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Original Articles

Oral Bacterial Therapy Reduces the Duration of Symptoms and of Viral Excretion in Children with Mild Diarrhea

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Abstract

Background: Oral administration of live *Lactobacillus casei* strain GG is associated with the reduction of duration of diarrhea in children admitted to the hospital because of diarrhea. The purposes of this work were to investigate the clinical efficacy of oral administration of *Lactobacillus* in children with mild diarrhea who were observed as outpatients, and to see whether *Lactobacillus GG* can reduce the duration of rotavirus excretion.

Methods: Duration of diarrhea was recorded in 100 children seen by family pediatricians and randomly assigned to receive oral rehydration or oral rehydration followed by the administration of lyophilized *Lactobacillus casei*, strain GG. Rotavirus was looked for in the stools of all children and, in those in whom results were positive, stools were examined again 6 days after the onset of diarrhea.

Results: In 61 children results were positive for rotavirus and in 39 results were negative. Duration of diarrhea was reduced from 6 to 3 days in children receiving *Lactobacillus GG*, with a similar pattern in rotavirus-positive and -negative children. Six days after the onset of diarrhea, stools in only 4 out of 31 children that received *Lactobacillus GG* were positive for rotavirus compared with positive findings in 25 out of 30 control subjects.

Conclusions: Oral administration of *Lactobacillus GG* is effective in rotavirus-positive and rotavirus-negative ambulatory children with diarrhea. Furthermore, it reduces the duration of rotavirus excretion.

Diarrhea is still a major problem in industrialized countries with 21 to 37 million diarrheal episodes occurring in the United States in 16.5 million children annually. The vast majority of these cases are mild and self-limiting, but 2.1 to 3.7 million lead to a physician's office visit and 200,000 required hospital admission. A similar epidemiologic pattern applies to European countries ^(1,2).

Rotavirus is the most common agent of infantile gastroenteritis worldwide. No specific therapy is available for rotavirus, and treatment is limited to rehydration. However, we have reported that oral administration of human serum immunoglobulin to children admitted because of rotavirus-induced diarrhea reduced the duration and severity of symptoms, the duration of viral excretion, and the length of hospital stay ^(3,4).

An alternative therapeutic approach, based on oral administration of live bacteria is currently under active investigation ⁽⁵⁾. Isolauro et al. have shown that oral bacterial therapy with *Lactobacillus casei strain GG* promotes clinical recovery from rotavirus gastroenteritis in hospitalized children ⁽⁶⁾. Oral bacterial therapy also reduced the stool frequency in Pakistani children with acute nonbloody diarrhea in whom rotavirus accounted for 20% of cases. However, the total duration of diarrhea was not reported in the results of that study nor were the other causes indicated ⁽⁷⁾.

Several clinical studies on the efficacy of *Lactobacillus* were conducted in children admitted to hospitals because of diarrhea ⁽⁶⁻¹¹⁾. Whether such treatment would be effective also in ambulatory children, who are less severely ill and are under observation as outpatients, is presently unknown.

This is an important matter, because it is obvious that the number of children seen in primary care or as outpatients greatly exceeds the number of inpatients. Therefore, a prospective study was conducted, in collaboration with family pediatricians, to evaluate the clinical efficacy of oral bacterial therapy in children with acute gastroenteritis, and to establish whether oral bacterial therapy reduced viral excretion.

PATIENTS AND METHODS

All children, between 3 and 36 months old, consecutively seen by three family pediatricians (AF, MIS, RBC) because of diarrhea in the period from November 1995 to January 1996, were enrolled in the study and randomly assigned to receive oral rehydration alone or oral rehydration therapy followed by oral bacterial therapy. The treatment was allocated by odd-on pairing from a random-number table. Informed consent was obtained from the parents of the children enrolled.

The bacterial preparation consisted of lyophilized *Lactobacillus casei strain GG* (3×10^9 CFU; DicoFlor 30, DicoFarm SpA; Rome, Italy), which was resuspended in 200 ml of milk or formula, according to the manufacturer's instructions. The solution was given twice a day for a maximum of 5 days, starting after 6 hours of oral rehydration with a 60-mmol Na

concentration in solution. This was offered ad libitum to patients until recovery from diarrhea was achieved. Full, age-appropriate feeding was reintroduced soon after initial rehydration ⁽¹²⁾. Diarrhea was defined as three or more watery stools per day.

Exclusion criteria were the administration of antibiotics in the previous 3 weeks, the onset of diarrhea more than 48 hours before the visit, breast-feeding, and a weight:height ratio below the fifth percentile.

Recovery from diarrhea was defined as the time since the last loose or liquid stools. The outcome of diarrhea was evaluated by the mothers of enrolled children, who had been appropriately instructed, and it was checked daily by telephone calls.

An enzyme-linked immunosorbent assay (Rotazyme II, Abbott Laboratories; Rome, Italy) was used to detect rotavirus in stools collected at the first visit and 6 days after the onset of diarrhea. This test was done because children with untreated rotavirus gastroenteritis excrete the virus for a mean of 7 days after the onset of diarrhea ⁽⁴⁾.

Statistical Analysis

An analysis of variance was used to evaluate inter-group differences. Duration of diarrhea was expressed as mean ± standard deviation. The *t*-test and the chi-square test were applied where appropriate.

RESULTS

A total of 100 children were enrolled in the study. All patients had mild to moderate dehydration. Forty-eight received oral rehydration therapy only and 52 received oral rehydration therapy and oral bacterial therapy. All children were fed again with full-strength, lactose-containing formula or milk, given soon after completion of rehydration, which usually lasted 6 to 8 hours. The two groups were similar in sex, age, and body weight. The duration of diarrhea before enrollment was also similar ^(Table 1). All children were well nourished and in no case was a risk factor for chronic diarrhea recorded.

	Control		Treatment	
	Mean	SD	Mean	SD
Age (days)	10.5	1.5	10.5	1.5
Weight (kg)	10.5	1.5	10.5	1.5
Duration of diarrhea (days)	5.5	1.5	2.5	1.5
Rotavirus positive (%)	50		50	
Rotavirus negative (%)	50		50	

Table 1

Diarrheal duration was reduced by approximately 50% (*p* < 0.01) in children receiving oral bacterial therapy compared with control subjects ^(Fig. 1).

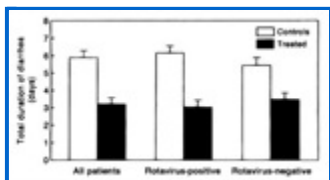


Fig. 1

Both control and treated children were divided into two groups, according to the presence or absence of rotavirus. In each group, the features of children receiving oral bacterial therapy,

as well as the duration of diarrhea at enrollment, were similar to the features and duration in control subjects (Table 1).

Within each group, the administration of oral bacterial therapy as an adjunct to rehydration was associated with a significant reduction of the duration of diarrhea compared with untreated control subjects (Fig. 1). The efficacy of *Lactobacillus GG* was slightly, though not significantly, greater in rotavirus-positive children than in those who were rotavirus-negative.

Finally, the number of children who were excreting the virus 6 days after the onset of diarrhea was significantly ($p < 0.01$) reduced in the treated group compared with the number in the control group (Fig. 2).

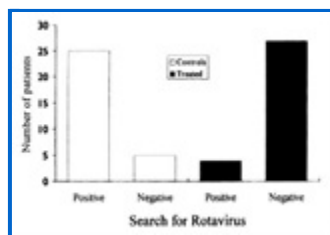


Fig. 2

DISCUSSION

Previous studies reporting the efficacy of *Lactobacillus GG*, included only hospitalized children (6-8), a population that represents only a minority of children with viral gastroenteritis, in that most children need only ambulatory care (1,2).

The results in this study show that oral administration of *Lactobacillus GG* is effective in reducing the duration of symptoms in well-nourished infants and children affected by mild diarrhea-the ones that are more commonly seen by primary pediatricians.

Lactobacillus GG was effective both in children with rotavirus gastroenteritis and in those whose fecal samples were negative for rotavirus. Cultures were not performed, thus we do not know the cause of the diarrhea in rotavirus-negative children. However, this finding suggests that the effect of oral bacterial therapy is not limited to rotavirus-induced diarrhea.

We also provide the first evidence that *Lactobacillus GG* administration is associated with a significant reduction of viral excretion. This finding is in agreement with the observed reduction of diarrhea and suggests that oral bacterial therapy may also inhibit spread of the disease in day care and health care centers. This finding has relevance in light of the major role of rotavirus as the agent of nosocomial infections (13).

We have recently shown that the efficacy of immunoglobulin against rotavirus is related to a direct neutralization of the virus (14). A similar mechanism could explain the efficacy of oral bacterial therapy, inasmuch as it has been suggested that the efficacy of *Lactobacillus GG* administration may be related to an enhancement of the immune response against rotavirus (15). Stimulation of immune response may be a nonspecific mechanism and could explain the efficacy of bacterial therapy observed in children with rotavirus-negative diarrhea. Alternatively, the efficacy of *Lactobacillus GG* in children without rotavirus could be related

to an antimicrobial substance produced by *Lactobacillus GG* that inhibits the growth of Gram-negative and Gram-positive bacteria ⁽⁴⁶⁾.

In the light of the relatively low cost (10 U.S. dollars per child) and of its proven efficacy, oral bacterial therapy, given as an adjunct to oral rehydration, may have a great impact on infantile gastroenteritis both in terms of health care and of its economic consequences. Finally, it would be useful to compare the efficacy of oral bacterial therapy with that of passive immunotherapy in children admitted to hospitals with viral diarrhea.

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