Postinfectious Chronic Gut Dysfunction: From Bench to Bedside

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The relationship between acute infectious gastroenteritis and the subsequent development of chronic gastrointestinal dysfunction has been established on the basis of clinical observations, prospective and epidemiological clinical studies, and from animal models. Clinically, two specific syndromes have been identified: postinfectious irritable bowel syndrome and postinfectious functional dyspepsia. These syndromes may develop in up to 30% of patients with gastroenteritis and both host and microbial risk factors have been identified. Initially, these conditions were considered to be short lived but recent epidemiological data indicate that they can persist for at least 8 years or more. Studies on animal models as well as in patients have identified changes in intestinal barrier and motor functions, as well as evidence of immune activation and low-grade inflammation. These findings prompt ongoing research into the role of anti-inflammatory medication treatment for these conditions. In addition, current research examines possible changes in the intestinal microbiota as a basis for the low-grade inflammation and symptom generation. The long-term consequences of these syndromes remain to be determined.

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INTRODUCTION

A significant fraction of the average gastroenterology practice is devoted to the management of functional gastrointestinal disorders, of which the most frequent are irritable bowel syndrome (IBS) and functional dyspepsia. These patients are highly heterogenous, and the lack of a known etiology and wide variability in treatment response makes them particularly challenging to manage. The ability to distinguish clear subgroups among these patients may assist in the selection of both short- and long-term treatment options and, potentially, improve treatment outcomes.

The relationship between infectious gastroenteritis and functional gastrointestinal disorders was first identified over 60 years ago. It has been clear for decades that patients who develop infectious gastroenteritis are at increased risk for functional gastrointestinal disorders. In 1950, Stewart (1) described "post-dysenteric colitis," a condition he encountered in patients following World War II. He recognized two types of postinfectious colitis: "type 1," did not have an inflammatory component and improved slowly without treatment; and type 2 postinfectious colitis, which was associated with significant inflammation and more serious disease. In 1962, Chaudhary and Truelove (2) described the "irritable colon syndrome," noting in their seminal publication that the syndrome was strongly linked with a history of dysentery. After 2 years, Connell *et al.* (3) were the first to identify an organic disorder in patients with postinfectious IBS, observing that motility in response to acetylcholinesterase inhibitor prostigmine, but not basal motility, was greater in patients with postinfectious IBS than in controls. Despite this evidence, the potential relationship between infectious gastroenteritis and functional gastrointestinal disorders was neglected until the past decade.

Postinfectious functional dyspepsia is a more recently recognized clinical entity. A 2002 study, conducted by Tack *et al.* (4) in 400 consecutive dyspepsia patients with unspecified-onset dyspepsia, found that the initial onset of dyspepsia symptoms occurred after a gastrointestinal infection in ~17% of patients.

Since these early studies, great strides have been made in our understanding of these disorders, although much remains to be uncovered. Today, postinfectious functional gastrointestinal disorders may be defined as the acute onset of new symptoms (IBS or functional dyspepsia) in an individual who has not previously met the Rome criteria for these disorders, immediately following an acute illness characterized by two or more of the following features: fever, vomiting, diarrhea, or a positive bacterial stool culture (5). It is possible that these patients may form a distinct group separable from patients with unknown etiology; in fact, the disease course

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and response to various treatments may distinguish these postinfectious patients from others with IBS and functional dyspepsia.

Epidemiology of postinfectious functional gastrointestinal disorders

At least 6 prospective studies have been conducted in patients with culture-positive infectious gastroenteritis. An early study by Gwee *et al.* (6) evaluated the incidence and persistence of IBS in a population of patients previously hospitalized with acute gastroenteritis. Of the 75 patients enrolled in the study, 29% had persistent symptoms compatible with IBS after their acute illness, and symptoms persisted for at least 6 months in 27%. Notably, all had significant abdominal pain associated with bowel movements; the majority of patients had diarrhea-predominant disease, but two patients with persisting symptoms had constipation, and one had mixed IBS. A subsequent, larger study conducted by Neal *et al.* (7) evaluated the prevalence of gastrointestinal symptoms in 544 outpatients 6 months after culture-positive bacterial gastroenteritis. In this study, ~7% of patients developed IBS. More recently, Marshall *et al.* (8) reported on the incidence of IBS following an outbreak of acute *Escherichia coli* 0157:H7 and *Campylobacter jejuni* gastroenteritis. Rome I criteria were met by 71 of 701 controls (10.1%) vs. 249 of 904 cases with self-reported gastroenteritis (27.5%) and 168 of 464 subjects with clinically suspected gastroenteritis (36.2%). Consistent with early data, patients with postinfectious IBS were more likely than those with IBS of unknown etiology to show diarrhea-predominant features. Other prospective studies examining the risk for IBS following an episode of bacterial gastroenteritis have fallen in this 7 to 29% range (5,9,10).

Postinfectious IBS can persist for the long term following an episode of bacterial gastroenteritis. In two long-term follow-up studies, less than half of postinfectious IBS cases recovered at 5 to 6 years (11,12). In a follow-up study of patients who developed acute gastroenteritis during a large outbreak in 2000, the prevalence of IBS at 8 years was 15.4% (compared with a 28.3% prevalence 2 to 3 years after the outbreak) and remained significantly increased compared with controls who did not have acute gastroenteritis (odds ratio, 3.12; 95% confidence interval 1.99–5.04) (13).

Notably, an increased risk for IBS does not appear to be confined to bacterial gastroenteritis. *Giardia* infection has been associated with an increased risk for IBS (14). In 2007, Marshall *et al.* (8) published a report of a prospective study conducted after a large outbreak of acute gastroenteritis at a medical meeting attributable to food-borne norovirus. Among the 89 subjects who experienced gastroenteritis during the outbreak, 23.6% reported symptoms consistent with postinfectious IBS at 3 months, compared with 3.4% of those who remained well during the outbreak. At 6, 12, and 24 months, the prevalence of IBS was similar among exposed vs. nonexposed individuals, suggesting that postinfectious IBS after presumptive viral gastroenteritis may be more transient than after bacterial dysentery.

Recently, a study using medical encounter data from the US military assessed the relationship between functional gastrointestinal disorders (including IBS, functional constipation, functional diarrhea, and dyspepsia) and infectious gastroenteritis (15)). A significant association was identified between infectious gastroenteritis and all functional gastrointestinal disorders (odds ratio, 2.64; $P<0.001$). The risk for functional diarrhea was most clearly elevated (odds ratio, 6.28; $P<0.001$), as was the risk for IBS (odds ratio, 3.72; $P<0.001$). Only moderate associations were identified for functional constipation (odds ratio, 2.15; $P<0.001$) and dyspepsia (odds ratio, 2.39; $P<0.001$). There was a strong relationship between the prevalence of functional gastrointestinal disorders and time after initial infection (**Figure 1**), with the strongest evidence of persistence for IBS.

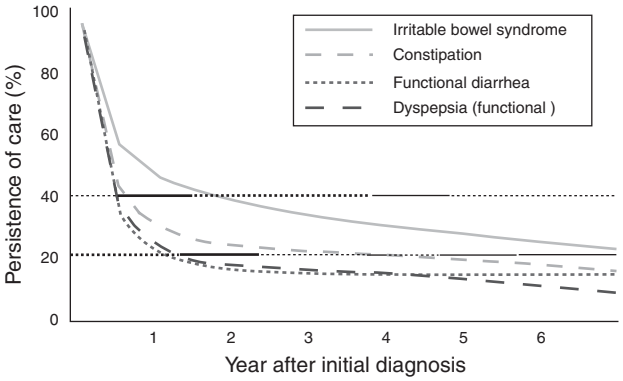

Figure 1. Prevalence of functional gastrointestinal disorder–associated medical visits after *initial* diagnosis of acute gastroenteritis among US military service members (21).

Meta-analyses have confirmed an increased risk for IBS following infectious gastroenteritis (16,17). In an analysis of eight studies, the median prevalence of IBS in all patients with a previous episode of infectious gastroenteritis was 9.8% as compared with 1.2% in control groups (16). Patients with an episode of infectious gastroenteritis were at 7.3-fold increased risk for developing IBS compared with the uninfected cohort.

A 2005 study elucidated the relationship between infection and functional dyspepsia (18). The study included 1,878 participants, of whom 677 had experienced acute gastroenteritis due to *Salmonella enteritidis*. Although the prevalence of dyspepsia was similar in cases and controls before the outbreak (2.5% vs. 3.8%), at 3 months, the respective prevalences were 17.7 and 2.0%; at 12 months, the number of case patients with dyspepsia remained substantially higher than among control patients (13.4% vs. 2.6%; **Figure 2**). There was significant overlap between symptoms of IBS and dyspepsia, such that at 12 months, 36% of patients had symptoms of both disorders, whereas 43% had dyspepsia alone and 21% had IBS alone. These data may suggest that there is a fundamental pathophysiologic underpinning for postinfectious dyspepsia and IBS.

Ford *et al.* (19) examined the prevalence of uninvestigated dyspepsia in a cohort of individuals, some of whom were exposed to bacterial dysentery. Of the 1,088 individuals who provided data for the analysis, 706 had reported acute gastroenteritis. At 8 years, patients with an episode of acute gastroenteritis were more than twofold more likely to have dyspepsia.

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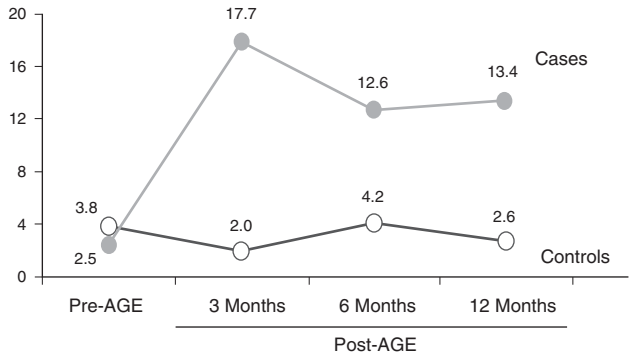

Figure 2. Changes in the prevalence of dyspepsia over time among patients experiencing an acute episode of gastroenteritis due to *Salmonella enteritidis* (reprinted from ref. 17 with permission from Elsevier).

Risk factors for postinfectious functional gastrointestinal disorders

A number of host risk factors—and protective factors—have been identified for postinfectious IBS. In the study conducted by Marshall *et al.* (13) (described above), biologic risk factors for persistent IBS at 8 years after an episode of bacterial gastroenteritis included female gender ($P<0.001$); abdominal cramps ($P=0.004$), fever ($P=0.002$), or blood in stools during the acute illness ($P=0.009$); diarrhea ≥6 days ($P=0.031$); and a peak stool frequency >10/day ($P=0.005$). In a separate study, tobacco use conferred a 4.8-fold increased risk for postinfectious IBS (20). Interestingly, being older than 60 years appears to be associated with a protective effect (adjusted relative risk, 0.36) (7). Among patients with postinfectious functional dyspepsia, female gender ($P=0.051$), vomiting during the acute episode ($P=0.003$), and a higher number of days with abdominal pain ($P=0.001$) were positively correlated with the development of dyspepsia (18). Notably, when compared with unspecified-onset dyspepsia, postinfectious dyspepsia is associated with earlier satiety and more weight loss, nausea, and vomiting (4).

Although biological factors are certainly important in the genesis of postinfectious functional gastrointestinal disorders, psychological factors may also play an important role. In the study conducted by Marshall *et al.* (13), pre-existing anxiety or depression was a strong ($P=0.016$) risk factor for the development of IBS (13). Similarly, a second study found that patients with postinfectious IBS reported significantly more negative life events and had higher hypochondriasis scores than patients without IBS; in fact, these psychological factors more clearly predicted postinfectious IBS than various biologic factors (21).

Pathophysiology of postinfectious IBS

The pathophysiology of postinfectious IBS is likely to be multifactorial. An early study found that, relative to controls, patients had increased rectal sensitivity and decreased rectal compliance 2 years after an episode of salmonella gastroenteritis (22). Similarly, Gwee *et al.* (21) demonstrated rectal hypersensitivity and hyperreactivity, as well as rapid colonic transit, in patients previously hospitalized for infectious gastroenteritis compared with controls. A small, retrospective 1997 study suggested that some patients with IBS may display bile acid malabsorption and that these patients respond positively to treatment with bile acid sequestrants (23). However, these results have not been confirmed in a larger prospective study. A number of changes in the gut mucosa have also been demonstrated in patients with postinfectious IBS, for example, enteroendocrine cell and T-lymphocyte numbers, as well as gut permeability, are markedly increased for ≥1 year following *Campylobacter* enteritis (24).

Risk factors for postinfectious IBS may provide clues to its underlying pathophysiology, even if the mechanisms underlying those risk factors remain incompletely understood. The inverse relationship between age and risk for postinfectious IBS may suggest a role for an aberrant immune response in the genesis of this condition, in that older individuals are generally less immunoreactive than younger individuals. The relationship between psychological and behavioral issues and IBS is telling in that they may relate to our current understanding of the pathophysiology of postinfectious IBS. For example, stress increases intestinal permeability (25) and depression increases vulnerability to inflammatory stimuli (26). These factors may result in an enhanced inflammatory response to the acute infection, thereby predisposing to the development of longer-term gut dysfunction.

Four genetic variants have been identified that may be associated with postinfectious IBS. Two variants are located in Toll-like receptor-9 that encodes a pattern recognition receptor expressed by monocytes/macrophages, plasmacytoid dendritic cells, and B lymphocytes that are specific for unmethylated CpG oligodeoxynucleotide DNA, a prominent bacterial pathogen-associated molecular pattern as well as the gene encoding the secretion of the cytokine IL-1β (27). Additional variants have been identified in CDH1, which, as a tight junction protein, plays a key role in epithelial barrier function, as well as the cytokine interleukin-6. These data are consistent with both abnormal activation of the immune system and increased intestinal permeability in postinfectious IBS. Additional evidence for an altered immune response in postinfectious IBS comes from a study by Gwee *et al.* (28) showing that levels of colonic mucosal interleukin-1β mRNA were significantly higher during gastroenteritis in individuals who subsequently developed IBS compared with those who recovered completely. Furthermore, at 3 months after infection, those patients who developed IBS did not downregulate IL-1β mRNA levels, suggesting inefficient control of the acute inflammatory response to the initial infection.

To date, no studies have profiled the microbiota in patients with postinfectious IBS. Recently, published data on the microbiota in IBS patients without a specified history of a precipitating infection have not identified a microbiotal "signature" other than a frequent reduction in *Lactobacillus* species. However, an emerging trend is a reduction in bacterial diversity and instability of the microbiota over time (for review see Salonen *et al.*(29)) The latter is of potential importance in that animal-based studies have shown that perturbation of a previously stable microbiota leads to changes in gut function (30) and behavior (31). The latter may be important given the association of psychiatric morbidity with postinfectious IBS.

Pathophysiology of postinfectious dyspepsia

It is generally accepted that functional dyspepsia is a heterogeneous disorder with different pathophysiologic mechanisms contributing to the symptom pattern. Putative mechanisms currently proposed include delayed gastric emptying, impaired gastric accommodation to a meal, hypersensitivity to gastric distention, altered duodenal sensitivity to lipids or acid, abnormal duodenojejunal motility, and others. Among the pathogenetic factors implicated are genetic susceptibility, *Helicobacter pylori* status, acute gastrointestinal infections, and psychosocial factors (32). Whether postinfectious dyspepsia pathophysiology differs from that of idiopathic dyspepsia is not clear.

Although recent studies have investigated various pathophysiological mechanisms, the pathogenesis of postinfectious dyspepsia remains obscure. Based on current data, the pathophysiology of postinfectious dyspepsia bears some resemblance to postinfectious IBS but also has some discrepancies. Moreover, results might be different depending on the investigated site (stomach or duodenum) and the offending agent (bacteria, protozoa, or virus). Most previous studies of postinfectious functional gastrointestinal diseases have focused on bacterial causes of gastroenteritis, which are characterized by inflammation and mucosal tissue destruction. However, they may occur also after *Giardia lamblia* infection (14) and viral gastroenteritis (8) where inflammation is mild or absent. Another controversial issue is how an infection involving a given segment of the gut (i.e., the colon) is able to induce chronic symptoms that seem to correspond to another part of the digestive system (i.e., dyspepsia). Several explanations come up: first, it is possible that the inflammation (or microinflammation) induced by the infective agent extends to other gut areas apparently not affected; second, enteroenteral reflexes might be induced, or impaired, producing motor or sensorial abnormalities of noninflamed zones; and third, central mechanisms such as hypersensitivity, hypervigilance, or descending sensorial inhibition loss could be involved and related to psychological factors including anxiety, depression, or somatization. **Figure 3** shows different hypotheses trying to explain postinfectious dyspepsia pathophysiology.

An early study suggested that there is no difference between patients with postinfectious dyspepsia and unspecified-onset dyspepsia in terms of *H. pylori* infection, gastric emptying, or gastric sensitivity; however, there was a significant difference between the two groups in impaired postprandial fundic accommodation (67% vs. 30%, respectively; $P < 0.05$) (4). More recently, Dizdar *et al.* (33) demonstrated gastric hyperalgesia, reduced gastric accommodation of liquid, and delayed gastric emptying in patients with postinfectious dyspepsia after *G. lamblia* infection.

A recent study found the degree of histological duodenitis in bacterial postinfectious dyspepsia to be significantly higher than that found in healthy volunteers and correlate with epigastric burning; however, no correlation was found with gastric emptying values (34). These authors also observed that CCR2-positive macrophage and eosinophil counts were significantly increased. According to these findings and previous studies (35,36), the researchers speculate that CCR2-positive macrophages-derived prostaglandins might lead to clinical symptoms through increasing the sensitivity of nerve terminals.

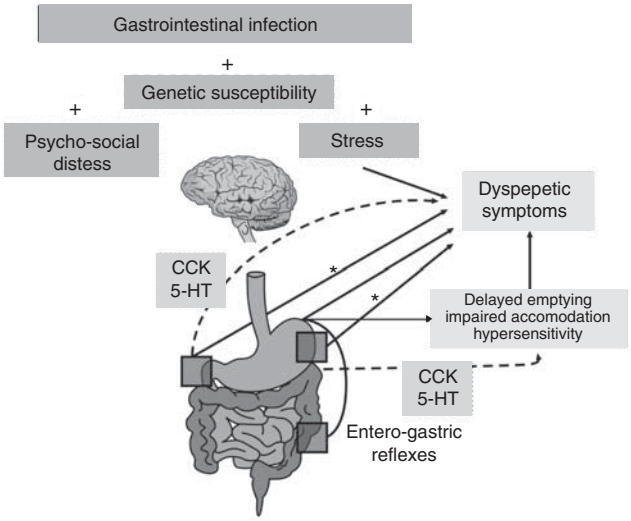

Figure 3. Several pathophysiological mechanisms might be involved in postinfectious dyspepsia. Symptoms could be directly (*) produced by gastric or duodenal inflammatory or immunological changes (□). It is also possible that the inflammation (or microinflammation) induced by the infective agent extends to other gut areas apparently not affected or that enteroenteral reflexes are induced, or impaired, producing motor or sensorial abnormalities of noninflamed zones. Central mechanisms such as hypersensitivity, hypervigilance, or descending sensorial inhibition loss could be involved and related to psychological factors. Circulating peptides may also contribute to symptom generation, either by direct interaction with nociceptive pathways or by influencing the normal physiology (including delayed gastric emptying and impaired gastric accommodation). 5-HT, 5-hydroxytryptamine; CCK, cholecystokinin.

Noteworthy, some other studies found only discrete changes in the cellular immunological response following a previous presumed inflammatory event (37): no increase in intraepithelial lynphocites or enterochromaffine cells but presence of focal aggregates of CD8+ T cells, decreased CD4+ cells, and increased macrophage counts surrounding the crypts. It is conceivable that these changes may contribute to symptom generation, either by direct interaction with nociceptive pathways or by influencing the normal physiology (including delayed gastric emptying and impaired gastric accommodation). On the other hand, low-grade lymphocytic and neutrophil infiltration in the antral mucosa and increases in other inflammatory components including enterochromaffin-like cells and mast cells have been observed by others, suggesting that changes in histamine, tryptase, and 5-hydroxytryptamine (5-HT) could be biological mechanisms inducing gastrointestinal disturbances after gastrointestinal infections (38). In addition, these investigators observed in postinfectious dyspepsia the numbers of activated mast cells and enterochromaffine cells in close proximity to the nerves to be significantly higher than in those with nonspecific functional dyspepsia or controls. This was consistent with the notion that proliferation and activation of both cell types adjacent to the nerves in postinfectious functional dyspepsia may lead to visceral hypersensitivity through a direct effect on perception (39). However, Mearin *et al.* (40) published that

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3 years after *Salmonella* acute gastroenteritis, the observed changes in the mast cell/nerve fiber anatomical interactions, in the stomach or in the colon, were not related to the presence of dyspepsia or IBS but to the infection itself.

A very interesting model to investigate postinfectious IBS and functional dyspepsia pathogenesis is that involving protozoan origin. Thus, *G. lamblia* resides in the lumen and attaches to the epithelium, but does not invade the mucosa and only occasionally causes mucosal inflammation. Dizdar *et al.* (33) found that patients with persisting abdominal symptoms after *Giardia* infection had lower number of 5-HT-containing enterochromaffin cells in duodenal mucosa as well as lower plasma 5-HT during a meal, but cholecystokinin-containing cells were increased and postprandial plasma cholecystokinin tended to be elevated. The authors concluded that cholecystokinin could have an important role in generating symptoms in patients with *Giardia*-induced postinfectious functional gastrointestinal diseases, whereas 5-HT seems less important.

Psychological factors also seem to play a role in postinfectious dyspepsia. Life events occurring during or after an infection are believed to be important cofactors for the development of postinfectious gut dysfunction. It has been published that the only clear difference between subjects who suffered from an acute gastroenteritis and developed chronic dyspepsia and those who did not was the presence of higher anxiety and somatization levels (40).

Treatment of postinfectious functional gastrointestinal disorders

It is beyond the scope of this review to discuss all of the specific treatments available for the management of IBS. A small study ($N=29$) specifically examined treatment of patients with postinfectious IBS. In this study, patients with postinfectious IBS were randomized to 3 weeks of oral prednisolone (30 mg/day) or placebo (41). There were no changes in enterochromaffin cell counts, although lamina propria T-lymphocyte counts decreased. Treatment did not have any effects on symptoms of IBS; however, it should be noted that treatment was initiated ≥3 months after acute gastroenteritis. In a second small ($N=61$) study, patients meeting Rome III criteria for IBS with diarrhea, including 18 patients with postinfectious IBS, received mesalazine 800 mg 3 times daily for 30 days. Among patients with postinfectious IBS, there was a significant reduction from baseline in total symptom scores, stool frequency, abdominal pain, and abdominal distension ($P<0.0001$ for all comparisons) (42). However, this study has some important limitations (open, noncomparative, and nonblinded), and the results should be confirmed in other well-designed investigations.

However, if postinfectious IBS leads to, or is a result of, an alteration in gut microbiota composition, several treatment modalities are available that may beneficially affect bacterial populations or physiology and have been demonstrated to relieve symptoms in general populations of patients with IBS. As discussed elsewhere in this supplement, dietary changes can influence the composition of the gut microbiota; in particular, restriction of FODMAPs (fermentable oligo-, di-, monosaccharides, and polyols) has been demonstrated to be beneficial in a subset of patients with IBS (43,44). Probiotics—discussed in detail in the article by Ringel and colleagues in this supplement—have the potential to alter the inflammatory response seen in patients with IBS and have been demonstrated to be effective for certain symptoms of IBS (45). Recently, a number of studies have been conducted that evaluate manipulation of the gut microbiota with the nonabsorbable antibiotic rifaximin (41). In a general population of patients with IBS without constipation, a 2-week course of rifaximin was effective for at least 10 additional weeks in the global relief of IBS symptoms (46).

Prevention of the development of postinfectious IBS altogether is an interesting possibility that deserves further exploration. Initial evidence from a rat model is promising (47). In this model, rats were randomly assigned to prophylaxis with rifaximin for 3 days, starting 1 day before gavage with *C. jejuni*. The mean duration of stool shedding of *C. jejuni* was lower in the rifaximin-treated group (10.3 days) compared with the control group (12.6 days). At 3 months, treated rats had less variability in stool percentage wet weight ($P<0.01$) and improved stool consistency ($P<0.00001$) compared with controls.

In addition, the presence of continued immune activation in postinfectious IBS raises the question as to whether anti-inflammatory medication might suppress or even reverse postinfectious IBS if provided soon after the onset of symptoms following recovery from the infection. A previous animal study showed that persistent gut dysfunction could be reversed by a short course of corticosteroid administered after infection (48). However, as indicated previously, a clinical study of a short course of a corticosteroid was insufficiently powered to detect changes in patients with mild postinfectious IBS symptoms following a short course of corticosteroid (41).

Treatment of postinfectious functional dyspepsia

There appears to be some difference in response to medication among patients with postinfectious functional dyspepsia compared with those with disease of unspecified origins. Specifically, sumatriptan appears to relax the stomach in controls and patients with unspecified-onset dyspepsia, but not in patients with postinfectious dyspepsia. These data suggest dysfunction at the level of gastric nitrergic neurons (4).

Unanswered questions and future directions

The fact that bacterial exposure and increased intestinal permeability have long been associated with inflammatory bowel diseases (IBD) and that these are features of postinfectious IBS raises concern that certain postinfectious IBS patients may be at risk for IBD. The presence of immune activation and low-grade inflammation, together with genetic abnormalities similar to those associated with IBD risk, prompt consideration of the notion that postinfectious IBS may be a *forme fruste* or a prodromal syndrome of IBD. A review of a large number of patients with postinfectious IBS 8 years after water contamination in the Canadian town of Walkerton, Ontario, suggests a higher than expected incidence of Crohn's disease and warrants ongoing surveillance of this population (49).

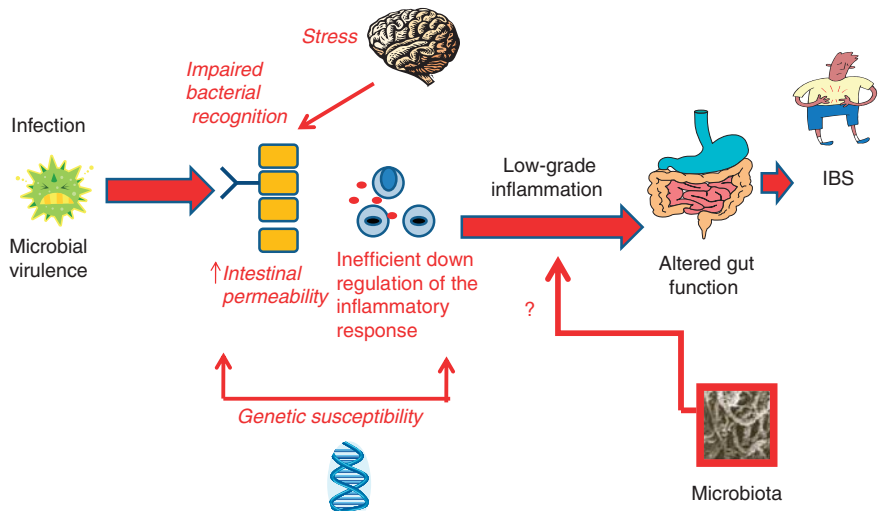

Figure 4. A conceptual model of postinfectious irritable bowel syndrome (IBS).

Accumulating evidence clearly links bacterial, viral, and parasitic infections with the long-term development of functional gastrointestinal disorders (a conceptual model is shown in **Figure 4**). Given the frequency with which patients develop postinfectious IBS, functional dyspepsia, and other functional gastrointestinal disorders, it is worthwhile to rethink the treatment paradigm for infectious gastroenteritis, which is conventionally considered a transient, though often serious, disease state. Preliminary evidence in animals suggests that prompt antibiotic use may have the potential to reduce or attenuate the development of postinfectious gastrointestinal disorders. Intestinal dysbiosis and specific changes in the gut microbiota resulting from gastroenteritis or antibiotics, although an attractive hypothesis to explain postinfectious IBS, remain uncharacterized in patients. Ultimately, differences demonstrated in the gut flora may be difficult to interpret or translate into therapy.

In contrast, low-grade inflammation and intestinal immune activation has been identified in patients with postinfectious IBS, suggesting that a disordered/prolonged immune response to the initial infection may, in fact, be responsible for eliciting and maintaining gastrointestinal symptoms over the long term. Although strong evidence supporting the use of anti-inflammatory treatment in postinfectious IBS is currently lacking, these data prompt consideration of well-designed clinical trials to evaluate the therapeutic benefit of anti-inflammatory treatment with, for example, low-dose steroids, 5-aminosalicylic acid agents, or probiotics following recovery from infectious gastroenteritis. Risk assessment tools that have recently been examined (50) may help accurately target aggressive anti-inflammatory treatment following an episode of acute gastroenteritis.

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CONFLICT OF INTEREST

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REFERENCES

1. Stewart GT. Post-dysenteric colitis. BMJ 1950;1:405–9.
2. Chaudhary NA, Truelove SC. The irritable colon syndrome. A study of the clinical features, predisposing causes, and prognosis in 130 cases. Q J Med 1962;31:307–22.
3. Connell AM, Gaafer M, Hassanei MA *et al.* Motility of the pelvic colon. 3. Motility responses in patients with symptoms following amoebic dysentery. Gut 1964;5:443–7.
4. Tack J, Demedts I, Dehondt G *et al.* Clinical and pathophysiological characteristics of acute-onset functional dyspepsia. Gastroenterology 2002;122:1738–47.
5. Dunlop SP, Jenkins D, Spiller RC. Distinctive clinical, psychological, and histological features of postinfective irritable bowel syndrome. Am J Gastroenterol 2003;98:1578–83.
6. Gwee KA, Graham JC, McKendrick MW *et al.* Psychometric scores and persistence of irritable bowel after infectious diarrhoea. Lancet 1996;347:150–3.
7. Neal KR, Hebden J, Spiller R. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. BMJ 1997;314:779–82.

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8. Marshall JK, Thabane M, Borgaonkar MR *et al.* Postinfectious irritable bowel syndrome after a food-borne outbreak of acute gastroenteritis attributed to a viral pathogen. Clin Gastroenterol Hepatol 2007;5:457–60.
9. Thornley JP, Jenkins D, Neal K *et al.* Relationship of Campylobacter toxigenicity in vitro to the development of postinfectious irritable bowel syndrome. J Infect Dis 2001;184:606–9.
10. Ji S, Park H, Lee D *et al.* Post-infectious irritable bowel syndrome in patients with Shigella infection. J Gastroenterol Hepatol 2005;20:381–6.
11. Neal KR, Barker L, Spiller RC. Prognosis in post-infective irritable bowel syndrome: a six year follow up study. Gut 2002;51:410–3.
12. Jung IS, Kim HS, Park H *et al.* The clinical course of postinfectious irritable bowel syndrome: a five-year follow-up study. J Clin Gastroenterol 2009;43:534–40.
13. Marshall JK, Thabane M, Garg AX *et al.* Eight year prognosis of postinfectious irritable bowel syndrome following waterborne bacterial dysentery. Gut 2010;59:605–11.
14. Dizdar V, Gilja OH, Hausken T. Increased visceral sensitivity in Giardia-induced postinfectious irritable bowel syndrome and functional dyspepsia. Effect of the 5HT3-antagonist ondansetron. Neurogastroenterol Motil 2007;19:977–82.
15. Porter CK, Gormley R, Tribble DR *et al.* The incidence and gastrointestinal infectious risk of functional gastrointestinal disorders in a healthy US adult population. Am J Gastroenterol 2011;106:130–8.
16. Thabane M, Kottachchi DT, Marshall JK. Systematic review and meta-analysis: the incidence and prognosis of post-infectious irritable bowel syndrome. Aliment Pharmacol Ther 2007;26:535–44.
17. Halvorson HA, Schlett CD, Riddle MS. Postinfectious irritable bowel syndrome--a meta-analysis. Am J Gastroenterol 2006;101:1894–9; quiz 1942.
18. Mearin F, Perez-Oliveras M, Perello A *et al.* Dyspepsia and irritable bowel syndrome after a Salmonella gastroenteritis outbreak: one-year follow-up cohort study. Gastroenterology 2005;129:98–104.
19. Ford AC, Thabane M, Collins SM *et al.* Prevalence of uninvestigated dyspepsia 8 years after a large waterborne outbreak of bacterial dysentery: a cohort study. Gastroenterology 2010;138:1727–36; quiz e12.
20. Parry S, Forgacs I. Intestinal infection and irritable bowel syndrome. Eur J Gastroenterol Hepatol 2005;17:5–9.
21. Gwee KA, Leong YL, Graham C *et al.* The role of psychological and biological factors in postinfective gut dysfunction. Gut 1999;44:400–6.
22. Bergin AJ, Donnelly TC, McKendrick MW *et al.* Changes in anorectal function in persistent bowel disturbance following salmonella gastroenteritis. Eur J Gastroenterol Hepatol 1993;5:617–20.
23. Niaz SK, Sandrasegaran K, Renny FH *et al.* Postinfective diarrhoea and bile acid malabsorption. J R Coll Physicians Lond 1997;31:53–6.
24. Spiller RC, Jenkins D, Thornley JP *et al.* Increased rectal mucosal enteroendocrine cells, T lymphocytes, and increased gut permeability following acute Campylobacter enteritis and in post-dysenteric irritable bowel syndrome. Gut 2000;47:804–11.
25. Söderholm JD, Perdue MH. Stress and gastrointestinal tract. II. Stress and intestinal barrier function [Review]. Am J Physiol Gastrointest Liver Physiol 2001;280:G7-G13 .
26. Ghia JE, Blennerhassett P, Collins SM. Impaired parasympathetic function increases susceptibility to inflammatory bowel disease in a mouse model of depression. J Clin Invest 2008;118:2209–18.
27. Villani AC, Lemire M, Thabane M *et al.* Genetic risk factors for post-infectious irritable bowel syndrome following a waterborne outbreak of gastroenteritis. Gastroenterology 2010;138:1502–13.
28. Gwee KA, Collins SM, Read NW *et al.* Increased rectal mucosal expression of interleukin 1beta in recently acquired post-infectious irritable bowel syndrome. Gut 2003;52:523–6.
29. Salonen A, de Vos WM, Palva A. Gastrointestinal microbiota in irritable bowel syndrome: present state and perspectives. Microbiology 2010;156 (Part 11): 3205–15.
30. Verdu EF, Bercik P, Verma-Gandhu M *et al.* Specific probiotic therapy attenuates antibiotic induced visceral hypersensitivity in mice. Gut 2006;55:182–90.
31. Bercik P, Denou E, Collins J *et al.* The intestinal microbiota affect central levels of brain-derived neurotropic factor and behavior in mice. Gastroenterology 2011;141:599–609, e3.
32. Mimidis K, Tack J. Pathogenesis of dyspepsia. Dig Dis 2008;26:194–202.
33. Dizdar V, Spiller R, Singh G *et al.* Relative importance of abnormalities of CCK and 5-HT (serotonin) in Giardia-induced post-infectious irritable bowel syndrome and functional dyspepsia. Aliment Pharmacol Ther 2010;31:883–91.
34. Futagami S, Shindo T, Kawagoe T *et al.* Migration of eosinophils and CCR2-/CD68-double positive cells into the duodenal mucosa of patients with postinfectious functional dyspepsia. Am J Gastroenterol 2010;105:1835–42.
35. Tajima T, Murata T, Aritake K *et al.* Lipopolysaccharide induces macrophage migration via prostaglandin D 2 and prostaglandin E 2. J Pharmacol Exp Ther 2008;326:493–501.
36. Bueno L, Fioramonti J. Visceral perception: inflammatory and non-inflammatory mediators. Gut 2002;51 (Suppl 1): 19–23.
37. Kindt S, Tertychnyy A, de Hertogh G *et al.* Intestinal immune activation in presumed post-infectious functional dyspepsia. Neurogastroenterol Motil 2009;21:832–e56.
38. Li X, Chen H, Lu H *et al.* The study on the role of inflammatory cells and mediators in post-infectious functional dyspepsia. Scand J Gastroenterol 2010;45:573–81.
39. Barbara G, Stanghellini V, De Giorgio R *et al.* Activated mast cells in proximity to colonic nerves correlate with abdominal pain in irritable bowel syndrome. Gastroenterology 2004;126:693–702.
40. Mearin F, Perelló A, Balboa A *et al.* Pathogenic mechanisms of postinfectious functional gastrointestinal disorders: results 3 years after gastroenteritis. Scand J Gastroenterol 2009;44:1173–85.
41. Dunlop SP, Jenkins D, Neal KR *et al.* Randomized, double-blind, placebo-controlled trial of prednisolone in post-infectious irritable bowel syndrome. Aliment Pharmacol Ther 2003;18:77–84.
42. Bafutto M, Almeida JR, Leite NV *et al.* Treatment of postinfectious irritable bowel syndrome and noninfective irritable bowel syndrome with mesalazine. Arq Gastroenterol 2011;48:36–40.
43. Shepherd SJ, Parker FC, Muir JG *et al.* Dietary triggers of abdominal symptoms in patients with irritable bowel syndrome: randomized placebo-controlled evidence. Clin Gastroenterol Hepatol 2008;6:765–71.
44. Ong DK, Mitchell SB, Barrett JS *et al.* Manipulation of dietary short chain carbohydrates alters the pattern of gas production and genesis of symptoms in irritable bowel syndrome. J Gastroenterol Hepatol 2010;25:1366–73.
45. Brandt LJ, Chey WD, Foxx-Orenstein AE *et al.* An evidence-based position statement on the management of irritable bowel syndrome. Am J Gastroenterol 2009;104 (Suppl 1): S1–35.
46. Pimentel M, Lembo A, Chey WD *et al.* Rifaximin therapy for patients with irritable bowel syndrome without constipation. N Engl J Med 2011;364:22–32.
47. Pimentel M, Morales W, Jee SR *et al.* Antibiotic prophylaxis prevents the development of a post-infectious phenotype in a new rat model of post-infectious IBS. Dig Dis Sci 2011;56:1962–6.
48. Barbara G, De Giorgio R, Deng Y *et al.* Role of immunologic factors and cyclooxygenase 2 in persistent postinfective enteric muscle dysfunction in mice. Gastroenterology 2001;120:1729–36.
49. Marshall JK. Post-infectious irritable bowel syndrome following water contamination. Kidney Int Suppl 2009;112: S42–3.
50. Thabane M, Simunovic M, Akhtar-Danesh N *et al.* Development and validation of a risk score for post-infectious irritable bowel syndrome. Am J Gastroenterol 2009;104:2267–74.