

Lactobacillus GG in the Prevention of Nosocomial Gastrointestinal and Respiratory Tract Infections

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KEY WORDS

LGG, probiotics, nosocomial infection, prevention, children

ABBREVIATIONS

LGG—*Lactobacillus rhamnosus* GG

RR—relative risk

CI—confidence interval

NNT—number needed to treat

OR—odds ratio

Drs Hojsak and Kolaček were responsible for study concept and design and drafting of the manuscript; Drs Hojsak, Abdović, Szajewska, and Kolaček were responsible for acquisition of data; Drs Hojsak, Abdović, Szajewska, Milošević, Krznarić, and Kolaček were responsible for analysis and interpretation of data; Drs Hojsak, Abdović, Szajewska, Milošević, Krznarić, and Kolaček were responsible for critical revision of the manuscript for important intellectual content; and Dr Hojsak were responsible for administrative, technical, and material support.

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WHAT'S KNOWN ON THIS SUBJECT: Hospitalized children are at greater risk for developing gastrointestinal and respiratory tract infections than children who stay at home. Efficacy of probiotic treatment in preventing nosocomial infections has been investigated in only a few small studies, with no uniform results.



WHAT THIS STUDY ADDS: The results of our randomized, double-blind, placebo-controlled trial suggests that *Lactobacillus* GG administration decreases the risk for nosocomial gastrointestinal and respiratory tract infections in hospitalized children.

abstract

OBJECTIVE: The incidence of nosocomial infections, predominantly gastrointestinal and respiratory, in children in developed countries is high, ranging from 5% to 44%. There is no effective strategy for preventing these infections. The objective of our study was to investigate the role of *Lactobacillus* GG (LGG) in preventing nosocomial gastrointestinal and respiratory tract infections at a pediatric hospital.

METHODS: We conducted a randomized, double-blind, placebo-controlled trial of 742 hospitalized children. They were randomly allocated to receive for their hospitalization LGG at a dose of 10^9 colony-forming units in 100 mL of a fermented milk product (LGG group, $n = 376$) or placebo that was the same postpasteurized fermented milk product without LGG (placebo group, $n = 366$).

RESULTS: In the LGG group, compared with the placebo group, we found a significantly reduced risk for gastrointestinal infections (relative risk [RR]: 0.40 [95% confidence interval (CI): 0.25–0.70]; number needed to treat: 15 [95% CI: 9–34]), respiratory tract infections (RR: 0.38 [95% CI: 0.18–0.85]; number needed to treat: 30 [95% CI: 16–159]), vomiting episodes (RR: 0.5 [95% CI: 0.3–0.9]), diarrheal episodes (RR: 0.24 [95% CI: 0.10–0.50]), episodes of gastrointestinal infections that lasted ≥ 2 days (RR: 0.40 [95% CI: 0.25–0.70]), and episodes of respiratory tract infections that lasted ≥ 3 days (RR: 0.4 [95% CI: 0.2–0.9]). Groups did not differ in hospitalization duration ($P = .1$).

CONCLUSIONS: LGG administration can be recommended as a valid measure for decreasing the risk for nosocomial gastrointestinal and respiratory tract infections in pediatric facilities. *Pediatrics* 2010;125:e1171–e1177

Nosocomial infections, “hospital-acquired infections” by definition, develop during a hospital stay, meaning that they are not present or incubating on admission. Infections that occur >48 hours after admission are usually considered nosocomial. This definition encompasses not only infections that are acquired in the hospital but also those that appear after discharge.¹ The incidence of nosocomial infections in children in developed countries is high, ranging from 5% to 44%^{2–4}; gastrointestinal infections (4.5–22.6 episodes per 100 admissions)^{5,6} and respiratory infections (incidence ranging from 13% to 53% in all hospitalized children)⁷ account for the predominant types of infections. Several reports from Croatian hospitals showed that incidence of respiratory nosocomial infection is similar to Western Europe and the United States.⁸ Nosocomial infections, besides mild infections, prolong the hospital stay, worsen the treatment outcome, and, therefore, significantly increase hospital expenses. Current measures for the prevention of nosocomial infections in pediatric settings, such as vaccinations, good hand hygiene, and visitor screening, are often ineffective,⁹ which highlights the necessity for additional research.

One of the potential strategies for the prevention of nosocomial infections is the use of probiotics. Although administered for a wide variety of clinical conditions,¹⁰ their role in the treatment and prevention of acute diarrheal disorders seems to be the most promising.^{11–16} Despite several published studies that have assessed the preventive effects of probiotics, results regarding their prevention of nosocomial diarrheal infections are controversial,^{17–20} and data regarding their prevention of nosocomial respiratory tract infections do not exist. We therefore performed a randomized,

double-blind, placebo-controlled trial with the aim of evaluating the role of *Lactobacillus GG* (LGG) administration in the prevention of nosocomial gastrointestinal and respiratory tract infections in a pediatric hospital setting.

METHODS

All patients who were older than 12 months and hospitalized at the Pediatric Department (Children’s Hospital Zagreb, Zagreb, Croatia) from November 2007 to May 2008 were eligible for the study. We excluded children with gastrointestinal and/or respiratory tract infections on admission, children with immunodeficiency, cow milk allergy, neoplasm, chronic severe illnesses, or an anticipated hospital stay of <3 days; children who had received probiotic and/or prebiotic products before enrollment (7 days before hospitalization); and children who disliked fermented milk products.

The study design was a prospective, randomized, double-blind, placebo-controlled trial. The tested probiotic, *Lactobacillus rhamnosus strain GG* (LGG strain [Valio Ltd, Helsinki, Finland]), was administered in 100 mL of a fermented milk product at a dose of 10⁹ colony-forming units. The placebo was the same postpasteurized fermented milk product (100 mL) without LGG. Both study products were administered for the duration of the hospitalization. Both products were supplied by Dukat Dairy Industry dd (Zagreb, Croatia), who had no role in the conception, design, or conduct of the study or in the analysis or interpretation of the data. The LGG product and placebo were packed in identical bottles; they were of the same color, weight, smell, and taste. Both the research staff and the patients were unaware of the real nature of the product. The unblinding procedure was performed after the study was completed and after the statistical analyses were finalized.

The primary end points were as follows: (1) gastrointestinal tract infections, defined as diarrhea with ≥ 3 loose or watery stools within 24 hours with or without vomiting; (2) respiratory tract infections, including upper respiratory tract infections (rhinitis, pharyngitis, sinusitis, otitis, and the common cold) and lower respiratory tract infections (pneumonia, bronchitis, and bronchiolitis). Both upper and lower respiratory tract infections had to be confirmed by the physician. Secondary end points were as follows: (1) number of vomiting episodes; (2) number of diarrheal episodes; (3) number of gastrointestinal infections that lasted >2 days; (4) number of respiratory tract infections that lasted >3 days; and (5) duration of hospitalization.

Patients were assigned to 1 of the treatment groups (experimental or control) after performance of a randomization procedure with computer-generated numbers. Under the supervision of pediatric residents, they received either the LGG preparation or placebo once daily during the morning from the day of admission until the day of discharge. During the test period, patients were not allowed to consume any other product that contained probiotics or prebiotics. A pediatric resident entered all data regarding product consumption, infections, or adverse effects into the patient’s study chart.

All gastrointestinal and respiratory tract infections were diagnosed by a pediatrician. Patients were checked every day for signs and symptoms of respiratory infections, and all data regarding nasal discharge, sore throat, erythema of pharynx, cough, fever, wheezing, and dyspnea were collected. All diagnoses concerning upper respiratory tract infections were based on clinical signs and symptoms. In children with symptoms and laboratory tests (complete blood count and

C-reactive protein) suggestive of bacterial infection, nasopharyngeal or pharyngeal swab were collected and tested for bacteria. In patients with symptoms of pneumonia, laboratory tests were done (complete blood count and C-reactive protein), as well as pharyngeal swab, blood culture, and chest radiograph.

All data for gastrointestinal infection regarding number of stools per day, number of vomiting episodes per day, fever, and dehydration risk were assessed, and data on need for parenteral rehydration were collected on a daily basis. Each patient who had gastrointestinal symptoms had his or her stool tested for bacteria, rotavirus, adenovirus, and norovirus. Antibiotic-associated diarrhea was excluded (diarrhea in patients who were treated with antibiotics and without positive stool test was not included as nosocomial infection). Seven days after the hospitalization, all patients were contacted to establish whether they had developed an infection that was in the incubation stage at discharge; however, no infections were recorded after discharge.

The study was conducted following the principles of the Helsinki Declaration and good clinical practice guidelines. The protocol was approved by the Children's Hospital Ethical Committee and the Central Ethical Committee of the Zagreb University Medical School. Written informed consent was obtained from the parent or guardian of each child included in the study.

Sample Size

We assumed a difference between the control and experimental groups of 15%, with parameters $\alpha = .05$, $\beta = .20$ (power = .90), and control subjects per case patient = 1; on this basis, the minimum total sample size for use of the Fisher's exact 2-tailed test would be 484 (242 subjects per group; GPower 3.0.9

[Institut für Experimentelle Psychologie, Düsseldorf, Germany]).

Statistical Analysis

Descriptive statistics were used to describe the basic features according to age, gender, duration of the intervention, and disease symptoms. Normality of the data distribution was analyzed with the Kolmogorov-Smirnov test. The χ^2 test was used to estimate differences in the distribution of qualitative variables. Differences in quantitative variables, according to their distribution, were analyzed with the parametric *t* test or the nonparametric Mann-Whitney test. Binary logistic regression was performed to determine significant predictors of gastrointestinal and respiratory tract infections. That regression model included age, gender, duration of the hospital intervention, and the examined groups as predictors and the existence of gastrointestinal and respiratory infections,

respectively, as dependent dichotomous variables. Cox proportional hazards regression was also preformed. All statistical tests were 2-tailed tests and performed at the 5% level of significance. Statistical software SPSS 15.1 (SPSS, Chicago, IL) was used for all statistical analyses. To calculate the relative risk (RR), 95% confidence interval (CI), and number needed to treat (NNT), we used StatsDirect 2.5.6. (Iain E. Buchan). The difference between the study groups was considered significant at $P < .05$ or when the 95% CI for RR did not exceed 1.0 (equivalent to $P < .05$). All analyses were performed on the intention-to-treat basis, in which all of the participants in a trial are analyzed according to the intervention to which they were assigned, regardless of whether they received it.

RESULTS

As shown in Fig 1, 742 children were enrolled in the study; 376 received

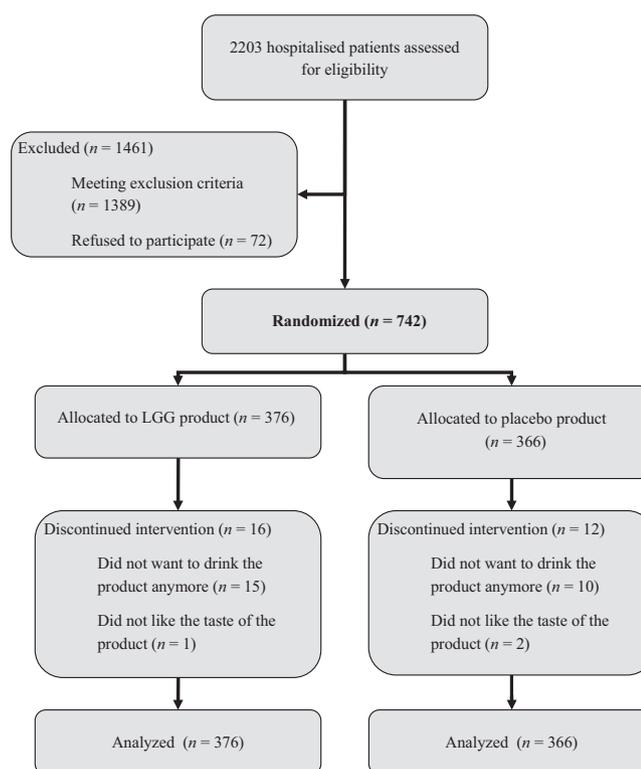


FIGURE 1

Diagram of the trial according to Consolidated Standards of Reporting Trials (CONSORT) statement.³⁴

TABLE 1 Baseline Characteristics and Differences Between Study Groups: χ^2 Test

Variable	LGG Group (n = 376)	Placebo Group (n = 366)	P
Age, mean \pm SD, y	9.9 \pm 5.1	10.6 \pm 5.0	.187
Female gender, n (%)	185 (49.2)	162 (44.3)	.087
Noninfectious gastrointestinal disorders, n (%) ^b	60 (16.0)	49 (13.4)	.370
Genetic disorders, n (%) ^b	34 (9.0)	44 (12.0)	.209
Cardiac disorders, n (%) ^b	36 (9.6)	29 (7.9)	.490
Urinary tract disorders, n (%) ^b	21 (5.6)	21 (5.7)	.920
Neurologic disorders, n (%) ^b	125 (33.2)	132 (36.1)	.567
Noninfectious pulmonary and immunologic disorders, n (%) ^b	73 (19.4)	70 (19.1)	.991
Intoxications, n (%) ^b	27 (7.2)	21 (5.7)	.495

^a Difference analyzed with Student *t* test.

^b Reason for hospitalization.

the LGG-supplemented fermented milk product, and 366 received the placebo product. There was no statistically significant difference between the groups in regard to age, gender, and the reasons for hospitalization (Table 1).

Considering the primary end points, the risk for gastrointestinal infections was significantly reduced in the LGG group compared with the placebo group (RR: 0.40 [95% CI: 0.25–0.70]; NNT: 15 [95% CI: 9–34]). Similarly, the risk for respiratory tract infections was significantly reduced in the LGG group compared with the placebo group (RR: 0.38 [95% CI: 0.18–0.85]; NNT: 30 [95% CI: 16–159]; Table 2). Moreover, secondary end points related to gastrointestinal infections

were significantly different between groups. Compared with the placebo group, children in the LGG group had a reduced risk for vomiting episodes (RR: 0.5 [95% CI: 0.3–0.9]) and diarrheal episodes (RR: 0.24 [95% CI: 0.10–0.50]; Table 3). They also had a reduced risk for episodes of gastrointestinal infections that lasted >2 days (RR: 0.40 [95% CI: 0.25–0.70]). None of the patients had a bacterial infection. In 5 patients, rotavirus (2 patients: both in the placebo group) or norovirus (3 patients: 2 in the placebo group and 1 in the LGG group) was isolated. All patients were treated symptomatically, and none required antibiotic treatment.

In regard to respiratory tract infections, patients in the LGG group had a

lower risk for episodes of respiratory tract infections that lasted >3 days than patients in the placebo group (RR: 0.4 [95% CI: 0.2–0.9]; NNT: 33 [95% CI: 17–257]; Table 3). All patients had upper respiratory tract infections, and only 1 patient in the placebo group also had a diagnosis of pneumonia. A bacterial cause was determined and treated with antibiotics in only 5 patients with upper respiratory tract infections (4 were from the placebo group). There was no significant difference regarding the duration of hospitalization between the 2 groups ($P = .1$; Table 3).

Patients who received the placebo had a 2.89 times higher chance of developing a gastrointestinal infection (odds ratio [OR]: 2.89 [95% CI: 1.63–5.15]; Table 4) than patients who received LGG. Nevertheless, the duration of hospitalization increased the risk for acquiring a gastrointestinal infection by 9% for every day after the third day (OR: 1.09 [95% CI: 1.04–1.15]). Cox analysis confirmed our results: patients in the LGG group had greater survival probability without gastrointestinal infection during hospitalization, which was almost 3 times greater for patients in the placebo group (OR: 2.73 [95% CI: 1.60–4.69]; Fig 2). In regard to respiratory tract infections, patients who received the placebo had a 3.17 times greater chance of acquiring an infection than patients who received LGG (OR: 3.17 [95% CI: 1.35–7.43]; Table 5); this risk was increased by the following: (1) longer duration of hospitalization by 6% for every day after the third day

TABLE 2 Primary Outcome Measures and Differences Between Study Groups: χ^2 Test

Variable	LGG Group (n = 376), n (%)	Placebo Group (n = 366), n (%)	RR (95% CI)	NNT (95% CI)
Gastrointestinal tract infections ^a	19 (5.1)	44 (12.0)	0.40 (0.25–0.70)	15 (9–34)
Respiratory tract infections ^a	8 (2.1)	20 (5.5)	0.38 (0.18–0.85)	30 (16–159)

^a Number of patients with nosocomial infection.

TABLE 3 Secondary Outcome Measures and Differences Between Study Groups: χ^2 Test

Variable	LGG Group (n = 376)	Placebo Group (n = 366)	RR (95% CI)	NNT (95% CI)
Vomiting episodes, n (%)	17 (4.5)	33 (9.0)	0.50 (0.30–0.90)	23 (13–110)
Diarrheal episodes, n (%)	7 (1.9)	28 (7.7)	0.24 (0.10–0.50)	18 (11–35)
Duration of gastrointestinal infection >2 d, n (%) ^a	19 (5.1)	45 (12.3)	0.40 (0.25–0.70)	14 (9–31)
Duration of respiratory infection >3 d, n (%) ^a	8 (2.1)	19 (5.2)	0.40 (0.20–0.90)	33 (17–257)
Duration of hospital intervention, median (interquartile range) ^b	5 (3–7)	4 (4–6)	—	—

^a Number of infections over 2 to 3 days.

^b Difference analyzed with Mann-Whitney *U* test.

TABLE 4 Predictors of Gastrointestinal Infections: Binary Logistic Regression

Predictor	OR (95% CI)
Placebo group	2.89 (1.63–5.15)
Duration of hospital intervention	1.09 (1.04–1.15)
Female gender	1.32 (0.77–2.25)
Younger age	1.04 (0.95–1.08)

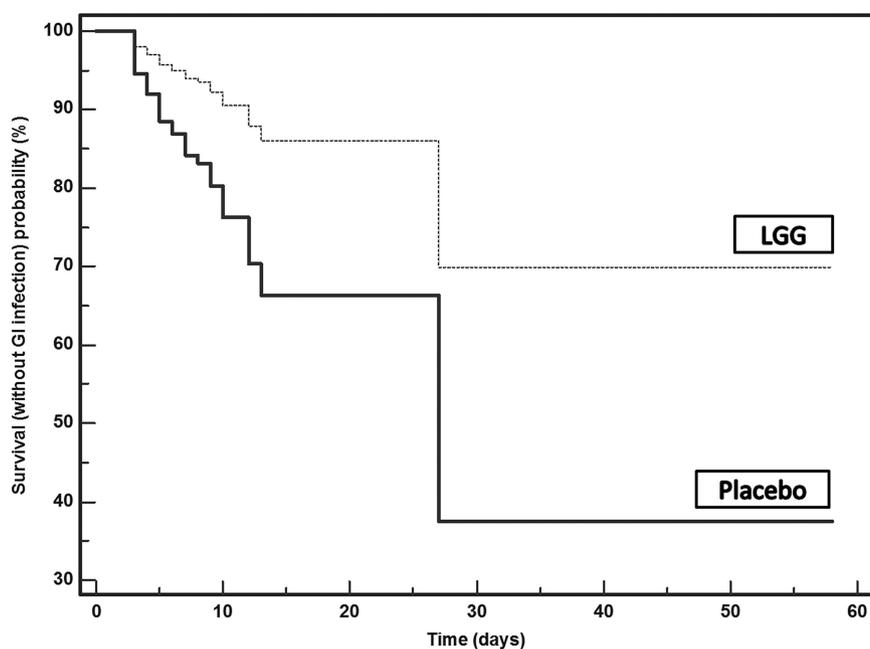


FIGURE 2

Cox proportional-hazards regression model for gastrointestinal infection. Probability of survival without gastrointestinal infection in relation to duration of hospitalization (days) for both groups.

(OR: 1.06 [95% CI: 1.01–1.12]); (2) younger age (12% for each lower year; OR: 1.12 [95% CI: 1.04–1.21]); and (3) female gender (OR: 2.52 [95% CI: 1.11–5.69]). Same was shown by using Cox analysis: the placebo group had greater probability for respiratory infection with prolonged hospitalization (OR: 3.3 [95% CI: 1.44–7.55]; Fig 3). No adverse effects were noted during study, and both products were well tolerated.

DISCUSSION

Our study shows that treatment with LGG significantly reduces the risk for developing nosocomial gastrointestinal and respiratory tract infections in children who were hospitalized on a pediatric ward. The efficacy of probiot-

ics in the prevention of nosocomial diarrhea in pediatric patients has been investigated in several studies, which have yielded contradictory results.^{17–20} In a randomized, double-blind compar-

ison (81 children aged 1–36 months), LGG administration significantly reduced the risk for developing nosocomial diarrhea compared with placebo.¹⁷ Conversely, results from a study to evaluate LGG versus placebo for the prevention of diarrhea in 220 children (1–18 months) did not confirm a preventive effect of treatment with LGG on the development of nosocomial rotavirus infections.¹⁸ In a substantially higher number of patients (aged 1–18 years), we have confirmed the beneficial effects of LGG; LGG treatment reduces not only the total number of nosocomial gastrointestinal infections but also the number of episodes of both diarrhea and vomiting as well as the duration of symptoms. The odds of acquiring a gastrointestinal infection in the placebo group was 2.89 times higher than that in the LGG group, and this risk increased with the increased duration of the hospital stay. Although the clinical picture was suggestive of a viral disease, the infective agent was

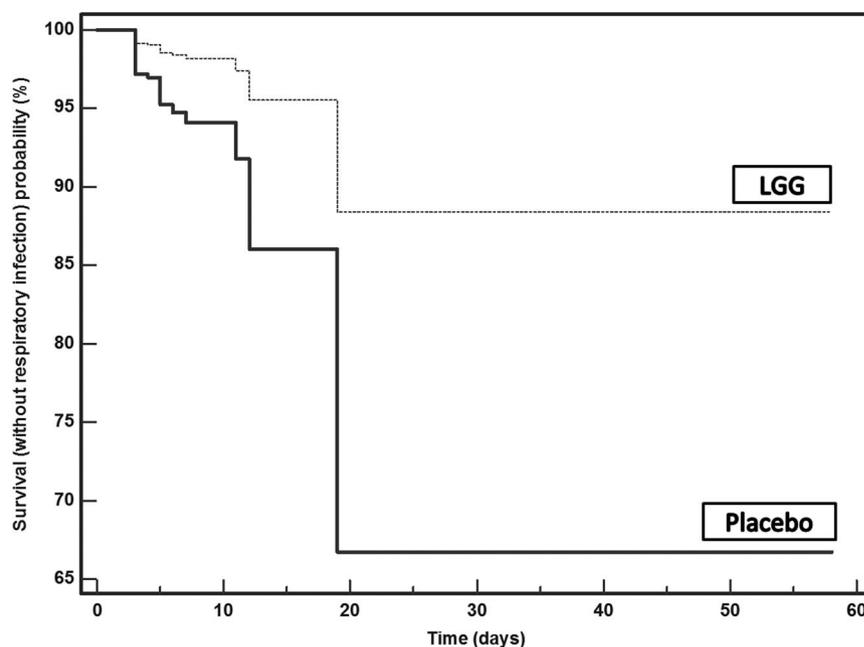


FIGURE 3

Cox proportional-hazards regression model for respiratory infection. Probability of survival without respiratory infection (%) in relation to duration of hospitalization (days) for both groups.

TABLE 5 Predictors of Respiratory Infections: Binary Logistic Regression

Predictor	OR (95% CI)
Placebo group	3.17 (1.35–7.43)
Duration of hospital intervention	1.06 (1.01–1.12)
Female gender	2.52 (1.11–5.69)
Younger age	1.12 (1.04–1.21)

not determined in the majority of patients.

In regard to the role of probiotics in the prevention of nosocomial respiratory tract diseases, only a few studies have examined this issue and all were conducted of critically ill patients with the aim of preventing pneumonia.^{21,22} Our study clearly shows that the use of LGG in pediatric wards successfully prevents hospital-acquired respiratory tract infections. Most of these infections were located in the upper respiratory tract (just 1 patient had pneumonia) and had a viral cause of the disease. In only 6 patients, a bacterial infection was diagnosed. The odds of acquiring a respiratory tract infection in the placebo group was 3.17 times higher than that in the LGG group and was increased by a prolonged hospital stay, younger age, and female gender. The last finding contradicts the results of previous studies that showed that young boys, not girls, are more prone to respiratory tract infections.²³

As for the mechanisms responsible for the beneficial role of probiotics, studies have documented direct antimicrobial effects and improvement in mucosal barrier function and immunomodulating activity as a result of the effects of probiotics on both innate and adaptive immunity but none of the mechanisms proved in upper respiratory infections.²⁴ Both in vivo and in vitro studies have shown that activa-

tion of macrophages²⁵; improvement in natural killer cell activity²⁶; increased numbers of immunoglobulin A-, immunoglobulin M-, and immunoglobulin G-secreting cells in the circulation; and increased fecal immunoglobulin A concentrations^{27–29} provide beneficial effects on the balance of proinflammatory and anti-inflammatory cytokine secretion (ie, decreases in fecal α -1 antitrypsin, urinary eosinophil protein X, and tumor necrosis factor α activity and increases in transforming growth factor β activity).^{28,30–32}

We are aware, however, of several limitations to our study. Infants, who are particularly prone to developing severe nosocomial infections could not be recruited because the study product contained 100 mL of fermented whole cow milk. Most of the nosocomial infections that were diagnosed during the study period in both groups of patients were of short duration and of unproven cause. In that respect and with the relatively high NNT of 15 for gastrointestinal infections and 30 for respiratory tract infections, it could be argued that LGG treatment for all hospitalized children may not be justified. Identifying the appropriate groups of patients for whom the prevention of nosocomial infections is most warranted could be the right direction, particularly because it has been shown that an NNT below even 40 is significant if just 1 severe infection is prevented.³³

CONCLUSIONS

Considering the significant decrease in the number of nosocomial gastrointestinal and respiratory tract infections achieved in our study with the administration of LGG in fermented milk products, treatment with LGG could be recommended as a valid measure for the prevention of hospital-acquired infections in children's facilities. We encourage future studies of children who are younger than 12 months.

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