



Technical Report

An Emerging Trend of High Dose Probiotic Use in Clinical Practice

A brief survey

October 2011

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The use of probiotics as bio-therapeutic agents is commonplace in the US and around much of the world. These probiotics are typically delivered in relatively low-dose functional foods (primarily yogurts) providing up to a few billion colony forming units (CFU); or in modest doses, in the form of dietary supplements of 5-25 billion CFU. Over the past several years, a trend has emerged in which much higher doses of probiotics are being used in both clinical practice and research.

Not surprisingly, the initial focus of the clinical research on high-dose probiotics has been on functional GI disorders such as inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and antibiotic-associated diarrhea (AAD). These conditions represent extreme examples of dysbiosis and dysfunction within the mucosal immune system of the gut; a system which is integrally associated with the microflora of the gut lumen. Although supplemental probiotics are only temporary members of the intestinal microbiota (perhaps 1-2 weeks), the introduction of large quantities of probiotics may sufficiently alter this environment allowing the probiotic to act as a potent bio-therapeutic agent in a manner that a lower dose would not. This short paper will explore this trend, discussing the limited, but positive, clinical trials on high-dose probiotics as well as potential mechanisms that explain the increasing potential benefits of this bio-therapeutic strategy

Inflammatory Bowel Disease

Probiotic use in patients suffering from inflammatory bowel disease (IBD) is now quite common, with numerous published clinical trials.¹ In particular, studies have shown that probiotic intervention has helped decrease immunological disturbances, modify disease activity, and assist in the normalization of increased intestinal permeability.

A commercial probiotic preparation (containing 3 strains of *Bifidobacteria*, 4 strains of *Lactobacilli*, and 1 strain of *Streptococcus salivarius* ssp.) used in many of these studies has shown benefit in patients with ulcerative colitis (UC). In one open-label pilot study, 20 patients in remission with UC were evaluated using very high doses of this preparation (3 trillion CFU/day). At the end of the study (12 months), 15 of 20 patients (75%) remained in remission. The authors of this study concluded that, "this probiotic preparation may be useful in maintaining the remission in UC patients intolerant or allergic to 5-ASA."² Another open-label study conducted by Bibiloni et al. involved testing this preparation (3.6 trillion CFU/day) on thirty-four patients with active mild-to-moderate UC who had not responded to conventional therapy. Over a six-week period, these patients experienced a combined remission/response rate of 77% with no adverse events.³ A longer 8-week randomized, multicenter trial with the same probiotic preparation was administered with balsalazide (a prodrug of mesalazine). This combination was found to be more effective in inducing remission of active UC than either mesalazine or standard-dose balsalazide. Patients with newly diagnosed (or recently relapsed) mild to moderate UC were randomized to receive balsalazide 2.25g/day in combination with this probiotic preparation (3g daily as 1g bags containing 300 billion bacteria per gram), balsalazide (4.5g/d), or mesalazine (2.4 g/day) for 8 weeks. A significant number of patients who received the probiotic preparation plus balsalazide (compared to those who received mesalazine or balsalazide alone) achieved remission.⁴ A larger double-blind, placebo-controlled study involving 144 patients found that supplementation of this preparation (3.6 trillion CFU/d) for 8 weeks was safe and able to reduce Ulcerative Colitis Disease Activity Index (UCDAI) scores and rectal bleeding in patients with relapsing mild to moderate UC.⁵ Some patients enrolled in the study were concomitantly administered mesalamine or an immunomodulator.

In the study, forty-one of the 71 patients (57.7%) in the active group met the primary end point of a 50% reduction in UCDAI at 8 weeks, compared to 29 of 73 (39.7%) in the placebo group. This analysis was repeated with exclusion of those on immunomodulators, with similar, significant results. For the secondary end points of a decrease of ≥ 3 points on the UCDAI scale and reduction in rectal bleeding, the active group had significantly higher rates compared with the placebo group. No significant differences were noted with regards to induction of remission, reduction of stool frequency, mean endoscopic scores, or physician rating of disease activity.

Table 1. Summary of high dose probiotics in ulcerative colitis

Type of Study	Author(s)	Duration	Treatment	No. of patients	Remission; No. of patients (%)	Response; No. of patients (%)	Relapse/No response; No. of patients	Worsening of disease activity; No. of patients	Lost to follow-up; No. of patients
UC in remission	Venturi et al.	12 mos	Probiotic blend (3 trillion CFU/d)	20	15 (75)	-	4 (20)	-	1 (5)
Active mild to moderate UC	Bibiloni et al.	6 wk	Probiotic blend (3.6 trillion CFU/d)	34	18 (53)	8 (24)	3 (9)	3 (9)	2 (5)
Active mild to moderate UC	Tursi et al.	8 wk	Balsalazide (2.25g/d) + probiotic blend (900 billion CFU/d)	30	24 (80)	-	-	-	-
			Balsalazide (4.5g/d)	30	21 (70)	-	-	-	-
			Mesalazine (2.4g/d)	30	16 (53)	-	-	-	-
Active mild to moderate UC	Tursi et al.	8 wk	Probiotic blend (3.6 trillion CFU/d)	144	57 (43.7)	-	-	-	13

Pouchitis

In addition to benefits seen with high-dose probiotics for UC, several trials have also shown positive benefits with this preparation for patients suffering from pouchitis. A study by Gionchetti et al. recruited 23 patients with mild pouchitis, all treated with this preparation (3.6 trillion CFU/day) for 4 weeks.⁶ Symptomatic, endoscopic, and histological evaluations were undertaken before and after treatment. Patients who were in remission after the initial treatment received a dose of 1.8 trillion CFU/day as maintenance treatment for six months. At the conclusion of the study, it was found that 16 patients (69%) were in remission after treatment. The median total Pouchitis Disease Activity Index and Inflammatory Bowel Disease Questionnaire scores significantly improved after treatment. All 16 patients who went into remission maintained remission during maintenance treatment.

Another study by the same group looked at the prevention of pouchitis in 40 patients between the ages of 18-65. These patients all underwent protective ileostomy closure after IPAA (ileal pouch-anal anastomosis) for UC. Patients received the probiotic preparation (900 billion CFU; administered every night) or placebo for 12 months with treatment initiated within a week of ileostomy closure. After 12 months, significantly fewer patients who received the probiotic preparation had developed pouchitis than those receiving placebo. Two of the 20 patients (10%) treated with probiotics had an episode of acute pouchitis, compared with 8 of the 20 patients (40%) treated with placebo. Patients who were treated with probiotics also experienced a significant improvement in the IBD Questionnaire score, which was not the case with placebo.⁷ The table below summarizes the studies, outcomes and doses of these published studies.

Table 2. Summary of high dose probiotics in pouchitis

Type of Study	Author(s)	Duration	Treatment	No. of patients	Development of active pouchitis or relapse; No. of patients (%)	Response to treatment or remission; No. of patients (%)
Mild pouchitis	Gionchetti et al.	4 wk	Probiotic blend (3.6 trillion CFU/d)	23	7 (31)	16 (69)
Prevention of pouchitis	Gionchetti et al.	12 mos	Probiotic blend (900 billion CFU/d)	20	2 (10)	18 (90)
			Placebo	20	8 (40)	12 (60)

IBS

A probiotic preparation containing 3 strains of *Bifidobacteria*, 4 strains of *Lactobacilli*, and 1 strain of *Streptococcus* (*S. salivarius* subspecies *thermophilus*) has also shown benefit in alleviating symptoms in IBS patients. In one ten-week study involving 25 patients, treatment with this preparation (450 billion CFU/day) showed a reduction in abdominal bloating scores in patients with IBS-D.⁸ A consequent trial (double-blind, placebo controlled study) was conducted by the same investigators. They found that after administration of the probiotic preparation for 4 weeks and 8 weeks (at the same dose), IBS patients had reduced flatulence scores and delayed colonic transit time.⁹ Another trial tested the efficacy of this probiotic combination in children (ages 4 to 18) with IBS for 6 weeks. The researchers found that the probiotic preparation was significantly associated with improvements in IBS symptoms (abdominal pain/discomfort, abdominal bloating/flatulence, and family assessment of life disruption).¹⁰

Table 3. Summary of high dose probiotics in IBS

Type of Study	Author(s)	Duration	Treatment	No. of patients	Significant findings
IBS (with predominant diarrhea)	Kim et al.	10 wk	Probiotic blend (450 billion CFU/day)	25	Reduction in abdominal bloating
IBS (with significant bloating)	Kim et al.	4 wk 8 wk	Probiotic blend (450 billion CFU/day)	31 17	Reduction of flatulence and delayed colonic transit time
Children with IBS	Guandalini et al.	6 wk	Children 4-11 y/o: Probiotic blend (450 billion CFU/day) Children 12-18 y/o: Probiotic blend (450 billion CFU/day)	59	Reduction in abdominal pain/discomfort, abdominal bloating/flatulence, and family assessment of life disruption

Diarrhea

It is well known that antibiotic therapy can severely disrupt the gut microbial ecology. Taking a probiotic during antibiotic therapy can often help preserve beneficial flora and improve stool consistency and frequency. A few controlled studies and several reports have shown high dose probiotics to be efficacious in the management of diarrhea. Basu et al, in one trial involving *Lactobacillus rhamnosus strain GG*,¹¹ found benefit in children who had acute, watery diarrhea. The investigators randomized 559 children into 3 groups. Those in group A (control) received an oral rehydration solution (ORS), group B received ORS and *Lactobacillus* powder (100 billion CFU), and group C received ORS and *Lactobacillus* powder (10 trillion CFU). During the duration of the study, none of the children received antibiotics or anti-diarrheal medication. The frequency and duration of diarrhea, requirement for IV therapy, and hospital stay were significantly lower in both the intervention groups compared with controls. No significant difference was found between the 2 intervention groups. In another double-blind, placebo-controlled randomized study involving 230 children, preliminary results found that use of a high-dose probiotic blend for 4 days resulted in earlier recovery and reduced frequency of oral rehydration administration, reflecting decreased stool volume loss during diarrhea.¹²

Table 4. Summary of high dose probiotics in diarrhea

Type of Study	Author(s)	Duration	Treatment	Total no. of patients	Significant findings
Acute, watery diarrhea in hospitalized children	Basu et al.	Minimum period of 7 days, or until the cessation of diarrhea	Oral rehydration solution (ORS) ORS+probiotic blend (100 billion CFU) ORS+probiotic blend (10 trillion CFU)	559	Significantly reduced frequency and duration of diarrhea, requirement for IV therapy, and hospital stay (equal in both groups receiving ORS + probiotic)
Rotavirus diarrhea	Dubey et al.	4d	Probiotic blend	230	Decreased stool volume loss during diarrhea

Proposed mechanisms of high-dose probiotic therapy

Numerous mechanisms are attributed to a wide dose range of probiotic therapies which mirror the mechanisms of beneficial commensal organisms.^{13,14} A major focus of this research is the interaction between bacterial organisms in the gut and specific cells within the gut associated lymphoid tissue (GALT), especially the dendritic cells which act as specialized antigen-presenting cells within the gastric mucosa. These dendritic cells are critical for both the maturation and tolerance of the immune system. A recent study suggest that by increasing the number of probiotic organisms interacting with the dendritic cells (this study used *Lactobacillus rhamnosus*), a much different response might be elicited.¹⁵ When researchers increased the multiplicity of infection (MOI), or the number of *L. rhamnosus* plated with immature human dendritic cells by 100 fold they induced a sharp increase in gene expression of over 1700 different genes compared to dendritic cells in the presence of fewer bacteria. Most of the changes in gene expression were within genes that control immune and inflammatory signaling. This genomic effect is an exciting new line of research that is likely to lead to a greater understanding of how commensal and probiotic organisms help regulate immune function- and attenuate numerous conditions related to the gut. In this case, a 100-fold increase in bacterial concentration was able to trigger a much different response than a lower concentration; suggesting one mechanism by which high dose probiotic therapies may differ from similar strains at lower doses.

Other published studies have also examined the efficacy of *Lactobacillus casei* strain GG in the treatment of IBD. Malin et al. reported that among pediatric patients with Crohn's disease (Cr), consumption of *Lactobacillus* GG was associated with increased gut IgA levels, which can promote the gut immunological barrier.¹⁶ Furthermore, Gupta et al. reported a similar finding in an open-label pilot study among a small number of pediatric Cr patients. At the end of the study, these patients had improved clinical scores, as well as improved gut barrier function.¹⁷

Safety and tolerability of high-dose probiotic therapy

Overall, oral administration of high-dose probiotic formulas is well tolerated and proven to be safe in most human clinical trials. Extremely rare cases of local or systemic infections have occurred with probiotic therapy, mainly in immune-compromised individuals.^{18,19,20} In

particular, septicemia and endocarditis were found to occur in immune-compromised patients with aplasia,²¹ HIV,^{22,23} and organ transplantation²⁴ who had been administered *Lactobacilli*. Further investigation revealed that in most of these cases, the source of the infection was the commensal *Lactobacillus* flora. It is safe to assume that most *Bifidobacteria* and *Lactobacilli* used in the food industry, as well as those reported in clinical trials, are safe for the general adult and pediatric populations.²⁵

Conclusion

While the available clinical research on high-dose probiotic therapy is rather recent, a trend is emerging in clinical practice to begin increasing probiotic doses, primarily for GI-related dysfunctions. More data is needed in order to discern whether specific GI disorders would be better supported using specific probiotic strains or combinations of strains (at different doses). Until such a time, doses of between 200 billion and several trillion CFU of products consisting of mixed probiotic strains should be considered safe for adjunct therapies for patients with IBD, IBS and AAD. This approach should be considered short term (4-8 weeks for functional bowel disorders or until symptoms cease for AAD), although cost may limit the utility of this therapy for some patients.

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