

Traveler's Diarrhea Due to Intestinal Protozoa

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Intestinal protozoa account for a minority of cases of acute traveler's diarrhea, but they are common pathogens in travelers who experience protracted diarrhea during or after travel. Evaluation of the traveler with chronic diarrhea should include a careful examination for typical infecting organisms, such as *Giardia* and *Entamoeba* species, as well as for emerging parasites, such as *Cryptosporidium* species, *Cyclospora* species, and microsporidia. The microbiology, epidemiology, clinical presentation, and treatment of the most common intestinal parasites found in travelers are presented in this minireview.

It has long been recognized that most cases of traveler's diarrhea are acute in nature and tend to resolve within 5–10 days after the onset of symptoms. Common organisms that cause acute traveler's diarrhea are enterotoxigenic *Escherichia coli*, *Campylobacter jejuni*, *Shigella* species and *Salmonella* species. For patients who are infected with these species, the duration and severity of illness are shortened with antimicrobial treatment. Contrary to popular belief, only a small percentage of cases of acute traveler's diarrhea are due to parasites. Numerous studies have identified intestinal protozoa in only 0%–12% of cases of acute travelers diarrhea (summarized in Peltola and Gorbach [1]). In contrast, intestinal protozoa are the most common infecting organisms identified in travelers with chronic diarrhea. For example, studies performed in Nepal demonstrated that giardiasis was more frequently diagnosed in travelers with diarrhea of >2 weeks' duration than it was in those with diarrhea of <2 weeks' duration [2].

The risk factors for acquisition of intestinal parasites have not been well defined. In general, duration of stay, hygiene, and level of socioeconomic development in the host country have been thought to be associated with the acquisition of intestinal protozoa [3]. The most common infecting organisms identified are *Giardia intestinalis*, *Cryptosporidium parvum*, and

Entamoeba histolytica, although a smaller proportion of infections are due to the microsporidiae and to *Isospora belli*. In recent years, *Cyclospora cayetanensis* has been recognized as a causative organism of chronic diarrhea in returning travelers. In this minireview, I present the microbiology, epidemiology, clinical presentation, and treatment of the most common intestinal parasites found in travelers.

GIARDIA SPECIES

Giardia lamblia, also known as *G. intestinalis* or *Giardia duodenalis*, can produce infection in humans and is also a zoonotic agent. Molecular analysis of isolates of *Giardia* species has shown that these parasites belong to distinct genotypes, some of which demonstrate host preferences and will probably be reclassified as a new species [4]. Infections with *Giardia* species occur worldwide. The ingestion of cysts found in contaminated water or food results in asymptomatic infection, acute self-limited diarrheal illness, or chronic gastrointestinal complaints with intermittent diarrhea. Urticaria and eosinophilia are rarely associated with giardiasis, as is the case with other atopic manifestations.

Giardia species can be visualized in trichrome iodine stains of fecal smears or by use of direct immunofluorescence. However, detection by means of ELISA is becoming the preferred diagnostic tool [5]. The antiparasitic agent of choice remains metronidazole. However, isolates with decreased susceptibility to metronidazole have been described. Albendazole is an alternative to metronidazole that appears to be effective [6]. Two other effective agents, tinidazole and quinacrine, are not available for use in the United States.

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CRYPTOSPORIDIUM SPECIES

Cryptosporidium parvum is a protozoan parasite with zoonotic potential that preferentially infects the small bowel of many animal species, including humans. Oocysts are resistant to chlorinated water and can survive in aquatic environments for a long time [7]. At least 2 distinct transmission cycles occur in nature and are related to specific genotypes. Genotype 1 causes infection in humans, whereas genotype 2 favors a zoonotic transmission [8]. In addition to genotypic differences, phenotypic differences have been demonstrated in vivo and in vitro, as determined by variable degrees of infectivity in humans and in tissue culture systems, which suggests that additional genetic pleomorphisms within the known genotypes exist [9, 10].

Risk factors for the acquisition of cryptosporidiosis include transmission via the fecal-oral route, contact with farm animals or pets, drinking contaminated water [11], and eating contaminated food [12]. As few as 10 oocysts can cause infection in healthy people [13]; perhaps even fewer oocysts can cause infection in immunocompromised patients. Few studies have been performed to assess the prevalence of cryptosporidiosis in long-term travelers. A survey of Peace Corps volunteers who were residing in West Africa demonstrated a 13.6% increase in seroprevalence during a 2-year period [14]. Symptoms of cryptosporidial infection include watery stools, fatigue, abdominal pain, general malaise, and in 20% of patients, nausea and vomiting. Low-grade fever can also occur. Healthy adults with antibodies to whole-oocyst preparations of the parasite, as determined by means of ELISA or Western blot test, are less susceptible to infection [15, 16]. However, the utility of serodiagnosis is limited because of lack of standardization, potential cross-reactivity with other parasites, and the fact that seroconversion after primary and secondary exposures is uncommon [17]. It is likely that the acquisition of specific antibodies and an effective protective cellular response requires repeated exposure.

In HIV-infected people with CD4 cell counts of >200 cells/mL, *C. parvum* infection may resolve spontaneously; however, in the later stages of HIV disease (CD4 cell count, <100 cells/mL), chronic infection can lead to dehydration, malnutrition, and wasting, frequently resulting in death. Patients with HIV and low CD4 T cell counts should exert particular caution when traveling abroad to prevent cryptosporidiosis. Specifically, travelers should avoid drinking water that has not been boiled, and clarithromycin therapy for *Mycobacterium avium* complex prophylaxis should be taken when indicated because this has been shown to have a protective effect for infection with *Cryptosporidium* species [18]. Infection can be diagnosed by identification of oocysts with a modified acid-fast stain of a fresh fecal specimen, but the level of sensitivity is low. Recently, a more sensitive, monoclonal-based direct immunofluorescence assay has been introduced, but it also has a low sensitivity. Commercially available ELISAs have been recently introduced that

are sensitive and specific. Nevertheless, because oocyst excretion is variable, the analysis of several stool specimens may be necessary to confirm the diagnosis.

Treatment of the immunocompetent host is supportive because cryptosporidiosis is self-limited. A small study that used bovine anti-*Cryptosporidium* immunoglobulin in healthy adults who were exposed to *C. parvum* demonstrated a decrease in parasite excretion but no significant decrease in diarrhea [19]. Few options exist for patients with AIDS in whom highly active antiretroviral therapy fails or is not an option. Monotherapy with paromomycin has not been effective; an open-label study of paromomycin and azithromycin demonstrated some efficacy in relieving symptoms and parasitic burden [20]. Nitazoxanide, a broad-spectrum antiparasitic agent, was found to be effective in a double-blind study performed in Mexico [21]; however, the drug demonstrated little efficacy in clinical trials performed in the United States, and it has not been approved by the US Food and Drug Administration.

ENTAMOEBIA SPECIES

Infections with *Entamoeba histolytica* and *Entamoeba dispar* are especially prevalent in Mexico, India, Africa, and Central and South America. The species are morphologically indistinguishable but can be differentiated by zymodeme patterns, monoclonal antibodies, and DNA probes [22]. Infections with *E. dispar* are characteristically asymptomatic, do not elicit a serological response, and are responsible for the majority of infections with *Entamoeba* species. In contrast, infections with *E. histolytica* result in symptomatic illness (80%–98%) or invasive disease (2%–20%) and the production of serum antibodies. However, in indigenous populations, asymptomatic carriage of *E. histolytica* is common [23]. Major routes of transmission are consumption of contaminated water and food or by direct fecal-oral contact. Individuals at highest risk for infection include persons who travel to developing nations, immigrants or migrant workers, immunocompromised persons, and persons housed in mental institutions.

E. histolytica release a pore-forming protein, soluble toxic molecules, and a cysteine proteinase, which can degrade matrix proteins. Host leukocytes, neutrophils, and macrophages also play a role in cell damage when they are lysed and release their toxic products. Ulcerative lesions in the intestinal mucosa and liver abscesses are characterized by a moderate inflammatory response. Advanced lesions have necrotic centers with amoebae concentrated at the outer zone of normal tissue.

E. histolytica can cause intestinal syndromes including the following: (1) a dysenteric syndrome with production of small volumes of bloody, mucoid stools without fecal leukocytes; (2) colitis characterized by ulcerations of the colonic mucosa with typical flask-shaped abscesses; and (3) the formation of a fi-

brotic mass in the intestinal wall (ameboma). Chronic amebic colitis is clinically indistinguishable from inflammatory bowel disease, and those persons who receive corticosteroids are at risk for toxic megacolon and perforation. Infective trophozoites can migrate hematogenously to the right lobe of the liver, causing abscess formation, abdominal pain, jaundice, and fever. Adjacent anatomical structures, such as the pulmonary parenchyma, peritoneum, and pericardium, can become involved. Amoebae can also disseminate to the brain. Immunosuppressed or malnourished individuals, those at the extremes of age, patients with malignancy, and women who are pregnant or in postpartum stages are especially at risk for invasive amebiasis. Indications for surgical drainage of an amebic abscess include large abscess dimensions, impending rupture, location in the left lobe, or lack of therapeutic response.

Identification of *E. histolytica* cysts and trophozoites requires examination of a fresh stool sample and a trichrome stain. New fecal antigen detection methods (e.g., ELISA) may also prove useful. Periodic acid–Schiff–stained tissue obtained by means of colonoscopy may be required to confirm the diagnosis. An episode of dysentery may not necessarily precede abscess formation. Newer serologic assays may improve the detection of invasive disease [24]. After invasive disease occurs, immunity develops to subsequent invasion with *E. histolytica*, but not to colonization, and this immunity is thought to be mediated by cellular mechanisms. The identification of cysts in an asymptomatic host should prompt treatment with diloxanide or paromomycin. Invasive disease, such as severe colitis or parenchymal abscess, should be treated with metronidazole, followed by a luminal agent, such as diloxanide or paromomycin, to prevent future invasion with any remaining cysts. Tinidazole has also been found to be highly effective.

MICROSPORIDIA

Microsporidia are small, obligate, intracellular parasites that infect vertebrate and invertebrate hosts. Only a few of the >1000 species known to belong in this phylum have been identified as pathogenic organisms for humans. Microsporidia have been sporadically reported as a cause of chronic diarrhea that occurs after travel in both otherwise healthy adults and HIV-infected patients [25, 26]. Infection with microsporidia should be considered in cases of chronic diarrhea.

Two species are associated with enteric infection, *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* (formerly known as *Septata intestinalis*). The former is more common. Microsporidia share several common characteristics, including specialized polar tubes, intracellular asexual reproduction, and the formation of thick-walled spores that are able to survive for months in the environment. *E. bieneusi* and *E. intestinalis* can be distinguished morphologically by use of electron mi-

croscopy of small-bowel biopsy specimens or by use of PCR techniques. To date, *E. bieneusi* has only been reported in humans, but it is apparently found worldwide. The prevalence of infection in selected groups of HIV-infected patients in different countries has a range of 1.7%–30%.

Infections with both *E. bieneusi* and *E. intestinalis* are most frequently identified by the presence of diarrhea in persons with CD4 counts <100 cells/mL and, frequently, also in asymptomatic carriers. *E. bieneusi* infects the enterocytes of the proximal jejunum and occasionally spreads to the biliary tract. In comparison, *E. intestinalis* is found in enterocytes, macrophages, and fibroblasts and may also disseminate to the mesenteric nodes and kidney.

Free and intracytoplasmic spores can be stained with Giemsa, Weber's trichrome, or fluorochrome stains (e.g., calcofluor, Uvitex 2B) that have affinity for chitin, but identification of the specific species requires electron microscopy or PCR. Infection of immunocompetent individuals is self-limited. Preliminary data suggests that albendazole may be of use in the treatment of infections with *E. intestinalis* and *Encephalitozoon* species.

ISOSPORA SPECIES

Isoospora belli produces large, oval-shaped oocysts that sporulate outside the body. This process takes 2–3 days before the oocysts become infectious. The organism is endemic in tropical and subtropical environments, it is associated with outbreaks of diarrheal disease, and it has been implicated as a cause of traveler's diarrhea. *I. belli* infection is confined to humans and, perhaps, dogs. No other animal reservoir has been identified. Transmission is associated with contaminated water, although that route is not proven. The watery diarrhea caused by this organism suggests that an enterotoxin is responsible, but no evidence for this molecule yet exists. The clinical features of *I. belli* infection in immunocompetent hosts are abdominal pain; cramping; nausea; and watery diarrhea, occasionally with eosinophilia. In immunodeficient hosts, prolonged diarrhea and malnutrition may occur. Several case reports have documented dissemination to the mesenteric lymph nodes or acalculous cholecystitis in patients with advanced HIV infection.

Oocysts can be visualized with an acid-fast stain. Symptomatic infection responds to treatment with trimethoprim-sulfamethoxazole (TMP-SMZ). In patients with AIDS who experience recurrent disease, secondary prophylaxis with TMP-SMZ and pyrimethamine in combination with sulfadoxine prevents relapses. Nitazoxanide, a thiazoline compound, and its desacetyl derivative, tizoxanide, have antimicrobial properties against anaerobic bacteria as well as against helminths and protozoa, and they are promising agents in the treatment of patients with this and other parasitosis [21, 27].

CYCLOSPORA SPECIES

Unlike *Cryptosporidium* species, which are readily infectious after excretion, *Cyclospora cayentanensis* requires sporulation in the environment before becoming infectious. This coccidian parasite was originally identified as a cause of diarrhea in developing countries, Nepal and Peru in particular, and was previously referred to as a “*Cyanobacteria*-like body.” It appears that humans are the only reservoir for infection, because extensive evaluation of domestic animals has failed to reveal carriage in regions where infection is endemic [28]. However, it is genetically related to *Eimeria* species (a common cause of infection in avian species), and it possible that an as-yet-undiscovered avian reservoir exists. The vehicles of transmission are most likely contaminated water [29] and food. Cases in developed countries have been acquired mostly during outbreaks of infection that have been related to imported raspberries [30] or they have been diagnosed in travelers who returned from developing nations [31]. Studies in developing countries, such as Peru and Haiti, have demonstrated a high frequency of asymptomatic excretion in indigenous populations. After an incubation period of ~7 days (range, 2–11 days), diarrhea occurs, accompanied by cramping, abdominal pain, nausea, vomiting, fatigue, and occasionally fever. In general, infection is self-limited in otherwise healthy adults, but diarrhea can be prolonged and, if untreated, it appears to be more severe than that experienced with *Cryptosporidium* species. In the immunocompromised host, infection with *Cyclospora* species, if untreated, may also result in chronic diarrhea; in some patients, such as those with AIDS, this infection requires long-term suppressive therapy.

Cyclospora species and *Cryptosporidium* species appear similar on stains, but *Cyclospora* oocysts are twice as large (8–10 μm vs. 3–5 μm). *Cyclospora* species can also be identified in fecal samples by its ability to autofluoresce at 330–380 nm [32] under ultraviolet microscopy. A 10-day course of therapy with TMP-SMZ results in clinical improvement and eradication of this parasite.

OTHER CONSIDERATIONS

The role of *Dientamoeba fragilis* as a causal organism of traveler's diarrhea remains a subject of debate; some authorities suggest treatment of symptomatic infections [33]. A number of nonpathogenic protozoa are commonly identified in travelers with acute or chronic diarrhea; however, their role as causative organisms of diarrhea has not been established. Patients in whom parasites such as *Balantidium coli*, *Endolimax nana*, and other species of *Entamoeba* are identified do not require specific treatment.

The evaluation of diarrhea in travelers who do not respond to antimicrobial therapy or who experience prolonged illness

requires a careful parasitologic examination of several stool specimens. In cases in which a specific organism cannot be identified, other diagnoses should be considered, such as Brainerd diarrhea, *Clostridium difficile* antibiotic-associated colitis, tropical sprue, celiac disease, postinfective irritable bowel syndrome, HIV infection, or inflammatory bowel disease, among others.

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