

# Persistent Traveler's Diarrhea

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**T**his is the first in a new series of columns dedicated to travel medicine. In these times of evolving geopolitical and microbiologic crises, knowledge of issues in travel medicine has become more important than ever. Treating patients in pretravel and post-travel settings requires a knowledge of emerging infections and new diagnostic, preventive, and therapeutic modalities, as well as a return to the venerated principles of a thorough history and physical examination. No subject within travel medicine more clearly demonstrates these points than does persistent traveler's diarrhea (PTD).

Traveler's diarrhea affects 20% to 50% of persons who travel to tropical and semitropical areas, including Latin America, parts of the Caribbean, southern Asia, and Africa, and is the most common ailment encountered by travelers.<sup>1,2</sup> Fortunately, most of these cases are self-limited to a duration of less than 1 week. However, a minority of patients will experience a more protracted course—an overview of several studies found that between 3% and 10% of travelers may have diarrhea that lasts for more than 2 weeks and that 0.8% to 3% will have symptoms that last for more than a month.<sup>3-7</sup> PTD may be defined as diarrhea that arises in the traveler or recently returned traveler and lasts for more than 3 to 4 weeks.

The usual concern is to rule out a persistent bacterial infection or parasitic infestation. This clearly remains the first task in the evaluation, and we should remain vigilant for emerging pathogens. However, when results of stool studies are negative, the physician needs to broaden his or her differential diagnosis and to apply basic principles of gastroenterology as well as infectious disease. Many patients who have PTD will have cleared the offending pathogen long ago and may present with postinfectious sequelae, be they inflammatory, malabsorptive, or func-

tional. Others may have a chronic noninfectious GI disease that has been unmasked and brought to medical attention by a superimposed enteric infection. One can broadly subdivide the syndrome of PTD into several pathogenetic subsets: persistent infection or infestation, postinfectious processes, and chronic GI illnesses unmasked by an infection (Table 1).

## Persistent infection or infestation

Parasites are the pathogens most likely to be isolated from patients with PTD, and their probability relative to bacterial infections grows with increasing duration of symptoms. In a study of travelers to Nepal, protozoa were detected in 10% of patients with GI symptoms that lasted less than 14 days and in 27% of patients with symptoms that lasted more than 14 days.<sup>8,9</sup> After the 2-month mark of symptom duration is passed, however, it becomes decreasingly likely that one will encounter a persistent parasite and more likely that one is dealing with a postinfectious phenomenon.

*Giardia lamblia* is, by far, the most commonly encountered pathogen in patients with PTD. Suspicion of giardiasis should be particularly high when upper GI tract symptoms and malabsorption predominate.<sup>10,11</sup> Bacteria and viruses, common causes of acute traveler's diarrhea, figure far less prominently in PTD; however, a list of relevant ones can be found in Table 1. *Clostridium difficile* deserves a special mention, since many patients with PTD have taken malaria prophylaxis—including mefloquine, chloroquine, or doxycycline—or antibiotics for treatment of acute traveler's diarrhea, which place them at risk for infection with this opportunist.<sup>12</sup>

Although its precise cause remains unclear, tropical sprue bears the clinical and epidemiologic characteristics of a persistent infectious disease. Tropical sprue is a syndrome of PTD associated with malabsorption, steatorrhea, fatigue, and deficiencies of vitamins absorbed in both the proximal and distal small bowel (folate and vitamin B<sub>12</sub>, respectively).<sup>13</sup> The incidence of tropical sprue,

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however, has declined dramatically over the years; consequently, therapy for this syndrome, consisting of tetracycline, 250 mg qid for at least 6 weeks with folate supplements, should not be prescribed empirically.<sup>14</sup>

#### Postinfectious processes

Maldigestion may persist after an acute infectious gastroenteritis has cleared, as a result of deficiency of disaccharidases, such as the enzymes used to digest lactose and sucrose, which normally reside in the fragile brush border overlying the intestinal epithelium.<sup>15,16</sup>

Enteric infection of the type acquired during travel may also leave the host with an altered neurogastroenterologic milieu and altered GI motility, leading to postinfectious irritable bowel syndrome (PIBS).<sup>17</sup> Like IBS more generally, PIBS is defined clinically by the absence of constitutional symptoms or weight loss and the presence of abdominal pain that is associated with an alteration of bowel habits and that is relieved by defecation. PIBS can be subcategorized into syndromes of diarrhea predominance, constipation predominance, and pain-gas-bloat predominance; patients in the latter 2 groups often do not have diarrhea at all.

As with IBS, psychological factors play a contributing role, at least in those patients who seek medical care.<sup>18-22</sup> Why is it important to give this entity a name and definition? From the physician's standpoint, once a diagnosis has been made, attention can be appropriately focused away from diagnostic efforts and onto symptomatic therapy and reassurance. Psychologically, many patients find comfort in receiving a diagnosis.

Finally, from a more global perspective, giving this syndrome a name may help facilitate research in the area, which is sorely lacking. Consider the diagnosis of PIBS in the young PTD patient with a typically lower GI tract symptom complex and without constitutional symptoms; rule out a structural cause or persistent pathogen with reasonable certainty, reassure the patient, and offer symptomatic relief in the form of antidiarrheal or antispasmodic medications.

#### Chronic GI diseases unmasked by enteric infection

Traveler's diarrhea has an important potential to uncover latent noninfectious GI disease. Idiopathic inflammatory bowel disease was diagnosed in 25% of patients in a retrospective British review of 129 cases of bloody diarrhea acquired during or within 2 weeks after return from a tropical sojourn.<sup>23</sup> Before initiating anti-inflammatory therapy for suspected ulcerative colitis in the returned traveler, it is important to be extremely thorough in ruling out the presence of *Entamoeba histolytica* with both colonic

biopsies and serology, as well as with multiple microscopic examinations of stool. The use of immunosuppressive drugs, such as corticosteroids, in the setting of an active parasitic infestation could lead to profound illness.<sup>24</sup>

Celiac sprue is a disease of the small bowel, in which genetically susceptible persons sustain villous atrophy and crypt hyperplasia in response to exposure to antigens found in many grains, leading to malabsorption. Rather than initiating the disease, an acute infection acquired during travel, superimposed on diseased bowel with fri-

**Table 1 – Differential diagnosis of chronic traveler's diarrhea**

#### Persistent infection or infestation

- Protozoa
  - Mastigophora: *Giardia lamblia*
  - Coccidia: *Cryptosporidium parvum*, *Isospora belli*
  - Ciliophora: *Balantidium coli*
  - Microspora: *Enterocytozoon bieneusi*, *Septata intestinalis*
  - Eimeriina: *Cyclospora cayetanensis*
  - Rhizopoda: *Entamoeba histolytica*
  - Trichomonadida: *Dientamoeba fragilis*
- Helminths
  - Strongyloides stercoralis*
  - Schistosoma* species
  - Ascaris lumbricoides*
  - Capillaria philippinensis*
- Bacteria
  - Enterobacteriaceae: *Escherichia coli* (especially enteroadherent), *Shigella* species, nontyphoidal *Salmonella*, *Campylobacter* species, *Yersinia enterocolitica*
  - Vibrionaceae: *Aeromonas* species, *Plesiomonas* species
  - Clostridium difficile*
- Viruses
- Unknown pathogens
- Brainerd diarrhea
- Tropical sprue

#### Postinfectious processes

- Postinfectious malabsorptive states
  - Disaccharide intolerance
  - Subacute tropical malabsorption
  - Bacterial overgrowth
- Postinfectious irritable bowel syndrome
- Postdysenteric colitis

#### Chronic GI diseases unmasked by enteric infection

- Idiopathic inflammatory bowel disease
  - Ulcerative colitis
  - Crohn disease
  - Microscopic colitis
- Celiac sprue
- Colorectal adenocarcinoma
- AIDS

**Table 2 – Noninvasive evaluation for traveler’s diarrhea**

**Blood**

All patients

- Complete blood cell count with differential
- Electrolyte levels
- Albumin level
- Prothrombin time
- Folate concentration
- Iron studies
- Vitamin B<sub>12</sub> concentration
- Thyroid-stimulating hormone level
- Erythrocyte sedimentation rate or C-reactive protein level

Selected patients

- Celiac serologies
- Thyroid-stimulating hormone level
- Amebic serology
- D-xylose (after 25-g load, urinary level also acceptable)
- HIV (ELISA)

**Stool**

All patients

- Culture and sensitivity
- Ova and parasites (3 specimens)
- Giardia* antigen ELISA
- Clostridium difficile* toxin assay
- Fecal occult blood
- Fecal fat (qualitative)
- Fecal leukocytes

Selected patients

- Fecal  $\alpha_1$ -antitrypsin clearance

ELISA, enzyme-linked immunosorbent assay.

ability or impaired reserve function, probably just brings the patient to medical attention. Findings compatible with celiac sprue on gross and microscopic duodenal examination and the presence of antiendomysial, antigliadin, anti-tissue transglutaminase, and antireticulin antibodies<sup>25,26</sup> confirm the diagnosis. Celiac sprue is treated with a very effective, although difficult-to-maintain, gluten-free diet.

Colorectal cancer also must be a consideration in patients with PTD, particularly those who pass blood per rectum or are found to have fecal occult blood or new iron deficiency anemia.<sup>27</sup> In any such patient over the age of 50, a full colonoscopy should be performed, even if the symptoms seem consistent with infectious colitis.

**Clinical approach**

As with the assessment of any other medical complaint, the most important diagnostic tools in PTD remain the

complete history and physical examination. Complementing these in the initial evaluation is a battery of stool and blood tests listed in Table 2. If a persistent infection is not uncovered, endoscopic evaluation and empiric therapy for *Giardia* or bacterial illness are equally acceptable first-line approaches, with advantages and disadvantages to both. There exist selected groups of patients in whom an endoscopic evaluation should be performed, including:

- Patients in whom 1 or 2 unsuccessful empiric courses of therapy fail.
- All patients older than 50 years with occult or gross fecal blood.
- Patients with symptoms or signs of malabsorption.

It is essential to develop a level of comfort in the absence of a specific microbiologic diagnosis, since the majority of patients with PTD will not have a specific diagnosis. In such cases, one must implement the tools of a thorough history and physical examination, blood and stool evaluations, empiric therapy, and endoscopy to characterize the problem as a persistent infection, postinfectious syndrome, or the unmasking of a chronic GI disease that resides in the small or large bowel, and treat the patient accordingly.

Symptomatic therapy begins with diet modifications. A trial of sequential avoidance of dairy products, sorbitol-containing products, fruit juices, concentrated sweets, and high-fat items, in that order, should be undertaken. In patients with colitis, a low-residue, low-fiber diet should be advised. Based on the nature of the symptoms, antispasmodics and other drugs useful in IBS, such as hyoscyamine, a chlordiazepoxide/clidinium combination, and a chlordiazepoxide/amitriptyline combination, and fiber in the form of psyllium or methylcellulose may be helpful. For the patient with predominant symptoms of diarrhea, loperamide, diphenoxylate, and tincture of opium are invaluable. Probiotics such as *Lactobacillus* and *Saccharomyces boulardii* also seem to improve symptoms in some patients.<sup>28</sup> ♦

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