Lactobacillus GG as Treatment for Diarrhea During Enteral Feeding in Critical Illness: Randomized Controlled Trial
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D iarrhea is a common problem in critically ill patients. The reported incidence of diarrhea in enterally fed intensive care unit (ICU) patients varies according to the criteria used to define diarrhea, but may be between 15% and 40% or higher.1-4 It can be a serious clinical problem, with potential significant detrimental effects on fluid and electrolyte balance, hemodynamic stability, skin integrity, wound healing, and nutrition status. Bowel management protocols can reduce the incidence of diarrhea,1 but probiotics remain an untested treatment in the ICU setting.

Probiotics are defined as beneficial bacteria found in a healthy human gut.5 Critical illness is likely to cause significant disturbance to the gut microbiota because of the effects of the illness itself6 as well as various interventions, including antibiotics and gastric acid suppressants, and medications that alter gut motility. The systemic inflammatory response affects gut motility and absorption and thus can contribute to diarrhea. Probiotics may have beneficial effects in ICU patients, including modulation of immune function and inflammatory response,7 improvement in gut barrier function,8 and prevention of colonization by harmful bacteria.9-11 Many studies support the effectiveness of probiotics (particularly Lactobacillus rhamnosus GG [LGG] and Saccharomyces boulardii) in preventing antibiotic-associated diarrhea,12-15 including in critically ill patients,16 but in everyday clinical practice, it is more common to administer probiotics only once the diarrhea has started. Although there is some evidence that such treatment of established diarrhea can reduce the duration and/or severity of diarrhea in children,17,18 there are very few supportive studies of probiotic therapy in adults with diarrhea19,20 and no published studies of probiotics as a diarrhea treatment in critically ill patients.

A difficulty with probiotic studies is the large number of different bacterial species available, singly and in various combinations. It is possible that there are disease-specific benefits confined to particular species. LGG was selected for this study because of its strong antibacterial effects,21 its ability to colonize the gut during antibiotic

Original Communication

**Lactobacillus GG as Treatment for Diarrhea During Enteral Feeding in Critical Illness: Randomized Controlled Trial**

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**Results by intention-to-treat analysis:** No significant difference was observed for any end point. There was a trend toward more diarrhea in the probiotic treatment group. Mean (standard deviation) duration of diarrhea was 3.83 (2.39) days for the probiotic group and 2.56 (1.85) days for the placebo group (P = .096). Mean number of loose stools per day during the 14 days from the first capsule was 1.58 (0.88) in the probiotic group and 1.10 (0.79) in the placebo group (P = .150). **Conclusions:** This study does not support the use of Lactobacillus GG as a treatment for established diarrhea in enterally fed critically ill patients. **Keywords:** probiotics; diarrhea; enteral nutrition; critical illness.
treatment, LGG appears to be resistant to antibiotics, including vancomycin, gentamicin, metronidazole, and co-trimoxazole, but unlike enterococci, probiotic lactic acid bacteria do not appear to have transferable antibiotic resistance properties. Previous studies using LGG to treat diarrhea have used daily doses ranging from 1 billion to 2 billion bacterial colony-forming units (CFU). Each capsule used in this study contained at least 10 billion CFU, and 2 capsules per day were administered. The aim of this study was to investigate whether probiotic treatment, in the form of an LGG supplement, reduces the duration or severity of diarrhea in tube-fed critically ill patients.

Materials and Methods

Study Population

Consecutive critically ill patients who were reported to have diarrhea were assessed for inclusion in the study. The hospital’s Ethics Review Committee approved the protocol. Written informed consent was obtained from the person responsible for making decisions for each enrolled patient.

Inclusion Criteria

Patients were included if they were receiving gastric tube feeding in the ICU and had diarrhea according to the following definition: in the absence of known or suspected malabsorption, the patient’s records indicated, in any 24-hour period, 3 or more loose or unformed stools or greater than 200 mL of liquid stool. If a patient had received any laxative medication, they were included only if diarrhea was still present 48 hours after this medication was ceased.

Exclusion Criteria

Patients were excluded from the study if they did not have diarrhea according to the above definition, had an ongoing need for laxative medications, had any evidence of gastrointestinal bleeding, had received any concentrated probiotic product within the past 28 days, or were not expected to survive for 48 hours after screening. Patients with diarrhea were not included if they were receiving an oral diet or parenteral nutrition.

Randomization Process and Treatment

The treatment capsule was a size #1 clear gelatin capsule containing 280 mg inulin powder with $10^{10}$ CFU LGG (Culturelle, ConAgra Foods, Omaha, NE). The placebo capsule was made up to replicate the treatment capsule as closely as possible, using the same capsule type, and the same amount and type of inulin powder reported by ConAgra Foods as forming the base of their product. The placebo capsule therefore consisted of a size #1 clear gelatin capsule containing 280 mg inulin powder (Raftiline, Orafti, Paris, France), filled under pharmacologic conditions in the hospital pharmacy. Independent laboratory testing (AMS Laboratories, Sydney, Australia) confirmed that the treatment capsules contained at least the stated number of L rhamnosus CFUs and that the placebo capsules were commercially sterile. The patients, clinicians, and data collectors were all blinded to treatment group. The hospital’s independent pharmacy Clinical Trials Department randomized (using a random-numbers list) and dispensed the capsules in identical bottles for administration in the ICU to each study patient. For administration, the contents of each capsule were dispersed in 50 mL sterile water and delivered as a bolus into the patient’s gastric feeding tube along with the regular water flush.

All patients with diarrhea received the usual treatments and investigations for diarrhea in accordance with the unit’s normal bowel management protocol. In addition, patients entering the study received 1 study capsule every 12 hours for 7 days via gastric feeding tube. All patients were fed continuously with a 24-hour feeding regimen using closed-system enteral feeds. All feeds were initially commenced on the ICU’s standard feeding formula, which is a 1-calorie per mL oat fiber–containing formula, but were changed to alternative enteral formulas as needed (eg, to restrict electrolyte or fluid input).

Study End Points

The primary end point was duration of diarrhea, measured as the number of consecutive days of diarrhea starting from the first day of capsule administration. The secondary end point was severity of diarrhea (stool volume/frequency), measured as (1) number of stools per day and (2) average number of loose stools per day, both averaged over the 14 days starting from the first day of capsule administration.

Determination of Sample Size

Although there are no previous treatment studies in critically ill patients, the available studies suggest that probiotics can reduce the duration of diarrhea in non–critically ill patients by 0.6 to 2.7 days. Using a standard sample size formula for continuous data in a 2-tailed test, a study population of 36 patients would have 90% power ($\beta = 0.1$) to detect a 1.1-day difference in diarrhea duration (standard deviation [SD] = 1 day; $\alpha = 0.05$). This sample size would have 90% power to detect a difference of 1 loose stool per day, again assuming an SD of 1.
**Statistical Analysis**

Intention-to-treat analysis was performed using SPSS for Windows version 11 (SPSS Inc, Chicago, IL) using the Student t test. A per-protocol analysis was also performed. χ² tests were used to analyze nonparametric data.

**Results**

**Study Population**

A total of 238 patients with reported diarrhea while receiving enteral nutrition were screened, starting in June 2003 (Figure 1). Of these patients, 36 met the inclusion criteria for the study (intention to treat: 18 randomized to treatment group and 18 to placebo group). Nine patients were excluded from the per-protocol evaluation: 4 patients in the treatment group and 2 patients in the placebo group did not receive the full number of capsules, and 3 patients (1 treatment group and 2 placebo group) received laxatives during the study period. Thus, 27 patients formed the per protocol group (13 treatment group and 14 placebo group). The demographic and clinical characteristics between groups were similar at randomization (Tables 1 and 2).

**Effect of LGG**

No significant differences were observed between the 2 groups in either the duration or the severity of diarrhea (Table 3). There was a trend toward increased incidence of diarrhea in the probiotics group. Mean (SD) duration of diarrhea from day 1 of study was 3.83 (2.39) days for the probiotic group and 2.56 (1.85) days for the placebo group (P = .096). Mean number of loose stools per day during the 14-day study period was 1.58 (0.88) in the probiotic group and 1.10 (0.79) in the placebo group (P = .150).

**Adverse Events**

No adverse events related to probiotic therapy were identified during the study period. Because of recent concerns about
the safety of probiotics in critically ill patients, a 6-month follow-up of study participants was performed. Two patients from each group died during the study. The recorded causes of death were cardiac arrest and sepsis/respiratory failure in the treatment group patients and ischemic gut and septic shock/end-stage renal failure in the placebo group patients. An additional 5 patients in the treatment group and 3 patients in the placebo group died within 6 months of being enrolled in our study. The difference between the 2 groups was not statistically significant (P = .480).

**Discussion**

In this study, LGG therapy did not have a significant effect on the duration or severity of diarrhea based on an
intention-to-treat analysis. There was a trend toward increased incidence of diarrhea in the treatment group, suggesting that probiotics may be not helpful in treating established diarrhea in critically ill patients. The dropout rate (9 of 36 participants) affected the power of the study, but the results (and direction of effect) were similar in a per-protocol analysis.

Until recently, probiotics have been considered a promising therapy in the hospital setting, possibly reducing incidence of infection and length of stay. Small beneficial effects of probiotics in modulating the immune response have also been observed. However, a recent meta-analysis of 8 randomized controlled trials did not find any preventive effect of probiotic therapy on nosocomial infections in adult ICU patients. Another recent study found no significant effect in pediatric ICU patients. Published case reports have raised concerns about the safety of probiotics in critically ill patients. Because probiotics are, by definition, indigenous to the human gut, it may be impossible to establish a definite causal link between probiotic supplementation and Lactobacillus bacteremia. A large epidemiological survey in Finland showed a sharp increase in the use of LGG without any corresponding increase in Lactobacillus bacteremia, but this survey did not focus on critically ill or immunosuppressed patients. A study of severe acute pancreatitis raised concerns about the possible harmful consequences of probiotic use in critically ill patients. Although it is possible that these concerns cannot be generalized to our study, because our study used the gastric route (rather than jejunum) for delivery of all probiotics in our study, we performed a 6-month follow-up to address these concerns. No adverse events associated with the probiotics were identified either during the study or in follow-up.

There are limitations to this study that may prevent any conclusions from being drawn. First, it could be argued that, with hundreds of different probiotic products on the market, a lack of effect could simply be a result of choosing the wrong product. However, the selection of species and dose for this study was based on the best evidence available. LGG is one of the only probiotics that has been successfully used in treating established diarrhea (albeit mostly in pediatric studies), and the dosage used in this study, 20 billion CFU per day, was at the upper end of the range used successfully in previous studies. The LGG product used contained inulin as a base, which has been associated with gastrointestinal symptoms in some people, but it is unlikely that this affected the results as the dose was very small and was the same for both the placebo and treatment groups.

Second, the duration of probiotic treatment was only 7 days. These results follow those of previous studies using LGG as a treatment for established diarrhea, which all used a treatment period of 2 to 7 days. Previous meta-analyses of probiotic treatment for diarrhea showed a significant difference within 3 to 4 days, suggesting that 7 days should be sufficient to see an effect. However, most of these studies were in children, not critically ill adults. It may be the case that a longer treatment period is required to obtain a significant effect in critically ill patients or those who are concomitantly receiving antibiotics or other medications that may affect gastrointestinal functioning.

Third, the small study population made the data vulnerable to a lack of power. Demographic differences that were not statistically significant (eg, the proportion of gastrointestinal/liver patients, the Acute Physiology and Chronic Health Evaluation II score, or incidence of feeding intolerance) may in fact reflect real differences between the groups that could have affected the results. For example, the treatment group included 1 gastrointestinal/liver medical patient (with hepatic failure due to a paracetamol overdose) and 2 gastrointestinal/liver surgical patients (1 post–partial gastrectomy, 1 post–jejunal volvulus resection and anastomosis), whereas the placebo group included only 1 gastrointestinal surgical patient (post laparotomy with no abnormal findings). Similarly, there were more
treatment patients than placebo patients with C difficile–positive stool cultures, which again might have been expected to increase the incidence of diarrhea in the treatment group. Persistent diarrhea was managed the same way in both groups, but because there were more patients with diarrhea in the treatment group, more of the treatment patients received fiber supplements or loperamide as part of diarrhea management. Significantly more treatment patients received enteral feeding formula with osmolality >500 mOsm/kg, usually to restrict fluid input. Although it has been suggested that the hyperosmolar formula does not contribute to diarrhea in patients with normal gastrointestinal functioning, it is possible that it could make a difference in critically ill patients.

The power calculation for duration of diarrhea included a standard deviation of 1 day based on a previous audit of diarrhea incidence in our ICU. In the current study, the standard deviation for duration of diarrhea was much larger than expected, which means the study was potentially underpowered to detect a significant difference between the groups. A difference of less than 2.7 days in the duration of diarrhea would not have been found significant. Previous probiotic treatment studies have found a significant decrease in diarrhea duration, but the difference in all cases was less than 2.7 days. For number of loose stools per day, however, the standard deviation was slightly less than expected, and the power of the study should have been adequate to detect the effect size seen in previous studies, which was not replicated in this study.

Finally, only a small proportion of the patients screened were enrolled in the study, and this sample may not be fully representative of the ICU patient population. There were several reasons for the large number of excluded patients. Some of those reported to have diarrhea did not fulfill the inclusion criteria for our definition of diarrhea, which exemplifies the difficulty in imposing an objective definition on something that may often be described subjectively. Nearly half of the excluded patients had received laxatives (many of whom had diarrhea that resolved promptly, resulting in formed stools, once laxatives therapy was ceased). This confirms a previous finding that unnecessary laxatives may be a significant, preventable contributor to diarrhea.

Overall, it appears that further investigation is needed to confirm whether LGG has a significant effect on established diarrhea in critically ill patients. Future research, particularly with a larger group of patients, standardized feeding, and perhaps a longer duration of treatment, may elucidate the answer to this question more satisfactorily.

Conclusions

This study does not support the use of LGG as a treatment for established diarrhea in enterally fed critically ill patients.

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References


