Clinical Studies of Probiotic Agents

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GENERAL CONCEPTS

The deliberate addition of microorganisms to the diet of humans dates back to ancient times. Initially, these were probably ingested in the form of fermented milk products, where the bacteria were used to preserve dairy foods. The popularity of dairy products containing "cultures," in the form of yogurt and other fermented milks, has not only withstood the test of time, but their consumption has actually increased over the last few decades due to numerous factors. The recent increase in health consciousness of some populations and the purported health benefits touted in the lay literature and popular culture have boosted this popularity.

The concept that these products confer health benefits beyond their dietary value is not new (1). The idea that microorganisms are part of our environment and that our intestinal lumen is a continuum with that environment led individuals like Metchnikoff (2) around the turn of the century to suggest that the ingestion of specific organisms (lactobacilli) could displace toxin-producing "putrefactive" microorganisms in the intestinal tract and thus promote health and prolong life. Later in this century, the concept that preserving a normal gut flora was beneficial ensued. Subsequently, other important clinical roles of normal gut flora were described. A "healthy" flora is necessary to maintain the health of the intestine, particularly the colon, to prevent the establishment or activity of potential pathogens and maintain adequate nutritional status of the B vitamins and vitamin K. Eventually, a scientific literature emerged, supporting the potential of some of these microorganisms to prevent or treat specific disease conditions when consumed orally, both in animals and in humans (3,4). All this led to the current concept of "health-promoting bacteria."

Unfortunately, the wide range of purported benefits, the many nonpathogenic bacteria and other microorganisms that have been implicated in these benefits, and the relative paucity until recently of adequately conducted research have all made it difficult to establish a clear role for these agents in health promotion or disease management. Their apparent safety and thus the lack of need for regulation may also have hindered adequate research.
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These shortcomings have led to a plethora of terms, names, and neologisms that has made the picture even more confusing. A few terms warrant some comment:

1. **Probiotics.** Coined in the 1970s, probiotics has generally been defined as a “live microbial feed supplement which beneficially affects the host animal by improving its microbial balance” (3). Unfortunately, this definition has multiple caveats: (i) It has yet to be proven that some of the beneficial effects are not due to metabolites or components of the microorganisms (which do not necessarily require that they be viable); (ii) the proposed benefits are completely open to interpretation; (iii) what constitutes a balanced flora remains to be determined (in fact, we may be unbalancing the flora for a particular host by ingesting microorganisms); and (iv) some effects of these organisms (e.g., immunostimulation of gut-associated lymphoid tissue) may be quite independent of modifications in the indigenous flora of an individual. For the purpose of this chapter, I will use a broader definition of the term: *a defined microbial feed supplement that, when ingested, has a positive effect on the prevention or treatment of a specific pathological condition.*

2. **Prebiotics.** The term is used in general to describe agents that, when ingested, will promote the growth, establishment, or activity of the probiotic microorganisms mentioned above. The term therefore shares similar problems of definition.

3. **Colonic foods.** Probiotics, prebiotics, and synbiotics are considered in some published reports under this common term. However, it is clear that a significant portion of the effects of these agents, such as modifications of the mucosal barrier, immunomodulation, and effects on small bowel digestion and absorption, do not occur at the colonic level.

4. **Biotherapeutic agents.** This rather broad term has been used as such in recent reviews (4). There is a strict implication that agents described by this term are used for the treatment of illness or disease. On the basis of the specific activities and mechanisms that may result in health benefits, it is clear, however, that many of these agents are actually “bioprophylactics” or may simply facilitate certain functions of the gut in entirely normal individuals. An example is the decline in lactase activity (not a disease, but a normal part of development in most humans) that leads to lactose intolerance in the majority of normal mammals. This can be improved or circumvented by the use of lactase-producing microbial agents ingested orally.

5. **Functional foods.** These agents cause a change in function in the human economy that leads to a “health benefit.” This has led to even more ill-defined terms such as “nutraceuticals,” “vitafoods,” “pharmafoods,” and “designer foods.” A discussion of these is beyond the scope of this chapter. Suffice it to say that the effect of these terms on health education, research, and ultimately on clinical applications of probiotic agents has made the picture more chaotic and difficult to interpret.
The extraordinary body of anecdotal and testimonial literature added to a significant number of uncontrolled reports and an increasing number of adequately conducted studies over the last few years has led to the recognition of the true potential of these agents in health maintenance and promotion (1,4). In this chapter, we focus on the two specific clinical benefits that have been most widely studied and documented in humans: the effects of probiotics on lactose digestion and on diarrheal disease.

**LACTOSE DIGESTION**

Most human adults, and all other adult mammals, undergo a decline of lactase activity in the intestinal brush border following weaning. The great majority of individuals worldwide are lactose maldigesters. The lack of adequate lactose absorption when lactase activity is low and lactose delivery to the gut is relatively high will lead to signs and symptoms of lactose intolerance, including increased abnormal gas, bloating, and diarrhea, which can be voluminous, watery, and contain a significant amount of organic acids as the product of the fermentation of unabsorbed carbohydrates by colonic bacteria (5). Kolars et al. (6) showed that a number of microorganisms, specifically *Lactobacillus bulgaricus*, *Streptococcus thermophilus*, and subsequently *Lactobacillus acidophilus*, can exert their lactase activity in vivo following ingestion. Thus, the activity of these microorganisms in the intestine can facilitate the digestion of lactose and its subsequent absorption, with amelioration of the clinical signs of lactose intolerance.

Recently, we reported that this effect, which had been demonstrated in adults, can be replicated in children (7). Twelve children with lactose malabsorption documented by standard lactose breath hydrogen test underwent a controlled trial with milk, pasteurized yogurt, and yogurt containing similar amounts of lactose. When the children ingested yogurt with active live cultures, they had significantly lower symptom scores than with milk. Pasteurized yogurt had an intermediate effect. The ingestion of yogurt with active live cultures significantly changed the kinetics of gas formation, inducing a slower rate of hydrogen production in the colon, and this probably led to a reduced symptom score in these subjects. Subsequently, we also demonstrated a significant improvement in symptom scores when yogurt starter culture or *L. acidophilus* was added to milk directly and ingested by lactose-malabsorbing children (8). The improvement in lactose absorption may be responsible for the improvement in signs and symptoms of enteritis in children with carbohydrate malabsorption who take fermented milk products, particularly yogurt, as part of their dietary regimen during an episode of acute diarrheal disease.

**CLOSTRIDIUM DIFFICILE DIARRHEA**

*C. difficile* diarrhea is an opportunistic infection that typically follows antibiotic disruption of the intestinal flora. It usually responds to treatment with metronidazole or vancomycin. However, relapses are quite common. Several investigators have
reported, in uncontrolled observations, resolution of *C. difficile* diarrhea with *Lactobacillus casei* strain GG (L.GG) in a small number of adults (9, 10) and four children (11). Another study reported similar potentially positive results in a larger number of adults (12). Typical doses were $10^{10}$ colony-forming units (CFU) per day for 1 to 2 weeks. L.GG was originally isolated from a healthy human and may have the ability to establish itself in the colon following regular ingestion. The organism is stable in acid and bile and has been found to produce an antimicrobial substance that inhibits several enteropathogens *in vitro*, including *C. difficile* (13).

In an uncontrolled trial, Surawicz et al. (14) reported that *Saccharomyces boulardii*, a yeast, in combination with vancomycin was effective in treating *C. difficile* in 11 of 13 patients. Later, in a placebo-controlled trial done by the same investigators, 124 patients were randomized to receive oral *S. boulardii* or placebo in combination with vancomycin or metronidazole (15). The patients treated with *S. boulardii* and standard antibiotics had a significantly lower relative risk of recurrence than those with placebo and standard antibiotics. The ability to decrease the recurrence rate was significant in patients who had a history of recurrent *C. difficile* diarrhea, but not in those who had an initial episode of the illness.

**PROPHYLAXIS FOR TRAVELER’S DIARRHEA**

Several placebo-controlled studies for prophylaxis of traveler’s diarrhea have been reported. In one, L.GG was evaluated in 756 Finnish tourists traveling to Turkey (16). The overall rates of traveler’s diarrhea were similar in patients receiving L.GG and placebo (41% vs. 46.5%). Two specific destinations were studied, and in only one of them were the rates significantly lower (23.9% vs. 39.5%). Thus, the overall effectiveness was questionable, and unfortunately the etiologies were not documented.

Another study found promising results using L.GG (17). In this study, the investigators studied 245 subjects attending a clinic in the United States who had journeyed to a developing country for a period of 1 to 3 weeks. Of 2743 travel days, the risk of having diarrhea on any given day was 7.4% in the placebo group, compared to 3.9% in the L.GG group—a statistically significant protection rate of 47%. Finally, in another placebo-controlled trial, a different *Lactobacillus* preparation was not found to be protective against traveler’s diarrhea (18), while in a placebo-controlled trial in volunteers, Clements et al. (19) were not able to show a difference in protection against toxigenic *Escherichia coli* with a preparation of *L. acidophilus* and *L. bulgaricus*.

In a double-blind placebo-controlled study using *S. boulardii* in 3000 Austrian travelers, there were reported rates of diarrhea of 39.1% in the placebo group versus 28.7% in the group receiving 1 g/day of *S. boulardii* (20), a small but statistically significant difference, although only 1016 subjects were compliant with the study protocol. The protection rate appeared less effective with 250 mg/day of the yeast. The poor compliance and lack of etiological studies were weaknesses in this study.
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ANTIBIOTIC-ASSOCIATED DIARRHEA

The prevention of diarrhea associated with the use of antibiotics has been the focus of several studies. The likely disruption of the normal flora by antimicrobials is a natural scenario for demonstrating the potential role of microbial agents such as the probiotics discussed here.

Several volunteer studies have been reported. In a crossover study with healthy volunteers receiving erythromycin, Colombel et al. (21) showed that Bifidobacterium longum in yogurt reduced stool weight (208 g/day vs. 145 g/day) and stool frequency (1.9 vs. 1.2 per day). Abdominal discomfort was also less. However, the treatment time was only 3 days, and while the differences were statistically significant, they were of doubtful clinical relevance (63 g less stool per day and 0.7 fewer days of diarrhea). Orrhage et al. (22) reported a significant decrease in gastrointestinal discomfort in 10 volunteers receiving clindamycin plus a fermented milk product with B. longum and L. acidophilus versus a fermented milk product without these organisms.

Enterococcus faecium SF68 was given prophylactically for 7 days to 45 patients receiving antibiotics in a multicenter double-blind trial (23). Diarrhea was observed in 27.2% of the placebo group compared to 8.7% of the treated group. Siitonen et al. (24) reported improvement of erythromycin-induced diarrhea in 16 volunteers randomized to receive L.GG in a yogurt product or placebo. In eight of the volunteers receiving L.GG, only 2 days of diarrhea were observed, compared to 8 days of diarrhea in eight controls receiving pasteurized yogurt. Using a combination of L. acidophilus and L. bulgaricus, Gotz et al. (25) found that none of 36 hospital inpatients receiving ampicillin developed diarrhea, compared with 6 of 43 who received ampicillin and placebo. Other studies, however, have failed to find a protective effect of L. acidophilus and L. bulgaricus in antibiotic-associated diarrhea (26).

In a large double-blind placebo-controlled trial using S. boulardii (27), 388 ambulatory adult patients received either tetracycline or β-lactam antibiotics for at least 5 days. Significantly fewer patients developed antibiotic-associated diarrhea (9 of 199, 4.5%) compared with those receiving placebo (33 of 189, 17.5%). In two other double-blind placebo-controlled studies, S. boulardii also appeared effective. In one trial, 180 hospital inpatients who received antibiotics were assigned to either S. boulardii 0.5 g twice a day (1 × 10¹⁰ CFU) or placebo concurrently with their antibiotic and continued for 2 weeks after discontinuation of the antibiotic (28). Significantly fewer patients receiving the yeast developed antibiotic-associated diarrhea (9.5% vs. 22%). In a subsequent trial, the same investigators showed that only 7.2% versus 14.6% of 97 patients receiving a broad-spectrum antibiotic developed diarrhea if they took S. boulardii simultaneously (29).

TREATMENT OF DIARRHEA

The potential treatment of acute diarrhea (not related to antibiotics or C. difficile) with probiotic agents is currently receiving greater attention. Given the fact that
diarrheal disease continues to be a major cause of infant mortality, most studies have been done in pediatric populations.

Only a few trials in adults have been reported. Two have used *E. faecium* SF68 in similar doses to treat acute diarrhea, with opposite results. Wunderlich et al. (23) used *E. faecium* to treat 78 patients with acute diarrhea. Those treated reported less diarrhea on day 7 than those on placebo. In another study, 183 adults in Bangladesh with diarrhea (114 with *Vibrio cholerae*, 41 with enterotoxigenic *E. coli*, and 28 of unknown etiology) were treated with *E. faecium* SF68 or placebo (nonviable *E. faecium*) for only 3 days (30). There was no difference in resolution of diarrhea between the two groups.

In a double-blind placebo-controlled trial, 35 patients with human immunodeficiency virus (HIV) disease and chronic diarrhea were given *S. boulardii* 1.5 g twice a day for 1 week or placebo. Of 18 patients given *S. boulardii*, 10 (56%) had resolution of diarrhea, compared with 1 of 17 (6%) of those on placebo (31).

In two reports, Boudra et al. (32) and Touhami et al. (33) showed improved clinical outcome, by stool output and weight gain, in children with persistent diarrhea fed yogurt instead of milk. These studies were open trials, and the effect could be attributed to dietary management of diarrhea independent of the probiotic agents used.

In a well controlled study, Isolauri et al. (34) studied children in the hospital with acute diarrhea. After oral rehydration, patients were randomly assigned to receive either L.GG-fermented milk, L.GG as a freeze-dried powder, or pasteurized yogurt as a placebo for 5 days. The duration of diarrhea was reduced from 2.4 days in the placebo group to 1.4 days in the supplemented groups. In this study, 82% of the subjects had rotavirus infection, and the reduction in duration of diarrhea with L.GG was greater when only patients with confirmed rotavirus infection were analyzed.

In another prospective placebo-controlled trial (35), 40 children in Pakistan were enrolled after rehydration to receive either oral L.GG or placebo twice daily for 2 days. Most children had moderate to severe diarrhea and varying degrees of malnutrition. The percentage of children with persistent watery diarrhea at 48 hours was significantly less in the treated group (31% vs. 75%). There was no significant difference in those presenting with bloody diarrhea.

Two recent studies show positive results with L.GG. In one, Majamaa et al. (36) showed a small but significant shortening of the course of rotaviral diarrhea and a higher secretory immunoglobulin A (IgA) response in children receiving L.GG compared to groups receiving *L. rhamosus* or *L. delbrueckii* with *S. thermophilus*. In another trial, L.GG also shortened the duration of acute watery diarrhea, but not bloody diarrhea, in a group of Thai children (37). On the other hand, a previous study using a different *Lactobacillus* preparation did not find an improved outcome in children in hospital for acute diarrhea (38).

*S. boulardii* has been used in several treatment trials. A dose of 0.5 g daily for 5 days, with standard oral replacement therapy (ORT), was compared with ORT alone in 38 children with acute diarrhea (39). The treated group showed a decrease in stool weight and an increased transit time of carmine red. In another large placebo-
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controlled double-blind study in 130 Mexican children with acute diarrhea, S. boulardii reduced stool output and improved overall treatment success (40).

PREVENTION OF INFANTILE DIARRHEA

Two studies giving L.GG to premature infants for short periods (1 week) did not show a reduction in stool intestinal pathogens or an apparent clinical benefit in this population (41,42). These studies underline the fact that agents such as L.GG can be present in increased quantity in the gut lumen and their excretion augmented, but true colonization does not always occur, nor are there necessarily any marked changes in the indigenous flora. Thus, it appears that a beneficial prophylactic effect can only be expected with regular consumption of the probiotic agent.

We recently conducted a double-blind placebo-controlled trial in infants aged 5 to 24 months who were chronically in hospital for nongastrointestinal conditions (43). Fifty-five subjects were randomized to receive a standard infant formula or the same formula supplemented with bifidobacteria and S. thermophilus. Over a 17-month period, 31% of the patients receiving control formula but only 7% of those receiving the supplemented formula developed diarrhea. Interestingly, and independently of the occurrence of diarrhea, 39% of the subjects who received the control formula and only 10% of those who received the supplemented formula shed rotavirus at some time during their hospital admission. This is the first study that has shown a preventive effect of continued administration of probiotics for pediatric diarrheal disease, as well as an effect on the occurrence of viral pathogens.

The potential effects of several of these agents in the management of rotaviral diseases are particularly exciting because they do not seem to be mediated by a simple modification of intestinal bacterial flora, but instead reflect a more complicated system that prevents infection by a virus rather than a bacterium. Recently, Isolauri et al. (44) showed an improved immunogenicity of oral rotavirus vaccine in 2- to 5-month-old infants when they received vaccine with L.GG. The treated infants showed an increased response in rotavirus-specific IgM-secreting cells on day 8 after vaccination. IgM seroconversion was not significantly different in the groups, but IgA seroconversion was reported as 93% versus 74%, which was significant. These findings suggest that L.GG has an immunostimulating effect on oral rotavirus vaccination. In a previous study in children with acute rotaviral diarrhea, this same group of investigators showed that treatment with L.GG was associated with an enhanced nonspecific humoral response during the acute phase of the infection, reflected in IgG-, IgA-, and IgM-secreting cell numbers (45). At convalescence, 90% of the study group versus 46% of the placebo group had developed an IgA-specific antibody-secreting cell response to rotavirus. These studies indicate that certain probiotic agents may promote recovery from rotaviral diarrhea by augmenting the local immune defense (36,45).

The possibility that probiotic agents such as bifidobacteria and L.GG decrease rotaviral shedding by enhancing the immune response during rotavirus diarrhea is of importance, signifying a departure from the simplistic concept that good bacteria
override bad bacteria to promote intestinal health. Interestingly, other studies have recently documented the effectiveness of bifidobacteria in ameliorating rotaviral diarrhea and in decreasing rotavirus shedding in animals (46). In another study, Yasui et al. (47) showed passive protection against rotavirus-induced diarrhea in mouse pups born to and nursed by dams fed *Bifidobacterium breve*. This passive protection was associated with increased concentrations of antirotavirus IgA in the milk of the dams who were fed *B. breve* and immunized orally with rotavirus, compared with the dams immunized with rotavirus and not supplemented with *B. breve*. It is an intriguing possibility that regular ingestion of some of these agents may enhance antigen-specific IgA antibody production in the milk of the mother-infant pair and thus provide a more efficient mechanism for protection against rotaviral disease, the most important and significant cause of diarrhea worldwide.

In summary, several probiotic agents have been shown to be effective in the control of diarrheal disease; in particular, the treatment of recurrent *C. difficile* diarrhea and the control of antibiotic-associated diarrhea appear to be rewarding. The potential for preventing traveler’s diarrhea remains to be substantiated. Some agents, including L.GG and *S. boulardii*, appear promising for ameliorating the course of acute diarrhea in children, when used therapeutically. Finally, the use of bifidobacteria given as a supplement in regular infant feeding appears to protect against acute diarrheal disease; this suggests an immunological mechanism that decreases viral infection. Table 1 summarizes the most relevant studies reviewed.

### SAFETY CONCERNS

Many decades of consumption of lactobacilli, bifidobacteria, and other agents worldwide with no reports of significant side effects should ease safety concerns. However, caution is warranted where large numbers of viable nontraditional strains or strains of human or animal origin are given, because of the potential for genetic transfer of antibiotic resistance (48). Recently, fungemia in a 1-year-old child treated with *S. boulardii* for prolonged diarrhea was reported (49). There is a particular need to consider the safety of using probiotic agents in immunocompromised populations, such as HIV disease patients. In our study, we enrolled two children with HIV disease, who received bifidobacteria and *S. thermophilus* for prolonged periods with no adverse effects and with improvement in their nutritional status (43).

### MECHANISMS OF ACTION

Various mechanisms can be proposed for the potential effects of microbial agents in the prevention and treatment of diarrheal disease. Table 2 summarizes these, with supporting references.

It is possible that several different mechanisms may be operative at the same time. The potential mechanisms will also vary with the different pharmacodynamics or biodynamics of the organism. It is obvious that if a metabolite is necessary for a protective or therapeutic effect, the organisms would need to be viable. On the other
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<th>TABLE 1. Clinical studies of probiotic agents</th>
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L. GG, lactobacillus GG.
TABLE 2. Effect of probiotics in diarrheal disease

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<td>Production of antimicrobial substances by</td>
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<td>various biotherapeutic agents</td>
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hand, immunostimulation by any structural component of the agent may be all that is necessary in some situations. Similarly, the ability to colonize would be of importance if competition with pathogens for adhesion at colonic level is the critical factor. However, for immunostimulation, regular interval dosing to achieve certain levels in the small bowel to protect from agents such as rotavirus may be all that is necessary. Studies to optimize dose regimens and delivery vehicles are badly needed. Once we know more about these potential mechanisms, we will be in a position to make recommendations about dose, concurrent diet, and prophylactic and therapeutic indications.

REFERENCES

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**DISCUSSION**

*Dr. Fuller:* My definition has been around for about 10 years, and it certainly needs updating and improving, no doubt, but I'm reluctant to see live bacteria disappear from the definition. As far as I know, the few studies that have been done comparing viable and nonviable preparations have shown that they lose their activity if you kill them. I'm prepared to see the rest of the definition change. This old problem of microbial balance has been with us for a long time, and a lot of people have suggested that it is not the right way to define things, but they haven't come up with anything better. I'm not sure that what you've come up with is any better either!

*Dr. Saavedra:* The fact is that the studies remain to be done, and the more we learn about mechanisms, the more we know about what we don't know. I believe there is probably more to it than the simple fact that these organisms are alive. Effects may be due to the way we react to components or parts of that microorganism, such as the capsule or its metabolites. If we believe that the organisms have to be live, it poses a practical problem from the point of view of delivering them. If we were able to show that effects resulted from a response to some part of the organism, the practical difficulty of putting them into a feed in live form might disappear.

*Dr. Szajewska:* The American Academy of Pediatrics published recommendations for the treatment of acute gastroenteritis 2 years ago. It stated that probiotics are not recommended. I would appreciate your opinion on that.

*Dr. Saavedra:* I don’t know of any specific recommendation about probiotics, nor are we ready to make a recommendation. There is no question that a number of other agents, including antidiarrheal drugs, are not recommended. From the point of view of probiotics, fermented milk products could be part of the recommendation of continued feeding during the diarrheal episode, which is one thing that everybody does agree on. From a treatment point of view, the results are promising but very variable. A lot has to do with the fact that since we don’t know the mechanism, we don’t know when the introduction of a probiotic may be effective. If we think of it as simply overriding a large population of disease-causing bacteria, then perhaps it would be reasonable to give a very high dose as early as possible. But that’s obviously not the case for rotaviral diarrhea, where these agents do seem to have a role. If the mechanism of this is an enhancement of the immune system, it would make more sense to give the agents prophylactically, which is one reason for the trials we are currently doing. On the other hand, I don’t know of any detrimental effects of giving many of these probiotic agents at any time.
Dr. Isolauri: I have two comments. First to Dr. Szajewska about the American Academy of Pediatrics' recommendation. That paper accepted for the first time the concept of rapid refeeding, 15 years after the first clinical studies showed this was desirable. That demonstrates the kind of time lag we are faced with with this kind of consensus paper. In fact, they mentioned that more research was needed on probiotics; they did not say that they should not be used. I think that showed a positive attitude toward more research in this field. My second comment is to Dr. Saavedra. I liked your definition of probiotics, first because we have clinical results showing that killed bacteria have an effect on rotaviral diarrhea, even though this was apparently not immunologically mediated, and second because you introduced the idea of specific clinical conditions where probiotics should be used and what diseases we want to prevent with them. That's better than promoting health benefits.

Dr. Heller: I would like to comment on the clinical application of *S. boulardii*, which is used for *C. difficile* diarrhea. I have the feeling in this meeting that the whole emphasis is on bifidobacteria. I know there are studies on *S. boulardii* in acute diarrhea. I would like your opinion.

Dr. Saavedra: *S. boulardii* has been used, and there is at least one reasonably good controlled trial showing that this organism does decrease the likelihood of recurrence of *C. difficile* diarrhea (1). There is very little work on antibiotic-associated diarrhea before the development of *C. difficile* diarrhea as a first episode. So the majority of trials in the literature are for recurrent *C. difficile* colitis after standard treatment with antibiotics, including vancomycin and metronidazole. In those studies, even though they were poorly controlled, *L. acidophilus* and a particular strain GG, which is the one that has been most used, seemed to be reasonably efficient. All those have been open trials (2,3).

The same group of investigators subsequently took a cohort of about 30 older patients in nursing homes and gave them L.GG over a period of weeks after a first episode of *C. difficile* diarrhea. Again, in this open trial, there did appear to be benefit (4). On the other hand, with *S. boulardii* there has only been one placebo-controlled trial. This was of *S. boulardii* with an antibiotic. It did not take the place of vancomycin or metronidazole in the treatment. This showed a decreased rate of recurrence.

Finally, about risk-benefit ratios, as we've heard earlier in relation to *S. boulardii*, there is potential pathogenicity that might favor L.GG over *S. boulardii*. However, I don't think there is enough information on this. There are no studies comparing both to say that one is better than the other.

Dr. Zoppi: I think the biggest difficulty in judging the effects of probiotics on health is that their survival in the large intestine is quite brief. After suspension of treatment, lactobacilli and the bifidobacteria will disappear within 2 weeks.

Dr. Saavedra: The gut ecosystem in the healthy individual is relatively resilient. It is not easy to change it. As we've heard, we might even consider it a "fingerprint" for a particular individual from the pattern of fecal strains. So I agree that makes it difficult to interpret the effects. On the other hand, we've also heard that maybe you don't need to colonize the colon; maybe there are other mechanisms whereby repeated dosing of an agent simply to the small bowel, forgetting the colon, may be enough to obtain a particular benefit. Once we have defined what benefits we are talking about for each one of these agents, and what dose, it will be easier to make a statement.

Dr. Gibson: Your new definition may cause more difficulties than you think, because if you start talking about specific clinical or pathological disorders, we have to know the mechanism of those disorders. For instance, we have heard this week that probiotics could be useful
in lowering cholesterol. But we don’t really know that cholesterol causes coronary heart disease. So you need to know the mechanism of the disease you’re looking at as well.

Dr. Saavedra: I agree, and that is precisely why we need to say that a probiotic should be defined by its specific benefit, which of course means knowing at least something about the mechanism. At the same time, we also need to demonstrate reproducibly in a double-blind way to prove that you get a health benefit with a particular bacterium. This puts the onus on us to be able to say: this is the health benefit brought about by this bacterium, and not just make broad “health benefit” claims.

Dr. Kratky: You may not be defining probiotics, but rather drugs derived from microbial fermentation that are useful in the treatment of certain health disorders.

Dr. Saavedra: That may be the way some probiotics work.

Dr. Bohles: I would like to emphasize from a practical point of view that probiotics do work in preventing antibiotic-induced diarrhea. I learned this 25 years ago in America when we used a lot of ampicillin and we were always getting ampicillin-induced diarrhea. Once we began using a spoonful of yogurt at the same time as each dose of ampicillin, I never saw the problem again. Two years ago, I read in the Lancet a brief comment suggesting that this was something very new. It’s not new: it’s an old experience, and it really works.

Dr. Saavedra: I also have personal experience with that. My father, who is a pediatrician, used to recommend yogurt to everybody to whom he prescribed antibiotics. I asked him, and still ask him, where is the double-blind trial!

REFERENCES