

Sequelae of Traveler's Diarrhea: Focus on Postinfectious Irritable Bowel Syndrome

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Traveler's diarrhea is usually an acute, self-limited illness; however, in some patients, enteric symptoms can persist for weeks, months, or years. It has been estimated that up to 3% of patients with traveler's diarrhea have symptoms for >30 days. The differential diagnosis includes persistent infection, coinfection, temporary postinfection phenomena, or malabsorptive syndromes. Once these possibilities are excluded, and if symptoms persist, a diagnosis of postinfectious irritable bowel syndrome (PI-IBS) becomes more likely. PI-IBS has recently become a topic of considerable clinical and investigative interest, because evidence validating it as a diagnosis and elucidating its pathophysiological mechanisms has accumulated. Epidemiological evidence suggests that PI-IBS is a relatively common sequela of acute gastroenteritis. Experimental evidence suggests that chronic inflammation following acute bacterial infection has a pathophysiological role in the development of PI-IBS. A fuller understanding of these pathophysiological mechanisms will lead to a more directed therapeutic approach and, perhaps, a reevaluation of prophylaxis for traveler's diarrhea as a means of primary prevention of PI-IBS.

Traveler's diarrhea is an acute infectious disease that is responsive to antibiotic therapy and is self-limited in nature. In certain instances, however, diarrhea persists, or permanent changes in gastrointestinal function develop after an episode of traveler's diarrhea. It has become apparent that, after acute traveler's diarrhea, subacute or chronic diarrheal syndromes are not uncommon, and, in some cases, the symptoms persist for weeks, months, or years [1–4].

Limited data are available on the incidence and natural history of and predisposing factors for persistent traveler's diarrhea. A recent review of 3 different studies found that 3%–10% of travelers with acute diarrhea have symptoms lasting >2 weeks and that up to 3% of travelers have persistent symptoms lasting >30 days. A Peace Corps study of 4607 American volunteers who worked in 21 different countries for a 2-year period showed that the prevalence of persistent traveler's di-

arrhea was 1.7% [5]. A study of 7886 Swiss travelers on short-term (<3 months) trips noted a 0.9% prevalence of persistent traveler's diarrhea [6]. The third study found that persistent diarrhea occurs in 2.9% of students traveling to several Latin American cities [7].

Specific etiologies for continued symptoms may be discovered during the period early after the development of traveler's diarrhea. However, in the vast majority of patients, as time passes from the initial bout of traveler's diarrhea, no specific etiology will be found. Concurrent with the recognition of the importance of persistent traveler's diarrhea as a presenting complaint has been the observation that, in a certain number of patients with irritable bowel syndrome (IBS), the onset of symptoms can be traced to an acute bout of gastroenteritis. IBS that develops after acute enteritis has been termed "postinfectious IBS" (PI-IBS) [8]. PI-IBS has recently become a topic of considerable clinical and investigative interest, as evidence validating it as a diagnosis and elucidating its pathophysiological mechanism has accumulated. PI-IBS may be the cause of symptoms in the large numbers of patients with persistent traveler's diarrhea for which no specific etiology is found. This review will consider traveler's diarrhea

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as a risk factor for PI-IBS, with a specific emphasis on the epidemiological profile, clinical presentation, pathophysiological mechanism, and management of PI-IBS.

DIAGNOSTIC CONSIDERATIONS

Before a diagnosis of PI-IBS can be made, other causes of persistent traveler's diarrhea must be excluded, including persistent infection, coinfection, temporary postinfection phenomena, malabsorption, postinfectious inflammatory bowel disease, and noninfectious causes. These specific etiologies or conditions are more likely to be discovered during the acute (weeks) or subacute (weeks to months) period after the development of traveler's diarrhea, rather than in subjects with more chronic or long-standing symptoms.

Persistent infection. Although some bacterial pathogens may persist in a carrier state (e.g., *Salmonella* species), rarely are persistent symptoms associated with this carriage. As a group, the microbial pathogens more likely to be isolated in persistent traveler's diarrhea are protozoans. In general, the clinical syndrome associated with intestinal protozoan pathogens is more insidious and indolent, compared with that associated with bacteria. As a rule, the probability of discovering a protozoan pathogen relative to a bacterial one increases with an increasing duration of symptoms. In travelers to Nepal, for example, protozoans were detected in 10% of patients whose symptoms lasted <14 days, as opposed to 27% of patients whose symptoms lasted >14 days [9–11]. *Giardia* species appear to be the most common protozoan pathogen in returned travelers. Other protozoans associated with persistent and indolent symptoms in travelers include *Cyclospora* and *Cryptosporidium* species and *Dientamoeba fragilis*. *Entamoeba histolytica*, which also is a diagnostic possibility, appears to be less common in travelers than in indigenous populations [12].

Coinfection. Persistent diarrhea may be seen in cases of coinfection, especially when one pathogen (e.g., a bacterium) is effectively treated with an antibiotic, leaving an untreated second infection, such as infection with *Giardia* species. Likewise, *Clostridium difficile* may account for persistent diarrhea, especially in subjects who have already been treated with antibiotics [13].

Temporary postinfection phenomena. In some cases in which the offending microorganism is no longer present, persistent gut damage or compromise may lead to continued symptoms. An acute episode of infectious diarrhea may precipitate an intestinal disaccharidase deficiency, with lactase deficiency as the most common form, although sucrase deficiency may be seen as well [14, 15].

Patients with this postinfection phenomenon will usually complain of continued diarrhea, abdominal pain, cramping, and gaseous distention. In most individuals, these symptoms resolve within a few weeks, but, in a small minority, a per-

manent disaccharidase deficiency may ensue, especially in those who are genetically predisposed.

Small intestinal bacterial overgrowth (SIBO) syndromes may be another temporary postinfection phenomenon. Enteric infections may cause temporary changes in bowel motility, resulting in stasis and secondary bacterial overgrowth [16].

Malabsorption. In patients with persistent diarrhea, especially those with weight loss, malabsorption may be present. Screening for malabsorption may be done by D-xylose testing. Tropical sprue is a classic travel-related cause of intestinal malabsorption and is an infectious disease of unknown etiology. Tropical sprue has been described in travelers returning from many parts of the world [17]. More common, however, in recent years has been the diagnosis of an underlying celiac sprue unmasked by an acute episode of traveler's diarrhea in patients with persistent diarrhea and malabsorption. There are specific serological markers for celiac sprue, including tissue transglutaminase antibody. The reference standard for diagnosis, however, is a small-bowel biopsy specimen that shows duodenal mucosa, with villous blunting, crypt hyperplasia, and increased intraepithelial lymphocytes [18].

Postinfectious inflammatory bowel disease. Postinfectious inflammatory bowel disease, both as ulcerative colitis and Crohn disease, has been described after traveler's diarrhea [19]. It appears that the acute enteric infection may serve as a trigger for the development of inflammatory bowel disease in subjects who are genetically predisposed.

Noninfectious causes. In a study of returned travelers with bloody diarrhea who were admitted to the Hospital for Tropical Diseases (London, UK), 25% of patients were found to have either IBS or colon cancer as a cause of their symptoms [20, 21]. The clinician should be particularly sensitive to appropriate clinical investigation of symptoms that may be unrelated to traveler's diarrhea.

PI-IBS

For patients for whom a specific etiology for diarrhea is not found, one should consider a diagnosis of PI-IBS. There is now increasing evidence that supports PI-IBS as a specific diagnosis [8]. Acceptance of this diagnosis requires a paradigm shift: a peripheral event (i.e., infection) leads to prolonged, permanent changes in gastrointestinal function.

The bulk of the research on PI-IBS involves cases that occur after episodes of acute gastroenteritis not necessarily related to travel. That research, as well as data on PI-IBS specifically associated with traveler's diarrhea, is reviewed here. Because the studies of PI-IBS after gastroenteritis not related to travel predominantly involve patients who are acutely infected with some of the same pathogens that are responsible for traveler's diarrhea (e.g., *Campylobacter*, *Salmonella*, and *Shigella* species) and with acute gastroenteritis clinically indistinguishable from

traveler's diarrhea, the data from those studies are relevant to the consideration of PI-IBS developing after traveler's diarrhea.

CLINICAL MANIFESTATIONS

PI-IBS has been defined as the onset of IBS symptoms after an episode of enteric infection [8]. The enteric infection can be characterized by fever, diarrhea, vomiting, and often, but not always, a stool culture positive for bacteria or a clinical response to an appropriate antibiotic [8, 22]. In most studies, PI-IBS has been linked to acute infection with bacterial pathogens, but it may also occur after viral infection [23] or protozoal infection [24].

IBS that is not known to arise from an acute infection is characterized by an insidious onset of symptoms, but PI-IBS is characterized by the acute or new onset of symptoms in the presence of previously normal bowel function [8]. In individuals with PI-IBS, abnormal bowel habits typically persist continuously after the acute infectious episode, although they may wax and wane. Although the severity of symptoms diminishes, compared with that during the acute infectious episode, bowel function before the episode is not regained. Weight loss and bleeding with defecation, which may occur during the acute diarrheal episode that precipitates PI-IBS, do not characterize PI-IBS. Persistent weight loss and/or rectal bleeding should stimulate investigation of alternative diagnoses.

PI-IBS is more often characterized by diarrheal symptoms than by constipation [25, 26] (author's unpublished data). In a sample of 90 patients reporting persistently altered bowel habits after an episode of gastroenteritis, the frequencies of abdominal pain, loose or watery stools, rectal urgency, mucus in the stool, and bloating significantly increased during the 6-month period after the episode of gastroenteritis relative to the 6-month period before the episode [26]. Persistent diarrhea may occur with both IBS and PI-IBS; however, constipation-predominant and alternating subtypes also exist in both syndromes [25] (author's unpublished data).

The prognosis of PI-IBS has not been systematically assessed, but results of one study suggest that symptoms may persist for years in many patients. In a long-term follow-up of 192 individuals, 6 years after an episode of gastroenteritis, recovery of normal bowel function was observed in only 6 (43%) of 14 individuals who developed PI-IBS after the episode of gastroenteritis and in 4 (31%) of 13 individuals who had IBS that began before the episode of gastroenteritis [27].

INCIDENCE: HISTORICAL PERSPECTIVE

The term "postdysenteric colitis" was coined by Stewart in 1950 to describe continued symptoms of diarrhea in British troops after successful treatment of amebic dysentery [24]. Two forms were described, an "ulcerative" form, which, in retrospect, was probably ulcerative colitis or colitis due to *C. difficile* infection,

and a functional nonulcerative form in which continued symptoms predominated but no obvious pathological abnormality could be found by use of sigmoidoscopy. A decade later, Chaudhary and Truelove described 130 patients with IBS, 34 of whom dated the onset of their symptoms to an episode of bacterial or amebic dysentery [8, 28]. They suggested that "psychological" factors played a role in this in these patients. Since then, others have suggested a high incidence of IBS after gastrointestinal infection, with estimates ranging from 4% to 31%.

Studies assessing the incidence of PI-IBS differ with respect to the definition of PI-IBS, the length of time between acute infection and follow-up, geographic and clinical settings, and methods for determining the presence of IBS. This heterogeneity may account for the variability among studies in the incidence of PI-IBS. Across studies, 4%–31% of individuals assessed up to 12 months after an episode of gastroenteritis have PI-IBS (table 1) [22, 26, 29–38].

The studies described in table 1 quantify the number of individuals who developed PI-IBS relative to the total number of patients with an episode of infectious gastroenteritis, rather than relative to the total number of cases of IBS. The few studies that have assessed the number of cases of PI-IBS as a fraction of the total number of cases of IBS suggest that a minority of patients with IBS attribute it to an acute infectious origin. Across studies, the proportion of patients with IBS who also have PI-IBS ranges from 6% to 35% [8].

The incidence data summarized in table 1 should be interpreted with an appreciation of the limitations of the studies. Many of the studies were retrospective and, therefore, subject to bias. In addition, most of the studies did not include a control group to define the incidence of new cases of IBS in the absence of preceding infection [39]. Furthermore, although most of the studies relied on the widely accepted Rome I or Rome II criteria for diagnosing IBS, alternative causes of persistent bowel symptoms were often not assessed or were not reported to have been assessed. This is especially true for patients thought to have PI-IBS during the first 3 months after travel, when other causes, such as *C. difficile*, protozoan pathogens, and temporary post-infection phenomena, may be found.

The dependence of most studies on patients' recollection of the relationship between an episode of infectious gastroenteritis and a long-standing change in bowel habits also constitutes a limitation. This measure is unreliable, particularly when patients are asked to recollect their bowel habits over a period of years. Because patients may fail to perceive a link between a past episode of gastroenteritis and persistent abnormal bowel habits, may have forgotten an episode of acute gastroenteritis, or may have had mild or subclinical acute infection that they did not perceive to be gastroenteritis, the data might underrepresent the number of patients with IBS associated with an acute infectious origin. On the other hand, because the ten-

Table 1. Summary of studies assessing the incidence of postinfectious (PI) irritable bowel syndrome (IBS).

Year, study	Description of study	Incidence of PI-IBS
1994, McKendrick and Read [29]	Prospective study of development of new-onset IBS symptoms after an outbreak of salmonellosis in 38 patients	31% had IBS at assessment 6 months after acute infection.
1996, Gwee et al. [30]	Prospective study in Sheffield, England, of 75 patients with gastroenteritis who consulted an infectious disease clinic	20 (27%) had persistent symptoms compatible with IBS 3 months after the acute illness.
1997, Neal et al. [26]	Community-based, retrospective survey in Nottingham, England, of 357 individuals with culture-positive bacterial gastroenteritis	7% met Rome I criteria for IBS 6 months after infection, and 25% reported persistent change in bowel habit 6 months after infection.
1999, Rodriguez and Ruigomez [31]	Prospective study of 318 patients with documented <i>Campylobacter</i> or <i>Salmonella</i> gastroenteritis from a general practice database of 584,308 patients in the United Kingdom	Relative risk of a new diagnosis of IBS over the 12 months after infection was 11.9 times greater than that for uninfected control subjects (incidence of new IBS cases, 4% in patients vs. 0.35% in uninfected control subjects)
2001, Thornley et al. [32]	Community-based, prospective study in Nottingham, England, of 189 individuals with gastroenteritis caused by <i>Campylobacter</i> species	9% met Rome I criteria for IBS 6 months after infection.
2003, Dunlop et al. [33]	Prospective study of 747 individuals after gastroenteritis caused by <i>Campylobacter</i> species	PI-IBS developed in 13.8% of patients surveyed 3 months after infection.
2003, Ilnyckij et al. [34]	Prospective cohort study of 109 healthy adults traveling outside of Canada or the United States	The incidence of IBS (by Rome criteria) was higher (but not statistically significantly so) among the 44% of the cohort that developed traveler's diarrhea than among those who did not develop traveler's diarrhea (4.2% vs. 1.6%; relative risk, 2.5; 95% CI, 0.2–27.2; $P = .41$).
2003, Parry et al. [35]	Prospective, community-based, case-control study of 108 patients with confirmed bacterial gastroenteritis and 206 control subjects	The incidence of new IBS (defined by Rome II criteria) over 6 months was 17% in individuals with previous infection, compared with 2% in control subjects (OR, 10; 95% CI, 3–31).
2004, Ji et al. [36]	Prospective study of 101 patients after a shigellosis outbreak and of 102 age- and sex-matched healthy control subjects	15% developed IBS by 12 months after shigellosis infection, compared with 6% of healthy control subjects.
2004, Lee et al. [22]	Retrospective study of 129 patients (selected from a larger group of 236) who had acute diarrhea and underwent colonoscopy from January 2001 to September 2002	11% of patients had IBS when interviewed by telephone (time of interview relative to time of acute diarrheal episode not specified).
2004, Mearin et al. [37]	Prospective study of incidence of IBS in 468 patients with acute <i>Salmonella</i> gastroenteritis, compared with that in an age-, sex-, and geography-matched cohort not affected in the outbreak of acute <i>Salmonella</i> gastroenteritis	Before the outbreak of acute <i>Salmonella</i> gastroenteritis, the incidence of IBS was comparable in case patients and control subjects (~3%). Three, 6, and 12 months after the outbreak of acute <i>Salmonella</i> gastroenteritis, the incidence of IBS was significantly higher in case patients (~10%) than in control subjects (~1%–2%).
2004, Okhuysen et al. [38]	Prospective study of 97 healthy students traveling from the US to Mexico	Of the 60 patients who acquired diarrhea in Mexico, 10% had newly diagnosed IBS 6 months after the diarrheal episode.

dency to underreport the frequency and/or severity of abnormal bowel habits may be greater before an acute infectious episode than afterward [40, 41], the data might overrepresent the number of patients with IBS associated with an acute infection.

The ability to generalize the data across regions is limited by the fact the studies were conducted in Western countries, particularly in England. The incidence of PI-IBS has not been systematically investigated in non-Western countries. Gastrointestinal infections are more common in tropical countries than in Western countries. Furthermore, the severity of illness is often decreased because of partial immunity conferred by frequent infection and/or infection early in life [8]. Both of these factors could influence the probability of developing PI-IBS such that risk differs in tropical countries, compared with Western countries; this a possibility that has not been assessed to date.

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 who had an acute episode of gastroenteritis with matched control subjects who did not have gastroenteritis consistently show an elevated incidence of IBS among the individuals with a preceding episode of gastroenteritis [31, 34–37]. Across these studies, subjects with acute gastroenteritis were ~2.5–12 times more likely than control subjects without acute gastroenteritis to develop IBS over follow-up periods of up to 1 year. The differences were statistically significant in all but one study [34], which, the authors point out, may have been inadequately powered to demonstrate statistical significance.

RISK FACTORS

Host factors. In the Nottingham study [26], women were significantly more likely than men to develop PI-IBS, but other researchers have observed that PI-IBS predominantly occurs among men (author’s unpublished data). Age >60 years exerts a protective effect, versus ages 19–29 years (adjusted relative risk, 0.36).

Pathogen factors. The type of organism responsible for the acute bacterial infection may also influence the risk of developing PI-IBS. PI-IBS is more common after infection with *Campylobacter* and *Shigella* species than it is after infection with *Salmonella* species [8]. The chances of developing PI-IBS are estimated to be 1 in 10 with *Campylobacter* or *Shigella* species, compared with 1 in 100 with *Salmonella* species. This difference may be attributed to the more severe mucosal injury and/or the longer duration of initial diarrheal illness caused by *Campylobacter* and *Shigella* species, compared with *Salmonella* species. Consistent with this speculation, bacterial toxicity in vitro was a strong determinant of the probability of developing PI-IBS by 3 months after *Campylobacter jejuni* enteritis infection in one study [32]. Data are lacking on pathogens commonly

associated with traveler’s diarrhea, such as enterotoxigenic *Escherichia coli* and enteroaggregative *E. coli*.

Host pathogen interaction. Research to date suggests that the duration of acute infectious illness may be the strongest risk factor for PI-IBS [26, 36]. In a community-based, retrospective survey of individuals with culture-positive bacterial gastroenteritis in Nottingham, England, the number of days that acute infectious diarrhea lasted was directly related to the risk of development of PI-IBS (table 2) [25]. Compared with individuals with acute infectious diarrhea that lasted ≤7 days, individuals with acute infectious diarrhea that lasted 8–14 days, 15–21 days, and ≥22 days were 2.9, 6.5, and 11.4 times, respectively, more likely to develop PI-IBS. The reason that longer duration of illness confers greater risk of developing PI-IBS, compared with shorter duration of illness, is not known. Insofar as longer duration of illness is a marker for more-severe illness, it may be that greater severity of illness, rather than duration of illness, per se, confers a risk of developing PI-IBS. This would explain the development of PI-IBS after acute traveler’s diarrhea, which is usually an illness of relatively short (<7 days) duration. This possibility is further supported by the finding that vomiting during acute gastroenteritis appears to protect against the subsequent development of PI-IBS, possibly by reducing the amount of inoculum and, thereby, the severity of illness [26]. Some consider this finding to be an argument for the early self-treatment or prophylaxis of traveler’s diarrhea.

PATHOPHYSIOLOGICAL ROLE

Experimental evidence suggests that chronic inflammation following acute bacterial infection has a pathophysiological role in the development of PI-IBS. Subjects with PI-IBS appear to be unable to down-regulate intestinal inflammation. In a recent study of unselected patients with IBS, there was a decreased prevalence of the anti-inflammatory cytokines IL-10 and transforming growth factor-β among these patients, which implies that they were more susceptible to prolonged and severe inflammation. Markers of mucosal inflammation are consistently elevated in patients with PI-IBS. Both during and 3 months after an episode of acute gastroenteritis, the inflammatory cy-

Table 2. Effect of duration of diarrhea on self-reported changes in bowel habits after gastroenteritis [26].

Duration of diarrhea, days	Onset of syndrome after illness (n = 23)	No syndrome (n = 324)	Adjusted relative risk (95% CI)
0–7	2	104	1.0
8–14	7	123	2.94 (0.6–15)
15–21	7	44	6.46 (1.3–34)
≥22	7	38	11.37 (2.2–58)

NOTE. Data are no. of subjects.

tokine IL-1 β was present in higher levels in the rectal mucosa of 8 patients who developed PI-IBS, compared with 7 patients whose bowel habits returned to normal [42]. Moreover, at the 3-month assessment, IL-1 β levels were elevated in the patients with PI-IBS, but not in the patients whose bowel habits normalized after acute gastroenteritis, compared with 18 control subjects who had not had gastroenteritis for at least 2 years before the study. On the basis of these findings, the authors suggest that inflammation plays a role in causing PI-IBS and that patients who develop PI-IBS may be more susceptible to inflammatory stimuli than those who do not [42].

The results of macroscopic and conventional histological assessments of the intestinal mucosal of patients with PI-IBS generally appear to be normal within 2 weeks of the acute infectious illness, but chronic inflammation as revealed by quantitative histological analysis persists [8, 43]. In a study of 21 patients who had experienced acute *Campylobacter* enteritis and 12 control subjects with no bowel symptoms after *Campylobacter* enteritis, numbers of intraepithelial T lymphocytes and enterochromaffin cells in rectal biopsy specimens were elevated, compared with cell counts in control subjects, at 2, 6, and 12 weeks after the episode of enteritis (figure 1) [43]. In a subset of 7 patients who had symptoms for 1 year after the episode of enteritis, counts of both cell types remained significantly higher than those noted for control subjects. Intraepithelial T lymphocytes and enterochromaffin cells were also increased in a separate group of 10 patients with PI-IBS. Cell counts in the latter group were comparable to those in the 7 patients who had symptoms 1 year after the episode of *Campylobacter* enteritis (figure 1) [43]. These signs of persistent local inflammation were accompanied by increased small-bowel permeability, as reflected by an elevated ratio of urinary excretion of lactulose to mannitol. Together, the increases in T lymphocytes and enterochromaffin cells and in small-bowel permeability reflect persistent mucosal inflammation.

These findings are corroborated by results of a study of 28 patients with newly diagnosed PI-IBS after *Campylobacter* infection, 28 age- and sex-matched control subjects who were asymptomatic after *Campylobacter* infection, and 34 healthy volunteers [33]. Enterochromaffin cell counts and T lymphocyte counts in rectal biopsy specimens were higher in patients with PI-IBS than in either recovered control subjects or healthy volunteers (figure 2) [33]. Enterochromaffin cell counts were 35.8 cells/high-power field (hpf) in patients with PI-IBS, 30.6 cells/hpf in recovered control subjects ($P = .022$, vs. IBS), and 29.1 cells/hpf in healthy volunteers ($P = .006$, vs. IBS). T lymphocyte cell counts were 127.1 cells/hpf in patients with PI-IBS, 113.4 cells/hpf in recovered control subjects (not significant, vs. IBS), and 97.1 cells/hpf in healthy volunteers ($P = .006$, vs. IBS).

Enterochromaffin cell hyperplasia, which is thought to be a

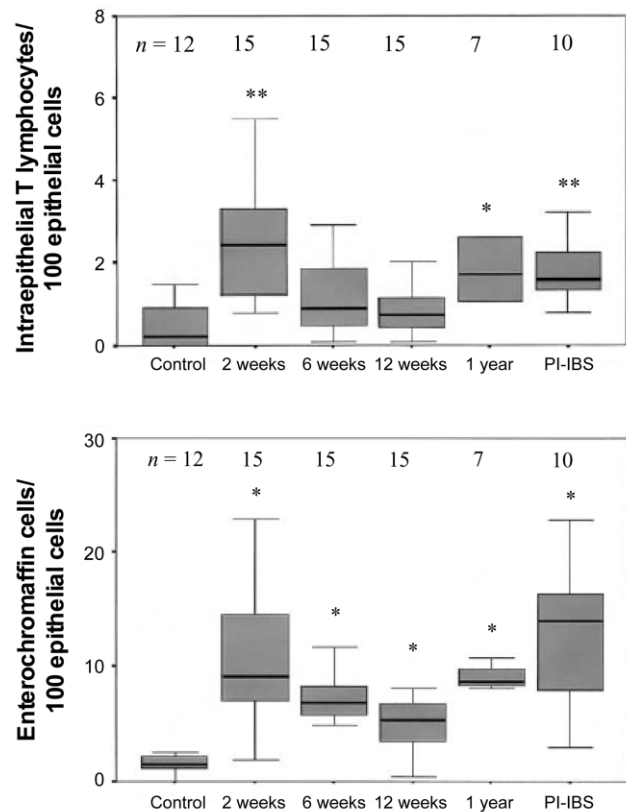


Figure 1. Analysis of rectal biopsy specimens obtained 2, 6, and 12 weeks and 1 year after *Campylobacter* enteritis [43]. Control subjects were asymptomatic individuals who underwent colonoscopy with negative results. *Top*, intraepithelial T lymphocytes (* $P < .01$; ** $P < .05$). *Bottom*, enterochromaffin cells (* $P < .001$). PI-IBS, postinfectious irritable bowel syndrome.

relatively nonspecific response to mucosal injury and inflammation, possibly contributes to the symptoms of PI-IBS through serotonin-mediated effects [8]. Enterochromaffin cells are the source of nearly all intestinal mucosal serotonin, which stimulates enteric secretions, activates visceral sensory afferents, and mediates peristalsis.

Like PI-IBS, IBS in individuals with no history of preceding infection is associated with histological evidence of chronic inflammation. However, the pattern of inflammatory manifestations differs between the 2 syndromes. In a study of 23 patients with PI-IBS, 52 patients with IBS and no history of preceding infection, and 36 healthy control subjects, (1) levels of enterochromaffin cells in rectal biopsy specimens were elevated in patients with PI-IBS, compared with both of the other groups; (2) levels of T lymphocytes were elevated in both IBS subgroups, compared with the control subjects; and (3) levels of mast cells were elevated, compared with such levels in control subjects, in patients with IBS and no history of preceding infection, but not in patients with PI-IBS [25]. Biopsy results evaluated with conventional criteria were normal for both IBS

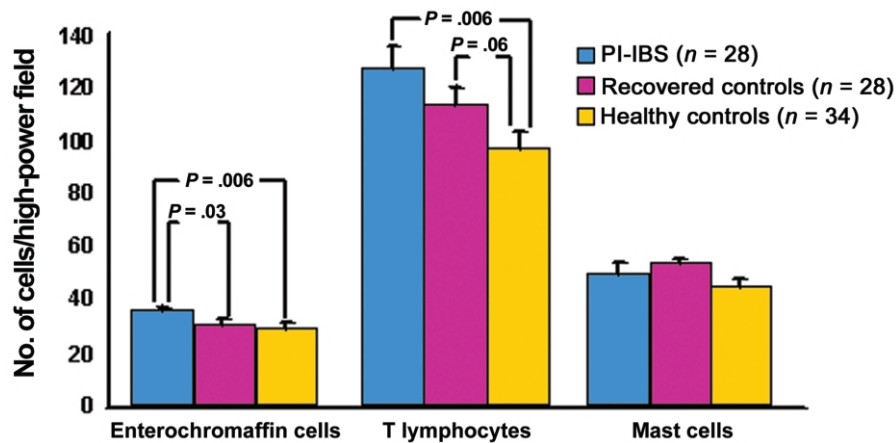


Figure 2. Enterochromaffin cells, T lymphocytes, and mast cells in rectal biopsy specimens obtained 4 months after acute *Campylobacter* infection from patients who went on to develop postinfectious irritable bowel syndrome (PI-IBS), patients who recovered from acute *Campylobacter* infection with no PI-IBS (i.e., “recovered controls”), and healthy controls [33].

groups. On the basis of these findings and results showing greater diarrhea predominance and different psychological histories among the IBS subgroups, the authors concluded that individuals with PI-IBS constitute a subgroup clinically distinct from patients with IBS with no history of preceding infection. This possibility, which appears to be supported by the results of this single study, warrants further investigation in both physiological and clinical studies.

In addition to inflammation, a plethora of other abnormalities, including altered gastrointestinal motility, visceral hypersensitivity, altered brain-gut interaction, and autonomic dysfunction, characterizes IBS in patients with no history of preceding infection. Little research has been conducted to investigate the degree to which these pathophysiological changes are also observed in PI-IBS. Patients who developed IBS after being hospitalized for gastroenteritis ($n = 22$) did show heightened visceral sensitivity and reduced colonic transit time relative to patients whose bowel habits had returned to normal after being hospitalized for gastroenteritis ($n = 72$) in one study [42]. Both heightened visceral sensitivity and reduced colonic transit time are observed in diarrhea-predominant IBS in patients with no history of preceding infection.

MANAGEMENT AND TREATMENT

If traveler’s diarrhea is a risk factor for the development of PI-IBS, what interventions can we offer to prevent this complication? If observations that the duration and/or severity of the acute infection somehow predispose to PI-IBS, then 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 postinfection complication should be considered, in ad-

dition to the other known benefits resulting from the use of antibiotic therapy of traveler’s diarrhea. The options for treatment or self-treatment involve standard antibiotics, such as fluoroquinolones and macrolides, and nonabsorbable antibiotics, such as rifaximin. Extending this logic further, a reevaluation of prophylaxis for traveler’s diarrhea with antibiotic therapy, as a means of primary prevention of PI-IBS, is also warranted. Such antibiotics as fluoroquinolones and macrolides have been proven to be effective in the prevention of traveler’s diarrhea but are associated with potential adverse events and with potential development of resistance. The nonabsorbable antibiotic rifaximin has been proven to be effective in prophylaxis for traveler’s diarrhea in students in Mexico [44]. Because it is a nonabsorbable antibiotic with a low potential for the development of resistance and a low adverse event profile, prophylaxis with rifaximin may become a standard recommendation for the prevention of traveler’s diarrhea.

At present, there is no widely accepted strategy for the management of PI-IBS. Treatment may be empirical, symptomatic, or directed [1]. Patients with PI-IBS may be helped by a host of empirical treatments, such as elimination diets, increasing dietary fiber, digestive enzymes, and probiotics, including *Lactobacillus* GG, VSL3 (Seaford Pharmaceuticals), or *Saccharomyces boulardii*. In addition, symptomatic therapies, such as antispasmodics (e.g., hyoscyamine) or the judicious use of an antidiarrheal agent, such as loperamide, may reduce symptoms. Low doses of tricyclic antidepressants may help reduce the occurrence of diarrhea by antagonizing the actions of serotonin and acetylcholine. Serotonin 3 (5HT3) antagonists that increase colonic transit time and improve symptoms in patients with diarrhea-predominant IBS may be helpful in the management of PI-IBS [45, 46]. In addition, 5HT4 agonists, such as tegaserod, may be helpful in patients with PI-IBS that is predom-

inantly characterized by constipation and bloating. If low-grade inflammation underlies PI-IBS, then anti-inflammatory treatments are logical.

In the only placebo-controlled clinical study of drug therapy for PI-IBS, the effects of the corticosteroid prednisolone (30 mg/day orally for 3 weeks), which is potentially anti-inflammatory, on symptoms and inflammatory cell numbers in rectal biopsy specimens were assessed in 29 patients [47]. Prednisolone, but not placebo, was associated with a significant decrease in T lymphocyte counts, versus pretreatment cell counts. However, neither prednisolone nor placebo improved bowel symptoms or reduced enterochromaffin cell counts, compared with pretreatment cell counts. These data are consistent with a lack of clinically significant effects associated with the use of prednisolone for treating PI-IBS, but the small sample size of that study precluded definitive conclusions. Given the strong histological evidence of mucosal inflammation in patients with PI-IBS, more research regarding a potential role of anti-inflammatory drugs in the treatment and prevention of PI-IBS, especially consideration of the use of anti-inflammatories concurrent with antibiotics at the onset of acute traveler's diarrhea, is warranted. In addition, budesonide, a partially absorbed corticosteroid, might be of benefit. The role of other anti-inflammatories, such as nonsteroidal anti-inflammatory drugs or cyclo-oxygenase-2 inhibitors, needs to be evaluated.

Insofar as bacteria contribute to the pathophysiological mechanism of PI-IBS, antibiotics might be useful in its management. Antibiotics could be useful both in treating established IBS and, when they are used either to treat or to prevent acute episodes of bacterial diarrhea, in preventing the development of IBS. With the exception of several promising investigations, few studies to date have examined the effects of antibiotics in the treatment or prevention of IBS. However, potential applications of antibiotics in treating IBS (including PI-IBS) are being actively researched.

Antibiotics might prove to be effective in the treatment of established IBS by eradicating bacteria that cause or exacerbate symptoms. Research suggests that SIBO, which is associated with a constellation of symptoms similar to those of IBS, may underlie some of the gastrointestinal symptoms in patients with IBS. In a recent meta-analysis undertaken to assess links between SIBO and IBS, abnormal lactulose breath test results, which indicate the presence of SIBO, were found for 84% of patients with IBS, and eradication of SIBO improved IBS symptoms by 75%, on average [48].

Antibiotic therapy that reduces SIBO also reduces or eliminates symptoms of IBS in many patients [49, 50]. In a study of 111 patients with IBS who met Rome I criteria, 84% of whom had abnormal lactulose breath test results at study entry, a course of treatment with the poorly absorbed antibiotic neomycin was associated with a 35% improvement in the Rome

composite symptom score, compared with an 11% improvement associated with placebo. Improvement with neomycin versus placebo on the Rome composite symptom score was more marked in the subgroup of patients with an abnormal lactulose breath test result at study entry (rate of improvement, 35% with neomycin vs. 4% with placebo). A similar pattern of results was reported for global improvement in IBS. The greatest improvements in symptoms of IBS were observed among neomycin-treated patients with normal lactulose breath test results 7 days after completion of treatment.

These data support the potential utility of antibiotics in the treatment of established IBS, particularly that associated with SIBO, as reflected by an abnormal lactulose breath test result. Because these data were collected from patients with IBS who were not selected with respect to whether or not they had PI-IBS, the findings cannot necessarily be generalized to patients with PI-IBS. Given the promising results associated with the use of antibiotics in unselected patients, further study of patients with PI-IBS is warranted. Antibiotics with proven efficacy in treating SIBO are good candidates for additional research. Results of small studies with the poorly absorbed (<0.4% absorption), gut-selective antibiotic rifaximin support further testing of the drug as therapy for IBS. In a randomized, double-blind, parallel-group study of 21 patients with SIBO, rifaximin given for 7 days (1200 mg/day) normalized lactulose breath test results in 70% of patients, compared with 27% of patients treated with chlortetracycline [51]. Improvement in functional gastrointestinal symptoms was greater with rifaximin treatment than with chlortetracycline treatment. Likewise, in a randomized, double-blind, parallel-group study of 34 patients with functional gastrointestinal symptoms (but who had not necessarily had IBS diagnosed), rifaximin, but not activated charcoal, improved lactulose breath test results and functional gastrointestinal symptoms [52].

The increasing recognition that acute bacterial gastroenteritis can frequently cause long-term sequelae, including PI-IBS, elevates the importance of effective treatment of the acute bacterial illness as a means of preventing the syndrome. Effective treatment of acute bacterial diarrheal illness with antibiotics might reduce the risk of PI-IBS by reducing the duration and severity of acute bacterial diarrheal illness and the associated chronic inflammation that may underlie functional bowel symptoms. The quinolones, azithromycin, and rifaximin are effective in the treatment of acute diarrheal illness, including traveler's diarrhea.

CONCLUSIONS

Epidemiological evidence suggests that PI-IBS is a relatively common sequela of acute gastroenteritis, particularly that caused by *Campylobacter*, *Salmonella*, and *Shigella* species. Experimental evidence suggests that chronic inflammation after acute bacterial

infection has a pathophysiological role in the development of PI-IBS. The increasing recognition that acute bacterial gastroenteritis can frequently cause PI-IBS elevates the importance of considering effective prevention and treatment of the acute bacterial illness as a means of preventing the syndrome. Antibiotics also are potentially useful in treating established IBS associated with SIBO. Additional research on the several potential applications of antibiotics and anti-inflammatories in the prevention and treatment of PI-IBS is warranted.

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