
Irritable bowel syndrome

Elena F. Verdu* MD, PhD

Stephen M. Collins MD, FRCP

Head of Division-Gastroenterology

Intestinal Research Programme, McMaster University, Hamilton, Ont., Canada

The intestinal microbiota interacts with several aspects of gastrointestinal function that may affect the expression or progression of disease. For example, a role for bacterial metabolism of bile acids and food has been linked to colorectal cancer development. Studies have also shown a potential role of the intestinal microbiota in the modulation of inflammation in the intestine and joints. Normal gut physiology is molded by the interaction between the intestinal microbiota and the host's gastrointestinal tissues, including motility, absorption and secretion, and intestinal permeability. Early studies in axenic mice demonstrated gross morphological abnormalities and gut motor dysfunction related to the absence of a normal microflora, raising the possibility that shifts in commensal bacterial populations could play a role in the development of altered motility states including functional disorders of the gut. This chapter concentrates on the experimental evidence for a role of intestinal microbiota and the potential therapeutic value of probiotics in functional diseases such as irritable bowel syndrome.

Key words: intestinal microflora; irritable bowel syndrome; gut function; motility; probiotics.

IS THE INTESTINAL MICROBIOTA ALTERED IN IRRITABLE BOWEL SYNDROME?

There are limitations to the study of the gastrointestinal flora by conventional microbiological techniques as most resident bacteria cannot be cultured. There is, however, evidence that the intestinal microbiota is altered in patients with irritable bowel syndrome (IBS) when compared to normal individuals. A number of studies have reported lower numbers of lactobacilli and bifidobacteria in IBS patients, and a shift from the dominant anaerobic species such as *Bacteroides* spp and *Bifidobacterium* spp to *Clostridium* spp.^{1,2} It has been suggested that the differences in the intestinal microbiota

* Corresponding author. Tel.: +1-905-525-9140; Fax: +1-905-522-3454.
E-mail address: bercikp@mcmaster.ca.

between healthy subjects and patients with IBS may underlie symptom generation by promoting abnormal colonic fermentation.³ It is possible that some symptoms in IBS patients are caused by fermentation by an altered intestinal microbiota. Following an exclusion diet, thereby modifying substrates for fermentation, patients with IBS had a decreased rate of gas production, which correlated with an improvement in symptoms.⁴ Although this may be true for a subset of patients with IBS, we must bear in mind the multifactorial essence of IBS. *discusses* some of the possible mechanisms through which alteration of the intestinal microbiota can affect gut function.

MECHANISMS LEADING TO IBS: IS THE INTESTINAL MICROBIOTA THE LINK?

IBS comprises an heterogeneous group of patients and is multifactorial in its pathogenesis and pathophysiology. The role of bacterial infection in the initiation of IBS has recently received much attention and the clinical entity referred to as post-infective IBS (PI-IBS) is now widely accepted. Since the large retrospective analysis of an association between a history suggestive of an acute gastroenteritis and the subsequent development of IBS⁵, several prospective studies have shown that acute bacterial gastroenteritis leads to IBS in 7–30% of patients.^{6,7} These studies, however, lacked control groups and estimates of relative risks were not provided. A recent cohort study comparing the incidence of IBS in a large sample of patients without gastroenteritis and patients with diagnosed gastroenteritis has shown a relative risk of IBS after bacterial gastroenteritis of 11.9.⁸ Thus, bacterial gastroenteritis is a major independent risk factor for IBS. Studies in non-selected IBS patients have suggested that IBS patients may be genetically susceptible to inflammatory stimuli^{9–11} and may exhibit low-grade inflammatory signals or cells.¹² A retrospective study has shown that the risk of PI-IBS is largely independent of the bacterial species that caused the initial gastroenteritis episode.⁷ This suggests that a common mechanism triggered by infection and inflammation, possibly in a genetically predisposed host, may also lead to PI-IBS. Moreover, it opens the possibility that other causes of gastroenteritis such as virus and parasites may also lead to PI-IBS. *Figure 1* depicts the multiple mechanisms that may underlie symptom generation in PI-IBS.

It is well known that antibiotics disrupt the intestinal microbiota. Antibiotic use leads to diarrhoea and patients treated with antibiotics for non-gastrointestinal complaints have been shown to be three times more likely to report functional bowel symptoms.¹³ This raises the possibility that qualitative or quantitative changes in resident bacterial populations by antibiotic use or infection may be involved in the generation of chronic gut dysfunction. Interestingly, there are other studies supporting a beneficial role of antibiotics in IBS. In particular, antibiotic treatment was associated with improvement of IBS symptoms in patients with bacterial overgrowth syndrome.¹⁴ Taken together, these studies indicate that perturbation of the delicate balance between commensal bacteria and host tissue can influence gastrointestinal physiology and promote the expression and maintenance of chronic functional disorders.

During infection and inflammation, 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 luminal content through a permeable epithelium and could involve the microbial flora either in the development and/or maintenance of IBS.

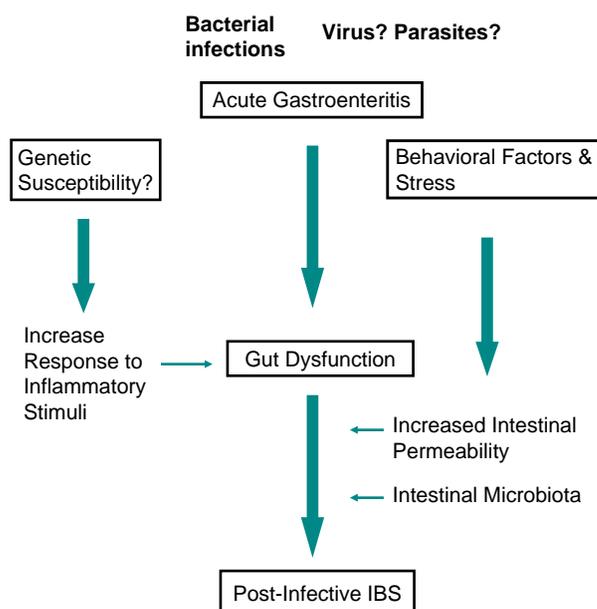


Figure 1. Symptom generation in post-infective IBS.

This is also a potential basis for the development of IBS in patients in remission from inflammatory bowel disease.¹⁵

Finally, the intestinal microbiota can affect gut motor function, which in turn can alter the intestinal microbiota composition. This was demonstrated in physiological studies showing that germ-free animals exhibit profound altered motility patterns that are normalized upon reconstitution with normal flora.¹⁶ Interestingly, the influence of the intestinal microbiota on small intestinal myoelectric activity was species-dependent.¹⁷ On the other hand, motility disorders frequently result in bacterial overgrowth.^{18,19}

The precise mechanism through which the intestinal microbiota modulates this variety of gastrointestinal functions remains unknown. Under normal conditions, bacteria interact with the gastrointestinal tract through receptors on the epithelial cell such as Toll-like and NOD receptors, and bacterial translocation, defined as passage of viable bacteria to mesenteric lymph nodes or other organs, is minimal.²⁰ However, secreted products of bacteria normally gain access to the submucosa to stimulate the mucosal immune system. Moreover, even in normal individuals, passage of bacteria to the submucosa occurs periodically without consequences for the individual, because bactericidal mechanisms are in place.²¹ However, this penetration may be sufficient to induce changes in intestinal immunity and physiology that are independent of bacterial interaction with the epithelial cell. *Bacteroides thetaiotaomicron*, a common gut commensal in mice and humans, was recently found to alter expression of genes involved in smooth-muscle function and neurotransmission.²² To what extent this altered gene expression can affect intestinal function, and its precise pathway, remains unclear. Our laboratory has pioneered the concept that an interplay between the mucosal immune and intestinal motor systems exists. The possible interface between the immune and motor or sensory systems, and between luminal antigens and inflammation, has not been recognized until recently. Because intestinal inflammation is

affected by the presence of bacterial flora and can be modulated by probiotics, we hypothesized that intestinal function is highly sensitive to changes in intestinal inflammation, and consequently changes in gut function can be modulated by probiotics.

CLINICAL EVIDENCE OF THE EFFECTIVENESS OF PROBIOTICS IN IRRITABLE BOWEL SYNDROME

Conclusions drawn from clinical studies on the effect of probiotics in IBS are conflicting. Differences in probiotic composition and the heterogeneous and multifactorial nature of patients with IBS may account, in part, for this. Abnormal colonic fermentation may be greater in a subset of patients with IBS.⁴ However, a double-blind, placebo-controlled, cross-over trial using *Lactobacillus plantarum* 299v did not show improvement of symptoms or of colonic fermentation in patients with IBS.²³ Another study using *L. plantarum* and oat flour in patients with IBS showed a reduction in the number of days with flatulence with respect to placebo-treated patients, but no improvement in bloating. Interestingly, abdominal pain was reduced both in patients that had received *L. plantarum* or placebo.²⁴ A number of clinical studies have investigated the presence of functional abdominal symptoms after antibiotic therapy. Although a clear beneficial role of antibiotics remains controversial, these studies indicate a potential relationship between a perturbed bacterial flora by antibiotic therapy and functional abdominal symptoms.^{14,15}

A controlled, double-blind study, randomized 20 patients with IBS to *L. plantarum* 299v in liquid suspension or placebo for 4 weeks. It was concluded that *L. plantarum* decreased abdominal pain and tended to normalize stool frequency in constipated patients.²⁵ On the other hand, *Lactobacillus casei* GG, administered as entero-coated tablets to patients with IBS and bloating symptoms, seemed to improve stool consistency in patients with IBS and diarrhoea.²⁶ Finally, a randomized controlled trial using the probiotic formulation VSL#3 improved abdominal bloating in patients with diarrhoea-predominant IBS, although no differences in gastrointestinal transit measurement, bowel function scores or satisfactory global symptom relief were shown.²⁷

In order to rationalize the use of probiotics in IBS, an understanding of the effects of different strains and formulations of probiotics on gut function, including neuromuscular function, is required.

INSIGHT FROM STUDIES IN A MOUSE MODEL OF PI-IBS: MODULATION OF NEUROMUSCULAR FUNCTION BY PROBIOTIC BACTERIA

Previous work from our laboratory, using the *Trichinella spiralis* infection mouse model, has shown increased muscle contractility and decreased excitatory neurotransmission, which persists after infection has resolved.²⁸ In this model, gut dysfunction is initiated by Th2 cytokines induced by the *T. spiralis* infection, and is maintained, at the post-infective state, by production of mediators such as COX-2, PGE2 and TGF β 1 in the muscular layer.^{29,30}

In order to investigate whether administration of probiotic bacteria influences post-infective dysfunction, *T. spiralis*-infected mice were given unfermented growth medium as control, or the probiotic spent culture media (SCM) containing 10⁹ *Lactobacillus paracasei*, *Lactobacillus johnsonii*, *Bifidobacterium longum* or *Bifidobacterium lactis* from day

10 to day 21 after *T. spiralis* infection. Contractility of whole-muscle strips showed that *T. spiralis*-infected mice that had received *L. paracasei* in SCM displayed significantly lower maximal contraction when compared to control mice. *B. lactis* and *B. longum* tended to attenuate post-infective hypercontractility but this did not achieve statistical significance. *L. johnsonii* did not attenuate post-infective hypercontractility. These results suggest that the effect of probiotic bacteria on post-infective gut dysfunction is strain-specific.

To determine whether normalization of hypercontractility was induced by the bacteria or their fermentation metabolites, groups of *T. spiralis*-infected mice were given live *L. paracasei* in their SCM, the filtered SCM free of live organisms (*L. paracasei*-free SCM) or heat-inactivated *L. paracasei* in SCM from day 10 to 21 after infection. Oral administration of *L. paracasei* or *L. paracasei*-free SCM significantly attenuated post-infective hypercontractility. This was accompanied by a decrease in mediators in the *muscularis externa* that have been shown to perpetuate muscle dysfunction in the *T. spiralis* mouse model of PI-IBS. Fourteen days post-infection, mice receiving *L. paracasei* or *L. paracasei*-free SCM had lower protein levels of IL-4 and message for COX-2. On day 21 post-infection, mice treated with *L. paracasei* or *L. paracasei*-free SCM had reduced protein TGF- β 1, PGE-2, COX-2 and message for COX-2 and TGF- β in the *muscularis externa*. Because administration of both live bacterium, and *L. paracasei*-free SCM, led to attenuation of post-infective hypercontractility, it is possible that a heat-labile factor released by the bacterium is responsible for the observed effect.³¹

SUMMARY AND CONCLUSION

A delicate balance exists in which intestinal microbiota interact with host tissues to determine gut physiological function under normal conditions. Factors that perturb this equilibrium, such as infections or antibiotic treatment, will promote gut dysfunction and are likely to be involved in symptom generation in IBS. Primary motility disturbances can induce changes in the intestinal bacterial content and thereby further perturb intestinal physiology. Although patients with IBS appear to have quantitative differences in the intestinal microbiota when compared to normal individuals, it is still unclear whether a causal relationship exists, or whether the altered flora is a consequence of the gut dysfunction. Also, the precise pathways through which the intestinal microbiota modulate gut function, in particular neuromuscular and sensory function, remain largely unknown. Using a mouse model of post-infective IBS, we have demonstrated the potential value of probiotic bacteria in restoring normal gut function, and that this is a strain-dependent effect. This supports the hypothesis that disruption of the intestinal microbiota may be involved in IBS and that restoration of this equilibrium may be of therapeutic benefit.

Practice points

- IBS is one of the most common diseases encountered by gastroenterologists and family physicians
- gastroenteritis is the most important environmental risk factor identified to date for the development of IBS
- there is emerging evidence of abnormal flora composition in IBS
- probiotics may be useful in the treatment of IBS

Research agenda

- identification of intestinal flora patterns in patients with IBS
- systematic evaluation of the contribution of specific components of the intestinal flora to gut physiology and functional disorders

REFERENCES

1. Balsari A, Ceccarelli A, Dubini F et al. The fecal microbial population in the irritable bowel syndrome. *Microbiologica* 1982; **5**: 185–194.
2. Bradley HK, Wyatt GM, Bayliss CE & Hunter JO. Instability in the faecal flora of a patient suffering from food-related irritable bowel syndrome. *Journal of Medical Microbiology* 1987; **23**: 29–32.
3. Cummings JH & Macfarlane GT. The control and consequences of bacterial fermentation in the human colon. *Journal of Applied Bacteriology* 1991; **70**: 443–459.
4. King TS, Elia M & Hunter LO. Abnormal colonic fermentation in irritable bowel syndrome. *Lancet* 1998; **352**: 1187–1189.
- * 5. Chaudhary NA & Truelove SC. The irritable colon syndrome. *Quarterly Journal of Medicine* 1962; **123**: 307–322.
- * 6. McKendrick MW & Read NW. Prevalence of gastrointestinal symptoms six months after bacterial gastroenteritis and risk factors for development of the irritable bowel syndrome: postal survey of patients. Irritable bowel syndrome-post salmonella infection. *Journal of Infection* 1999; **29**: 1–33.
7. Neal KR, Hebden J & Spiller R. Prevalence of gastrointestinal symptoms six month after bacterial gastroenteritis, and risk factors for development of the irritable bowel syndrome: postal survey of patients. *British Medical Journal* 1997; **314**: 779–782.
- * 8. Rodriguez LA & Ruigomez A. Increased risk of irritable bowel syndrome after bacterial gastroenteritis: cohort study. *British Medical Journal* 1999; **318**: 565–566.
9. Gonsalkorale WM, Perrey C, Pravica V et al. Interleukin 10 genotypes in irritable bowel syndrome: evidence for an inflammatory component? *Gut* 2003; **52**: 91–93.
10. Morris-Yates A, Talley NJ, Boyce PM et al. *American Journal of Gastroenterology* 1998; **93**: 1311–1317.
- * 11. Levy RL, Jones KR, Whitehead WE et al. Irritable bowel syndrome in twins: heredity and social learning both contribute to etiology. *Gastroenterology* 2001; **121**: 799–804.
- * 12. Chadwick VS, Chen W, Shu D et al. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002; **122**: 1778–1783.
13. Maxwell PR, Rink E, Kumar D & Mendall MA. Antibiotics increase functional abdominal symptoms. *American Journal of Gastroenterology* 2002; **97**: 104–108.
14. Pimentel M, Chow EJ & Lin HC. Eradication of small intestinal bacterial growth reduces symptoms of irritable bowel syndrome. *American Journal of Gastroenterology* 2000; **95**: 3503–3506.
15. Isgar B, Harman M, Kaye MD & Whorwell PJ. Symptoms of irritable bowel syndrome in ulcerative colitis in remission. *Gut* 1983; **24**: 190–192.
- * 16. Caenepeel Ph, Janssens J, Vantrappen G et al. Interdigestive myoelectric complex in germ-free rats. *Digestive Diseases & Sciences* 1989; **34**: 1180–1184.
- * 17. Husebye E, Hellstrom PM, Sundler F et al. Influence of microbial species on small intestinal myoelectric activity and transit in germ-free rats. *American Journal of Physiology, Gastrointestinal and Liver Physiology* 2001; **280**: G368–G380.
- * 18. Husebye E, Hellstrom PM & Midtvedt T. Intestinal microflora stimulates myoelectric activity of rat intestine by promoting cyclic initiation and aboral propagation of migrating myoelectric complex. *Digestive Diseases & Sciences* 1994; **39**: 946–956.
19. Nieuwenhuijs VB, Verheem A, van Duijvenbode-Beumer H et al. The role of interdigestive small bowel motility in the regulation of gut microflora, bacterial overgrowth, and bacterial translocation in rats. *Annals of Surgery* 1998; **228**: 188–193.
20. Berg RD. Bacterial translocation from the gastrointestinal tract. *Advances in Experimental Medicine & Biology* 1999; **473**: 11–30.
21. McPherson AJ. Immune regulation of the normal intestinal bacterial flora. The host response to the normal intestinal flora. In: Uhr T, editor. *Gut Ecology* 2002.
- * 22. Hooper LV, Wong MH, Thelin A et al. Molecular analysis of commensal host-microbial relationships in the intestine. *Science* 2001; **291**: 881–884.

23. Sen S, Mullan MM, Parker TJ et al. Effect of *Lactobacillus plantarum* 299v on colonic fermentation and symptoms of irritable bowel syndrome. *Digestive Diseases & Sciences* 2002; **47**: 2615–2620.
24. Nobaek S, Johansson M-L, Molin G et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *American Journal of Gastroenterology* 2000; **95**: 1231–1238.
25. Niedzielin K, Kordecki H & Birkenfeld B. A controlled, double-blind, randomized study on the efficacy of *Lactobacillus plantarum* 299v in patients with irritable bowel syndrome. *European Journal of Gastroenterology & Hepatology* 2001; **13**: 1143–1147.
26. O'Sullivan MA & O'Morain CA. Bacterial supplementation in the irritable bowel syndrome. A randomized, double-blind placebo-controlled cross-over study. *Digestive and Liver Disease* 2000; **32**: 302–304.
27. Kim HJ, Camillieri M, McKinzie S et al. A randomized controlled trial of a probiotic, VSL#3, on gut transit and symptoms in diarrhoea-predominant irritable bowel syndrome. *Alimentary Pharmacology & Therapeutics* 2003; **17**: 895–904.
- * 28. Barbara G, Vallance BA & Collins SM. Persistent intestinal neuromuscular dysfunction after acute nematode infection in mice. *Gastroenterology* 1997; **113**: 1224–1232.
29. Akiho H, Deng Y, Blennerhasset P et al. The roles of TGF β and COX-2 in the maintenance of muscle hypercontractility in a murine model of post infective irritable bowel syndrome. *Gastroenterology* 2002; **122**. abstract S958.
30. 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**: 1729–1736.
31. Verdu EF, Bercik P, Blennerhasset P et al. Strain dependent effects of probiotics on intestinal muscle dysfunction in an animal model of post-infective irritable bowel syndrome. *Gastroenterology* 2003; **124**: A197. (abstract).