Probiotics in the Treatment of Human Inflammatory Bowel Diseases

Update 2011

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Abstract: Crohn's disease, ulcerative colitis, and pouchitis after ileal pouch anal anastomosis in ulcerative colitis patients are often refractory to standard therapy. Over the last decade, the rational to use probiotics and its beneficial efficacy in the treatment of chronic inflammatory bowel disease (IBD) is increasingly under scrutiny. Although it has become clear that intestinal epithelial-mucosal immune interactions and enteric bacteria play a critical role in the development of IBD, the substantial clinical efficacy of probiotics in these disorders is less evident. This review outlines the clinical studies regarding probiotics before October 2007. These studies formed the foundation of probiotic clinical trials in IBD, but they also indicated the need of larger and better-controlled studies than the past experimental approaches. Furthermore, this review also examines in-depth the probiotic clinical trials published between 2007 and December 2010, providing new insights into the role of probiotics for inducing and maintaining remission of IBD, and highlighting some of the breakthroughs, especially regarding induction of remission for ulcerative colitis.

Key Words: Crohn's disease, inflammatory bowel diseases, pouchitis, probiotics, ulcerative colitis, lactobacillus, bifidobacterium, intestinal bacteria

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Since 1997, when the treatment of chronic inflammatory bowel disease (IBD) with *Escherichia coli Nissle 1917*[1,2] was studied, probiotic treatment for human IBD, including pouchitis, has been investigated and reviewed numerously. At present, accumulating evidence suggests that the dynamic balance between microbes, particularly commensal flora, and host defensive responses at the mucosal frontier has a pivotal role in the initiation and pathogenesis of chronic IBD.[3] In addition, susceptibility genes and environmental agents have shown importance in a dysfunctional mucosal immune system in IBD. Despite an increased understanding of its pathogenesis, the present therapies are still relatively insufficient to cure IBD. Patients often become intolerant or refractory to standard treatments, some of them with significant adverse effects. As a result, novel treatments have been studied to abrogate patients' debilitating symptoms. Some of the alternative treatment options have included modulation of the intestinal microflora using probiotics.

The aim of this review is to provide a brief historical perspective of the available evidence for the use of probiotics in IBD followed by a recent update of the literature. The intent is to enhance the clinician perspective about the role of probiotic therapy within the array of conventional medical treatments.

LITERATURE SEARCH

A systematic literature search was conducted in the following databases: EMBASE, BIOSIS Previews, Medline, and PubMed. The following terms were used for searching: Crohn's disease, ulcerative colitis, pouch, pouchitis, inflammatory bowel diseases, and probiotic. Search results were separated into 2 groups with the first group consisting of results published before October 2007, and the second group consisting of publications from 2007 through December 2010. Results were restricted to human patients, written in the English language, and original research articles using only larger randomized controlled trials (RCT).

OVERVIEW OF PROBIOTIC CLINICAL STUDIES FOR IBD BEFORE OCTOBER 2007

Crohn's Disease (CD)

For CD, a total of 9 studies were conducted before October 2007. However, only 2 small studies were associated with inducing remission for CD.[4,5]

Maintenance of Remission

Bousvaros et al[6] reported no significant difference in probiotic efficacy [4×10^{10} colony forming units (CFU)] when compared with a placebo. In this RCT, 18 of the 75 patients relapsed, 33% of these relapsing patients had earlier surgery, 22% had not. Guslandi et al[7] randomized 32 patients to either treatment with *Saccharomyces boulardii* or mesalamine (3 g/d). Both research arms were homogenous for previous bowel resection, the probiotic group showed an increased time to relapse relative to the mesalamine control group.[7] In a 1-year trial in patients who did not undergo surgery,[2] oral administration of *E. coli Nissle 1917* did not significantly increase the time to relapse relative to placebo.

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Prevention of Postoperative Relapse

Prantera et al[8] reported no significant difference in probiotic efficacy (*Lactobacillus GG*, 1.2×10^{10} CFU) when compared with a placebo. Similarly, Marteau et al[9] and van Gossum et al,[10] respectively, reported that *Lactobacillus johnsonii* did not prolong the time to relapse after surgery for CD, indicating that this probiotic strain was ineffective for maintenance therapy in CD, although these results were weakened due to a high dropout rate.

In addition, a synbiotic preparation was studied by Chermesh et al[11] in 2007, who conducted a RCT to examine the efficacy of Synbiotic 2000 (a commercial mixture containing 4 probiotics and 4 prebiotics) to extend the duration of remission after surgery for CD. This was a small study and also suffered from a lot of dropouts. During this 2-year follow-up, there were no significant differences with respect to either endoscopic or clinical relapses. However, the majority of patients had fistulizing CD, and their response to this treatment may differ from those who have inflammatory nonpenetrating disease behavior.[11]

Ulcerative Colitis (UC)

Two large randomized controlled studies examining probiotic treatment for inducing remission in UC concluded that there were significant reductions in disease activity relative to the control groups.[12,13] One of these studies, conducted by Tursi et al,[12] studied the efficacy of balsalazide and a high potency probiotic mixture (VSL#3) and compared it to a group-administered balsalazide, or to a group-administered mesalamine. The combination treatment was most effective; it outperformed the comparator groups on symptoms assessment, endoscopic appearance, and histologic evaluation. The other study on preventing mild-to-moderate UC flares, conducted by Matthes et al,[13] explored the effect of dosing probiotics, randomizing 90 patients to either 40 mL, 20 mL, or 10 mL enemas containing *E. coli Nissle 1917* (1×10^8 CFU/mL) or placebo, concluding that remission rates significantly decreased according to dosing; 53%, 44%, and 27%, respectively.[13] A third large randomized controlled study concluded that probiotic treatment was as effective as the standard mesalamine treatment,[14] but this study suffered from a subtherapeutic mesalamine dose in the control group. In addition, findings on reductions in disease activity when comparing probiotics to a mesalamine control group were supported by Kato et al[15] in a smaller RCT and in 2 open-label studies.[16,17]

For maintaining remission, 2 studies concluded independently that *E. coli Nissle 1917* did not significantly increase the time to relapse[1,14] versus 1.2 or 1.5 g/d mesalamine. A third larger study also found that the same probiotic strain was as effective as the control group receiving mesalamine (significant equivalence, $P = 0.003$).[18] The low dose of mesalamine in the control group may have generated a "placebo" effect, thereby casting doubt as to the efficacy of *E. coli* treatment for this indication. Two large studies using *Lactobacillus salivarius* or *Bifidobacterium infantis* did not show significant difference in preventing UC relapse versus placebo or 2.4 g mesalamine,[19,20] but Zocco et al[20] concluded that *Lactobacillus GG* did prolong the length of remission. A combination of this probiotic and mesalamine did not induce a synergistic therapeutic effect on the trial patients.

Pouchitis

Pouchitis is a relatively common occurrence in patients with UC who undergo ileal pouch anal anastomosis after colectomy. Trials examining the use of probiotics for inducing remission of pouchitis have either been too small or uncontrolled to draw any conclusions regarding probiotics.[21–23]

In maintaining remission, probiotic therapy was beneficial in all larger placebo-controlled studies using VSL#3[24–27] and 1 study using *Lactobacillus rhamnosus GG*.[28] Each study found significant improvements in extending the time to relapse. In fact, the placebo-controlled study by Gionchetti et al[26] was the first report on the efficacy of probiotics for an indication related to IBD (Table 1).

CLINICAL STUDIES FROM OCTOBER 2007 THROUGH TO DECEMBER 2010

CD

Induction of Remission

No RCTs were found in which probiotics were used to induce remission in patients with CD.

Maintenance of Remission

There were no studies regarding probiotics to prevent relapses in patients with CD. However, it is noteworthy to mention that Vilela et al[29] researched the effects of *Saccharomyces boulardii* on the intestinal permeability of patients with CD in remission. A small RCT with 15 patients on *S. Boulardii* versus 19 patients on placebo demonstrated that patients treated with *S. Boulardii* and who remained in remission also improved their abnormal intestinal barrier function.

UC

Induction of Remission

Adding to open-label studies reported by Bibiloni et al[17] and Tursi et al[12] on the beneficial therapeutic effect of VSL#3 in inducing remission for UC, Sood et al[30] performed a large randomized placebo-controlled trial in 2009 on adults with mild-to-moderate activity of UC, administering 3600×10^9 CFU of VSL#3. Concomitant treatment with oral mesalamine, azathioprine, or 6-mercaptopurine, was continued on a stable dose. After 12 weeks of treatment the remission rates in VSL#3 versus placebo were 42.9% and 15.9%, respectively. Although this study was well designed, a large dropout in the placebo group (20%) was an important limitation for this study.

Tursi et al[31] randomly assigned 144 adults with relapsing mild-to-moderate UC to either 3600×10^9 CFU of VSL#3 or placebo, as an adjunct to standard maintenance treatment. Although there were no significant differences in obtaining clinical remission, there was a significant clinical response in the VSL#3 group.

In addition, VSL#3 was investigated in children. Miele et al[32] studied the efficacy of VSL#3 in adjunct to standard treatment with steroids and 5-aminosalicylic acid in the induction and maintenance of remission in 29 newly diagnosed patients with UC in a small randomized placebo-controlled trial. After steroid induction therapy, a high induction remission rate (92.8%) was achieved in patients on VSL#3 (dose range from 450 to 1800×10^9CFU based on age) while on a stable dose of oral 5-aminosalicylic acid. In the placebo group, only 36.4% of patients obtained clinical

TABLE 1. Summary of Studies Investigating the Effect of Probiotic Treatment on the Induction and Maintenance of Remission in Inflammatory Bowel Disease Published Before October 2007

First Author	Design Duration	Group (Dose/d)		Concomitant Therapy	Results
		Probiotic	Comparator		
Crohn's Disease					
Maintenance of remission					
Bousvaros et al[6]	DB, R, C 2 y	LGG (4×10^{10} CFU) n = 39	Placebo n = 36	Aminosalicylate 6-MP, azathioprine, corticosteroids	NSD
Prantera et al[8]	DB, R, C 1 y	LGG (1.2×10^{10} CFU) n = 23	Placebo n = 22	Loperamide, cholestyramine	NSD
Marteau et al[9]	DB, R, C 6 mo	*Lactobacillus johnsonii* LA1, Nestle (2×10^9 CFU) n = 43	Placebo n = 47	Loperamide, cholestyramine, corticosteroids tapered to nil by week 3	NSD for endoscopic scores
Van Gossum et al[10]	DB, R, C 12 wk	*Lactobacillus johnsonii* LA1, Nestle (1×10^{10} CFU) n = 27	Placebo n = 22	None	NSD for endoscopic score High dropout rate (n = 21)
Ulcerative colitis					
Induction of remission					
Tursi et al[12]	R, C 8 wk	Balsalazide (2.25 g) and VSL#3 (1×10^{11} CFU) n = 30	Balsalazide (4.5 g) n = 30 Mesalamine (2.4 g) n = 28	None	Balsalazide and VSL#3 outperformed the 2 comparator groups (symptoms assessment, endoscopic appearance, and histologic evaluation)
Matthes et al[13]	DB, R 4 wk	*E. coli Nissle 1917* ($> 10^8$ CFU/mL) 10, 20, or 40 mL Enema n = 20	Placebo n = 20	None	Remission induced in 18.2% (placebo), and varied by dose in the treatment group: 27.3% (10 mL); 44.4% (20 mL), and 52.9% (40 mL)
Rembacken et al[14]	DB, R, C 1 y	*E. coli Nissle 1917* (1×10^{11} CFU) n = 57	Mesalamine (2.4 g) n = 59	Prednisolone or hydrocortisone enemas	As effective as mesalamine at attaining remission
Ulcerative Colitis					
Maintenance of remission					
Kruis et al[1]	DB, R, C 3 mo	*E. coli Nissle 1917* (CFU $> 10^{10}$) n = 50	Mesalazine (1.5 g) n = 53	None	NSD for relapse rates, CAI scores, global assessment
Rembacken et al[14]	DB, R, C 1 y	*E. coli Nissle 1917* (CFU $> 10^{10}$) n = 39	Mesalamine (1.2 g) n = 44	Prednisolone (tapered to nil over 4 mo)	NSD
Kruis et al[18]	DB, R, C 1 y	*E. coli Nissle 1917* (2.5-25×10^9 CFU) n = 162	Mesalamine (1.5 g) n = 165	None	As effective as mesalamine at maintaining remission ($P = 0.003$)
Shanahan et al[19]	DB, R, C 1 y	*L. salivarius* or *Bifidobacterium infantus* (1×10^9 CFU) n = 52/group	Placebo n = 53	Aminosalicylate	NSD
Pouchitis					
Maintenance of remission					
Gionchetti et al[25]	DB, R, C 12 mo	VSL#3 (1×10^{11} CFU) n = 20	Placebo n = 20	None	Increased duration of remission ($P < 0.05$)
Gionchetti et al[26]	DB, R, C 9 mo	VSL#3 (6 g) n = 20	Placebo n = 20	None	Increased duration of remission ($P < 0.001$)
Gosselink et al[28]	R, C 3 y	*L.* GG (CFU $> 10^{10}$) N = 78	Placebo n = 39	Not indicated	Increased duration of remission ($P = 0.011$)

VSL#3: commercial mixture containing *Bifidobacterium longum, B. infantis, B. breve. Lactobacillus acidophilus, L. casei, L. delbrueckii subsp bulgaricus, L. plantarum, and Streptococcus salivarius subsp thermophilus*.

C indicates controlled; CAI, clinical activity index; CFU, colony forming units; DB, double-blind; L.GG, Lactobacillus rhamnosus GG; L. salivarius, Lactobacillus salivarius subsp Salivarius UCC118 strain; MP, mercaptopurine; NSD, no significant difference; R, randomized.

remission. VSL#3 was well tolerated in both adults and children.

In 2004, Tursi et al[12] studied a dose effect of *E. coli Nissle 1917* for the induction of remission. A larger trial by Matthes et al[33] confirmed Tursi previous findings; time to remission was indeed shortest in the *E. coli Nissle 1917* 40 mL high-dose group. However, this trial was hampered by the high number of excluded patients.

Maintenance of Remission

In 2009, Miele et al[32] reported that 21.4% of the children treated with VSL#3 relapsed within 1 year after corticosteroid induction or response. A relapse was defined if the Lichtiger colitis activity index score had increased > 3 points. The relapse rate was 73.3% in the placebo arm.

TABLE 2. Summary of Studies Investigating the Effect of Probiotic Treatment on the Induction and Maintenance of Remission in Inflammatory Bowel Disease Published After October 2007

First Author Date	Design Duration	Group (Dose/d)		Concomitant Therapy	Results
		Probiotic	Comparator		
Crohn's Disease					
Maintenance of remission					
Vilela et al[29]	DB, R, C 3 mo	S. Boulardii (4×10^8 CFU) n = 15	Placebo n = 19 Healthy controls n = 15	Mesalamine, Azathioprine Prednisone, metronidazol/ thalidomide	Improved permeability ($P = 0.0005$) and maintenance of remission
Ulcerative colitis					
Induction of remission					
Sood et al[30]	DB, R, C 12 wk	VSL#3 (3.6×10^{11} CFU) n = 77	Placebo n = 70	Mesalamine, Azathioprine, 6-MP	6wk Decreased UCDAI > 50% in 32.5%VSL#3 vs. 10% in placebo ($P = 0.001$). 12 wk Decreased UCDAI > 3 in 51.9% VSL#3 vs. 18.9% placebo ($P < 0.001$). 42.9% remission in VSL#3 vs. 15.7% in placebo ($P < 0.001$).
Tursi et al[31]	DB, R, C 8 wk	VSL#3 (3.6×10^{12} CFU) n = 71	Placebo n = 73	Mesalamine, Azathioprine, 6-MP	UCDAI > 50% decrease in 63.1% VSL#3 vs. 40.8% placebo ($P = 0.01$). Decreased UCDAI > 3 in 60.5% VSL#3 vs. 41.4% placebo ($P = 0.017$). NSD for remission and endoscopic scores
Miele et al[32]	DB, R, C 1 y	VSL#3 (4, 5-18×10^9 CFU) n = 14	Placebo n = 15	Mesalamine, Steroid-induction therapy	Remission induced by corticosteroids in 92.8% (VSL#3) vs. 36.4% (placebo) ($P < 0.001$). Lower endoscopic and histologic scores ($P < 0.05$)
Matthes et al[33]	DB, R, C 4-8 wk	EcN (1×10^8CFU/ mL) Group 1 = 40 mL n = 24 Group 2 = 20 mL n = 23 Group 3 = 10 mL n = 23	Placebo n = 20	Aminosalicylate Corticosteroisds Loperamide drops	Dose-dependent remission, resp.; 52.9%, 44.4%, 27.3%, 18.2% ($P = 0.0446$) Shorter time to remission in 40 mL and 20 mL vs. 10 mL and placebo
Ulcerative colitis					
Maintenance of remission					
Miele et al[32]	DB, R, C 1 y	VSL#3 (4, 5-18×10^9 CFU) n = 14	Placebo n = 15	Mesalamine, Corticosteroids	Relapse within 1 y in 21.4% (VSL#3) vs. 73.3% (Placebo) ($P = 0.014$) Lower endoscopic and histologic scores ($P < 0.05$)
Fujimori et al[34]	R, C 4 wk	*Bifidobacterium longum* (2×10^9 CFU) n = 40	Synbiotic N = 40 Prebiotic (psyllium 4 g) n = 40	Aminosalicylate prednisolone	NSD IBDQ compared with baseline for probiotics Improvement in IBDQ with symbiotic ($P = 0.04$)
Pouchitis					
Maintenance of remission					
Pronio et al[35]	O, R, C 12 mo	VSL#3 (3.9×10^{11} CFU) n = 18	No treatment (control) n = 13	None	Decreased PDAI (1.5 to 0.3) after 3,6, and 12 mo in patients on VSL#3 ($P < 0.01$) Increased T-reg. cells.

VSL#3: commercial mixture containing *Bifidobacterium longum, B. infantis, B. breve, Lactobacillus acidophilus, L. casei, L. delbrueckii subsp bulgaricus, L. plantarum, and Streptococcus salivarius subsp thermophilus*.

6-MP indicates 6-mercaptopurine; C, controlled; CFU, colony forming units; DB, double-blind; EcN, E. Coli Nissle 1917; IBDQ, inflammatory bowel disease questionnaires; NSD, no significant difference; O, open label; PDAI, pouchitis disease activity index; R, randomized, UCDAI: ulcerative colitis disease activity index.

The effects of *Bifidobacterium Longum* on the quality of life was investigated by Fujimori et al[34] by assessing inflammatory bowel disease questionnaire (IBDQ) scores from 120 randomly assigned patients with UC who were in remission or had only mildly active UC. These patients were randomly assigned to either probiotics (2×10^9CFU of *Bifidobacterium Longum*), prebiotics (8 g psyllium), or their combination, also called synbiotics.[34] After 4 weeks, there was no improvement in IBDQ scores in the prebiotic or probiotic group. However, there was a significant improvement in the synbiotic group. The authors also reported that hemoglobin and hematocrit increased overtime ($P = 0.04$) in the probiotic group, C-reactive protein decreased in the synbiotic group, and that no such changes were found using prebiotics (Table 2).

Pouchitis

Induction of Remission

Between 2007 and 2010 no RCTs were found in which probiotics induced remission in patients with chronic pouchitis.

Maintenance of Remission

In 2008, a randomized controlled study by Pronio et al[35] reported that VSL#3, administered at various times after ileal pouch anal anastomosis, reduced the Pouchitis Disease Activity Score slightly but significantly in patients without acute pouchitis (n = 18) compared with the placebo arm (n = 13). This beneficial effect was accompanied by an expansion of regulatory T lymphocytes in the pouch.

CONCLUSIONS

Over the past 3 years we have seen a more robust efficacy of probiotics, such as VSL#3, to induce remission in mild-to-moderately active UC by virtue of well designed and adequately powered clinical trials in patients who failed standard treatment. The efficacy of probiotics as an adjunct therapy for patients who fail standard therapy and who otherwise have to step up to steroids and/or immunosuppressives is an important contribution to the clinical field. It is even more important that this beneficial effect was also reported in children with UC, a group in which we would like to avoid the use of steroids that could lead to further growth retardation.

The rational to use probiotics is supported by research demonstrating the involvement of microbiota and their influence on the host response in both rodent IBD models and in human IBD. It is interesting to note that probiotics are beneficial for UC and pouchitis after colectomy for UC, strengthened with level B recommendation for the use of *E. coli Nissle 1917* in maintenance of remission in UC, and level A recommendation for VSL#3 in the maintenance of remission in pouchitis and induction of remission in UC, but that probiotics fail to treat or prevent CD. This confirms our suspicion that the pathogenesis of UC and CD, especially the role of microbes-host interaction, is different between these 2 disease entities.

Despite the positive reports regarding probiotics and UC, many studies regarding probiotics in IBD should be interpreted cautiously due to methodologic limitations. Similar to our conclusions 3 years ago,[36] many studies are still confounded by small cohort populations, different probiotic doses, variation in treatment duration, range of probiotic strains or combinations thereof, and the inconsistent use of conventional adjuvant medicines. Moreover, some studies often lack appropriate randomization, blinding, and control groups.

Long-term maintenance studies using probiotics are still lacking. As a result, the effectiveness of prolonged probiotic use and potential adverse events over an extended period of time still remains unknown.

The clinician has a responsibility to communicate the use of probiotic treatment to patients with IBD as a potential treatment option, especially for UC.[37] Many patients with IBD do not disclose probiotic usage to their clinicians either voluntarily, or in response to a direct question.[38–40] Indeed, a German survey indicated that 43% of patients with IBD consumed probiotic treatments on a regular basis.[37] This situation is not restricted to adult or adolescent patients with IBD, as a large proportion of patients are provided with probiotics by their fellow patients.[38–40] However, patients with IBD should be informed that for some indications, such as CD, the improvements may be marginal and that probiotic treatment does not replace standard medicines. By providing sufficient information on their use and efficacy, the patient is less prone to be confused by online information, "patient testimonies," and the "media hype" that may be misleading or false.

Future studies to investigate probiotics regarding their clinical efficacy in IBD, and studies on the pathogenesis of IBD and bacterial species in the gut biome, will provide necessary information and help develop more effective and rational probiotic therapies in the quest to find a cure for IBD.

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