Probiotics for Prevention and Treatment of Diarrhea

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Abstract: Probiotics have been extensively studied over the past several years in the prevention and, to a larger extent, in the treatment of diarrheal diseases, especially in pediatric populations. Diarrhea is a symptom, and not a disease. This review will not address chronic disorders associated with diarrhea, or *Clostridium difficile*-induced diarrhea. Rather it will focus on published clinical trials performed on acute-onset, likely infectious diarrhea occurring in the settings of day-care centers, in the community, acquired in the hospital, antibiotic-associated diarrhea, and treatment of acute infectious diarrhea. For prevention of diarrhea acquired in day-care centers, 9 randomized and placebo-controlled trials have been published, conducted in different parts of the world. Probiotics tested were *Lactobacillus* GG, *Bifidobacterium lactis* (alone or in combination with *Streptococcus thermophilus*, and *Lactobacillus reuteri*, *Lactobacillus rhamnosus* (not GG), and *Lactobacillus acidophilus*, in various trials either alone or in comparison with each other. The evidence of their efficacy in these settings is only modest for the prevention of diarrhea, although somewhat better for prevention of upper respiratory infections. In the community, new trails conducted in underprivileged areas of India, again with modest efficacy. Previous trials that examined the potential role of probiotics in preventing the spreading of diarrhea in hospitalized children had yielded conflicting results. More recently, a large trial in Poland showed, however, rather good evidence of efficacy for *Lactobacillus* GG. The prevention of antibiotic-associated diarrhea has been the subject of many investigations, both in children and in adults. Most commonly used probiotics were *Lactobacillus* GG, *Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium* ssp, *Streptococcus* ssp, and the yeast *Saccharomyces boulardii*. In general, most of these trials do show clear evidence of efficacy, with the 2 most effective strains being *Lactobacillus* GG and *S. boulardii*. Evidence is also emerging on the importance of the dose in reducing the incidence of this type of diarrhea, and the incidence of *Clostridium difficile*-associated postantibiotic diarrhea. As for treatment, a large body of data is available, especially in children, on the effect of several strains of probiotics in treating sporadic infectious diarrhea. The vast majority of the published trials show a statistically significant benefit and moderate clinical benefit of a few, well-identified probiotic strains—mostly *Lactobacillus* GG and *S. boulardii*—in the treatment of acute watery diarrhea, and particularly those due to rotavirus. Such a beneficial effect results, on average, in a reduction of diarrhea duration of approximately 1 day. The effect is strain-dependent and dose-dependent.

Key Words: probiotics, diarrhea, children, *Lactobacillus* GG, *Saccharomyces boulardii*

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The authors declare that they have nothing to disclose.

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This review is an update on current knowledge on the efficacy of probiotics in preventing and/or treating diarrhea. As diarrhea is a symptom, and not a disease, it is necessary to point out that I will focus only on published clinical trials performed on acute-onset, likely infectious diarrhea occurring in the settings of day-care centers; in the community; acquired in the hospital; after the use of antibiotics; and on the treatment of acute infectious diarrhea. Thus, the review will not address chronic disorders where diarrhea is a manifestation of other disorders such as inflammatory bowel disease, irritable bowel syndrome, malabsorption syndromes, human immunodeficiency virus/acquired immunodeficiency syndrome, diarrhea after radiation or chemotherapy. In addition, as *Clostridium difficile*-induced diarrhea is a topic of another review in this issue, this condition will also not be discussed here.

The areas of investigations examined are reported in Table 1.

PREVENTION OF DIARRHEA ACQUIRED IN DAY-CARE CENTERS

Children in day-care centers are notoriously exposed to an increased risk of infectious disease. Among them, upper respiratory tract infections[1] and acute gastroenteritis[2] seem to be very common although rarely serious.

Randomized, placebo-controlled trials (RCT) have been published beginning in 2001, conducted in Europe,[3–6] North America,[7] Israel,[8] Australia,[9] and Asia.[10] The studies differ in respect to strains of probiotic used, vehicle of administration, length of administration, and comparisons are therefore hard. However, some generalizations can be made.

- Probiotics most studied: *Lactobacillus* GG; *Bifidobacterium lactis* Bb 12; *Bifidobacterium lactis* Bb 12 and *Streptococcus thermophilus*; other Lactobacilli (*Lactobacilli reuteri*, *Lactobacilli rhamnosus*, *Lactobacilli acidophilus*)
- Most common vehicles: yogurt, fermented milk
- Periods of administration: between 3 months and 1 year
- Total number of children in the trials: approximately 1100

TABLE 1. Probiotics in the Prevention and Treatment of Diarrhea—Conditions Included

Prevention of:
Acute infectious diarrhea acquired in day-care centers
Community-acquired diarrhea in developing countries
Nosocomial diarrhea
Antibiotic-associated diarrhea
Treatment of:
Acute infectious diarrhea
Protracted infectious diarrhea

- Main results: Minimal-to-modest efficacy on reducing number of diarrheal episodes. When the parameter was examined, better outcome on incidence of upper respiratory tract infections.

In summary, while all probiotics tested were found to be completely safe, the evidence of their efficacy in preventing diarrheal episodes in infants and children attending day-care centers is only modest: statistically significant for some strains only, and in any case of questionable clinical importance. Recently, the American Academy of Pediatrics reached similar conclusions in a position study.[11]

PREVENTION OF DIARRHEA ACQUIRED IN THE COMMUNITY IN DEVELOPING COUNTRIES

The high impact of infectious diarrhea in the settings of developing countries in terms of mortality and morbidity[12] is well known. A number of sanitary intervention strategies are known to be potentially very effective, their implementation has been proven difficult in economically challenged societies. Therefore, alternative strategies are being actively sought for their efficacy and feasibility. Among them, the use of probiotics has been explored too. Two RCTs have been recently published. The first[13] was conducted in Kolkata, India on 3758 children of 1 to 5 years in an urban slum community. The enrolled children received *Lactobacillus casei* Shirota for 12 weeks, and were followed additionally for another 12 weeks. Diarrheal surveillance was conducted by community health workers for 24 weeks, and diarrhea was defined as 3 or more loose or liquid stools within the last 24-hour period. During the 24-week study period, there were 608 children with diarrhea (0.88 cases/child/y) in the probiotic group and 674 children with diarrhea (1.029 cases/child/y) in the placebo group, for a probiotic protective efficacy of 14% [95% confidence interval (CI), 4-23, $P < 0.01$] and a number needed to treat of 14. The Kaplan-Meier survival curves of the cumulative proportion of children without diarrhea in the probiotic and placebo groups (Fig. 1) showed that after 12 weeks of drink consumption the "survival" curve in the probiotic group was significantly higher. No differences were found in the etiology of diarrhea or in growth parameters.

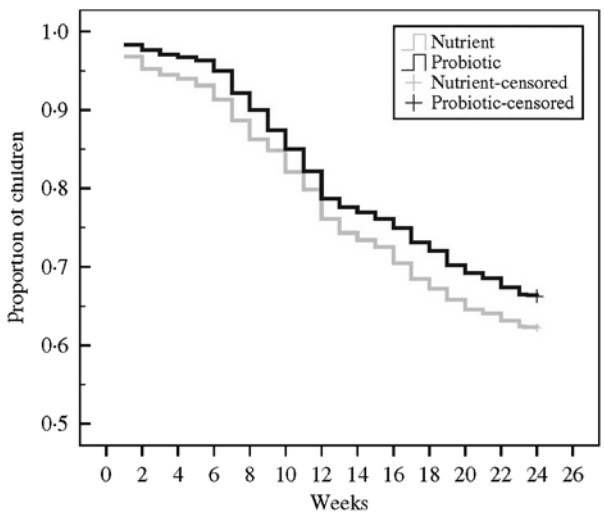

FIGURE 1. Survival curve for "free of diarrhea" time. Kaplan-Meyer plot of proportion of children in the community remaining free of diarrhea during the 24 weeks of observation related to the regimen (probiotic vs. placebo).

The second trial[14] assessed the efficacy of the combination of a probiotic oligosaccharide and *B. lactis* HN019 added to milk, in preventing diarrhea and respiratory infections in 624 children aged 1 to 3 years in New Delhi, India. Biweekly, household surveillance was conducted to gather information on compliance and morbidity. Overall, there was no effect of the symbiotic preparation on diarrhea (6% reduction, 95% CI, 21%-12%; $P = 0.08$). Of note, however, if the analysis is restricted to children older than 24 months, then those in the study group had significantly fewer episodes of diarrhea ($P < 0.02$). In addition, and interestingly, the incidence of dysentery episodes in the whole group was reduced by 21% (95% CI, 0%-38%; $P = 0.05$). Incidentally, it is worth noticing that also the incidence of pneumonia and that of severe acute lower respiratory infections were both reduced ($P = 0.05$).

PREVENTION OF NOSOCOMIAL DIARRHEA

Children admitted to the hospital for other causes often acquire diarrhea during their hospitalization.[15] The agents most commonly responsible for this occurrence and leading to a prolonged hospital course,[16] are rotavirus and, less commonly, *C. difficile*. The latter is particularly worrisome not only for its possible severity, but also because spores from this anaerobe are highly resistant to common anti-infectious practices such as alcohol-based disinfectants. Thus, there is an obvious need for agents that may be safe and effective in limiting this bothersome phenomenon, and probiotics seem as potentially useful.

The few RCTs that evaluated probiotics to prevent diarrhea in infants and young children admitted to hospitals for reasons other than diarrhea published previously[17–19] and reviewed in 2008[20] produced somewhat conflicting results. However, a recent large RCT[6] seemed more convincing. Hojsak et al[21] examined 742 hospitalized children in a randomized, double-blind, placebo controlled trial. They were randomly allocated to receive *Lactobacillus* GG (at a dose of 10^9 CFU in 100 mL of a fermented milk product) or placebo throughout their hospital stay. The risk for gastroenteritis was significantly reduced [relative risk (RR) = 0.40; (95% CI, 0.25-0.70)], as was the number of vomiting episodes [RR = 0.5 (95% CI, 0.3-0.9)]. Episodes of gastrointestinal infections lasting more than 2 days were also significantly reduced by the probiotic [RR = 0.40 (95% CI, 0.25-0.70)]. The 2 groups, however, did not differ in hospitalization duration.

Figure 2 reports the "survival" curve for gastrointestinal infections, showing clearly the advantage of being on probiotic for these hospitalized children.

Overall, therefore it is reasonable to conclude, with these investigators,[21] that considering the significant decrease in the number of nosocomial gastrointestinal and respiratory tract infections with the administration of *Lactobacillus* GG, this treatment could be recommended as a valid measure for the prevention of hospital acquired.

PREVENTION OF ANTIBIOTIC-ASSOCIATED DIARRHEA

Antibiotics administration is followed in up to 40% of cases by the appearance of diarrhea.[22] Although this complication is often self-limited, it may become occasionally worrisome, especially if it is due to *C. difficile* that is

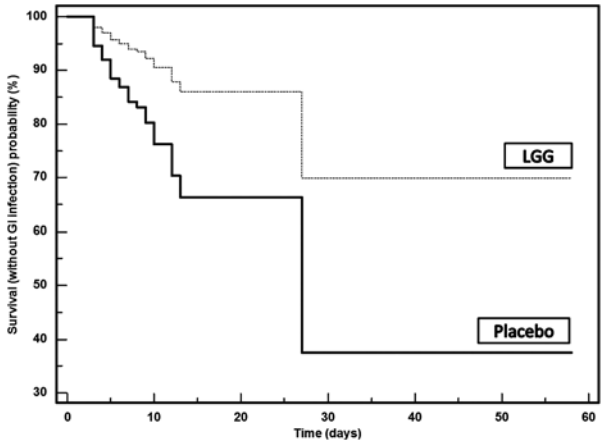

FIGURE 2. Survival curve for "free of diarrhea" time. Kaplan-Meyer plot of percentages of children in the hospital that remained free of diarrhea related to the regimen (*Lactobacillus* GG vs. placebo).

responsible for such complication in approximately 25% of cases. A Cochrane library meta-analysis published in 2007 on the capacity of probiotics to prevent this symptom in children[23] included 10 RCTs with 1015 treated and 971 control children, varying in age from 1 month to 15 years of age.

Overall, the authors reported a statistically significant reduction in the incidence of antibiotic-associated diarrhea (AAD) from 37.5% to 8.9% (RR = 0.49; 95% CI, 0.32-0.74). Of interest, the strength of the reported preventive efficacy was directly related to the quality of the study as judged by the Jadad et al[24] score, with the studies assigned a Jadad score of more than 3 reporting the highest efficacy of the probiotics in preventing AAD. It would seem that once a child on antibiotics has developed diarrhea; however, whether or not he/she was also on probiotics does not make any difference. In fact, when looking at the duration of the AAD, no difference was found between placebo and any of the tested probiotics. Finally, as for the efficacy of individual strains of probiotics in limiting the incidence of AAD, the 2 most effective strains were found to be *Lactobacillus* GG and *Saccharomyces boulardii*.

In conclusion, and in accordance with recent conclusions by the American Academy of Pediatrics,[11] there is reasonable evidence to recommend the use of either probiotic at the start of the antibiotic treatment to limit the incidence of AAD in children. Seven to 10 children need to be treated to prevent 1 case of AAD. Lastly, the importance of a right dosing cannot be overemphasized. A recent study on 255 adult inpatients divided in 3 groups[25] has in fact shown that those receiving 2 probiotic capsules per day of 50 billion CFU of live organisms (*Lactobacillus acidophilus* CL1285 + *Lactobacillus casei* LBC80R Bio-K + CL1285) had a lower AAD incidence (15%) than those who received only 1 capsule (28.2%); each probiotic group had a lower AAD incidence than placebo (44.1%).

TREATMENT OF ACUTE INFECTIOUS DIARRHEA

The potential for probiotics improve the treatment of diarrhea by either shortening its duration and/or preventing its complications has been quite extensively examined in a large number of clinical trials using widely different strains, doses, and methods of analysis. As a result, we have today a large number of published clinical trials, many of which randomized and controlled, to the point that our review here can again be based on available accurate meta-analyses. Allen et al[26] examined 63 studies that met their inclusion criteria with a total of more than 8000 participants. Of these, 56 trials recruited infants and young children. As it is often the case, the trials varied in the definition used for acute diarrhea and the end of the diarrheal episode, and were conducted in widely different settings. In addition, they noticed wide variations in microorganisms tested, dosage, and participants' characteristics. Despite this lack of homogeneity, some clear conclusions could be reached: first, no adverse events were attributed to the probiotic intervention. Second, probiotics reduced the duration of diarrhea, with the size of the effect being different between studies. A significant effect was seen for the mean duration of diarrhea (replicating a previously reported average difference of approximately 24 h in favor of the intervention groups in a total of 4555 patients and 35 trials). In addition, probiotics were efficacious in reducing the risk of diarrhea running a course equal or longer than 4 days (n = 2853, trials = 29) and in reducing stool frequency on day 2 (mean difference 0.80; n = 2751, trials = 20). Of note, the differences in effect size between studies were not explained by study quality, probiotic strain, the number of different strains, the viability of the organisms, dosage of organisms, the causes of diarrhea, or its severity. Even the size of the effect of probiotics on diarrheal duration (as mentioned: approximately 1 d less) seems to be surprisingly constant in time and across different species of probiotics used.[27–29]

The authors concluded, "Used alongside rehydration therapy, probiotics seem to be safe and have clear beneficial effects in shortening the duration and reducing stool frequency in acute infectious diarrhea."

Of notice, among the probiotics, most widely tested with consistent favorable results are *Lactobacillus* GG and *S. boulardii*. The latter has recently been found—in combination with metronidazole—more effective than metronidazole alone in the treatment of bloody diarrhea due to Amoeba in Turkey.[30] This finding is of interest, as so far most studies had shown that probiotics were more effective in treating viral than bacterial diarrheas. For instance, when the efficacy of *Lactobacillus* GG was analyzed in a meta-analysis,[31] as for separate etiologies, it was evident that this probiotic was most effective for rotavirus diarrhea, where it induced an average reduction of diarrhea duration of −2.1 d, 95% CI, between −3.6 and −0.6.). In our multicenter RCT involving 287 patients,[29] we found no effect of *Lactobacillus* GG on diarrheas of bacterial etiology, whereas overall this probiotic significantly reduced the risk of diarrhea running a protracted course of more than 7 days (relative risk 0.25, 95% CI, 0.09-0.75).

Similar to *Lactobacillus* GG, *S. boulardii* too was shown in a meta-analysis performed in 2007[32] to significantly reduce the risk of diarrhea running a protracted course.

Of interest from the epidemiological standpoint is the fact that probiotics (documented for strains of *Lactobacillus rhamnosus)* seem to have the capability of reducing the shedding of rotavirus[33] in a dose-dependent manner,[34] thus allowing reducing the risk of spreading of the infection.

TABLE 2. Summary Recommendations for the Use of Probiotics in Diarrhea in Children

Condition	Patients and Controls	Most Studied Probiotics	Evidence of Efficacy (− to + + +)
Prevention of diarrhea acquired in day-care centers	2000	*Lactobacillus* GG *Bifidobacterium lactis* *Lactobacillus Reuteri* *Lactobacillus Casei* *Bifidobacterium bifidum* + *Streptococcus thermophilus*	±
Prevention of nosocomial diarrhea	1000	*Lactobacillus* GG	+ +
Prevention of acute diarrhea in community settings	5000	*Lactobacillus* GG	+
Prevention of antibiotic-associated diarrhea	2000	*Lactobacillus* GG *Saccharomyces boulardii*	+ + +
Treatment of acute infectious diarrhea	3500	*Lactobacillus* GG *Saccharomyces boulardii* Possibly several other strains, including mixtures of probitics	+ + +
Persistent diarrhea	464	*Lactobacillus* GG *Saccharomyces boulardii*	+

Given the sheer number of the RCTs performed and their quite consistent results, it would seem that such conclusions are now well established, and further studies would be needed not so much for establishing probiotic efficacy in acute diarrhea, but rather—again quoting the authors—"to guide the use of particular probiotic regimens in specific patient groups."

Although the reduction of approximately 1 day of diarrhea may not seem a worthwhile health benefit, in reality the resulting improvement in absenteeism, lower cost of treatment (lesser need for oral or intravenous rehydration solutions), reduced risk of protracted course with its nutritional and economical implications, and additionally the likelihood of reduced risk of spreading of the gastrointestinal infections make in my opinion the use of selected, well dosed probiotics a very appealing adjunct to the cornerstone of diarrhea management[35]: the use of oral rehydration solution.

Thus, the evidence for the size of effectiveness of probiotic intervention in acute diarrhea seems—especially in children—well documented. Much less is known on the potential role of these agents in cases of persistent diarrhea (a diarrheal episode lasting more than 14 d). Recently, a meta-analysis published in the Cochrane Library[36] could only include 4 trials, with a total of 464 participants. This meta-analysis showed that probiotics reduced the duration of persistent diarrhea (mean difference 4.02 d, 95% CI, 4.61-3.43 d, n = 324, 2 trials). In addition, stool frequency was reduced by probiotics in 2 of the trials. Given the small number of trials, however, these results cannot be considered definitive.

CONCLUSIONS

Probiotics have moved from the field of alternative medicine slowly but surely over the past decade. It is now possible to produce evidence-based recommendations on their use in various areas. Table 2 reports a summary of the evidence currently available on the efficacy of probiotics in diarrhea, with a special emphasis on children, where most of the data have been generated. A judicious use of selected strains seems nowadays definitely justified in some of these settings.

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