Single-Strain Probiotics For The Management Of Acute Diarrhea In Children: A Randomized Comparative Study

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Abstract

Goals
To assess the efficacy of probiotics in managing acute gastroenteritis in children, including reducing the need for inpatient care and antibiotics, repeat visits to emergency or private clinics, and incidence of adverse events.

Background
Acute gastroenteritis is characterized by diarrhea, vomiting, and occasionally, abdominal pain and fever. Treatments include oral rehydration solutions to prevent dehydration and nutritional damage and zinc supplementation to reduce the severity of diarrhea and reoccurrence. Probiotics are effective in reducing the intensity and duration of acute gastroenteritis; however, their efficacy in the Indian population needs further investigation.

Study
In this single-center open-label randomized study, the efficacy of 3 single-strain probiotics, *Bacillus clausii*, *Saccharomyces boulardii*, and *Lactobacillus rhamnosus GG*, as adjuvant therapy along with oral rehydration solution and zinc supplements in the management of acute gastroenteritis, were compared in 150 children aged 6 months to 16 years.

Results
B. clausii was the most effective single-strain probiotic in our study for the management of acute diarrhea in children across various parameters, including time to first formed stool, reduction in the duration of diarrhea, reduced hospital admissions, and earlier recovery.

Conclusions
All 3 probiotics demonstrated no adverse effects. Readmission and revisit rates after treatment with these probiotics were extremely low. *B. clausii* is strongly recommended as adjuvant therapy in children with acute gastroenteritis.

Keywords: acute gastroenteritis in children; single-strain probiotics; Bacillus clausii; Saccharomyces boulardii; Lactobacillus rhamnosus GG

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Introduction

Acute gastroenteritis (AGE) is mainly characterized by diarrhea of ≤7 days duration[1]; other symptoms include vomiting, abdominal pain, and fever.[2] Dehydration, a consequence of vomiting, diarrhea, and fever, is a major risk factor, particularly in children, and the main reason for medical visits, hospitalization, and mortality.[3]

Gastroenteritis affects 3–5 billion children annually worldwide, and 12% of mortalities occur in children aged <5 years, which is equivalent to approximately 611,000 childhood mortalities and 2 million hospitalizations. Although the global mortality rate due to diarrheal diseases has substantially declined (39%) during the last 2 decades, it continues to remain high.[1]

The etiologies of AGE include bacterial, viral, and parasitic enteropathogens. Globally, rotavirus is the most common cause of AGE among children,[1-7] and the cause of severe diarrhea requiring hospitalization in Indian children aged <5 years.[8]

AGE is usually self-limiting in healthy children, regardless of the etiology. The treatment objectives are to prevent dehydration, treat dehydration (if present), improve feeding during and after diarrhea to prevent nutritional damage, and prescription of zinc supplementation to reduce the duration and severity of diarrhea and occurrence of future episodes.[2] Active treatment should be initiated during the early stage of disease to maximize its efficacy.
Probiotics are live microorganisms that boost gut health when consumed adequately.[9] Moreover, they effectively reduce the intensity and duration of AGE symptoms by increasing the number of beneficial gut bacteria and decreasing the number of the pathogenic ones.[3] However, evidence of their efficacy in the Indian population needs further investigation.
Different probiotic strains are available; however, the efficacy and safety of single-strain probiotics, including *Lactobacillus rhamnosus GG*, *Bacillus clausii*, and *Saccharomyces boulardii*, have consistently been established in managing acute diarrhea in children.[10]

This study investigated the efficacy of 3 single-strain probiotics (*B. clausii*, *S. boulardii*, and *L. rhamnosus GG*) in the management of AGE, as an adjuvant therapy along with oral rehydration solution (ORS) and zinc (WHO recommendation) supplementation, specifically among children aged 6 months to 16 years in a tertiary care children's hospital. [11-14] Additionally, the efficacy of each probiotic was assessed based on the following variables: reduction of inpatient management, need for antibiotics, repeat visits to emergency or private clinics, and incidence of any adverse events.

Study Design

In this open label, randomized, comparative study, a total of 150 children with AGE who visited Apollo Children's Hospital, Chennai, India, were assigned to 3 groups (50 in each group), and the probiotic to be administered was randomly allotted by selecting labeled (probiotics' strain/brand name) and sealed envelopes. The study was conducted between January 2019 and June 2022 (18 months). Probiotics' preset proforma (50 each) were kept in the emergency and in 2 OP (outpatient) departments.
Parents of all the participants provided informed written consent. The study participants' demographics is presented in Table 1 and Figure 1.

Inclusion and exclusion criteria

Children with diarrhea of >48 h duration with or without dehydration who visited the OP and emergency departments were included in the study.

Exclusion criteria

Children already on probiotics and with a history of probiotic usage within the past 7 days, any known allergies or hypersensitivity to any probiotics.

Methods

All children were prescribed ORS, zinc supplements, and one of the randomly selected single-strain probiotics *S. boulardii* CNCMI-1745 (ECONORM®; Dr. Reddy's Laboratories Ltd., Hyderabad, India), *B. clausii* (O/C, N/R, SIN and T) (ENTEROGERMINA®; Sanofi India Ltd., Raipur, India), and *L. rhamnosus* ATCC 15503 (SUPERFLORA GG®; Sundyota Numandis Pharmaceuticals Pvt. Ltd., Ahmedabad, India) for 5 days.
The participants' parents were instructed to maintain a daily record the number of fecal outputs and their consistency, the presence of vomiting and fever, any necessity for hospital admission/revisits, use of any antibiotics, and all adverse events. The participants were followed-up for 5 days from the day of commencement of the therapy and monitored for the number of episodes of loose stools, stool consistency, time since last loose stool, time taken for the first formed stool, and any adverse events. The collected data were statistically analyzed to ascertain the probiotic with the best outcome.

Ethical approval

This study was approved by the appropriated Institutional Review Board (NBEMS/THESIS/2021/A-211947).

Data analyses

Data were analyzed using the statistical package SPSS (version 22.0; SPSS Inc., Chicago, IL), and the level of significance was set at p<0.05. Descriptive statistics were used to assess the mean and standard deviations of the respective groups. The normality of the data was assessed using the Shapiro–Wilk test. Inferential statistics to determine the difference between the groups were performed using the one-way analysis of variance (ANOVA) and Tukey's Honest Significant Difference test. Differences in frequency between categorical variables were analyzed using the Chi-square test.

Results

The majority of participants in the three groups were aged 1–5 years, followed by 6–16 years and <1 year. No significant difference was noted in the proportion of population per age group among the three probiotic groups. The mean age of the participants was 4.314 ± 3.465, 4.214 ± 3.494, and 4.27 ± 3.074 in the econorm, enterogermina, and superflora GG groups, respectively (p=0.98), and the male-to-female ratio was 1.08:1, 1:1.2, and 1:1.2, respectively (p=0.22).

Stool consistency after the intervention was monitored in each group for 5 days. Accordingly, no changes in loose stools were observed during the first 24 h among the 3 groups. On day 5, in the econorm group, only 10% (5/50) of the patients passed loose stools, while 50% (25/50) passed normal stools; in the enterogermina group, 88% (44/50) and 6% (3/50) passed normal and loose stools, respectively; and in the superflora GG group, 88% (44/50) 26% (13/50), 24% (12/50) passed normal, loose, and semisolid stools, respectively. (Figure 2)

Regarding the mean stool frequency for 5 days, in the econorm group, it was 5.2 ± 1.87 on day 1 and reduced to 0.16 ± 0.024 on day 5; in the enterogermina group, it was 4.2 ± 0.54 on day 1 and significantly reduced to 0.22 ± 0.004 on day 5; and in the superflora GG group, it was 5.03 ± 1.22 on day 1 and 0.89 ± 0.18 on day 5, revealing that all 3 probiotics were equally effective in reducing loose stool frequency in AGE (Figures 3 and 4).

Further, the mean duration of vomiting after the intervention was 2.19 ± 1.15 days, 1.64 ± 0.89 days, and 2.12 ± 1.04 days in the econorm, enterogermina, and superflora GG groups, respectively. Among the 3 groups, the best results were obtained in the enterogermina group, and a significant difference was observed between the econorm and enterogermina groups (Figure 5).

The mean duration of diarrhea after the intervention was 3.19 ± 0.65 days, 3.04 ± 0.57 days, and 3.68 ± 0.35 days in the econorm, enterogermina, and superflora GG groups, respectively. Additionally, significant results were obtained in the enterogermina group after group comparison.

In this study, among the econorm cohort, 4% (2/50) of the patients were admitted after 5 days of intervention, 10% (5/50) were admitted after 55 days, and 12% (6/50) were admitted during the Day 1 to 5 of intervention for various reasons. No significant difference was observed between the 3 groups.

Regarding the reduction in antibiotic use with the administration of probiotics, unless otherwise indicated, 1/50 (2%), 1/50 (2%), and 4/50 (8%) of patients in the econorm, enterogermina, and superflora GG groups, respectively, required antibiotics for various reasons. Among the three groups, the lowest incidence of antibiotic use was observed in the econorm and enterogermina groups.

Furthermore, the number of patients who revisited the hospital was evaluated. In the econorm group, 2 of 50 patients revisited the hospital after 5 days of intervention due to dehydration and complaints of abdominal pain requiring admission. S. boulardii reduced the frequency of hospital revisits; however, the results were not significant (P=0.25). In the enterogermina group, 4 of 50 patients revisited the hospital: 1 was admitted for dehydration, and the remaining had visited for non-specific reasons. In the superflora GG group, 5 of 50 patients revisited the hospital for reasons, including severe dehydration requiring admission, bloody stools, and diarrhea with poor oral intake. None of the participants reported any adverse reactions to the probiotics.

Discussion

Most of the children in this study were aged 1–5 years because gastroenteritis is more frequent in this age group; and AGE is a most common cause of mortality among children <5 years. In this study, the mean age of the patients was 4 years in all three probiotic groups, which made it a comparable variable. To the best of our knowledge, this is the first study to compare the efficiency of three single-strain probiotics. Das et al.[13] conducted a study on *S. boulardii* and compared its efficacy with that of a placebo in 115 children aged 3 months to 5 years, whereas Salloju et al.[14] investigated the efficacy of *B. clausii* and *S. boulardii* in 104 children aged 1 month to 6 years.

In the present study, no significant changes were observed in the consistency of loose stools among the 3 groups during the first 24 h; however, *B. clausii* elicited a significant outcome (p= -0.0001). Studies that corroborated the present study's methodology of comparison of three single-strain probiotics could not be found; however, Das et al.[13] reported in their placebo-controlled trial that the mean duration of diarrhea in the *S. boulardii* group was significantly less than that of the control group by approximately 29 h (95% confidence interval [CI], -41.2–-16.8). In contrast, when Salloju et al.[14] compared *S. boulardii* and *B. clausii*, the mean duration of diarrhea was 94.8 h (2.9 days) and 69.6 h (3.95 days), respectively; hence, the total duration of diarrhea was significantly shorter (25.2 h) in children administered *S. boulardii* than in those administered *B. clausii*.[15,16] The largest cohort study was conducted by Canani et al.[16] who compared the efficacy of five different probiotics: *L. rhamnosus GG*; *S. boulardii*; *B. clausii*; mix of *L. delbrueckii var bulgaricus*, *Streptococcus thermophilus*, *L. acidophilus*, and *Bifidobacterium bifidum*; and *Enterococcus faecium* SF68. They concluded that the median duration of diarrhea and the daily number of stools were significantly less in children administered the *L. rhamnosus* strain GG than in those administered other probiotics; however, *S. boulardii* and *B. clausii* demonstrated no significant effects on the duration of diarrhea. Bhat et al[17]. reported in their study that the group administered *S. boulardii* had a significantly lesser duration of diarrhea than the control and *B. clausii* groups. The duration of diarrhea was 15.97 h less in the *S. boulardii* group than in the control group. The difference in the duration of diarrhea between the *B. clausii* and control groups was 4.32 h. Therefore, *S. boulardii* had a better outcome than *B. clausii*. The longer duration of diarrhea in this study could be because most of the study participants had diarrhea >36 h prior to admission.[18,19,20]

Based on the present study's results, *B. clausii* was more efficient in reducing the duration of vomiting (P=0.016).No significant difference was identified in the duration of vomiting in several previous studies.[21,22,23,24] However, Bhat et al.[17] reported that *S. boulardii* had a significantly better outcome in reducing the duration of vomiting than *B. clausii*, though both probiotics were no more effective than the placebo (p>0.05).

No significant difference (p=0.11) was found among the three study groups regarding admission following the intervention, probably due to the relatively low incidence of hospital admissions; this is consistent with the study by Canani et al,[16] wherein the number of hospital admissions in all five groups of probiotics were studied; however, the results were not significant.
Among the three groups, the lowest frequency of antibiotic use was observed in the *S. boulardii* and *B. clausii* groups (p=0.04). None of the previous studies reported the use of antibiotics as a secondary outcome. In the present study, *S. boulardii* reduced revisits to the hospital; however, the results were not significant. There are no studies reporting on revisits.[23,24,25]

None of the participants in any of the three groups in this study reported adverse events. However, adverse events have been reported in four previous studies[15,25,26,27]. A study by Canani et al.[16] reported three adverse effects in 3/3178 patients (0.09%) during the study, including vomiting, for which the relationship with the study medication could not be determined. Moreover, hypersensitivity reactions, including skin rashes that were reported by one patient in this study, were listed as possible adverse events of *B. clausii* in the probiotic's prescribing information. Although there have been sporadic adverse events, no life-threatening events were triggered by any of the probiotics studied thus far; hence, they have a good safety profile.

This study has a few limitations. First, the sample size was small (50 in each group), which was mostly due to the current pandemic and difficulty in recruiting study participants. Second, since this was an open-label study, it is theoretically prone to selection bias; however, this was addressed by randomizing the patients blindly. Third, as a single-center study, the findings may not represent the true effects of these probiotics in the community.

In conclusion, this study demonstrated that *B. clausii* is the most effective single-strain probiotic for the control of acute diarrhea in children. Additionally, *B. clausii* is effective in controlling vomiting. All three probiotics administered in this study demonstrated no adverse effects and the readmission/revisit to hospital rates were negligible. Moreover, the lowest rate of antibiotic use was observed among children administered *S. boulardii* and *B. clausii*; overall, the number of children needing antibiotic therapy was negligible. This study augments the existing evidence that probiotics are useful adjuvants for the management of AGE in children and hence, could be a first-line treatment for most children managed in outpatient settings. Furthermore, single-strain probiotics are effective in controlling gastroenteritis, and the use of any of the aforementioned probiotics is acceptable in general practice. Nevertheless, further large-scale multicenter studies among the Indian population are needed to validate our study findings.

FIGURE LEGENDS

Figure 1. Stool consistency
Figure 2. Stool frequency
Figure 3. Stool frequency (mean)
Figure 4. Frequency of vomiting
Figure 5. Cessation of loose stools (Frequency)

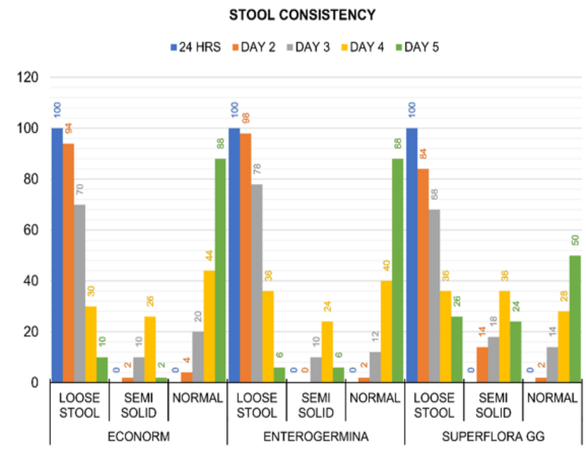

Figure 1. Stool consistency

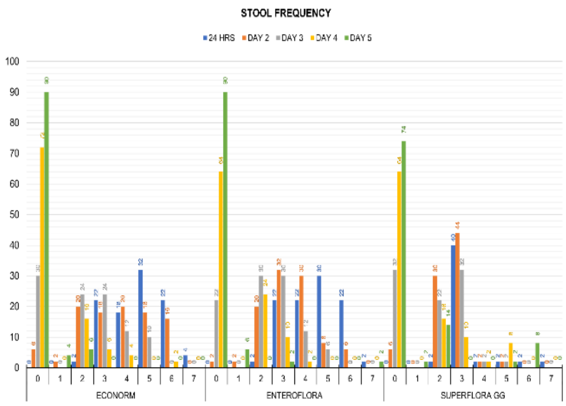

Figure 2. Stool frequency

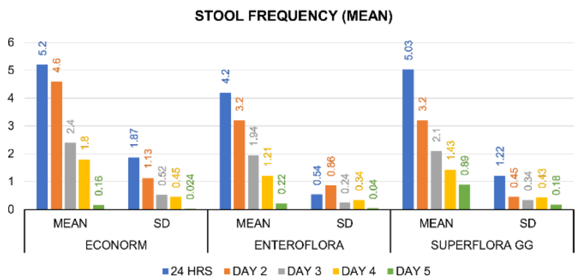

Figure 3. Stool frequency (mean)

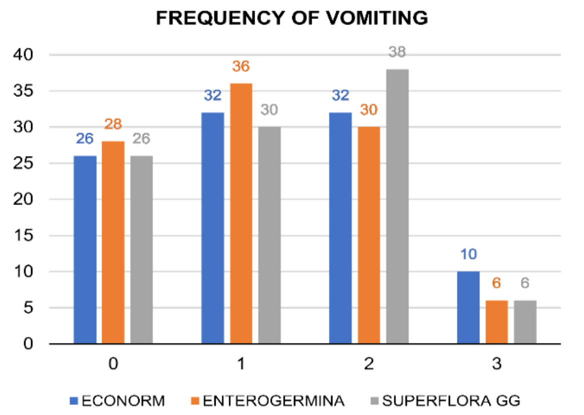

Figure 4. Frequency of vomiting

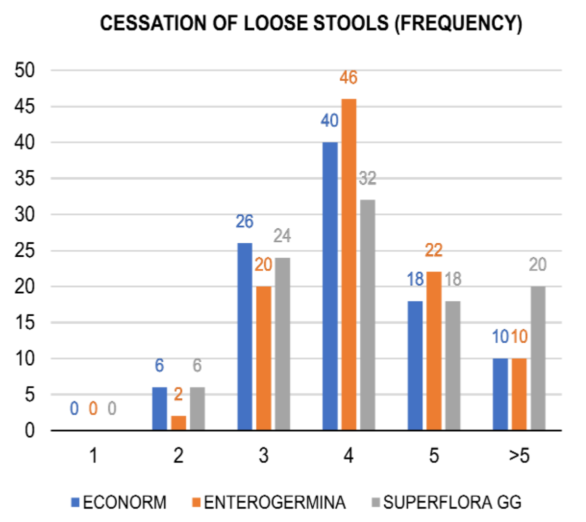

Figure 5. Cessation of loose stools (Frequency)

Table 1 showing the schematic flow

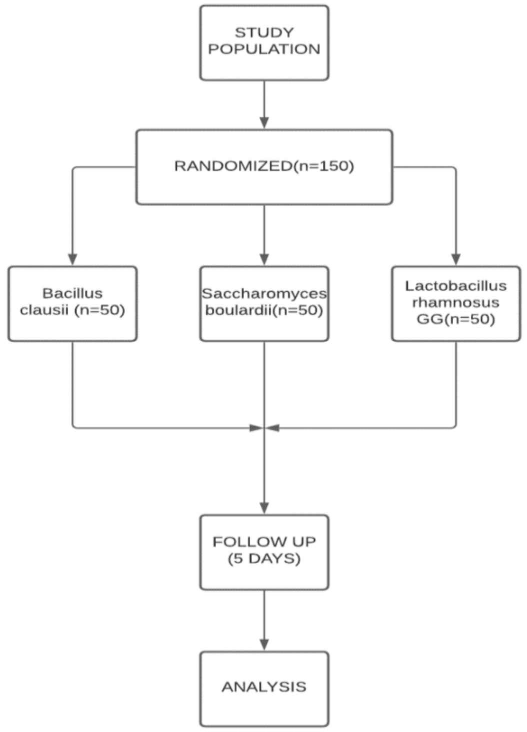

Table 2- Inclusion and Exclusion criteria

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Presentation: None

Data Availability

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Inclusion criteria:

All children between 6 months to 16 years of age group diagnosed with Acute gastroenteritis attending the paediatric outpatient clinics and emergency department at Apollo Hospitals, Chennai. 5282

Exclusion criteria

1.Children with chronic diarrhoea (due to any known or unknown etiology)
2.Diarrhoea secondary to Inflammatory bowel disease
3.Diarrhoea secondary to irritable bowel syndrome
4.Diarrhoea with dehydration needing admission (necessitating intravenous antibiotics)
5.Children with suspected or confirmed congenital or acquired immunodeficiency
6.Children on immuno- suppressants (steroids, biologicals and immunomodulators)
7.Known hypersensitivity to the drug or any of the excipients.

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