The Role of Probiotic Cultures in the Control of Gastrointestinal Health

Rial D. Rolfe

Department of Microbiology and Immunology, Texas Tech University Health Sciences Center, Lubbock, TX 79430

ABSTRACT The use of probiotics to enhance intestinal health has been proposed for many years. Probiotics are traditionally defined as viable microorganisms that have a beneficial effect in the prevention and treatment of specific pathologic conditions when they are ingested. There is a relatively large volume of literature that supports the use of probiotics to prevent or treat intestinal disorders. However, the scientific basis of probiotic use has been firmly established only recently, and sound clinical studies have begun to be published. Currently, the best-studied probiotics are the lactic acid bacteria, particularly Lactobacillus sp. and Bifidobacterium sp. However, other organisms used as probiotics in humans include Escherichia coli, Streptococcus sp., Enterococcus sp., Bacteroides sp., Bacillus sp., Propionibacterium sp. and various fungi. Some probiotic preparations contain mixtures of more than one bacterial strain. Probiotics have been examined for their effectiveness in the prevention and treatment of a diverse spectrum of gastrointestinal disorders such as antibiotic-associated diarrhea (including Clostridium difficile–associated intestinal disease), infectious bacterial and viral diarrhea (including diarrhea caused by rotavirus, Shigella, Salmonella, enterotoxigenic E. coli, Vibrio cholerae and human immunodeficiency virus/acquired immunodeficiency disorder, enteral feeding diarrhea, Helicobacter pylori gastroenteritis, sucrase maltase deficiency, inflammatory bowel disease, irritable bowel syndrome, small bowel bacterial overgrowth and lactose intolerance. Probiotics have been found to inhibit intestinal bacterial enzymes involved in the synthesis of colonic carcinogens. There are many mechanisms by which probiotics enhance intestinal health, including stimulation of immunity, competition for limited nutrients, inhibition of epithelial and mucosal adherence, inhibition of epithelial carcinogens, and promotion of antimicrobial substances. Probiotics represent an exciting prophylactic and therapeutic advance, although additional investigations must be undertaken before their role in intestinal health can be delineated clearly. J. Nutr. 130: 396S–402S, 2000.

KEY WORDS: probiotics, intestinal disorders

Despite numerous therapeutic improvements, especially in the field of antibiotics, gastrointestinal infections and their consequences remain a major clinical problem. In addition, there has been a dramatic increase in the incidence of antibiotic-resistant microbial pathogens. There is a concern that industry will no longer be able to develop effective antibiotics at a rate sufficient to compete with the development of microbial resistance to old antibiotics. These factors have renewed interest in the possibility of deliberately feeding beneficial microorganisms to humans as an alternative to antibiotic therapy in gastrointestinal disorders. Probiotics are also an attractive treatment alternative because antibiotics, which further delay recolonization by normal colonic flora, can be avoided. This paper will focus on the evidence that probiotics are useful in the prevention and treatment of gastrointestinal disorders in humans.

Probiotics have been defined as viable microorganisms that (when ingested) have a beneficial effect in the prevention and treatment of specific pathologic conditions (Havenaar and Huis in’t Veld 1992). The principle of using harmless bacteria for conquering pathogens has been recognized for many years. In fact, probiotics have been used for as long as people have eaten fermented foods. However, it was Metchnikoff at the turn of the century who first suggested that ingested bacteria could have a positive influence on the normal microbial flora of the intestinal tract (Metchnikoff 1907). He hypothesized that lactobacilli were important for human health and longevity, and promoted yogurt and other fermented foods as healthy.

The belief in the beneficial effects of probiotics is based on the knowledge that the intestinal flora can protect humans against infection and that disturbance of this flora can increase susceptibility to infection. Numerous in vivo and in vitro studies have shown that the normal intestinal flora is an extremely effective barrier against pathogenic and opportunistic microorganisms (Fuller 1991). Probiotics are usually targeted for use in intestinal disorders in which specific factors
(such as antibiotics, medication, diet or surgery) disrupt the normal flora of the gastrointestinal tract, making the host animal susceptible to disease. Examples of such diseases include antibiotic-induced diarrhea, pseudomembranous colitis and small bowel bacterial overgrowth. The goal of probiotic therapy is to increase the numbers and activities of those microorganisms suggested to possess health-promoting properties until such time that the normal flora can be reestablished. There are also intestinal disorders in which probiotics have been used prophylactically and/or therapeutically in which the role of disruption of normal flora in the disease process is less clear. These diseases include traveler’s diarrhea, *Helicobacter pylori* gastrenteritis and rotavirus diarrhea.

Many microorganisms have been used or considered for use as probiotics. A probiotic preparation may contain one or several different strains of microorganisms. Because viable and biologically active microorganisms are usually required at the target site in the host, it is essential that the probiotic be able to withstand the host’s natural barriers against ingested bacteria. The most commonly used probiotics are strains of lactic acid bacteria (e.g., *Lactobacillus*, *Bifidobacterium* and *Streptococcus*). The beneficial effects of *Lactobacillus* and *Bifidobacterium* have been discussed for decades. Bacteria in these two genera resist gastric acid, bile salts and pancreatic enzymes, adhere to intestinal mucosa and readily colonize the intestinal tract. They are considered important components of the gastrointestinal flora and are relatively harmless. Lactic acid bacteria have been demonstrated to inhibit the *in vitro* growth of many enteric pathogens including *Salmonella typhimurium*, *Staphylococcus aureus*, *Escherichia coli*, *Clostridium perfringens* and *Clostridium difficile* and have been used in both humans and animals to treat a broad range of gastrointestinal disorders (Meurman et al. 1995, Silva et al. 1987).

*Saccharomyces boulardii*, a patented yeast preparation, is used in many countries as both a preventive and therapeutic agent for diarrhea and other gastrointestinal disorders caused by the administration of antimicrobial agents. *S. boulardii* possesses many properties that make it a potential probiotic agent; i.e., it inhibits the growth of a number of microbial pathogens in vivo and *in vitro*; its temperature optimum is 37°C; it survives transit through the gastrointestinal tract; it is rapidly eliminated, however, when therapy is discontinued; and it is unaffected by antibiotic therapy (Blehart et al. 1989, Boddy et al. 1991, Brugier and Patte 1975). This last property is important because many patients administered a probiotic are receiving concurrent antimicrobial therapy for conditions unrelated to the gastrointestinal tract.

There have been hundreds of publications describing the use of probiotics to prevent and treat a variety of gastrointestinal disorders. However, only a few have contributed convincingly to our knowledge of the health effects of probiotics in humans. The majority of studies have been poorly designed (e.g., inadequately defined strains of microorganisms, variation in preparation and storage of probiotics, patient groups that are too small in size for statistical analysis or imprecise definitions of end points) and therefore not reproducible by other investigators. Only a relatively few studies have been conducted with sufficient subjects, proper controls and statistical analysis of the results.

### Intestinal disorders treated with probiotics

Probiotics have been studied in the treatment and prevention of various intestinal disorders. However, as will be described below, evidence that probiotics are useful therapeutically or prophylactically is available for only a few of these disorders.

**Antibiotic-induced diarrheal disease.** Diarrhea is the most common side effect of antimicrobial therapy, with ~20% of patients receiving an antibiotic developing this condition (Bartlett 1992). The pathogenesis of antibiotic-induced diarrhea is not understood but is undoubtedly related to quantitative and qualitative changes in the intestinal flora (Nord et al. 1986).

Many of the studies that have attempted to demonstrate the usefulness of probiotics in antibiotic-associated diarrhea have used it prophylactically. However, because of the low incidence of antibiotic-associated diarrhea and the variable intensity of the diarrhea, it is not practical from a cost-benefit viewpoint to treat all patients receiving antibiotic therapy in this way with a probiotic. Furthermore, it is not possible to predict which patients will develop antibiotic-associated diarrhea. Nonetheless, several probiotics have been used in an attempt to prevent antibiotic-associated diarrhea. These agents include *Saccharomyces*, *Lactobacillus*, *Bifidobacterium*, and *Streptococcus*. However, only *S. boulardii*, *E. faecium* and *Lactobacillus* have been shown to be clinically effective in preventing antibiotic-associated diarrhea.

Surawicz et al. (1989), in a prospective, double-blind, placebo-controlled study, treated 180 hospitalized patients receiving antibiotic therapy concurrently with either placebo or *S. boulardii*. The overall incidence of diarrhea in these patients was 26%; 22% of the patients receiving placebo developed diarrhea compared with 9% of patients receiving *S. boulardii*, a statistically significant difference. Adam et al. (1977) prospectively treated 388 ambulatory patients, receiving either tetracycline or a β-lactam, concurrently with placebo or *S. boulardii*. The incidence of diarrhea in patients receiving the placebo was 17.5%, whereas in patients receiving *S. boulardii*, it was 4.5%. These results were confirmed in another study of 193 patients receiving at least one broad-spectrum β-lactam antibiotic (McFarland et al. 1995). Of the 97 patients receiving *S. boulardii*, only 7.2% developed antibiotic-associated diarrhea compared with 14.6% of the 96 patients receiving placebo.

Lactinex, a commercial preparation containing *Lactobacillus acidophilus* and *Lactobacillus bulgaricus*, was used in a placebo-controlled study of 79 hospitalized patients receiving ampicillin (Gotz et al. 1979). The rationale for using *Lactobacillus* in these patients is based on the observation that antibiotic therapy often causes a loss or reduction in the number of intestinal *Lactobacillus*. Thirty-six patients received concurrent Lactinex and 43 patients received placebo. None of the patients receiving Lactinex developed ampicillin-induced diarrhea, whereas 14% of the placebo group developed diarrhea.

In a multicenter, double-blind, placebo-controlled clinical trial involving 10 hospitals, Wunderlich et al. (1989) randomly assigned 45 antibiotic-treated patients to receive either concurrent placebo or *Enterococcus faecium*. Differences in the incidence of diarrhea were significant; 27% of the placebo group developed diarrhea compared with 9% of the group receiving *E. faecium*.

The general conclusion from these studies is that patients at risk of developing antibiotic-associated diarrhea would benefit from prophylactic probiotic therapy. However, this becomes impractical because there is no way to identify these patients.

**Clostridium difficile–associated intestinal disease.** *C. difficile* is a classic example of the opportunistic proliferation of an intestinal pathogen after breakdown of colonization resistance due to antibiotic administration. After antibiotic intake by animals and humans, *C. difficile* colonizes the intestine and releases two protein exotoxins, toxin A and toxin B, which...
mediate the diarrhea and colitis caused by this microbe. Toxinogenic C. difficile is the cause of ~20–40% of cases of antibiotic-associated diarrhea (Clabots et al. 1992, Fekety and Shah 1993, McFarland et al. 1989). In fact, this microorganism is the major identifiable cause of nosocomial diarrhea in the U.S., infecting 15–25% of adult hospitalized patients. C. difficile can have serious consequences, particularly in the elderly and debilitated; these include pseudomembranous colitis, toxic megacolon, intestinal perforation and death.

Standard treatment of C. difficile–associated intestinal disease, which involves either vancomycin or metronidazole, can be expensive and difficult. In addition, ~25% of patients relapse with disease once treatment is discontinued (Bartlett et al. 1980, Fekety et al. 1989, Walters et al. 1983, Young et al. 1985). Multiple relapses can occur and the relapses can be more severe than the original disease. The mechanism of relapse is unknown but is probably due to the survival of C. difficile spores in the intestinal tract until the antibiotic is discontinued (Walters et al. 1983). The spores then germinate and produce toxin. The antibiotic therapy prevents the normal flora from reestablishing itself. There is no uniform effective therapy to prevent further C. difficile recurrences in intractable patients.

An attractive alternative to antibiotic therapy is to use probiotics to restore intestinal homeostasis. Patients at risk of C. difficile intestinal disease can be identified in the sense that individuals that have had a previous relapse of C. difficile disease are more likely to have another relapse. Several alternative treatments have been used in C. difficile–associated intestinal disease. Rectal administration of feces from healthy adults has been examined in a very limited number of uncontrolled studies (Bowden et al. 1981, Schwan et al. 1984). This treatment appears to be moderately successful, but there is obvious concern about the use of a complex, mixed undefined flora that could contain a number of potential pathogens. Additional uncontrolled studies have examined rectal infusion of 10 different aerobic and anaerobic bacteria as well as the use of a nontoxigenic strain of C. difficile (Borriello 1988, Tvede and Rask-Madsen 1989). Presumably these bacteria occupy niches that the toxigenic strain would expect to find available.

S. boulardii has demonstrated the most promise for use in C. difficile–associated intestinal disease. In a placebo-controlled study, McFarland et al. (1994) examined standard antibiotic therapy (metronidazole or vancomycin) with concurrent S. boulardii or placebo in 124 adult patients, 64 patients with an initial episode of C. difficile disease and 60 patients with a history of at least one prior episode of C. difficile disease. The investigators found that in patients with an initial episode of C. difficile, there was no significant difference in the recurrence of C. difficile disease in the placebo or S. boulardii groups. However, in patients with prior C. difficile disease, S. boulardii significantly inhibited further recurrences of disease. The investigators concluded that in combination with standard antibiotics, S. boulardii is an effective and safe therapy for patients with recurrent C. difficile.

**Probiotic treatment of infectious diarrhea**

It is very difficult to perform a critical analysis of studies that have examined the use of probiotics for the treatment and/or prevention of infectious diarrhea. First, there are many etiological agents that cause infectious diarrhea (e.g., *Shigella, Salmonella, C. difficile, rotavirus, enterotoxigenic E. coli*), and the majority of the studies do not attempt to define the cause of the diarrhea. In addition, many of the studies involved only a small number of patients. Two of the more common types of infectious diarrheal diseases will be described in greater detail below, i.e., traveler's diarrhea and rotavirus diarrhea.

**Traveler's diarrhea.** The incidence of diarrhea in travelers to foreign countries varies from 20 to 50% depending on the origin and the destination of the traveler, as well as the mode of travel. Although various infectious agents can cause traveler's diarrhea, enterotoxigenic *E. coli* is the most common. Even small attacks can interrupt a holiday, and the traveling public has a great interest in medications that could be used to prevent traveler's diarrhea. Thus, a safe, inexpensive and effective drug against traveler's diarrhea would have important public health implications. Several probiotics have been examined for their ability to prevent traveler's diarrhea, including *Lactobacillus, Bifidobacterium, Streptococcus* and *Saccharomyces* (Hilton et al. 1997, Oksanen et al. 1990, Scarpignato and Rampal 1995). These studies have involved several different groups of travelers such as Finnish travelers to Turkey, American travelers to Mexico, British soldiers to Belize and European travelers to Egypt. The results from these studies have been extremely variable. For example, in the study of Finnish travelers to Turkey, the travelers had two different destinations (Oksanen et al. 1990). In one destination, *Lactobacillus GG* provided protection against traveler's diarrhea, but failed to protect travelers at the other destination. Different etiologic agents may have involved in these two locations, but this possibility was not examined.

**Rotavirus diarrhea.** Rotaviruses are a significant cause of infant morbidity and mortality, particularly in developing countries (Majamaa et al. 1995, Middleton et al. 1977). The principal means of treatment is oral rehydration, although an effective vaccine that should decrease dramatically the health impact of rotavirus infections has recently become available. *Lactobacillus* has demonstrated some promise as a treatment for rotavirus infection (Isolauri et al. 1994, Kaila et al. 1992, Majamaa et al. 1995). Isolauri et al. (1991) treated 74 children (ages 4–45 mo) with diarrhea with either *Lactobacillus GG* or placebo. Approximately 80% of the children with diarrhea were positive for rotavirus. The investigators demonstrated that the duration of diarrhea was significantly shortened (from 2.4 to 1.4 d) in patients receiving *Lactobacillus GG*. The effect was even more significant when only the rotavirus-positive patients were analyzed.

**Helicobacter pylori gastroenteritis**

*H. pylori* has recently been shown to be an important etiologic agent of chronic gastritis as well as gastric and duodenal ulcers. It has also been postulated that chronic *H. pylori* infection leads to stomach carcinoma. *Lactobacillus* has been shown to be antagonistic to *H. pylori* both in vitro and in a gnotobiotic murine model (Aiba et al. 1998, Kabir et al. 1997, Midolo et al. 1995). The results of the few studies with *Lactobacillus* that have been performed in humans are conflicting, with some showing modest protection and others showing no protection.

**Hepatic encephalopathy**

Hepatic encephalopathy is a neurologic disorder caused by increased blood levels of ammonia. The ammonia is produced in the intestine by the action of bacterial ureases. The ammonia is absorbed and, in healthy individuals, is detoxified by the liver. However, in patients with liver failure, the blood concentration of ammonia can reach toxic levels. Investigators have postulated that it may be possible to use probiotics to decrease intestinal urease activity. For example, patients
treated with L. acidophilus and neomycin show a greater decrease in fecal urease activity than patients treated with neomycin alone (Loguercio et al. 1987, Read et al. 1966, Scevola et al. 1989). The decreased fecal urease activities corresponded to lower serum ammonia levels and improvements in the clinical status of patients.

HIV/AIDS diarrhea

Diarrhea is a very serious consequence of human immunodeficiency virus (HIV) infection. The etiology of this diarrhea is frequently unknown and there are no effective treatment modalities. However, S. boulardii was recently used to treat 33 HIV patients with chronic diarrhea (Born et al. 1993, Saint-Marc et al. 1991). In these double-blind studies, 56% of patients receiving S. boulardii had resolution of diarrhea compared with only 9% of patients receiving placebo.

Sucrase-isomaltase deficiency

Sucrase-isomaltase deficiency is the most frequent primary disaccharidase deficiency seen in humans. It is an inherited condition that leads to malabsorption of sucrose. The resulting bacterial fermentation of the sucrose leads to an accumulation of hydrogen in the colon, producing diarrhea, abdominal cramps and bloating. A sucrose-free diet causes a disappearance of symptoms. However, not all patients will follow such a diet. Harms et al. (1987) used Saccharomyces cerevisiae to treat eight children with sucrase-isomaltase deficiency. These investigators demonstrated that in children given sucrose followed by S. cerevisiae, there was an improvement in both their hydrogen breath test and gastrointestinal symptoms. The investigators postulated that S. cerevisiae was supplying the missing enzymes.

Lactose intolerance

People throughout the world suffer from a congenital deficiency of the enzyme β-galactosidase. This deficiency results in an inability to digest and absorb lactose. Bacteria metabolize the lactose and the resulting by-products cause abdominal cramping, bloating, diarrhea and nausea. Lactose-negative strains of bacteria (e.g., Lactobacillus, Bifidobacterium and Streptococcus) are commonly added to pasteurized dairy products to increase digestibility of the lactose present in the dairy product (Gilliland and Kim 1984, Kim and Gilliland 1983, Pettoello et al. 1989). There are two probable mechanisms by which the addition of these bacteria is beneficial, i.e., the reduction of lactose in the dairy product through fermentation and the replication of the probiotic in the gastrointestinal tract, which releases lactase.

Inflammatory bowel disease

There are two inflammatory bowel diseases, Crohn’s disease and ulcerative colitis; their etiologies are unknown but may be related to disturbances of the intestinal microflora (Fabia et al. 1993). Crohn’s disease is an idiopathic inflammatory bowel disease that occurs from the mouth to the anus, although the terminal ileum is most common site of disease. The most common clinical manifestation of ulcerative colitis is an inflammation of the colon. No specific treatment is available for either disease. Kruis et al. (1997) examined the Nissle strain of nonpathogenic E. coli (serotype O6:K5:H1) for its ability to prevent relapses of ulcerative colitis. Preliminary results look promising and suggest that this may be another option for maintenance therapy of ulcerative colitis.

Pouchitis

Pouchitis is a complication of ileal reservoir surgery occurring in 10–20% of the patients who undergo surgical treatment for chronic ulcerative colitis. Bacteria overgrow in the pouch, resulting in degradation of the epithelial cells (Madden et al. 1990, Mortensen 1992, Ruseler-Van Embden et al. 1995). This results in inflammation and symptoms that include bloody diarrhea, lower abdominal pain and fever. Investigators have postulated that Lactobacillus GG may be an effective therapeutic agent for pouchitis because it does not demonstrate mucus-degrading properties (Ruseler-Van Embden et al. 1995).

Irritable bowel syndrome

Irritable bowel syndrome is characterized by chronic, recurrent pain that occurs primarily during childhood. There is no specific treatment of this condition. However, a small, double-blind, placebo-controlled, crossover study in Poland demonstrated a slight but significant reduction in the severity of abdominal pain in individuals receiving L. plantarum (Niedzielin and Kordecki 1996).

Small bowel bacterial overgrowth

Overgrowth of bacteria in the small intestine can have many causes, including blind loops, stenosis of the intestines, diverticula and motility disorders. Symptoms of small bowel overgrowth are frequently chronic and relapsing. Response to antibiotic treatment is often inadequate or incomplete. Surgical treatment is occasionally possible, but in many cases the underlying cause is not accessible for permanent treatment. Limited studies have suggested that L. plantarum and Lactobacillus GG may be helpful in eliminating the symptoms of small bowel bacterial overgrowth (Vanderhoof et al. 1998).

Enteral feeding–associated diarrhea

Patients receiving nasogastric tube feeding frequently develop diarrhea. The mechanism of the diarrhea is not known, but investigators postulate that enteral feeding causes changes in normal flora that result in altered carbohydrate metabolism and subsequent diarrhea (Guenter et al. 1991). Two separate studies (both placebo-controlled and double blind) demonstrated a significant reduction in diarrhea in these patients when they were given S. boulardii (Bleichner et al. 1997, Tempe et al. 1983).

Carcinogenesis

Evidence is accumulating that the normal intestinal flora can influence carcinogenesis by producing enzymes that transform precarcinogens into active carcinogens. These enzymes include glycosidase, β-glucuronidase, azoreductase and nitroreductase (Goldin et al. 1980, Goldin 1990, Ling et al. 1994, Marteau et al. 1990, Pedrosa et al. 1995). There is some evidence that selected microorganisms may actually protect the host from this carcinogenic activity. There are three postulated mechanisms for this protection as follows: 1) the probiotic may inhibit the bacteria that are responsible for converting precarcinogens into carcinogens; 2) animal studies have shown that some probiotics inhibit tumor cell formation directly; and 3) some bacteria have been shown to bind and/or inactivate carcinogens (Orlhage et al. 1994, Rowland and Grasso 1975). Human volunteers receiving either L. acidophilus or L. casei have reduced levels of enzymes that convert...
precarcinogens to carcinogens in their fecal specimens (Hayatsu and Hayatsu 1993, Lee and Salminen 1995, Lidbeck et al. 1992). Whether this leads to a reduced incidence of cancer is unknown. Obviously, more extensive investigations and clinical trials must be conducted before probiotics can be considered for cancer prevention.

Mechanisms of action

There are many proposed mechanisms by which probiotics may protect the host from intestinal disorders. The sum of all processes by which bacteria inhibit colonization by other strains is called colonization resistance. Much work remains to classify the mechanisms of action of particular probiotics against particular pathogens. In addition, the same probiotic may inhibit different pathogens by different mechanisms. Listed below is a brief description of mechanisms by which probiotics may protect the host against intestinal disease.

Production of inhibitory substances. Probiontic bacteria produce a variety of substances that are inhibitory to both gram-positive and gram-negative bacteria. These inhibitory substances include organic acids, hydrogen peroxide and bacteriocins. These compounds may reduce not only the number of viable cells but may also affect bacterial metabolism or toxin production.

Blocking of adhesion sites. Competitive inhibition for bacterial adhesion sites on intestinal epithelial surfaces is another mechanism of action for probiotics (Conway et al. 1987, Goldin et al. 1992, Kleeman and Klaenhammer 1982). Consequently, some probiotic strains have been chosen for their ability to adhere to epithelial cells.

Competition for nutrients. Competition for nutrients has been proposed as a mechanism for probiotics. Probiotics may utilize nutrients otherwise consumed by pathogenic microorganisms. However, the evidence that this occurs in vivo is lacking.

Degradation of toxin receptor. The postulated mechanism by which S. bouardii protects animals against C. difficile intestinal disease is through degradation of the toxin receptor on the intestinal mucosa (Castagliuolo et al. 1996 and 1999, Pothoulakis et al. 1993).

Stimulation of immunity. Recent evidence suggests that stimulation of specific and nonspecific immunity may be another mechanism by which probiotics can protect against intestinal disease (Fukushima et al. 1998, Kaila et al. 1992, Link-Amster et al. 1994, Malin et al. 1996, Perdigon et al. 1986, Pouwels et al. 1996, Saavedra et al. 1994). For example, peroral administration of Lactobacillus GG during acute rotavirus diarrhea is associated with an enhanced immune response to rotavirus (Kaila et al. 1992). This may account for the shortened course of diarrhea seen in treated patients. The underlying mechanisms of immune stimulation are not well understood, but specific cell wall components or cell layers may act as adjuvants and increase humoral immune responses.

Prebiotics and synbiotics

As described above, the oral feeding of external microorganisms is one mechanism to increase the number of beneficial bacteria in the intestine. Prebiotics is another mechanism. Prebiotics are defined as food supplements that are nondigestible by the host but that improve health by selectively stimulating the growth and/or activities of selected intestinal bacteria (Ballongue et al. 1997, Gibson and Roberfroid 1995). This increase in indigenous bacteria may in turn inhibit the growth of pathogenic species. Prebiotics are not hydrolyzed or absorbed in the small intestine but are available as substrates for indigenous bacteria in the large intestine (Molis et al. 1996). All prebiotics to date have been carbohydrates, ranging in size from small sugar alcohols and disaccharides, to oligosaccharides and large polysaccharides. A probiotic can be combined with a prebiotic to form what is called a synbiotic (Gibson and Roberfroid 1995, Lewis and Freedman 1998). Colonization by an exogenous probiotic could be enhanced and extended by simultaneous administration of a prebiotic that the probiotic could utilize in the intestinal tract. To date, no well-conducted clinical trials in humans have tested prebiotics or synbiotics for prevention or treatment of intestinal disorders.

SUMMARY

Probiotics represent a potentially significant therapeutic advance. In an effort to decrease reliance on antimicrobials, the time has clearly come to increase the exploration of the therapeutic applications of probiotics. There are too many reports describing the beneficial effects of probiotics to dismiss this concept for preventing and treating a variety of intestinal disorders. Probiotics offer dietary means to support the balance of the intestinal flora. They may be used to counteract local immunological dysfunction, to stabilize the intestinal mucosal barrier function, to prevent infectious successions of pathogenic microorganisms and to influence intestinal metabolism.

However, any postulated benefit from consumption of probiotics or prebiotics should be accepted as fact only after extensive, multicenter testing in human clinical trials. There are still many unresolved issues that can be answered only by well-designed and well-controlled clinical trials. It is important to remember that in vitro and animal studies are frequently not transferable to humans.

There are many potential advantages to probiotics over conventional therapy, including relatively low cost, the fact that probiotics are unlikely to increase the incidence of antibiotic resistance, and the multiple mechanisms by which probiotics presumably inhibit pathogens, thereby decreasing the chances for development of resistance against the probiotic.

In the future, probiotics must be subjected to the identical, rigorous scientific studies that are required of chemical drug entities, including randomized, placebo-controlled, double-blind studies, pharmacokinetic studies (i.e., dose-dependent efficacy, absorption, distribution, metabolism, excretion and duration of effect) and multicenter trials to establish reproducibility. In the past, once efficacy had been demonstrated, few researchers have gone on to define a pharmacodynamic profile of the probiotic nor have extensive efforts been directed at identifying mechanisms of action. The synbiotic concept must be tested more rigorously as must the use of multiple probiotic strain combinations. It will also be important to define more clearly the mechanisms of action of various probiotics. This will permit the scientific rationale for the selection of the best species or strains to use against a particular pathogen. It may also permit the application of genetic engineering to enhance the activity of probiotics (Tannock 1997, Wagner et al. 1997). It should be possible to bring together the ability to survive in the intestinal tract with the ability to produce metabolites that are responsible for the probiotic effect.

LITERATURE CITED


