

ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Diseases

Section Editor: Stephen B. Hanauer, MD

The Role of Probiotics in IBD

Jeffrey Katz, MD
Associate Professor of Medicine
Case Western Reserve University
School of Medicine

G&H What is the rationale for probiotic therapy in inflammatory bowel disease?

JK There are several reasons why the use of probiotics is a logical therapeutic approach for inflammatory bowel disease (IBD). Evidence from animal models of IBD points to the critical role of the intestinal microflora in the development of chronic gut inflammation. When raised in a germ-free environment, these genetically manipulated animals do not develop intestinal inflammation, however, when they are raised in a normal microbial environment, inflammatory disease develops. Furthermore, in some of these models the risk and severity of the intestinal inflammation is determined by the genetic background of the experimental animal, as well as the specific bacterial exposure. A particular strain of bacterium in one species of mice might lead to severe inflammation, but a different bacterium may lead to no inflammation, and a third bacterium may result in only mild-to-moderate inflammation. Studies have also shown that certain probiotic bacteria can prevent or minimize intestinal inflammation in some animal models.

Clinical evidence also adds support for the use of probiotics in IBD. It is well known that diversion of the fecal stream in Crohn's disease typically leads to mucosal healing. However, once intestinal continuity is restored and fecal contents are reintroduced to the healed bowel, inflammation rapidly returns. It is also known that antibiotics can often be effective in the treatment of IBD. Finally, patients with IBD seem to have an abnormal immunologic reactivity to their own bacterial flora, while people without IBD remain tolerant of their flora, suggesting that some distortion of the interaction between the gut and gut bacteria contributes to the disease. These observations provide direct patient-based evidence

of the importance of intestinal microbiota in chronic gut inflammation.

Taking into account the evidence from these various areas, there is a strong rationale supporting the concept that bacteria are important in gut inflammation and that probiotic bacteria may modulate the host-microbe interaction in a way that is directly beneficial to patients.

G&H In what specific conditions might probiotics be effective?

JK The best data, thus far, are in pouchitis. Two placebo-controlled studies of patients with recurrent or refractory pouchitis utilizing the probiotic VSL#3 (VSL Pharmaceuticals) have been conducted. In both studies, patients were first brought into remission with antibiotic therapy, followed by 9–12 months of treatment with VSL#3. As long as patients were receiving the probiotic, their pouchitis remained in remission; however, once this therapy was stopped, patients relapsed. In addition, a small placebo-controlled study of VSL#3 and a case-controlled study of *Lactobacillus rhamnosus* GG showed a decrease in the development of pouchitis with the prophylactic use of probiotics. Finally, there are some small studies evaluating high-dose probiotics for the treatment of acute pouchitis. However, at the current time, probiotics appear to be more appropriate for preventing pouchitis onset or for maintaining remission, rather than for the treatment of acute, active disease.

G&H Have other studies provided evidence regarding the efficacy of probiotic therapy in maintaining remission?

JK Several large studies of the nonpathogenic *Escherichia coli* strain Nissle 1917 (Mutaflor, Ardeypharm) have shown that it is useful for maintaining remission in ulcerative colitis. Although the methodology of these studies has been criticized, they nonetheless add to the weight of evidence suggesting a beneficial effect of probiotic therapy.

There have been a number of small uncontrolled studies evaluating both *Saccharomyces boulardii* and VSL#3 for the maintenance of remission in patients with ulcerative colitis. There was also a recently published

uncontrolled trial of VSL#3 for the treatment of mild to moderate ulcerative colitis that reported remission in 53% and response in 24% of patients (*Am J Gastroenterol.* 2005;100:1539-1546). Although small, these studies suggest some benefit from these treatments and point toward the need for a larger placebo-controlled study.

G&H What studies have been conducted in the setting of Crohn's disease?

JK Unfortunately, there are thus far few data to support a role for probiotics in Crohn's disease. Small studies with around 30 patients suggest that a variety of probiotics, including lactobacilli, bifidobacteria, and *S. boulardii*, might be beneficial in maintaining remission, but there have been no placebo-controlled trials published yet. Some data have shown a protective effect of probiotics by delaying severe endoscopic recurrence after surgical resection for Crohn's disease, but other studies have not found this effect. Currently, there is no solid evidence supporting the efficacy of probiotics in the treatment of active Crohn's disease, and data are limited regarding their benefit in maintenance of remission.

G&H What do all of these studies indicate about the potential application of probiotics in IBD?

JK The scientific evidence supports the potential benefit of probiotics in IBD, but the clinical trials data remain weak. Until we have definitive data, probiotics are best considered adjunctive therapies in the treatment of most patients with IBD. Their safety and overall tolerance make them attractive to both patients and physicians, but they are best used in conjunction with other therapies.

It is important to realize that not all probiotics are equal. Although one probiotic may be useful in maintaining remission of pouchitis, one cannot assume that the same probiotic will be effective in ulcerative colitis or Crohn's disease.

G&H What are the potential mechanisms of action of probiotics in IBD?

JK There are a variety of hypothesized mechanisms of action supported by in vitro cell culture studies and in vivo studies. Probiotics have direct antimicrobial activity and effects on the barrier integrity of the gut. In addition, probiotics show immune activity, such as increasing secretory immunoglobulin A secretion, decreasing proinflammatory cytokines, inducing the upregulation of regulatory cytokines, and, possibly, an effect on dendritic cell modulation and T cell apoptosis. Interestingly, live probiotics may not be necessary to achieve these effects. Probiotic DNA has been shown to interact with Toll-like receptors and to play a role in the modulation of innate immunity.

G&H What are the next steps for the research of probiotics in IBD?

JK There are several areas that need to be investigated simultaneously. Whether in large or small clinical trials, we need to focus rigorously on better defining the mechanisms of action and the local gut effects of the various probiotics that have preliminarily shown efficacy in IBD. This requires careful study of the mechanism of action at the mucosal-luminal interface. We need to be certain that the administered probiotic is present in the gut and having some local effect, and we also need to understand the more complicated issues of pre- and post-therapy mucosal immune function, barrier function, and local antimicrobial effects.

It is critically important to perform well-designed randomized clinical trials to evaluate efficacy. A multicenter, randomized controlled Canadian study is evaluating VSL#3 in the postoperative maintenance of remission in Crohn's disease, and two large placebo-controlled studies of *Lactobacillus salivarius* and *Bifidobacterium infantis* in both ulcerative colitis and Crohn's disease are ongoing in the European Union. These studies will provide the sort of rigorous clinical trials data necessary to move the probiotic field forward.

Dose-ranging studies are also needed. It is not known, for example, if some of the potential benefits of these organisms might be related to dose. The optimal dosing of these products is not known and could range widely between different organisms and different populations of patients.

Comparison studies are needed as well. The probiotics industry is unregulated; neither the US Food and Drug Administration nor European regulatory bodies closely monitor the production of these products. It is not clear that all probiotics are equivalent, and some may not contain the levels of bacteria stated on the package, or the bacteria may not even be alive. Direct comparison of different probiotics is a logical next step.

G&H What specific probiotics appear to be most effective in IBD based on studies thus far?

JK Based on data currently available, the probiotics that appear to have the most potential in IBD include *L. rhamnosus GG*, *E. coli* Nissle 1917, *S. boulardii*, and VSL#3. There are some studies to support activity in IBD for each of these probiotics.

G&H What other potential applications of probiotics in IBD warrant further study?

JK Areas that warrant study include further evaluation of probiotics in pouchitis and mild-to-moderate ulcerative

colitis—comparing probiotics to antibiotics or comparing different probiotics for both treatment and maintenance of remission. In Crohn's disease, it is important to continue to study these agents for maintaining medical and postoperative remission. In addition, it is important to evaluate the potential cumulative beneficial effects of probiotics paired with other therapies, such as 5-aminosalicylates, corticosteroids, immunomodulators, and biologic agents. Finally, probiotics have been suggested as a means of decreasing colon cancer risk and should be evaluated in patients at high risk for IBD-related colonic neoplasia.

Suggested Reading

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