Probiotic Therapy for Irritable Bowel Syndrome

George Aragon, MD, Deborah B. Graham, MD, Marie Borum, MD, EdD, MPH, and David B. Doman, MD, FACP, FACG

Drs. Aragon and Graham are Gastroenterology Fellows at the George Washington University School of Medicine in Washington, DC, where Dr. Borum serves as Professor of Medicine and Director of the Division of Gastroenterology, and Dr. Doman serves as Clinical Professor of Medicine.

Address correspondence to:
David B. Doman, MD
12012 Veirs Mill Road
Silver Spring, MD 20906;
Tel: 301-942-3550;
Fax: 301-933-3621;
E-mail: drdbd@aol.com

Keywords
Irritable bowel syndrome, probiotics, small-bowel bacterial overgrowth

Abstract: The etiology of irritable bowel syndrome (IBS) is thought to be multifactorial, with several factors (including alterations in gut motility, small-bowel bacterial overgrowth, microscopic inflammation, and visceral hypersensitivity) potentially playing a role. Recent studies have suggested that probiotics may be useful in the treatment of IBS. Although the exact mechanism for how probiotics may aid in the reduction of symptoms commonly found in IBS is unknown, the effects of probiotics on alterations in gut bacteria appear to play a part. This review focuses on recent studies examining the role of probiotics in the treatment of IBS.

Irritable bowel syndrome (IBS) is a common disorder affecting millions of people worldwide. Over the past few years, there has been an emergence of new concepts related to the pathophysiology of IBS. These concepts include alterations in gut motility, small-bowel bacterial overgrowth, microscopic inflammation, visceral hypersensitivity, and changes related to the brain-gut axis. This changing paradigm may allow for probiotic therapeutic opportunities in IBS. Probiotics are defined as "live microorganisms, which, when administered in adequate amounts, confer a health benefit on the host."[1] This paper reviews the potential benefits of probiotics in patients with IBS.

Pathophysiology of Irritable Bowel Syndrome

Recent research suggests that IBS has a multifactorial etiology that includes alterations in gut motility, small-bowel bacterial overgrowth, microscopic inflammation, and visceral hypersensitivity. Some of these postulated components of IBS pathophysiology may potentially lend themselves to probiotic therapeutic benefits.

Alterations in Gut Motility

Disorders in gut motility have been observed in the stomach, small intestine, colon, and rectum of IBS patients.[2-5] Within the gut,

there is a cyclic pattern of motility known as the major migrating complex, which consists of periodic, luminal contractions that propel intestinal contents from the stomach to the terminal ileum. Several studies in the literature have shown that patients with IBS tend to have abnormalities in these contractions. Vassallo and colleagues examined colonic tone and motility by measuring electronic barostat and perfusion manometry in 16 patients to assess for changes in IBS. The study showed that patients with IBS had a greater frequency of high amplitude prolonged contractions and greater preprandial colonic motility, which may account for the increased perception of pain in these patients.[3] Another study, which used radiopaque markers to assess colonic transit times in IBS, showed that patients with diarrhea-predominant IBS had accelerated colonic transit.[5] Although these alterations were seen in patients with IBS, as compared to normal controls, their findings are likely qualitative, rather than quantitative, and lack specificity. Additionally, the alteration in gut motility found in some patients with IBS appears to place them at risk for small-bowel bacterial overgrowth, which is another proposed etiology for IBS.

Small-Bowel Bacterial Overgrowth

Small-bowel bacterial overgrowth has emerged as a possible cause of IBS. In 1977, Vantrappen and associates described a reduction in the major migrating complex in patients with bacterial overgrowth.[6] Further studies have confirmed this finding in patients with IBS and abnormal lactulose breath testing.[7] However, studies showing the presence of small-bowel bacterial overgrowth in patients with IBS have been conflicting. A large study of 202 patients with IBS found that 78% of these patients had evidence of bacterial overgrowth via breath testing. In the study, 25 of 47 patients experienced eradication of bacterial overgrowth on follow-up after treatment with antibiotics. Analysis of this subset of patients revealed that those who were successful in the eradication of bacterial overgrowth reported improvement in their IBS symptoms.[8] Another study, which was conducted by Pimentel and coworkers, looked at 111 patients with IBS and found that 84% had abnormal breath testing. These patients were randomized to neomycin or placebo for a total of 7 days. A follow-up questionnaire revealed that patients in the neomycin group reported a 35% reduction in symptomatology as compared to 11.4% in the placebo group.[9] More recently, Peralta and colleagues assessed 97 patients who met Rome II criteria and found that 56% of these patients had positive lactulose breath tests.[10] Fifty-four patients with positive tests were treated with a 7-day course of rifaximin (Xifaxan, Salix). Follow-up after 3 weeks revealed that 50% of patients had a subsequent negative lactulose breath test and a statistically significant improvement in their IBS-related symptoms. These results were similar to those found in a recent study by Majewski and associates, in which a 4-week course of rifaximin led to improvement in IBS-related symptoms and a negative breath test in patients who previously had positive tests.[11] Although these results are encouraging, further research is needed in this area.

Microscopic Inflammation

Interest has recently emerged regarding the possibility of microscopic inflammation as a cause of IBS.[12] Several studies have shown that patients with IBS have low-grade inflammation throughout the small bowel and colon.[13-15] It has been postulated that the release of certain inflammatory mediators, including interleukins and histamine, may affect nearby enteric nerves, causing alteration in gut function and sensory perception.[14,16] Although this theory shows promise, efforts to treat low-level inflammation to improve symptoms have been disappointing. A study of 29 patients with postinfectious IBS who were randomized to either prednisolone 30 mg daily versus placebo showed that, although T lymphocytes decreased by 22% as compared to 11.5% in the placebo group, no improvement was noted in IBS symptoms.[17]

Visceral Hypersensitivity

Visceral hypersensitivity has been recognized as one of the potential contributing etiologies of pain associated with IBS. It has long been known that patients with IBS have poor tolerance to rectal distention.[18-21] Other studies have confirmed that increased perception in visceral stimuli in patients with IBS can also be seen throughout the length of the gastrointestinal tract.[22-24] Interestingly, however, compliance and wall tone are similar in patients with IBS and in healthy control patients.[25] Although increases in the perception of pain are common in patients with IBS, hypersensitivity has not been found to be a consistent indicator of disease. In fact, some studies show that only 60% of IBS patients perceive hypersensitivity to bowel distention.[19,26] An additional confounder is that patients with IBS may be hypervigilant to pain, which may act as a potential bias in these studies.[21]

Psychological factors have long been known to exacerbate symptoms of patients with known IBS. Although the exact effects of stress, depression, and anxiety on the gut remain unclear, serotonin appears to play a role. Serotonin is known to regulate secretory, motility, and sensory events in the gut; thus, changes in its concentration may contribute to the sensorimotor function in IBS.[27] This mechanism provides the rationale for the use of selective serotonin reuptake inhibitors in the treatment of IBS.

Physiologic Benefits of Probiotics in Irritable Bowel Syndrome

Probiotics are live microorganisms with a vast array of therapeutic potential for gastrointestinal disease. They have been studied and used in many gastrointestinal disorders, with growing evidence for use in pouchitis, *Clostridium difficile* colitis, antibiotic-associated diarrhea, inflammatory bowel disease, and IBS. The emerging multifactorial pathophysiologic paradigm of IBS may create adjunctive probiotic therapeutic opportunities.

Probiotics have a beneficial effect on intestinal mucosa via several proposed mechanisms that include suppression of the growth and binding of pathogenic bacteria, improvement of the barrier function of the epithelium, and alteration of the immune activity of the host.[28,29] Probiotics secrete short chain fatty acids, an action that results in decreased luminal pH and production of bactericidal proteins.[29] Butyric acid, a byproduct of bacterial fermentation of fiber, has been shown to nourish colonic enterocytes, enhancing mucosal integrity.[30,31] The DNA of probiotic organisms has also been shown to inhibit apoptosis of epithelial cells.[32,33] In addition, probiotics may improve bowel dysmotility.[30]

A study by Desbonnet and coworkers investigated the probiotic *Bifidobacterium infantis* on rats that were chronically subjected to a stressor (a forced swim test) for 14 days.[34] The results were reductions in the levels of tumor necrosis factor alpha, interferon gamma, and interleukin 6 after stimulation of peripheral blood monocytes. Plasma levels of tryptophan and kynurenic acid were also significantly increased in the rats treated with *B. infantis* compared to controls. There was no improvement in performance during the stressor, though *B. infantis* may have had a role as an antidepressant by increasing the levels of tryptophan, a serotonergic precursor, and reducing proinflammatory markers. These raised levels of tryptophan can potentially reduce depressive overlay and aberrant enteric nervous system effects in IBS.

Studies on Probiotics

There is a limited amount of quality evidence for the empiric use of probiotics in IBS. The randomized controlled trials that have been performed are typically small and are limited by publication bias. Previous trials have typically included strains of *Lactobacillus* species, *Bifidobacterium* species, and *Propionibacterium* species, along with different probiotic combinations such as VSL#3 and SCM-III.

VSL#3

Kim and colleagues performed two double-blind, placebo-controlled trials examining VSL#3 for the treatment of IBS symptoms.[35,36] VSL#3 is a combination of probiotics that contains live bacteria including *Bifidobacterium* (*B. longum, B. infantis,* and *B. breve*); *Lactobacillus* (*L. acidophilus, L. casei, L. delbrueckii ssp. bulgaricus,* and *L. plantarum*); and *Streptococcus salivarius ssp. thermophilus.* The first trial by Kim, in 2003, evaluated the effect of VSL#3 on gastrointestinal transit and symptoms of diarrhea-predominant IBS. Twenty-five IBS patients were randomized to receive VSL#3 or placebo for 8 weeks. With VSL#3, the decrease in bloating was borderline significant, but there was no effect on gastrointestinal transit or other individual symptoms of IBS. Kim and associates performed a second placebo-controlled trial studying VSL#3 and its effects on IBS symptoms and colonic transit in 48 IBS patients, with abdominal bloating as the primary endpoint.[36] VSL#3, as compared to placebo, led to a reduction in flatulence and a delay in colonic transit.

SCM-III

SCM-III is another probiotic combination of 3 different strains (*L. acidophilus, Lactobacillus helveticus,* and *Bifidobacterium sp.*), which was evaluated by Tsuchiya and coworkers in a study of 68 IBS patients.[37] The study participants were randomly assigned to receive SCM-III or placebo for 12 weeks. There was an improvement in overall efficacy in 80% of patients at 12 weeks ($P<.01$), as well as improvement in bloating, abdominal pain, and bowel habits at different time intervals throughout the 12-week period. However, the limitations of this study included its single-blinded design, small study population, and use of pseudo-randomization.

Lactobacillus *and* Bifidobacterium *Species*

Saggioro performed a study with 70 IBS patients, randomizing them to 3 different treatment groups for assessing improvements in abdominal pain and severity scores of 7 IBS symptoms.[38] These treatment arms included Group 1 (*L. plantarum* LP01 and *B. breve* BR0); Group 2 (*L. plantarum* LP01 and *L. acidophilus* LA02); or placebo. Both treatment cohorts showed significant decreases in abdominal pain and severity scores at 2 and 4 weeks; however, the major limitation of this study was the inability to perform statistical evaluation due to its small number of patients and its short duration of follow-up.

O'Mahony and associates performed a study in 77 patients diagnosed with IBS (based upon Rome II criteria) and grouped them into 3 different treatment arms.[29] The patients received *Lactobacillus salivarius* UCC4331, *B. infantis* 35624, or placebo for a total of 8 weeks and then were assessed for the cardinal symptoms of IBS (abdominal pain/discomfort, bloating/distension, and difficulty of bowel movement), quality of life, and blood sampling for interleukin-10 and -12. Those patients randomized to the *B. infantis* 35624 arm showed a significant reduction in

composite symptom score as well as a reduction in each individual symptom, with the exception of bowel movement frequency and consistency. The interleukin-10/-12 ratio, which is abnormal in IBS patients in the proinflammatory state, was normalized in the *B. infantis* 35624 arm, suggesting that the mechanism of action of this particular probiotic may have an immune-modulating effect. The limitations of this trial, as with other trials involving probiotics, include its small size and lack of power calculation; otherwise, it was a well-designed trial. The authors concluded that additional larger, randomized, controlled trials studying *B. infantis* 35624 are needed, along with further research regarding the mechanism of immune regulation in IBS patients.

A larger study by Whorwell and coworkers evaluating different doses of *B. infantis* 35624 was performed in 362 women diagnosed with IBS.[39] The study participants were randomized to low or high doses of *B. infantis* or placebo and were followed for a total of 4 weeks. In the treatment group, there was a significant decrease in abdominal pain/discomfort (the primary endpoint) at 4 weeks, along with improvement in the secondary endpoints of bloating/distension, sensation of incomplete evacuation, passage of gas, straining, bowel habit satisfaction, and a reduction in composite symptom score. These benefits were only noted in the high-dosing group containing 1×10^{10} CFU/mL of *B. infantis*, and not 1×10^{8} CFU/mL of *B. infantis*. The authors concluded that the discrepancy in the efficacy of the higher and lower concentrations may have been secondary to the methods that the different formulations use to release the active agent within the intestine.

A study by Guyonnet and colleagues assessed 274 constipation-predominant IBS patients and randomized them to placebo or fermented milk yogurt (Activia, Dannon), which contains *Bifidobacterium animalis (regularis)* DN-173 010 for 6 weeks.[30] In the treatment group, the health-related quality-of-life discomfort score improved, as well as bloating symptoms (both of which were primary endpoints), and there was an increase in stool frequency in patients with fewer than 3 stools per week. This yogurt (ie, *B. regularis*) may have promotility benefits for the alleviation of IBS bowel dysmotility and may shorten intestinal transit time.[30]

Past studies involving the *Lactobacillus* species as either a single probiotic agent or in combination with other probiotics have been less impressive. A 6-month double-blind, placebo-controlled study by Kajander and associates evaluated 103 patients with IBS and randomized them to a probiotic mixture containing *Lactobacillus rhamnosus* GG, *L. rhamnosus* LC705, *B. breve* Bb99, and *Propionibacterium freudenreichii ssp. shermanii* JS, or to placebo and then followed them for 6 months.[40] A 44% reduction in the symptom score (consisting of abdominal pain, distension, flatulence, and borborygmi) was seen in the probiotic group at the end of the trial. A recent meta-analysis by Moayyedi and coworkers reviewed 4 trials evaluating single strains of *Lactobacillus* and found no significant benefit in alleviating IBS symptoms in 200 patients.[29,31-33,40,41]

Nine trials evaluated different probiotic combinations (most often including *Bifidobacterium, Lactobacillus,* and *Streptococcus*) in 772 patients and showed a significant effect in improving IBS symptoms.[30,35-37,40,42-45] Two trials involving *Bifidobacterium*, conducted by O'Mahony and associates and Whorwell and colleagues (both of which were previously mentioned in this article), were included in this meta-analysis and showed a trend toward improving IBS symptoms in 379 patients.[29,39]

Brenner and coworkers conducted a meta-analysis in 2009 that included 16 randomized controlled trials evaluating the efficacy, safety, and tolerability of probiotics in IBS patients.[46] *B. infantis* 35624 was the only probiotic that showed any significant benefit in the composite symptom score of IBS patients. *Bifidobacterium* likely has a beneficial effect in the symptom relief of IBS either as a single agent or in combination with other probiotics, though the available data are inadequate and further well-designed trials are still needed.

Future Directions

Probiotics will likely have an emerging adjunctive therapeutic role in treating IBS. The studies to date simultaneously provide interesting observations and raise fundamental questions. Overall, many of the studies involved were small in size, of short duration, and had significant design flaws, but there is growing evidence that *B. infantis* is becoming the frontrunner for treatment of IBS. If larger, well-controlled studies involving other strains of probiotics are performed, we may begin to have other options regarding different probiotic species and for the treatment of more specific subsets of IBS symptoms.[47]

Additional issues that still need to be determined include the most effective probiotic strain, dose, and duration of therapy; whether patients should be treated for specific IBS symptoms only; and whether there is a role for maintenance IBS therapy or only IBS therapy on an as-needed basis. In addition, cost-effectiveness analysis and safety profiles still need to be addressed in large, well-designed trials. As probiotics are not considered pharmaceutical drugs, they are not currently regulated by the US Food and Drug Administration, which would promote standardization for consistent clinical trials in the future.

Probiotics may have a role as a delivery vehicle for therapeutic payloads that are released at targeted areas of inflammation throughout the intestinal tract. The majority of this research has involved probiotics in the treatment of inflammatory bowel disease, but these studies may translate into future studies for IBS. One such example is the study conducted by Steidler and Neirynck in which recombinant *Lactococcus lactis*, engineered to secrete interleukin-10, was administered to mice with experimental inflammatory bowel disease, which showed that the probiotic was similar to steroids.[48]

A recent systematic review performed by the American College of Gastroenterology Task Force on the management of IBS concluded that *Lactobacillus* does not appear to be effective in single organism studies and studies involving combinations of probiotics, though *Bifidobacterium* demonstrates some efficacy (Grade 2C evidence).[47] Future avenues of research should focus on treating subtypes of IBS; evaluation of patients according to the Rome III criteria; safety, dosing, and concentrations of certain probiotics; and duration of treatment.

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