CORRESPONDENCE

Lactobacillus for Gastroenteritis in Children

TO THE EDITOR: Schnadower et al. (Nov. 22 issue)[1] report that preschool children with acute gastroenteritis who received a 5-day course of *Lactobacillus rhamnosus* GG did not have better outcomes than those who received placebo. The authors did not highlight a crucial limitation of the trial: stool samples were obtained from 78.4% of the participants, with 45.6% of these samples positive for viruses. A therapeutic benefit of probiotics has been documented mostly in acute gastroenteritis of a viral origin.[2,3]

Furthermore, probiotics are more effective when administered early in the course of diarrhea rather than later,[2,3] whereas in most participants in this trial, therapy was initiated on the third or fourth day of diarrhea. Finally, some of the participants received antibiotics, although many strains of lactobacilli are susceptible to antimicrobial agents.[4] Moreover, after antibiotic therapy, probiotics induced a markedly delayed and incomplete reconstitution of the intestinal mucosal microbiome.[5]

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TO THE EDITOR: Schnadower et al. found that *L. rhamnosus* GG was ineffective in acute gastroenteritis in children. They provided several explanations for their negative results, which contrasted with available data supporting the use of *L. rhamnosus* GG in children.[1,2]

Unfortunately, the authors did not report important weaknesses of their trial. For example, data show that probiotics should ideally be initiated early in the course of gastroenteritis.[3,4] In this trial, the median duration of diarrhea before treatment was 53.2 hours (range, 29.0 to 81.3). This delay seems too long for a disease that typically lasts less than 7 days. With such a delay in the beginning of treatment, it is hard to show a difference in the duration of diarrhea. In addition, with the use of a primary outcome based on a score of 9 or higher on the Vesikari scale (scores range from 0 to 20, with higher scores indicating more severe disease), which was determined at any time point during the 14-day follow-up period after enrollment, it is hard to determine the effect of *L. rhamnosus* GG on the duration and severity of gastroenteritis. Previous studies used the total duration of diarrhea (in hours) as the primary outcome. To provide solid guidance on the use of probiotics in acute gastroenteritis, it would be important to perform a large trial to confirm previous data from smaller studies. However, to confirm the results of previous trials, it would be better to adopt the same trial design and clinical outcomes. Otherwise, there is a risk that "bigger" will not become "better."

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TO THE EDITOR: A Cochrane systematic review[1] concluded that the use of specific probiotics along with rehydration therapy has beneficial effects in reducing the duration and stool frequency of acute infectious diarrhea. Cochrane experts acknowledged variability among studies and stated that research is needed to guide the use of particular probiotic regimens in specific patient groups.

The results of the trial by Schnadower et al. and those of the trial by Freedman et al., which were published in the same issue of the *Journal*,[2] should be interpreted with caution because of the late use of probiotic therapy and the unverified viability of strains in liquid suspension in both trials. Most children had mild gastroenteritis and were recruited after they had had diarrhea for 2 days. Guidelines recommend probiotic use within the first 24 to 48 hours after symptom onset in order to be effective.[3] Infectious gastroenteritis in Western societies is typically mild and self-limiting, and the use of probiotics may not be critical.[4] This is not the same in less developed areas. It would be advisable to perform a subanalysis focusing only on severe cases of diarrhea treated with reliable probiotic dosing within the first 48 hours after the onset of symptoms in order to properly assess the effectiveness of the intervention.

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No potential conflict of interest relevant to this letter was reported.

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DR. SCHNADOWER AND COLLEAGUES REPLY: All three letters express the oft-stated belief that the sooner probiotics are initiated in acute gastroenteritis, the greater the effect. However, the references cited in these letters do not provide specific data supporting this contention. The only relevant data we found for the use of *L. rhamnosus* GG for the treatment of acute gastroenteritis in a population similar to ours showed a nonsignificant benefit in patients with symptoms lasting more than 48 hours.[1] We stratified participants according to the duration of symptoms (<48 hours vs. ≥48 hours) and identified no significant differences according to the time of initiation of the probiotic (Fig. S1 in the Supplementary Appendix, available with the full text of our article at NEJM.org).

Weizman contends that the inclusion of participants who were receiving antibiotics was a weakness of the trial and that viruses were detected in stool samples obtained from fewer than half the participants. We chose to include participants who were receiving antibiotics because probiotics are often used (with limited evidence) to prevent antibiotic-associated diarrhea, treat it, or both. No bona fide enteric pathogens are detected in stool samples obtained from many patients with acute gastroenteritis in North America, even with the use of multiplex polymerase-chain-reaction assays containing more viral targets than the one we used and in populations with sparse rotavirus vaccine penetration.[2] Figure S1 in the Supplementary Appendix of our article addressed antibiotic use and a viral cause of diarrhea as possible determinants of the efficacy of probiotics, and we found no such influences.

Berni Canani questions the use of a total score of 9 or higher on the modified Vesikari scale as our primary outcome instead of the duration of diarrhea. We prefer the Vesikari scale score because it includes multiple aspects of gastroenteritis severity and we think it better reflects the burden of the disease in our population.[3] However, we also addressed the duration of diarrhea as a secondary outcome, and we found no difference between the treatment group and the placebo group (Table 3 of our article).

Alvarez-Calatayud et al. express concern that viability was lost because the probiotics were suspended in a liquid form. Because most young participants cannot swallow capsules, we sprinkled the contents of each capsule in 20 ml of liquid at the time of administration; this common practice was recommended by the manufacturer. We independently tested all batches of *L. rhamnosus* GG at regular intervals to ensure purity and viability. Alvarez-Calatayud et al. state that probiotics may be less effective in Western societies, where gastroenteritis is usually mild; this statement contradicts the findings reported in one of their references.[4] We agree that the burden of gastroenteritis is greater in less developed areas. However, we will not know whether *L. rhamnosus* GG or probiotics improve patients' outcomes in such environments until rigorous studies are conducted in those settings.

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DR. FREEDMAN AND COLLEAGUES REPLY: Alvarez-Calatayud et al. cite a review[1] that is prone to the same limitations as all systematic reviews,[2] and the outcomes of ensuing large, randomized, controlled trials are poorly predicted by such reviews.[3] Studies reporting positive results are more often published than those that report negative results[4]; this leads subsequent systematic reviews[2] to overestimate the treatment effect size. Although we limited eligibility in our trial to participants who had had symptoms for less than 72 hours, only 17% of our trial population presented within 24 hours after symptom onset, and 53% presented within 48 hours after symptom onset. In these subgroups, the respective odds ratios for the development of moderate-to-severe disease among participants who received probiotics were 1.05 (95% confidence interval [CI], 0.47 to 2.33) and 1.20 (95% CI, 0.79 to 1.83).

Evidence of the viability of the probiotic strain in liquid preparations has been published[5] and is available from the manufacturer, which also confirmed colony-forming unit counts for all trial batches at the end of the shelf life. The disease severity effect was assessed by evaluating the interaction between the treatment and the baseline Vesikari scale score, and it was not significant ($P=0.86$). We performed subgroup analyses involving children who presented less than 48 hours after symptom onset with varying degrees of baseline severity. An analysis involving 134 children who had a baseline Vesikari scale score of 11 or higher yielded an odds ratio for moderate-to-severe gastroenteritis of 1.26 (95% CI, 0.61 to 2.61), whereas the analysis involving 256 children with a Vesikari scale score of 9 or less yielded an odds ratio of 0.89 (95% CI, 0.48 to 1.66).

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