

Prophylactic *Lactobacillus GG* Reduces Antibiotic-Associated Diarrhea in Children With Respiratory Infections: A Randomized Study

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ABSTRACT. *Objectives.* Antimicrobial treatment may disturb the colonization resistance of gastrointestinal microflora, which may induce clinical symptoms, most commonly diarrhea. The severity of antibiotic-associated diarrhea may range from a brief, self-limiting disease to devastating diarrhea with electrolyte disturbances, dehydration, crampy abdominal pain, pseudomembranous colitis, toxic megacolon, or even death. The incidence of diarrhea in children receiving a single antimicrobial treatment is unclear. In addition to more critical use of antimicrobials, adjunctive preventive measures to antibiotic-associated diarrhea are needed. The objective of this study was to evaluate the incidence of diarrhea after antimicrobial treatment in children with no history of antimicrobial use during the previous 3 months. Another aim of this study was to assess the preventive potential of *Lactobacillus rhamnosus GG* (*Lactobacillus GG*; American Type Culture Collection 53103), a probiotic strain with a documented safety record and a therapeutic effect in viral gastroenteritis on antibiotic-associated diarrhea.

Methods. Oral antimicrobial agents were prescribed for the treatment of acute respiratory infections at the clinics of the Health Care Center of the City of Tampere or Tampere University Hospital, Finland, to 167 patients who were invited to participate in the study. Of the patients, 48 were lost to follow-up; therefore, the final study population consisted of 119 children from 2 weeks to 12.8 years of age (mean: 4.5 years). All study subjects met the inclusion criteria: they had not received any antimicrobial medication during the previous 3 months, they did not suffer from gastrointestinal disorders, and they did not need intravenous antimicrobial treatment.

The patients were randomized to receive placebo or 2×10^{10} colony-forming units of *Lactobacillus GG* in capsules given twice daily during the antimicrobial treatment. *Lactobacillus GG* and placebo capsules were indistinguishable in appearance and taste. The parents kept a daily symptom diary and recorded stool frequency and consistency at home for 3 months. Diarrhea was defined as at least three watery or loose stools per day for a

minimum of 2 consecutive days. In the case of diarrhea, viral (adenovirus, rotavirus, calicivirus and astrovirus) and bacterial (*Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Clostridium difficile*, *Staphylococcus aureus*, and yeasts) analyses were studied in fecal samples. The metabolic activity of the gut microflora was assessed by analysis of fecal urease, β -glucosidase, and β -glucuronidase activities. The primary outcome measure was diarrhea during the first 2 weeks after the beginning of the antimicrobial treatment, because this period most likely reflects the effects of antimicrobial use. Secondary outcome measures were the activities of fecal urease, β -glucuronidase, and β -glucosidase.

Results. On the entire follow-up, 80% of any gastrointestinal symptoms were reported during the first 2 weeks after the beginning of the antimicrobial treatment. The incidence of diarrhea was 5% in the *Lactobacillus GG* group and 16% in the placebo group within 2 weeks of antimicrobial therapy ($\chi^2 = 3.82$). The treatment effect (95% confidence interval) of *Lactobacillus GG* was -11% (-21% – 0%). In diarrheal episodes, the viral and bacterial analyses were positive for *Clostridium difficile* in 2 cases and for Norwalk-like calicivirus in 3 cases. The age of the patients with diarrhea was between 3 months and 5 years in 75% of cases in both groups. The severity of diarrhea was comparable in the study groups, as evidenced by similar stool frequency (mean: 5 per day; range: 3–6) and the duration of diarrhea (mean: 4 days; range: 2–8).

The activities of fecal urease and β -glucuronidase, but not β -glucosidase, changed significantly after the beginning of the antimicrobial treatment in the *Lactobacillus GG* group and in the placebo group alike. The decrease in urease and β -glucuronidase activities was reversible in patients with no diarrhea, but in patients with diarrhea, the modifications in gut microflora were more profound and prolonged. The activities of the three enzymes were normalized within 3 weeks, evidenced by stable enzyme activities in samples collected 3 weeks, 1 month, and 3 months after the beginning of the antimicrobial treatment, compared with those obtained before treatment.

Discussion. In the present study, after a single antimicrobial treatment, the incidence of diarrhea was 16%. The higher incidence of antibiotic-associated diarrhea in previous reports may be attributable to a recent antimicrobial therapy that disturbs intestinal flora and exposes to complications. Also, in the present study, changes in the metabolic activity of the intestinal flora were observed, evidenced by a transient decline in fecal enzyme activities.

Different probiotic preparations, including lactobacilli, are recommended frequently to prevent antibiotic-associated diarrhea. Although probiotics have been shown to be efficient in the prevention and the treatment of viral gastroenteritis, their usefulness during antimicrobial therapy in children has not been elucidated be-

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fore. We observed that the administration of *Lactobacillus GG* to children receiving antimicrobial therapy for respiratory infection reduced the incidence of antibiotic-associated diarrhea to one third. The beneficial effect may be mediated by a number of functions of probiotics, ie, production of antimicrobial substances, local competition of adhesion receptors and nutrients, and stimulation of intestinal antigen specific and nonspecific immune responses.

Conclusion. A probiotic strain, *Lactobacillus GG*, is effective in the prevention of diarrhea in children receiving antimicrobial treatment to respiratory infections. *Pediatrics* 1999;104(5). URL: <http://www.pediatrics.org/cgi/content/full/104/5/e64>; antibiotic-associated diarrhea, *Lactobacillus*, *glucuronidase*, *glucosidase*, *urease*.

Antimicrobial agents are the most frequently prescribed medicines in children, because acute infectious diseases are prevalent in this age group. The demonstration that acute infections are primarily of viral origin¹ has not reduced the use of antibiotics, nor has the fact that antibiotics afford only marginal alleviation of the clinical symptoms.²

Antimicrobial treatment may disturb the colonization resistance of gastrointestinal microflora,³ which may induce clinical symptoms, most commonly diarrhea. The incidence of antibiotic-associated diarrhea has been estimated to vary between 5% and 25% in adults⁴ and between 8% and 30% in children.^{5,6} The discrepancies in the incidence may have been attributable to differences in the definition of diarrhea, the antimicrobial agent used, the number of daily doses, the duration of the treatment, and the time from previous antimicrobial treatments.^{5,6} The severity of antibiotic-associated diarrhea may range from a brief, self-limiting disease to devastating diarrhea with electrolyte disturbances, dehydration, crampy abdominal pain, pseudomembranous colitis, toxic megacolon, or even death.⁴

In addition to more critical use of antimicrobials, adjunctive preventive measures to antibiotic-associated diarrhea are needed. The objective of this randomized, double-blind, placebo-controlled follow-up study was to evaluate the incidence of diarrhea after antimicrobial treatment in children with no history of antimicrobial use during the previous 3 months, because recent antimicrobial treatments may cause confusion.⁷ Another aim of this study was to assess the preventive potential of probiotics on antibiotic-associated diarrhea. For this purpose, we applied *Lactobacillus rhamnosus GG* (*Lactobacillus GG*; American Type Culture Collection 53103), a probiotic strain with a documented safety record⁸ and a therapeutic⁹ effect in viral gastroenteritis, as the probiotic for the treatment of children receiving antibiotics.

METHODS

Patients

Oral antimicrobial agents were prescribed for the treatment of acute respiratory infections at the clinics of the Health Care Center of the City of Tampere or Tampere University Hospital to 167 patients, who were invited to participate in the study. Of the patients, 20 receiving placebo and 28 receiving *Lactobacillus GG* during antimicrobial treatment were lost to follow-up or discontinued because of difficulties in the transportation of the study samples. Therefore, the final study population consisted of 119

children (Table 1) from 2 weeks to 12.8 years of age (mean: 4.5 years, with 72% <6 years of age). All study subjects met the inclusion criteria: they had not received any antimicrobial medication during the previous 3 months, they did not suffer from gastrointestinal disorders, and they did not need intravenous antimicrobial treatment. Five patients were hospitalized; all others were treated as outpatients.

Design

All patients received the same information and the follow-up was conducted in a similar manner. Antibiotic use was continued for 7 to 10 days, and the dosage was divided into two or three doses and given every 8 to 12 hours. The patients were randomized by means of a computer program to receive placebo (microcrystalline cellulose) in capsule or 2×10^{10} colony-forming units of *Lactobacillus GG* in capsules given twice daily during the antimicrobial treatment. If the patient was unable to swallow the capsule, the capsules were opened and the contents were dissolved in a small amount of water. *Lactobacillus GG* and placebo capsules also were indistinguishable in appearance and taste when opened.

The parents kept a daily symptom diary and recorded stool frequency and consistency (solid, loose, watery) at home for 3 months. Diarrhea was defined as at least three watery or loose stools per day for a minimum of 2 consecutive days. In the case of diarrhea, the parents were requested to bring a fecal sample for viral and bacterial analyses. The primary outcome measure was diarrhea during the first 2 weeks after the beginning of the antimicrobial treatment, because this period most likely reflects the effects of antimicrobial use. Secondary outcome measures were the activities of fecal urease, β -glucuronidase, and β -glucosidase.

The parents were informed verbally and in writing about the nature and requirements of the study. Written informed consent was obtained from the parents, and the study was approved by the ethics committees of Tampere University Hospital and the City of Tampere.

Samples

Stool specimens were obtained before antimicrobial treatment or within 24 hours of its beginning and after 1 and 2 weeks. In 14 randomly selected patients, late fecal samples were collected additionally 3 weeks, 1 month, and 3 months after the beginning of the antimicrobial treatment to evaluate the long-standing effects of antimicrobials on intestinal microecology.

Stool specimens were cooled immediately at 6°C to 8°C and within 24 hours frozen at -70°C until analysis.

Determination of Fecal Bacterial Enzyme Activities

The alteration in gut microecology was studied using fecal urease, β -glucosidase, and β -glucuronidase activities as indica-

TABLE 1. Clinical Characteristics of the Patients

	<i>Lactobacillus GG</i> (n = 61)	Placebo (n = 58)
Diagnosis		
Otitis	45	43
Tonsillitis	6	6
Pneumonia	5	4
Bronchitis	4	3
Sinusitis	1	2
Antimicrobial agent		
Penicillin	9	10
Amoxicillin	41	38
Kephalosporins	3	2
Erythromycin	3	2
Trimetoprim-sulpha	5	6
Previous antibiotics		
None	9	10
0-1 prescription/y	40	36
2 or more prescriptions/y	12	12
Child care		
Home	30	29
Kindergarten	12	10
Private family	4	5
School	13	14

tors. Intestinal bacterial enzyme activities reflect both the metabolic activity and the quantitative composition of intestinal bacteria.¹⁰ Fecal samples were prepared and the enzyme activities were measured as previously described.¹¹ Enzyme activities are expressed as nmol of substrate metabolized per minute per milligram of protein in the fecal supernatant.

Detection of *Lactobacillus GG* in Feces

To study colonization, the recovery of *Lactobacillus GG* in feces in 23 randomly selected patients from samples collected 7 days after the start of antimicrobial treatment was studied as previously described.¹² Analysis showed that the patients in the *Lactobacillus GG* group were colonized by *Lactobacillus GG*. Two patients were not colonized with the organism with a detection limit of 10^3 colony-forming units per gram of feces. These were not excluded, because biopsy studies have indicated mucosal colonization even in cases in which fecal counts were below detection limit.¹³

Viral and Bacterial Analyses

Adenovirus-antigen and rotavirus-antigen were assessed using the enzyme-linked immunoassay. Fecal samples were cultured for *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, *Clostridium difficile*, *Staphylococcus aureus*, and yeasts. *Clostridium difficile* toxin A was analyzed by enzyme immunoassay. These analyses were studied from fresh fecal samples. Frozen fecal samples negative under electron microscopy were analyzed further by reverse transcription polymerase chain reaction for Norwalk-like (genogroup I and II) caliciviruses¹⁴ (with confirmation by hybridization with specific probes) and for astroviruses.¹⁵

Statistical Methods

The results are presented as means with range. The χ^2 test, Wilcoxon signed-rank test, and analysis of variance for repeated measurements were used in statistical comparisons.

RESULTS

Clinical Characteristics of the Patients

The mean age of the patients in the *Lactobacillus GG* group was 4.7 years (range: 2 weeks to 11.8 years of age), and in the placebo group, 4.4 years (range: 2 weeks to 12.8 years of age). The groups were also comparable in clinical diagnosis, antimicrobial agents used, history of antibiotic use, and mode of day care (Table 1). The parents reported no adverse effects of *Lactobacillus GG* or placebo.

The Frequency of Diarrhea After the Beginning of the Antimicrobial Treatment

On the entire follow-up, 80% of any gastrointestinal symptoms were reported during the first 2 weeks after the beginning of the antimicrobial treatment. In 3 (5%) patients in the *Lactobacillus GG* group and in 9 (16%) patients in the placebo group, the change in stool consistency and frequency during the first 2 weeks fulfilled the criteria of diarrhea ($\chi^2 = 3.82$; $P = .05$). The treatment effect (95% confidence interval) of *Lactobacillus GG* was -11% (-21% – 0%). In diarrheal episodes, the viral and bacterial analyses were positive for *Clostridium difficile* in 2 cases (1 in both groups with toxin A-positive in the patient in the *Lactobacillus GG* group) and Norwalk-like calicivirus in 3 cases (1 in the *Lactobacillus GG* group and 2 in the placebo group), whereas, the viral and bacterial analyses were negative for rotavirus, astrovirus, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter coli*, *Campylobacter jejuni*, *Staphylococcus aureus*, and yeasts. The age of the patients with diarrhea was between 3 months and 5 years in 75% of cases, in both groups

alike. The severity of diarrhea was comparable in the study groups, evidenced by similar stool frequency (mean: 5 per day; range: 3–6) and the duration of diarrhea (mean: 4 days; range: 2–8). In all cases, the diarrhea was self-limiting.

Fecal Urease, β -Glucosidase, and β -Glucuronidase Activity

The activities of fecal urease and β -glucuronidase, but not β -glucosidase, changed significantly after the beginning of the antimicrobial treatment ($P = .0001$ and $P < .0001$, respectively) in the *Lactobacillus GG* group and in the placebo group alike. The decrease in urease and β -glucuronidase activities was reversible in patients with no diarrhea, but in patients with diarrhea, the modifications in gut microflora were more profound and prolonged (Fig 1). The activities of the three enzymes were normalized within 3 weeks, evidenced by stable enzyme activities in samples collected 3 weeks, 1 month, and 3 months after the beginning of the antimicrobial treatment, compared with those obtained before treatment (data not shown).

DISCUSSION

The most common complication of antimicrobial therapy is antibiotic-associated diarrhea. In the present study, the incidence of diarrhea after a single antimicrobial treatment was 16%. We chose to analyze only the diarrhea episodes that occurred during the first 2 weeks after the beginning of the antimicrobial treatment, because the later that diarrhea occurs, the more unlikely it is caused by an antimicrobial agent. The higher incidence of antibiotic-associated diarrhea in previous reports may be attributable to a recent antimicrobial therapy that disturbs intestinal flora and exposes to complications. Also, in the present study, changes in the metabolic activity of the intestinal flora were observed, evidenced by a transient decline in fecal enzyme activities.

Different probiotic preparations, including lactobacilli, are recommended frequently to treat and prevent disturbances in intestinal microflora and antibiotic-associated diarrhea. Although probiotics have been shown to be efficient in the prevention¹⁶ and the treatment⁹ of viral gastroenteritis, their usefulness during antimicrobial therapy in children has not been elucidated before. We observed that the administration of *Lactobacillus GG* to children receiving antimicrobial therapy for respiratory infection reduced the incidence of antibiotic-associated diarrhea to one third. This is in agreement with a previous study demonstrating beneficial effect of *Lactobacillus GG* in the treatment of relapsing *Clostridium difficile* colitis.¹⁷ The profitable effect may be mediated by a number of functions of probiotics,¹⁸ ie, production of antimicrobial substances, local competition of adhesion receptors and nutrients, and stimulation of intestinal antigen specific and nonspecific immune responses.¹⁹

The most effective way to prevent antibiotic-associated diarrhea is still critical use of antimicrobials, as recommended recently for the treatment of acute otitis media in children.²⁰ However, when antimicro-

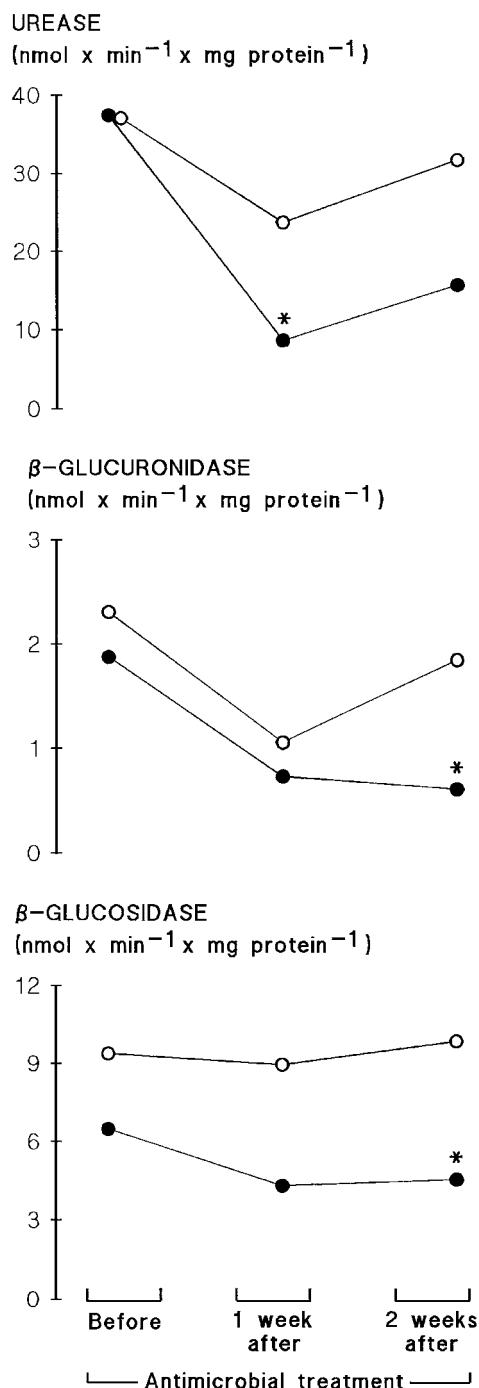


Fig 1. The mean activities of fecal urease, β -glucuronidase and β -glucosidase in patients with diarrhea (closed circle) and in those with no diarrhea (open circle) before antimicrobial treatment and 1 and 2 weeks after the beginning of the antimicrobial treatment. Asterisks indicate significantly different ($P \leq .05$) from patients with no diarrhea.

bial treatment is indicated, *Lactobacillus GG* is a safe and useful adjunctive therapy to prevent diarrhea.

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