Probiotics and Irritable Bowel Syndrome: Rationale, Putative Mechanisms, and Evidence of Clinical Efficacy

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Abstract: The irritable bowel syndrome (IBS) follows an acute, presumably infectious diarrheal illness in ~15% of patients. There may be a persistent, mild inflammatory state with changes in mucosal function or structure. Changes in the colonic bacterial flora reported in IBS seem related to predominant bowel. Colonic bacteria normally metabolize nutrients with the formation of gas and short chain fatty acids. The latter may induce propulsive contractions and accelerate colonic transit or they may enhance fluid and sodium absorption in the colon. This review addresses the mechanisms, rationale and current evidence for the efficacy of probiotics, including *Lactobacilli*, *Bifidobacteria*, and VSL#3, in the treatment of IBS. The mechanisms influenced by probiotics include immune function, motility, and the intraluminal milieu. Probiotics may suppress the low-grade inflammation associated with IBS or restore normal local immune function. *Lactobacilli* and *Bifidobacteria* subspecies are able to deconjugate and absorb bile acids, potentially reducing the colonic mucosal secretion of mucin and fluids that may contribute to functional diarrhea or IBS with diarrhea. Therapeutic trials show the potential benefit of *Bifidobacteria or Lactobacilli* species alone or in the specific probiotic combination, VSL#3, on symptoms in IBS. Colonic transit was retarded in IBS patients treated with VSL#3 without induction of significant changes in bowel function. In summary, probiotics are promising therapies in IBS.

Key Words: irritable bowel syndrome, probiotics, *Lactobacilli*, *Bifidobacteria*, VSL#3, bloating, flatulence, immune, inflammation

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Probiotics are preparations that contain viable microorganisms that confer potential health benefits by preventing or treating specific pathologic conditions.[1,2] They are used extensively for the relief of abdominal symptoms[1–6] and do not require prescription. The scientific basis of probiotic use has been investigated recently, and clinical studies have documented efficacy in the treatment of inflammatory bowel disease or pouchitis[6–8] or irritable bowel syndrome (IBS[9–11]).

The mechanism of such benefit is not entirely clear; this review addresses the rationale, putative mechanisms of action, and current evidence for the efficacy of probiotics in the treatment of IBS. The studies to date have examined *Lactobacilli*, *Bifidobacteria*, and VSL#3.

WHAT IBS MECHANISMS MAY BE INFLUENCED BY TREATMENT WITH PROBIOTICS?

The mechanisms influenced by probiotics that are of potential relevance to the development and treatment of IBS include immune function, motility, and the intraluminal milieu.

Immune Function

IBS follows an acute, presumably infectious diarrheal illness in ~15% of patients. These patients may have a persistent, mild inflammatory state, which may result in changes in mucosal function such as increased mucosal permeability, change in mucosal structure, or increases in serotonin-containing enteroendocrine cells, or infiltration with inflammatory cells in bowel mucosa biopsies.[12] One study showed proximity of mast cells to nerve cells in the lamina propria.[13] The latter cells seem to produce substances that activate receptors involved in visceral sensation such as proteinase-activated receptors (PAR-2[14,15]).

Changes in the Colonic Bacterial Flora Seem Related to Predominant Bowel Function and Unrelated to Prior Infection

Genomic DNAs examined in 1-g fecal samples of patients with different bowel functions[16] showed lower numbers of *Lactobacillus* species in the samples of patients with diarrhea-predominant irritable bowel syndrome (IBS-D), whereas increased numbers of *Veillonella* species were detected in those with constipation-predominant irritable bowel syndrome (Fig. 1). In contrast, counts of *Bifidobacterial* species were unaltered (Ref. 16, Fig. 1). These are intriguing observations given the fact that a therapeutic trial suggests that a particular *Bifidobacterial* species rather than a *Lactobacillus* species was efficacious in the treatment of IBS symptoms (see below).

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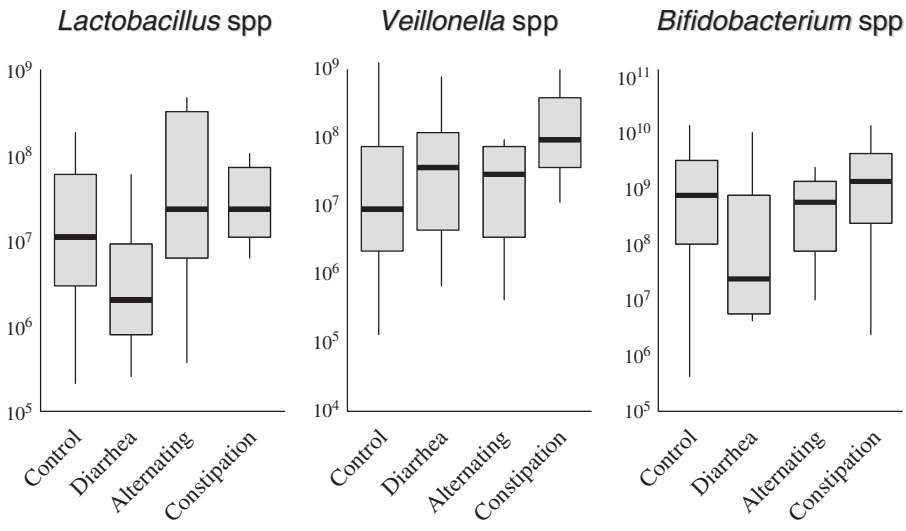

FIGURE 1. Fecal flora in IBS subgroups: genomic DNAs in 1-g fecal samples lower amounts of *Lactobacillus* spp in the samples of IBS-D patients, whereas they increase *Veillonella* spp in constipation-predominant irritable bowel syndrome. Reproduced from Ref. 16, Malinen et al. Am J Gastroenterol. 2005;100:373–382.

Colonic Bacterial Formation of Gas and Production of Short Chain Fatty Acids

Colonic bacteria normally metabolize nutrient substrates, reaching the colon with the formation of gas and production of short chain fatty acids. The latter may induce propulsive contraction[17] and accelerate transit, or enhance fluid and sodium absorption in the colon.[18]

Idiopathic Bile Acid Catharsis

Some patients with functional diarrhea show evidence of bile acid malabsorption[19]; di–α hydroxy bile acids (chenodeoxycholic and deoxycholic acid) induce colonic secretion[20] or propulsive contractions in the colon.[21] *Lactobacilli* and *Bifidobacteria* subspecies are able to deconjugate and absorb bile acids.[22,23] This may reduce the bile acid load to the colon and potentially reduce the colonic mucosal secretion of mucin and fluids or the induction of propulsive colonic contractions that may be contributing to the symptoms of patients with functional diarrhea or IBS-D.

DIFFERENCES IN PROBIOTIC PREPARATIONS

One of the challenges presented in the literature is that there are several preparations of these bacterial species, some of which have been tested for efficacy in symptom relief, and they are often assumed to be interchangeable. There are great differences in the content, the medium in which the probiotic is administered (eg, water, yogurt, fruit juice), and the bowel colonization capability of the preparations. Variation in the degree of pasteurization of the frequently coadministered yogurt and in the time between preparation and ingestion may additionally result in variation in the total bacterial load administered.

VSL#3 is a composite probiotic that has been the subject of several investigations in recent years. Each sachet contains 450 billion viable lyophilized bacteria: *Bifidobacterium* (*B. longum, B. infantis,* and *B. breve*); *Lactobacillus* (*L. acidophilus, L. casei, L. delbrueckii* subsp. *bulgaricus,* and *L. plantarum*); and *Streptococcus salivarius* subsp. *thermophilus*. The preparation is a powder miscible in yogurt, which facilitates dissolution and enhances palatability of the preparation. Studies have shown PCR detection of *Bifidobacterium* strains and *Streptococcus thermophilus* in the feces of human subjects (healthy and inflammatory bowel disease) after VSL#3, and the recovery of *S. thermophilus* by PCR was around one log higher with VSL#3 than with yogurt alone.[24]

Other studies have addressed the effects of single organisms (eg, *E. coli 1917 Nissle*, *L. salivarius UCC4331* and *B. infantis 35624*) in IBS. Enrichment of colonic or adherent bacterial flora is not always demonstrated for the different preparations. Although the popular press sometimes equates yogurt with probiotics, it is important to note that the bacterial loads achievable with pasteurized or unpasteurized yogurts are unknown or unstandardized, and the positive effects of one preparation should not be assumed to be generalizable to the class of probiotics or to yogurts in general. Commercially available probiotic preparations contain different bacteria and varying bacterial colony counts and, to some extent, these vary with the clinical indication. For example, *S. boulardii* and *Lactobacillus GG* tend to be dominant components of probiotics tested for travellers' and antibiotic-associated diarrhea.[25,26] On the other hand, *S. salivarius, Clostridium butyricum*, and selected *E. coli* strains (eg, *Nissle 1917*) are used in inflammatory bowel disease research studies,[27] in addition to the *Lactobacilli* and *Bifidobacteria* species used in IBS.

MECHANISTIC EFFECTS OF PROBIOTICS

Immune Function

In a study from Cork, Ireland, assessing individual bacterial species, improvement in symptoms with *Bifidobacteria* was associated with changes in the relative production of anti-inflammatory interleukin (IL)-10 to

TABLE 1. Summary of Literature on Effects of Bacterial Species on Inflammatory Responses*

Species	Cytokines	Reference	Present in VSL#3
Lactobacillus			
Plantarum	↑ IL-10	Pathmakanthan S et al[31]	+
Casei	↓ TNF-α	Borruel N et al[30,32]	+
Bulgaricus	↓ TNF-α	Borruel N et al[30,32]	+
Reuteri	↓ IL-8	Ma D et al[29]	–
Salivarius	↓ IFN-γ	McCarthy J et al[33]	–
Bifidobacterium			
Breve	↓ TNF-α, ↑ IL-10	Menard S et al[34]	+
Infantis	↓ TNF-α, ↓ IL-12, ↑ IL-10/IL-12 ratio	McCarthy J et al[33] O'Mahony L et al[11]	+
Streptococcus thermophilus	↓ TNF-α	Menard S et al[34]	+

*Reproduced from Ref. 36, Kim et al. *Neurogastroenterol Motil.* 2005;17:687–696.

proinflammatory (IL-12) cytokines. The observations from Cork suggest that probiotics have an anti-inflammatory effect,[11] and this is consistent with the demonstrated benefit in inflammatory bowel diseases, including pouchitis.[28] Animal model and human studies have evaluated the immunologic modulation with specific probiotic bacteria. In brief, the potential anti-inflammatory effect of *Lactobacillus reuteri* in an experimental rodent study demonstrated an inhibition of tumor necrosis factor-α (TNF-α)-induced production of IL-8.[29] *Lactobacillus casei* significantly decreased TNF-α release in ileal tissues from patients with Crohn disease.[30] Other papers,[31–35] summarized in Table 1, evaluated the anti-inflammatory effects of probiotic organisms and demonstrated activity against cytokines, including interferons.

Colonic Transit and Motility

Effects of probiotics on colonic transit have been reported in 2 studies, 1 in patients with IBS-D[10] and the second in IBS with predominant baseline bloating.[36] There was no significant effect on transit in patients with IBS-D.

In IBS patients with predominant bloating, the colonic transit [geometric center (GC) at 24 h, primary transit end point] was significantly retarded with VSL#3 relative to placebo, after adjusting for baseline transit (Ref. 36, Fig. 2). This effect on transit was not associated with the worsening of bowel function. Bazzocchi et al[37] showed that the colon's reflex motor responses to balloon distension were reduced during an open-label study with VSL#3. Further studies are indicated to explore the mechanism of the retarded transit of stool and potential effects on colonic sensation and fermentation of nutrients reaching the colon.

Effect on Intraluminal Milieu

Lactobacilli and *Bifidobacteria* subspecies are able to deconjugate and absorb bile acids.[22,23,38–40] This may result in a reduced bile salt load to the colon. It is known that reduced ileal retention (and therefore increased colonic delivery) of bile acids may be a potential cause for symptoms in patients with functional diarrhea.[41] It is conceivable that another role of probiotics is that they may serve to inactivate the bile salts delivered to the colon and, thus, avoid the potential colonic secretion and mucosal permeability changes induced by the bile salts.[20]

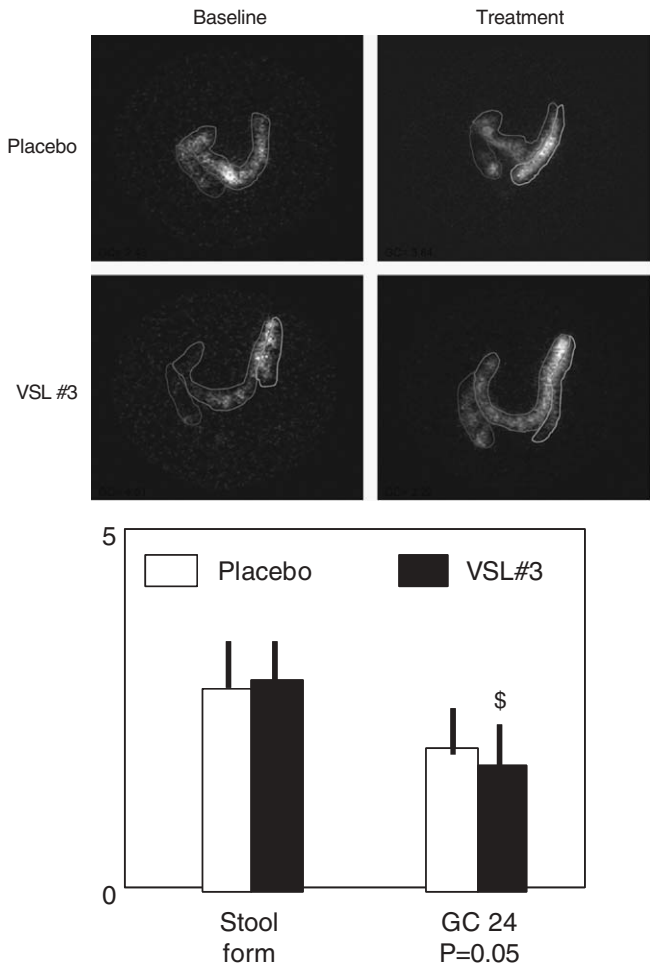

FIGURE 2. Effect of VSL#3 on colonic transit in patients with significant bloating associated with IBS. VSL#3 significantly delays colonic transit without altering overall stool form or consistency. Reproduced from Ref. 36, Kim et al. *Neurogastroenterol Motil.* 2005;17:687–696.

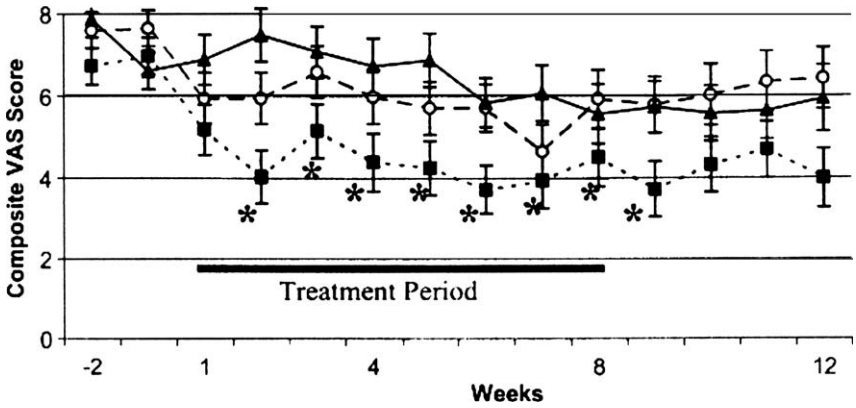

FIGURE 3. Effect of *L. salivarius UCC4331* and *B. infantis 35624* in IBS. The scores are derived from the sum of scores for abdominal pain/discomfort, bloating/distension, and bowel movement difficulty, adjusted for any differences in baseline symptom score. Reproduced from Ref. 11, O'Mahony et al. *Gastroenterology* 2005;128: 541–550.

Colonic bacteria normally metabolize nutrient substrates reaching the colon with the formation of gas and production of short chain fatty acids. The latter may induce propulsive contractions[17] and accelerate transit or enhance fluid and sodium absorption in the colon.[18] Thus, alteration in the resident colonic flora with administration of probiotics may modify the colonic metabolism of nutrient substrates to alter colonic transit and fluid fluxes.

THERAPEUTIC EFFECTS OF PROBIOTICS ON SYMPTOMS IN IBS

Three recently published studies have assessed the effects of probiotics on IBS symptoms.

In a 4-week, randomized, controlled trial, 5×10^7 cfu/mL of *Lactobacillus plantarum* and 0.009 g/mL (3.6 g) of oat flour in a rose hip drink were compared with placebo (rose hip syrup) in 60 patients with IBS.[9] Flatulence was significantly lower in the *Lactobacillus*-treated group compared with the placebo-treated group. Abdominal pain was lower than at baseline in both groups, but no significant difference between the 2 treatments was observed. Overall gastrointestinal function at 1 year was reported to be significantly better in the active treatment group. In this study, the test product contained fiber, and this may have confounded the observed results. Further evaluation, without the addition of fiber, is warranted to assess the effect specifically

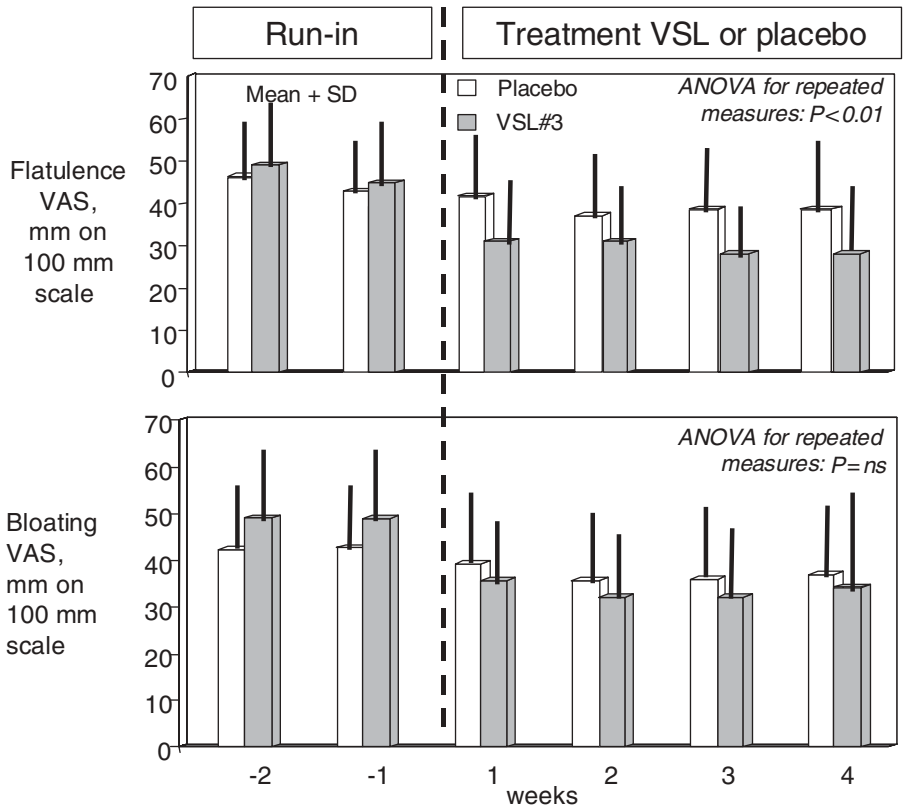

FIGURE 4. Weekly scores of flatulence and bloating during run-in and in response to placebo or VSL#3. Reproduced from Ref. 36, Kim et al. *Neurogastroenterol Motil.* 2005;17:687–696.

attributable to the probiotic in the improvement of symptoms.

In an 8-week, randomized, placebo-controlled trial, comparing VSL#3 with placebo in 24 IBS–D patients, there was no significant clinical efficacy, although a trend toward improvement in abdominal bloating was documented.[10]

The largest trial to date demonstrated a significant effect of *Bifidobacteria* species, but not of *Lactobacilli* species or placebo (Ref. 11, Fig. 3). It is unclear why *Lactobacilli* were ineffective in the Cork study, given the experimental data (discussed below) and the efficacy of *Lactobacilli* species in the study by Nobaek et al.[9] The primary end point used in the trial from Cork was novel, a composite Likert score of pain/discomfort, bloating, and difficulty with bowel movements. The secondary end points were significantly different for *Bifidobacteria* versus placebo in different weeks during the 12-week trial.

In the second study from the Mayo Clinic, the mean posttreatment scores were numerically lower for the VSL#3 treatment group for virtually all symptoms, with the score for flatulence being statistically significant [($P = 0.01$) Fig. 4]. The score for bloating was also reduced, although it was not statistically significant [($P = 0.11$) Fig. 4]. The proportions of the 2 groups that reached the threshold of 50% of weeks with satisfactory relief, thus fulfilling the a priori set criterion for responders for abdominal bloating, were 46% (11/24) for the VSL#3 group and 33% (8/24) for the placebo group (Fisher exact test, $P = 0.27$).

CONCLUSIONS

In summary, the literature confirms the potential benefit of *Bifidobacteria* alone or the specific probiotic combination, VSL#3, on symptoms in IBS without the induction of significant changes in bowel function; the mechanisms supporting these beneficial effects are the subject of ongoing research and the combination of immune effects, changes in the intraluminal milieu and secondary effects on colonic transit seem likely to result in beneficial effects for patients, particularly when safety is paramount in nonlethal disorders like IBS.

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