Probiotics and Prebiotics: Effects on Diarrhea[1,2]

Michael de Vrese[3]* and Philippe R. Marteau[4]

[3]Institute of Physiology and Biochemistry of Nutrition, Federal Research Centre for Nutrition and Food, 24103 Kiel, Germany and [4]Digestive Diseases, Hopital Lariboisière, 75010 Paris, France

Abstract

Probiotics have preventive as well as curative effects on several types of diarrhea of different etiologies. Prevention and therapy (or alleviation) of diarrhea have been successfully investigated for numerous dietary probiotics to establish probiotic properties and to justify health claims (the medicinal use of probiotic food and the therapy of gastrointestinal diseases itself may not be advertised under current food laws). Other probiotic microorganisms (e.g., *Lactobacillus rhamnosus* GG, *L. reuteri*, certain strains of *L. casei*, *L. acidophilus*, *Escherichia coli* strain Nissle 1917, and certain bifidobacteria and enterococci (*Enterococcus faecium* SF68) as well as the probiotic yeast *Saccharomyces boulardii* have been investigated with regard to their medicinal use, either as single strains or in mixed-culture probiotics. However, the effects on humans have been assessed mainly in smaller ($n < 100$) randomized, controlled clinical studies or in open label trials, but large intervention studies and epidemiological investigations of long-term probiotic effects are largely missing. Perhaps with the exception of nosocomial diarrhea or antibiotic-associated diarrhea, the results of these studies are not yet sufficient to give specific recommendations for the clinical use of probiotics in the treatment of diarrhea.   J. Nutr. 137: 803S–811S, 2007.

Diarrhea (Greek $\delta\iota\alpha\rho\rho o\iota\alpha$ = flowing through) means the increased liquidity or decreased consistency of stools usually associated with an increased frequency of stools and an increased fecal weight. The WHO defines diarrhea as 3 or more watery stools on 2 or more consecutive days. According to the main mechanisms involved, there are several types of diarrhea, which are summarized in **Table 1**, together with therapeutic measures.

Treatment of diarrhea by administering living or dried bacteria to restore a disturbed intestinal microflora has a long tradition. Interestingly, yogurt had originally been developed in Spain and introduced into the market as an inexpensive, easy to prepare, and easily available remedy against diarrhea in children and was sold in pharmacies. However, earlier reports on the successful use of *Enterococcus faecium/faecalis*, strains of *Escherichia coli*, or freshly isolated members of the patients' own intestinal microflora were mostly case reports and open studies rather than well-documented, randomized, double-blind, controlled clinical studies. But in the last 2 decades, investigations in probiotic microorganisms by in vitro studies, animal experiments, and appropriate well-designed clinical studies have put this "bacteriotherapy" on a more rational basis.

Probiotics in prevention and treatment of diarrhea

The use of probiotic microorganisms for the prevention or therapy of gastrointestinal disorders is an obvious measure and perhaps the most usual application of probiotics because most health effects attributed to them are related directly or indirectly (i.e., mediated by the immune system) to the gastrointestinal tract. The mechanisms and the efficacy of a probiotic effect often depend on interactions with the specific microflora of the host or immunocompetent cells of the intestinal mucosa. The gut (or its associated lymphoid system, GALT)[5] is the largest immunologically competent organ in the body, and maturation and optimal development of the immune system after birth depend on the development and composition of the indigenous microflora and vice versa.

Many strains of probiotic microorganisms have been shown to inhibit growth and metabolic activity as well as the adhesion to intestinal cells of enteropathogenic bacteria (*Salmonella*, *Shigella*, enterotoxigenic *E. coli*, or *Vibrio cholerae*) (1–3) to modulate (temporarily) the intestinal microflora and to have immunostimulatory or -regulatory properties.

Suggested mechanisms for the effects on the intestinal microflora are lowering the intestinal pH, the production of bactericidal substances such as organic acids (lactic, acetic, butyric

TABLE 1 Types of diarrhea and therapeutic measures

Diarrhea	Characterization
Type of diarrhea	
Osmotic diarrhea	Insufficient absorption of osmotically active substances in the gut (e.g., lactose malabsorption in lactase deficiency)
Secretory diarrhea	Most cases of viral and bacterial enteritis are accompanied by increased secretion or decreased absorption of ions into the gut
Inflammatory diarrhea	Accompanied by exsudation of proteins and blood
Motility-associated diarrhea	Diarrhea with accelerated gastrointestinal motility
Therapeutic measure	
Rehydration alone	Replacement of water losses only
Treatment of symptoms	By use of antisecretory agents (loperamide, enkephalinase inhibitors) or by measures to avoid liquid stools (argile, fiber)
Causal therapy	Cholestyramine, antibiotics, intestinal antiinflammatory agents, probiotics?

acid) (4), H_2O_2 and bacteriocines, agglutination of pathogenic microorganisms, adherence to the cellular surface of the mucosa, and competition for fermentable substrates or receptors, strengthening the barrier effect of the intestinal mucosa (5,6), release of gut-protective metabolites (arginine, glutamine, short-chain fatty acids, conjugated linoleic acids), binding and metabolism of toxic metabolites (7–11), immunologic mechanisms (12,13), or regulation of the intestinal motility (14) and mucus production (15).

In human and animal experiments, bacterial counts in stool samples and in samples from the small bowel taken from ileostomized patients, have been altered by probiotics. All these methods, however, have drawbacks and only indirectly reflect the real situation in the gastrointestinal tract and its microflora.

The interactions between probiotic microorganisms and the GALT or the respective mucosal receptors and signaling pathways as well as the mechanisms of immunomodulation and antiinflammatory probiotic effects are not yet fully understood, but the use of modern techniques such as molecular biology lead to a rapidly growing knowledge of the relations among probiotics, the immune system, and health.

Preventive or curative effects of probiotic microorganisms with evidence of the effects on the gastrointestinal microflora and antibacterial, immunostimulatory, and antiinflammatory properties have been investigated in diarrhea caused by (primary) lactose intolerance; acute diarrhea from viral and/or bacterial infections, e.g., nosocomial rotavirus infections in children, gastrointestinal infections in children in day-care centers, and travelers' diarrhea; antibiotic-associated diarrhea (AAD); *Clostridium difficile* gastroenteritis; diarrhea in tube-fed patients; chemo- or radiotherapy-induced diarrhea; inflammatory bowel diseases (Crohn's disease, ulcerative colitis, pouchitis); small bowel bacterial overgrowth; and irritable bowel syndrome (IBS) with diarrhea.

Reduced diarrhea and other gastrointestinal symptoms in lactose intolerance

The most thoroughly investigated health effect of fermented milk products is the enhancement of lactose digestion and the avoidance of intolerance symptoms in lactose malabsorbers, that is, in persons with insufficient activity of the lactose-cleaving enzyme β-galactosidase in the small intestine. This effect is based mainly on the fact that fermented milk products with living bacteria contain microbial β-galactosidase that survives the

passage through the stomach to be finally liberated in the small intestine and to support lactose hydrolysis there (16).

However, depending on the definition of "probiotic," this is not a specific probiotic effect because it does not depend on survival of the bacteria in the small intestine. Yogurt is usually more effective (17,18), and, last but not least, primary or adult-type hypolactasia (the reason for lactose malabsorption) is not a disease but actually the normal physiological state. Many probiotic bacteria show either a lower β-galactosidase activity or, because of their high resistance against acid and bile salts, do not release their enzymes in the small intestine (16).

There is no strong correlation, however, between lactose malabsorption and the occurrence of intolerance symptoms such as flatulence, bloating, abdominal cramping and pain, or diarrhea in any case. Many persons with alleged nonallergenic milk intolerance can digest lactose, and some truly maldigesting persons live without symptoms of intolerance. Thus, it may be imagined that probiotic bacteria do not significantly improve lactose digestion in the small intestine but rather avoid symptoms of intolerance directly in the large intestine (16,19). The latter effect depends on the specific strain, concentration, and preparation of the probiotic as well as on the subject's susceptibility to gas and osmotic pressure or, for unknown reasons, the individual responsiveness to probiotics (20).

In conclusion, probiotics promote lactose digestion in lactose malabsorbers no better than conventional yogurt. No independent reduction of diarrhea and other gastrointestinal complaints in lactose intolerance has yet been definitely proven.

Prevention or alleviation of acute diarrhea caused by viral or bacterial infection

Acute diarrhea from viral (mostly rotaviruses) or bacterial infection is still a major health problem worldwide and a frequent cause of death, especially in hospitalized children and in developing countries. But infectious diarrhea is not only a problem of developing countries. Up to 30% of the population in developed countries are affected by food-borne bacterial diarrheas each year.

Protection by probiotic bacteria and yeasts with immunostimulatory properties or the alleviation of symptoms and shortening of acute infections are perhaps the best-documented probiotic effects, and these have been demonstrated many times in the past in clinical studies fulfilling scientific requirements. Beneficial effects such as decreased frequency of infections, shortening of the duration of episodes by 1–1.5 d, decreased shedding of rotaviruses or promotion of systemic or local immune response, and an increase in the production of rotavirus-specific antibodies have been demonstrated for a number of food (*Lactobacillus rhamnosus* GG, *L. casei* Shirota, *L. reuteri*, *L. acidophilus* spec., *Bifidobacterium animalis* ssp. *lactis* BB-12, and others) (21–31) and nonfood probiotics (*E. coli*, *Enterococcus faecium* SF68, *Saccharomyces boulardii*) (32–34). In numerous studies probiotics were administered as nonfood preparations, e.g., as a powder or suspended in oral rehydration solutions (35). For reviews see Fonden et al. (9), de Roos and Katan (36), or Marteau et al. (37).

Prevention of infectious diarrhea in healthy children and adults

In large part, studies demonstrating positive effects on the prevention and alleviation of infectious diarrhea in healthy human populations have been performed in infants and children. Young children may be particularly responsive to probiotics because of the immaturity of their immune system and the greater

simplicity of their intestinal microflora compared with that of adults. Malnourished children or children attending child-care centers are exposed to a higher risk of gastrointestinal and respiratory tract infections (38), which may be reduced by the consumption of probiotic milk products or milk formulas supplemented with probiotic bacteria.

Administration of *L. rhamnosus* GG (LGG) or a placebo to 204 malnourished children in Peru (6–24 mo old) was associated with a significantly lower incidence of diarrhea in the treated compared with the placebo group (5.2 vs. 6.0 episodes per child per year) (39).

In a prospective, randomized, controlled French study, 287 children (18.9 ± 6.0 mo) in day-care nurseries were administered daily either unfermented jellied milk, conventional yogurt, or a probiotic yogurt product containing 10^8 cfu/mL *L. casei* spec. Each product was given over 1 mo, each month being followed by 1 mo without supplementation. The conventional yogurt brought the mean duration of diarrhea from 8.0 d down to 5 d, and the probiotic product brought it down to 4.3 d ($P <$ 0.01); the incidence of diarrhea was not different between groups (40).

This study was expanded to a randomized, controlled multi-center clinical trial in a total of 928 children (6–24 mo). During administration of *L. casei*–containing fermented milk (daily for 2 mo), a lower frequency of diarrhea was observed compared with the administration of conventional yogurt (15.9 vs. 22%; $P < 0.05$) (41).

Finnish children from day-care centers who consumed milk containing a probiotic *L. rhamnosus* strain during the winter had 16% fewer days of absence from day care because of diarrhea and gastrointestinal and respiratory tract infections then controls (42). However, the nature of the causative pathogens was not examined in these studies.

When healthy term infants (4–10 mo) from child-care centers in Israel were fed milk formulas containing no bacteria (controls, $n = 60$) or 10^7 cfu/g formula powder of *B. lactis* BB12 ($n = 73$) or *L. reuteri* SD2112 ($n = 68$), respectively, over 2 winter and 2 summer periods, a significant reduction in episodes of diarrhea was observed in the *L. reuteri* and BB12 groups compared with controls (mean values 0.15/0.02 and 0.37/0.13 vs. 0.59/0.31). A reduction in febrile days or in days with respiratory illness was observed only in the *L. reuteri* group (43).

Clearly fewer studies show preventive effects of probiotics on diarrhea and other gastrointestinal complaints in healthy adults. Administration of fermented milk products containing between 5×10^5 and 10^7 cfu/g LGG, CRL438, or LA5 plus BB12 plus *S. thermophilus* to healthy adults (20–65 y old) significantly reduced severity and frequency of mild, occasional episodes of diarrhea, abdominal pain, bloating, and flatulence compared with chemically acidified milk without bacteria (37,44). Yet, in a study in Israeli soldiers, diarrhea frequency (from 16.1% down to 12.2%) and duration (from 3.0 down to 2.6 d) was non-significantly decreased following consumption of probiotic yogurt containing *L. casei* ($n = 254$) compared with yogurt without probiotics ($n = 275$) (45).

Investigations of the effect of probiotic bacteria on traveler's diarrhea in the past showed inconsistent results (46) because of differences between probiotic strains, the traveled countries, the local microflora, eating habits of the travelers, or time point (before or during travel) and means (i.e., as a capsule or a fermented milk product) of administering the probiotic. Whereas some studies revealed fewer or shorter episodes of diarrhea in subjects consuming the probiotic (47–49), others found no such effect (50).

Altogether there is evidence that some probiotic strains are efficacious in preventing infectious diarrhea in healthy subjects. This was confirmed by a recent meta-analysis of the available data from 34 randomized placebo-controlled trials evaluating the efficacy of selected strains of probiotic bacteria in different types of acute diarrhea (51). The data suggested a significant reduction of the risk of acute diarrhea among children (-57%), of acute diarrhea among adults (-26%), of travellers' diarrhea (-8%), and of acute diarrhea of various causes (-34%). All microorganisms tested (*Saccharomyces boulardii*, *L. rhamnosus* GG, *L. acidophilus*, *L. delbrückii* ssp. *bulgaricus*, and other strains) showed similar effects, alone or used in combination.

Treatment of infectious diarrhea using probiotics

The majority of successful treatments of infectious diarrhea by probiotic microorganisms (or biotherapeutic agents, as clinically utilized probiotica are also called) (52) were performed in young children. Many of them suffered from nosocomial rotavirus infections, or both viral and bacterial infections were diagnosed in the cohort studied.

The analysis of 9 or 18, respectively, eligible randomized, controlled, blind studies on acute diarrhea in otherwise healthy infants showed a mean reduction in the duration of episodes by 0.7 or 1 d (53,54) and a reduction in stool frequency of 1.6 stools on d 2 of treatment (53) in the groups receiving probiotics (mainly lactobacilli).

However, it has been been published that strains of *L. rhamnosus* were effective only in the treatment of rotavirus-induced diarrhea in children but not in the treatment of diarrhea of other etiology (55). In other clinical trials in infants, LGG, 1 of the most successful probiotics altogether, was ineffective in nosocomial rotavirus infections (56) and in severe dehydrating diarrhea (57). It was therefore concluded that the therapeutic efficacy of probiotic microorganisms is not sufficient in cases of severe infectious diarrhea or that probiotics display their therapeutic effect too slowly.

This is in accordance with a recent review (58) that states that therapeutic effects of probiotics in children with acute diarrhea seem to be 1) moderate, 2) strain- (LGG, *L. reuteri*, *B. lactis* Bb12) and 3) dose-dependent, 4) more evident when probiotics are applied early in the episode, and 5) significant only in watery diarrhea and viral gastroenteritis but not in invasive bacterial diarrhea.

Clearly fewer randomized controlled trials have been performed in healthy adults. A meta-analysis of 23 randomized controlled studies in adults and children with a total of 1917 subjects came to the conclusion that probiotics reduce the mean duration of diarrheal episodes by 30.5 h and appear to be useful adjuncts to rehydration therapy in the treatment of acute infectious diarrhea (59).

In conclusion, the preventive and curative effects of certain dietary probiotics, particularly LGG, toward (nosocomial) rotavirus infections in children are relatively well supported. The use of dietary or medicinal probiotics against other pathogens, in adults, in children in Third-World –countries, and for very severe (dehydrating) diarrhea was less successful. Therefore, at the moment, results of randomized controlled clinical studies are too conflicting to give specific recommendations for the clinical use of probiotics. Also, with respect to the prophylaxis of traveler's diarrhea, none of the probiotics examined can be recommended without any reservation, particularly because of contradictory study results related to the diversity of travel destinations and to the locale-specific pathogens.

Alleviation or prevention of diarrhea caused by antibiotic treatment

Disturbance or destruction of the indigenous microflora caused by antibiotic treatment as well as a subsequent excessive growth of normally harmless bacteria (e.g., *Clostridium difficile*) often lead to diarrhea and symptoms related to toxin production. Antibiotic-associated diarrhea (AAD) is a common clinical problem, occurring in 25–30% of patients with 25% of cases caused by *C. difficile*.

Prevention and treatment of AAD is a frequently used model to test the effectiveness of (potential) food probiotics and the justification of health claims. Of higher importance is the testing of possible clinical applications of selected probiotic microorganisms (LGG, Bb12, SF68, *S. boulardii*, strains of *L. reuteri* and *L. acidophilus*) and multiple-strain probiotics (Lactinex, VSL#3) to reduce use of antibiotics for prevention or treatment of undesirable side effects (diarrhea, *Clostridium difficile* infections or relapses). Administration of LGG, *Saccharomyces boulardii*, and other probiotic strains before and during antibiotic treatment reduced the frequency and/or duration of episodes and the severity of symptoms in many cases (60–68) but was not always effective (69).

Eradication of the gastric pathogen *Helicobacter pylori* using clarithromycin, amoxicillin, and omeprazol (triple therapy) is a rather mild therapy and leads to diarrheas in only ~10–20% of cases. Coadministration of *S. boulardii* during *H. pylori* eradication did reduce AAD from 11.5 to 6.9% of patients (70). Administration of fermented milk containing 10^7–10^8 per day *B. animalis* ssp. *lactis* and *L. acidophilus* 4 wk before and during a *H. pylori* eradication therapy led to significantly fewer episodes of diarrhea compared with the placebo group (7 vs. 22% of the subjects) (44,71).

Application of probiotics also significantly decreased the number of relapses after successful treatment of *Clostridium difficile* infections (72), but the analysis of other trials yielded no clear-cut results because of inconsistent data and the heterogeneity in study design and choice of probiotics (73).

Careful reviews of the literature (74–77) support an efficacy of *L. rhamnosus* GG and mixed-strain probiotics in prevention and treatment of AAD in children and adults but not in the treatment of *C. difficile* infections, whereas *S. boulardii* is not effective or only moderately effective in the prevention of AAD but more efficacious in prevention and treatment of *C. difficile*–associated diarrhea.

In conclusion, there seems to be a potential role for probiotics in prevention of AAD. The same is true for diarrheas during triple therapy for *H. pylori* eradication. In particular, *S. boulardii* may be effective as an adjunct in the treatment of *C. difficile*–associated diarrhea.

Diarrhea in tube-fed patients

Diarrhea is a frequent complication in enteral tube feeding. The reasons for this are manifold, but the effectiveness of probiotics has been little studied to date. Although administration of *S. boulardii* did reduce the frequency of diarrhea in critically ill tube-fed patients from 20% of enteral feeding days in the placebo to 14% in the treated group ($P < 0.01$) in a randomized, placebo-controlled study (78), a mixed-strain preparation of *L. acidophilus* plus *L. delbrückii* ssp. *bulgaricus* had no effect on the frequency or incidence of diarrhea in subjects who were tube-fed <5 d (79).

In conclusion, at the moment there is not enough evidence from clinical trials to recommend the use of probiotics in the prevention of diarrhea in tube-fed patients.

Diarrhea in immunocompromised subjects

Chemo- and radiotherapy frequently cause severe disturbances of the immune system and the indigenous intestinal microflora accompanied by diarrhea and/or increased cell counts of the mold *Candida albicans* in the gastrointestinal tract and other organs. Side effects were ameliorated by the administration of probiotic bacteria before and during chemo- (80) or radiotherapy (81,82).

Whether regular consumption of probiotics exerts beneficial effects in HIV patients has not been studied up to now, but it has been shown that probiotic products are well tolerated by these patients (83).

In conclusion, although results of a few studies indicate that probiotics can be effective in the prevention of radiation-induced diarrhea, there is not enough evidence from clinical trials to recommend the prophylactic or therapeutic use of probiotics in immunocompromised subjects.

Inflammatory bowel diseases

Although their exact causes are not yet fully understood, disturbances of the autochthonous intestinal microflora and the stimulation of proinflammatory immunological mechanisms seem to play a role in a number of inflammatory diseases of the intestine. Therefore, numerous efforts have been undertaken to improve the health and well-being of affected patients by the administration of probiotics with antiinflammatory properties and a proven positive impact on the intestinal flora. Extensive investigations have been performed on the effect of nonfood probiotics, particularly nonpathogenic strains of *Escherichia coli*.

Studies in experimental animals give a clue about the potential application of lactobacilli, bifidobacteria, or *Lactococcus lactis* to prevent or treat colitis (84–88).

Patients with inflammatory bowel diseases (Crohn's disease, ulcerative colitis, diverticulitis, necrotizing enterocolitis, or inflammation of an ileal pouch after colectomy) also showed a positive response to probiotics such as LGG, *E. coli* Nissle 1917, or a mixed culture preparation containing 4 strains of lactobacilli, 3 strains of bifidobacteria, and *Streptococcus thermophilus* (VSL#3). Beneficial effects were a decreased expression of inflammatory markers ex vivo (89), increased immune response (90), improvement of gut barrier function (91), maintenance of remission (92–96), and a lower drug consumption (92,97). All in all fewer symptoms and a higher quality of life of children and adult patients were observed, although mainly in preliminary studies (98). In other studies LGG and other probiotics failed to induce or maintain remission and did not extend the time to a new relapse in Crohn's disease (99–102). This is discussed in greater detail in the article by Sheil et al. in this issue.

In conclusion, accumulating evidence from randomized, controlled, but relatively small clinical studies suggests the potential of probiotics for inducing or maintaining remission in inflammatory bowel diseases. In particular, a mixed strain preparation of lactobacilli plus bifidobacteria was effective in ulcerative colitis and pouchitis. However, further investigations and a deeper insight into the role of the autochthonal microflora and the host immune system, targets for probiotic effects, in the development of inflammatory bowel diseases are needed.

Small bowel bacterial overgrowth

Certain circumstances such as insufficient production of gastric acid (anacidity), extented gastrointestinal transit time, resection of the small intestine, or, most frequently, terminal renal failure can lead to an excessive growth of single bacterial strains in the

small intestine and to increased, partly life-threatening concentrations of D-lactic acid and toxic metabolites of the bacterial protein metabolism. Only a few successful approaches to normalizing the small intestinal microflora have been reported (103), e.g., decreased frequency of diarrheas (104) following administration of *L. acidophilus* and *L. casei* to patients with small bowel bacterial overgrowth.

In conclusion, the few reported clinical trials are not yet sufficient to recommend the use of probiotics in the treatment of small bowel bacterial overgrowth.

Irritable bowel syndrome

The irritable colon is a functional disorder of the colon without provable biochemical or structural irregularity and is characterized by intermittent abdominal pain and an alternating succession of diarrhea and obstipation. Reports on effects of probiotics in this disorder are still rather contradictory. Although in some trials a positive modulation of the intestinal flora, less motility disorder, and the alleviation of functional diarrhea were found (105–109), a randomized, placebo-controlled study on 362 primary-care female patients with IBS showed an improvement in bowel dysfunction and other symptoms only if 10^8 cfu of the freeze-dried probiotic bacteria *B. infantis* spec. were administered, but not at any other dosage level (110). Other studies failed to confirm significant effects on stool frequency or consistency (111–113), so further investigations are required to advance from hopeful findings to conclusive results (114–116).

In conclusion, because of small numbers of patients, poor compliance, and other methodological inadequacies, currently there is not enough evidence from clinical trials to recommend the routine use of certain probiotic strains in the treatment of IBS.

Effects of prebiotics

Prebiotics were originally defined by Gibson and Roberfroid (117) as "nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of 1 or a limited number of bacteria in the colon, and thus improve host health," and this criterion is fulfilled only by some indigestible but fermentable carbohydrates (inulin, lactulose, and certain oligosaccharides). They have been redefined by the same group (118; this issue) as "selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confer benefits upon host well-being and health."

According to these authors, only 2 indigestible oligosaccharides fulfill the criteria for prebiotic classification to date: *1)* inulin and inulin-type fructans, produced by partial hydrolysis of inulin or synthetically from the monomers, and *2)* (*trans-*)galactooligosaccharides. Investigations in other candidate prebiotics to date did not yield enough meaningful information to make conclusive assessments.

The main characteristics of a prebiotic are resistance to digestive enzymes in the human gut but fermentability by the colonic microflora, and bifidogenic and pH-lowering effects (119, 120). By this last effect prebiotics inhibit certain strains of potentially pathogenic bacteria, especially *Clostridium*, and prevent diarrhea (121). A symbiotic combination of inulin plus oligofructose with *L. plantarum* plus *B. bifidum* increased the growth of bifidobacteria but inhibited human pathogenic strains of *Campylobacter jejuni*, *E. coli*, and *Salmonella enteritidis* in vitro more than any other carbohydrate tested (122). Similarly, the combination of *trans*-galactooligosaccharides plus bifidobacteria did protect mice against lethal infections with *Salmonella enterica* serovar *typhimurium* (123). A symbiotic composed of a probiotic *L. paracasei* strain and oligofructose increased counts of *Lactobacillus* spp., *Bifidobacterium* spp., total anaerobes, and total aerobes in the feces of weanling piglets significantly more than a pure *L. plantarum* preparation and significantly decreased fecal concentrations of *Clostridium* spp. and *Enterobacterium* spp. compared with the control group (124). Inulin and oligofructose (125) or prebiotic treatment with germinated barley foodstuff (126) had beneficial effects on experimental colitis and the composition of the intestinal microflora of rats. Galactooligosaccharides, on the other hand, failed to attenuate inflammation in experimental colitis in rats (127).

Despite the promising results of animal experiments, there was no report of a successful preventive or therapeutic use of prebiotics in patients with diarrhea and/or inflammatory diseases of the gut. This is possibly a result of side effects such as gas, borborygmus, pain, or diarrhea, which can sometimes be observed when therapeutic doses of prebiotics are administered to particularly sensitive subjects, IBS patients, or in cases of a maladapted intestinal flora. In AAD, the bifidogenic effect of prebiotics may be suppressed by the antibiotic.

However, when small amounts (2 g/d) of oligofructose or a placebo (maltodextrin) were administered over 4 wk to 35 healthy infants (aged 6–24 mo), greater numbers of bifidobacteria (NS) and lower numbers of clostridia ($P < 0.05$) were found in the

TABLE 2 Established and proposed probiotic health effects

Probiotic effect	Validity of scientific knowledge
Modulation of the autochthonous (usually intestinal) microflora	Well-established effect. However, because of methodological difficulties and complex interactions between regulatory mechanisms, the correlation with true health effects is not clear
Prevention and/or reduction of duration and complaints of rotavirus-induced diarrhea	Effect well established by clinical studies and accepted by the scientific community
Prevention or alleviation of antibiotic-associated diarrhea	
Alleviation of complaints caused by lactose intolerance	
Beneficial effects on microbial aberrancies, inflammation, and other complaints in connection with inflammatory diseases of the gastrointestinal tract, *Helicobacter pylori* infection, bacterial overgrowth	Effects established in certain target groups. However, more studies are necessary to find out which section of the population may profit from a probiotic and under which conditions
Prevention and alleviation of unspecific and irregular complaints of the gastrointestinal tract in healthy subjects	
Normalization of passing stool and stool consistency in subjects suffering from an irritable colon	Effects cannot be classified as well established and scientifically proven because of insufficient clinical and/or epidemiological data

stool. Fewer children were afflicted with diarrhea, and fewer diarrheal episodes were observed, in the oligofructose compared with the placebo group (0 vs. 3 children and 0 vs. 13 episodes; $P < 0.05$). Significantly fewer episodes of flatulence (4 vs. 27), vomiting (0 vs. 10), and fever (5 vs. 13) were observed in the oligofructose group as well (128). Furthermore, partially hydrolyzed guar gum, a bifidogenic, water-soluble, nongelling fiber, improved symptoms in constipation-predominant and in diarrhea-predominant IBS (129).

In other studies a prebiotic effect on diarrhea was less clear. Coadministration of 12 g/d oligofructose during antibiotic therapy reduced the occurrence of relapses of successfully treated *C. difficile*–associated diarrhea to 8%, compared with 34% in controls ($P < 0001$) (130), but the same amount of oligofructose failed to protect elderly subjects receiving broad-spectrum antibiotics from AAD (development of diarrhea in 56 of 215 in the oligofructose and in 60 of 220 patients in the placebo group) (131). And 10 g/d oligofructose (given 2 wk before and during a 2-wk journey) was only moderately successful in preventing traveler's diarrhea, reducing the percentage of subjects with diarrhea attacks to 11% compared with 20% in the placebo group ($P = 0.08$) (132).

Other clinical studies failed to show a significant reduction of diarrhea in IBS (133), infantile infectious diarrhea (134), and AAD in children (135).

In conclusion, despite established positive effects of inulin, oligofructose, and galactooligosaccharides on the intestinal microflora, and despite some promising results of animal experiments, there is not enough evidence to medically recommend prebiotics for the prevention or treatment of diarrhea.

Table 2 lists beneficial effects of probiotic microorganisms on the gastrointestinal tract and particularly on diarrhea.

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