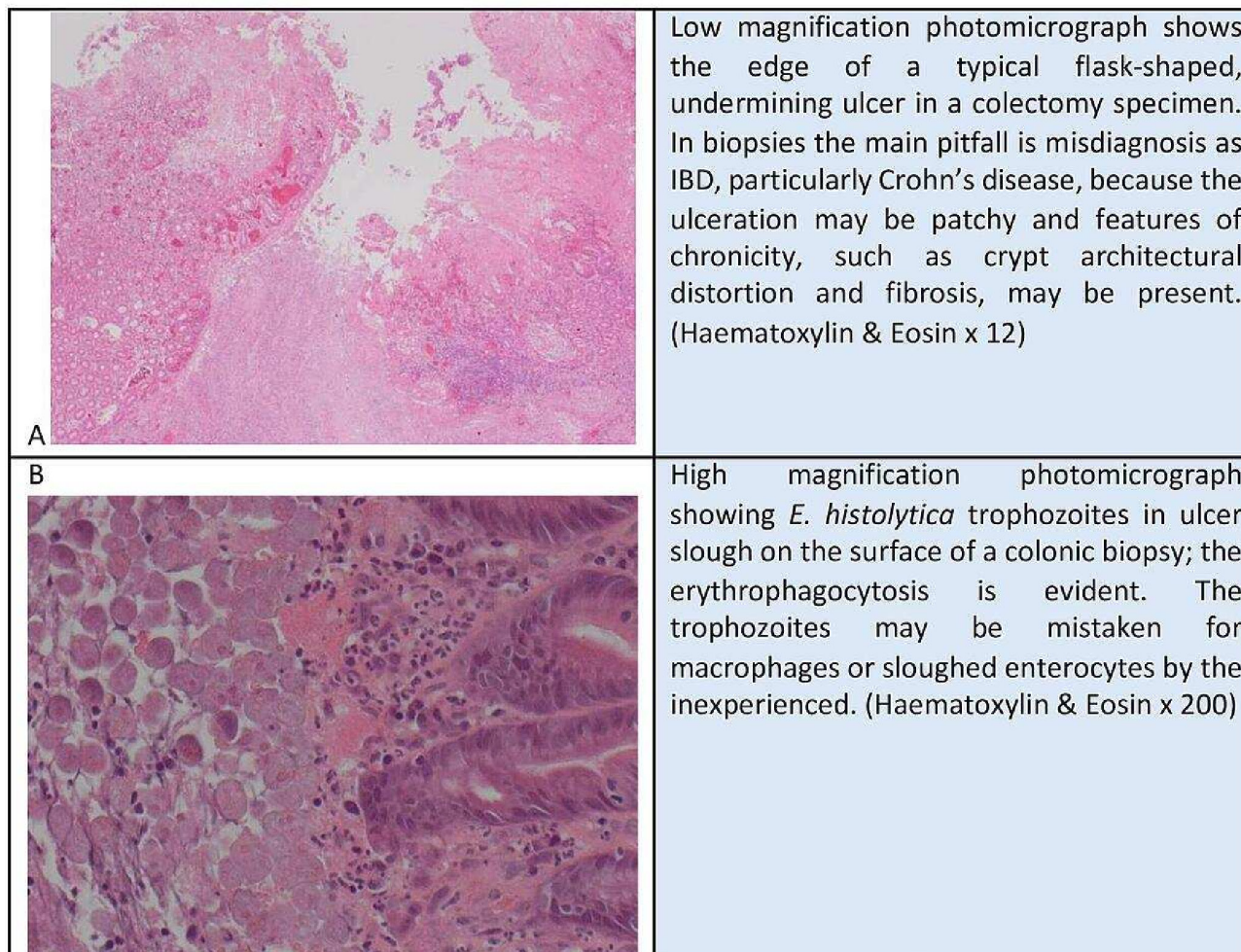


Figure 3 Histopathological findings in amoebic colitis. We thank Guys and St Thomas' NHS Foundation Trust Histopathology Department for allowing access to histopathology images. NHS, National Health Service.

histolytica infection on mucosal biopsy.⁸⁵ However, correlation does not necessarily imply causation.

Histopathology

The histopathological findings in amoebic colitis are described in [figure 3](#).

Imaging

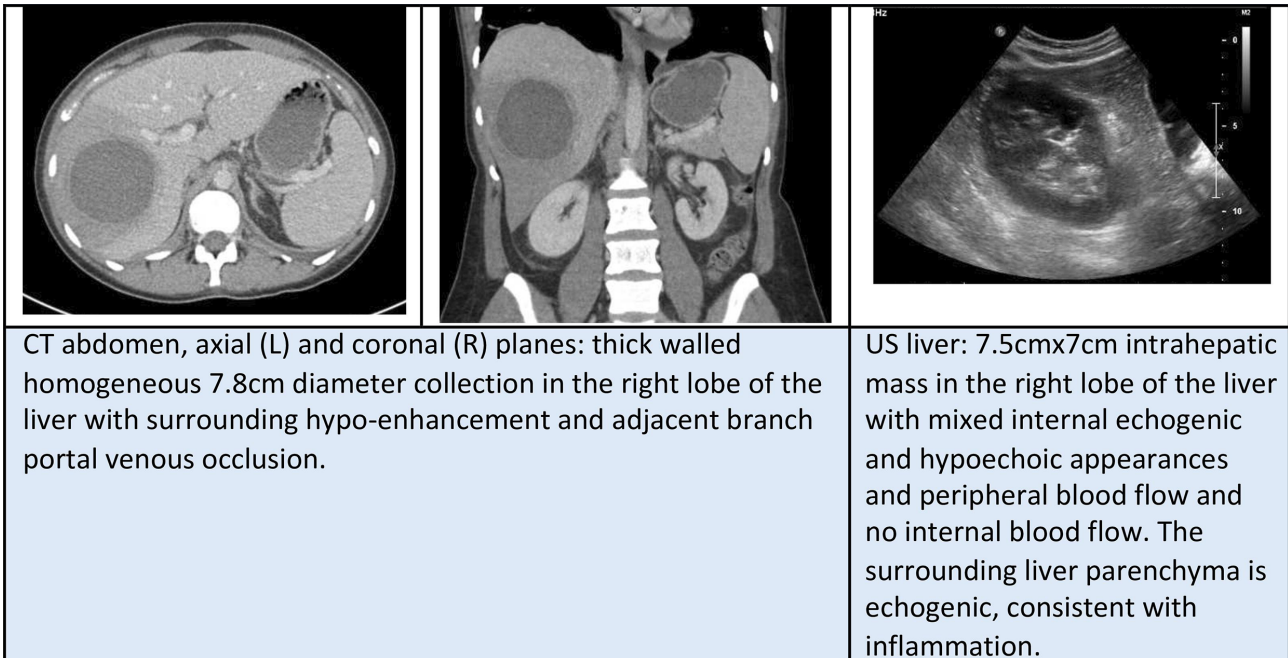
Imaging may be performed alongside laboratory tests to support diagnosis. Plain abdominal radiography may show non-specific features of colitis, with colonic wall thickening, gaseous distension and loss of haustral folds.²⁸ CT may help identify features of amoebic colitis, including deep ulceration, patchy distribution of colitis and omental wrapping.²⁸ CT alone should not be made to diagnose amoebic colitis since features may be indistinguishable from IBD.

CT, MRI and ultrasonography are good modalities to diagnose ALA. It is most commonly unilocular compared with pyogenic abscess, which is most commonly multilocular, but appearances may be indistinguishable. ALA will appear on US as a

cystic intrahepatic hypoechoic lesion with thick walls, often in the right hepatic lobe near the capsule, and by CT there will be a non-enhancing centre with an inflammatory ring following administration of contrast.^{6 108} The right hemidiaphragm may be elevated.¹⁰⁹ [Figure 4](#) illustrates the typical radiological features of ALA.

Treatment

All patients with *E. histolytica* infection should be treated, whether or not they have symptoms. The goal of therapy is to eliminate invading trophozoites and eradicate intestinal carriage. Treatment consists of two agents—a systemically absorbed tissue amoebicide,¹¹⁰ and a luminal amoebicide, to eliminate cysts from the intestinal lumen. Tissue amoebicidal agents are nitroimidazole antibiotics, such as metronidazole and tinidazole, with a Cochrane review finding the latter more effective (metronidazole 5% failure rate vs tinidazole 1% failure rate) with fewer adverse events,²⁴ however, tinidazole is no longer available in the UK.¹¹¹ Alcohol



CT abdomen, axial (L) and coronal (R) planes: thick walled homogeneous 7.8cm diameter collection in the right lobe of the liver with surrounding hypo-enhancement and adjacent branch portal venous occlusion.

US liver: 7.5cmx7cm intrahepatic mass in the right lobe of the liver with mixed internal echogenic and hypoechoic appearances and peripheral blood flow and no internal blood flow. The surrounding liver parenchyma is echogenic, consistent with inflammation.

Figure 4 Radiological features of amoebic liver abscess in a patient with right upper quadrant pain and weight loss.

ingestion should be avoided during and for 4 days after metronidazole or tinidazole therapy due to unpleasant disulfiram-like side effects. Luminal amoebicides include paromomycin, diloxanide furoate (no longer available in the UK), iodoquinol and nitazoxanide. Paromomycin, an aminoglycoside which works by disrupting RNA translation, is the agent used in the UK.^{112 113} Combination therapy has been shown to prevent disease recurrence, so while asymptomatic amoebic cyst passage is treated with a luminal amoebicide, treatment of symptomatic amoebiasis requires a tissue amoebicide followed by a luminal amoebicide.²⁴

Previous national guidelines recommended giving tinidazole or metronidazole, followed by paromomycin.¹¹³ Since 2021, tinidazole has not been available in the UK and therefore metronidazole is recommended.¹¹¹ Longer duration of treatment is recommended for extraintestinal amoebiasis, including liver abscess (see table 5).^{6 96} ALA does not routinely require percutaneous drainage, but it may be considered if clinical response is not seen after three or 4 days medical treatment, or when the abscess is >10 cm (which carries an increased risk of abscess rupture) or if the abscess is in the left lobe, where rupture

Table 5 Treatment for *Entamoeba histolytica* infection

Amoebic colitis ¹¹³	<ul style="list-style-type: none"> ▶ Metronidazole 800 mg three times per day PO for 5 days OR Tinidazole 2 g once daily for 3 days (no longer available in UK) followed by a luminal amoebicide ▶ Paromomycin 25–35 mg/kg/day in three divided doses PO for 7 days OR ▶ Diloxanide furoate for 10 days (no longer available in UK)
Amoebic liver abscess	<ul style="list-style-type: none"> ▶ Metronidazole 800 mg three times a day orally for 5–10 days OR Tinidazole 2 g once daily for 5 days (no longer available in UK) followed by a luminal amoebicide ▶ Paromomycin 25–35 mg/kg/day in three divided doses orally for 7 days OR Diloxanide furoate for 10 days (no longer available in UK) <p>ONLY consider drainage of ALA, if:</p> <ul style="list-style-type: none"> ▶ Imminent rupture ▶ No clinical response after three or 4 days of medical treatment ▶ Abscess diameter >10 cm ▶ ALA in left lobe of liver
Extraintestinal/extrahepatic amoebiasis	▶ Consult with infectious diseases team
ALA, amoebic liver abscess.	

may involve the pericardium.⁶ The abscess may take many months to resolve fully on imaging, but this does not require extended periods of drug therapy.⁶ Table 5 summarises the treatment for *E. histolytica* infection.

In patients with IBD for which there is a high index of suspicion for amoebiasis, it is reasonable to commence metronidazole therapy once a stool sample has been collected and confirmed to be sent for amoebic stool PCR testing.

Clinical care requires universal enteric precautions which can be discontinued 48 hours after resolution of diarrhoea.²⁶ Both symptomatic and asymptomatic household, cotraveller and sexual contacts (any sexual contact of the case following the suspected time of initial infection (especially in MSM) should undergo stool PCR testing and treatment if positive.²⁶ Amoebic clearance should be checked with a stool PCR test at least 1 week following completion of treatment with both tissue and luminal amoebicides.^{26 114} This is done to demonstrate treatment success, although symptomatic relapses after an initial course of treatment are very rare. The literature suggests that asymptomatic carriage persists beyond 15 months after initial identification in untreated individuals.²

More than 90% of the patients with amoebiasis respond to nitroimidazoles, but parasite persistence is seen in 40%–60% of patients after nitroimidazole treatment (as they are tissue, not luminal, amoebicides). Luminal amoebicides like paromomycin have up to 85% cure rate in asymptomatic carriers.² A Cochrane review showed reduction in parasitological failure by a third after completion of combination treatment over metronidazole alone (RR 0.36).²⁴

Additional, general supportive measures may be required, depending on the patient's clinical needs and may include intravenous fluids, electrolyte replacement and nutritional supplementation.⁶ Prevention remains paramount, with personal hygienic measures, avoidance of contaminated food and water supplies and education regarding sexual transmission.¹¹¹

There are currently no licensed vaccines for amoebiasis but the Gal/GalNAc lectin has been the subject of research as a potential antigenic target.^{113 115} Several novel drug targets involving different amoebic cellular processes have been suggested but these drugs are not yet in routine practice.¹¹⁰ There have been shown to be alterations in the microbiome that may trigger amoebae to switch from commensal bystander to invasive pathogen, raising a theoretical role for probiotics as preventative or adjunctive treatment, but further research in this area is required.¹¹⁵

CONCLUSION

Misdiagnosis of intestinal amoebiasis as IBD in non-endemic regions can easily occur, be that clinically, endoscopically and histologically, leading to potential inadvertent treatment with steroids or immunosuppressants. This can lead to life-threatening complications and so gastroenterologists, infectious diseases physicians and surgeons in particular need to have an awareness of it as a potential differential diagnosis. Establishing a detailed life-long travel history is essential, with the diagnosis of intestinal amoebiasis best achieved using stool *E. histolytica* PCR which must be requested specifically. Clinicians should consider routine stool PCR testing for *E. histolytica* in all new IBD cases, especially prior to commencing immunosuppression. Testing should be considered particularly in patients with established IBD who have travelled to endemic areas, particularly in the context of a worsening acute colitis. Empirical treatment for amoebiasis should be offered once samples are sent if there is a high index of suspicion. Routine colonic histopathology may be diagnostic if trophozoites are present, but sampling error or failure to recognise trophozoites may contribute to low sensitivity overall. If a patient treated for IBD with immunosuppressants fails to improve or deteriorate, it would be appropriate to request review of the histology, to search particularly for trophozoites, if necessary, by a specialist infectious disease histopathologist. ALA will appear on ultrasound as a cystic intrahepatic hypoechoic lesion with thick walls and on CT there will be a non-enhancing centre with an inflammatory ring following administration of contrast. This should be suspected especially if patients have right upper quadrant pain, fever and deranged liver function tests. Treatment of intestinal amoebiasis should comprise both tissue and luminal amoebicides to avert disease recurrence.

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Key points

- ⇒ Clinical, endoscopic and histological misdiagnosis of intestinal amoebiasis as inflammatory bowel disease (IBD) in non-endemic regions can easily occur.
- ⇒ Inadvertent treatment with steroids or immunosuppressants can lead to life-threatening complications.
- ⇒ Diagnosis of intestinal amoebiasis is best achieved using stool *Entamoeba histolytica* PCR and needs to be requested specifically, giving full travel history.
- ⇒ Recommend stool PCR testing for *E. histolytica* in all new IBD cases regardless of previous travel history to an endemic area, especially prior to commencing immunosuppression. Testing should be performed in patients with established IBD who have had travel to endemic areas particularly with a worsening colitis. Empirical treatment for amoebiasis should be offered once samples sent if there is a high index of suspicion.
- ⇒ Routine colonic histopathology may be diagnostic if trophozoites are present, but sampling error or failure to recognise trophozoites may contribute to low sensitivity.
- ⇒ Treatment should comprise both tissue and luminal amoebicides to avert disease recurrence.

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