Probiotics in gastroenterology
Paolo Gionchetti, MD, Fernando Rizzello, MD, and Massimo Campieri, MD

Recent evidence has suggested the potential therapeutic role for probiotics in the prevention or treatment of gastrointestinal diseases. Several studies have shown that probiotics are of benefit in gastrointestinal infections, including viral diarrhea, *Clostridium difficile*–associated diarrhea, traveler’s diarrhea, and antibiotic-associated diarrhea. Recent data support the potential beneficial therapeutic effect in inflammatory bowel disease as well. Other possible indications for probiotic treatment include *Helicobacter pylori* infection, irritable bowel syndrome, and radiotherapy-associated diarrhea. It is important to select well-characterized preparations; in fact, the viability and survival of many available preparations are unproven. More precise information on the mechanisms by which probiotic strains exert their beneficial effects in vivo is needed. This may provide the scientific rationale for the selection of the best probiotic strains to use in the performance of large, double-blind, controlled clinical trials. Curr Opin Gastroenterol 2002, 18:235–239 © 2002 Lippincott Williams & Wilkins, Inc.

Probiotics are living microorganisms that determine important health effects if ingested in sufficient number [1]. Bacteria associated with probiotic activity are most commonly lactobacilli, bifidobacteria, and streptococci, but other nonpathogenic bacteria such as some strains of *Escherichia coli* and nonbacterial organisms such as the yeast *Saccharomyces boulardii* have been used.

For clinical application, probiotic strains must be both acid-resistant and bile-resistant, and they must have the ability to be metabolically active within the intestinal lumen, where, ideally, they should survive but not persist in the long term. These strains should be antagonistic against pathogenic bacteria. Obviously, they must be safe and tested for human use and should maintain their viability and other beneficial properties during the manufacturing processes.

Several mechanisms have been proposed to account for the action of probiotics. They include the following:

- Antagonistic activity against pathogenic bacteria either by inhibition of adherence and translocation or by production of antibacterial substances such as antimicrobial peptides and hydrogen peroxide.
- Stimulation of mucosal defense at the level of both immune and epithelial functions with increase of sIgA production, blockade of proinflammatory cytokines, enhancement of antinflammatory cytokine levels, stimulation of intestinal mucin expression, and improvement of gut permeability.
- Production of nutrients of special importance to the intestine, such as short-chain fatty acids and vitamins.

The most studied indications for the use of probiotics are in the treatment or prevention of gastrointestinal infections, including *Clostridium difficile*–induced diarrhea, viral enteritis, certain forms of bacterial enterocolitis, and nonspecific infections such as traveler’s diarrhea.

The best established benefit of using probiotics has been in the management of acute pediatric diarrheal disease. Several studies have shown that probiotic treatment can shorten the duration and reduce the severity of viral diarrhea in children [2–5]. Probiotics have also been reported to be effective in the prevention of acute viral diarrhea [6–10]. The occurrence of *C. difficile*–associated diarrhea may also be reduced by treatment with probi-
otics; in particular, *Lactobacillus GG* and *S. boulardii* were shown to reduce the risk of recurrence of the infection [11–14]. Several studies have investigated the efficacy of taking prophylactic probiotics together with antibiotics in preventing antibiotic-associated diarrhea. *L. GG* was shown to reduce the incidence of diarrhea in children in two placebo-controlled studies [15,16] and while *S. boulardii* was effective in the prevention of antibiotic-associated diarrhea in adults [17,18].

The incidence of traveler’s diarrhea varies between 20 and 50%. Although the results of studies may suggest a protective effect of probiotics, the different probiotics preparations used, the lack of etiologic documentation in many studies, and the variability of incidence in the different geographic areas make it difficult to draw definitive conclusions [19]. The effects of probiotics in gastrointestinal infections have been reviewed recently by Vanderhoof and Young [20•].

The rationale for using probiotics in inflammatory bowel diseases (IBD) is based on convincing evidence implicating intestinal bacteria in their pathogenesis. The distal ileum and the colon are the areas with the highest bacterial concentrations and represent the sites of inflammation in IBD; similarly, pouchitis appears to be associated with bacterial overgrowth and dysbiosis. There is evidence of a loss of immunologic tolerance to the enteric flora in IBD [21]. Decreasing bacterial concentration with antibiotics or fecal stream diversion decreases activity in Crohn disease [22,23]. Patients with pouchitis may also be effectively treated with antibiotics [24]. In addition, the ability of luminal contents, presumably dominated by bacteria, to trigger postoperative recurrence of Crohn disease in the neoterminal ileum within a few days has recently been demonstrated [25]. However, the most compelling evidence is derived from animal models. Despite great diversity in genetic defects and immunopathology, a consistent feature of many transgenic and knockout mutant murine models of colitis is dependence on the presence of normal enteric flora for full expression of inflammation [26]. All of these observations suggest that IBD can be prevented or treated by manipulation of the intestinal microflora, and increasing evidence supports the potential therapeutic role of probiotics in IBD [27].

Encouraging results have been obtained with probiotic therapy in experimental colitis. The administration of *L. reuteri* was shown to considerably reduce inflammation in acetic acid–induced and methotrexate-induced colitis in rats [28,29]. The administration of *Lactobacillus* species was shown to prevent the development of spontaneous colitis in interleukin (IL)-10 knockout mice [30], and continuous feeding with *L. plantarum* attenuated the severity of inflammation in the same model of colitis [31].

Very recently, Madsen et al. [32•] reported that treatment with VSL-3, a highly concentrated probiotic preparation containing eight different bacterial strains, brought about significant improvement of inflammation together with a reduction in mucosal levels of proinflammatory cytokines (tumor necrosis factor-α and interferon-γ) and a normalization of colonic physiologic function and barrier integrity in IL-10 knockout mice.

A nonpathogenic strain of *E. coli* (Nissle 1917) has been found to exhibit efficacy similar to that of mesalamine in the maintenance treatment of ulcerative colitis [33–35]. An open-label pilot study has recently suggested that *L. GG* may improve gut barrier function and clinical status in children with mild to moderately active Crohn disease [56]. Gionchetti et al. [37••] have tested a probiotic preparation (VSL#3) characterized by a very high bacterial concentration (300,000,000,000 live microorganisms/g) and a cocktail of eight different bacterial species (four lactobacilli, three bifidobacteria, and one *Streptococcus* species). Forty patients with chronic pouchitis who went into remission after 1 month of antibiotic treatment with ciprofloxacin (1 g/d) plus rifaximin (2 g/d), were randomly selected to receive VSL#3, 6 g/day, or placebo for 9 months in a double-blind trial. Patients were assessed clinically every month and assessed endoscopically and histologically every 2 months; fecal samples were also collected for stool culture every month. Relapse was defined as an increase of at least two points in the Pouchitis Disease Activity Index and was confirmed by endoscopic and histologic examination. Microbiologic determination showed a notable increase in the concentrations of lactobacilli, bifidobacteria, and *Streptococcus thermophilus*, which was already evident by 1 month and persisted through the treatment period; a return to basal levels was observed within 15 days after the end of treatment with no modification of fecal concentrations of *Bacteroides* species, enterococci, coliforms, clostridia, and total anaerobes and aerobes. All 20 patients treated with placebo had a relapse during the follow-up period. By contrast, 17 of the 20 patients treated with VSL#3 were still in remission after 9 months, and all 17 patients had a relapse within 4 months after suspension of the treatment. Prolonged treatment of pouchitis with VSL#3 brought about a significant increase of tissue levels of IL-10; a significant decrease of tissue levels of proinflammatory cytokines tumor necrosis factor-α, interferon-γ, and IL-1; and a decrease in inducible nitric oxide synthase and matrix metalloproteinase activity [38•].

Shanahan [39•] and Marteau [40•] have recently discussed the potential therapeutic role of probiotics in IBD. Both researchers emphasize that the encouraging results obtained with probiotics in IBD should be confirmed in larger studies, and that a better understanding of intestinal flora composition and of the mechanisms of
action of probiotics is needed. Hamilton-Miller [41] recently reviewed the clinical trials of probiotics in the management of IBD and emphasized that questions remain about dosing, duration of treatment, and the selection of the most appropriate probiotic strains.

*L. salivarius* (WB1004) has recently been shown to be able to inhibit the *in vitro* attachment of *Helicobacter pylori* to gastric epithelial cell lines and the release of IL-8; moreover, *H. pylori* could not colonize the stomach of *L. salivarius*-infected gnotobiotic BALB/c mice, but it colonized in large numbers and caused active gastritis in germ-free mice. The administration of *L. salivarius* could eliminate colonization by *H. pylori*, which suggests that probiotics could be used to eradicate *H. pylori* [42]. Moreover, *L. acidophilus* strain LB spent-culture supernatant has been shown to dramatically decrease the viability of *H. pylori* both *in vitro* and *in vivo*, independently of pH and lactic acid level [43]. The effect of *L. acidophilus* La1 supernatant on *H. pylori* was then tested in a randomized, double-blind, controlled clinical trial, using a drinkable spent-culture supernatant. *H. pylori*-infected volunteers were treated for 2 weeks with La1 supernatant with either omeprazole 20 mg or with placebo. A marked decrease in $^{13}$C-urea breath test values was observed immediately after treatment with *La1* supernatant in all volunteers. In addition, persistent suppression of *H. pylori* was observed in the volunteers treated with *La1* supernatant alone [44]. The addition of an inactivated preparation of *L. acidophilus* was effective in improving the efficacy of standard anti-*H. pylori* therapy [45]. More recently, Sakamoto et al. [46] tested the efficacy of *L. gasseri* OLL2716 (LG21) in 51 *H. pylori* infected subjects. The volunteers were treated with yogurt containing LG21 daily for 8 weeks; the $^{13}$C-urea breath test and assays of serum pepsinogen revealed a significant improvement, suggesting the efficacy of LG21 both in suppressing *H. pylori* and in reducing gastric mucosal inflammation.

In a recent editorial, Michetti [47•] emphasized that antibiotic-based triple therapy would be not cost effective and would lead to widespread antibiotic resistance. For these reasons, the probiotic approach may represent a suitable alternative, at least playing an adjuvant role in the treatment of *H. pylori* infection.

**Other indications for probiotics**

Some data suggest the presence of altered gut flora in irritable bowel syndrome (IBS). Coliforms, lactobacilli, and bifidobacteria have been reported to be decreased in the feces of patients with IBS [48], and another study has shown an increase in anaerobes, *Bacteroides* species, and *E. coli* in colon biopsy specimens [49]. More recently, patients with IBS were shown to produce more colonic gas as a result of abnormal bacterial fermentation of foods [50]. These observations have suggested the possibility that patients with IBS may be treated with probiotics in an attempt to restore the altered gut flora. Halpern et al. [51] reported a significant improvement in IBS symptoms in a double-blind, placebo-controlled trial, using a strain of *L. acidophilus* in 50% of patients. More recently, *L. GG* was not superior to placebo in improving symptoms in a subgroup of patients with IBS and bloating [52], whereas in a double-blind trial, a symbiotic preparation containing fructo-oligosaccharides plus a bacterial mix of *S. thermophilus* and *L. acidophilus* was effective in reducing symptoms in patients with diarrhea-predominant IBS [53]. Given that IBS is a complex syndrome, further studies are needed to identify particular subgroups of patients with IBS who can benefit from treatment with probiotics.

Diarrhea frequently occurs after radiotherapy for malignancies in the abdomen and pelvis. In a double-blind trial, the effect of *L. rhamnosus* was compared with that of placebo in a group of patients with mild to moderate diarrhea induced by radiation therapy. At the end of the study, there was a favorable risk/benefit ratio in favor of probiotic treatment [54].

**Conclusions**

Probiotics may provide a simple and attractive way to treat gastrointestinal disease; patients find the probiotic concept appealing because it is a natural, safe, and non-toxic therapeutic approach. It is important, however, to select a well-characterized probiotic preparation; in fact, the viability and survival of many available preparations have not been demonstrated. It should be also remembered that the efficacy of one preparation does not imply efficacy of other probiotics containing different strains, because each strain possesses very specialized functions. Further larger controlled studies are needed to establish the therapeutic effect of probiotics in gastrointestinal disease. Future research on probiotic bacteria needs to be focused on a better understanding of the composition of enteric flora, of the neglected organ, and of intestinal physiology and its relation with the luminal ecosystem. This information will allow the therapeutic potential of probiotics to be fulfilled.

**References and recommended reading**

Papers of particular interest, published within the annual period of review, have been highlighted as:

* Of special interest
** Of outstanding interest


