Beyond O&P Times Three

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Although examination of the stool for ova and parasites times three (O&P × 3) is routinely performed in the United States (US) for the evaluation of persistent and/or chronic diarrhea, the result is almost always negative. This has contributed to the perception that parasitic diseases are nearly non-existent in the country unless there is a history of travel to an endemic area. The increasing number of immigrants from third-world countries, tourists, and students who present with symptoms of parasitic diseases are often misdiagnosed as having irritable bowel syndrome or inflammatory bowel disease. The consequences of such misdiagnosis need no explanation. However, certain parasitic diseases are endemic to the US and other developed nations and affect both immunocompetent and immunocompromised patients. Testing for parasitic diseases either with O&P or with other diagnostic tests, followed by the recommended treatment, is quite rewarding when appropriate. Most parasitic diseases are easily treatable.


INTRODUCTION

Microscopic examination of independently collected fresh specimens of stool for ova and parasites is the cornerstone of clinical parasitology. Luminal enteric parasitic diseases are considered to be rare in the US except in high-risk population groups such as recent immigrants, travel to endemic areas, adopted children from highly endemic nations, college students from Afro-Asian countries, and immunocompromised patients. However, a few misconceptions exist regarding parasitic diseases. For example, if a person has not traveled outside the US or any developed nation, he is unlikely to acquire a parasitic infection. In reality, although uncommon, parasites such as *Giardia* and *Cryptosporidium* exist within the US and are even implicated in small, sporadic outbreaks [1]. The population of the US or any affluent Western nation currently comprises millions of individuals born and raised in developing nations. With facilities for rapid travel and fast import of foods from developing nations, the phrase “traveler’s diarrhea comes to your local grocery store” is both meaningful and humorous. It is another misconception that parasitic diseases can almost always be excluded by microscopic examination of the stool.

Because intestinal parasites are shed intermittently, parasitologists recommend three or more stool samples for examination to maximize the sensitivity of detection of ova and parasites. However, a recent study demonstrated detection of 91% of parasites in the first stool sample with only 10% yield by the examination of additional specimens, suggesting to avoid reflexive submission of multiple stool samples for ova and parasite testing [2]. The result of this study is found to be consistent with multiple other studies [3–7]. Similar result was also reported in a multicenter College of American Pathologists-sponsored Q-Probe investigation which showed only 2.7% parasitic detection and over 90% of parasites identification in the first specimen [8]. In developed nations, clinicians routinely perform the ova and parasites times three (O&P × 3) test in almost all patients with persistent and/or chronic diarrhea; however, they almost always expect the results to be negative based on prior experience. Given the overuse of stool O&P × 3 coupled with the inappropriateness of performing the stool tests, there is a legitimate concern about the cost-effectiveness of the test. Furthermore, many of us are unaware that the standard stool examination by microscopy for detection of ova and parasites has been replaced by more sensitive diagnostic tests. For example, a multiplex real-time polymerase chain reaction (PCR) assay is available for the simultaneous detection of *Entamoeba histolytica* (*E. histolytica*), *Giardia lamblia* (*G. lamblia*) and *Cryptosporidium parvum* (*C. parvum*) in stool sample tests, the three of the most important diarrhea-causing parasitic protozoa [9].

The luminal parasites can be divided into two groups: protozoa and helminths. The protozoa are single-celled, motile, free-living parasitic organisms, whereas the helminths are large, multicellular organisms that can be seen with the naked eye. The aim of this review is to provide helpful information, solely on luminal para-
sites that one might encounter in clinical practice in the West in high-risk groups based on clinical manifestations, country of origin, and immune status. We have also provided data on the clinical resemblance of parasitic diseases to the more frequently encountered GI problems and thus the common parasites to consider testing for in such cases.

DESCRIPTION OF COMMON LUMINAL GI PARASITES
Protozoa

The intestinal pathogenic protozoa include amebae, coccidia (Cryptosporidium, Cystoisospora, and Cyclospora), ciliates (Balantidium coli), and flagellates (G. lamblia) (Table 1). Transmission of protozoa occurs from one individual to another through the fecal-oral route. The life cycle of a protozoan parasite has two major stages: the cyst stage (excreted in feces, contains protective walls, and responsible for the transmission of the parasite) and the trophozoite stage (responsible for intestinal pathology and clinical manifestations). G. lamblia (0.2–29.2% of cases), Cryptosporidium spp. (0.1–9.1% of cases), Entamoeba spp. (0.2–12.5% of cases), and Cyclospora cayetanensis (C. cayetanensis) (0.2–4.3% of cases) are the frequent causes of watery diarrhea in the US [10]. The prevalence of the common pathogenic protozoal species was challenged by the controversial pathogens Blastocystis spp. (0.4–18.1% of cases) and Dientamoeba fragilis (D. fragilis) (0.4–6.3% of cases), which are more frequently associated with asymptomatic infection [10]. The protozoal causes of luminal GI diseases are listed alphabetically in the following paragraphs.

Amebiasis. Amebiasis, caused by the protozoa E. histolytica, affects ~50 million people worldwide and results in as many as 100,000 deaths each year [11]. Amebiasis is highly prevalent in Central and South America, Africa, and Asia. In the US, after giardiasis and cryptosporidiosis, amebiasis is the third most common parasitic infection (1.2 cases per 100,000 US population) and the second most common cause of diarrhea in travelers returning from other countries [12]. Transmission of infection occurs by ingestion of the quadrinucleate cyst of E. histolytica by fecal contamination. An increased incidence of amebiasis has been reported in homosexual men [13]. However, recent evidence suggests that many of these men are colonized with the non—pathogenic Entamoeba dispar rather than E. histolytica [14]. Returned travelers, elderly, malnourished, pregnant, and immunocompromised patients are at increased risk of severe amebiasis.

The majority of infections (>90%) remain asymptomatic. Amebic diarrhea without dysentery is the most common clinical manifestation, although ~15–33% of infections are accompanied by amebic dysentery or amebic colitis [15]. Amebic colitis typically presents with crampy abdominal pain, mucous or bloody diarrhea, weight loss and, rarely, fever. The onset is often insidious, with several weeks of symptoms. This is different from bacterial causes of dysentery, in which patients are usually symptomatic for only 1–2 days.

Acute necrotizing colitis is a rare (occurs in <0.5% of cases) and severe complication of intestinal disease characterized by fever, bloody mucoid diarrhea, diffuse abdominal pain, and signs of peritoneal irritation [16]. Other complications of the intestinal disease include toxic megacolon, ameboma, stricture, bowel obstruction, and perianal ulceration with potential fistula formation [14, 16]. Ameboma, the localized inflammatory mass that commonly involves cecum or ascending colon, results in obstructive symptoms mimicking carcinomas.

The most common extraintestinal manifestation is liver abscess. Extra-abdominal amebiasis likely follows direct extension from liver abscesses rather than direct transmission from the intestine. Thoracic amebiasis (empyema, bronchohepatic fistulas, or extension of a pleuropulmonary abscess, and acute pericarditis) is the most common type of extra-abdominal amebiasis. Other forms of extra-abdominal amebiasis include cerebral and cutaneous amebiasis.

The TechLab E. histolytica II ELISA fecal antigen detection test has sensitivity and specificity superior to stool O & P examination and distinguishes E. histolytica from E. dispar and Entamoeba moshkovskii [17]. Real-time PCR is superior in sensitivity compared to stool antigen detection; however, it is technically complex and expensive [9]. Serological tests for intestinal E. histolytica infection are generally less sensitive than those of amebic liver abscess but can be used as an important adjunct in the diagnosis of intestinal amebiasis. Serological tests can be particularly useful when E. histolytica—specific stool diagnostic techniques (antigen detection or PCR) are not available, because infection with E. histolytica, and not E. dispar or E. moshkovskii, results in seroconversion [16]. Colonoscopy and biopsy can be useful in the diagnosis of intestinal amebiasis. Colonoscopy typically shows diffuse edema and granularity, which can be mistaken for ulcerative colitis. In the setting of presumed ulcerative colitis, E. histolytica infection must be excluded before the initiation of corticosteroid therapy since the therapy can lead to hyperinfection and have fatal consequences [18, 19]. In chronic amebiasis, there may be involvement of cecum with rectal sparing. Biopsy of colonic mucosa from an ulcer margin provides a high yield of erythrophagocytic trophozoites. Histologically, the ulcer is typically flask-shaped, and the broad base is composed of fibrin and cellular debris (Fig. 1).

Asymptomatic E. histolytica infections are treated with paromomycin (25–35 mg/kg/day PO QID for 5–10 days), diloxanide furoate or iodoquinol [20]. Asymptomatic infections should be treated in non-endemic areas for two reasons: first, there is a risk of the disease becoming invasive; and second, the presence of cysts in the feces is a public health concern. For symptomatic intestinal or extraintestinal disease (amebic liver abscess), metronidazole 750 mg PO three times a day for 7–10 days or tinidazole 800 mg orally three times a day for 5 days (better tolerated, shorter periods of treatment, and available in the US) are the treatment options [16]. Although 90% of amebic colitis patients respond to nitroimidazoles, luminal agents like paromomycin or diloxanide should be added to prevent relapse [21].

Balantidiasis. Balantidiasis is caused by Balantidium coli (B. coli) and has a worldwide prevalence of less than 1% [22]. Areas of high prevalence include Latin America, Philippines, Papua New...
<table>
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<th>Parasitic disease (Name of the parasites)</th>
<th>Epidemiology</th>
<th>Clinical manifestations</th>
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<tr>
<td><strong>Amebiasis</strong> Entamoeba histolytica [16]</td>
<td>Worldwide but most commonly reported in Central and South America, Africa, and Indian subcontinent</td>
<td>Amebiasis (90% asymptomatic) Intestinal amebiasis Crampy abdominal pain Weight loss Watery or bloody diarrhea Ameboma Amebic strictures Hepatic amebiasis Fever Right upper quadrant pain</td>
</tr>
<tr>
<td><strong>Balantidiasis</strong> Balantidium coli [23]</td>
<td>Worldwide but most frequently reported in Latin America, Southeast Asia, Papua New Guinea, and parts of Middle East</td>
<td>Mostly asymptomatic Intestinal amebiasis • Intermittent diarrhea, pain abdomen, and weight loss • Fulminant colitis (rare) • Traveler’s diarrhea</td>
</tr>
<tr>
<td><strong>Blastocystis</strong> Blastocystis hominis [26, 27]</td>
<td>Worldwide</td>
<td>Mostly asymptomatic Acute or chronic diarrhea Urticaria</td>
</tr>
<tr>
<td><strong>Cryptosporidiosis</strong> Cryptosporidium parvum Cryptosporidium hominis [29]</td>
<td>Worldwide except Antarctica</td>
<td>Enteric cryptosporidiosis Watery or mucoid diarrhea Abdominal cramps Biliary cryptosporidiosis (in AIDS patients)</td>
</tr>
<tr>
<td><strong>Chagas disease</strong> Trypanosoma cruzi [53, 55]</td>
<td>Southern part of North America • South America</td>
<td>Megalocytosis Megaeosinophils</td>
</tr>
<tr>
<td><strong>Cystoisosporiasis</strong> Cystoisospora bellii [41]</td>
<td>Worldwide but predominantly in tropical and subtropical climates especially South America, Africa, and Southeast Asia</td>
<td>Self-limited or severe watery diarrhea (immunocompetent hosts) Chronic watery diarrhea in immunocompromised hosts Hemorrhagic colitis (AIDS) • Biliary tract disease in AIDS (very rare)</td>
</tr>
<tr>
<td><strong>Dientamebiasis</strong> Dientamoeba fragilis [44, 46]</td>
<td>Worldwide</td>
<td>Mostly asymptomatic Intestinal amebiasis</td>
</tr>
<tr>
<td><strong>Giardiasis</strong> Giardia lamblia [47]</td>
<td>Worldwide</td>
<td>Acute giardiasis • Foul-smelling diarrhea • Watery diarrhea • Abdominal cramps • Chronic giardiasis</td>
</tr>
<tr>
<td><strong>Microsporidiosis</strong> Microsporidian spp. Enteroctozaon bienesi [51, 52]</td>
<td>Central and South America • Asia • Africa</td>
<td>Intestinal microsporidiosis Persistent diarrhea • Loss of appetite • Acalculous cholecystitis</td>
</tr>
</tbody>
</table>

**Table 1** Epidemiology and manifestations of protozoan gastrointestinal parasites and their clinical mimics
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Guinea, and the Middle East [23]. Human infection occurs with close contact with pigs, poor sanitary hygiene, and in tropical or subtropical regions that favor survival of cysts.

Most patients are asymptomatic. Clinical manifestations include intermittent diarrhea, abdominal pain, and weight loss. Fulminant colitis is rare, manifesting as bloody diarrhea that may lead to intestinal perforation with peritonitis or extraintestinal disease (B. coli pneumonia) [24].

The diagnosis of balantidiasis involves examination of the stool for rapidly motile trophozoites; cysts are infrequently observed. Endoscopic findings in invasive intestinal disease include necrosis and ulceration resembling invasive amebiasis, bacterial dysentery, and inflammatory bowel disease. Tetracycline (500 mg four times daily for 10 days), metronidazole (750 mg three times daily for 5 days), or iodoquinol (650 mg three times daily for 20 days) are the drugs of choice.

Blastocystosis. The prevalence of blastocystosis is higher in developing countries (30–50%) than in developed countries (1.5–10%) [25]. However, Blastocystis is the most common parasite identified in stool samples in the US, and is more common than G. lamblia or D. fragilis [26]. The pathogenicity regarding Blastocystis spp. is controversial. The risk factors for the infection include travel to and immigration from developing countries, immunocompromised state, and exposure to contaminated food and water. Symptoms include acute or chronic watery diarrhea, abdominal cramps, bloating, flatulence, and fatigue. Blastocystis hominis (B. hominis) infection has shown to be associated with irritable bowel syndrome [27]. There may be virulent and avirulent strains of B. hominis, which would explain the variability of symptoms.

Diagnosis is based on the demonstration of O&P in the stool. B. hominis is not easily seen in concentrated wet mount preparation; hence, permanent stains (trichrome) are preferred for microscopic diagnosis [28]. In a symptomatic patient, if the stool sampling shows the parasite, it should prompt a thorough evaluation for other parasitic causes of the patient’s GI complaints as there is a possibility of co-infection.

Symptoms due to B. hominis infection are often self-limited, and therapy for symptomatic infections should be withheld until other causes of intestinal symptoms are ruled out [26]. Metronidazole (750 mg, thrice daily for 10 days) is considered the first line of treatment. When there is resistance to metronidazole, treatment with trimethoprim/sulfamethoxazole (TMP/SMX) and iodoquinol offers variable success. Asymptomatic individuals do not need treatment.

Cryptosporidiosis. Cryptosporidium is endemic in North, Central and South America, Africa, and Australia [29]. In the immunocompetent population, cryptosporidium infection accounts for 2.2% cases of diarrhea in developed countries and 6.1% in developing countries [29]. It is a common occurrence in waterborne outbreaks, among children in daycare centers, childcare and healthcare workers, international travelers, backpackers, hikers, swimmers swallowing infected water, and people handling infected cattle. The infection is spread by animals, the fecal–oral route, and indirectly through contaminated water. More than 100 outbreaks of cryptosporidiosis have been associated with contaminated drinking water; the largest documented waterborne outbreak of diarrhea occurred in Milwaukee in 1993 [30]. Its pathogenesis is multifactorial, with effects on the immune system causing inflammation, and apoptosis of the intestinal epithelium. Interferon gamma and declining CD4 counts are directly related to the severity of the disease.

In the immunocompetent, the infection causes self-limiting, watery diarrhea lasting 2 weeks; however, it is potentially life-threatening in immunocompromised patients, especially those with acquired immunodeficiency syndrome (AIDS). There are four patterns of disease in AIDS: asymptomatic infection, with no change in bowel habits; transient infection, with diarrhea limited to 2 months; chronic diarrhea, with diarrhea for more than 2 months; and fulminant infection [29]. Fulminant infection occurs.
in patients with a CD4 count of <50 cell/µl. The diarrhea is watery, with a frequency of ten stools per day, and is accompanied by abdominal pain, nausea, vomiting, and fever.

The parasite can invade through the wall and spread extraintestinally, especially in patients with AIDS. The disease has extra-gastrointestinal manifestations in the biliary tree, pancreas, and lungs, as seen in the immunocompromised population [31]. The most common cholangiographic pattern is papillary stenosis with intrahepatic sclerosing cholangitis; this is usually seen in patients with CD4 count below 100/mm³.

Acid-fast staining, with or without stool concentration on microscopic examination, is the simplest method of detecting oocysts. However, immunofluorescent and enzyme immunoassay tests are superior in sensitivity and specificity, and are now commonly used in diagnostic laboratories [32]. Clinicians should keep in mind that routine O&P stool examinations do not always include tests for cryptosporidium; a special request is often required [4]. PCR-based techniques are available as research tests [9]. The value of serological testing is limited.

The treatment options vary. The clinical course largely depends on the immune status of the patient. Asymptomatic immunocompetent patients need no specific therapy. Supportive therapy (which should include a lactose-free diet) is the key component in symptomatic immunocompetent patients, most of whom spontaneously recover. Treatment with oral nitazoxanide 500 mg twice daily for 3 days can be moderately effective in immunocompetent individuals [33]. However, in the case of HIV-positive individuals, the combination of antiparasitic medications (e.g., nitazoxanide or paromomycin combined with azithromycin) with anti-retroviral therapy is most beneficial [34].

**Cyclosporiasis.** Cyclosporiasis is an intestinal infection caused by the protozoan parasite *C. cayetanensis*. The disease is prevalent in tropical and subtropical regions and is not uncommon in the US. Around 32 foodborne outbreaks of cyclosporiasis reported in the US from 2000 to 2015 were associated with various types of imported fresh produce, including raspberries, basil, snow peas, mesclun lettuce, and cilantro [35]. The Centers for Disease Control (CDC) has identified the disease in patients who did not report international travel. The risk of infection tends to be seasonal and peaks during the summer months [36].

Cyclosporiasis is characterized by profuse, watery diarrhea, anorexia, fatigue, weight loss, nausea, flatulence, abdominal cramping, myalgia, vomiting, and low-grade fever (less common) [37]. Symptoms typically start at an average of 7 days (range 2–14 days) after ingestion of the infective form of the parasite (sporulated oocysts) and, if left untreated, may last weeks to months with remitting and relapsing symptoms. In immunocompromised hosts, the infection causes severe, intractable, voluminous diarrhea which may persist from weeks to months. Extrainestinal manifestation is uncommon. Post infectious arthritis and Guillain-Barré syndrome have been reported post-infection [38, 39]. Biliary tract involvement has been described in AIDS patients.

Cyclosporiasis is diagnosed by examining stool specimens; however, diagnosis can be difficult because patients might not shed enough oocysts in their stool even if symptomatic. Acid-fast staining is often used to identify *Cyclospora* oocysts and is superior to the examinations of routine wet mounts. The demonstration of blue autofluorescence of the oocyst under ultraviolet microscopy is quick and sensitive [37]. Although real-time PCR is more sensitive than conventional diagnostic methods, it is not widely available and needs additional validation in clinical settings [40].

Cyclosporiasis is treated with double-strength TMP/SMX twice daily for 7–10 days. Patients who do not tolerate TMP/SMX may be treated with ciprofloxacin 500 mg twice daily for 7 days.

**Cystoisosporiasis.** *Cystoisospora belli* (C. belli), formerly known as *Isospora belli*, causes an intestinal disease known as cystoisosporiasis. The distribution of this protozoan parasite is worldwide, but is mainly found in tropical and subtropical areas of the world such as the Caribbean, Central and South America, India, Africa, and Southeast Asia. In the US, it is usually associated with daycare centers, psychiatric institutions, immigrants from Latin America, HIV infection and other immunosuppressed conditions [41]. *C. belli* transmitted from person to person through the fecal–oral route.

Immunocompetent individuals are usually asymptomatic. However, clinical symptoms such as mild diarrhea, abdominal discomfort, and low grade fever for approximately one week have been observed in certain individuals. Immunocompromised people experience acute, nonbloody diarrhea associated with crampy abdominal pain, malabsorption, and weight loss; symptoms can last from weeks to months. *Cystoisospora belli* is diagnosed by microscopic identification of the oocyst in the stool sample. If stool examination is negative, examination of duodenal specimens by biopsy or string test may be required. The oocysts can be visualized on wet mounts by microscopy with bright-field differential interference contrast and epifluorescence [42]. They can also be stained by modified acid-fast stain[43].

The typical treatment regimen comprises TMP 160 mg plus SMX 800 mg (one double-strength tablet), orally twice a day for 7–10 days. Immunosuppressed patients may need to be treated longer and/or with higher daily doses. Patients who are allergic to (or are intolerant of) TMP/SMX are usually treated with a daily dose of 50–75 mg of pyrimethamine. Ciprofloxacin, 500 mg, orally, twice a day for 7 days is a second-line alternative.

**Dientamebiasis.** *Dientamoeba fragilis* has a worldwide distribution with a prevalence ranging from 0–82% [44]. The role of *D. fragilis* as a pathogen is controversial because the trophozoites are not invasive and patients are usually asymptomatic [45]. Recent studies on patients infected only with *D. fragilis* have found an association with diarrhea, abdominal pain, nausea, weight loss, anorexia, and flatus, which resolve after eradication [46].

Infection is diagnosed through identification of trophozoites in permanent stain fecal smears (e.g., trichrome). The drug of choice is iodoquinol (650 mg orally, 3 times/day for 20 days). Paromomycin (25–35 mg/kg/day orally, in three divided doses for 7 days), tetracycline (500 mg orally 4 times/day for 10 days), or metronidazole (500 mg to 750 mg 3 times/day for 10 days) are also effective.
Giardiasis. *Giardia intestinalis* (also named *G. lamblia* and *G. duodenalis*) is the most commonly identified cause of parasitic diarrhea, with a prevalence of 2–7% in high-income countries and up to 30% in low-income countries [47]. It is the most common intestinal parasitic disease affecting humans in the US [48]. The infection occurs through ingestion of the cyst during the infectious stage via waterborne, foodborne, and person-to-person transmission. Risk factors for giardia acquisition in the US include foreign travel to regions such as South and Southeast Asia, North Africa, the Caribbean, and South America, day-care settings, immunodeficiency disorders, and sexually active homosexual men [47]. Hikers, backpackers, and campers who drink untreated or improperly treated water from lakes, streams or wells are at high risk of contracting giardia. The disease commonly affects children under age 5 and adults aged 25–44 years.

Clinical manifestations of giardiasis are widely variable but mainly present as acute or chronic diarrhea associated with abdominal cramps, nausea, malabsorption, and weight loss. Bloody bowel movement suggests another disease. Severe disease occurs in children younger than 2 years and patients with hypogammaglobulinemia. Lactose intolerance occurs in up to 40% of patients and might even persist months after the infection is cured [47]. In malnourished children, the infection leads to growth retardation. Recent evidence suggests that it might be a risk factor for zinc deficiency in school-aged children [10]. There is a link between secretory IgA deficiency, giardiasis, and nodular lymphoid hyperplasia [49].

The first test for giardiasis is stool examination of cysts and trophozoites or stool antigen tests. The sensitivity of antigen detection assays is superior to stool microscopy. Currently, examination of duodenal aspirate and/or biopsy for the parasite is seldom performed. Real-time PCR in developed settings is a superior test, recently approved in the US [50]. These molecular methods are highly sensitive with sensitivity greater than 90% and specificity nearly 100% [9, 50]. However, they are not yet widely available. Serological tests are not appropriate for clinical diagnosis of giardiasis.

The treatment of choice for giardiasis includes metronidazole, tinidazole, and nitazoxanide. A single 2g dose (equivalent in children) of tinidazole is proven to have superior clinical efficacy and compliance compared to metronidazole. When the clinical suspicion is high, even if stool test is negative, an empiric therapy with metronidazole is appropriate. Alternate medications include paromomycin, quinacrine, and furazolidone; however, Quinacrine is no longer available in the US. If symptoms persist, lactose intolerance should be ruled out before repeating the therapy [47]. In treatment failures, repeat therapy with the same drug (higher doses) or combination therapy might work. Nitazoxanide alone appears to be as effective as metronidazole. Patients with multiple treatment failures should be evaluated for common variable immunodeficiency [47].

**Microsporidiosis.** The microsporidia are a group of obligate intracellular parasitic spore-forming fungi that were historically classified as protozoans. Infection is mainly of zoonotic origin, but human-to-human transmission can occur by ingestion of spores. Microsporidiosis is most common among patients with AIDS and less common in other immunocompromised states [51].

In immunocompetent hosts, the infection is rare. It most commonly presents as self-limiting diarrhea, although ocular infections have also been reported. In patients with AIDS, intestinal infections with *Enteroctozytozoon bieneusi* (*E. bieneusi*) and *Encephalitozoon* have been reported in 10–40% of the patients, causing chronic diarrhea with anorexia, bloating, weight loss, and wasting. Fever is unusual. Extraintestinal manifestations in immunocompromised persons associated with microsporidians (including the genera *Enteroctozytozoon*, *Encephalitozoon*, *Brachiola*, *Vittaforma*, *Pleistophora*, *Trachipleistophora*, and *Microsporidium*) include biliary tract disease (AIDS cholangiopathy), genitourinary infection with cystitis, kidney disease, hepatitis, peritonitis, myositis, respiratory infections including sinusitis, central nervous system infections including granulomatous encephalitis, and disseminated infections [52]. Ocular infections with *Encephalitozoon* species cause conjunctivitis and stromal keratitis (associated with trauma in immunocompetent patients), presenting as redness, photophobia, and loss of visual acuity.

Diagnosis of intestinal microsporidiosis by modified trichrome or chromotrope 2R-based staining and Uvitex 2B or calcofluor fluorescent staining reveals spores in smears of feces or duodenal aspirates [51]. Immunofluorescence assays (IFAs) and species-specific PCR assays are also available for microsporidia detection.

For intestinal and disseminated (not ocular) infection due to microsporidia other than *E. bieneusi*, the drug of choice is albendazole 400mg orally, twice daily; treatment should continue until immune reconstitution has been maintained for at least 6 months. Although albendazole is likely less effective against *E. bieneusi*, there are reports of success with albendazole therapy in immunosuppressed patients. Initiation and optimization of antiretroviral therapy is the cornerstone of treatment of microsporidiosis in HIV-infected patients. Immune restoration to CD4 cell count >100 cells/mm³ is associated with resolution of symptoms of enteric microsporidiosis.

**Luminal protozoal disease with special consideration**

*Chagas disease.* Chagas disease is endemic to rural populations of Central and South America [53]. With the initiative of compulsory blood-bank screening, there is a decreased burden of Chagas disease in Latin America. *Trypanosoma cruzi* (*T. cruzi*) transmission primarily occurs when humans are exposed to contaminated feces of infected, hematophagous triatomine (large, blood-sucking insects) vectors. Alternate transmission mechanisms are congenital, blood transfusion, organ transplants, and to a lesser extent, ingestion of uncooked food contaminated with feces of infected bugs. Up to 20 years after the infection, nearly 30–40% of patients develop cardiomyopathy, peripheral nervous system damage or dysfunction of the digestive tract, often leading to megaesophagus and megacolon [53]. The megaesophagus resembles idiopathic achalasia in symptomatology and imaging studies. An increased incidence of esophageal cancer has been reported in patients with megaesophagus.

The history of exposure to *T. cruzi* is the first consideration in the diagnosis of acute Chagas disease. The diagnosis of acute Chagas disease is made by detection of circulating parasites, which
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<th>GI manifestations mimic</th>
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<td><strong>Ascaris</strong> A. lumbricoides [58, 84]</td>
<td>• Worldwide but most common in tropical and temperate areas</td>
<td>Intestinal ascariasis • Abdominal pain • Nausea and vomiting Hepato-biliary and pancreatic Ascaris Appendicular ascariasis Gastric ascariasis</td>
<td>• Ascaris pneumonia • Loeffler’s syndrome • Growth retardation • Cognitive dysfunction • Malnutrition</td>
</tr>
<tr>
<td><strong>Capillaria</strong> C. philippinensis [59, 60]</td>
<td>• Philippines • Japan • Korea • India • Thailand</td>
<td>Intestinal capillariasis • Cardiomyopathy (rare)</td>
<td>• Chylothorax • Chylopericardium • Cervical granulomas • Tubovarian abscess</td>
</tr>
<tr>
<td><strong>Diphyllobothriasis</strong> Diphyllobothrium latum [85]</td>
<td>• Europe • Asia (Palearctic distribution)</td>
<td>Abdominal pain • Megaloblastic anemia</td>
<td>• Diarrhea • Megaloblastic anemia</td>
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<td><strong>Enterobius</strong> E. vermicularis [18, 62]</td>
<td>• Worldwide</td>
<td>Perianal itching • Enterobiasis</td>
<td>• Enuresis • Vulvovaginitis • Cervical granulomas • Tubovarian abscess</td>
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<td><strong>Hookworm disease</strong> A. duodenale</td>
<td>• Tropical and subtropical countries • Southern US</td>
<td>Iron deficiency anemia • Diarrhea • Protein malnutrition</td>
<td>• Ground itch • Loeffler’s syndrome • Waskana disease • Chlorosis</td>
</tr>
<tr>
<td><strong>Hymenolepis</strong> Hymenolepis nana [86]</td>
<td>• Latin America • Egypt • India</td>
<td>Abdominal pain • Pruritis ani • Intestinal schistosomiasis</td>
<td>• Cysticercosis of the brain, spinal cord, eye, and heart</td>
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<td><strong>Strongyloides</strong> S. stercoralis [69, 87]</td>
<td>• Southeastern US • Europe • Australia • Japan • Tropical and subtropical countries</td>
<td>Abdominal pain • Diarrhea • Protein malnutrition • Intestinal schistosomiasis</td>
<td>• Enterobiasis • Gall bladder cancer</td>
</tr>
<tr>
<td><strong>Schistosomiasis</strong> S. mansoni</td>
<td>• Africa • South America • Caribbean • Indonesia • China • Southeast Asia</td>
<td>Intestinal schistosomiasis • Diarrhea • Weight loss • Strongyloides hyper infection syndrome • Profuse watery or bloody diarrhea with signs of sepsis</td>
<td>• Enterobiasis • Gall bladder cancer</td>
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<tr>
<td><strong>Taenia</strong> T. saginata T. solium</td>
<td>• North America • Europe • Australia • New Zealand</td>
<td>Taeniasis • Loss of appetite • Change in stool pattern</td>
<td>• Cysticercosis of the brain, spinal cord, eye, and heart</td>
</tr>
<tr>
<td><strong>Trichinellosis</strong> T. spiralis</td>
<td>• North and South America • Europe • Russia</td>
<td>Intestinal trichinellosis • Fever • Diarrhea • Systemic trichinellosis</td>
<td>• Canker sores • Metastatic infection • Inflammation of the skin • Dermal inflammation • Skin rash • Skin ulceration • Skin abscess • Skin abscesses</td>
</tr>
<tr>
<td><strong>Trichuriasis</strong> T. trichiura [84, 91]</td>
<td>• Worldwide but common in tropical and temperate zones</td>
<td>Lower abdominal pain • Mucoid or bloody diarrhea • Rectal prolapse (rare)</td>
<td>• Impaired growth • Chronic anemia</td>
</tr>
</tbody>
</table>
are often seen in wet preparation of anticoagulated blood or a buffy coat viewed under a cover slip. Testing for IgM is not useful in diagnosing acute disease. Diagnosing the chronic infection is also based on the patient’s clinical findings and his likelihood of being infected, along with at least two different serological methods (usually ELISA, indirect immunofluorescence, or indirect hemagglutination) to confirm the diagnosis to detect IgG antibodies to *T. cruzi* antigens [53–55]. PCR assays for the detection of *T. cruzi* infection have shown variable sensitivity and are not commercially available [55].

Nifurtimox (8–10 mg/kg daily for 90–120 days) and benznidazole (better tolerated, 5–10 mg/kg daily in two or three divided doses for 60 days) are the only drugs that have shown benefit in acute and congenital Chagas disease. The treatment of megaesophagus is similar to that of idiopathic achalasia.

**Helminths**

The helminths of clinical importance are the nematodes (roundworms, e.g., *Schistosomes*), cestodes (tapeworms, e.g., *Taenia saginata*, *Taenia solium*, and *Diphyllobothrium*) and nematodes. The nematodes are roundworms (*Ascaris lumbricoides*), hookworm (*Ancylostoma duodenale* and *Necator americanus*), pinworms (*Enterobius vermicularis*), and whipworm (*Trichuris trichiura*) (Table 2).

**Ascaris.** The infection is endemic to Sub-Saharan Africa, South America, Asia, and the Western Pacific, with a world prevalence of 25% (0.8–1.22 billion people) [56]. It is commonly associated with poor personal hygiene, crowding, poor sanitation and places where human feces are used as fertilizer. Cases of ascariasis in non-endemic areas occur in immigrants and travelers. The infection occurs fecal–orally by the ingestion of eggs. The eggs attach to the mucosa of the small intestine and the larvae migrate via the portal circulation into the pulmonary circuit and to the alveoli, giving rise to a pneumonitis-like illness. They can be coughed up the respiratory tract and enter back into the GI tract; from there, they migrate to the duodenum, hepatobiliary tree, pancreas, and the small intestine giving rise to obstructive symptoms.

The symptoms of ascariasis depend on the worm load and the location of the parasite. Most patients with Ascaris infections are asymptomatic, or produce only mild abdominal discomfort, nausea, dyspepsia or loss of appetite. A heavy worm load may cause weight loss and malnutrition. Complications of chronic ascariasis include intestinal obstruction, obstruction of bile and pancreatic ducts, appendicitis, intestinal perforation, intussusception, and bowel necrosis requiring emergent surgical intervention. Although the adult worms mostly live in the jejunum, they can migrate up into the common bile duct and reach the intrahepatic ducts and the gallbladder (Fig. 2). This migration may result in biliary colic with severe pain in the right upper quadrant that is continuous or recurrent. Hepatobiliary ascariasis (HBA) is now a recognized clinical entity with varied symptomatology. The obstruction of the biliary tree causes jaundice, cholecystitis, cholangitis, acute pancreatitis, and liver abscess [57]. Intestinal and appendicular ascariasis are other forms of ascariasis with acute obstructive presentation [58]. The diagnosis of Ascaris is made by stool examination for eggs (usually sufficient) along with peripheral eosinophilia (during the tissue migration phase of infection).

It is preferable to treat all infections, including mild or asymptomatic, with oral albendazole 400 mg single dose, mebendazole 500 mg single dose or 100 mg twice daily for 3 days.

**Capillariasis.** Capillariasis is an infection caused by two species of nematodes, *Capillaria hepatica*, which causes hepatic capillariasis, and *Capillaria philippinensis* (*C. philippinensis*), which causes intestinal capillariasis. According to the CDC, only 1500 cases of intestinal capillariasis have been reported since 1963 worldwide. Although rare in the US, it is more common in Asia, especially in Thailand and the Philippines. The infection occurs when human beings consume raw or undercooked fish that contains capillaria larvae [59]. The larvae of *C. philippinensis* reside in the human small intestine, where the female deposits unembryonated eggs. Some of these eggs can become embryonated, which leads to autoinfection and in turn to hyperinfection.

Clinical features of the disease at onset include borborygmi and intermittent diarrhea, followed by voluminous diarrhea (8–10 stools daily), anorexia, malaise, and vomiting that can culminate into protein-losing enteropathy [59]. The diagnosis is established by detection of eggs and parasites in the stool or via a small intestinal mucosal biopsy [60]. Capillariasis is treated with metronidazole 200 mg orally twice a day for 20 days.

**Enterobiasis.** *Enterobius vermicularis* (*E. vermicularis*), a small, thin, white roundworm frequently called pinworm, is a common parasitic infection worldwide, particularly in temperate climates (Fig. 3). It is also frequently observed in institutionalized individuals and household members of infected persons. Pinworm is the most common worm infection in children between 5 and 10 years of age in the US [61].

The spread of infection is accelerated by overcrowding and lack of hygiene. The eggs are deposited around the anus by the worm. Infestation is by contamination of food with the eggs or through contaminated clothing. Autoinfection also occurs as a result of scratching the perianal area and contaminated food, thumb-
Hookworm disease. Hookworm disease is caused by *Ancylostoma* sp. and *Necator americanus*. *Ancylostoma duodenale* (A. duodenale) is more prevalent in North Africa, the Middle East, and Europe. Infection occurs by skin penetration when walking barefoot in soil contaminated with hookworms. *A. duodenale* can also be transmitted orally. The larvae migrate to the right heart and then to the pulmonary vasculature. From lung capillaries, the larvae rupture and enter lung parenchyma, where they are coughed up and swallowed into the GI tract.

Hookworm disease manifests with varying GI and pulmonary symptoms. Classic hookworm disease is a GI infection that causes iron deficiency anemia and protein malnutrition when the blood loss by the worm exceeds the host's intake and reserves of iron and protein [64, 65]. The adults attach to the mucosa of the small intestine and cause anemia by ingesting blood, rupturing erythrocytes, and degrading hemoglobin in the host with hemoglobinases [66]. There is an intestinal inflammation with epigastric pain, nausea, vomiting, and diarrhea [67]. In children, hookworm infection may cause growth retardation, intellectual and cognitive impairment. The pulmonary manifestations resemble allergic asthma.

The standard method for diagnosis is by stool examination for hookworm eggs and peripheral eosinophilia on complete blood count [67]. An iron supplement alone can restore the normal hemoglobin level; however, anemia recurs unless antihelminthic therapy is given. Oral albendazole 400 mg single dose is the treatment of choice [68].

*Strongyloidiasis.* Strongyloidiasis infection is caused by *Strongyloides stercoralis* (S. stercoralis), which is endemic to Asia, Africa, Oceania, South America, and Southern Europe. In the US, the parasite has been reported in the southeastern states (Kentucky, Virginia, Tennessee, and North Carolina). Predisposing factors include immigrants from endemic areas, military veterans who have lived in endemic areas, malnutrition, chronic obstructive pulmonary disease (COPD), chronic renal failure, alcoholism, and patients with underlying malignancies [69]. The primary mode of infection is through contact with soil contaminated with free-living larvae. The larvae on contact with skin penetrate it and migrate through the body, first to the lungs and eventually to the small intestine, where they burrow and lay their eggs. Strongyloidiasis can be a chronic, life-long infection, due to its autoinfective cycle, and remain asymptomatic [70]. In the majority of infected individuals, *Strongyloides* causes a chronic, asymptomatic infection, but with changes in immune status and parasite load, hyperinfection syndrome (HIS), and disseminated disease can occur [71]. Strongyloidiasis can be severe and life-threatening (i.e., HIS) in those who are on steroid therapy (asthmatics or COPD exacerbations, lupus, gout, or inflammatory bowel disease (IBD)), human T-cell leukemia-lymphoma virus (HTLV-1) infected individuals, with hematologic malignancies and transplant recipients [69, 70, 72]. Peripheral eosinophilia is a feature of *Strongyloides* infection, but it is frequently absent in a disseminated infection and in patients who are receiving corticosteroids [73]. Although HIS can occur in any person, disseminated infection occurs mainly in the immunocompromised host.

Adult worms and larvae migrating to the small bowel mucosa may produce epigastric pain that mimics peptic ulcer pain. In patients with HIS, the GI manifestations include abdominal pain, nausea, vomiting, diarrhea, ileus, and edema of the bowel, which can lead to intestinal obstruction. The clinical picture may resemble that of ulcerative colitis. Extraintestinal manifestations include maculopapular or urticarial rashes, pulmonary symptoms such as pneumonitis, and CNS symptoms such as meningitis and brain abscesses.

Uncomplicated strongyloidiasis can be diagnosed by identification of larvae in the stool and duodenal fluid; however, the test is relatively insensitive. A serological test such as enzyme-linked immunoassay (EIA) is currently recommended by the CDC because of its greater sensitivity (90%) [74]. However, the specificity of the test is lower because of the crossreactivity with other helminthic infections. An assay that uses a luciferase immuno precipitation system to identify IgG antibodies to a recombinant

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Fig. 3 Demonstration of pinworms (*Enterobius vermicularis*) on colonscopic examination.
Strongyloides antigen and S. stercoralis immunoreactive antigen has 100% sensitivity and specificity [75]. HIS can be readily diagnosed by examining stool, sputum, other body fluids and tissues, which typically contain large numbers of filariform larvae. Upper GI series show prominent mucosal folds in the gastric antrum and an irritable, spastic, duodenal bulb and C-loop with prominent, thickened, spiked transverse mucosal folds (valvulae conuventes).

The endoscopic appearance of strongyloidiasis ranges from normal-appearing mucosa to ulcerative and catarrhal duodenitis [76, 77]. Patients with a clinical and histopathologic diagnosis of “idiopathic” eosinophilic gastroenteritis need to be promptly evaluated for Strongyloides because larvae may not always be apparent on initial evaluation, and therapy with corticosteroids may lead to fatal hyperinfection if the diagnosis of strongyloidiasis is missed [73]. The first-line therapy for uncomplicated strongyloidiasis is ivermectin single dose 200µg/kg orally for 1–2 days; this is better tolerated than thiabendazole 25mg/kg twice daily. Albendazole PO 400mg twice a day for 10–14 days is an alternative. HIS or severe, complicated strongyloidiasis requires treatment with ivermectin for at least 7 days until the stool, sputum, and urine examinations are negative for the infection [69]. Resolution of eosinophilia does not always indicate clearance of Strongyloides. For both uncomplicated and complicated strongyloidiasis, the goal is to eradicate the infection; hence, follow-up examinations are indicated. Repeat treatment is necessary if larvae are identified in the feces 2 weeks after completion of the therapy.

Schistosomiasis. Schistosomiasis is a major public health problem in many countries of the developing world. The five species of organisms causing the disease in humans are Schistosoma mansoni (S. mansoni), Schistosoma haematobium (S. haematobium), Schistosoma japonicum (S. japonicum), Schistosoma intercalatum (S. intercalatum), and Schistosoma mekongi (S. mekongi). The endemic countries for S. mansoni are mainly in Africa, the Middle East, the Caribbean, Brazil, Venezuela, and Suriname; the organism primarily resides in the mesentery of the large intestine. S. japonicum is endemic in China, Indonesia, and the Philippines; here, it resides chiefly in the mesenteric veins of the small intestine.

Acute schistosomiasis is mostly asymptomatic in endemic areas. Patients from non-endemic areas may develop symptoms of acute schistosomiasis (katayama fever) 2–12 weeks after exposure, especially to S. japonicum and S. mansoni. Onset of fever is acute and often associated with chills, fatigue, headache, myalgia, abdominal pain, diarrhea, and sometimes bloody stools [78]. The clinical picture may resemble IBD. The symptoms and signs usually resolve in 2–10 weeks, but persistent and more severe disease may occur with heavy infection. Chronic schistosomiasis results from the eggs retained in the intestinal wall and mesentery, which provoke granulomatous inflammation and lead to microulcerations, pseudopolyps, muscular irritation, and microscopic bleeding. This manifests as colicky, hypogastic pain or pain in the left iliac fossa, diarrhea that may alternate with constipation, and hematochezia. Chronic intestinal disease may result in colonic or rectal stenosis. Colonic polyposis may manifest as protein-losing enteropathy and an inflammatory mass in the colon which may mimic cancer.

A diagnosis of schistosomiasis is made by finding schistosome eggs in feces, urine, or a rectal biopsy specimen, or by demonstrating circulating antigens in serum and urine [79, 80]. Praziquantel, a pyrazinoisoquinoline derivative, is the drug of choice for the treatment of schistosomiasis, given at 60 mg/kg orally in divided doses (3 × 20 mg/kg every 4 h) for 1–2 days [80].

Taeniais. Taenia is a zoonotic disease caused by the tapeworms, Taenia saginata (T. saginata), or beef tapeworm), Taenia solium (T. solium, or pork tapeworm) and Taenia asiatica (T. asiatica, or Asian tapeworm). Although T. saginata has a worldwide distribution, in the US the prevalence is less than 1%. The infection is associated with people who have traveled to rural areas outside the US where the infection is endemic or in the immigrants from Latin America. Locally acquired infections are rare but have been diagnosed in Los Angeles, New York, Chicago, and Oregon.

The infection occurs upon ingestion of raw or undercooked meat and manifests as abdominal discomfort or weight loss. The reported sequelae to intestinal taeniasis include gall bladder perforation, appendicitis, and bowel obstruction. The aberrant encystment of the larval stage of T. solium eggs can occur in muscles, eyes, subcutaneously, and in the central nervous system (CNS); the most common manifestations are ocular and in the CNS. The presence of the cysts in the CNS, also known as neurocysticercosis (NCC), is associated with the highest mortality.

The diagnosis of adult Taenia carriers relies upon direct microscopy of expelled eggs in feces; however, due to the intermittent nature of egg shedding, the sensitivity of the test is low and ranges from 3.9–52.5% [81]. With the advent of coproantigen ELISA test, a sensitivity/specificity of 96.4/100%, respectively, has been achieved for detection of T. solium [82]. Currently, PCR and antibodies toward T. solium excretory secretory (TSES) antigens are used [81].

The drug of choice for the infection is Albendazole 400mg orally thrice daily for 3 days and has demonstrated a cure of 100%.

Trichuriasis. Trichurus trichiura (T. trichiura, or whipworm) is the third most common roundworm in humans. It occurs in areas where human feces are used as fertilizer or where defecation onto soil happens. The infection spreads from person to person by the fecal–oral route. Worldwide, the infection occurs more frequently in the tropics with poor sanitation practices among children. Trichuriasis is also seen in the southern US. People with mild infections are usually asymptomatic with evidence of peripheral eosinophilia [83]. However, patients with heavy worm burden can experience frequent, painful Passage of stool that contains a mixture of mucus, water, and blood (Trichuris dysentery syndrome). Rectal prolapse can also occur. Heavy infection in children can lead to iron deficiency anemia, growth retardation, and impaired cognitive development [83]. Trichuriasis is diagnosed by microscopically identifying whipworm eggs in a stool sample or adult worms on the mucosa of the prolapsed rectum or colonoscopy. Anthelmintic medications, such as albendazole and mebendazole, are effective and generally given for 3 days (Table 3).
<table>
<thead>
<tr>
<th>Name of the parasitic disease</th>
<th>Stool O&amp;P (sensitivity/specificity)</th>
<th>Peripheral eosinophilia</th>
<th>Fecal immunoassay (sensitivity/specificity)</th>
<th>Serology (sensitivity/specificity)</th>
<th>Polymerase chain reaction (sensitivity/specificity)</th>
<th>Other tests specific for infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal amebiasis [1, 92]</td>
<td>Cysts and trophozoites (25-60/10-50%)</td>
<td>–</td>
<td>TechLab <em>Entamoeba histolytica</em> II (100/94.7%)</td>
<td>ELISA (90/85%)</td>
<td>Real-time PCR 95/100%</td>
<td>Colonoscopy and biopsy</td>
</tr>
<tr>
<td>Balantidiasis [23]</td>
<td>Trophozoites (wet mount)</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Colonoscopy and biopsy</td>
</tr>
<tr>
<td>Blastocystosis [28, 93]</td>
<td>Parasites (Trichrome stain) (82/100%)</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>–</td>
<td>Xenic in vitro culture (Jones' medium)</td>
</tr>
<tr>
<td>Chagas disease [53, 55]</td>
<td>Motile trypomastigotes (Acute phase)</td>
<td>–</td>
<td>NA</td>
<td>Positive IgG (ELISA) (Chronic infection)</td>
<td>Varially detectable</td>
<td>Blood culture or specimen culture, Microscopic examination of lymph node, pericardial and cerebrospinal fluid</td>
</tr>
<tr>
<td>Cryptosporidiosis [1, 9]</td>
<td>Oocyst (modified ZN stain)</td>
<td>–</td>
<td>TechLab 98-100/94-100%</td>
<td>NA</td>
<td>Real-time PCR 100/100%</td>
<td>Intestinal biopsy</td>
</tr>
<tr>
<td>Cyclosporiasis [1, 41]</td>
<td>Oocyst (modified ZN stain or autofluorescence)</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>Real-time PCR 87/100%</td>
<td>Jejunal aspirates and biopsy, Flow cytometry</td>
</tr>
<tr>
<td>Cyclosporiasis [1, 41]</td>
<td>Oocyst (modified ZN stain or autofluorescence)</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Duodenal biopsy or string test</td>
</tr>
<tr>
<td>Dientamebiasis [44, 46]</td>
<td>Trophozoites (Permanent stained smear)</td>
<td>+</td>
<td>NA</td>
<td>Not commercially available</td>
<td>Real time PCR 88-100/100%</td>
<td>Xenic in vitro culture</td>
</tr>
<tr>
<td>Giardiasis [1, 50]</td>
<td>Cysts and trophozoites (Permanent stained smear) (66.4/100%)</td>
<td>–</td>
<td>TechLab Giardia 98-100/94-100%</td>
<td>NA</td>
<td>Real-time PCR 98/100%</td>
<td>Duodenal aspiration and biopsy</td>
</tr>
<tr>
<td>Microsporidiosis [51]</td>
<td>Endospore (Modified trichrome stain)</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>Available</td>
<td>Small intestinal biopsy with or without electron microscopy examination</td>
</tr>
<tr>
<td>Ascariasis [58]</td>
<td>Eggs (Simple smear is sufficient)</td>
<td>+(Acute phase)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Larvae can be found in gastric aspirates, Worms readily visible in USG, CT scan</td>
</tr>
<tr>
<td>Capillariasis [60]</td>
<td>Ova or larvae</td>
<td>+(uncommon)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>Enterobiasis [62]</td>
<td>Eggs (low yield)</td>
<td>–</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Scotch tape test</td>
</tr>
<tr>
<td>Hookworm disease [67]</td>
<td>Eggs (Direct fecal smear/direct wet mount)</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Iron deficiency anemia</td>
</tr>
<tr>
<td>Schistosomiasis [80, 84]</td>
<td>Eggs (Concentration procedures needed)</td>
<td>+</td>
<td>NA</td>
<td>FAST-ELISA Immunoblot techniques</td>
<td>Real-Time PCR 84/100%</td>
<td>Liver &amp; rectal biopsy</td>
</tr>
<tr>
<td>Strongyloidiasis [74, 95]</td>
<td>Rhabditiform larvae (Direct smear/concentration methods)</td>
<td>+</td>
<td>NA</td>
<td>(ELISA) 83-93/95% LIPS (100/ 100%)</td>
<td>Varies, low sensitivity but high specificity</td>
<td>Duodenal aspiration and biopsy</td>
</tr>
<tr>
<td>Taeniaiasis [81, 82]</td>
<td>Eggs and proglottids</td>
<td>+</td>
<td>NA</td>
<td>Useful in early invasive stages</td>
<td>NA</td>
<td>Examination of proglottids required for species determination</td>
</tr>
<tr>
<td>Trichuriasis [83]</td>
<td>Eggs (Simple smear is sufficient)</td>
<td>+</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>Colonoscopy (adult worms seen)</td>
</tr>
</tbody>
</table>

NA Not available, ZN Ziehl–Neelsen stain, USG Ultrasonography, CT Computed tomography, ELISA Enzyme-linked immunosorbent assay, LIPS Luciferase immunoprecipitation systems, FAST-ELISA Falcon assay screening test-enzyme-linked immunosorbent assay.

aPCR sample from blood
1. Restrict stool examination to patients with persistent diarrheal illness with a duration greater than 7 days. Utility of the O&P examination in long term hospitalized patients (>3 days) is not recommended. Eliminating O&P examinations on hospitalized patients would decrease hospital and patient costs without altering patient care.

2. Giardiasis and cryptosporidiosis are the most common parasitic infections causing diarrhea in the US. When these infections are suspected, a stool immunoassay (EIA) or direct immunofluorescence assay (DFA) test is rapid, highly sensitive and superior to traditional O&P examination. Both these methods are available in commercial kits. *E. histolytica* is the third most common parasite in the US and has been reported in some US populations (e.g., men who have sex with men, children in day care, institutionalized patients). We suggest *E. histolytica* antigen, EIA over O&P examination for detection of *E. histolytica*. Furthermore, traditional O&P cannot routinely distinguish between pathogenic *E. histolytica* and non-pathogenic *E. dispar*. Although TaqMan-based real-time PCR assay for identification of *C. parvum*, *C. hominis* and *E. histolytica* is highly sensitive and validated at CDC, the test is not widely available.

3. If the above tests are negative and diarrhea persists in an immunocompetent patient, it is unlikely that the diarrheal illness is secondary to parasitic infections and non-infectious causes need to be considered highly. However, in patients who are persistently symptomatic with a history of recent travel or residence in a parasitic region, O&P with wet mount/AFB stain/special stain for detection of rare parasites (e.g., helminthes, *Strongyloides*, *Cyclospora*, *Cystoisospora*) is reasonable to consider. Although stool concentration methods are recommended to better diagnose few of the parasites, the technique is unpopular in most of the clinical laboratories in the US. Various conventional and real time PCR have been developed to detect *C. cayetanensis*, which can be useful in the context of a possible outbreak of diarrheal illness (e.g., multiple people with diarrhea who shared common food or a sudden rise in observed diarrheal cases). Antibody detection tests for *Strongyloides* can be used in symptomatic patients because of its higher sensitivity. Routine testing for organisms such as *D. fragilis* and *B. hominis* is not recommended because these organisms are generally considered as non-pathogenic and rarely associated with symptoms.

4. Immunocompromised patients (such as patients with HIV/AIDS, transplant recipients) usually present with severe, recurrent and persistent diarrhea with a higher rate of complications. Common parasitic infections associated with an immunocompromised state are either well-established enteric pathogens, e.g., *E. histolytica*, *G. lamblia*, and *S. stercoralis* or an opportunistic pathogen, e.g., *Cryptosporidium*, *Microsporidia*, *Cystoisospora*, and *Cyclospora*. The rate of parasitic infection in HIV/AIDS patient also largely depends upon the endemicity of a particular parasite in the community. Therefore, we suggest stool EIA for common pathogens such as *E. histolytica*, *G. lamblia*, and *Cryptosporidium* and stool O&P with and without special stains (AFB) for detection of above mentioned rare parasites.

5. Given the very low incremental yield of second and third samples we discourage repeating the O&P test which subsequently result in increase hospital costs, laboratory workloads, and burden on patients.

6. Peripheral eosinophilia is common in helminthic infections and usually more pronounced early in the disease. In contrast, protozoal infections do not cause peripheral eosinophilia with the exception of *C. belli* and *D. fragilis*.

7. Endoscopic procedures are seldom used in diagnosing parasitic diseases. Demonstration of edema, granularity, and small discrete ulcers by colonoscopy and presence of erythrophagocytic trophozoites in biopsy has been proven useful in diagnosing disseminated *E. histolytica* infection. Few case reports and case series have demonstrated endoscopic features of *Strongyloides* (Please refer to text for details). Although demonstration of trophozoites/oocysts/larvae in the duodenal aspirates (String test or Enterotest) and biopsy is an alternative to O&P for parasites such as *Giardia*, *Cystoisospora*, and *Strongyloides*, the utility of string test in detection of parasitic infections in a low prevalence setting is unknown. An advantage of biopsy especially in patients with HIV/AIDS or symptoms of malabsorption is the ability to detect a histologic abnormality that is not caused by parasite such as *Giardia* and to identify other pathogens or non-infectious causes.

8. The need for empiric treatment in parasitic infections is very limited. Special situations need to be considered. For example, empiric treatment for *E. histolytica* before administering high dose steroid therapy in patients with acute ulcerative colitis with a history of recent travel or residence in a parasitic region.

The above approach will substantially reduce the abuse of stool O&P but will not totally negate the utility of the test. At this time, there is no strong evidence to recommend one or the other diagnostic tests. We believe that our recommendations are supported by data on the sensitivity, specificity and cost effectiveness of various tests for parasitic diseases in the US. This article also briefly summarizes the clinical manifestations of GI parasites and their clinical mimics.

**CONFLICT OF INTEREST**

**Guarantor of the article:** Dr. C.S. Pitchumoni, MD.

**Specific author contributions:** SM wrote the paper with the help of other co-authors. DPS analyzed the literature for the tables. DA
reviewed the paper for scientific accuracy. CSP formulated the idea, structure and the content for the paper.

Financial support: None.

Potential competing interests: None.

REFERENCES

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1. Regarding amebiasis, which statements are correct:
   a. It is the third most common parasitic infection in the U.S.
   b. Most infections are symptomatic and lead to diarrhea
   c. Dysentery is the most common clinical presentation
   d. Symptoms usually last for weeks if left untreated
2. Giardiasis
   a. most commonly identified cause of parasitic diarrhea
   b. upper GI symptoms such as nausea are common
   c. persistent diarrhea despite therapy usually implies a resistant strain
   d. is more common in IgA deficient patients

True or False

3. Cryptosporidia can cause sclerosing cholangitis and papillary stenosis in AIDS patients with CD4 counts <50
4. Protozoa cysts are responsible for the clinical symptoms of the infection
5. The initial O&P study detects a parasitic infection in over 90% of cases; additional O&P’s only add 10% to the yield of the test.
6. Cryptosporidia is routinely tested for during O&P tests.
7. Blastocystis is a common parasite identified in the US, it is usually self-limited and therapy is not always needed
8. An ameboma is usually located in the right colon, mimics cancer, and can cause intestinal obstruction
9. A luminal amebicide such as paromomycin or diloxanide should be used to prevent recurrent infection.
10. Cyclosporiasis typically resolves without medical therapy
11. Pruritus ani is a common symptom in ascariasis
12. Esophageal dysmotility caused by Trypanosoma cruzi usually develops within weeks after initial infection
13. Peripheral eosinophilia, a common feature of strongyloides infection is often absent in disseminated disease or during treatment with corticosteroids
14. Cystoisosporiasis can be diagnosed with duodenal biopsies if the diagnosis is suspected but stool examination is negative
15. Blastocystis species, Entamoeba dispar and Dientamoeba fragilis may be found on O&P exams but rarely cause symptoms
16. When amebiasis is suspected, ulcers should be biopsied at the margins and histologically, flask shaped ulcers are typically found