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Parasitic causes of prolonged diarrhoea in travellers

Diagnosis and management

Background
Prolonged infectious diarrhoea in the returning traveller is generally caused by protozoal and occasionally by helminth parasites.

Objective
This article provides a framework for the diagnosis, management and prevention of the diseases that cause persistent diarrhoea in the traveller.

Discussion
A large proportion of disease is caused by *Giardia lamblia, Cryptosporidium parvum* and *Entamoeba histolytica*. However, given the ease of travel with comorbid conditions such as human immunodeficiency virus, there is an expanding list of organisms that can cause persistent diarrhoea. An awareness of the likely aetiological agents and their clinical features enables a more effective diagnosis and management of the patient's condition using an appropriate antiparasitic agent. Prevention strategies need to be initiated before travel and should consist of simple but memorable advice. Noninfectious causes of diarrhoea should be considered as diarrhoea can be a prominent feature of conditions such as hyperthyroidism or coeliac disease.

Keywords
diarrhoea; travel; intestinal diseases, parasitic; diagnosis, differential

Diarrhoea remains the largest infectious risk posed to the traveller while abroad or on their return home. A large percentage is due to bacterial infections such as enterotoxigenic *Escherichia coli* and resolve within days of onset. A small percentage of the travelling population will have prolonged symptoms that may disrupt either a long term holiday or a return to normal activities when they are at home.

Prolonged diarrhoea (typically defined as >14 days) occurs in 1–3% of travellers with diarrhoea.[1] Of the infectious causes, protozoan infections would account for the majority of the cases.[2]

Determination of the cause of persistent diarrhoea follows the usual format of history, examination, 'targeted' laboratory investigations and, very rarely, diagnostic imaging or invasive testing such as colonoscopy.

The consequences of infection with organisms such as *Cryptosporidium parvum* or microsporidia in an immunocompromised host is that they may cause ongoing and debilitating symptoms that may be difficult to control or eliminate. Alternatively, organisms such as *Strongyloides* may cause infections quite some time in the future when the host's immunological status changes.

Underlying all of these infections is that none of them is vaccine preventable, unlike some of the bacterial infections, such as typhoid. Nevertheless, they can be prevented when the traveller is aware of the risk and can avoid potential infections.

Diagnosis

As with all diagnostic processes, it begins with a complete history focusing on the onset and nature (volume, character, consistency) of the diarrhoea as well as the presence of blood or mucus in the stool. Associated symptoms can be explored to give the full presentation and should include the presence of fever, chills/rigors and jaundice. Other important elements of history and physical examination are highlighted in *Table 1* and *Table* 2.[1,3,4]

Investigations

The role of laboratory investigations is twofold: first, to define the aetiological agent of the diarrhoea, and second, to delineate comorbid conditions such as malaria or thyroid disorders.

First line testing should involve testing of fresh stool specimen collected by the patient. Ideally, the stool should be unformed or the liquid component, collected close to the time of delivery to the laboratory and a portion placed in sodium acetate-acetic acid-formalin (SAF) fixative. The stool should be kept a room temperature rather than refrigerated. Multiple stool collections are warranted as the increase in volume and distribution of stool increases the probability of

Table 1. Key history points in the returned traveller with diarrhoea

- How long have the symptoms been occurring? What is the nature and character of the stool? Have you noticed any other changes with your bowel habit (eg. abdominal distension or tenesmus)?
- What were your bowels like previously?
- Had you previously had episodes of this type of stool?
- Have you ever been investigated for any gastrointestinal disease (eg. inflammatory bowel disease, coeliac disease, bowel cancer or irritable bowel syndrome)?
- Do you have any medical conditions? Do you know your HIV status?
- What medications have you been taking? Have you taken antibiotics in the past 2 months?
- What about vaccinations/malaria prophylaxis?
- Travel history is very important. Ask the patient to bring in their itinerary so nothing is missed. Systematically go through the patient's journey – when, where and what they did. Look for potential risks or behaviours regarding eating, drinking or exposure

Table 2. Physical examination in the patient with persistent diarrhoea

- Assess hydration status – with a large volume of diarrhoea comes a loss of total body water and subsequent hypovolaemia
- Assess nutritional status – malabsorptive diarrhoea could result in loss of muscle mass, fat wasting or vitamin deficiencies
- General physical examination – look for localising signs that may indicate a contributing disease such as malaria (hepatosplenomegaly) or a noninfective disease such as hyperthyroidism (tachycardia, tremor)

a pathogen being isolated. If multiple stools are to be collected then this should be done with an interval of 2–3 days in between, with transport to the laboratory occurring with each sample. That being said, Medicare only reimburses for one faeces microscopy culture and sensitivity (MCS) and two faeces microscopy for ova, cysts and parasites (OCP) in a 7 day period. If a third sample is required, then a period of 7 days must elapse before a sample for OCP can be requested.

Knowing the capabilities of the testing laboratory is important, as clinical suspicion must guide what additional testing may be needed to make a diagnosis. For instance, enzyme immunoassays are available for the testing for *Giardia lamblia, C. parvum* and *Entamoeba histolytica*. Special stains are required for the diagnosis of microsporidia. Polymerase chain reaction (PCR) testing for these pathogens are likely to become routinely available in the future. *Clostridium difficile* testing is warranted in those who have received broad spectrum antibiotics recently. Communication either directly with the laboratory or via detailed clinical notes on the request form can facilitate the correct testing.

Peripheral blood should be taken for full blood count with differential, electrolytes/liver function tests, and additional serum should be taken for *Strongyloides* antibodies if appropriate. In patients with a fever: blood cultures, thick and thin films for malaria and erythrocyte sedimentation rate/C-reactive protein (ESR/CRP) as markers of inflammation.[1,3,4]

Giardia lamblia

Giardia lamblia (also known as *G. duodenalis* or *G. intestinalis*) is the most common aetiological agent of persistent diarrhoea. It has a worldwide distribution but it is typically and increasingly found in areas of low sanitation. It can be found in 5–7% of stools in the United States and in 15–30% of stools in endemic areas.[5,6] Given its distribution and prevalence, *Giardia* is the most likely pathogen to infect travellers.

Transmission is via the faecal–oral route or via ingestion of contaminated water sources – both recreational and potable sources. It is particularly prevalent in children and men who have sex with men. Less commonly it can be acquired through food contamination.

Symptoms of *Giardia* infection include diarrhoea, malaise, flatulence, foul smelling greasy stools, bloating/distention and, less commonly, nausea, anorexia and vomiting. The greasy stools are a result of a malabsorptive state that appears to be multifactorial in aetiology.[6]

Post-*Giardia* infection, lactase deficiency is common; it may persist for several weeks after treatment. The patient should be warned about the potential of lactose intolerance post-treatment and that it probably represents a transient change in the digestive system and should recover in a few weeks.[7]

Diagnosis of *Giardia* infection is via microscopy of wet preparation using fresh stool or via a concentration method. Sensitivity and specificity of detection is dependent on the microscopist and the stool specimen. *Giardia* antigen enzyme immunoassays have been gaining increasing popularity with laboratories and have a specificity and sensitivity approaching greater than 90%.[8,9] Treatment of giardiasis and other organisms is shown in *Table 3*.

Cryptosporidium parvum

Cryptosporidium parvum is the second most commonly isolated protozoal pathogen in travellers. Like *Giardia*, it has a worldwide distribution with sporadic outbreaks occurring in developed countries as well as endemic infections in developing countries.[10,11] Travel to southeast Asia, in particular India, is associated with higher rate of travel related infections.

Cryptosporidium is a water and food-borne pathogen; symptoms of infection include abdominal pain, fatigue, flatulence, anorexia, fever, nausea and weight loss.[12] *Cryptosporidium* infections are generally self limiting with a median duration of 5–10 days.[12] However, it has been implicated in persistent and intractable diarrhoea in those with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) or other immunocompromising diseases.

Diagnosis is performed using a modified acid-fast stain of preserved stool. Similar to *Giardia*, immunoassay tests are now available and have improved sensitivity over microscopy.[13] *Cryptosporidium* is associated with a postinfection irritable bowel syndrome that may occur in up to 40% of patients.[12]

Table 3. Treatment options for aetiological agents of persistent diarrhoea

Organism	First line	Alternative agents	Reference
Giardia lamblia	Metronidazole or tinidazole	Paromomycin, mebendazole, albendazole and nitazoxanide*	28, 29
Cryptosporidium parvum	Supportive therapy. Restitution of immunity with CD4+ >200		12
Entamoeba histolytica	Metronidazole, tinidazole ± paromomycin (invasive disease)*		15, 29
Cyclospora cayetanensis	Trimethoprim + sulfamethoxazole	Ciprofloxacin	29
Isospora belli	Trimethoprim/sulfamethoxazole		21
Microsporidium	Supportive therapy. Restitution of immunity with CD4+ >200		22
Blastocystis hominis	Metronidazole or tinidazole	Trimethoprim + sulfamethoxazole	23, 24
*Strongyloides stercoralis**	Albendazole	Ivermectin	25, 26

* Specialist advice should be sought before the institution of therapy wherever possible

Entamoeba histolytica

Entamoeba histolytica is the causative agent of amoebiasis. It is an organism that has been implicated in both diarrhoeal disease and invasive disease such as liver abscesses. *E. histolytica* is thought to cause many million infections and up to 100 000 deaths in populations where it is endemic. The majority of these infections occur in Central and South America, Africa and the Indian subcontinent. The risk to travellers is paralleled to the local endemicity of the organism.[14]

The majority of patients will have asymptomatic or low level disease with a gradual onset of diarrhoea with generalised abdominal tenderness. Fever is not usually associated with amoebic disease. Mucus and/or blood may be present if the organism penetrates the bowel wall and causes mucosal damage.

Invasive diseases, specifically liver abscesses, are rare; symptoms include fever, malaise and right upper quadrant pain. Pleural, pericardial or peritoneal disease is thought to be due to extension of liver abscesses. Imaging of the liver, using ultrasound or computed tomography (CT) scanning, is used to characterise abscesses. Confirmation of diagnosis is by fine needle aspiration.[15]

Diagnosis of *E. histolytica* by microscopy is poor, with sensitivity ranging from 30–50% even when special staining techniques are used. Several other nonpathogenic *Entamoeba* species closely resemble *E. histolytica*, making it difficult to correctly identify. Commercial immunoassays are available and have much improved sensitivity and specificity compared to microscopy. These assays are not routinely performed on all faecal specimens, unlike the *Giardia/Cryptosporidium* assays, and need to be specifically requested from the testing laboratory.[15]

Cyclospora cayetanensis

Cyclosppora cayetanensis is a coccidian organism endemic to Mexico, Haiti, Peru and Nepal. It is likely that it is found in surrounding countries. It has been found in the United States, typically in imported foods from endemic countries.[16]

Clinical features of *Cyclospora* infections include diarrhoea, anorexia, nausea, flatulence, fatigue, cramping, fevers and weight loss. Diarrhoea can last up to 3 weeks and patients typically have 5–15 bowel motions per day, however, asymptomatic infections are possible. Human immunodeficiency virus patients typically have more severe disease, with increased weight loss and longer duration of diarrhoea.[10] Diagnosis is by modified acid fast staining of fixed stool samples.[17]

Isospora belli

Isospora belli has been found predominantly in immunocompromised travellers in the tropics, especially those with HIV/AIDS or other acquired T-cell immunity defects,[13] but has been also found in immunocompetent travellers.[19,20] It causes profuse and watery diarrhoea. It has not been found in the family members of those infected, indicating that person to person transmission is unlikely.[21] Isolation rates in AIDS patients indicate that infection rates are higher in developing countries.

Microsporidium

Enterocytozoon bieneusi and *Encephalitozoon intestinalis* are pathogens commonly associated with diarrhoea in HIV/AIDS patients.[22] Infections have also been found in immunocompetent patients in countries such as Mexico, Argentina and Niger.[21] As in *I. belli*, infection causes profuse watery diarrhoea and associated weight loss. Detection of these organisms is via special staining of fixed stool samples and is generally only performed on those with HIV/AIDS. Restitution of the immune status using antiretroviral therapy may allow clearance of the organisms.

Blastocystis hominis

Blastocystis hominis is an organism that courts much controversy in terms of its pathogenicity, given that asymptomatic carriage has been widely noted. Likewise, studies have noted its association with symptoms such as diarrhoea, bloating, abdominal pain and excessive flatus. Its presence in stool is a likely indicator that exposure to other organisms has occurred. Where *Blastocystis* has been solely isolated and clinical symptoms are present, then a trial of treatment is warranted.[23,24]

Strongyloides

While not a common cause of persistent diarrhoea, *Strongyloides* certainly is an organism that has long term consequences in those infected. Risk factors include travel to endemic areas, consuming contaminated water or contact with infected soil, usually through barefoot travel. Acute or chronic infections are usually asymptomatic, but can present with diarrhoea, urticaria and abdominal pain. Chronic infections in patients with a cell mediated immunity defect due to high dose corticosteroid use, organ

transplantation and HTLV-1 can potentially result in *Strongyloides* hyperinfection syndrome, which has a high mortality.[25,26]

Screening for the presence of *Strongyloides* in returned travellers with persistent diarrhoea or with eosinophila is warranted given that co-infection is possible. Current screening method includes agar plate culture or serology. Seek specialist advice for the treatment of *Strongyloides* if an infection is detected.[25,26]

Table 4. Nonparasitic causes of persistent diarrhoea in the traveller

- Coeliac disease
- *Clostridium difficile*
- Medication induced
- Hyperthyroidism
- Inflammatory bowel disease
- Postinfectious lactase deficiency
- Carbohydrate malabsorption
- Colorectal cancer

Nonparasitic causes of chronic diarrhoea

It is important to remember that diarrhoea is a common symptom of many other diseases; it may be a coincidence that travel preceded the episode. Patients who have persistent diarrhoea despite negative screening for stool parasites should be further investigated. Further aetiologies to consider are shown in *Table 4*. Referral for specialist follow up is warranted when the history and examination are suggestive of potential cancer (ie. change of bowel habit associated with bleeding, family history of cancer, abdominal or rectal mass), inflammatory bowel disease, coeliac disease or ongoing symptoms unexplained by initial investigations.[27]

Table 5. Advice before travel regarding avoidance of parasites

- Use extra caution when travelling in areas of low sanitation and poor sewage treatment
- Consume only bottled water (make sure that the lids are sealed)
- If necessary, water can be made safe by boiling, filtering or iodination/chlorination
- Avoid high risk foods such as unpeeled vegetables, fruits and items washed in untreated water
- Clean hands frequently – consider ethanol-based handwash
- Avoid contact such as swimming in suspected contaminated lakes/rivers or other water sources, especially where there is no sanitation – the faeces has to go somewhere, and where better to wash your bum than in the local river?
- Avoid walking around in bare feet in mud or rainforest areas
- If HIV positive or immunocompromised, you are at a greater risk of more chronic debilitating disease. Know your status and your CD4+/viral load before travelling

Table 6. Simple advice for patients to avoid diarrhoeal illness while travelling

The ABCD of avoiding diarrhoea

A	Avoid anything that may be contaminated with faecal material. Water and food are the biggest culprits
B	Bottled water is the safest option. Check seals and method of purification
C	Clean and Cover: Wash hands thoroughly using an alcohol based cleanser. Cover your feet
D	Disease: if you are immunocompromised, you are at risk of a wider range of disease. Take extra caution and tell your physician this when you get unwell so they can look for different pathogens

Remember: it's all about hands, feet and mouth when it comes to diarrhoea

Hands	Wash your hands using an alcohol-based cleanser before and after toileting and eating
Feet	Parasites can burrow their way into your body: shoes are a great way to stop this happening
Mouth	Think about what you put in your mouth: is it likely to be contaminated with unseen faeces?

Prevention of parasitic infections in the traveller

Many of the axioms for the prevention of traveller's diarrhoea remain true for the prevention of parasitic infections. *Table 5* shows advice that can be given before travel. The advice should be memorable and to the point rather than long winded or overly detailed. A brochure or a travelling item such as a bookmark or a post-travel booking card can help reinforce this advice. *Table 6* provides examples of simple messages that can be given to travellers.

Key points

- Persistent diarrhoea in the traveller is most commonly caused by protozoan parasites.
- *Giardia* is the most common organism, followed by *Cryptosporidium* and *E. histolytica*.
- Stool microscopy combined with antigen-specific enzyme immunoassays give the highest sensitivity of detection.
- Infection with *E. histolytica* and *Strongyloides* can cause systemic disease such as liver abscess and hyperinfection syndrome respectively.
- Be alert for postinfection lactase deficiency causing ongoing diarrhoea after effective treatment.
- HIV/AIDs patients are at a greater risk of prolonged infections with potentially debilitating symptoms.
- Consider nonparasitic causes of diarrhoea in your differential diagnoses, including *C. difficile*, coeliac disease, inflammatory bowel disease and carbohydrate malabsorption.
- Prevention is achieved by educating travellers before travel and advising on simple strategies to avoid infections, namely avoiding contaminated water and food sources and covering the feet.

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Conflict of interest: none declared.

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