The Rationale and Clinical Effectiveness of Probiotics in Irritable Bowel Syndrome

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Abstract: The pathophysiology of irritable bowel syndrome (IBS) is still unknown. However, several lines of epidemiological, physiological, and clinical data suggest a role for intestinal bacteria in the pathogenesis of the disorder. Recent microbiology studies demonstrated differences in the composition of the intestinal microbiota between patients with IBS and healthy individuals. In addition, physiological studies have shown that manipulation of the intestinal microbiota by antibiotics, prebiotics, or probiotics can affect intestinal functions (eg, motility and sensation) relevant in the pathogenesis of IBS. Several randomized control trials comparing the effects of probiotics versus placebo in IBS have been published. Despite considerable differences in study design, dosing regimens, probiotic species used, and reported clinical end points, the current data indicate improving IBS symptoms and reducing the risk of persistent IBS symptoms. The data on the use of probiotics in children with IBS is more limited but is also suggestive for beneficial effects. The inconsistencies between the studies underline the need to look at each probiotic product separately for specific conditions, symptoms, and patient populations. This review article discusses the rationale for targeting the intestinal microbiota in patient with IBS and provides an overview and a critical evaluation of the currently available clinical data on the use of probiotics in the treatment of patients with IBS.

Key Words: probiotics, irritable bowel syndrome (IBS), intestinal microbiota

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THE RATIONALE FOR TARGETING THE INTESTINAL MICROBIOTA IN IBS

The adult human's intestine harbors more than 500 different species with a large diversity of aerobic and anaerobic bacteria. However, our knowledge of the human intestinal microbiota is still limited as the majority of the normal bacteria in the gut have not yet been identified.[1]

Evidence for the role of intestinal bacteria in the pathogenesis of irritable bowel syndrome (IBS) comes from epidemiological, physiological, and clinical data.[2,3] Epidemiological studies have identified gastrointestinal (GI) infection (eg, acute gastroenteritis) as a predictor for the development of IBS and that patients who recover from intestinal infection may continue to have chronic GI symptoms consistent with IBS.[4] Other studies have documented the presence of small-bowel bacterial overgrowth in a portion of IBS patients,[5] and in some of these studies treatment with antibiotics led to significant improvement in symptoms.[6] Further support for a possible role of bacteria in functional GI conditions comes from physiological studies of animals and humans, which show a profound effect of alterations in the composition of the intestinal microbiota on the intestinal physiological functions.[7]

The evidence for differences in the composition of the intestinal microbiota between patients with IBS and healthy individuals is still emerging. Earlier studies using classic culture techniques were able to investigate only a limited number of cultureable bacteria. However, recent studies using new DNA-based molecular techniques investigate a broader spectrum of bacteria in the gut and provide more detailed information, demonstrating subtle, but statistically significant differences in the composition of the intestinal bacteria between patients with IBS and healthy individuals.[8,9]

Despite the current limited understanding of the role of microbiota in the pathogenesis of IBS, there is a growing interest in the manipulation of the intestinal microbiota as a mean of treatment of patients with this disorder. Recent clinical data have shown that manipulation of the intestinal microbiota by antibiotics,[10] prebiotics,[11] or probiotics can affect human intestinal functions, which may be directly relevant to the pathogenesis of IBS symptoms (eg, intestinal motility and sensation); and that some patients can experience relief of symptoms with these interventions.

THE SCIENTIFIC BASIS FOR THE USE OF PROBIOTICS IN IBS

The probiotic concept suggests that supplementation of the intestinal microbiota with the right types and numbers of live microorganisms can improve the microbiota characteristics and promote health.[12] Probiotic products are available in different preparations, including fermented milk drinks, yogurts, food products (snacks, chocolate, etc.), capsules, pills, and powders. The number, variability, and availability of these products are increasing as new products are constantly being developed and marketed with various beneficial health claims. In theory, certain probiotics (at the right dose and in the right formulation) can help restore the proper balance of the intestinal microbiota, lead to better digestive and intestinal function, and possibly improve GI symptoms.

Several randomized control trials comparing the effects of probiotics versus placebo in IBS have been published. Comparing and summarizing these studies is difficult due to considerable differences in study design, dosing regimens,

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TABLE 1. Important Randomized Controlled Trials Investigating Probiotics Vs. Placebo in IBS

Probiotic Intervention	No. of Studies [Ref]	No. of Patients	Intervention Duration	Study Outcome	Recommendation†/‡
Single probiotics					
LGG	1.*Bausserman and Michail[22]	50	6 wk	No benefit over placebo	
	2.*Gawronska et al[23]	104	4 wk	Reduction in abdominal pain in IBS not in FAP or FD	B/C (in children)
	3.*Francavilla et al[24]	141	8 wk	Reduction in abdominal pain	
VSL#3	1. Kim et al[28]	25	8 wk	Reduction in bloating or symptoms No significant change in gut transit	
	2. Kim et al[29]	48	4/8 wk	Significant reduction in flatulence and slower transit	C
	3.*Guandalini et al[25]	59	6 wk	Improvement of IBS symptoms	C (in children)
B. infantis 35624	1. O'Mahony et al[18]	77	8 wk	Reduction in abdominal pain, bloating, bowel satisfaction, and composite score	B/C
B. infantis 35624	2. Whorwell et al[19]	362	4 wk	Improvement in IBS symptoms and IBS global assessment score for 1×10^8	
L. Plantarum (DSM 9843)	1. Nobaek et al[30]	60	4 wk	Reduction in flatulence	C
L. Plantarym 299V	1. Niedzielin et al[31]	40	4 wk	Resolution of pain	C
L. reuteri ATCC 55730	1. Niv et al[32]	54	6 mo	No benefit over placebo	
B. animalis DN 173010	1. Guyonnet et al[33]	274	6 wk	No benefit over placebo. Subanalysis (n = 19) increase in stools frequency	C
Bacillus coagulans GBI-30, 6086	1. Dolin[34]	55	8 wk	Reduction in number of BM per day	C
Synbiotic					
Lactobacillus paracasei B21060 with prebiotics vs. prebiotics	1. Andriulli et al[35]	135	12 wk	No benefit of synbiotic over prebiotic. Significant reduction in BM, pain, IBS Score in D-IBS (n = 47)	C
Mixed probiotics					
LGG, *L. rhamnosus* LC705, *B. breve* Bb99	1. Kajanda et al[20]	103	6 mo	Reduction in total symptom scores in intervention	
Propionibacterium freudenreichii spp shermanii JS	2. Kajanda et al[21]	86	5 mo	Reduction in GSS	B/C
L. acidophilus SDC 2012 and 2013	1. Sinn et al[36]	40	2 wk	Reduction in abdominal pain	C
B. longum LA 101, *Lb. acidophilus* LA 102, *L. lactis* LA 103 and *S. thermophilus* LA 104	1. Drouault-Holowacz et al[37]	100	4 wk	No benefit over placebo. Some benefit in subgroup analysis	C
E. coli (DSM 17252) and *En. faecalis* (DSM 16440)	1. Enck et al[38] 2. Enck et al[39]	297	8 wk	Reduction in GSS by 50% Reanalysis of previous data	C
Lactobacillus acidophilus CUL60 (NCIMB 30157) and CUL21 (NCIMB 30156), *Bifidobacterium lactis* CUL34 (NCIMB 30172)	1. Williams et al[40]	52	8 wk	Significant reduction in Symptom severity score	C
L. paracasei, ssp. paracasei F19, *L. acidophilus* La5 and *B. lactis* Bb12	1. Simrén et al[41]	74	8 wk	No benefit over placebo	
L. acidophilus NCFM and *B. lactis* Bi-07	1. Ringel-Kulka et al[42]	60	8 wk	Significant reduction in bloating	C

*Study done in children.

†Recommendation is based on: A = strong, positive, well-conducted, controlled studies in the primary literature, not abstract form; B = some positive, controlled studies but presence of some negative studies or inadequate amount of work to establish the certainty; C = some positive studies but clearly inadequate amount of work to establish the certainty of "A" or "B."

‡Recommendations relate to the specific strains that were tested and reported to be effective.

B indicates Bifidobacretium; BM, bowel movements; E, Escherichia; En, Enterococcus; FAP, functional abdominal pain; FD, functional dyspepsia; GSS, global symptom score; IBS, irritable bowel syndrome; L, Lactobacillus.

probiotic species used, and reported clinical end points. Despite these limitations, few recent systematic reviews and meta-analyses concluded that probiotics appear to be effective, to varying extent, in patients with IBS.[13–17] It should be noted, however, that less than half of the published studies satisfied the selection criteria for inclusion in these meta-analyses and systematic reviews (McFarland n = 12; Hoveyda n = 14; Moayyedi n = 18). Additional analyses of the data have indicated significant heterogeneity among studies ($I^2 = 68\%$; >25% indicate high levels of heterogeneity), possible publication bias, and small studies effects.[13] In addition, some of the studies included in recent reviews suffer from suboptimal study design with regard to inadequate blinding, trial length, sample size, and clear acceptable end points.[14] Nevertheless, taken together these meta-analyses have found that probiotics are better than placebo with regard to improving IBS symptoms [odds ratio 1.63 (95% CI, 1.23-2.17); $P = 0.001$][15] and reducing the risk of persistent IBS symptoms with a risk reduction of 0.77 (95% CI, 0.62-0.94; $P < 0.001$)[16] and 0.72 (95% CI, 0.57-0.88; $P = 0.002$), and a number needed to treat of 4.[13] However, as grouping all studies together for systematic reviews and meta-analyses may dilute the effect of a specific intervention, it is important to also evaluate each study separately. Careful review of the individual studies reveal that most of the reported studies were relatively small, of short duration, and used various primary end points, often not clinically applicable. Many of the studies found improvement in primary end points compared with baseline, but few were able to demonstrate significant improvement over placebo. Overall, the quality of evidence based on the quality of studies, number of studies, consistency of results among studies, and clinical applicability of study end points is low for most of the investigated probiotics. However, 2 probiotic interventions seem to have better data in IBS. *Bifidobacterium infantis* 35624 was studied in 2 well-designed clinical trials.[18,19] The first study compared *B. infantis* 35624 or *Lactobacillus salivarius* UCC4331 versus placebo in 77 patients with IBS and found significant reduction in pain, bloating, bowel movement difficulty, and composite score (study primary end points) in the group receiving *B. infantis* 35624 ($P < 0.05$) compared with placebo.[18] A larger follow-up multicenter trial further supported these findings by demonstrating significant improvement in pain (the study primary end point) at 4 weeks in *B. infantis* 35624 (10^8) group versus placebo group (1.73 vs. 1.48 respectively, $P < 0.03$). There was also improvement in global relief of IBS symptoms in *B. infantis* 35,624 (10^8) group versus placebo group (62.3 vs. 42.0 respectively, $P < 0.02$) and in other individual IBS symptoms.[19] The multispecies probiotic containing *L. rhamnosus* GG (LGG), *L. rhamnosus* LC705, *B. breve* Bb99, and *Propionibacterium freudenreichii* spp shermanii JS has also been tested in 2 clinical trials.[20,21] Both studies have shown a significant reduction in IBS total symptom (abdominal pain, distension, flatulence, borborygmi) score over placebo (42% vs. 6% respectively, $P = 0.015$[20]; and 37% vs. 9% respectively, $P = 0.01$[21]).

Only few studies examined the effect of probiotics in children with IBS. LGG was studied in 3 randomized clinical trials.[22–24] Two of the 3 studies showed significant benefit of LGG over placebo.[23,24] A study of 6 to 16 year olds with IBS, functional abdominal pain, and functional dyspepsia found that only in the IBS group children receiving LGG had greater likelihood of treatment success (no pain) than those receiving placebo (33% vs. 5%; RB 6.3; 95% CI, 1.2-38; $P = 0.04$) and the number needed to treat 4 (95% CI, 2-36), as well as reduced frequency of pain ($P = 0.02$).[23] A second study with LGG of 5 to 14 year olds with IBS and functional abdominal pain, showed that the LGG group compared with placebo had lower frequency (1.6 vs. 3.2 respectively; $P < 0.01$) and severity (2.5 vs. 3.6 respectively, $P < 0.01$) of abdominal pain.[24] Another clinical trial using VSL#3 in children 4 to 15 years with IBS showed a significantly higher magnitude of improvement in relief of IBS symptoms (primary end point) in the VSL#3 group compared with placebo ($P < 0.05$).[25]

REGULATORY PERSPECTIVE

The regulatory authorities (eg, Food and Drug Administration) regard probiotics as dietary supplements that are not intended to diagnose, treat, cure, or mitigate the effects of diseases and recommend that consumers will consult with a health care professional before using these products. However, the ability of health care providers to provide knowledgeable evidence-based advice with regard to the appropriate use of probiotics is limited due to the lack of high-quality data on commercially available probiotic products. Indeed, most of the probiotic products currently available on the market have not been adequately tested for their effectiveness in IBS in acceptably designed clinical trials. Furthermore, despite the Food and Drug Administration recommendation, <30% of probiotics consumers do so with the advice of a health care provider.[26]

CONCLUSIONS AND CLINICAL IMPLICATIONS OF CURRENT DATA

The data emerging from epidemiological, physiological, and clinical trials provide the rationale for the use of probiotics in the treatment of IBS. However, the currently available data, from well-designed randomized controlled clinical trials in patients with IBS, is still limited and is not sufficient to support a general recommendation for the use of probiotics in general or a specific probiotic bacteria/product in adults or in children[27] with IBS. Further research is needed to help identify the targeted patients and symptoms, the most effective probiotic species and strains, and the preferred regimen of intervention. Nevertheless, in view of the paucity of available treatments for IBS and their limited efficacy, the overall safety of probiotics lowers the bar for trying probiotic products in patients with IBS and possibly other functional GI disorders. Although probiotics should not be used as a single therapy, they may be worth trying in symptomatic patients in combination with current conventional treatments. When choosing a product for such patients, it is recommended that providers and patients look for products that were specifically tested in IBS. Table 1 summarizes the probiotic bacteria tested compared with placebo in recent randomized control trials in patients with IBS.

REFERENCES

1. Marchesi J, Shanahan F. The normal intestinal microbiota. *Curr Opin Infect Dis*. 2007;20:508–513.
2. Ringel Y, Carroll IM. Alterations in the intestinal microbiota and functional bowel symptoms. *Gastrointest Endosc Clin N Am*. 2009;19:141–150.
3. Salonen A, de Vos WM, Palva A. Gastrointestinal microbiota in irritable bowel syndrome: present state and perspectives. *Microbiology*. 2010;156:3205–3215.

4. Spiller RC. Postinfectious irritable bowel syndrome. *Gastroenterology*. 2003;124:1662–1671.
5. Choung RS, Ruff KC, Malhotra A, et al. Clinical predictors of small intestinal bacterial overgrowth by duodenal aspirate culture. *Aliment Pharmacol Ther*. 2011;33:1059–1067.
6. Peralta S, Cottone C, Doveri T, et al. Small intestine bacterial overgrowth and irritable bowel syndrome-related symptoms: experience with Rifaximin. *World J Gastroenterol*. 2009;15: 2628–2631.
7. Husebye E, Hellström PM, Sundler F, et al. Influence of microbial species on small intestinal myoelectric activity and transit in germ-free rats. *Am J Physiol Gastrointest Liver Physiol*. 2001;280:G368–G380.
8. Carroll IM, Chang YH, Park J, et al. Luminal and mucosal-associated intestinal microbiota in patients with diarrhea-predominant irritable bowel syndrome. *Gut Pathogens*. 2010;2:19.
9. Carroll I, Ringel-Kulka T, Keku TO, et al. Molecular Analysis of the Luminal and Mucosal-Associated Intestinal Microbiota in Diarrhea-Predominant Irritable Bowel Syndrome. *Am J Physiol Gastrointest Liver Physiol*. 2011. [Epub ahead of print].
10. 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.
11. Roberfroid M, Gibson GR, Hoyles L, et al. Prebiotic effects: metabolic and health benefits. *Br J Nutr*. 2010;104(suppl 2):S1–63.
12. Reid G, Younes JA, Van der Mei HC, et al. Microbiota restoration: natural and supplemented recovery of human microbial communities. *Nat Rev Microbiol*. 2011;9:27–38.
13. Moayyedi P, Ford AC, Talley NJ, et al. The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Gut*. 2010;59:325–332.
14. Brenner DM, Moeller MJ, Chey WD, et al. The utility of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Am J Gastroenterol*. 2009;104:1033–1049.
15. Hoveyda N, Heneghan C, Mahtani KR, et al. A systematic review and meta-analysis: probiotics in the treatment of irritable bowel syndrome. *BMC Gastroenterol*. 2009;9:15.
16. McFarland LV, Dublin S. Meta-analysis of probiotics for the treatment of irritable bowel syndrome. *World J Gastroenterol*. 2008;14:2650–2661.
17. Parkes GC, Sanderson JD, Whelan K. Treating irritable bowel syndrome with probiotics: the evidence. *Proc Nutr Soc*. 2010;69:187–194.
18. O'Mahony L, McCarthy J, Kelly P, et al. Lactobacillus and bifidobacterium in irritable bowel syndrome: symptom responses and relationship to cytokine profiles. *Gastroenterology*. 2005;128:541–551.
19. Whorwell PJ, Altringer L, Morel J, et al. Efficacy of an encapsulated probiotic *Bifidobacterium infantis* 3,5624 in women with irritable bowel syndrome. *Am J Gastroenterol*. 2006;101:1581–1590.
20. Kajander K, Hatakka K, Poussa T, et al. A probiotic mixture alleviates symptoms in irritable bowel syndrome patients: a controlled 6-month intervention. *Aliment Pharmacol Ther*. 2005;22:387–394.
21. Kajanda K, Myllyluoma E, Rajilic-Stojanovic M, et al. Clinical trial: multispecies probiotic supplementation alleviates the symptoms of irritable bowel syndrome and stabilizes intestinal microbiota. *Aliment Pharmacol Ther*. 2008;27:48–57.
22. Bausserman M, Michail S. The use of *Lactobacillus* GG in irritable bowel syndrome in children: a double-blind randomized control trial. *J Pediatr*. 2005;147:197–201.
23. Gawrońska A, Dziechciarz P, Horvath A, et al. Randomized double-blind placebo-controlled trial of Lactobacillus GG for abdominal pain disorders in children. *Aliment Pharmacol Ther*. 2007;25:177–184.
24. Francavilla R, Miniello V, Magistà AM, et al. Randomized controlled trial of Lactobacillus GG in children with functional abdominal pain. *Pediatrics*. 2010;126:e1445–e1452.
25. Guandalini S, Magazzù G, Chiaro A, et al. VSL#3 improves symptoms in children with irritable bowel syndrome: a multicenter, randomized, placebo-controlled, double-blind, crossover study. *J Pediatr Gastroenterol Nutr*. 2010;51:24–30.
26. Jackson JP, Palsson O, Fedor-Hammonds L, et al. Prevalence and characteristics of probiotic use in subjects with functional GI symptoms. *JPEN*. 2010;34:224.
27. Ringel-Kulka T. Probiotics role in children with irritable bowel syndrome. *European Gastroenterology & Hepatology Review*. 2011. (In press).
28. Kim HJ, Camilleri 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. *Aliment Pharmacol Ther*. 2003;17:895–904.
29. Kim HJ, Vazquez Roque MI, Camilleri M, et al. A randomized controlled trial of a probiotic combination VSL#3 and placebo in irritable bowel syndrome with bloating. *Neurogastroenterol Motil*. 2005;17:687–696.
30. Nobaek S, Johansson ML, Molin G, et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol*. 2000;95:1231–1238.
31. Niedzielin K, Kordecki H, Birkenfeld B. A controlled, double-blind, randomized study on the efficacy of Lactobacillus plantarum 299 V in patients with irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2001;13:1143–1147.
32. Niv E, Naftali T, Hallak R, et al. The efficacy of *Lactobacillus reuteri* ATCC 55730 in the treatment of patients with irritable bowel syndrome: a double blind, placebocontrolled, randomized study. *Clin Nutr*. 2005;24:925–931.
33. Guyonnet D, Chassany O, Ducrotte P, et al. Effect of a fermented milk containing *Bifidobacterium animalis* DN-173 010 on the health-related quality of life and symptoms in irritable bowel syndrome in adults in primary care: a multicentre, randomized, double-blind, controlled trial. *Aliment Pharmacol Ther*. 2007;26:475–486.
34. Dolin BJ. Effects of a proprietary *Bacillus coagulans* preparation on symptoms of diarrhea-predominant irritable bowel syndrome. *Methods Find Exp Clin Pharmacol*. 2009;31:655–659.
35. Andriulli A, Neri M, Loguercio C, et al. Clinical trial on the efficacy of a new symbiotic formulation, Flortec, in patients with irritable bowel syndrome: a multicenter, randomized study. *J Clin Gastroenterol*. 2008;42(suppl 3):S218–S223.
36. Sinn DH, Song JH, Kim HJ, et al. Therapeutic effect of *Lactobacillus acidophilus*-SDC 2012, 2013 in patients with irritable bowel syndrome. *Dig Dis Sci*. 2008;53:2714–2718.
37. Drouault-Holowacz S, Bieuvelet S, Burckel A, et al. A double blind randomized controlled trial of a probiotic combination in 100 patients with irritable bowel syndrome. *Gastroenterol Clin Biol*. 2008;32:147–152.
38. Enck P, Zimmermann K, Menke G, et al. A mixture of *Escherichia coli* (DSM 17252) and *Enterococcus faecalis* (DSM 16440) for treatment of the irritable bowel syndrome: a randomized controlled trial with primary care physicians. *Neurogastroenterol Motil*. 2008;20:1103–1109.
39. Enck P, Zimmermann K, Menke G, et al. Randomized controlled treatment trial of irritable bowel syndrome with a probiotic E.coli preparation (DSM17252) compared to placebo. *Z Gastroenterol*. 2009;47:209–214.
40. Williams E, Stimpson J, Wang D, et al. Clinical trial: a multistrain probiotic preparation significantly reduces symptoms of irritable bowel syndrome in a double-blind placebo-controlled study. *Aliment Pharmacol Ther*. 2009;29:97–103.
41. Simrén M, Ohman L, Olsson J, et al. Clinical trial: the effects of a fermented milk containing three probiotic bacteria in patients with irritable bowel syndrome: a randomized, double-blind, controlled study. *Aliment Pharmacol Ther*. 2010;31: 218–227.
42. Ringel-Kulka T, Palsson OS, Maier D, et al. Probiotic bacteria: probiotic bacteria *Lactobacillus acidophilus* NCFM and *Bifidobacterium lactis* Bi-07 versus placebo for the symptoms of bloating in patients with functional bowel disorders-a double-blind study. *J Clin Gastroenterol*. 2011;45:518–525.