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Postinfectious Irritable Bowel Syndrome

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After acute bacterial gastroenteritis, up to one-third of patients will have prolonged gastrointestinal complaints, and a portion of those affected will meet the diagnostic criteria for postinfectious irritable bowel syndrome. After resolution of the acute infection, patients with postinfectious irritable bowel syndrome appear to have chronic mucosal immunologic dysregulation with altered intestinal permeability and motility that can lead to persistent intestinal symptoms. Both host- and pathogen-related factors, such as preexisting psychological disorders and duration of initial infection, have been associated with an increased risk for the development of postinfectious irritable bowel syndrome. Current treatments for postinfectious irritable bowel syndrome are typically targeted at specific symptoms, although studies evaluating therapies directed at preventing or reducing the duration of the initial infection are ongoing.

The majority of individuals who develop acute bacterial diarrhea will have self-limited symptoms lasting <5 days; however, a subset of patients will have prolonged symptoms that may last for years [1]. A portion of patients with postinfectious symptoms will receive diagnoses of irritable bowel syndrome (IBS), a chronic, episodic medical condition associated with abdominal pain or discomfort and altered bowel habits. Postinfectious IBS, which develops in 4%–32% of patients with bacterial gastroenteritis [2], appears to be a nonspecific response to infection caused by a variety of enteric pathogens and has been documented after illness due to *Campylobacter* species, *Salmonella* species, diarrheagenic strains of *Escherichia coli,* and *Shigella* species [3–5].

Postinfectious IBS is diagnosed on the basis of the acute onset of symptoms meeting diagnostic criteria for IBS (with Rome III criteria being the most recently defined; table 1) [6] following an episode of acute infectious gastroenteritis characterized by ⩾2 of the following symptoms and findings: fever, vomiting, diarrhea, and a positive stool culture result [7]. Typically, the acute infectious symptoms of vomiting and fever resolve after several days with resolution of the infection; however, abdominal discomfort, bloating, and diarrhea persist. Several factors, such as duration and severity of initial illness, may increase the risk of developing postinfectious IBS [8, 9]. Although a unifying set of pathophysiologic characteristics has not been established, ongoing intestinal inflammation, motility alterations, and intestinal permeability appear to be associated with mucosal presence of serotonin-containing enterochromaffin cells, intestinal T lymphocytes, mast cells, and proinflammatory cytokines. The clinical aspects, pathophysiologic characteristics, prevention, and management of postinfectious IBS are the focus of this article.

INCIDENCE

It has been >45 years since Chaudry and Truelove [10] evaluated 130 cases of "irritable colon syndrome" and reported that 26% of patients with IBS attributed their onset of IBS to an episode of dysentery. In contrast to patients who developed symptoms without preceding infection, less psychological disturbances and a better prognosis were reported in patients with postinfectious IBS. More recently, the risk of IBS following acute enteric infection has been substantiated following outbreaks of enteric infection in western nations and in travelers to developing countries, with a 4%–32% reported incidence of postinfectious IBS (table 2) [1, 8, 9, 11–23]. This wide range of reported incidence is because of considerable variability in study design (including in the duration of follow-up), in the definition of gastroenteritis, and in the criteria used for diagnosis of IBS. The diagnostic criteria for IBS have been updated over the past 30 years, with recent changes being made in an attempt to exclude other "functional" gastrointestinal disorders

Received 28 August 2007; accepted 7 October 2007; electronically published 9 January 2008.

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Clinical Infectious Diseases 2008; 46:594–9

1058-4838/2008/4604-0019$15.00

DOI: 10.1086/526774

Table 1. Rome III diagnostic criteria for irritable bowel syndrome.

Criteria
Recurrent abdominal pain or discomfort[a] at least 3 days per month in the previous 3 months that is associated with ⩾2 of the following variables
Improvement with defecation
Onset associated with a change in frequency of stool
Onset associated with a change in form (appearance) of stool

NOTE. Criteria fulfilled for the previous 3 months, with symptom onset at least 6 months prior to diagnosis. From [6].

[a] Discomfort means an uncomfortable sensation not described as pain.

and to establish a required duration of symptoms. Of note, it has been generally accepted that, for research purposes, symptoms need only to be present for 3 months.

Importantly, most studies have lacked control groups, which would have made it possible to compare the incidence of IBS in an otherwise similar population without preceding infection. Among the studies that included control groups, the incidence of IBS after acute bacterial enteritis has been 10%–15%. The study by Rodríguez and Ruigómez [21] reported a comparatively lower incidence (4%) of postinfectious IBS among patients with culture-proven bacterial infection; however, after the 12-month follow-up period, only 0.35% of uninfected control subjects were found to have developed IBS—a rate lower than the 1% incidence rate seen in a subsequent study [24]. Recently, in a meta-analysis in which 8 studies were included, Halvorson et al. [25] reported a mean prevalence of IBS of 9.8% among patients with a history of infectious gastroenteritis, compared with a mean prevalence of IBS of 1.2% among control subjects (pooled OR, 7.3%; 95% CI, 4.7–11.1).

Three studies have specifically evaluated the risk of postinfectious IBS in patients with travelers' diarrhea (TD) [14, 19, 22]. Ilnycky et al. [14] prospectively observed 109 healthy adults who were traveling outside Canada or the United States, with the majority of travel destinations listed as developing countries. Consistent with expected attack rates, 44% of these adults developed TD. Interestingly, only 2 (4.2%) of 48 of those who experienced an episode of TD were subsequently found to have IBS after a 3-month follow-up period. In contrast, the incidence of IBS among the travelers who remained healthy was 1.6% (1 of 61 travelers). Okhuysen et al. [19] evaluated 97 healthy US college students studying in Mexico for 5 weeks and reported that 10% of those who acquired diarrhea during their stay in Mexico developed newly diagnosed IBS according to diagnostic criteria during the 6 months after returning from Mexico. Although not all of the students met the diagnostic criteria for IBS, 17% of those with TD had chronic gastrointestinal symptoms (e.g., loose stools and abdominal discomfort) during the 6 months after leaving Mexico. The incidence of postinfectious IBS found in these 2 studies is lower than typically reported for nontravelers who develop bacterial gastroenteritis. One potential explanation for this finding might be that the bacteria causing the infections may have been more-virulent pathogens, such as *Campylobacter, Salmonella,* or *Shigella* species, which are associated with outbreaks in western countries, rather than diarrheagenic *E. coli,* which is more typically seen in travelers. A larger, more recent study of travelers prospectively evaluated in a travel medicine clinic found that nearly 14% of patients with TD developed new IBS during the 6 month follow-up period, compared with 2.4% of those who remained healthy during their travel [22].

Viral gastroenteritis is typically associated with a short duration of symptoms with little residual injury and might be predicted to be associated with a decreased incidence of postinfectious IBS, compared with infection due to bacterial pathogens. In a recent analysis of an outbreak of presumed viral gastroenteritis, 18 (23.6%) of 107 patients who experienced gastroenteritis reported symptoms that were consistent with those associated with postinfectious IBS at 3 months after the outbreak, compared with 1 (3.4%) of 29 individuals who experienced gastroenteritis and remained healthy [26]. However, at 6, 12, and 24 months of follow-up, the prevalence of IBS was similar in both groups.

RISK FACTORS

Both host- and pathogen-related factors have been shown to predispose to the development of postinfectious IBS. Similar to IBS without an infectious onset (nonpostinfectious IBS), preexisting psychological disorders have repeatedly been associated with an increased risk of postinfectious IBS [11, 13]. However, a history of anxiety or depression has been shown to be less common among patients with postinfectious IBS than among those with nonpostinfectious IBS (26% vs. 54%). In addition, similar to patients with IBS overall, female sex has been associated with an increased risk of developing postinfectious IBS [8, 13]. However, when controlling for psychological variables, Gwee et al. [13] found that female sex was no longer a significant independent risk factor. One of the strongest risk factors for the development of postinfectious IBS is the duration of initial infection. Compared with those with illness duration of ⩽1 week, those with symptoms lasting >3 weeks have been shown to have an 11-fold increase in the risk of developing postinfectious IBS [8]. Younger age has also been associated with an increased risk of postinfectious IBS [8, 27] and has been documented to increase the risk of developing TD [28].

Specific pathogens may also influence the risk of developing postinfectious IBS. Compared with infection due to *Salmonella* species, infection due to *Campylobacter* or *Shigella* species may induce more-severe mucosal damage in the gastrointestinal

Table 2. Incidence of postinfectious irritable bowel syndrome (IBS).

Study (year)	Duration of follow-up	No. of patients with acute infectious gastroenteritis	Incidence of postinfectious IBS, %
Borgaonkar et al. [9] (2006)	3 months	191	4
Dunlop et al. [11] (2003)	3 months	747	14
Gwee et al. [12] (1996)	3 months	75	27
Gwee et al. [13] (1999)	12 months	94	23
Ilnyckyj et al. [14][a,b] (2003)	3 months	109	4
Ji et al. [15][a] (2005)	12 months	101	15
Marshall et al. [16][a] (2006)	2–3 years	1368	30
McKendrick and Read [17] (1994)	12 months	38	32
Mearin et al. [18][a] (2005)	12 months	467	12
Neal et al. [8] (1997)	6 months	386	6
Neal et al. [1] (2002)	6 years	192	4
Okhuysen et al. [19] (2004)	6 months	97	7
Parry et al. [20][a] (2003)	6 months	128	14
Rodríguez and Ruigómez [21][a] (1999)	12 months	318	4
Stermer et al. [22][a,b] (2006)	6 months	483	14
Thornley et al. [23] (2001)	6 months	188	9

[a] Study with control group.
[b] Study without pathogen identification.

tract and may lead to longer duration of acute illness [29], which may increase the risk of postinfectious IBS. In a 3-month follow-up study comparing *Campylobacter* infection with *Salmonella* infection, 5 (4.2%) of 119 patients with *Campylobacter* infection developed postinfectious IBS, compared with 1 (2.6%) of 38 patients with *Salmonella* infection [9]. Although an increased risk of subsequent postinfectious IBS due to specific infecting pathogens has been suggested by some researchers, other researchers have found no association between specific bacterial species and development of postinfectious IBS [8, 19].

Vomiting during initial enteric infection may decrease the risk of postinfectious IBS [12], possibly by decreasing the pathogen load in the distal gastrointestinal tract. Although possibly protective against postinfectious IBS, vomiting has recently been associated with an increased risk of postinfectious dyspepsia [17], which might suggest that persistent postinfectious complications may be related to the predominant site of initial infection. In contrast, vomiting associated with viral gastroenteritis has been associated with an increased risk of postinfectious IBS at 3 months after initial infection [26]; however, because vomiting is frequently the predominant symptom seen in viral gastroenteritis, this may merely signify more-severe initial illness.

PATHOPHYSIOLOGIC CHARACTERISTICS

Serotonin (5-hydroxytryptamine) released from enterochromaffin cells affects gastrointestinal motililty, enterocyte secretion, and visceral sensation [30]. *Campylobacter* infection has been shown to lead to an increase in the number of enterochromaffin cells [3], possibly as a response to mucosal injury and inflammation. A 25% increase in the number of rectal enterochromaffin cells has been documented in patients with postinfectious IBS, compared with patients with nonpostinfectious IBS and control subjects [7]. Significant increases in the number of rectal enterochromaffin cells and in lymphocyte counts have also been reported in patients with postinfectious IBS, compared with matched control subjects who recovered from their acute illness without subsequent IBS [11]. In addition, an increase in postprandial plasma serotonin levels has been seen in patients with postinfectious IBS, compared with healthy control subjects and patients with constipation-predominant IBS without an infectious onset [31].

There is increasing evidence that symptoms of postinfectious IBS may originate and be perpetuated by immunologic factors. Although macroscopically normal, microscopic alterations have been documented in the gastrointestinal tract of patients with postinfectious IBS. Patients with postinfectious IBS have been reported to have increases in intraepithelial lymphocyte and lamina propria lymphocyte counts that have persisted for at least a year after infection and have been associated with increased intestinal permeability [3].

The recent evaluation of cytokine profiles has also supported the idea that inflammation plays a role in postinfectious IBS. Increased expression of IL-1β, a proinflammatory cytokine, in rectal biopsy specimens has been reported in patients with infectious enteritis who developed postinfectious IBS, compared with individuals with infectious enteritis who did not subsequently develop IBS [4]. Levels of IL-1β remained elevated at 3

months after initial infection in patients with postinfectious IBS, and those who did not develop IBS had levels similar to those in healthy control subjects. Increased IL-1β expression in the rectosigmoid and ileum has been found in patients with postinfectious IBS following *Shigella* infection, and normal levels have been seen in patients with IBS without an infectious onset [5]. Increased levels of IL-1β support the concept of ineffective downregulation of the inflammatory response seen after acute infectious enteritis, which may contribute to the perpetuation of symptoms seen in patients with postinfectious IBS.

In addition to increased numbers of inflammatory cells and cytokines, increased small intestinal permeability may also be involved in the pathogenesis of postinfectious IBS. Increased intestinal permeability, defined by an increase in the urine lactulose-to-mannitol ratio, has been reported in patients with postinfectious IBS [3, 32]. In a waterborne outbreak of acute gastroenteritis due to *Campylobacter jejuni* and *E. coli* 0157:H7, Marshall et al. [32] reported an increase in intestinal permeability in 35% of patients with new IBS, compared with 13% in those who did not subsequently develop IBS following infection ($P = .03$). Increased intestinal permeability may enhance neuromuscular exposure to bacterial and other luminal antigens, which, in turn, may lead to altered visceral sensitivity and enteric dysmotility through chronic inflammatory mechanisms.

Bile salt malabsorption has been reported following acute infectious enterocolitis, including salmonellosis [33]. Patients with this condition may present with acute onset of infection, large-volume stools, and nocturnal defecation [34] and frequently respond to cholestyramine therapy [35]. Although well documented in the pediatric population [36], clinically significant lactose intolerance following acute bacterial infection appears to be less common in adults. In a small study from the United Kingdom, no cases of lactose intolerance were documented by breath testing in 16 patients with postinfectious IBS following bacterial enteritis [37].

DIAGNOSIS

The diagnosis of postinfectious IBS should be considered in previously asymptomatic individuals with acute onset of symptoms, persistent abdominal pain or discomfort, and altered bowel habits. The diagnosis of acute gastroenteritis is based on the presence of at least 2 of the following signs of infection: fever, vomiting, diarrhea, or a positive stool culture result [7]. Alternatively, TD has been defined as $\geqslant$3 loose stools combined with $\geqslant$1 symptom of infection (e.g., vomiting and abdominal pain/cramps) within a 24 h period beginning at least 48 h after arrival at the destination country [38]. Prior to the onset of acute illness, patients should not meet the diagnostic criteria for IBS (table 1). However, there appears to be a subpopulation of patients with mild chronic gastrointestinal complaints who will meet the diagnostic criteria for IBS after developing significant worsening of symptoms following acute enteritis (author's unpublished observation). In patients with postinfectious IBS, symptoms other than abdominal pain or discomfort and altered bowel habits typically resolve after the acute infection, with the predominant bowel alteration usually being diarrhea [39], whereas individuals with IBS without infectious onset are more likely to have alternating diarrhea and constipation [40]. In the presence of persistent systemic complaints, such as fever or weight loss, or other alarm symptoms (bleeding, anemia, significant nocturnal symptoms, and elevated sedimentation rate), alternative diagnoses should be investigated. Organic diseases that should be considered in individuals with persistent symptoms following presumed acute enterocolitis include inflammatory bowel disease, microscopic colitis, chronic enteric infection (e.g., giardiasis), and celiac disease, and colonoscopy, stool studies, and celiac antibody testing (for antiendomysial and tissue transglutaminase antibody concentrations) may be indicated. IBS has traditionally been considered to be a diagnosis of exclusion; however, Vanner et al. [41] reported a positive predictive value of nearly 100% in individuals who met diagnostic criteria for IBS without alarm symptoms when observed for a period of 2 years.

TREATMENT AND MANAGEMENT

Currently, there are no widely accepted treatment options for postinfectious IBS, and management, similar to that for IBS in general, focuses on the alleviation of specific symptoms. Dietary fiber and fiber supplementation improve constipation associated with IBS through the addition of bulk and water to stools with an acceleration of intestinal transit; however, bloating, discomfort, and diarrhea, which commonly occur in the context of postinfectious IBS, may worsen. Opiates are effective for the treatment of diarrhea through prolongation of intestinal transit, which leads to electrolyte absorption and inhibition of intestinal secretion. Loperamide, the generally preferred opiate because of its rapid onset of action and lack of sedating effects, is especially useful to prevent postprandial fecal urgency associated with IBS, and treatment can be scheduled 30 min before meals. Simethicone and/or antispamodics, such as the anticholinergic agents hyoscyamine and dicyclomine, are often prescribed for bloating and abdominal discomfort. Tricyclic antidepressants and selective serotonin reuptake inhibitors, through their effects on nociception, have been used to treat chronic abdominal pain in patients with IBS and are generally given at a lower dose than is given for treatment of depression. In addition to neuromodulatory and analgesic properties, antidepressants also affect intestinal transit [42]. Selective serotonin reuptake inhibitors have the potential to cause diarrhea, whereas tricyclic antidepressants slow intestinal transit, which may be beneficial in patients with postinfectious IBS.

After establishing the importance of serotonin in the path-

ophysiology of IBS, serotonergic agents have been shown to be modestly effective in the management of IBS. The 5-hydroxytryptamine$_3$ antagonist alosetron enhances small intestinal absorption, slows colonic transit, reduces visceral pain, and has been shown to be effective in female patients with diarrhea-predominant IBS [43]. Because of the adverse effects of severe constipation, ischemic colitis, and bowel perforation, alosetron is currently only available in the United States through a restricted prescribing program for female patients with diarrhea-predominant IBS. Tegaserod, a selective partial 5-hydroxytryptamine$_4$ agonist, accelerates orocecal transit, increases the frequency of bowel movements, and improves abdominal pain [44], and it has traditionally been used for constipation-predominant IBS. Recently, because of a small but statistically significant increased risk of cardiovascular complications, tegaserod has been withdrawn from the market.

Antibiotics have been reported to benefit patients with IBS who have suspected small intestinal bacterial overgrowth by lactulose breath testing [45]. The prevalence of small intestinal bacterial overgrowth in patients with postinfectious IBS has not yet been evaluated; however, antibiotics should be considered in those patients with a positive breath test result. Antibiotics that have shown efficacy in this patient population include rifaximin, neomycin, metronidazole, and fluoroquinolones [45, 46].

In 2005, Hungin et al. [40] reported that only 14% of patients with IBS were completely satisfied with their current therapy. Therefore, effort should be made to prevent the disease when feasible. Travelers to developing countries represent a group at risk for the subsequent development of IBS following infectious enterocolitis. It is possible to decrease the attack rate from TD by careful food and beverage selection; however, travelers typically fail to comply with available recommendations [47]. Antibiotic prophylaxis may reduce the risk of developing postinfectious IBS by preventing the initial mucosal insult and subsequent persistent immunologic dysregulation. Bismuth subsalicylate and antibiotics, including fluoroquinolones and rifaximin, have been evaluated for the prevention of TD [48]. Bismuth subsalicylate has been shown to decrease the occurrence of TD, with a protection rate of 65% [49] (compared with a protection rate of up to 80% with fluoroqinolones [50]); however, concerns regarding bacterial resistance and occurrence of adverse effects have limited the use of bismuth subsalicylate for this indication [48]. Rifaximin, a poorly (<0.4%) absorbed antibiotic, has been approved in the United States for the treatment of TD due to noninvasive *E. coli* [51], and the efficacy of rifaximin has been suggested by 2 double-blind, randomized, placebo-controlled studies [52, 53]. The possibility that preventing TD with rifaximin reduces the risk of postinfectious IBS during long-term follow-up is currently being evaluated.

PROGNOSIS

Early data suggested an increased remission rate in patients with IBS with acute onset of symptoms, compared with those with insidious onset of symptoms [54]. In a more recent 6-year prospective analysis, Neal et al. [1] reported only a slightly improved recovery rate in patients with postinfectious IBS, compared with patients with IBS without infectious onset (43% vs. 31%). McKendrick [55] reported a similar poor prognosis, with 80% of patients with postinfectious IBS following *Salmonella* infection still having symptoms after 5 years. Long-term remission rates appear to be inversely related to underlying psychiatric comorbidities [1, 10]—a finding that is also seen in patients with unspecified IBS [56]. In general, patients with postinfectious IBS appear to have a prognosis that is similar to that for those with IBS without an infectious onset, and most patients will have chronic episodic symptoms.

CONCLUSIONS

Enteric infection leads to the occurrence of postinfectious IBS in a subset of individuals. Future research is needed to define the host and microbial factors that predispose to postinfectious IBS. Clearly, postinfectious IBS is a chronic illness in most cases, which underscores the importance of prevention of the initial inciting illness if possible.

Acknowledgments

Potential conflicts of interest. A.D.P. has received financial support from and honoraria for speaking for Salix.

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