



Probiotics – Scope and Promise in Inflammatory Bowel Disease

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Crohn's disease and ulcerative colitis are inflammatory diseases of the alimentary tract. Both share some clinical, pathologic and epidemiologic features and are diverse in others. The etiology of both diseases is multifactorial. Genetics and environmental factors probably play a crucial role in their etiology, as well as in the interaction between them. Among the etiologic factors associated with Crohn's disease are smoking, measles and possibly food ingredients, e.g., *Saccharomyces cerevisiae* [1,2]. An association of *Listeria*, *Escherichia coli* and *Streptococcus* antigens with Crohn's disease has also been suggested [3]. Studies have searched extensively for an infectious agent as the cause of both diseases. There is indirect evidence that bacteria, including the normal intestinal flora, may contribute to the development of IBD, but no specific agent has been found [1]. Gaffer et al. [4] showed that the intestinal flora of patients with active CD is different from that of inactive CD, UC and normal controls. The gut flora of patients with active CD is rich in *E. coli* and depleted of bifidobacteria. CD patients have more aerobic bacteria than found in normal controls.

It is logical to assume that even if there is no specific agent causing IBD, an imbalance in the gut flora of these patients contributes to the disease state either by promoting its emergence or contributing to its activity. Another theory is that the disease is mediated by an abnormal response of the immune system to resident microbacteria of the gut. This is supported by the fact that antibiotics have been shown to alleviate disease symptoms in IBD [5] and are efficacious in treating postoperative pouchitis and fistulae [6,7]. Moreover, some animal models of IBD, such as the interleukin-10 knockout mouse [8], ultimately develop jejunitis and colitis unless they are kept in a sterile environment [9].

After performing a Medline search using the key words probiotics, inflammatory bowel disease, ulcerative colitis, and Crohn's disease, we summarize here the concept of probiotics as a means of treatment with special emphasis on their role in IBD.

The concept

The concept of probiotics relates to some bacteria as 'good' agents that help maintain health and treat disease. Several definitions have been suggested over the years. Parker [10] defined probiotics as "organisms and substances which contribute to intestinal microbial balance." This definition continued to evolve and has been broadened considerably. Schrezenmeir and de Verse [11] defined probiotic as "a preparation of or product containing viable, defined microorganisms in sufficient numbers, which alter the microflora by implantation or colonization in a compartment of the host and by that exert beneficial health effects in this host." This definition expresses the concept that viable microflorae are a prerequisite for an agent to be considered a probiotic, and that it has to affect the host in a positive manner so that the host's health is benefited. Most of the probiotic bacteria belong to a group of lactic acid-forming bacteria (e.g., lactobacilli) [12]. Other probiotic organisms include the yeast *Saccharomyces boulardii* or the gram-negative *E. coli* [13,14]. Dunne and colleagues [15] defined the following prerequisites for a bacterium to be able to serve as a probiotic.

- Human origin
- Non-pathogenic behavior
- Resistance to technologic process, i.e., viability in delivery vehicles
- Resistance to gastric acidity and bile acid toxicity
- Adhesion ability to target epithelial tissue
- Ability to persist within the gastrointestinal tract
- Production of antimicrobial substances
- Ability to modulate immune responses
- Ability to influence metabolic activities

The requirement for adhesion ability to target epithelium has been challenged, as some of the known probiotics seem to pass in the feces without having adhered or multiplied. For this reason the probiotic substance must be ingested continuously [16].

Proven clinical benefit

Lactose intolerance

Persons with lactose intolerance have a lower concentration of the brush-border enzyme lactase. Hypolactasia might cause symptoms such as diarrhea, flatulus and abdominal distension after the consumption of lactose-containing dairy products. Persons who

IBD = inflammatory bowel disease
CD = Crohn's disease
UC = ulcerative colitis

suffer from lactose intolerance experience better digestion and tolerance when consuming lactose in yogurt (which contains probiotics) than in milk [17].

Antibiotic-associated diarrhea

Diarrhea occurs in up to 20% of patients who receive antibiotic treatment. Adam et al. [18] showed that treatment with *Saccharomyces boulardii* lowered the risk of developing diarrhea in patients consuming antibiotics from 17.5 to 4.5%; while in the study by Surawicz and associates [19], treatment with *S. boulardii* lowered the symptoms from 21.8% in untreated patients to 9.5% in the group treated with the probiotic. Probiotics have also been used to treat *Clostridium difficile* colitis with partial success; most of the studies were performed in small numbers of patients experiencing recurrent *C. difficile* infection.

Viral enteritis

Numerous studies have shown *Lactobacillus rhamnosus* GG to be effective in the treatment of infant rotavirus diarrhea [20–22]. Overall, more than 200 infants were enrolled in these studies.

Traveler’s diarrhea

Studies assessing the role of probiotics in the treatment or prevention of traveler’s diarrhea have produced conflicting results. Some using lactobacilli showed no effect, whereas others showed a beneficial effect using *Lactobacillus* strains or *Saccharomyces boulardii* [12,23,24].

Probiotics and IBD

A great part of the etiology of inflammatory bowel disease is obscure. As outlined above, pathogenic bacteria, a pathologic response to the normal flora of the gut, or an imbalance within the gut flora may play a major role in the etiology and pathogenesis of IBD. Probiotics may act in one or more of the following ways: counteracting the inflammatory process by enhancing the degradation of enteral antigens, reducing the secretion of inflammatory mediators, and promoting the

exclusion of antigens in the gut by enhancing mucosal immunoglobulin A response to enteral antigens or even by normalizing the intestinal microflora composition or permeability [25–28] [Table 1]. Since its benefit has been proven in other inflammatory and infectious states of the bowel, there seems to be sufficient rationale to determine whether probiotics can be used in inflammatory bowel disease.

Three studies have shown a decrease in probiotic bacteria in either experimental colitis or IBD patients. Fabia et al. [29] showed this to be true in rats. Favier and co-workers [30] reported a decrease in bifidobacteria in feces of patients with CD, and Ruseler-van-Emden [31] found reduced fecal concentration of lactobacilli and bifidobacteria in patients with pouchitis.

To date, few studies have attempted to assess the role of probiotics in the treatment of IBD [Table 2]. Some used animal models and some used humans. Madsen et al. [32] conducted a study using IL-10 knockout mice. Ileum and colon from IL-10 knockout mice were scored histologically, cultured at various time points from the age of 2 to 16 weeks, and compared to wild-type mice. At 2 weeks of age, the IL-10 knockout mice showed no signs of colitis, but there was evidence of abnormal bacterial colonization and translocation as well as reduced level of *Lactobacillus* sp. at this time point. By the age of 4 weeks, the mice showed signs of colitis. No injury was found in the ileum. Treating the IL-10 knockout mice once daily with an enema containing *Lactobacillus reuteri* resulted in normal levels of lactobacilli adhering to the mucosa and attenuation of the colitis [32]. Mao et al. [33] demonstrated in rats with methotrexate-induced enterocolitis that administration of *Lactobacillus reuteri* R2LC and *L. plantarum* DSM 9843 was associated with

IL = interleukin

Table 1. Potential mechanisms of action of probiotics in IBD

Competitive colonization with harmful bacteria
Binding of bacterial toxins
Production of antibacterial compounds
Reinforcement of mucosal barrier
Promotion of recovery from infections
Promotion of immunologic memory and secretion of specific immunoglobulins
Increased quantity of short chain fatty acids in the colon

Table 2. Summary of the studies on probiotics and IBD

Type of study	No. of patients	Type of disease	Probiotic used	Results	Comments	Ref no.
Open	14	CD	<i>L. rhamnosus</i>	Increase in IgA secreting cells, no clinical benefit	Small number of patients, uncontrolled	34
Open	20	UC in remission	VSL #3	75% of patients maintained remission after 1 year	Open, small numbers	36
Randomized double-blind placebo-controlled	40	Chronic relapsing pouchitis	VSL #3	15% vs. 100% relapse rate in treated vs. placebo-treated patients	Well-designed study	35
Randomized double-blind mesalazine vs. probiotic	116	UC in remission	Non-pathogenic <i>E. coli</i>	Both drugs maintained similar remission rates at 1 year (70%)	Higher than expected remission rates in both groups	14
Double-blind double-dummy mesalazine vs. <i>E. coli</i>	120	UC in remission	Non-pathogenic <i>E. coli</i> (Nissle 1917)	No significant differences at 3 months	Well-designed study	37

low intestinal permeability, bacterial translocation, and plasma endotoxin concentrations compared with rats not treated with probiotics.

Several studies were also performed in IBD patients. In an open study, Malin and team [34] administered *L. rhamnosus* GG orally to 14 children with active or inactive CD. This resulted in an increase in IgA secreting cells to beta-lactoglobulin and casein, indicating that there is an interaction between the probiotic and the local immune system. The lactobacilli treatment did not influence disease activity, but the study group was too small and the study too short for assessing clinical effect. Gionchetti et al. [35] report the results of a study that explored the use of a new probiotic preparation. This preparation, numbered VSL#3, contains four strains of lactobacilli, three strains of bifidobacteria and one of *Streptococcus salivarius*. The preparation has a high bacterial concentration and a mixture of bacteria with potential synergistic activity. In this study the efficacy of VSL#3 was compared with placebo in the maintenance treatment of chronic relapsing pouchitis [35]. Forty patients were enrolled and received VSL#3 or an identical-appearing placebo. All placebo-treated patients relapsed, whereas 17 of the 20 patients treated with the probiotic complex VSL#3 retained their remission at the 9 month follow-up ($P < 0.001$) [35]. Ventury and colleagues [36] used VSL#3 to treat 20 patients with ulcerative colitis in remission who were intolerant or allergic to 5-ASA. The authors found that fecal concentration of *Salivarius* spp *thermophilus*, lactobacilli and *Bifidobacterium* increased significantly in the treated patients. Fifteen of the 20 treated patients remained in remission throughout the 12 month period of the study [36].

The effect of non-pathogenic *Escherichia coli* on the course of ulcerative colitis was studied by Rembacken et al. [14]. In a double-blind randomized study of 116 patients with active ulcerative colitis, all patients received standard therapy and oral gentamycin. After remission was achieved patients were maintained on either mesalazine or *E. coli*. After a follow-up of 12 months, approximately 70% of the patients in both groups maintained their remission (75% in the mesalazine group and 68% in the *E. coli* treated group). There was no significant difference between the two treatment groups. Kruis and co-workers [37] compared mesalazine and *E. coli* (Nissle 1917) treatment in UC patients who were in remission. After 3 months the authors found no significant difference in the relapse rate between the two groups of patients.

Side effects

With any therapeutic intervention one should always be aware of unwanted side effects. To date few, if any, side effects have been reported for probiotics. Theoretically some side effects could develop [38], but their relevance in clinical practice is unknown:

Treatment with probiotics is aimed at changing the bacterial balance within the intestine. Most of the probiotics are gram-positive bacteria. Theoretically, disequilibrium between gram-negative and gram-positive bacteria can result in D-lactic acidosis. D-lactic acidosis occurs in patients suffering from malabsorption

with an intact colon. In these patients, carbohydrates that reach the colon are processed by colonic bacteria possibly producing D-lactic acid and thus metabolic acidosis [39].

S. boulardii is used as a probiotic. A few cases of fungemia have been reported [40]. Some reports refer to HIV-infected patients and were presented at The Fifth European Conference on Clinical Aspects and Treatment of HIV Infection in Copenhagen in 1995. All patients reported with fungemia had intravenous lines, most of them central, suggesting that the infection might have been caused by an exogenous route. All patients received antimycotic treatment and recovered.

Limitations of studies

The studies summarized here assessed the role of various probiotics mainly on ulcerative colitis in remission, or on pouchitis. Most are small-scale, non-controlled studies that used different probiotics and are thus of limited value, though promising. What is needed are further large-scale controlled trials exploring the role of probiotics in these and other aspects of ulcerative colitis and Crohn's disease, i.e., active disease, maintenance of remission, etc.

Conclusions and future perspectives

Probiotics seem to have beneficial effects in some diarrheal and inflammatory conditions in the gastrointestinal tract, where there seems to be an imbalance between 'good' and 'bad' bacteria and/or an excessive immune response to an offender. Probiotics may be of benefit in the treatment of IBD, either as maintenance treatment or as part of the treatment of flare-ups. Until now, only a few small studies have been undertaken to define the role of probiotics in clinical practice, the results of which are encouraging. We believe that probiotics will prove to be an important addition to our arsenal of drugs for IBD, but this awaits additional large-scale studies.

Randomized clinical trials examining the effect of probiotics on mild to moderate ulcerative colitis and Crohn's disease should be carried out, as well as maintenance of remission studies in CD. The role of probiotics on postoperative maintenance of remission in Crohn's disease should also be investigated. Studies using various probiotics on transgenic mice (IL-10 knockout etc) will add to our understanding of the mechanism whereby probiotics exert their effects. There is still a long but promising way to go.

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Ig = immunoglobulin

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I find television very educational. Every time someone switches it on I go into another room and read a good book.

Groucho Marx (1895-1977), American comic actor and one of the famous Marx brothers