JPPT | Prospective Randomized Pilot Study

Lactobacillus GG in the Prevention of Antibiotic-Associated Diarrhea in the Pediatric Intensive Care Unit: A Prospective Randomized, Double-Blind Placebo Controlled Intervention

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OBJECTIVE The objective of this study was to assess the efficacy of lactobacillus GG (LGG) to prevent antibiotic-associated diarrhea (AAD) in the pediatric intensive care unit (PICU).

METHODS This was a prospective randomized, double-blind, placebo-controlled pilot trial in an academic PICU over 1 year. Patients ≤ 17 years who required antibiotic therapy ≥ 72 hours were randomly assigned to receive placebo or LGG. Exclusion criteria included antibiotics ≥ 48 hours prior, prior probiotics, pre-existing diarrhea, laxative therapy, immunocompromise, and gastrointestinal (GI) disorders. LGG (30×10^9 colony forming units) or a matching placebo capsule was administered twice daily for the duration of antibiotic therapy. Diarrhea was defined as 3 or more loose stools in 24 hours.

RESULTS A total of 36 patients were enrolled with 19 patients eligible for final analysis; 10 in the LGG group and 9 in the placebo group. Median age and weight of LGG vs placebo groups were 0.4 (0.17–1.42) vs 0.86 (1.21–10.92) years, p = 0.48, and 6 (3.4–9.9) vs 9.8 (3.71–39.6) kg, p = 0.31, respectively. Antibiotic associated diarrhea was experienced in 30% vs 55.5% of patients in the LGG groups vs placebo (p = 0.375), respectively. The median PICU length of stay for the patients with AAD was 6 days compared with 7.5 days in placebo group (p = 0.033). The RR ratio for AAD when using LGG was 0.59 (95% CI, 0.21–1.6). No adverse events were reported or attributed to LGG.

CONCLUSION Results of this pilot study indicate that LGG is safe and could potentially reduce the incidence of AAD in the critically ill pediatric patients at this academic institution. Our findings suggest clinicians should consider the use of LGG in appropriate PICU patients.

ABBREVIATIONS AAD, antibiotic associated diarrhea; ANC, absolute neutrophil count; CFU, colony forming units; GI, gastrointestinal; IV, intravenous; LGG, lactobacillus GG; PICU, pediatric intensive care unit; VAP, ventilator associated pneumonia

KEYWORDS antibiotic-associated diarrhea; critical illness; Lactobacillus; pediatrics; PICU; probiotic

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Introduction

Antibiotic associated diarrhea (AAD) is a common complication of antibiotic use due to disruption of the normal intestinal microbiota and has a reported incidence of 11% to 62% depending on the location (inpatient, outpatient, intensive care unit [ICU]), age and antibiotic type.[1,2] Antibiotic associated diarrhea can be attributed to increased costs and length of hospital stay.[2] In pediatrics, AAD appears to have a more rapid onset, shorter duration, and fewer complications. It is still reported to have a median incidence of 22% and a reported outpatient range of 6% to 75%.[3] In critically ill ICU patients, broad spectrum antibiotics are commonly administered empirically due to the severity of potential infectious processes. In this population, AAD can be more severe and more frequent due to the use of these antibiotics.[4]

Currently, no studies have examined the impact of probiotics on the prevention of AAD in the PICU population as their primary outcome. One study by Roshanzamiri et al[5] examined the impact of probiotic, *Limosilactobacillus reuteri* DSM 17938 on the prevention of ventilator associated pneumonia (VAP) in the pediatric ICU (PICU) and had diarrhea as a secondary outcome.[5] Due to the limited data on the use of probiotics for the prophylaxis of AAD in the PICU, this prospective study was conducted to determine if *Lactobacillus rhamnosus* (LGG) was beneficial in the prevention of

AAD in patients admitted to the PICU at a stand-alone academic pediatric hospital.

Objective

The objective of this study was to assess the efficacy of LGG to prevent AAD in the PICU. This study utilized LGG and a standardized definition of diarrhea to assess and determine the incidence of diarrhea in a lactobacillus group vs a placebo-controlled group of critically ill pediatric patients.

Materials and Methods

This was a prospective randomized, double-blind, placebo-controlled trial which compared the efficacy of LGG to placebo in preventing AAD in critically ill pediatric patients. The study took place in a 20-bed PICU, with trained PICU nurses, pharmacists, physician assistants, and physicians.

Settings and Participants. Patients admitted to the PICU over the 1 year of enrollment in the study required antibiotic therapy and met the inclusion/exclusion criteria, were identified as eligible to participate in the study by attending physicians, physician assistants, pharmacists, and residents.

Patients were eligible for the study if they were 17 years of age or younger and were considered to require antibiotic therapy (IV or enteral) for more than 72 hours. All patients who were started on oral feeds within 24 to 48 hours of admission to the PICU were also eligible for inclusion into the study. Patients were excluded if they had previously been on antibiotics for greater than 48 hours prior to time of admission, had pre-existing diarrhea upon admission or 24 hours prior, was on laxative therapy 48 hours prior to admission or upon admission, severely immunocompromised (defined as HIV with CD4 <250, ANC<100, >10 days of chronic steroid therapy), those with pre-existing gastrointestinal disorders (such as intussusception, lower bowel disease, bowel resection, irritable bowel syndrome, bowel resection, irritable bowel syndrome, ulcerative colitis, or Crohn disease), those receiving post-surgical antibiotics for prophylaxis, or those who were not able to take medications by either mouth or enterally. Patients were further excluded from analysis if they had < 48 hours of antibiotics, < 6 doses of LGG and incomplete data.

Randomization. Upon enrollment, patients were randomly assigned to receive study drug (*lactobacillus GG* 30 × 10^9 colony forming units (CFUs) every 12 hours) or matching in appearance placebo by computer-generated randomization. Treatment with LGG or placebo was initiated within 24 hours of the initiation of antibiotic therapy and continued for the duration of antibiotic therapy. All investigators, nurses, physician attendings, physician assistants, and residents were blinded to treatment. Randomization occurred in the pharmacy at the time of dispensing. The capsules could be opened and dissolved with water to administer through orogastric/nasogastric tubes if needed. If opening occurred, blinding was retained as the internal components appeared similar in color.

Diarrhea Definition. For the purpose of this study diarrhea was defined as stools >200 mL or 200 g per day in patients over 10 kg and > 20 mL/kg/day or > 20 g/kg/day in patients ≤ 10 kg or 3 or more loose stools in 24 hours if the stools were not able to be weighed.[6]

Primary Outcomes and Statistical Analysis. The primary outcome was the incidence of AAD after 3 days of LGG, with secondary outcomes being tolerability (ADRs attributed to LGG, e.g., flatulence, GI upset/bloating, constipation, vomiting, nausea, elevated blood pressure, fever, sepsis, rash or headache), the length of PICU stay, antibiotics that patients were on and number of stools. Our estimated sample size was 67 to achieve a statistically significant result, with the power of 0.8 (based on Fisher z-transformation). Outcomes were evaluated using a χ^2 analysis and Mann-Whitney *U* test. Logistic regression was utilized for variables. The RR, 95% CI, and number needed to treat was calculated. The difference between study groups were considered significant when the p value is <0.05 or when 95% CI for RR does not exceed 1.0 (equivalent to $p < 0.05$). Any patients with missing data on the primary outcomes was removed from analysis.

Results

A total of 36 patients met the initial inclusion criteria and were enrolled in the study. After the exclusion criteria were applied, 19 patients were eligible for final analysis with 10 randomly assigned to the LGG group and 9 to the placebo group. A majority of patients were excluded from final analysis due to receiving less than 48 hours of antibiotics, less than 6 doses of LGG or incomplete data collection. Most patients enrolled were male (57.9%). Median (IQR) age and weight of LGG vs placebo groups were 0.4 (0.17–1.42) vs 0.86 (1.21–10.92) years, p = 0.48, and 6 (3.4–9.9) vs 9.8 (3.71–39.6) kg, p = 0.31, respectively. The PICU patients were administered 1 to 3 intravenous (IV) antibiotics. Clindamycin was utilized in 52.6% of the patients. Further demographics are shown in the Table. A majority of patients were receiving enteral feeds of some type, 18/19 (94.7%).

For the primary outcome of diarrhea, there was a 30% occurrence in the LGG groups vs 55.5% in the placebo group (p = 0.37). The RR ratio for diarrhea with the LGG group vs placebo was 0.589 (95% CI, 0.21–1.6, p = 0.37). Diarrhea was not statistically significant with use of clindamycin alone or with the number of antibiotics patients were on.

The median (IQR) length of stay for the patients with diarrhea was 8 days (7–10) compared with 6 days (4–7.25) in patients without diarrhea (p = 0.033). The duration of LGG therapy ranged from 3 to 8.5 days. The overall number of stools ranged from 4 to 35 in

Table. Demographic Characteristics of LGG vs Placebo

Variable	LGG (n = 10)	Placebo (n = 9)	p value
Age, median (IQR), yr	0.4 (0.17–1.42)	1.43 (1.32–10.71)	0.26
Sex, female, %	30	55.5	0.65
Race, Caucasians, %	36.4	40	*
Weight (in kg)	6 (4–9.9)	9.8 (3.71–39.6)	0.18
Length of PICU stay, days	6 (4.5–7)	8 (5.5–8.0)	0.031
No. of antibiotics:			
• 3	5	3	
• 2	3	3	
• 1	1	1	
• Unknown	1	2	
Antibiotics (all IV):			
• Cephalosporins	9	9	
• Clindamycin	4	7	
• Vancomycin	3	4	
• Ampicillin	5	1	

IV, intravenous; LGG, lactobacillus GG; PICU, pediatric intensive care unit

* Data involves more than 2 independent variables and sample size is insufficient to do multivariable logistic regression to calculate p value.

the probiotic group and 5 to 53 in the control group, with the overall mean for number of stools was 16.9 and 17.5, respectively. No adverse events were reported or attributed to LGG. The incidence of sepsis, bacteremia, and fungemia due to LGG were specifically assessed and did not occur in any patients.

Discussion

This is the first study to prospectively assess the efficacy of LGG for AAD in critically ill pediatric patients who are treated with broad spectrum antibiotics. Other studies have looked at use of probiotics for pediatric outpatients, inpatient, non-critical care or mixed (inpatient and outpatient) settings.[7–10] These studies have demonstrated efficacy of probiotics in stool consistency, duration of diarrhea, and incidence of AAD. One other study that occurred in the PICU, reported on AAD but it was not the primary outcome.[5] Their primary outcome was prevention of VAP in mechanically ventilated patients and AAD was a secondary outcome. They utilized *L reuteri* DSM 17938 in 72 children and their definition of AAD was similar to this study (3 loose stools/24 hours). The incidence of AAD was 20.59% vs 2.63% for placebo vs probiotic (p = 0.023), respectively.[5] That study demonstrated a marked difference between placebo and probiotic compared with what our study demonstrated (30% vs 55.5%) despite it being a secondary outcome.[5]

In our study, the incidence of AAD in the LGG group was about half the incidence in the placebo group (30% vs 55.5%, respectively), but this difference was not statistically significant, likely due to the low number of patients and not meeting power. We did demonstrate a RR of 0.59 and a statistically significant difference in length of PICU admission (p < 0.033). However, we realize that length of PICU admission is affected by so many other factors that were not tested and thus cannot be fully attributed to incidence of AAD or LGG administration.

Several systematic reviews and meta-analysis have been conducted to determine the pooled incidence of AAD. The 2017 Cochrane Review determined an incidence of 1.5% vs 4% in the probiotic vs placebo groups, respectively with an RR of 0.4.[11] Similarly, the 2019 Cochrane Review calculated a RR of 0.45.[12] Our study had a similar RR at 0.59. However, the overall incidence of AAD was higher (55.5% and 30% for placebo vs LGG, respectively) than others have reported in the literature for both placebo and LGG groups. Reported incidences of AAD in patients on broad spectrum antibiotics range from 11% to 40%.[1,12] The increase we observed may be due to the amount of IV broad-spectrum antibiotics our patients were on in addition to the stress of being in the PICU. All the Cochrane Reviews included both inpatient and outpatient children together.

A strength of our study was that it was randomized and double-blinded to decrease bias. We utilized a strict criterion to define AAD and had a strict inclusion criterion which limited enrollment. The Cochrane reviews noted the heterogeneity of the definition of diarrhea (more than 9 different definitions) utilized in different studies.[11–13] We chose to use the World Health Organization definition of diarrhea. Since stool quantity and consistency in an infant differs from a toddler or 10-year-old, our definition of diarrhea was specific for patient weight as well.[6] The European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and a 2019 Cochrane Review identified that the difference of AAD based on probiotic dose was significant with higher doses (≥ 5×10^9 CFU/day) being more beneficial with a RR 0.37 (95% CI, 0.3–0.46) and number needed to benefit of 6.[12,14] We also maintained high standard doses of LGG in this study at 60×10^9 CFUs per day.

Moreover, we analyzed the specific antibiotics that the patients received. The risk of AAD is typically considered higher for aminopenicillins, cephalosporins, and clindamycin.[15] In our analysis, a majority of patients were on cephalosporins and clindamycin, but it did not appear that use of these antibiotics affected the incidence of AAD.

Limitations for this study include it being in 1 institution and 1 PICU, the small sample size and the variability of diarrhea description by nurse and/or reliance on nurses charted data for bowel movements. Another limitation was the availability of LGG as enteral only. Many patients were started on antibiotics prior to ability to administer enteral LGG and thus could not be included in the study. Furthermore, we did not gather data if our patients had a central line or not. We also did not assess duration of diarrhea systematically, but it is something that could have been addressed and compared. Due to the low number of patients in this study, it may not have been as relevant.

We did not enroll patients who were immunocompromised. As such we did not have any lactobacillus-related incidences of bacteremia, fungemia or positive blood cultures. There have been some studies and case reports questioning the safety of probiotics for routine use in inpatient settings or at-risk populations.[16,17] One of the reasons being due to the risk of plasmid-mediated antibiotics resistance transfer or direct clonal transmission.[16,17] A majority of the incidences of adverse events have occurred in immunocompromised children or those with central venous catheters. In this study, we had a strict inclusion criterion which did not allow for severely immunocompromised children. This decreased our overall enrollment but also likely precluded any incidence of antibiotic resistance transfer or sepsis. Moreover, our population in this current study was likely too small to detect such plasma-mediated antibiotic resistance transfer but our institution has been routinely administering LGG to PICU and other inpatient pediatric patients since 2006. Lactobacillus is included in our standard PICU admission order set and is often routinely started when patients start antibiotics. We are also unaware of any known antibiotic resistance transfer. We have not done a systematic study on this, but this could be a future investigational pursuit.

Due to the small sample size and large number of lost patients, this was a hypothesis generating pilot study involving critically ill pediatric patients receiving broad spectrum antibiotics. We believe that this supports lactobacillus efficacy at our institution, but it may not be generalizable to other institutions. Our PICU is a tertiary referral PICU with most of the subspecialties except cardiac/thoracic surgery and extracorporeal membrane oxygenation. Thus, these results may not be generalizable to all PICUs. Other future studies could include multi-institutions, involve a larger sample size, longer duration, and determination of *Clostridium difficile* incidence.

Conclusion

Results of this pilot study are hypothesis-generating and appear to indicate that LGG is safe and could potentially reduce the incidence of AAD in the critically ill pediatric patients. This information may only be applicable to other similar PICUs. Further research is warranted.

Article Information

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Ethical Approval and Informed Consent. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation and have been approved by the appropriate committees at our institution (University of South Alabama and Auburn University). All patients and/or parents/caregiver(s) provided written informed consent and/or assent (>8 years old) at enrollment.

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