

## Original Article



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# Lactobacillus rhamnosus GG Usage in the Prevention of Gastrointestinal and Respiratory Tract Infections in Children with Gastroesophageal Reflux Disease Treated with Proton Pump Inhibitors: A Randomized Double-Blinded Placebo-Controlled Trial

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## ABSTRACT

**Purpose:** Proton-pump inhibitors (PPIs) are frequently used to treat gastroesophageal reflux disease (GERD) in children, but recent evidence suggests a potential association between PPI treatment and some types of infections. The aim of this study was to assess the effectiveness of *Lactobacillus rhamnosus* GG (LGG) for the prevention of gastrointestinal and respiratory tract infections in children with GERD treated with PPI (omeprazol).

**Methods:** Children younger than 5 years with GERD were assigned by a computer-generated list to receive LGG ( $10^9$  colony-forming units) or placebo, twice daily, concomitantly with PPI treatment for 4–6 weeks; they were followed up for 12 weeks after therapy. The primary outcome measures were the percentage of children with a minimum of one episode of respiratory tract infection and the percentage of children with a minimum of one episode of gastrointestinal infection during the study.

**Results:** Of 61 randomized children, 59 patients (LGG n=30; placebo n=29, mean age 11.3 months) were analyzed. There was no significant difference found between the LGG and placebo groups, either for the proportion of children with at least one respiratory tract infection (22/30 vs. 25/29, respectively; relative risk [RR] 0.85, 95% confidence interval [CI] 0.66–1.10) or for the proportion of children with at least one gastrointestinal infection (9/30 vs. 9/29, respectively; RR 0.97, 95% CI 0.45–2.09).

**Conclusion:** LGG was not effective in the prevention of infectious complications in children with GERD receiving PPI. Caution is needed in interpreting these results, as the study was terminated early due to slow subject recruitment.

**Keywords:** *Lactobacillus rhamnosus*; Gastroesophageal reflux disease; GERD; Infant

## INTRODUCTION

Currently, proton-pump inhibitors (PPIs) are among the most commonly used drugs in the world [1]. They are the first-choice treatment for peptic ulcers, gastroesophageal reflux disease (GERD), specific dyspepsia subtypes, eosinophilic esophagitis, nonvariceal upper gastrointestinal hemorrhage, and as a part of *Helicobacter pylori* therapy [2-6]. Studies analyzing the prescription pattern of PPI in infants and small children show that they are most frequently used as a therapeutic agent for GERD [7-9].

PPIs are generally well tolerated; however, there is mounting evidence that these medications are not without adverse effects. Data on the safety of PPI in children are limited, but some studies have reported an association between PPI treatment and increased risk of respiratory tract and gastrointestinal infections [10]. The underlying biological mechanisms involved in PPI-associated infections are complex and still not fully understood. However, it is postulated that they depend on several factors affecting the complex balance between the host defense and gut microbiota [11]. It was shown that PPIs decrease gastric mucus viscosity, increase mucosal permeability, have direct effects on the activity of neutrophils and monocytes, and inhibit leukocyte adhesion [12,13]. Compared to that of PPI naïve subjects, patients treated with PPIs had significantly altered richness and structure of the oral and gastric mucosal microbiota, which may increase their vulnerability to gastrointestinal and respiratory tract infections [14].

Taking into account the widespread use of PPI, there is a need to identify therapies addressing risks and complications secondary to their use with potential preventive effects. Probiotic supplementation can potentially reverse alterations in patients treated with antisecretory drugs for GERD [15]. It has been shown that probiotics modulate local and systemic immunological responses, enhance gastrointestinal barrier function, and have the ability to antagonize pathogens directly [16]. Several studies and systematic reviews with meta-analyses have assessed the effect of probiotics in reducing the risk of respiratory and gastrointestinal tract infections in children [17-19]. Among probiotics, *Lactobacillus rhamnosus* GG (LGG) is well characterized, widely used, has a good safety profile, and has proven efficacy in treating and preventing diseases [20-22]. While the exact mechanism of action of LGG remains to be determined, it includes alterations of the gut microbiota, displacement of pathogenic bacteria, increasing the number of intestinal cells, and inhibition of TNF- $\alpha$  production [23]. We performed a randomized controlled trial (RCT) to assess the effectiveness of LGG for preventing PPI-associated gastrointestinal and respiratory tract infections in children with GERD.

## MATERIALS AND METHODS

### Study design

This was a randomized, double-blind, placebo-controlled trial conducted in a pediatric tertiary hospital (The Medical University of Warsaw) from February 1, 2013 to October 15, 2016. The study protocol was developed following the Declaration of Helsinki, approved by the local Ethics Committee, and registered at ClinicalTrials.gov (NCT01782118) before patient enrollment. Parents or legal guardians were fully informed about the aims of the trial, and informed written consent was obtained before patients began the study. The guidelines from the Consolidated Standards of Reporting Trials were followed for reporting this trial.

### Participants

Children eligible for study entry were younger than 5 years of age with a diagnosis of GERD and assigned to PPI treatment. Diagnosis of GERD was based on the patient's history, physical examination, and either significant distal esophageal acid exposure during 24-pH monitoring (intraesophageal pH <4 for  $\geq 10\%$  of the time) or histopathologically-proven esophagitis. Exclusion criteria included the use of PPI within the last 4 weeks for at least 2 weeks before enrollment in the study, use of probiotics within 7 days before the study, acute or chronic respiratory tract infections, acute or chronic gastrointestinal tract infections, neurological disorders, and/or immunodeficiency.

### Intervention

The study period included three appointments with the investigators and two telephone contacts during the follow-up period. At the inclusion visit, after checking inclusion/exclusion criteria and obtaining informed consent, participants were randomly assigned to receive either LGG ( $1 \times 10^8$  colony-forming units, CFU) or a comparable placebo, twice a day, orally, for 4–6 weeks, concomitantly with PPI treatment. During the subsequent two visits (3 and 4–6 weeks after the beginning of the study), patients were checked for, both, compliance with the study product and clinical improvement, and outcome measures were assessed. In the case of prolonged PPI treatment, the study product was also provided up to the end of the therapy. During the follow-up period, investigators made two telephone contacts (6 and 12 weeks after the end of PPI treatment) to review the study outcome measures.

### Outcome measures

The primary outcome measures were the percentage of children with a minimum of one episode of respiratory tract infection and the percentage of children with a minimum of one episode of gastrointestinal infection. The secondary outcome measures included the number of patients with a minimum of one episode of pneumonia, the number of respiratory tract infections/child, the number of gastrointestinal infections/child, and the number and type of adverse events. All the outcome measures were assessed during the intervention and up to 12 weeks after treatment.

### Allocation concealment and blinding

A computer-generated randomization list was used to allocate participants to the study groups in blocks of four. Consecutive randomization numbers were given to participants at enrollment. To ensure allocation concealment, a person independent from the study prepared the randomization schedule. The study products (both LGG and placebo) were prepared and delivered free of charge by the Dicofarm SpA (Rome, Italy) as a powder, with an identical taste, smell, and appearance, in indistinguishable sachets. The manufacturer had no role in the conception, protocol design, or conduct of the study, or in the analysis or interpretation of the data. Researchers, caregivers, outcome assessors, and the person responsible for the statistical analysis were blinded to the intervention until the completion of the study and the analysis of the data.

### Sample size calculation

Based on the results of the Canani et al. [24] study, we assumed that, after the intervention, the frequency of gastrointestinal infections in children in the placebo group would be 47%, while that of the group receiving the active preparation would be 20%. To detect such difference, with a power of 80% and  $\alpha=0.05$  and including 20% loss of patients, 60 subjects should be allocated to each of the study groups. For respiratory tract infections, we expected a reduction in the risk

of respiratory tract infections to 36% in the placebo group and to 6% in the active preparation group. Assuming a 20% loss of patients and a study power of 80% with  $\alpha=0.05$ , 60 patients should be allocated to each of the study groups. In October 2016, due to poor recruitment, study recruitment was terminated prior to reaching the desired sample size.

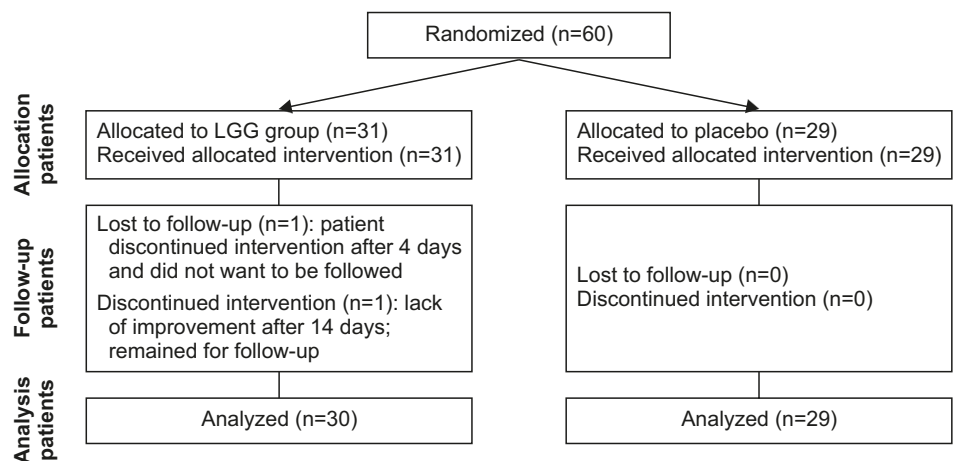
### Statistical analysis

The statistical analyses were conducted using StatsDirect V.3.0.181 (November 1, 2016, StatsDirect) computer software. The Shapiro-Wilk test was used to investigate whether the data followed a normal distribution. Student's *t*-test was used to compare means of continuous variables approximating a normal distribution. For non-normally distributed variables, the Mann-Whitney U-test was used. The  $\chi^2$  test or Fisher's exact test was used, as appropriate, to compare percentages. The same computer software was used to calculate the relative risk (RR) and mean or median difference (MD), as appropriate, both with a 95% confidence interval (CI). The difference between study groups was considered significant when the 95% CI for RR did not include 1.0 and the 95% CI for MD did not include 0 (equivalent to  $p<0.05$ ). All statistical tests were two-tailed and performed at the 5% level of significance. All analyses were conducted on an intention-to-treat basis, including all patients in the groups to which they were randomized for whom outcomes were available.

## RESULTS

**Fig. 1** presents the participants' flow through the study. A total of 60 children were enrolled. The number of available children receiving PPIs for GERD, thus eligible for enrollment in the study, decreased over time, prompting the investigators to stop the recruitment phase of the study early.

Among the children who entered the study, 31 were randomized to the LGG group and 29 were randomized to the placebo group. At baseline, groups were comparable in regard to age, gender, weight, and length/height (**Table 1**). Except for one subject who withdrew their consent after only 4 days of intervention, data from all remaining patients were analyzed. There were no significant differences found between the placebo and the probiotic (LGG) groups for any of the predefined infectious outcome measures (**Table 2**). Both groups also showed a comparable number and type of adverse events.



**Fig. 1.** Flow diagram.  
LGG: *Lactobacillus rhamnosus* GG.

## LGG for Prevention of Infections during PPI Treatment in Children

**Table 1.** Baseline and study characteristics of the placebo and LGG groups

Patients characteristics	Placebo	LGG
Boys/girls	11/18	19/12
Mean age (mo)	11.7 (0.5–48)	11.37 (2–15)
Weight (kg)	8.36 (4.3–19)	8.78 (4.8–13)
Height (cm)	70.3 (52–109)	72.6 (53–85)
Patients treated with omeprazole (%)	100	100
Mean omeprazole dose (mg/kg)	1.2 (0.8–2)	1.3 (0.9–2)
Treatment period (wk)	5.5 (4–6)	5.13 (4–6)
Follow-up period (wk)	12.1 (11–13)	11.9 (11–13.5)

Values are presented as number only, mean (range), or number (%).  
LGG: *Lactobacillus rhamnosus* GG.

**Table 2.** Primary and secondary outcome measures

Outcome measure	Placebo (n=29)	LGG (n=30)	RR1/MD2 (95% CI)	p-value
Number of children with at least one episode of respiratory tract infection	25 (86.2)	22 (73.3)	0.85 (0.66–1.10)*	0.505
Number of children with at least one episode of gastrointestinal infection	9 (31.0)	9 (30.0)	0.97 (0.45–2.09)*	>0.999
Number of children with at least one episode of pneumonia	0 (0.0)	1 (3.3)	NA	>0.999
Number of upper+lower respiratory tract infections/child	1.0 (1.0–2.0)	1.0 (0.3–2.0)	0.0 (–1.0–0.00002)*	0.248
Number of gastrointestinal infections/child	0.0 (0.0–1.0)	0.0 (0.0–1.0)	0.0 (–0.00005–0.00005)†	0.673
Colic/abdominal pain	3 (10.3)	0 (0.0)	NA	0.112
Refusal to eat	7 (24.1)	3 (10.0)	0.41 (0.12–1.45)*	0.181
Weight gain faltering	2 (6.9)	0 (0.0)	NA	0.237
Eczema	1 (3.4)	4 (13.3)	3.87 (0.46–32.57)*	0.353
Asthma	1 (3.4)	0 (0.0)	NA	0.492
Urinary tract infection	1 (3.4)	1 (3.3)	0.97 (0.06–14.74)*	>0.999

LGG: *Lactobacillus rhamnosus* GG, RR: relative risk, MD: median difference, CI: confidence interval, NA: not available.

\*Relative risk with 95% CI (Placebo vs. LGG)

†Median difference between groups with 95% CI.

## DISCUSSION

### Summary of findings

This randomized, double-blind, placebo-controlled trial found no evidence that the administration of LGG at a dose of  $10^9$  CFU, twice daily, was effective in the prevention of gastrointestinal and respiratory tract infections in children younger than 5 years treated with PPIs for GERD. Caution is needed in interpreting the results, as due to slow subject recruitment, the study was terminated early.

### Strengths and limitations

The strengths of the study lie in its design, which is randomized, double-blinded, and placebo-controlled with intention-to-treat analysis, performed in a specifically defined population. Nevertheless, the trial has some limitations. As stated earlier, we did not reach the predefined number of study participants despite a prolonged recruitment phase. After almost 3.5 years of the study, we barely achieved half of the number of participants required based on our sample size calculations. The null results of this study could be the effect of beta-error, because of the smaller sample size and relatively short follow-up period compared to previous reports. However, our findings are of importance, and may be useful for future meta-analysis. Moreover, the assessment of infections was based on parent/guardian reports, which are prone to recall bias. To minimize the risk of recall bias, the caregivers of children who entered the study were clearly instructed on the aim of the study, the ambulatory checks were made every 3 weeks, and the telephone contacts were made every 6 weeks.

### Comparison with other studies

There is no prior trial assessing the efficacy of administering probiotics to patients treated with antisecretory drugs for GERD. The evidence for a possible link between PPI use and gastrointestinal or respiratory tract infections in children is limited. The few RCTs performed in pediatric populations have shown conflicting results, and none were designed to evaluate the safety issues of PPI therapy [25-27]. Only one prospective, open-label, non-RCT by Canani et al. [24] specifically evaluated infectious complications as an outcome of treatment with gastric acidity inhibitors. This study showed that children treated with gastric acidity inhibitors (either ranitidine or omeprazole) more frequently developed community-acquired pneumonia and acute gastroenteritis than healthy controls. However, the influence of confounding factors (comorbidities, antibiotic use, and previous hospitalization) on these results could not be excluded. The only recently published, large RCT (>17,000 participants) evaluating the adverse effects of PPI treatment in adults showed that there was no evidence of harm from pantoprazole therapy except for an increased risk of enteric infections [28]. However, the prevalence of gastroenteritis in this study was low (1.4% in the pantoprazole group and 1.0% in the placebo group), and the odds ratio for the difference between groups was of statistically borderline significance (1.3, 95% CI 1.01–1.75%) [24].

In conclusion, LGG, as dosed in this trial, did not reduce the risk of PPI-associated gastrointestinal or respiratory tract infections in children. As the study is underpowered, further trials are needed.

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