

Almost All Irritable Bowel Syndromes Are Post-Infectious and Respond to Probiotics: Consensus Issues

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Abstract

Several reports have described post-infectious irritable bowel syndrome (Pi-IBS), while many animal and human studies have shown the presence of increased infiltration of inflammatory cells and hyperplasia of enterochromaffin cells in the intestinal mucosa after acute gastroenteritis. The potential value of probiotic bacteria in restoring normal gut function has been demonstrated by animal models of Pi-IBS. In humans, Pi-IBS can be prevented utilizing probiotics to reduce the duration of acute gastroenteritis, despite the variable efficacy shown in randomized control trials evaluating unspecified IBS. Here, advances in the pathophysiology supporting the post-infectious hypothesis are considered. In addition, the current role of probiotics in the management of Pi-IBS is discussed.

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Irritable bowel syndrome (IBS) is one of the most common causes of gastroenterological visits. This syndrome is mainly characterized by disturbances correlated to defecation in terms of irregular bowel movements, time spent in the restroom, alteration of stools and urgency to

defecate. Specifically, the definition of IBS is based on the presence of abdominal pain, change in bowel habits and a poorly identifiable organic etiology [1].

Several factors have been identified from a pathophysiological point of view [2]. IBS patients may exhibit an altered gastrointestinal motility with an increased recto-sigmoid motor activity up to 3 h after eating. Psychological issues are documented in up to 80% of IBS patients who are cared for at referral centers. Visceral afferent hypersensitivity has indeed been shown: in several patients a normal physiologic gut stimuli, not perceived by healthy individuals, may produce pain. Autonomic hyperactivity and microscopical inflammation have been shown in some cases, although in the last few years the post-infectious hypothesis has been gaining ground.

Does Gastroenteritis Cause Irritable Bowel Syndrome?*Epidemiological Data*

The first descriptions of post-infectious IBS (Pi-IBS) like symptoms were reported more than five decades ago. Indeed, during the Second World War, British soldiers stationed in North Africa developed diarrhea and abdominal discomfort following amoebic dysentery [3]. In another report, Chaudhary and Truelove [4] described Pi-IBS in 26% of a population that had amoebic dysentery.

In two case-controlled studies the authors reported an increased risk of IBS after gastroenteritis. The first study was carried out on a general practice database in the UK, and involved 128 cases with documented bacterial gastroenteritis and 219 controls. After a follow-up of 6 months, IBS was diagnosed in about 17% of cases and in 2% of controls with an odds ratio of 10.1 [5]. In another study performed using a Chinese Hospital database, 295 cases with bacillary dysentery and 243 controls consisting of patients' siblings or spouses who had not been infected, were enrolled. In this study the authors analyzed all the diagnoses of IBS alone or functional bowel disorders (FBD) encompassing IBS, functional diarrhea, functional constipation, functional bloating and unspecified FBD. They found about 22% of FBD and up 8% of IBS among cases, and up to 7% FBD and about 1% IBS among controls. The risk for FBD and IBS after gastroenteritis was 1.6 and 10.7, respectively [6].

A meta-analysis published in 2006 analyzed eight articles that had appeared in the literature, and showed a 3- to 11-fold higher risk of IBS after a gastroenteritis episode [7].

Clinical Symptoms, Risk Factors and Pathophysiological Data

What are the symptoms reported after a gastroenteritis episode? Abdominal pain, watery stool, urgency, mucus in the stool and bloating are more frequent 6 months after gastroenteritis. Moreover, there are some physiological changes in Pi-IBS compared to unspecified IBS. Intestinal transit appears more accelerated and rectal sensitivity appears increased. Malabsorption of bile salt was also observed in Pi-IBS patients. Indeed, in a study on patients who had had gastroenteritis, 16 out of 29 responded well to cholestiramine, experiencing a decrease in stool frequency [8, 9].

Are there risk factors for developing Pi-IBS? Some studies have explored the possible causes of an increased risk for developing Pi-IBS. Female sex, psychological features as hypochondriasis or presence of adverse life events and younger age are some of the several factors that may be related to the development of Pi-IBS [10]. Lack of vomiting during an acute episode is also another risk factor, as vomiting may partly rid the body of the infecting agent. Moreover, the duration of the gastroenteritis episode influences the development of Pi-IBS. Data of a Chinese study showed that if the diarrhea lasted >7 days, the risk increased by 3.5 times, whereas if it lasted >15 days, the risk increased by 4.6 times [6]. The role of pathogens is also important, as the risk of developing IBS after *Cam-*

pylobacter and *Shigella* is 10 times greater than after *Salmonella* infections [8]. There is scanty information on the risk of Pi-IBS after episodes of gastroenteritis due to viral or parasitic infection.

An interesting field of research to define increased risk for developing Pi-IBS is genetic polymorphism. Preliminary results suggest that at least some patients with IBS may be genetically predisposed to produce lower amounts of the anti-inflammatory cytokine interleukin (IL)-10 [11]. Furthermore, a change in the activity of inducible nitric oxide synthase related to a genetic polymorphism could be responsible of an increased risk of post-infectious disease [12].

Are there organic signs of Pi-IBS? Spiller et al. [13] showed persisting intraepithelial lymphocyte infiltration 1 year following a *Campylobacter jejuni* infection. Moreover, the same group also showed changes in IL-1 β mRNA expression in patients who had developed IBS after acute gastroenteritis [14]. Basically, a hyperplasia of enterochromaffin cells and an increase in post-prandial serotonin have been shown in rectal biopsies of patients 3 weeks after acute infection [15]. Still in relation to serotonin metabolism, we must also highlight changes in SERT (serotonin transporter), the major determinant of serotonin inactivation following release at synapses. In an experimental study the authors showed that *Trichinella spiralis* infection produces a marked inflammation associated with a decrease in jejunal SERT and enterochromaffin cell hyperplasia [16].

Persistent neuromuscular changes have been shown in animal models of post-infectious disease. The persistence of an increased muscle contractility after inflammation resolution measured by myeloperoxidase in the inflamed jejunum at 6 days post-infection has been shown [17].

Does Post-Infectious Irritable Bowel Syndrome Respond to Probiotics?

Normally, bacteria are present in the gastrointestinal tract. Their presence increases from the proximal to the distal zone. Changes in resident bacterial populations by antibiotic use or due to infection may be involved in the generation of chronic gut dysfunction, although some other studies support a beneficial role of antibiotics in IBS [18]. Hence the perturbation of the delicate balance between commensal bacteria and host tissue can promote the expression and maintenance of chronic functional disorders.

Probiotics are microorganisms that have beneficial effects on their host. This term is commonly used for microorganisms that survive the passage through the gastrointestinal tract and might prevent, or even cure, some gastrointestinal diseases as diarrhea. The effects of probiotics are dependent on several mechanisms: modifications of intestinal mucus; competition for nutrients; trophic effect on the epithelium; enhancement of immune response-secretory IgA; competitive inhibition of adhesion; receptor hydrolysis; nitric oxide production; bacteriocins and organic acids production, and toxin hydrolysis.

During an acute gastroenteritis, mucosal permeability is enhanced, and bacterial translocation is increased. As a result, it is possible that the state of altered physiology is maintained, at least in part, by the luminal content through a permeable epithelium and this could involve the microbial flora in either the development and/or maintenance of IBS [19].

Two aspects are relevant to define the rationale of probiotic use in Pi-IBS. Firstly, the evidence for immune activation as well as low-grade inflammation in IBS patients [20]. Secondly, the emerging evidence of abnormal microbiota composition in these patients. The possible therapeutic effects of probiotics in Pi-IBS derive from their antibacterial and antiviral effects, which may be able to prevent or modify the course of Pi-IBS. Moreover, some authors have described an anti-inflammatory effect on the mucosal surfaces achieved by reducing mucosal inflammation, decreasing immune-mediated activation of enteric motor and sensory neurons and modifying neural traffic between the gut and the central nervous system [19, 21].

Probiotics can influence gut function by modifying the composition of the gut flora directly, through the increase in commensal lactobacilli or bifidobacteria or the elimination of pathogens or, indirectly, through a reduction in either pathogen-related inflammation or bacterial fermentation [22]. Furthermore, probiotics could alter the volume and/or composition of stool and gas or increase intestinal mucus secretion. These effects could influence intestinal handling of its contents and thus modulate symptoms such as constipation and diarrhea.

Another aspect of the rationale underlying the usefulness of probiotic therapy in Pi-IBS regards the effect of some bacteria on intestinal function. Experimental studies on germ-free animals exposed to lactobacilli, bifidobacteria and *Clostridium tabificum*, but not to *Escherichia coli*, showed an influence on intestinal motility patterns [23]. Moreover, the exposure of cultured cell to

Streptococcus thermophilus and *Lactobacillus acidophilus* prevents the decrease in transepithelial resistance induced by *E. coli* [24]. Hence, these experiments showed the protective effect of probiotics on the intestinal damage caused by *E. coli*. Probiotics are also capable of decreasing visceral hypersensitivity in an animal model. In fact, pretreatment with *Lactobacillus paracasei* in mice decreases hypersensitivity and inflammation induced by non-absorbable antibiotic [25].

In clinical experience, the most efficacious utilization of probiotics in this field is the prevention of the Pi-IBS, and probiotic therapy reduces the duration of infectious diarrhea in children [26]. The shorter duration of an episode of gastroenteritis or the prevention of colonization by pathogens may reduce the risk of the subsequent development of IBS.

Among eight placebo-controlled studies exploring the probiotic effects of various bacteria strains in patients with unspecified IBS, three reported an improvement in the overall symptoms score and another three on a single symptom (flatulence, bloating and pain), while in two there was no improvement of symptoms [27]. Two of these studies need more attention. In the first study, the authors used a mix of seven bacteria strains and showed an improvement in abdominal bloating. In the other study the authors showed an improvement in the overall symptoms score with *Bifidobacterium infantis* but not with *Lactobacillus salivarius* [28]. However, the most interesting result of the latter study was the effect of probiotics on cytokines; indeed, treatment with *B. infantis* but not *L. salivarius* increased the IL-10/IL-12 ratio before and after treatment, showing an anti-inflammatory effect related to the increase in IL-10, which can be thus considered an anti-inflammatory cytokine [29].

In conclusion, several studies have shown that the development of IBS following an enteric infection is common, that Pi-IBS is associated with increased chronic inflammatory cells of the mucosa and hyperplasia of enterochromaffin cells, and that enteric infections can affect the neuromuscular function of the bowel long after the infection has cleared. Regarding probiotic therapy of Pi-IBS, we can summarize that factors determining an unbalance of intestinal microbiota can promote gut dysfunction, and the potential value of probiotic bacteria in restoring normal gut function has been shown in animal models of Pi-IBS. Moreover, prevention of Pi-IBS can be achieved utilizing probiotics to reduce the duration of acute gastroenteritis despite the variable efficacy shown in randomized control trials evaluating unspecified IBS.

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