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Chronic Diarrhea in Travelers

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Abstract As a rule, travelers' diarrhea is a self-limited bacterial infection that affects approximately 40 % of travelers to developing countries. Health-care professionals who see returning travelers have noted that some travelers afflicted with diarrhea do not recover completely but, instead, develop chronic diarrhea or a persistent change in gastrointestinal function. Concurrent with this observation has been the recognition that in many patients with long-standing irritable bowel syndrome, an episode of traveler's diarrhea or gastroenteritis preceded the onset of symptoms. Before a diagnosis of postinfectious irritable bowel syndrome is considered, other diagnostic considerations must be excluded. This review will examine an approach to the patient with chronic diarrhea posttravel.

Keywords Travelers' diarrhea · Chronic diarrhea · Persistent diarrhea · Bacterial diarrhea · Clostridium difficile · Enteric parasitic infection · Celiac disease · Inflammatory bowel disease · Brainerd diarrhea · Postinfectious irritable bowel syndrome

Introduction

One of the more perplexing challenges for clinicians who see returned travelers is the patient with chronic diarrhea posttravel. Travelers' diarrhea is, by definition, a short-term malady, affecting approximately 40 % of travelers to developing countries [1]. Persistent diarrhea in returned travelers manifests itself in several forms. Some travelers develop diarrhea that seems to persist beyond the usual 3–5 days. As some have pointed out, especially in long-term travelers, these may, in fact, be consecutive or successive bouts of diarrhea from new pathogens, rather than a prolonged course of diarrhea resulting from the initial microbial agent [2].

In some patients who return from travel, their bout of diarrhea persists, sometimes less intense and often with a waxing and waning course. In others, their symptoms resolve initially, but after a variable period of time, they begin to have diarrhea again. In other patients, the diarrhea has resolved, but ongoing symptoms of bloating, gas, and abdominal distention persist, sometimes for variable and prolonged periods of time. In yet other patients, a considerable gap occurs between the bout of diarrhea and the onset of altered bowel habits and gastrointestinal function. All of these patients fall within the rubric of *posttravel chronic diarrhea*, but the clinical manifestations differ, as well as the diagnostic approach and management.

A conceptual framework that we employ would categorize patients with chronic gastrointestinal symptoms into one of three categories: (1) either persistent and ongoing infection or coinfection, (2) an unmasking of a previously undiagnosed gastrointestinal disease or syndrome by the bout of travelers' diarrhea, or (3) a postinfectious sequela of the enteric infection.

Another important factor is duration of symptoms in relation to the index episode of travelers' diarrhea. Travelers who are seen shortly after return—for example, in the first 4–6 weeks posttravel—may present with diarrhea of different etiology than patients who present 3–6 months later or 1–3 years or more later (Table 1).

Persistent Infection or Coinfection

Parasitic Infection

Although bacterial pathogens are the most common cause of acute travelers' diarrhea, the contribution of bacterial

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Table 1 Diagnostic possibilities by duration of symptoms or time from initial episode to medical provider visit

First 3 to 4 weeks:
Persistent infection or coinfection
Work-up: stool O & P X 3
C. difficile stool toxin assay
Temporary postinfectious malabsorption
Trial lactose free diet
Unmasked GI disease
Antigliadin, endomysial, tissue transgluatminase antibodies
ASCA, ANCA serologies for IBD
1 month to 3 months:
Coinfection:
Stool O & P
C. difficile stool toxin assay
Unmasked GI disease
Antigliadin, endomysial, tissue transgluatminase antibodies
ASCA, ANCA serologies for IBD
Nonceliac gluten sensitivity
Trial gluten-free diet
Empiric treatment for *Giardia*
Greater than 3 months:
Coinfection:
Stool O & P
C. difficile stool toxin assay
Unmasked GI disease
Antigliadin, endomysial, tissue transgluatminase antibodies
ASCA, ANCA serologies for IBD
Nonceliac gluten sensitivity
Trial gluten-free diet
Empiric treatment for *Giardia*
PI-IBS: treatrment for SIBO, ±GI dysmotility

O & P ova and parasites, *ASCA* anti-saccharomyces cerevisiae antibodies, *ANCA* perinuclear antineutrophil cytoplasmic antibodies, *IBD* inflammatory bowel disease, *PI-IBS* post infectious irritable bowel syndrome, *SIBO* small intestinal bacterial overgrowth

pathogens in patients with chronic or persistent symptoms appears to be limited. As a group, parasites as pathogens are most likely to be isolated from patients with persistent travelers' diarrhea, with their probability relative to bacterial infection increasing with increasing duration of symptoms. In a study of travelers to Nepal, protozoans were detected in 10 % of travelers with gastrointestinal symptoms for less than 14 days and in 27 % with symptoms lasting more than 14 days [3, 4]. Protozoan parasites, which inhabit the proximal small bowel, are of particular concern. The most common of these is *Giardia lamblia* [5]. Suspicion for giardiasis should be raised when upper gastrointestinal symptoms predominate, such as epigastric distress, eructation, belching, and gastroesophageal reflux. Untreated symptoms of giardiasis may persist for a prolonged period of time, weeks or months. The diagnosis can be made by stool microscopy, with immunofluorescence increasing the yield of recovery [6]. However, since Giardia is an inhabitant of the proximal small bowel, it is often degraded prior to defecation to be recognized at microscopy, and even multiple stool samples may not always be successful in making the diagnosis. Upper gastrointestinal endoscopy with aspiration of duodenal fluid and duodenal biopsy is probably the most sensitive means of making the diagnosis but requires the invasive use of fiberoptic endoscopes [7].

An alternative option is empiric therapy. Therapeutic options include metronidazole 250 mg three times daily for 7–10 days or tinidazole as a single 2-g dose. Occasionally, a repeat course may be required. Recently, resistance to both metronidazole and tinidazole has been reported. Alternative therapies include nitazoxanide 500 mg twice daily for 3 days or albendazole 400 mg daily for 5 days. Quinacrine 100 mg three times daily is another option.

Other protozoan parasites that cause persistent diarrhea include *Cyclospora cayetanensis*. This coccidian parasite is of particular concern because, in the untreated state, symptoms may be prolonged, lasting for as long as 6–12 weeks [8]. Symptoms of cyclosporiasis are usually upper gastrointestinal, and the illness is associated with profound fatigue, anorexia, weight loss, and malabsorption [9]. *Cyclospora* responds to trimethoprim/sulfamethoxazole double-strength tablet for 10–14 days [10]. *Cryptosporidium parvum* is another protozoan parasite, which, although closely linked with persistent diarrhea in immunosuppressed patients, may also cause persistent diarrhea in the immunocompetent. Treatment of these infections with nitazoxanide 500 mg twice daily can be effective. Other enteric parasites less commonly associated with persistent diarrhea include *Entamoeba histolytica, Dientamoeba fragilis, microsporidia*, and *Isospora belli*.

Bacterial Infection

There is some evidence that Enterobacteriaceae, such as enteroadherent *Escherichia coli*, play a role in persistent diarrhea in children and the immunosuppressed. A prolonged course of diarrhea in the immunocompetent is unusual [11, 12]. One bacterial pathogen that should be searched for in the returned traveler with persistent diarrhea is *Clostridium difficile*. *C. difficile* is often associated with antecedent use of antibiotic therapy, such as for travelers' diarrhea or malaria chemoprophylaxis [13]. The initial workup of the patient with persistent travelers' diarrhea should always include a *C. difficile* stool toxin assay. Therapy with metronidazole, oral vancomycin, or fidaxomicin is generally successful, although resistant and recurrent *C. difficile* infection is becoming an increasing problem.

Coinfection

It is important for the clinician to consider the possibility of coinfection in someone with persistent diarrhea posttravel. An example would be the patient with a treated bacterial infection with a relapse of symptoms, only to be found to have a *Giardia* coinfection perhaps acquired through the same contaminated meal.

Other Pathogens

There are patients with persistent diarrhea who possess the clinical and epidemiologic characteristics of a persistent infection and in whom extensive microbiological analysis fails to reveal the responsible pathogen. Given the history of new pathogen discovery over the past few decades, it is entirely possible some of these patients indeed have microbial infections that are beyond our diagnostic capabilities. Examples of this are tropical sprue and Brainerd diarrhea.

Tropical sprue is a syndrome of persistent travelers' diarrhea often associated with malabsorption, steatorrhea, folate, and vitamin B12 deficiency [14]. Tropical sprue is rare in short-term travelers and seems to be less frequent epidemiologically in recent surveys of returned travelers worldwide but bears all the hallmarks of an infectious disease and is successfully treated with tetracycline 250 mg four times daily for at least 6 weeks [15, 16].

Brainerd diarrhea was first described in 1983 when an epidemic of chronic diarrhea occurred in Brainerd, Minnesota, in which the unpasteurized milk of a local dairy was epidemiologically identified as the source [17]. Although presumably infectious, extensive microbiological analysis has failed to identify a responsible pathogen, and no antimicrobial agents have been found to be effective. Multiple subsequent Brainerd epidemics have been reported since its initial description, including several in the U.S. and one on a cruise ship in the Galapagos Islands of Ecuador [18]. The watery diarrhea, associated with urgency, frequency (10–20 stools/day), cramping, weight loss, and a waxing and waning pattern, lasts from 2 to 42 months. At 1-year follow-up of the initial outbreak, 12 % of patients were subjectively normal, 40 % were improved, and 48 % had unrelenting diarrhea. Biopsy specimens of the colon revealed a prominence of intraepithelial lymphocytes without markers consistent with microscopic or collagenous colitis.

Underlying Gastrointestinal Disease

In some cases, a bout of travelers' diarrhea unmasks an underlying gastrointestinal disease in a person who may be genetically predisposed. Examples of this include idiopathic inflammatory bowel disease (IBD), celiac sprue (gluten-sensitive enteropathy) or the recently described nonceliac gluten sensitivity, lactose intolerance, or in rare cases, colorectal neoplasia. In the cases of celiac sprue and colonic adenocarcinoma, it seems clear that the acute infection acquired in travel is not causative, but it allows the underlying pathology to become clinically apparent, bringing the patient to medical attention. In cases of IBD, the pathogenesis remains unclear. A prevailing hypothesis is that IBD is caused by an antecedent microbial infection, and a posttravel IBD may be an accelerated manifestation of this process [19].

Celiac Diasease

Celiac sprue is a systemic disease, which manifests as a small bowel enteropathy. In genetically susceptible individuals (those with HLA types DQ2 and DQ8), villous atrophy and crypt hyperplasia develop in response to antigens found in many grains, leading ultimately to malabsorption [20]. From studies of healthy blood donors, we know that clinically apparent disease with malabsorptive diarrhea accounts as only the tip of the iceberg, with the majority of cases being subclinical or presenting with associated symptoms such as osteoporosis or anemia. Somewhat less than 1 % of healthy Americans harbor latent celiac disease, and it is important to consider as a cause of persistent diarrhea in the returned traveler, especially because it can be relatively easily diagnosed by serologies (antiendomysial, antigliadin, and antitissue transglutaminase antibodies) or by endoscopic biopsies of the small bowel, which show intraepithelial lymphocytosis and variable degrees of villous atrophy and crypt hyperplasia [21–23]. Celiac disease can be effectively treated with a strict gluten-free diet, leading to resolution of chronic diarrhea and restitution of the small bowel architecture [20]. A more recently described condition of gluten hypersensitivity should also be considered in the population of returned travelers with persistent symptoms. Here, a gluten-free diet results in marked improvement or complete resolution of symptoms, but diagnostic serologies are negative and small bowel biopsies are normal [24–26].

Inflammatory Bowel Disease

Idiopathic IBD was diagnosed in 25 % of patients in a retrospective British review of 129 cases of bloody diarrhea acquired during or within 2 weeks of return from a tropical country [27]. These patients denied preexisting gastrointestinal symptoms prior to their travels. A prevailing hypothesis of IBD pathogenesis is the infectious trigger. Whether a genetically determined individual can develop IBD as an accelerated course of travelers' diarrhea is unknown [19]. Others believe that IBD may result from alterations in normal bowel flora, such as occur in travelers [28]. The

most common form of IBD uncovered in the posttravel setting is ulcerative colitis; however, Crohn's disease and microscopic colitis, including collagenous and lymphocytic colitis, have also been described [29].

Colorectal Cancer

Colorectal cancer must be a consideration in patients with persistent travelers' diarrhea, particularly in those who are found to have fecal occult blood or new iron deficiency anemia. This is especially true if these findings persist after the diarrhea has resolved. In many such patients, and especially those over the age of 50, a full colonoscopy should be performed even if the symptoms seem consistent with infectious colitis.

Postinfectious Irritable Bowel Syndrome (PI-IBS)

In the majority of patients with persistent travelers' diarrhea, as more time passes from the initial bout of diarrhea, no specific etiology will be found. Concurrent with the recognition of the importance of persistent diarrhea as a presenting complaint in travelers has been the observation that in certain patients with irritable bowel syndrome (IBS), the onset of symptoms can be traced to an acute episode of gastroenteritis. Irritable bowel syndrome, which develops after acute gastroenteritis, was originally called postinfectious enteropathy [30] but is now known as postinfectious IBS (PI-IBS) to conform to universal nomenclature. PI-IBS has become a topic of considerable clinical and investigative interest as evidence validating it as a diagnosis and elucidating its pathophysiology has accumulated [31]. The syndrome of PI-IBS may be a cause of symptoms in a large number of patients with persistent travelers' diarrhea in whom no specific etiology is found.

PI-IBS as a specific diagnosis requires a paradigm shift: A peripheral event—in this case, an infection—leads to prolonged and permanent changes in gastrointestinal function. PI-IBS has been defined as the new onset of IBS symptoms by modified Rome III criteria for IBS—at least 3 months of recurrent abdominal pain or discomfort associated with two or more of the following features: improvement with defecation and/or onset associated with a change in frequency of stool and/or onset associated with a change in form (appearance) of stool following an episode of gastroenteritis or travelers' diarrhea, with a workup for chronic enteric infection or underlying gastrointestinal disease being negative [31]. Adherence to rigid Rome III criteria (e.g., symptoms present for 6 months) may not apply to the posttravel IBS population—hence, the modification in duration of symptoms to conform to the usual travel clinic scenario. This is the definition currently used in GeoSentinel, the emerging infectious disease surveillance network of the Centers for Disease Control and Prevention and the International Society of Travel Medicine. PI-IBS may be characterized by diarrhea as its predominant symptom, but constipation and mixed IBS patterns with alternating diarrhea and constipation may be seen. In many patients, it is bloating, gas, and generalized abdominal discomfort that cause the most distress.

To put this condition in historical perspective requires a review of the medical literature from the post-WWII period, when it was observed that postdysenteric gastrointestinal symptoms occurred in British troops following successful treatment for amebic dysentery [32]. In more recent studies of IBS patients, 20 % retrospectively recalled diarrhea, vomiting, and fever at the onset of their symptoms, and in other studies, 6 %–17 % of IBS sufferers recalled acute diarrhea as a herald of IBS [33]. Whereas IBS in general is not known to arise from an acute infection but, rather, as the insidious onset of symptoms, in contradistinction PI-IBS is characterized by the acute or new onset of symptoms in the presence of previously normal bowel habits. In PI-IBS, abnormal bowel habits may persist continuously from the acute infectious episode, although they may wax and wane and symptoms may diminish in severity from those of the acute infectious episode. In other cases, symptoms begin after a period of feeling well. The incidence of IBS after any enteric infection has been reported to range from 4 % to 32 % [34–38]. This wide range may be related to differences across studies in the definition of PI-IBS, the time to follow-up between infections, and so forth. Many of the studies were retrospective and subject to bias. In addition, most of the studies did not include a control group to define the incidence of new IBS in the absence of preceding infection. Although most of the studies relied upon the widely accepted Rome I or Rome II criteria for diagnosing IBS, alternative causes of persistent bowel symptoms were often not assessed. This is especially true for patients labeled PI-IBS in the first 3 months after travel, when other causes such as *C. difficile*, protozoan pathogens, and temporary postinfective phenomena may be found.

The limitations of these studies notwithstanding, the data suggest that PI-IBS may be a relatively common sequela of acute gastroenteritis. The studies that did compare individuals having an acute episode of gastroenteritis with matched control individuals having no gastroenteritis consistently show an elevated incidence of IBS among the individuals with a preceding episode of gastroenteritis [39, 40]. Across these studies, those with acute gastroenteritis were approximately 2.5–12 times more likely than controls without acute gastroenteritis to develop IBS over follow-up periods of up to 1 year.

The incidence of PI-IBS specifically associated with travelers' diarrhea has been examined only in four studies. The most recent study was reported among 121 U.S. military travelers returning from routine deployment (>6-month follow-up) to the Middle East, where it was reported that

there was more than a 5-fold increase in incident IBS among those who experienced an episode of travelers' diarrhea during travel, as compared with those who did not (17.2 % vs. 3.7 %, p=.12) [41]. Another study among travelers from Israel reported that significantly more people (14 %) who had travelers' diarrhea developed IBS after 6 to 7 months, as compared with only 2 % of those who did not have diarrhea [42]. A third study reported an incidence of PI-IBS of 10 % in patients who had acquired travelers' diarrhea in Mexico [37]. The fourth study reported only a 4 % incidence of PI-IBS after travelers' diarrhea, which was not statistically different as compared with those who developed IBS who did not have diarrhea (2 %) [38]. However, this study may have been underpowered and unable to detect a statistical significance for such a small difference in incidence.

Risk Factors

The risk factors for PI-IBS are only now beginning to be understood, but host factors, genetic factors, pathogen factors, and host–pathogen interactions are felt to serve as a basis for risk for PI-IBS. In a study of unselected patients with IBS versus controls, fewer patients with IBS were noted to have antiinflammatory cytokines, IL-10, and TGF-beta implying more susceptibility to prolonged and severe inflammation [43]. This is consistent with an increase in inflammatory cells such as enterochromaffin cells and T lymphocytes in the lamina propria in rectal biopsies of patients with PI-IBS. In addition, PI- IBS patients have increased postprandial 5HT release, as compared with controls, and those with standard constipation predominant IBS (IBS-C). PI-IBS patients also have an increased IL-1 beta both during and after infection, as compared with controls [44].

Host risk factors for the development of PI-IBS have also been described. Psychological factors such as stress and anxiety have been shown to be associated with the development of PI-IBS in several studies [45–48]. Younger age has been shown to be a risk factor in some studies [48, 49], but not in another [50]. Host genetics may also be an important risk factor in PI-IBS; however, no studies to date have reported any relevant genes. Several studies suggest that individuals with a genetic background that results in the high production of the proinflammatory TNF-a and low production of the antiinflammatory IL-10 may be more susceptible to prolonged inflammation following gastroenteritis, which may be important in the pathophysiology of PI-IBS [51, 52].

Pathophysiology

The pathophysiology of PI-IBS appears to be related to dysregulation of an immune/inflammatory response. Affected individuals may be unable to down-regulate intestinal inflammation caused by enteric infection [31]. The chronic intestinal immune activation in PI-IBS may be caused by low-grade inflammation and increased intestinal permeability, which leads to disrupted intestinal barrier function, altered neuromuscular function, chronic inflammation, and ultimately to the symptoms of PI-IBS [53]. The mechanistic significance of this is that once mucosal inflammation begins, an alteration of function of the enteric nervous system occurs, leading to changes and excitability of muscle and nerves. A cascade starts in the mucosa and involves a series of mediators leading to activation of the visceral sensory system, with visceral hypersensitivity and alteration in GI transit times with disturbed motor function. (Fig. 1). As a result of altered motility specifically decreased interdigestive phase III waves, small intestinal bacterial overgrowth (SIBO) may occur, resulting in changes in the intestinal microflora. Interestingly, recent data have emerged from an animal model that appears to link *Campylobacter jejuni* infections with gut motor dysfunction, chronic inflammation, and SIBO [54]. A purported mechanism has been put forward that describes changes in the density of interstitial cells of Cajal in the intestinal mucosa and subsequent aberrations in dysmotility [55]. While a number of questions regarding the potential patho-etiology and relevance to human PI-IBS exist, this finding, if confirmed, may prove to be an initial understanding of the mechanism by which acute enteric infections may trigger functional

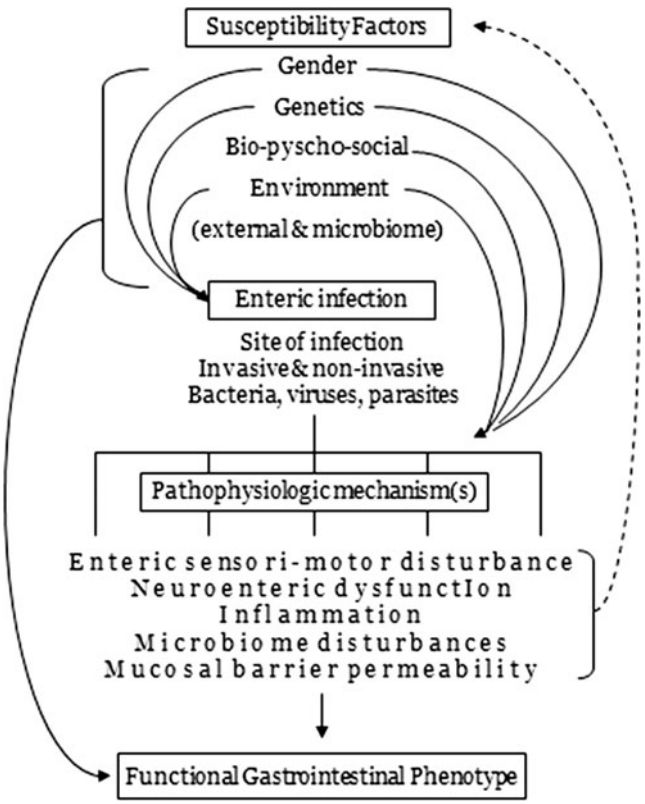

Fig. 1 Proposed analytic framework for evaluating the pathogenesis of PI-IBS

gastrointestinal disorders and be of great value in advancing our understanding of the genetics, immunology, and microbiomics behind this disease mechanism, as well as potentially evaluating mitigative host susceptibility factors and potential preventive interventions (e.g., chemoprophylaxis, vaccination).

There is substantial evidence for inflammation in the gut of patients with PI-IBS. Significantly greater numbers of chronic inflammatory cells were detected in rectal biopsies from patients with PI-IBS than from patients who had enteritis but did not develop PI-IBS [47]. Several other studies have also reported evidence of immune activation and inflammation in the GI system of patients with PI-IBS (Table 2) [43–45, 56]. Elevated levels of enterochromaffin cells are relevant to the pathogenesis of PI-IBS because they produce serotonin, which can stimulate enteric secretions, activate visceral sensory nerves, and regulate peristalsis, thus playing a role in mediating the symptoms of PI-IBS [31, 57]. Interleukin-1b may also be important in PI-IBS, since it can affect enteric nerve function and contribute to diarrhea [58].

These data support the potential utility of antibiotics in the treatment of established IBS, particularly those associated with SIBO, as reflected in a positive lactulose breath test. Since these data were collected from patients with IBS not selected with respect to whether or not they had PI-IBS, the findings cannot necessarily be generalized to those with PI-IBS [59]. Given the promising results with antibiotics in unselected patients, further study in patients with PI-IBS is warranted. Antibiotics with proven efficacy in SIBO are good candidates for additional research. Results of small studies with the poorly absorbed (<0.4 %), gut-selective antibiotic rifaximin support its further testing in IBS. In a randomized, double-blind parallel-group study of 21 patients with SIBO, rifaximin given for 7 days at a dose of 1,200 mg/day normalized lactulose breath tests in 70 % of patients, as compared with 27 % of patients treated with chlortetracycline. Improvement in functional gastrointestinal symptoms was greater with rifaximin than with chlortetracycline [60]. Likewise, in a randomized, double-blind parallel-group study of 34 patients with functional gastrointestinal symptoms (but not necessarily diagnosed with IBS), rifaximin, but not activated charcoal, improved lactulose breath test results and functional gastrointestinal symptoms. In two identically designed, phase III double-blind controlled studies in patients with IBS without constipation who were randomized to either rifaximin 550 mg three times daily or placebo for 2 weeks, significantly more patients in the rifaximin group had adequate relief of global IBS symptoms during the first 4 weeks after treatment (primary endpoint) and adequate relief of IBS-related bloating (key secondary endpoint) during the first 4 weeks after treatment [61]. Some have suggested that the addition of a prokinetic agent such as erythromycin or a 5HT4 agonist following antibiotic treatment will restore normal gastrointestinal motility—specifically, phase III interdigestive waves—and prevent relapse of symptoms [62].

If travelers' diarrhea is a risk factor for the development of PI-IBS, it stands to reason that early treatment, early self-treatment, or prophylaxis might provide a potential window of opportunity to prevent this complication. Although at present there are no data to support this hypothesis, the potential benefit in preventing this postinfective complication should be considered, in addition to the other known benefits from antibiotic therapy of travelers' diarrhea.

Conclusion

Although most cases of travelers' diarrhea are acute and self-limited, it is important for physicians who treat returned travelers to be aware of a significant percentage of patients who develop persistent gastrointestinal symptoms. The pathogenesis of persistent travelers' diarrhea generally falls into one of three broad categories: persistent infections, postinfectious processes, or chronic gastrointestinal illnesses unmasked by an enteric infection. Giardiasis is by far the most likely persistent infection to be encountered in these patients, making empiric therapy for it a reasonable

Table 2 Evidence for increased immune activation in intestines of patients with PI-IBS relative to controls[a]

Biopsy comparisons	EC cells	$CD3^+$ lymphocytes	Mast cells	IL-1b mRNA
Patients with PI-IBS vs. healthy controls, rectal [44]	++	++	—	—
Patients with PI-IBS vs. postinfection controls and healthy controls, rectal [43]	—	—	—	+++
Patients with PI-IBS vs postinfectious and noninfected controls, rectal [45]	+	+[b]	—	—
Patients with PI-IBS vs. non-PI-IBS and noninfected family controls [56]				
Rectal	—	—	ND	+
Ileal	—	—	+[b]	+

Note. EC, enterochromaffin; IL-1b, interleukin 1 beta; ND, no difference; PI-IBS, postinfectious IBS

[a] Results shown if significantly different from those for all listed controls

[b] Results only significantly greater than those for noninfected controls

option. Many patients with persistent travelers' diarrhea where no other cause is found suffer from PI-IBS, although many of these patients have gas, bloating, and constipation as their predominant symptoms. Patients with PI-IBS may benefit from antibiotics that eradicate SIBO.

Conflict of Interest Bradley A. Connor declares that he has no conflict of interest.

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