Published in final edited form as:
Pediatr Emerg Care. 2012 October ; 28(10): 1048–1051. doi:10.1097/PEC.0b013e31826cad9f.

The Effect of Lactobacillus GG (LGG) on Acute Diarrheal Illness in the Pediatric Emergency Department (PED)

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Abstract

Objective—The purpose of this study was to evaluate the effectiveness of the probiotic Lactobacillus GG (LGG) in reducing the duration of acute infectious diarrhea in the pediatric emergency department (PED).

Methods—We conducted a double blind randomized controlled trial of children 6 months to 6 years presenting to the PED with a complaint of diarrhea. Patients were randomized to receive either placebo or LGG powder twice daily for 5 days. With each dose, parents recorded the stool history in a home diary and were followed-up daily by a blinded researcher. Groups were compared in terms of time to normal stool and number of diarrheal stools.

Results—Of 155 patients enrolled, 129 completed the study: 63 in the LGG group and 66 in the placebo group. There was no significant difference in the median (IQR) time to normal stool (LGG 60 hrs [37,111] vs placebo 74 hrs [43,120] p=0.37) or the number of diarrheal stools (LGG 5.0 [1,10] vs placebo 6.5 [2,14] p=0.19). Among children who presented with >2 days of diarrhea, the LGG group returned to normal stool earlier (LGG 51 hrs [32, 78] vs placebo 74 hrs [45,120], p=0.02), had fewer episodes of diarrheal stools (LGG 3.5 [1.0,7.5] vs placebo 7 [3.0,16.3] p=0.02) and were 2.2 times more likely to return to normal stool (95%CI 1.3-3.9, p=0.01) than children in the placebo group.

Conclusion—LGG may reduce the duration of acute diarrheal illness among children presenting with >2 days of symptoms.

Introduction

There is growing evidence that probiotics may play a role in the treatment of certain illnesses. Probiotics are defined by the Food and Agriculture Organization of the United Nations and by the World Health Organization as “live microorganisms, which, when

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Conflicts of Interest

The study was sponsored by Amerfit Brands (Cromwell, CT), which provided the LGG and placebo powder, as well as a small monetary compensation for participants’ telephone airtime. The study investigators have no affiliation with, and were entirely independent from, Amerifit Brands and had full control over the data.

Portions of this article were presented at the Pediatric Academic Societies Annual Meeting, May 2010, Vancouver, Canada.

administered in adequate amounts, confer a health benefit to the host".[1] Of the probiotics, *Lactobacillus* GG (LGG) has been the most studied in children and has been shown to be particularly effective against *Rotavirus,* the leading cause of acute gastroenteritis in children worldwide.[2]

A 2004 Cochrane review documented a reduction in the duration of diarrhea by 30 hours in both adult and pediatric patients taking probiotics. [3] Meta-analyses of pediatric studies, done largely on inpatient populations, have found that patients treated with probiotics have a decrease in the duration of infectious diarrheal episodes.[4,5,6] Only a few studies, all performed outside of the United States, have demonstrated the effectiveness of probiotics in reducing the duration of acute infectious diarrhea in outpatient pediatric populations.[7,8,9] While the beneficial effect of LGG in treating acute infectious diarrhea in both pediatric inpatients and outpatients is well documented in other countries, to date, it has not been studied in an outpatient setting in the United States.[10] Our objective was to evaluate the effectiveness of LGG in reducing the duration of acute infectious diarrhea in the pediatric emergency department (PED).

Materials and Methods

Study Design

We conducted a double blind randomized controlled trial comparing a 5 day course of LGG to a placebo powder. This was a preliminary study designed to provide an estimate of the effect of LGG on acute diarrheal illness. The study was approved by the Institutional Review Boards of The Albert Einstein College of Medicine and Jacobi Medical Center. Written informed consent was obtained from the guardians of all enrolled patients.

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Study Setting and Population

Participants were recruited from November, 2008 through July, 2009 from the PED of an urban, public hospital with an annual census of approximately 40,000. Consecutive patients aged 6 months to 6 years presenting with a complaint of diarrhea, defined by the World Health Organization, as more than 2 loose stools in the preceding 24 hours, were assessed for eligibility. Patients were eligible if the parent was English or Spanish speaking, had access to a telephone and was available to receive calls daily for 5 days. Patients were excluded if they were admitted to the inpatient service, had risk factors for non-viral diarrhea (prolonged diarrhea more than 7 days, gross blood, antibiotic exposure or inflammatory bowel disease), immune compromise, risk factors for probiotic-associated systemic illness (indwelling central line, short gut syndrome) or an allergy to milk products.

Study Protocol

After written consent was obtained, patients were randomized to the placebo or LGG group. Providers were instructed to take the next packet in a series of sequentially numbered packets whose order was derived from a random numbers table. Packets, stored in a refrigerator in the PED, were labeled A or B, and contained LGG or placebo capsules along with written instructions and a home diary. All forms in the enrollment packet were in English and Spanish.

LGG powder, in capsule form, was compared to a physiologically inactive placebo, inulin. The LGG powder and the placebo were nearly identical, tasteless white powders, delivered in sealed foil blister packs, labeled A or B. All research personnel, including pharmacy, PED staff and research assistants were blinded to the group assignment until data analysis was completed.

In the PED, providers completed a baseline data collection form consisting of demographic and contact information and multiple choice questions detailing the patient's diarrheal illness. Patients received a home diary and 10 capsules of dissolvable powder. The first dose was given in the PED, where providers demonstrated to parents how to open the capsule and dissolve the powder. Parents were instructed to administer the powder twice daily for 5 days and to refrain from giving their child yogurt during the study period. With each dose, parents used the home diary to record the number of stools (normal vs. diarrheal) in the 12 hour interval prior to the dose,. Additionally they were asked to note the time of the first normal stool. A blinded researcher called the caregiver daily for 5 days and recorded the number of capsules administered in the prior 24 hours, the number of stools and the date and time of the first normal stool. On the fifth day of follow-up, in addition to the standard questions, parents were asked about the need to return to medical care, and the ability to return to routine daily activities for both themselves and their child. Parents were also asked their opinion of the ease of administration of the powder and its effectiveness in shortening the course of their child's diarrhea. Following the completion of the 5 days of telephone follow-up, parents were mailed a $25 cash compensation for their telephone airtime.

Data Analysis

Groups were compared in terms of the proportion of patients returning to normal stool, time to normal stool and number of diarrheal stools. Patients who never completed any telephone calls were coded as “Lost/No data” and were excluded from final analysis. Patients who either partially or fully completed the follow-up telephone interviews were used to compare the overall percentages of patients returning to a normal stool. To perform this analysis, patients who partially completed the study were censored at the last completed telephone call. Patients with unresolved diarrhea by the end of the study period were coded as having 5 days (120 hrs) of diarrhea. Patients who either had a normal stool during the follow-up period or who completed all 5 days of follow-up calls were considered to have fully completed the study. Patients who fully completed the study were used to compare the duration of diarrhea and the number of diarrheal stools between groups.

Statistical Analysis

The study was powered to detect a difference of 1 day in the duration of diarrhea, assuming the average duration of diarrhea was 4 days, with a standard deviation of 2 days. This estimated average duration was based on pilot data collected prior to designing the study . Using these estimates,, a beta of 0.20 and an alpha of 0.05, we calculated that a sample size of 64 patients in each group was required to detect this one day difference.

Statistical tests used for comparison included Chi-Square and the Mann-Whitney U. Because many of the continuous variables were not normally distributed, when a Mann-Whitney U was used to compare the groups, the medians and interquartile ranges (IQR) are presented. Hazard ratios were estimated using Cox Regression models in which time to return to normal stool was the outcome.

Data were analyzed using SPSS 15.0, Grad Pack for Windows. (SPSS Inc, Chicago, Illinois).

Results

Of the 217 patients approached, 155 (71%) met inclusion criteria and were enrolled. Twenty-two patients (10%) were excluded based on enrollment criteria and 40 (18%) refused to participate. Seventy-seven patients were randomized to the LGG group and 78 to the placebo group. Seventeen patients had no follow-up contact and were excluded from the final analysis, 10 in the LGG group and 7 in the placebo group, (p= 0.16). Sixty-seven patients in the LGG group and 71 patients in the placebo group, either partially or fully completed the follow-up telephone interviews. Of this group, 63 patients in the LGG group and 66 patients in the placebo group completed all 5 days of telephone calls or returned to normal stool within the study period.

The LGG and placebo groups differed only by age (28.5 vs 22.4 mos, p=0.02). There were no statistically significant differences between groups in terms of other demographic information or the severity of illness prior to presentation, including the number of days of diarrhea, the number of diarrheal stools and the presence of emesis or fever at home. (Table 1)

There was no statistically significant difference between groups in the proportion of patients returning to normal stool, (75% in the LGG group vs 65% in the placebo group, p=0.21). Among those patients who returned to normal stool or completed the 5 day study period, there was no significant difference in the median (IQR) time to normal stool (LGG 60 hrs [37,111] vs placebo 74 hrs [43,120], p=0.37) or the median (IQR) number of diarrheal stools, (LGG 5.0 [1,10] vs 6.5 [2,14], p=0.19). After adjusting for age there was a non-significant trend for the LGG group to be 1.4 times more likely to return to normal stool, (95% CI 0.9-2.1) (p=0.14).

Observing this trend toward a positive effect of LGG on the resolution of diarrhea, we performed a subgroup analysis to further explore the relationship. Among patients presenting with more than 2 days of diarrhea, a higher percentage of LGG patients returned to normal stool by the end of the study, (79% in the LGG group vs 58% in the placebo group, p=0.04). Additionally, the LGG group returned to normal stool nearly 24 hours earlier than the placebo group (LGG 51 hrs [32,78] vs placebo 74 hrs [45,120], p=0.02), and had half the number of diarrheal stools, (LGG 3.5 [1.0,7.5] vs placebo 7 [3.0,16.3], p=0.02). Adjusting for age, patients in the LGG group presenting with more than 2 days of diarrhea were twice as likely to return to normal stool as children in the placebo group, (95% CI 1.2-3.6) (p=0.01).

Among patients <12 mos (n=38), the LGG group was 2.5 times more likely to return to normal stool within the study period (95% CI 1.0-6.4, p=0.06). There were no significant differences in median time to normal stool (LGG 55 hrs [37,117] vs placebo 65 hrs [31,120], p=0.9) or in number of diarrheal stools (LGG 8 [5,13.5] vs placebo 6 [3,16], p=0.7) in this age group.

On examination of the secondary outcomes, the groups did not significantly differ in terms of the overall ability of patients or parents to return to their normal activities, return to medical care or the need for hospitalization. One hundred percent of the LGG patients (20/20) versus 92% of the placebo patients (11/12), who reported attending daily out of home activities (school, daycare, etc), were able to return to those daily activities (p=0.21). One hundred percent of both groups of parents (17/17 LGG vs 21/21 placebo), who reported that they attended work or school, were able to return to their obligations during the study period. Thirteen percent of the LGG group versus 17% of the placebo group had a return visit within the study period (p=0.79). Subsequent hospitalization rates were not significantly different between groups (LGG 3.0% vs placebo 1.4%, p=0.74)

During the final telephone interview, parents were asked their opinion of the ease of administration of the powder and of their perception of its effectiveness. Similar percentages of parents in both groups, 88% of LGG vs 86% of placebo found the powders to be “very” or “somewhat” easy to administer to their children (p=0.91). Parental perception of effectiveness was not significantly different between the placebo and LGG groups. In the LGG group, 88% of parents felt the powder to be effective in reducing the duration of their child's diarrhea, vs 77% in the placebo group (p=0.25).

Discussion

Our study found that LGG compared to placebo showed a consistent, albeit non-significant, trend towards reducing the duration and severity of diarrheal illness in the overall population of patients presenting to the pediatric ED. Our results are consistent with previously reported beneficial effects of the probiotic. We found, however, a statistically significant and clinically meaningful reduction of nearly 24 hours in the duration of diarrheal illness among children presenting with more than 2 days of symptoms. Although this finding was identified on post-hoc analysis, similar subgrouping by duration of symptoms was performed in prior studies.[8,11] Our findings differ from those reported by Rosenfeldt et al[8] of Danish daycare attendees using a different Lactobacillus preparation, which suggested that early initiation of probiotics, specifically within 60 hours of the start of illness, may have a more pronounced effect. A more recent study by Salazar-Lindo, et al[11] among Peruvian children diagnosed with mild acute diarrhea and randomized to treatment with oral rehydration solution and Lactobacillus LB or placebo, found no overall difference between groups in the rate of recovery, but did find a significant difference when examining the subgroup of patients presenting with more than 24 hours of symptoms. The exact mechanism by which probiotics improve diarrheal illness is not clear, and it is possible that each strain may have a different mechanism. The reduction reported in our study and that by Salazar-Lindo et al, suggests that the LGG may have a restorative effect on the intestinal flora, and therefore would preferentially benefit patients presenting with prolonged diarrhea. Additionally, it is possible that our study population contained a large percentage of patients with mild illness but high parental anxiety, who sought treatment early into the course of an illness that would likely have self-resolved. We would expect that this population would not benefit from the administration of probiotics and their inclusion might have weakened our ability to demonstrate an effect of LGG.

Additionally, posthoc analysis suggested that patients 6-12 months of age were more likely to improve during the 5 day course than the overall patient population; however, the number of these patients was very small, therefore the confidence intervals around the estimates were wide. This possible differential benefit may be of particular importance because infants are more susceptible to dehydration than older children. Therefore, reducing the duration of diarrhea in this group could result in meaningful improvements in morbidity and mortality. Interestingly, in our study population, despite randomization, the groups still differed significantly by age. The LGG group was, on average, 6 months older than the placebo group. We adjusted for this difference whenever possible, including in our survival analyses. Given that our subgroup analysis suggested that the benefit of the LGG might be greater in the younger population, if age had a clinically meaningful effect, we would expect it to weaken the observed effect of the LGG in our study.

Regarding the secondary outcomes, we found few substantial differences between groups. There was no meaningful difference between LGG and placebo groups with regard to return to daily activity or the need to return to medical care. This was largely due to the fact that the majority of patients in our study were cared for at home by a parent; therefore quantifying return to daily activity was difficult and our numbers were small. It is possible

that fewer patients than expected returned to medical care in both groups because parental anxiety was assuaged by the daily telephone calls. Finally, parents in general found the powder easy to administer and well tolerated by their children. No adverse effects were reported during daily telephone calls. Regardless of group randomization, a large majority of parents perceived a benefit from the powder. This speaks to the frustration that many parents feel when faced with a viral illness, for which “tincture of time” is the only cure and to the psychological benefit of administering a “treatment”.

Our study had several limitations. We relied on parental report for the majority of the data. Because the study was randomized and controlled, however, this potential bias should, in theory, affect both groups similarly. Additionally, our outcome measure was time to the first normal stool. Perhaps a better measure would have been time to the last diarrheal stool. In our study, patients who had resolution of diarrhea, but did not have a normal stool prior to the end of the study period, were included with those who had diarrhea throughout the 5 days; therefore, this may have falsely decreased the percentages returning to normal stool and increased the time to normal stool. Due to the manner in which data was collected, we did not have the information to perform this analysis.

The choice of inulin, provided as the placebo by the sponsoring company, may also have had an effect on our results. Touted by some as a “prebiotic”, functioning to nourish preexisting gut flora, the effect of inulin on diarrhea is not known. If in fact inulin is not an inert substance and has a beneficial effect, the differences we found between the groups would be underestimated. Finally, while a random number table was used to generate allocation sequence, our study lacked complete allocation concealment. The envelopes had a code on the outside, which was placed for the enroller to check against the packet contents in order to ensure accuracy of the contents. Theoretically, enrollers could notice and interpret the code, to which they were blinded. Because, however, our PED operates with numerous rotating clinicians, it is highly unlikely that the same individual enrolled multiple patients, nor did they have access to any of the follow-up data or outcomes.

Therefore, it would have been extremely difficult for a given clinician to form an opinion of the coded sequence.

In conclusion, as diarrhea accounts for more than 1.5 million pediatric outpatient visits and over 200,000 hospitalizations annually in the United States[12], a reduction in the time to resolution may have important public health implications in terms of missed work and lost revenue, school and daycare absenteeism, and the cost of diapers and other health related expenses. Our findings suggest that a larger randomized controlled trial, with predetermined subgroup analysis, will further define the usefulness of LGG in the outpatient setting.

Acknowledgments

Source of Funding

This publication was supported in part by the CTSA Grant UL1 RR025750, KL2 RR025749 and TL1 RR025748 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and NIH roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessary represent the official view of the NCRR or NIH.

References

1. Food and Agriculture Organization of the United Nations (FAO) and World Health organization (WHO). Health and nutritional properties of probiotics in food including powder milk with live lactic acid bacteria.. FAO and WHO Joint and Expert Committee Report, 2001. Available at: ftp://ftp.fao.org/es/esn/food/probio_report_en.pdf

2. Majamaa H, Isolauri E, Saxelin M, et al. Lactic acid bacteria in the treatment of acute rotavirus gastroenteritis. J Pediatr Gastroenterol Nutr. 1995; 20:333–338. [PubMed: 7608829]

3. Allen SJ, Okoko B, Martinez E, Gregorio G, Dans LF. Probiotics for treating infectious diarrhoea. Cochrane Database Syst Rev. 2004; (2):CD003048. [PubMed: 15106189]

4. Huang JS, Bousvaros A, Lee JW, et al. Efficacy of probiotic use in acute diarrhea in children: A meta-analysis. Dig Dis Sci. 2002; 47(11):2625–2634. [PubMed: 12452406]

5. Szajewska H, Skorka A, Ruszczynski M, et al. Meta-analysis: Lactobacillus GG for treating acute diarrhoea in children. Aliment Pharmacol Ther. 2007; 25(8):871–81. [PubMed: 17402990]

6. Van Niel CW, Feudtner C, Garrison MM, et al. *Lactobacillus* therapy for acute infectious diarrhea in children: A meta-analysis. Pediatrics. 2002; 109(4):678–684. [PubMed: 11927715]

7. Guarino A, Canani RB, Spagnuolo MI, et al. Oral bacteriotherapy reduces the duration of symptoms and of viral excretion in children with mild diarrhea. J Pediatr Gastroenterol Nutr. 1997; 25(5):516–519. [PubMed: 9360205]

8. Rosenfeldt V, Michaelsen KF, Jakobsen M, et al. Effect of probiotic *Lactobacillus* strains on acute diarrhea in a cohort of nonhospitalized children attending day-care centers. Pediatr Infect Dis J. 2002; 21(5):417–419. [PubMed: 12150179]

9. Canani RB, Cirillo P, Terrin G, et al. Probiotics for treatment of acute diarrhoea in children: randomised clinical trial of five different preparations. BMJ. 2007; 335(7615):340. [PubMed: 17690340]

10. Szajewska H, Mrukowicz JZ. Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: A systematic review of published randomized, double-blind, placebo-controlled trials. J Pediatr Gastroenterol Nutr. 2001; 33:S17–S25. [PubMed: 11698781]

11. Salazar-Lino E, Figueroa-Quintailla D, Caciano MI, et al. Effectiveness and Safety of Lactobacillus LB in the Treatment of Mild Acute Diarrhea in Children. J Pediatr Gastroenterol Nutr. 2007; 44:571–576. [PubMed: 17460488]

12. King CK, Glass R, Bresee JS, et al. Managing acute gastroenteritis among children: oral rehydration, maintenance, and nutritional therapy. MMWR Recomm Rep. 2003; 52(RR-16):1–16. [PubMed: 14627948]

Table 1

Baseline Characteristics of Patients in LGG and Placebo Groups

Category	Placebo (n=78)	LGG (n=77)	Total (n=155)	p value
Age, mos (SD)	22.4 (13.8)	28.5 (17.1)	25.5 (15.8)	0.02
Gender:				
Female	45%	49%	47%	0.57
Male	55%	51%	53%	
Ethnicity:				
Hispanic/Latino	58%	64%	61%	
Black	23%	13%	18%	0.26
Other	19%	23%	22%	
Prior Days of Diarrhea (SD)	2.8 (1.3)	2.5 (1.2)	2.7 (1.2)	0.17
Episodes of Diarrhea In Prior 24 hrs (SD)	5.4 (3.5)	5.2 (2.6)	5.3 (3.1)	0.23
Presence of Emesis	65%	78%	72%	0.08
Fever at Home	55%	45%	50%	0.39

For all continuous variables, the mean and standard deviation (SD) are given.

For all categorical variables, the percentages are given.