Invited Review

Probiotics: A Practical Review of Their Role in Specific Clinical Scenarios

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ABSTRACT: The use of probiotics (live viable microbial organisms) in the treatment of specific diseases has evolved into an extremely valuable option yet to be optimally used in clinical medicine. Probiotics have been shown to have immunomodulating properties and enhance the mucosal barrier. This review will briefly discuss the use of probiotics in inflammatory bowel disease, pancreatitis, liver transplantation, and various uses in diarrhea. When using probiotics, one must be cautious of the sometime overzealous claims that are commonly made when dealing with medical foods. As we begin to appreciate the degree of complexity that our indigenous microbial population has on health, it is only then that we can begin to understand the importance in disease. In the arena of probiotics, numerous fundamental questions remain unanswered.

There has been an exponential expansion in the quantity and quality of research and publications in the last several years involving use of probiotics in clinical medicine. A probiotic is defined as one of a vast group of microorganisms that constitute normal human gastrointestinal flora; they are viable in the gastrointestinal lumen, are acid- and bile-stable, adhere to the mucosa, and are safe. To meet the definition of probiotics, they also must have some clinically demonstrated benefit.[1] Numerous mechanisms of the proposed clinical benefits have been theorized. These range from prevention of clonal expansion of pathogens to enhancing mucous synthesis and secretion. The majority of the probiotics in use today are among the *Lactobacillus* group; however, other commonly used and studied probiotics include the bifidobacteria and the saccharomyces yeasts, particularly *Saccharomyces boulardii*.[2] As this paper will discuss, these organisms can be administered in varying media, mixtures, and dosages.

Current clinical and animal research is providing clinicians with an ever-increasing bank of evidence to suggest the crucial role of the gastrointestinal system as a vital immune organ. It is known that approximately 70% of immune function is derived from the gut, being composed of the mucosal barrier, the submucosal glands, and the mucosa-associated lymphoid tissue.[3] In addition, it is suggested that 80% of the immunoglobulin-producing cells are found within the gut and its associated lymphoid tissue, with a significant portion of the body's secretory immunoglobulin A being produced therein.[4] The immune benefits of enteral nutrition when compared with parenteral is now well accepted. In excess of 48 well-done prospective trials have compared enteral and parenteral feeding, with the general conclusion (in all but a few studies) that enteral feeding lowers infectious complications.[5,6] It is evidence such as this that is leading many to realize the importance of maintaining and stimulating the integrity of the gastrointestinal tract in order to optimize the patient's immune function.

Clinical and basic science research is beginning to demonstrate immunomodulating and mucosal barrier protective benefits of diets enriched with probiotic agents. Over a decade ago, Roszkowski et al[7] reported in a murine model that administration of broad-spectrum antibiotics not only increases the susceptibility to resistant bacteria but that macrophage function is actually suppressed. They later demonstrated that macrophage function can be significantly restored by administration of certain microflora, including *Lactobacilli* spp and other live lactic acid bacteria.[8] Similar results were demonstrated more recently in a rat model by Kilcullen et al.[9] His group showed that administration of either live bacteria or their cell wall components had the

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0884-5336/05/2002-0262$03.00/0
Nutrition in Clinical Practice 20:262–270, April 2005

ability to stimulate macrophage function and recruitment. Others have demonstrated the ability of *Lactobacillus acidophilus* and *Bifidobacterium longus* to enhance phagocytic properties of macrophages.[10] It is also becoming apparent that specific nutrition supplements, in particular probiotics, have an ability to enhance the mucosal barrier. Mangell et al[11] reported in a rodent model that *Escherichia coli* administration at the mucosal level increased mucosal permeability to mannitol. However, this increased permeability to mannitol was abolished almost completely if the rats had been given free access to water enhanced with *L plantarum* 299V for 1 week before the permeability study.

Beyond the scope of this article, but equally important, is the subject of prebiotics. Prebiotics are nondigestible fibers that essentially act as metabolic substrate for the normal intestinal flora.[12] The prebiotics include pectins, starches, oligosaccharides, and β glucans, among other substances.[3] When given with probiotics, these fuels seem to enhance the efficacy of probiotic supplementation (see Bengmark[13]).

Armed with an ever-increasing knowledge of the potential benefits of probiotic supplementation, researchers and clinicians are now beginning to elucidate specific clinical uses of these adjuncts to more traditional treatments. There is a growing body of data to suggest usefulness in medicine, pediatrics, and surgery and in both acute and chronic illnesses. In addition, there is evidence to suggest a role for these substances in the prevention of disease, including gastrointestinal cancers. Perhaps the most well-studied area of usefulness for probiotics is in the treatment of inflammatory bowel disease and related pouchitis. Additionally, data are available to support use of probiotics in the treatment of pancreatitis, chronic diarrhea and antibiotic-associated diarrhea, intraabdominal abscess and postoperative infection prevention, and in the treatment of liver transplant recipients. Most of the data for these indications are still representative of small trials or retrospective studies; however, there now exists a foundation for further studies and clinical applications. It is the intent of the remainder of this review to discuss these specific uses in individual detail and to summarize the best available data regarding these indications. It is beyond the scope of this review to include all the clinical arenas of potential use of probiotics.

Probiotics and Inflammatory Bowel Disease

Inflammatory bowel disease, ulcerative colitis, and Crohn's disease can difficult to treat, and in many cases, these disorders are quite disabling to those with this diagnosis. Unfortunately, the pathogenesis of these disorders is not well understood; therefore, advances in treatment have been slow to develop. Increasing evidence has implicated changes in the intestinal microflora in the pathogenesis of this disease.[14] Giaffer et al[15] demonstrated differences between the intestinal flora of patients with quiescent inflammatory bowel disease and those with active disease. If this is the case, then having the ability to restore a more "normal flora" may affect the disease process. One small double-blinded trial compared the use of *S boulardii*, along with conventional treatment, to conventional treatment alone in the management of active Crohn's disease. The trial included 20 patients who were assigned randomly to conventional treatment plus placebo for 7 weeks or to conventional treatment plus *Saccharomyces* supplementation for 7 weeks. In the group that received the *Saccharomyces*, the authors noted a significant reduction in the number of daily bowel movements during the study period.[16] In addition to treating active disease, there is reason to believe that the use of probiotic supplementation may play a role in maintaining remission of active disease. In a double-blind, randomized, controlled trial, Malchow[17] demonstrated an impressive and statistically significant reduction in relapse rates of Crohn's disease by treating with *E coli* Nissle 1917 *vs* placebo. Patients received approximately 5.0×10^{10} viable bacteria per day for 1 year. Recurrence rates were determined by Crohn's activity index. In a comparison of standard treatment with 5-ASA to treatment with 5-ASA plus *S boulardii* at a dose of 1 g daily, Guslandi et al[18] demonstrated superiority of the combined regimen over the standard regimen. Similarly, but in a slightly larger study, Campieri et al[19] were able to show that VSL #3 (VSL Pharmaceuticals, Inc, Newington, NH), a mixture of 8 strains of probiotic bacteria and prebiotic, when given after a course of rifaximin (an antibiotic with only luminal activity) was superior to rifaximin plus 5-ASA in the prevention of postoperative exacerbations. These studies clearly demonstrate some exciting potential for probiotics in treatment of acute disease and maintenance of disease-free state in individuals with inflammatory bowel disease. In addition, these studies suggest that there may be multiple probiotic regimens that are beneficial. It is imperative that research elucidate which regimen is most effective, most cost-efficient, and best tolerated. Indeed, several studies have shown no benefit of probiotics supplementation. One such study compared the use of *Lactobacillus* GG to placebo in the maintenance of Crohn's remission and showed no benefit, suggesting that all probiotic species are not equal in their ability to affect clinical processes[20] (Table 1). Several similar studies have been performed to evaluate the usefulness of probiotics with ulcerative colitis; however, the results of these studies (reviewed elsewhere) are mixed, and most failed to reach statistical significance.[2,21]

Although there are not yet significant data in the literature to support the routine addition of probiotics for maintaining remission of ulcerative colitis, there is evidence to suggest a role in treating long-term complications of this disease. Many patients

Table 1
Randomized controlled trials using probiotics to prevent recurrence of Crohn's disease

Author	Probiotic	Control	*N*	Duration, mo	Relapse probiotic/control, %	*p*
Malchow et al, 1997[16]	*E coli* Nissle 1917	Placebo	28	12	33/63	< .05
Guslandi et al, 2000[17]	*S boulardi* +5-ASA	5-ASA	32	6	6.3/37.5	< .05
Campieri et al, 2000[18]	VSL #3	5-ASA	40	12	20/40	< .05
Prantera et al, 2002[19]	LGG	5-ASA	45	12	60/35.3	.297

5-ASA, mesalamine; LGG, *Lactobacillus* GG.
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with a diagnosis of ulcerative colitis need proctocolectomy at a relatively early age. A common reconstruction associated with this operation is the ileal pouch–anal anastomosis (IPAA), which is an excellent option for this population, but it is not without a unique set of complications. Unfortunately, up to 10% of these patients have recurrent bouts of pouchitis. Pouchitis is described as "a non-specific, idiopathic inflammation of the ileal pouch," usually occurring within the first 2 years after creation of the pouch.[22] Symptoms include frequent loose stooling, hematochezia, tenesmus, fever, and stool incontinence. Like the underlying disease, the specific pathogenesis is not well understood. Traditional treatment of pouchitis has involved short courses of antibiotics, with moderate success. There are now several papers supporting a role for probiotics in managing this complication of the IPAA. Gionchetti et al[23] recently reported encouraging results of a randomized, double-blind, placebo-controlled trial that compared treatment with VSL #3 to placebo in 40 patients who had undergone closure of their diverting ileostomy after IPAA for ulcerative colitis. The treatment group received 1 packet of VSL #3 per day beginning 1 week postoperatively and lasting for a period of 12 months. VSL #3 is a mixture of prebiotics and probiotics and contained 900 billion bacteria in each sachet, made up of a mixture of 4 strains of *Lactobacillus*, 3 strains of *Bifidobacterium*, and a single strain of *Streptococcus*. In the placebo group, 40% of patients had an episode of pouchitis in the first 12 months after operation, whereas in the VSL #3 group, only 10% of patients experienced an episode of pouchitis. The degree of inflammation in the 2 patients in the latter group who developed pouchitis was less extensive than the inflammation observed in the placebo group. An additional benefit observed in the treatment group was a higher quality of life and lower stool frequency, as evidenced by higher Inflammatory Bowel Disease Questionnaire scores in this group. In an earlier study, these same authors documented excellent results with treatment of pouchitis with probiotics after inducing disease remission with antibiotics.[24] Of perhaps equal interest is the additional data that this study provided. The treatment group was found to have higher stool concentrations of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* during the treatment period and for approximately 1 month after cessation of treatment. The increase in stool frequency in these patients correlated to the decrease in concentration of these organisms. In addition, the concentrations of preexisting host flora, such as *Clostridium*, *Bacteroides*, coliforms, and *enterococci*, did not decrease, suggesting that the mechanisms of action involved more than simple suppression or competitive inhibition of these potentially pathogenic host flora. As evidenced by these studies, it is clear that probiotics seem to have a valuable role in the management of both inflammatory bowel disease and pouchitis after total colectomy. It is anticipated that probiotics will continue to provide useful alternatives to management of inflammatory bowel disease and its complications and that the developing understanding of their interaction with the disease process may help to elucidate the underlying pathogenesis of these disease entities.

Probiotics and Pancreatitis

Acute pancreatitis is a fairly common diagnosis treated by both primary care providers and surgeons. Fortunately, the clinical course of this disease is usually relatively benign and self-limited if prompt treatment is instituted. Perhaps the most important predictor of a lethal course of acute pancreatitis is the presence of pancreatic necrosis and, specifically, infected pancreatic necrosis. The exact mechanism by which the pancreatic tissue becomes infected, in the absence of instrumentation, is not entirely clear, but there has been recent literature to support the concept that the pancreas is seeded with bacteria by translocation from the gastrointestinal tract.[25–27] These luminal organisms traverse the vulnerable enteric mucosal barrier, are taken up into lymphoid tissue or engulfed by macrophages, and are transported to inflamed pancreatic tissue. Although this mechanism may not ever be definitively proven in humans, animal models consistently support this mechanism.[26,27] Enteric flora make up the vast majority of organisms isolated from infected pancreatic specimens. Additionally, as discussed earlier, acute stress conditions predispose the gastrointestinal mucosa to increased permeability and general loss of integrity of the gut mucosal

barrier. One study has shown that infected pancreatic necrosis is nearly always preceded by colonization of the patient's colon with non–*E coli* Gram-negative organisms.[28] It is known from abundant clinical experience that pancreatic necrosis becomes infected in approximately 25% of patients after 1 week and up to 75% of patients after 3 weeks.[29] Once pancreatic necrosis becomes infected, the mortality rate increases dramatically from 5%–19% for sterile pancreatic necrosis to up to 50% for infected pancreatic necrosis.[30] With the knowledge of the grim prognosis of infected pancreatitis necrosis, it is necessary that we devise treatment strategies to prevent the development of infected pancreatic necrosis and to curb its course once infection occurs.

Although early in its conception, the notion that probiotic organisms may play a pivotal role in the management of pancreatitis is gaining support in the literature. In a recent double-blind, randomized trial, Olah et al observed a statistically significant benefit with treatment that supplied *L plantarum* 299.[31] In this study, patients were randomized on admission to the hospital to receive either live *L plantarum* 299 plus an oat fiber or heat-inactivated *L plantarum* 299 with oat fiber. The supplements were administered *via* feeding tube twice daily for 1 week. After enrolling 45 patients, the study was terminated because the difference between the groups was so compelling. In the live-bacteria group, only 1 of 22 patients had developed infected pancreatic necrosis or a peripancreatic abscess. In contrast, of the 23 patients that received the heat-inactivated bacteria, 7 patients developed infection. The only patient in the treatment group to develop infection had evidence of a urinary tract infection that had developed 8 days after terminating the probiotic. These results suggest a possible role for supplementation with *L plantarum* 299 for patients with acute pancreatitis, and they also suggest that there may be a role for treatment longer than 7 days. To add support to this concept, Mangiante et al,[32] using a rodent model, demonstrated a marked decrease in translocation of enteric flora to mesenteric nodes and pancreatic tissue when probiotics were administered. Rats that were supplied with *L plantarum* before and after induction of pancreatitis had only 1 of 20 mesenteric nodes noted to contain enteric bacteria, whereas in the rats that were not supplied with the probiotic, 14 out of 20 nodes contained these bacteria. More important, 10 of these rats developed infected pancreatic tissue with the same organisms that were found in the mesenteric nodes. These results not only suggest a protective effect of the probiotic, they also support the theory of bacterial translocation in the pathogenesis of infected pancreatic necrosis. There are still no trials available in peer-reviewed literature investigating other probiotics in the management of pancreatitis, and it is not known what dose or treatment duration may be optimal, but it is likely that the success that this group had will initiate further work in this area.

Probiotics in Liver Transplantation

In the past 2 decades, patients with liver failure have seen new hope with the possibility of orthotopic liver transplantation. This procedure is a lifesaving procedure for many people, but, like any operation, it does not come without significant risks. Postoperative infections make up the majority of complications in this patient population, and studies have reported infection rates as high as 86%.[33] A recent study reported that surgical site infections increased mortality by 10% and hospital stay by an average of 24 days.[34] The impressive rate of infections noted in this severely immunocompromised host is no doubt related to the prolonged operative time, the mandatory immunosuppression, blood transfusions, and the derangement of normal gut function. In a recent prospective, randomized, double-blind trial, Rayes et al[35] reported significantly lower postoperative infection rates when patients received a probiotic mixture. In the study, 66 patients were randomized to receive immediate postoperative enteral feedings with either a probiotic mixture of 4 lactic acid bacilli plus 4 fibers or the mixture of fibers alone. The feeding began on the day before the operation and continued for 14 days. In the treatment group, the postoperative bacterial infection rate in the first 30 days was reduced dramatically to 3%. The group that received only the mixture of 4 fibers developed postoperative infections in 48% of cases. The majority of the infections were of enteric origin, being represented most commonly by *Enterococcus faecalis* and *E faecium*, further contributing to the idea that maintenance or restoration of a more normal gut flora may affect infection rates. None of the administered lactic acid bacteria were isolated in cultures of the infected patients. In addition, no statistically significant differences were seen in the rates of noninfectious complications between the 2 groups.

This study was a follow-up of a similar study by the same research group in which they compared treatment with lactic acid bacilli to selective digestive-tract decontamination.[36] In this study, 95 patients were randomized to the following groups:

1. selective digestive tract decontamination 4 times per day for 6 weeks (consisting of broad-spectrum antibiotic and antifungal agents);
2. administration of *L plantarum* 299 with 15 g of fiber for 12 days postoperatively; and
3. administration of heat-killed *L plantarum* 299 with 15 g of fiber for 12 days postoperatively.

The researchers found that the selective decontamination group had 23 infections (32 patients), the live *L plantarum* 299 group had 4 infections (31 patients), and the heat-killed *L plantarum* group had 17 infections (32 patients). In addition to the statistically significant reduced rate of infection in the probiotic group, these patients also required shorter intensive care unit stays, shorter hospital stays, and shorter lengths of time receiving antibi-

otics, although the data for these particular endpoints did not reach statistical significance. It is also interesting that, in the follow-up study that was referenced previously,[35] the researchers noted that nutrition parameters did not differ between the groups, disputing any suggestion that the improved infection rates were simply caused by better nutrition provided to the study patients.

If this study is supported by further significant studies, there exists significant potential for a vital role for probiotics in orthotopic hepatic transplantation. Although the studies are not available at this time, it is reasonable to extrapolate that there may be a similar role for probiotics in the transplantation of other organs, particularly other intraabdominal organs. In fact, there are already data to support improved clinical course in patients undergoing various intraabdominal operations unrelated to transplantation. Probiotics may indeed become a routine part of perioperative management.

Probiotics and Diarrhea

Chronic diarrhea is a problem faced by many patients, and it can be very difficult and frustrating to manage for both the patient and physician. This paper has discussed the role of probiotics in the management of inflammatory bowel disease, which often involves significant diarrhea, but many patients without this diagnosis had diarrhea. A multitude of studies are now targeted at the efficacy of probiotics in treatment of diarrhea. The following section will address the role of probiotics in antibiotic-associated diarrhea, acute infectious diarrhea, and chronic diarrhea.

Antibiotic-Associated Diarrhea

It is well known that even a single dose of antibiotics can predispose one to the development of diarrhea. The frequency of antibiotic-associated diarrhea can be staggering, affecting as many as 30% of patients. It is particularly alarming that, in the past decade, the frequency of antibiotic-associated diarrhea has skyrocketed by 500%.[37] The mechanism for this phenomenon seems to be related to an alteration in the normal intestinal flora brought about by excessive use of broad-spectrum antibiotics. The normal host flora provide protection against enteric pathogens by means of multiple mechanisms, including the production of bacteriocins, competitive inhibition of binding to mucosa, competition for nutrients, enhancing mucous synthesis and secretion, increasing secretion of secretory IgA, maintaining normal gastrointestinal motility, and inhibition of production of toxic metabolites.[38] Although numerous pathogenic bacteria can be responsible for the onset of antibiotic-associated diarrhea, the most common isolated pathogen is *Clostridium difficile*.[39]

The efficacy of probiotics in reducing the duration or incidence of antibiotic-associated diarrhea has been studied using several different agents. *Saccharomyces boulardii* has shown significant promise in several studies. MacFarland et al[40] randomized 124 patients with active *C difficile* colitis to receive *S boulardii* plus either vancomycin or metronidazole *vs* a placebo plus vancomycin or metronidazole. The study found improvement in patients with primary and recurrent *C difficile* colitis, but the most striking results were seen in those with recurrent infection. For those being treated for recurrent disease, the placebo group showed recurrence of their colitis in almost 65% of patients. In those treated with *S boulardii*, only approximately 35% of patients had recurrence of colitis. There have been subsequent studies that confirm such dramatic results.[41] Several small studies have also suggested, yet not at a statistically significant level, that *L rhamnosus* GG may have efficacy in the treatment of *C difficile* colitis.[42,43]

Saccharomyces boulardii has also been studied for treatment and prevention of antibiotic-associated diarrhea that is not related specifically to *C difficile* colitis. Surawicz et al[44] randomized 180 patients who had been given new prescriptions for antibiotics to receive either *S boulardii* in a dose of 1 g per day or a placebo for the duration of antibiotic usage and for 2 weeks after its completion. Only 9.5% of patients in the treatment group developed diarrhea, whereas almost 22% of patients in the placebo group developed diarrhea ($p < .038$). Not only does this study demonstrate efficacy in the prevention of diarrhea, it also provides important evidence that probiotics can be administered effectively during the period of antibiotic treatment. MacFarland et al[45] demonstrated similar results in 193 patients receiving β-lactam antibiotics.

Lactobacillus rhamnosus GG, another commonly used probiotic, has been extensively studied in the pediatric population. In 1 study, 119 children who were receiving treatment for respiratory infections were randomized to receive *L rhamnosus* GG or placebo for the duration of their antibiotic treatment.[46] The treatment group developed diarrhea in 5% compared with 16% in the placebo group. The results of this study were statistically significant and suggest a protective role of this particular probiotic.

Infectious Diarrhea

The rationale for probiotic use in infectious diarrhea has garnered support from numerous basic-science studies. Previously, the immunomodulatory effect of probiotics has been noted. This is particularly important with respect to the effect of probiotics on host defenses against infectious diarrhea. Improved mucosal barrier, immune cell function and IgA production, and neutralization of virulence factors all contribute to the potential benefits that probiotics have in cases of infectious diarrhea.

Human epithelial cell lines exposed to enteroinvasive *E coli* (EIEC) in the presence of *Streptococcus thermophilus* or *L acidophilus* "significantly limited adhesion, invasion, and physiologic dysfunction induced by EIEC." This defense was through maintenance or enhancement of the epithelial cytoskeleton, and tight junction phosphorylation.[47] *Lactobacillus plantarum* inhibits enteropathogenic *E coli* binding to epithelial cell lines in a similar manner.[48] Specific exometabolites of probiotics may work in direct opposition to bacterial products. For example, *Bifidobacterium bifidum* inhibits antilysozyme function in *Klebsiella* and *E coli* strains.[49] Serum immunoglobulin A anticholera toxin is increased in the colon of experimental mice when live *L acidophilus* and *Bifidobacterium* spp are present.[49]

Numerous studies have been performed in the pediatric population to evaluate new means by which to treat diarrhea. Diarrhea in children is unfortunately common and potentially life threatening. In this population, there exists a greater threat of severe dehydration and malnutrition than in the adult population. Probiotics, in addition to their apparent value in antibiotic-associated diarrhea, have shown significant promise in preventing and treating infectious diarrhea in the pediatric population.

Rotavirus has been the most extensively studied pathogen with respect to probiotic therapy and diarrhea in the pediatric population. A recent multicenter, double-blind, controlled study[50] compared the efficacy of a milk formula supplemented with viable *Bifidobacterium lactis* strain in the prevention of acute diarrhea in infants. The study revealed a reduced risk of contracting diarrhea by a factor of 1.9 in patients supplied with probiotic-fortified milk. This study, performed on outpatient children in day-care settings, suggests a role for prevention of infectious diarrhea, particularly in children. This becomes more important when the acute nature of most diarrhea is taken into account. The majority of diarrheal illnesses are self-limited, and their course is rapid. Many cases will have run their course before administration of probiotic therapy, emphasizing that prevention in at-risk populations may be the most effective role for probiotics in the future.[51]

Many studies have verified a decrease in severity and duration of rotavirus diarrhea in the pediatric population. In children 1 month to 3 years old who have contracted rotavirus diarrhea, administration of *L rhamnosus* GG was shown to reduce duration of the symptoms by approximately 20 hours compared with placebo ($p < .008$).[52] In another study, 130 children ages 3 months to 3 years were randomized to receive oral rehydration therapy, along with either *S boulardii* or placebo, in treatment of diarrhea of uncertain etiology.[53] By the fourth day of treatment, 85% of the children in the *S boulardii* group had recovered from their diarrhea, whereas only 40% of the children in the placebo group had recovered. Several other randomized, placebo-controlled trials have produced confirmatory data, but review of the entire literature in this area is beyond the scope of this brief review.

Although literature for the adult population is less developed than for children, similar results are beginning to bear out regarding the efficacy of probiotics in the treatment of infectious diarrhea. In a randomized, controlled pilot study by Turchet et al,[54] adult patients were given a 3-week supply of milk with ($n = 180$) and without ($n = 180$) *L casei* fortification during winter months. The incidence of pneumonia and gastrointestinal infection was not reduced over this time; however, a significant reduction in the duration and severity of illness was noted (7.4 ± 3.2 days *vs* 8.7 ± 3.7 days, $p = .024$). More studies are ongoing to assess the role of probiotics in prevention and treatment of infectious diarrhea. Case reports are numerous and show anecdotal benefit of probiotics in *E coli*, *Shigella*, cholera, *Entamoeba histolytica*, and cryptosporidium infections.[55,56]

Chronic Diarrhea

Many adults had chronic diarrhea without carrying a diagnosis of inflammatory bowel disease or other specific mucosa-based diseases. One such condition is characterized by chronic intestinal bacterial overgrowth. Small-bowel bacterial overgrowth may be associated with such underlying etiologies as chronic gastritis with achlorhydria, chronic hyposecretion of gastric acid secondary to gastric resection or acid suppression, surgically created blind loops, and partial bowel obstruction.[2] Traditional treatment of bacterial overgrowth has been with antibiotics, but this practice induces resistant flora and may also initiate an antibiotic-associated diarrhea. Newer data suggest that treatment with probiotics may have a role in treatment of chronic diarrhea related to bacterial overgrowth. There are 2 small nonblinded studies that suggest efficacy of lactic acid bacilli. In 1 study, 8 hemodialysis patients with small-bowel bacterial overgrowth were treated with *L acidophilus*.[57] After treatment, levels of 2 toxins, dimethylamine and nitrosodimethylamine, were significantly decreased from baseline. In contrast to this data, 2 small, blinded, placebo-controlled trials failed to show any advantage of *L fermentum* or *S boulardii* administration over placebo or antibiotic treatment.[58,59] All of these studies were very small and inadequate to resolve any definitive consensus on whether probiotics have a role in adults with chronic diarrhea that is related to small-bowel bacterial overgrowth. However, before dismissing the potential benefit, there is enough evidence to suggest that a larger randomized, controlled trial is necessary to provide guidance in this area.

Probiotics and Postoperative Infections

Postoperative intraabdominal abscess formation and other postoperative infections continue to occur

at a relatively constant rate over the last 30 years, despite the advances in bowel preparations and antibiotics. These postoperative infections are difficult to treat. Standard practices of infection prevention have included preoperative mechanical bowel preparations, antibiotics, and meticulous operative technique. However, the controversy continues on the issues of which antibiotics to use and how long they should be administered. Clearly, the trends in serious postoperative infections are to treat early, treat with broad-spectrum antibiotics, and use relatively high doses. When culture results then become available, adjust the antibiotic to specific bacterial populations. There is now evidence that prophylactic antibiotics may not be the only choice in prevention of infection and that, in fact, the administration of bacteria in the form of probiotic supplements may be a beneficial practice. There are limited, if any, data comparing probiotics with antibiotics in prophylaxis of perioperative infections, but there are early data evaluating efficacy of supplementation with probiotics. A German study has identified benefit with provision of lactic acid bacilli when compared with standard enteral nutrition alone in patients undergoing major intraabdominal operations.[60] Sixty patients were randomized to receive live *L plantarum* 299 with oat fiber or heat-killed *L plantarum* plus oat fiber. In addition, a third group of 30 patients received only standard enteral nutrition. The study found the rate of postoperative infections, particularly pneumonia, was significantly lower in the live-*Lactobacillus* group. Only 10% of patients who received either live or heat-killed *L plantarum* developed a postoperative infection, whereas 30% of the standard enteral nutrition group developed infections. The rate of non–infection-related complications was higher in the lactic acid bacilli groups, but the reason for this phenomenon is unclear. In another randomized, prospective trial, 129 patients were randomized to receive either PRO VIVA (Skane Dairy UK Ltd, Cevedone, UK), a premixed fruit drink that contains a relative low dosage of *L plantarum* 299V.[61] The test subjects were given the supplement for a minimum of 1 week preoperatively. Postoperatively, determinations of bacterial translocation, gastric colonization with enteric organisms, or septic complications were measured, and no significant differences were identified.

The discrepancies in the results of the 2 studies makes it clear that more research needs to be done in this arena to clarify the usefulness of such treatment and to elucidate any explanation for the increase in noninfectious complications seen in the first study. It is quite possible that the PRO VIVA study failed to show benefit because of its relatively low concentration of lactic acid bacilli (5×10^7), but one cannot be sure that other factors contributed. The varying results between these studies and the insignificant increase in noninfectious complications seen in the first study cited emphasize the need for more data guiding specific treatment with probiotics. It is obvious that the beneficial effects may, in fact, be dose related, and we know that not all probiotics species are equivalent. In addition to studies such as these, the data collected on liver transplantation patients, as discussed previously, would also suggest a prophylactic role for probiotics.

Discussion

The study of probiotics is an exciting and rapidly developing arena. The data presented in this review only scratch the surface of the subject and were meant to stimulate the reader to dig deeper into the literature and develop studies to help answer many of the yet-unanswered questions. For example, perhaps the most important question is that of which organism to use in each clinical situation. Adding to the lack of clarity in this regard is the fact that some probiotics have shown promise in certain conditions and not in others. Not only must we answer the question of which species or combination of species to use in each clinical scenario, it is also necessary to better define the necessary doses of these agents and the best vehicle for delivery.

If planning to prescribe any of the probiotic agents, a physician must also be aware of any potential hazards of the supplement. It is with great frustration that the authors observe companies marketing various supplements to the public as "natural" and, therefore, safe. As all health care providers know, some of the most hazardous medications that are prescribed are "natural" in origin. These probiotic supplements must be used with the same degree of caution with which one would use any other medication. Having stated this, we do have reasonable evidence that probiotics are safe in almost all setting in which they have been tested and, quite possibly, much safer than antibiotics. There are no reported cases of severe metabolic adverse events, such as hepatic or renal failure, as may often be observed with other pharmaceuticals. However, there have been several reports of systemic infection, including vascular catheter-related sepsis with cultures positive for the probiotic organism, but these have nearly all been in patients previously immunocompromised because of their underlying disease.[2]

After having reviewed the available data, several practice guidelines can be developed. First, in treating patients with inflammatory bowel disease, there is considerable evidence from well-designed studies to support the administration of *S boulardii* or VSL #3 to shorten the duration of an acute exacerbation of the disease or to augment remission. In addition, there is evidence from 1 study to support administration of a lesser-studied probiotic, *E coli* Nissle 1917, for the same indications. In contrast, the data would not support use of the much more common *Lactobacillus* GG for use in IBD. Similarly, in the management of acute pancreatitis, evidence sug-

gests that supplementation of enteral feeding with *L plantarum* 299 may decrease the progression from sterile pancreatic necrosis to infected pancreatic necrosis. If these data are confirmed, the morbidity and mortality of this potentially devastating disease could be dramatically curbed.

Although hepatic transplantation does not enter into the practice of many physicians, the principles learned from this research, such as decreased postoperative infections with probiotic usage, can be useful in other settings. In contrast, nearly every physician treats patients with diarrhea. The data from these studies support the use of *S boulardii* and several *Lactobacillus* species to prevent and treat diarrhea. The number of available well-controlled studies in adults is still limited, but this is certainly an important area to be followed. Finally, in the preparation and treatment of surgical patients, *L plantarum* 299 has shown benefit. According to these data, it is reasonable and considered safe to administer this probiotic perioperatively. The data from several groups would best support use of the supplement for 1 week before the operation and for at least 1 week postoperatively.

Conclusion

The data presented above reviews what may seem to be one of the greatest paradoxes in modern medicine: the treatment and prevention of infectious disease with viable bacteria. Physicians have long sought to overcome bacteria by developing better antibacterials, but it just may be that these very bacteria are far better than we are at controlling their existence. In fact, it may be true that rather than destroying bacteria, we should be nurturing their existence in the proper setting. Clinicians must begin to examine traditional thought regarding infection control and nutrition to further the understanding of probiotics and their potential benefits. It appears that what was once viewed as the physician's greatest enemy may now be a powerful ally and play a pivotal role in the prevention and treatment of numerous common diseases. This review makes no attempt at discussing the role of probiotics in prevention of neoplastic disease of the GI tract, yet another promising area by the early studies.[62,63]

The use of probiotics in clinical medicine can be summed up by the comment "so many questions, so few answers." The authors have no doubt that probiotics and prebiotics will play a major role in prevention and the treatment of numerous disease states.

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