CHAPTER 32

Amebiasis, Giardiasis, and Other Intestinal Protozoan Infections

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Entamoeba histolytica and *Giardia lamblia* are the most common protozoan pathogens of the human intestinal tract worldwide. In the United States, infections caused by *Giardia* and *Cryptosporidium* are most prevalent. *Giardia* and *E. histolytica* infection rates are significantly higher in developing countries. Despite this, neither protozoan is a common cause of disease in travelers. *Giardia* accounts for 1-4% of traveler's diarrhea, and *E. histolytica* for <1%. However, the prolonged illness and potential for serious complications in both diseases make it important to expeditiously diagnose and treat.

ENTAMOEBA HISTOLYTICA

Pathogenesis

E. histolytica is the only commonly recognized human intestinal pathogen in the subphylum Sarcodina, whose members are distinguished by the use of pseudopods for locomotion. *E. histolytica* exists in two forms: the cyst (infective form) or the ameboid trophozoite (invasive form). The cysts are round, 10-15 μm in size, and have four nuclei and a refractile wall. The trophozoites are larger (10 and 50 μm) and motile with a pleomorphic shape. Infection is usually acquired by ingestion of cysts present in fecally contaminated food or water or by direct person-to-person contact. Transmission can also occur by sexual exposure (either through oral-anal-genital contact or by direct inoculation of traumatized tissue) or from contaminated enema equipment.

The trophozoites are very labile and easily destroyed by gastric acid. Unlike the trophozoites, the cysts can survive for weeks in moist surroundings and are resistant to gastric acid and the low concentrations of chlorine commonly used in commercial water purification.

Intestinal Amebiasis

The initial site of amebic infection is the cecum and colon after *E. histolytica* excysts in the small bowel. Attachment of trophozoites to the colonic mucosa is followed by mucosal invasion, leading to both superficial and deep colonic ulcerations. Host cell lysis and proteolysis of the extracellular matrix by the amebae results in ulceration and tissue invasion. Virulent strains of *E. histolytica* possess lectins and adhesins for adherence, cytotoxins, proteolytic enzymes, and transmembrane ion channel proteins (porins). Strains from different geographic areas vary widely in their relative virulence. Certain isoenzyme patterns appear to serve as markers for strain virulence. A rapid assay for virulence would have great clinical significance, as clinically avirulent strains such as *E. dispar*, *E. moshkovskii*, or *E. bangladeshi*, while morphologically indistinguishable from virulent strains, do not require treatment. For instance, currently approximately 12% of the world population is estimated to have both *E. histolytica* and *E. dispar*; however, only 1% are estimated to have pathogenic *E. histolytica*. Presence of other bacteria in the colon, extremes of age, immunocompromised state, pregnancy, and malnutrition influence the virulence of the amebae.

Extraintestinal Amebiasis

Once local invasion is established in the colon, the amebae can gain access to the portal venous system to establish metastatic sites of infection. Symptomatic invasive amebiasis occurs in approximately 10% of patients with asymptomatic *E. histolytica* fecal carriage state. The most common location is the liver, but amebic abscesses of the lungs, brain, and, rarely, other organs do occur. These metastatic abscesses contain necrotic debris but few leukocytes or trophozoites. Trophozoites are most easily identified in the peripheral tissue. In addition to hematogenous dissemination, local spread of infection from the colon can result in cutaneous amebiasis or in paracolonic inflammatory masses referred to as amebomas.

Immunity

Infected individuals develop both humoral and cell-mediated immune responses to *E. histolytica*. The specific immunoglobulin response is helpful in diagnosis in non-endemic areas (see later discussions), but its importance in vivo is unknown. Cell-mediated responses are important in controlling the disease, particularly in invasive amebiasis, but only partial protection from reinfection is achieved after recovery from the primary episode. Host response determines the severity and relapses of disease. Acquired resistance to infection is thought to be linked to intestinal IgA against the carbohydrate-recognition domain of the *E. histolytica* galactose *N*-acetyl-d-galactosamine lectin. Host HLA class II-restricted immune responses also play a role in protection against *E. histolytica* infection. Recovery from amebiasis does not confer immunity to reinfection.

Epidemiology

Humans and some nonhuman primates are the only natural reservoirs. Therefore, the persistence of endemic disease in a population is dependent on crowding and poor standards of hygiene for water purification, food preparation, and waste disposal.

Amebiasis is a significant health problem in the developing world. Within the United States, risk groups include institutionalized individuals, promiscuous men who have sex with men (sexual transmission in which case trophozoites may be infective as well), recent immigrants, and travelers to high prevalence countries.

Travel to any developing country poses a risk of acquiring amebiasis, but travel to Mexico or to remote rural areas of Asia (e.g., trekking in Nepal) appears to bear the highest risk. The risk of amebiasis among travelers was 0.3% in one study.

Clinical Features

Intestinal Amebiasis

E. histolytica infection is most often asymptomatic. Asymptomatic cyst excretion can be self-limited or persist for years. Symptoms, when present, range from mild diarrhea to severe dysentery. Typically, there is gradual onset of colicky lower abdominal pain and diarrhea. Mucus, tenesmus, fever, and abdominal pain usually accompany diarrhea. Stools are often bloody and may be associated with signs of hypovolemia in severe cases. Spontaneous resolution after 1-4 weeks, sometimes with persistent asymptomatic cyst excretion, is the usual outcome. Persistent disease is not uncommon. Chronic disease may manifest cyclical relapses and remissions mimicking inflammatory bowel disease. Chronic amebic colitis results in anorexia, weight loss, and intermittent abdominal pain.

Several serious complications can develop in about 5% of patients with invasive intestinal amebiasis. Intra-abdominal complications include peritonitis secondary to perforation of a colonic abscess, intestinal hemorrhage from erosion of an abscess into an artery, or toxic megacolon from fulminant amebic colitis. The prognosis is poor in these situations, since the colon is often diffusely necrotic, rendering surgery difficult. Complications are more common in infants, pregnant women, and patients with alcohol abuse or diabetes or receiving corticosteroids. Amebomas are inflammatory mass lesions most common in the cecum, ascending colon, and descending colon; usually solitary, they can be radiologically indistinguishable from colonic neoplasms or intestinal tuberculosis. Involvement of the cecum can result in amebic appendicitis.

Extraintestinal Amebiasis

The liver is the most common site of extraintestinal amebic disease. Amebic liver abscesses (ALA) can present with the dysenteric phase of the illness or several years later. ALA are predominantly solitary (83%) and located in the right lobe (75%) of the liver. Right lobe predilection results from streaming of portal vein blood flow. ALA develops in 3-9% of cases of intestinal amebiasis. However, only 14% of patients with ALA will have active intestinal disease at the time of diagnosis, and majority will have neither active intestinal disease nor a history of dysentery. Incidence peaks in the 20- to 50-year-old age group with a male/female case ratio of 3:1.

The duration of symptoms before presentation is <2 weeks in the majority of cases. Virtually all patients present with right upper quadrant pain. Right lower chest pain, which may be pleuritic, is present in 25%. Other symptoms include upper abdominal swelling, weight loss, malaise, anorexia, pruritus, and cough (10-50%). Diaphragmatic irritation can result in referred pain to the right shoulder. High fever with chills and profuse night sweats may be present. Examination reveals tender hepatomegaly, sometimes with point tenderness. About half of the patients may have abnormal right lung auscultatory findings (rales or dullness). Jaundice is rare.

Primary amebic abscesses of the lung or brain are indistinguishable from pyogenic abscesses. Finally, extraintestinal disease can also result from rupture of a hepatic amebic abscess into the peritoneum, pleural cavity, or pericardium.

Diagnosis

Intestinal Amebiasis

Examination of the stool

Traditionally, intestinal amebiasis was diagnosed by the identification of trophozoites or cysts in fresh feces. However, owing to the more prevalent nonpathogenic, morphologically identical, but genetically distinct *E. dispar* in stool, *E. histolytica* is diagnosed using *E. histolytica*-specific tests. *E. histolytica* trophozoites survive only 2-5 hours at 37°C and 6-16 hours at 25°C, so prompt examination of specimens or refrigeration (survival 48-96 hours) is essential. In active infections, both cysts and trophozoites can be found on microscopic examination of the stool. The finding of ingested red blood cells (hematophagocytosis) is diagnostic of *E. histolytica* infection. More often, however, the number of organisms is small and excretion is sporadic, resulting in a yield of only 33-50% from the examination of a single specimen. Despite invasive disease, fecal leukocytes are not found because of the lytic activity of the amebae. Fecal blood (microscopic or gross) is seen in approximately 70% of patients.

Differentiation from nonpathogenic ameba species or fecal leukocytes can be difficult, and both false-positive and false-negative laboratory errors are common. Therefore, in addition to clinical and epidemiologic correlation, a specific *E. histolytica* test is advised for definitive diagnosis. Specific tests are available to detect and differentiate *E. histolytica* and *E. dispar*. Stool *E. histolytica*-specific antigen has a sensitivity of 87% and specificity of >90% compared with culture. Stool in vitro culture methods are not selective for *E. histolytica*. Isoenzyme analysis is specific but takes about 1-2 weeks. Molecular methods such as polymerase chain reaction (PCR) are also available and effective to identify *E. histolytica*.

Colonoscopy

Colonoscopy is preferred over sigmoidoscopy because amebic colitis lesions can be present in the ascending colon or cecum and be missed on a sigmoidoscopy. Endoscopy may be normal or reveal only nonspecific edema and inflammation of the mucosa. Characteristic ulcers are present only 25% of the time, but scrapings or brushings from the rectal mucosa or the edge of an ulcer frequently are positive for trophozoites (samples must be obtained with a glass pipette or metal implements, since the amebae adhere to cotton fibers). Endoscopic brushings or biopsy from the edge of the ulcer are more sensitive for the diagnosis of amebic colitis than fecal examination.

Radiographic studies

No pathognomonic pattern is present on radiographic studies. Barium studies in particular should be avoided, since barium interferes with stool examination for protozoa.

Blood tests

Several serologic tests are available for the diagnosis of amebiasis. Antibody detection is most useful in patients with extraintestinal disease (i.e., ALA). Of these the most widely used is the enzyme immunoassay (EIA), which has replaced indirect hemagglutination. The EIA detects antibody specific for *E. histolytica* in approximately 95% of patients with extraintestinal amebiasis, 70% of patients with active intestinal infection, and 10% of asymptomatic cyst carriers. Anti-ameba antibodies can remain elevated for years after the initial infection, hence should be evaluated carefully in persons from endemic countries. Serologic tests are particularly useful in excluding amebiasis as the etiology of chronic inflammatory bowel disease before initiating steroid therapy, especially in persons from non-endemic countries.

Extraintestinal Amebiasis (Especially Liver Abscesses)

Blood tests

Most patients with ALA will have a moderate degree of leukocytosis with neutrophilia. Transaminases may be slightly elevated in acute ALA with normal alkaline phosphatase. However, these are elevated in only 20% of patients with chronic ALA.

Radiographic studies

Chest radiography is abnormal in the majority of cases. Elevation of the right hemidiaphragm and right lung base atelectasis are the most common abnormalities. Pleural fluid may be present, despite absence of frank rupture of the abscess into the pleural space. Ultrasonography and computed tomography are equally sensitive in detection of ALA.

Special diagnostic considerations

None of the aforementioned tests will reliably differentiate ALA from pyogenic liver abscesses or from neoplastic masses with central necrosis. Serologic tests for anti-amebic antibodies are positive in 91-98% of patients with ALA, making these tests highly useful in persons from non-endemic areas. In one study of detection of circulating *E. histolytica* Gal/GalNAc lectin in the serum, the TechLab *E. histolytica* II test (TechLab, Blacksburg, VA) had a sensitivity of 96% to diagnose ALA and was helpful in follow-up care after treatment. In endemic areas, a therapeutic trial of metronidazole or a diagnostic aspiration of the lesion may be necessary to establish the diagnosis. Fluid from an amebic abscess is characteristically thin, brownish, and odorless, but amebae may be difficult to detect without a biopsy of the edge of the abscess. In biopsy specimens, detection of the trophozoites is diagnostic. PCR may be more rapid and sensitive where available. If possible, aspiration or surgery should be avoided because of the risk of complications, including secondary infection of the abscess cavity, and because of the excellent therapeutic outcome obtained with chemotherapy alone.

Diagnosis of amebic abscesses of other organs or of amebic peritonitis generally requires serologic evidence of amebiasis and consistent findings in aspirated fluid from the abscess or peritoneum.

Treatment

Treatment regimens for the various *E. histolytica* clinical syndromes are listed in **Table 32.1**. Common side effects associated with these antimicrobial agents are shown in **Table 32.2**. All patients with active intestinal or extraintestinal infection, especially those at high risk for severe complications (immunocompromised or individuals at either extreme of age), should be treated with a tissue agent followed by a luminal agent. Management of an asymptomatic individual who passes cysts is more controversial. Differentiating between *E. dispar* and *E. histolytica* helps clarify management options, as nonpathogenic *E. dispar* does not need treatment. Treatment is recommended for high-risk cyst carriers with either *E. histolytica*/*E. dispar* complex (where differentiation is not possible) or *E. histolytica* alone in the stool. Asymptomatic *E. histolytica* colonization can be treated with a luminal agent alone. In areas

TABLE 32.1 Treatment Regimens for *Entamoeba histolytica* Infections

Drug	Adult Dose	Pediatric Dose	Duration
Asymptomatic cyst passers			
Iodoquinol	650 mg t.i.d.	30-40 mg/kg per day in three doses	20 days
Diloxanide furoate	500 mg t.i.d.	20 mg/kg per day in three doses	10 days
Paromomycin	25-30 mg/kg per day in three doses. Can be used in pregnant women	25-30 mg/kg per day in three doses	7 days
Invasive colitis			
Metronidazole[a]	750 mg t.i.d.	35-50 mg/kg per day in three doses	10 days
	2.4 g q.d.		2-3 days
Tinidazole[a]	2 g orally q.d.	Children >3 years of age: 50 mg/kg per day[b] (up to 2 g a day)	3 days
Dehydroemetine[a]	1-1.5 mg/kg per day i.m. in two doses		5 days
Amebic liver abscess			
Metronidazole[a]	750 mg t.i.d.	35-50 mg/kg per day in three doses	10 days
Tinidazole[a]	2 g orally q.d.	Children >3 years of age: 50 mg/kg per day[b] (up to 2 g a day)	3-5 days
Dehydroemetine[a]	1-1.5 mg/kg per day i.m.	1-1.5 mg/kg per day i.m. in two doses	5 days
Chloroquine base	600 mg q.d. × 2 days, then 300 mg q.d. (may be added to other regimens)		14-21 days

[a]A luminal agent (paromomycin, diloxanide, or iodoquinol) should follow treatment with metronidazole, tinidazole, or dehydroemetine.
[b]Tinidazole tablets (available as 250 mg or 500 mg) can be crushed and mixed with cherry syrup.
i.m., intramuscularly; *q.d.*, one per day; *t.i.d.*, three times per day.

where the risk of reinfection is high, treatment of asymptomatic individuals may not be cost effective. Test-of-cure stool examinations after completion of therapy are important, as all of the recommended regimens have significant failure rates.

Intestinal Amebiasis

Metronidazole is the mainstay of therapy because of its availability and low toxicity. Unfortunately, it fails to eradicate luminal infection in 10-15% of cases because of its excellent absorption from the lumen into the tissues. Tinidazole, a structural analog of metronidazole, is effective for the treatment of intestinal amebiasis. It is also not indicated for the treatment of asymptomatic cyst passage. In four small randomized clinical trials of intestinal amebiasis, tinidazole was equally or more efficacious (one study) than metronidazole, with fewer side effects. Nitazoxanide, a thiazolide antiparasitic drug, has in vitro activity against *E. histolytica*/*dispar*. In clinical trials, parasitologic cure rates range from 69 to 96%. It is not yet approved by the US Food and Drug Administration (FDA) for the treatment of intestinal amebiasis. Following treatment with metronidazole or tinidazole for invasive amebiasis, all patients should receive a luminal amebicide to eliminate cysts from the colon. The following

TABLE 32.2 Side Effects Associated with Medications Used in the Treatment of Intestinal Protozoal Infections

Drug	Common	Uncommon
Metronidazole	Nausea, vomiting, bloating, metallic taste	Dizziness, vertigo, ataxia, stomatitis, peripheral neuropathy, Antabuse effect
Tinidazole	Nausea, vomiting, bloating, metallic taste	Rash, serum-sickness, peripheral neuropathy
Nitazoxanide	Abdominal pain, diarrhea, headache and nausea	
Diloxanide furoate	Flatulence	Nausea, vomiting, diarrhea, urticaria
Iodoquinol	Rash, acne, enlarged thyroid, nausea, diarrhea, cramps	Optic atrophy
Paromomycin	Nausea, vomiting, diarrhea	Eighth nerve damage, nephrotoxicity
Dehydroemetine	Nausea, vomiting, diarrhea, cardiac arrhythmias, precordial pain, muscle weakness (patients must be hospitalized and electrocardiographic changes monitored)	Dizziness, weakness, heart failure, hypotension
Quinacrine	Vomiting, diarrhea, dizziness, headache, abdominal cramps	Toxic psychosis, hepatic necrosis, blood dyscrasias
Furazolidone	Nausea, vomiting	Allergic reactions, polyneuritis, fever, hemolytic anemia

medications are primarily active against luminal stage of the protozoa. In the United States, the most common luminal amebicide is paromomycin. Diloxanide furoate is available in the United States only through the Centers for Disease Control and Prevention (CDC). Iodoquinol, although approved by the FDA, is difficult to obtain and has the potential for optic neuritis. Paromomycin and tetracycline have activity against luminal disease but have not been tested in rigorous controlled treatment trials with adequate follow-up monitoring. Documentation of cure should be undertaken after treatment. There is a 10% relapse rate if treated with a tissue agent but not followed by a luminal agent.

None of the drugs used in the treatment of amebiasis has been shown to be safe for use during pregnancy. The indications for treatment must be weighed against the potential risk to the fetus in each case.

Extraintestinal Amebiasis

Metronidazole or tinidazole, with or without a luminal amebicide, is the treatment of choice for all forms of extraintestinal amebiasis. Tinidazole is equally as efficacious as metronidazole (seven randomized studies with a total of 133 patients) or more efficacious than metronidazole (one study, 18 patients) for the treatment of ALA. The cure rates range from 86 to 93%. Dehydroemetine (available through the CDC) is extremely toxic and rarely indicated. Emetine is even more toxic and should be avoided.

In a series of ALA treated with metronidazole and followed by hepatic ultrasonography, resolution ranged from 2 to 20 months. After healing, the hepatic sonograph pattern was normal. Routine follow-up ultrasounds are not recommended, since the abscess cavity is likely to remain for months to years after appropriate therapy.

Antimicrobial therapy alone is successful in the majority of cases of amebic abscesses. The prognosis is excellent unless the patient is gravely ill at the initiation of treatment.

Needle aspiration or drainage may be useful in selected cases for symptomatic relief, left-lobe abscess, impending rupture, or abscess that does not respond to conservative medical therapy. Surgery should be reserved for emergent situations, such as impending rupture of ALA into the pericardium or peritoneum.

Prevention

The basic means for eradication of endemic amebiasis is to eliminate fecal contamination of food and water by improving waste disposal systems and water purification. For travelers, avoidance of uncooked, unpeeled fruits and vegetables and untreated drinking water is recommended. Adequate water treatment consists of boiling, filtration, or treatment with high concentrations of iodide. Chlorine is much less effective (see Chapter 7). Prophylactic chemotherapy is not recommended. One agent available for this purpose in some countries, iodochlorhydroxyquin (Entero-Vioform), has been associated with irreversible optic neuritis. In populations at risk of sexually transmitted amebiasis, altering sexual practices to avoid fecal-oral spread may reduce the risk of transmission of amebiasis and other enteric pathogens. Additionally, efforts should be made to decrease the transmission from a cyst-passer to family members or contacts. Contacts and family members of the index case of *E. histolytica* infection should be screened.

GIARDIA LAMBLIA

Pathogenesis

G. lamblia (also called *G. duodenalis* or *G. intestinalis*) is the human species and is acquired by ingestion of a very low inoculum (as few as 10-100) cysts in contaminated food or water. Cysts can survive up to 3 months in water at 4°C. The free-living trophozoite form is less infectious, since it is more labile in the environment and is easily killed by gastric acid. Excystation occurs in the duodenum and proximal jejunum, the regions predominantly involved in the infection. The incubation period is 3-25 days (median 7-10 days), after which the cysts can be detected in the stool.

The pathogenesis is poorly understood. Trophozoites have a prominent "sucking disk" on their ventral surface, but whether this structure is involved in adherence to the intestinal brush border is unknown. The severity of symptoms does not correlate with the extent of morphologic damage to the epithelial cells (usually limited to disruption of the brush border) or the number of organisms. Organisms have occasionally been noted to penetrate the wall of the gut to the submucosa, but invasiveness does not appear to play a role in pathogenesis. No enterotoxins have been associated with *Giardia*.

The host immune system plays an important role in giardiasis, as illustrated by the predisposition to chronic giardiasis observed in patients with malnutrition, IgA deficiency, agammaglobulinemia, and common variable immunodeficiency. Humoral immune system is important for recovery from the initial infection and protection from reinfection. Cellular immunity also plays a role, as shown in animal models. *Giardia* infection confers partial protection of variable duration.

Epidemiology

Giardiasis occurs as an endemic disease and in large, water-borne outbreaks. In developing countries, where prevalence is 7-10%, it is primarily a disease of children. *G. lamblia* is the most commonly diagnosed intestinal parasite in public health laboratories in the United States. In the United States, major water-borne outbreaks have been reported from many states. *G. lamblia* that infects humans has cross-species pathogenicity for other mammals, and vice-versa. Water-dwelling animals, such as beavers and muskrats, have been implicated as the source of the *Giardia* contamination in some of the outbreaks.

Direct person-to-person spread is also important in the transmission of giardiasis. An infected person may shed 1-10 billion cysts daily in their feces. Shedding may last for several months. High shedding and small infective inoculum contribute to high attack rates in developing countries and daycare centers. At-risk groups include men who have sex with

men, institutionalized persons, refugees or immigrants from developing countries, or travelers to those countries. Overall risk of *Giardia* among immigrants is 1180 per 100,000, with the highest risk associated with immigration from Afghanistan and Iraq.

All travelers are at some risk of acquiring *Giardia*, even when traveling in the United States or other industrialized countries. A Swedish study of imported giardiasis showed that the overall risk for acquiring *Giardia* during travel is 5.3/100,000, with the highest risk of acquisition related to travel to the Indian subcontinent (628 per 100,000) and East and West Africa. The largest proportion of imported giardiasis was seen among immigrants visiting friends and family in the country of their origin. Overall, however, it accounts for only a small percentage of cases of traveler's diarrhea. Hikers drinking untreated surface water have the greatest risk for acquisition of giardiasis.

Among the nontraveling patients in the United States, giardiasis is more common among children between 0 and 5 years old and among adults between 31 and 40 years old. There is a seasonal variation, with more cases during late summer and early fall, coinciding with increased water-related outdoor activities. There appears to be geographic variation as well, with higher number of cases reported from the northern states. Annually about 20,000 cases are reported in the United States.

Clinical Features

The acute phase of giardiasis is highly variable in severity, but typically there is sudden onset of diarrhea 7-21 days after ingestion of the cysts. The moderate to large volume of foul-smelling, loose stools accompanied by distention, flatulence, and midepigastric cramps helps to distinguish giardiasis from other infectious diarrheas. Bacterial pathogens of the small bowel, such as enterotoxigenic *Escherichia coli*, tend to cause a more watery diarrhea with less bloating and flatulence. Infectious colitis secondary to amebiasis or *Shigella* infection typically has smaller stool volume, more severe and diffuse cramps, and less abdominal bloating than seen with giardiasis. Dysentery is highly unusual with giardiasis and should prompt an evaluation for other pathogens. Other symptoms with acute giardiasis can include nausea, anorexia, vomiting, low-grade fever, and headache. The acute phase usually lasts 7-14 days but can then evolve into a chronic infection.

Chronic giardiasis symptoms may be persistent or relapsing and include loose, bulky, foul-smelling stools; distention; foul flatus; constipation; and substernal burning. Malabsorption can occur and lead to significant weight loss. Malabsorption results from trophozoites forming a physical barrier between the intestinal epithelial cells and the lumen of the intestine, interrupting the absorption of nutrients from the lumen. Spontaneous resolution is the rule, but occasionally infections can persist for years. Chronic infection most often occurs in patients with hypogammaglobulinemia or agammaglobulinemia. Some individuals become chronic, asymptomatic cyst-passers and become an important reservoir for spread to others. In developing countries, chronic giardiasis in children is associated with malnutrition and resultant growth and cognitive impairment.

Diagnosis

Giardiasis should be suspected in any patient with a diarrheal illness persisting >1 week or malabsorption. Epidemiologic data may be suggestive but do not exclude the diagnosis, since giardiasis is endemic in the United States and sporadic cases occur. Both the cyst and the trophozoite forms can be seen in diarrheal stool, but trophozoites are rare in formed stool. A minimum of three specimens should be examined, since cyst passage is erratic and the numbers may be small. The yield from a single specimen is 50-75% but increases to 90-95% with three or more specimens collected every other day during a 5-day period. *Giardia* antigen detection by enzyme-linked immunosorbent assay and direct fluorescent antibody (DFA) in stool specimens are the preferred diagnostic tests and more sensitive than standard morphologic identification of this parasite in stool specimens. Some of these antigen detection assays are available as combined *Cryptosporidium/Giardia* detection kits. The sensitivity and specificity approach 100% compared with microscopy. Newer stool PCR tests, where available, are more sensitive and specific for diagnosis.

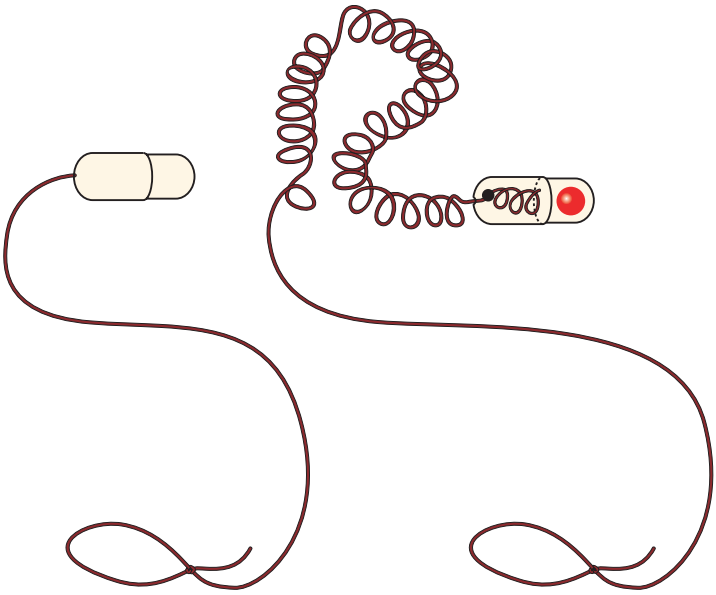

Fig. 32.1 The string test capsule.

If suspicion of giardiasis remains high and multiple stool specimens are negative, options include a therapeutic trial with antimicrobial agents or proceeding to the string test (Entero-Test, Hedeco, Palo Alto, CA); upper endoscopy for aspiration of duodenal fluid or biopsy may be helpful. The string test consists of a gelatin capsule containing a string (**Fig. 32.1**). One end of the string is held outside the patient, and the capsule is swallowed. The capsule is weighted with a small metal sphere and is passed into the duodenum, unwinding string from a hole in the proximal end. The gelatin capsule dissolves, leaving the distal end of the string free in the duodenum. After 4 hours it is withdrawn, and the material adhering to the bile-stained end is scraped off and examined for trophozoites (**Fig. 32.2**).

Small-bowel biopsy is most helpful in the evaluation of chronic giardiasis and associated malabsorption. It has little, if any, role in the diagnosis of acute giardiasis. The histopathologic examination of the small bowel in giardiasis is usually normal but may show some nonspecific blunting of the villi. Touch preparations of the biopsy specimen are necessary to see the trophozoites, which inhabit the mucoid layer overlying the epithelial cells.

Routine blood chemistry and hematologic values are normal, and specific serodiagnostic assays for antibodies to *Giardia* are still experimental. Radiographic procedures are unhelpful. Barium studies should be avoided, as barium interferes with detection of Giardia.

Treatment

The agents and appropriate dosage regimens used in the treatment of giardiasis are listed in **Table 32.3**. Common or severe side effects reported with these agents are shown in **Table 32.2**.

Metronidazole or tinidazole is the standard therapy for giardiasis. Metronidazole dosing of 250 mg three times a day for 5 days in uncomplicated giardiasis is associated with a higher failure rate; therefore, a minimum dose of 500 mg three times a day for 5-7 days appears appropriate. Short-course therapy with metronidazole has been tried, but the failure

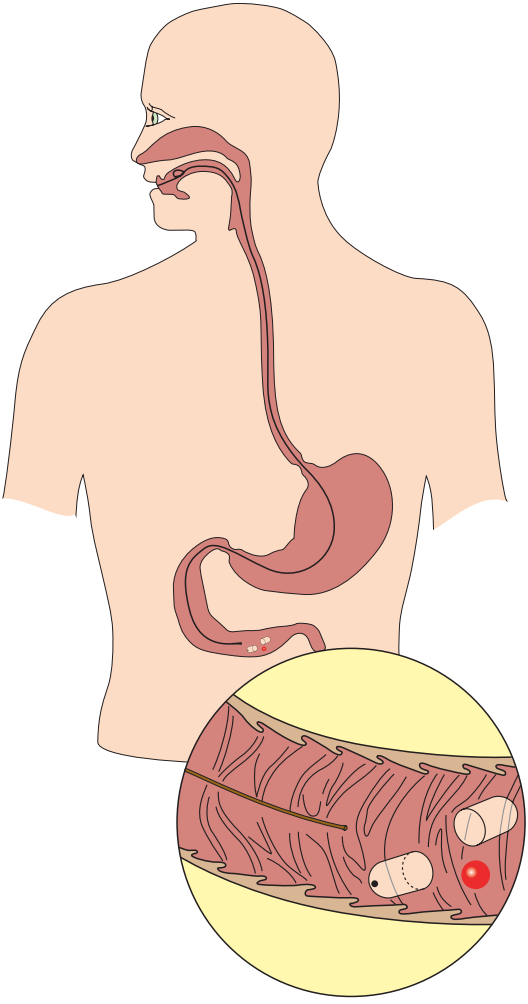

Fig. 32.2 **Route of the string test in the gastrointestinal tract.**

rates have been high with both the 2.0 g single-dose regimen (40-50% treatment failure) and the two-dose (2.0-2.4 g q.d. × 2 days) regimen (20-25% failure rate). A regimen of 2.4 g/day for 3 days has a 91% success rate but is associated with higher gastrointestinal toxicity.

Tinidazole, a second-generation nitroimidazole antiprotozoal agent, is FDA approved for the treatment of giardiasis. Tinidazole has in vitro and clinical activity against metronidazole-resistant strains of *Giardia*. A Cochrane Database Systematic Review showed that treatment with a single dose of tinidazole results in higher clinical cure (92% cure rate with a single 2.0-g dose) with fewer adverse effects than metronidazole.

TABLE 32.3 Treatment Regimens for Giardiasis

Drug	Adult Dose (Nonpregnant)	Pediatric Dose	Duration
Metronidazole	500 mg t.i.d.	5-7 mg/kg t.i.d.	5-10 days
Tinidazole	2 g orally	Children >3 years of age: 50 mg/kg per day[a] (up to 2 g a day)	Single dose
Nitazoxanide	>12 years of age: 500 mg tablet or 25-mL suspension twice daily with food	Children 1–3 years of age: 100 mg (5 mL) twice daily with food Children 4–11 years of age: 200 mg (10 mL) twice daily with food	3 days
Quinacrine HCl	100 mg t.i.d. p.c.	2 mg/kg t.i.d. p.c. (max. 300 mg/day)	5 days
Furazolidone	100 mg q.i.d.	1.25 mg/kg q.i.d.	7-10 days

[a]Tinidazole tablets (available as 250 mg or 500 mg) can be crushed and mixed with cherry syrup.
p.c., after meals; *q.i.d.*, four times per day; *t.i.d.*, three times per day.

In 2002, the FDA approved nitazoxanide for the treatment of giardiasis for persons ≥1 year of age. Nitazoxanide interferes with the pyruvate–ferredoxin oxidoreductase enzyme-dependent electron transfer reaction in *Giardia* or *Cryptosporidium*. Its metabolite, tizoxanide, is eight times more active than metronidazole against *Giardia* in metronidazole-susceptible strains and twice as active as metronidazole-resistant strains. In clinical trials, the parasitologic response rate with nitazoxanide varied from 64 to 94%.

Quinacrine, the official drug of choice for treatment of giardiasis, is associated with frequent severe gastrointestinal side effects that limit patient compliance. Few controlled studies have been performed comparing quinacrine with metronidazole. Although these studies had suboptimal follow-up for detection of late relapses, the data suggest that there is little difference in cure rates between these two agents, both being successful in approximately 90% of cases. In the United States, quinacrine can be acquired from a few compounding pharmacies on an individual basis.

Special Therapeutic Considerations

Children

Prior to the approval of tinidazole and nitazoxanide, the treatment of children was difficult owing to the lack of liquid preparations of quinacrine or metronidazole. However, treatment options for children have improved: tinidazole is approved for children >3 years of age (tablets can be crushed and mixed with cherry syrup); nitazoxanide is approved for children >1 year of age and is available as a suspension. Another drug, furazolidone, is FDA approved for treatment of giardiasis but with limited availability. It is less active against *Giardia* (cure rates of 70-80%).

Treatment Failures

Treatment success is generally better in acute giardiasis than in subacute or chronic cases. Drug resistance is not believed to be a major factor in treatment failures, and a second course of the same agent is as likely to be successful as switching to a second drug. Recurrent infections may be related to IgA deficiency and warrant further investigation. Metronidazole-resistant strains have been described. Options for treatment of drug-resistant giardiasis include using a different drug such as nitazoxanide or using a combination of medications with different mechanisms of action, such as metronidazole and albendazole or paromomycin. Tinidazole may still be effective, but since it shares a similar mechanism of

action it may not be effective. Additional options include using a higher dose, longer course, or combination of medications.

Pregnant Women

None of the drugs used in the treatment of giardiasis is approved for use in pregnancy. Unless severe or disabling symptoms are present, treatment should be deferred until after delivery. CDC recommends use of paromomycin, a non-absorbable aminoglycoside, in the treatment of giardiasis in pregnant women.

Chronic Gastrointestinal Symptoms

Some individuals, possibly as many as 5%, develop a poorly characterized symptom complex of persistent bloating, flatulence, and upper abdominal cramps after apparently successful therapy for giardiasis. Patients with this "post-giardiasis syndrome" do not have detectable persistent infections as assessed by stool examination and small-bowel aspiration and biopsy, and the giardiasis-like symptoms often persist despite repeated courses of therapy. Destruction of mucosal disaccharidases may play some role, but the symptoms may persist after recovery of the mucosal epithelium. Symptoms resolve slowly over 3-24 months. It is important to avoid repeated courses of antimicrobial agents in this disease if no evidence of ongoing infection is present. In refractory cases or in patients with chronic symptoms with evidence of active infection, a 14-day combination of metronidazole 750 mg, three times a day, and quinacrine 100 mg, three times a day, may be more effective.

Prevention

Contaminated water is the primary mode of transmission for *Giardia*. Boiling (30 s is sufficient at sea level; longer periods may be necessary at high elevations) and filtration are both adequate purification techniques (see Chapter 7). Inactivation by chlorination or by iodine treatment is less effective because these methods are affected by the pH, temperature, and cloudiness of the water, thereby decreasing the reliability of the purification method. The traveler should also avoid uncooked foods that may have been washed with tap water or untreated surface water. Hikers in mountainous regions should regard all surface water as potentially contaminated. Antimicrobial prophylaxis is not advised. Patients should also be advised to avoid fecal exposure and the potential of transmission during sex.

Outbreaks arising from daycare centers may be difficult to eradicate. The efficacy of epidemiologic screening or treatment of daycare staff and family members of infected children is unproven. Even the necessity for screening and treating asymptomatic children attending the daycare centers is unknown, although it would seem reasonable to screen and treat infants in diapers because of the greater potential for fecal-oral spread within and from this population.

OTHER PROTOZOA

Cryptosporidiosis

Protozoa of the genus *Cryptosporidium* are widely distributed among mammalian species, but only *Cryptosporidium parvum* and *C. hominis* are significant human pathogens. Infection, acquired by ingestion of cysts, primarily involves the small intestine, with highest concentration in the jejunum. Water or food contaminated with even a small inoculum (as low as 30 cysts) can cause an infection. Oocysts are highly resistant to chlorine or other common disinfectants.

In immunocompetent hosts, cryptosporidiosis is a self-limited illness that resolves spontaneously in 7-21 days. It is indistinguishable from giardiasis. Children less than 5 years of age are also more susceptible to symptomatic cryptosporidiosis. Immunocompromised hosts, especially patients with human immunodeficiency virus infection (HIV)/acquired immunodeficiency syndrome (AIDS), with cryptosporidiosis develop a prolonged intractable watery diarrhea associated with anorexia and weight loss. Among HIV/AIDS patients, it can also cause infection of the bile duct, gallbladder, pancreas, liver, or lung. Cell-mediated and humoral immunity seem to play a role in pathogenesis.

Cryptosporidium may cause as much as 5-7% of pediatric diarrhea in developing countries but is implicated in only 0.3-1.0% of outpatient diarrheal cases in the United States. The prevalence of cryptosporidiosis among HIV/AIDS patients ranges from 14% in developed countries to 24% in developing countries. Risk factors for cryptosporidiosis include travel to developing countries, use of swimming pools or water recreation parks, animal contact (zoo, farms, etc), daycare exposure, and contact with ill persons, especially children.

Stool *Cryptosporidium* antigen detection by EIA or DFA is the test of choice for detection of *Cryptosporidium* cysts and is more sensitive than modified acid-fast stain testing. Modified acid-fast stains of direct or concentrated stool are labor intensive and require more skill. Small-bowel biopsies and more elaborate stool purification techniques are rarely required. Patients with a clinical illness consistent with giardiasis but with multiple negative stool examinations for *Giardia* should undergo tests for *Cryptosporidium*.

Efficacious therapy against *Cryptosporidium* remains problematic. Nitazoxanide has a clinical efficacy of 72-88%, while the parasitological clearance rate is lower (60-75%). Its efficacy in immunocompromised hosts such as advanced HIV/AIDS patients remains unproven. In the United States, nitazoxanide is FDA approved for the treatment of cryptosporidiosis in immunocompetent persons ≥1 year of age. Paromomycin and high-dose azithromycin have modest efficacy in treating chronic cryptosporidiosis in immunocompromised patients. Subcutaneous octreotide helps control diarrhea in HIV/AIDS patients. Complete recovery is dependent on resolution of the immune deficit, as can occur with anti-HIV therapies. Immunosuppressive chemotherapy should either be delayed or transiently lowered if possible in a patient with cryptosporidiosis.

Prevention of fecal-oral transmission of *Cryptosporidium* oocysts can be achieved by strict personal hygiene, eating cooked food, and avoiding water theme parks, uncooked fruits and vegetables, oro-anal sexual exposure, and direct contact with animals, particularly calves and lambs. It is important to note that chlorination does not adequately kill the *Cryptosporidium* oocysts. Because of the lower parasite clearance rates, it is important to advise the patient to avoid public pools until symptom resolution and for at least 2 weeks after treatment. Retesting is unnecessary unless the patient is symptomatic. Boiling water for 1 minute is the best method of decontaminating water. In addition, using filters with 1 μm or smaller pore size are effective in removing the oocysts.

Balantidiasis

Balantidium coli is the only ciliated protozoan pathogen in humans. This parasite is very large (100 μm) and is easily identified in stool specimens. It is acquired by close contact with swine or, more rarely, transmitted within chronic care facilities for the developmentally disabled. It produces invasive disease of the colon with symptoms of colitis and dysentery. Tetracycline, iodoquinol, and high-dose metronidazole are all effective in treating balantidiasis.

OTHER PROTOZOAN PATHOGENS

Cystoisospora (Formerly *Isospora*) *belli*

Cystoisospora belli has been reported as a rare cause of enteritis. It is distributed worldwide but is more prevalent in South America and Africa. The clinical syndrome resembles giardiasis and is acquired by contact with contaminated water or food. Persistent diarrhea associated with *Cystoisospora* can occur in immunocompromised patients. Identifying the characteristic oocysts on modified acid-fast stool smears is diagnostic. Trimethoprim-sulfamethoxazole is the agent of choice; pyrimethamine may be useful in people allergic to sulfa. There are two reported cases of parasite clearance with nitazoxanide (not FDA approved for this indication).

Cyclospora cayetanensis

Cyclospora cayetanensis is an intestinal protozoan pathogen that causes diarrhea and is found in both developed and developing countries. It is presumably acquired through ingestion

of contaminated water or food and not likely to be transmitted person-to-person. It has marked seasonal variation, tending to occur more in the late spring and summer months. The oocysts are detected by modified acid-fast (Ziehl–Neelsen) staining or by ultraviolet autofluorescence microscopy. The spherical cyst-like organisms measure 8-10 μm in diameter and are larger than *Cryptosporidium* oocysts.

Cyclospora infection in immunocompetent patients results in a prolonged self-limited watery diarrhea lasting up to 10 weeks. During the acute phase, upper abdominal symptoms, nausea, and fever accompany diarrhea. This may be followed by anorexia, weight loss, and fatigue. Symptoms may wax and wane for up to 4-8 weeks. Cases of cyclosporiasis in immunocompromised patients have been incompletely characterized, but the clinical presentation is similar to cryptosporidiosis. Cyclospora may be able to cause biliary tract disease among people with HIV/AIDS. The diagnostic differentiation between the two protozoan pathogens is significant, because cyclosporiasis responds to trimethoprim-sulfamethoxazole (adults, 160 mg trimethoprim and 800 mg sulfamethoxazole twice a day; children, 4 mg/kg trimethoprim and 20 mg/kg sulfamethoxazole twice a day) given for ≥3 days, whereas *Cryptosporidium* infections do not. Albendazole, trimethoprim, azithromycin, nalidixic acid, norfloxacin, tinidazole, metronidazole, quinacrine, tetracycline, and diloxanide furoate have no or limited activity on *Cyclospora*. Alternatives for patients allergic to sulfonamide include either desensitization to sulfonamide or treatment trial with ciprofloxacin based on a randomized controlled trial in HIV-infected patients with *Cyclospora* or *Cystoisospora*. Nitazoxanide has also shown broad in vitro activity against *Cyclospora* but needs clinical validation.

Similar to *Cryptosporidium, Cyclospora* is resistant to chlorination. Therefore, it is important to advise travelers regarding water precautions. Cyclosporiasis can be prevented by drinking boiled or bottled water, avoiding raw vegetables and fruits, and adhering to strict hand washing.

Dientamoeba fragilis

Dientamoeba fragilis is a flagellate protozoan that has been associated with a mild, nonspecific enteritis syndrome. Iodoquinol is the treatment of choice; tetracycline and paromomycin are alternatives.

POSSIBLE PATHOGENS

Blastocystis hominis

Blastocystis hominis is a common stool commensal (up to 19% of normal controls in the United States are colonized). There is evidence that heavy infestations may be associated with cramps, vomiting, dehydration, abdominal pain, sleeplessness, nausea, weight loss, lassitude, dizziness, flatus, anorexia, pruritus, and tenesmus.

B. hominis infections in primates have been cured with trimethoprim-sulfamethoxazole. In vitro susceptibility tests show that the following drugs may be effective, in descending order: emetine, metronidazole, nitazoxanide, furazolidone, trimethoprim-sulfamethoxazole, iodochlorhydroxyquin (Entero-Vioform), and pentamidine. Chloroquine and iodoquinol have also been reported as effective treatments.

The role of *B. hominis* as a human pathogen is still controversial. Some published reports, based on clinical and laboratory studies, have suggested that when *B. hominis*-associated diarrhea appears to respond to therapy, improvement may, in fact, be due to some other undetected organism that is actually causing the problem.

NONPATHOGENIC PROTOZOA

Numerous other species of protozoa can be detected in human feces, including nonpathogenic protozoa such as *Entamoeba coli*, *E. polecki*, *E. hartmanni*, *Iodamoeba bütschlii*, and *Endolimax nana*. At the present time identification of one of these organisms in the stool is a useful marker of exposure to fecal-contaminated food or water. Their presence should prompt a more exhaustive search for other intestinal pathogens.

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