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Study of the Effectiveness and Safety of *Saccharomyces Boulardii* and *Lactobacillus Rhamnosus GG* in Infectious and Non-Infectious Disorders of the Gastrointestinal Tract in Children

[1] Chkhaidze Ivane, [2] Kavtaradze Marina, [3] Pirtskhalaishvili Ketevan, [4] Abutidze Maya, [5] Mazmishvili Elza, [6] Antelava Nana, [7] Ambroladze Medea, [8] Kiknadze Ketevan, [9] Ioseliani Maya

[1] Tbilisi State Medical University, Iashvili Central Children Hospital, Tbilisi, Georgia
[2] Tbilisi Adults' Polyclinic №19, Tbilisi, Georgia
[3] Evex Clinics, Tbilisi, Georgia
[4] Tbilisi Family Medicine Centre, Tbilisi, Georgia
[5] Tbilisi Medical Holding 23, Tbilisi, Georgia
[6] Tbilisi Medcapital, Tbilisi, Georgia
[7] Complex Type Policlinic #14, Tbilisi, Georgia
[8] Tbilisi Family Medical Centre #4, Tbilisi, Georgia
[9] Children's Policlinic #3, Kutaisi, Georgia

Corresponding Author: **Chkhaidze Ivane**

Abstract

Aim:

This study was designed to assess the efficacy and safety of the probiotics mixture *Saccharomyces boulardii* and *Lactobacillus rhamnosus* GG in the management of various infectious and functional disorders of the gastrointestinal tract in children.

Methods:

A total of 704 infants and children from 2 moths to 18 years of age with diagnoses to the following ICD 10 codes: Viral intestinal infection, unspecified A08.4; Antibiotic associated diarrhea K52.1; Noninfective gastroenteritis and colitis, unspecified K52.9 were allocated to the probiotic group [*Saccharomyces boulardii* 250 mg (5×10 9 CFU*) 500 mg (1×10 10 CFU*)] and *Lactobacillus rhamnosus* GG ATCC 53103 2×10 9 CFU* 4×10 9 CFU**S* once daily]. 43 patients were also selected, whose treatment will be carried out according to the standard scheme, without probiotics (control group). Primary endpoint was the frequency of diarrhea, decrease fever and degree of dehydration.

Results:

The administration of probiotics mixture *S. boulardii* and *Lactobacillus rhamnosus* GG was associated with beneficial effects on duration and severity of diarrhea. The frequency of diarrhea was significantly less in the probiotic group compared with the control group. Probiotics were well tolerated, no side effects were reported.

Conclusion:

Administration of probiotics mixture *S. boulardii* and *Lactobacillus rhamnosus* GG in children with acute viral diarrhea, antibiotic associated diarrhea and noninfective gastroenteritis and colitis was shown effective in reducing the duration and severity of diarrhea.

Keywords: Acute Diarrhea, Probiotic, Pediatric, *S. Boulardii*, *Lactobacillus Rhamnosus* GG

Introduction

Diarrhoea is a leading killer of children, accounting for approximately 9 per cent of all deaths among children under age 5 worldwide in 2019. This translates to over 1,300 young children dying each day, or about 484,000 children a year, despite the availability of a simple treatment solution. Children under three years old in low-income countries experience approximately three episodes of diarrhea each year. Each episode deprives the child of the necessary ingredients for growth. As a result, diarrhea is a major cause of malnutrition, and malnourished children are more likely to suffer from diarrhea [1, 2].

Gastrointestinal infections are a public health problem in both developing and industrialized countries. Despite changes in disease diagnosis and management, food safety regulations, and immunization, these diseases affect millions yearly. Rapid and accurate diagnosis is essential for the management and epidemiological surveillance of these infections. The main challenges

in diagnosing gastrointestinal infections include identifying etiological agents of viral, bacterial, and parasitic pathogens, as well as treatment issues.

Acute diarrhea is defined as the abrupt onset of 3 or more loose stools per day and lasts no longer than 14 days, which may be accompanied by fever and vomiting [3]. Changing the consistency of stool is a more informative feature than the frequency of defecation, especially in the first months of life. The leading etiological agents of acute viral diarrhea are Rotavirus, Norovirus, Astrovirus, Enteric adenovirus, Picornavirus. Rotavirus is the most common cause of severe diarrhea in children. The disease season is October-March, and the peak months are January-March.

Effective management of this problem is often a serious challenge for physicians. In recent years, special emphasis has been placed on the use of probiotics, the role of which has been confirmed by numerous studies and which are recommended by various international societies and associations - WGA, ESPGHAN, European Pediatric Association, Asia-Pacific Regional Recommendation. World Gastroenterology Organization, Food and Agriculture Organization under the United Nations and the World Health Organization define probiotics as "live microorganisms, when administered in adequate amounts, confer a health benefit on the host" [4].

Probiotic formulations are microecological products that improve the intestinal flora's architecture, diminish the growth of harmful microbes, and improve the immune response. Currently, most extensively researched probiotics include *Lactobacillus, Bifidobacteria, Escherichia coli, Enterococcus*, etc. Although probiotics' mechanism profoundly focuses on the GIT, the effect of probiotics is not confined to the initial infection site. Probiotics can act on the entire body via immune modulation. Probiotics and their antigenic metabolites are phagocytosed by microfold cells to form endosomes in gut-associated lymphoid tissues. These antigens are suddenly released and consequently activate naive T and B cells to differentiate into different effector subpopulations. This initiates the release of the relevant cytokines and various immune responses [5].

The mechanism of action of probiotics is to colonize the intestinal wall to alter the intestinal microflora. It competitively adheres to the intestinal mucosa and restores normal intestinal flora. Probiotics release antimicrobial products, intestinal mucin, and bacteriocins that inhibit pathogens and promote immunomodulation at the intestinal level to reduce the duration of diarrheal symptoms.

The clinical effect and safety of one probiotic microorganism should not be extrapolated to another. The probiotic effect is strain-specific, and its efficacy and safety remain to be established. Furthermore, very few combination probiotics on the market have been studied to determine their safety and clinical efficacy.

Probiotics are effective and widely used against acute watery diarrhea and antibiotic-associated diarrhea. A meta-analysis of several randomized controlled trials has shown that certain probiotic strains at adequate doses have antidiarrheal effects in children [6, 7]. World Health Organization and the European Society for Infectious Diseases of Children evidence-based guidelines recommend active treatment with specific probiotic strains supplemented with oral rehydration salts [8].

Probiotic consumption caused a significant reduction in antibiotic-associated diarrhea (AAD) and *Clostridioides difficile* infection (CDI), also, clinical trials highlighted the considerable effects of probiotics on the reduction or prevention of ventilator associated pneumoniae [9]. Probiotics are associated with a reduction in ventilator-associated pneumonia (VAP), as well as the duration of mechanical ventilation, ICU length of stay, and bacterial colonization in ICU [10]. Probiotic utilization is effective in preventing the incidence of VAP and diarrhea in children under mechanical ventilation in the PICU. [11, 12]; Probiotics have potential ability in the prevention and treatment of colorectal cancer [13]; Probiotic intervention may provide an effective means of preventing atopic dermatitis in children. [14]; There is growing evidence that probiotic treatment promotes a protective environment for commensal bacteria and generates an interface for immune response, thus improving clinical outcomes in pediatric patients with different gastrointestinal diseases [15].

Saccharomyces boulardii has been widely studied worldwide for acute watery diarrhea in various age groups. Studies have shown a reduction in the duration and frequency of diarrheal symptoms within about 24 hours [16, 17]. Because of its proven efficacy and safety, *S. boulardii* CNCM I-745 is recommended by ESPGHAN and other global bodies for the prevention and treatment of acute diarrhea. Thus, *S. boulardii* CNCM I-745 is one of the preferred choices of probiotics for the management of AAD and pediatric acute gastroenteritis due to its distinct advantages over bacterial probiotics as well as its favorable efficacy and safety profile [18].

Another probiotic that has been studied extensively is *Lactobacillus rhamnosus* GG (LGG). In India, 2 types of probiotics (*S. boulardii* CNCM I-745 and *L. rhamnosus GG*) significantly shortened both the duration of diarrhea and hospitalization stays in pediatric patients with pediatric acute gastroenteritis [17]. *Lactobacillus rhamnosus* effectively prevent and treat AAD in children [19]; The ESPGHAN recommends LGG as an adjuvant therapy for gastrointestinal infections in children [20].

Based on the above, it is clear that studies conducted in the last decade indicate the effectiveness of *Saccharomyces boulardii* and *Lactobacillus rhamnosus* in the treatment of various forms of diarrhea in children. If we consider the necessity of purposeful selection of probiotics strains, a formulation containing these two probiotics should be maximally effective in managing diarrhea.

The aim of the study was **e**valuation of the effectiveness and safety of a 5-day course of probiotics mixture Active Flora duo (producer: Dr.GustavKlein GmbH & Co.KG, Germany): *Saccharomyces boulardii* [*Saccharomyces boulardii* 250 mg (5×10 9 CFU*) 500 mg (1×10 10 CFU*)] and *Lactobacillus rhamnosus* [*Lactobacillus rhamnosus* GG ATCC 53103 2×10 9 CFU* 4×10 9 CFU*] once daily in various infectious and functional disorders of the gastrointestinal tract in children.

Materials and methods

Study design

Open, observational, parallel, non-randomized, prospective, multicenter study.

Statistical methods

In consideration of the non-normal distribution and ordinal scales characterizing the dataset, the choice of statistical methodology for comparing each patient group to itself—

both at admission to the clinic and after treatment—falls upon the Wilcoxon signed-rank test. The Wilcoxon signed rank test is non-parametric alternative to the Student's t-test. The Wilcoxon signed rank test is commonly used as a non-parametric method for analyzing paired data, such as pre- and post-treatment measurements. This makes it particularly advantageous for assessing changes within patient groups over time - from admission to post-treatment. The null hypothesis consistently posits that these groups exhibit no significant differences. The P value equal to or less than 0.05 allows us to reject the null hypothesis, signifying the presence of meaningful distinctions. This suggests that when the P value is equal to or less than 0.05, there is evidence to reject the null hypothesis, implying a potential significant difference between pre- and post-treatment measurements.
For enhanced visualization, average scores for each symptom were utilized in the construction of graphs. This approach provides a concise representation of the central tendency within each group and facilitates a clearer understanding of the trends in symptomatology before and after treatment. Notably, our analysis encompassed both a study group and a control group, each subjected to the same rigorous statistical evaluation.
All statistical analyses were performed using the R statistical programming language (version 4.2.1).

Criteria for inclusion in the study
Age from 2 months to 18 years; acute diarrhea (acute onset of three or more loose or watery stools a day lasting for 14 days or less); Antibiotic-associated diarrhea (diarrhea that develops any time from a few hours after the onset of antibiotic therapy to eight weeks following antibiotic cessation [21].

Exclusion criteria from the study
Inability to take medication orally, severe course of the disease with signs of severe dehydration.

Patients
Children from 2 moths to 18 years of age with diagnoses to the following ICD 10 codes:
- Viral intestinal infection, unspecified A08.4;
- Antibiotic associated diarrhea K52.1;
- Noninfective gastroenteritis and colitis, unspecified K52.9.

Table 1: Main characteristics of the study and control group

	Study Group (n=704)	Control (n=43)
Age, years ± SD	5.4	4.1
Sex, male/female	359/345	16/27
Bowel frequency (score)	1.6	1.5
Degree of dehydration (score)	1.4	1.0
Fever	1.25	1.18

Between September 2022 and April 2023, 704 patients with the above-mentioned diagnoses were hospitalized or were under ambulatory care in 10 medical institutions of Tbilisi and Kutaisi under the observation of 16 doctors, who were prescribed the drug Active Flora Duo (main group). In all medical centers, 43 patients were also selected, whose treatment will be carried out according to the standard scheme, without probiotics (control group). Main characteristics of the study and control group is shown in Table 1.

Medication
Patients received Active Flora Duo in the following dosages: from 2 months (up to 3 years): 1 capsule per day for 5 days; from 3 years to 18 years: 2 capsules per day for 5 days.

Clinical assessment
The study started on September 1, 2022, and ended on April 1, 2023. Patients were evaluated twice: before the start of treatment and after the end of treatment (5 days). All patients underwent the necessary clinical and laboratory/instrumental examination (in hospitalized patients) on the first day before treatment.
In case of diarrhea [Viral intestinal infection, unspecified A08.4; Antibiotic-associated diarrhea K52.1; Noninfectious gastroenteritis and colitis, unspecified K52.9] severity was graded using a modified scoring system of the scheme provided by Lee OJ *et al* [22]. A similar assessment was performed after the end of treatment (day 5).

Table 2: Diarrhea severity score

Score component	Indicator	Score
Duration of diarrhea	1-4 days	1
	5-7 days	2
	≥8 days	3
Max number of loose stools/day	2-4	1
	5-7	2
	≥8	3
Duration of vomiting, days	2 days	1
	3-5 days	2
	≥6 days	3
Duration of reported fever, days	1-2 days	1
	3-4 days	2
	≥5 days	3
Confirmed temperature	38.0-38.2	1
	38.3-38.7	2
	≥38.8	3
Dehydration	Moderate dehydration	2
	Severe dehydration	3
Total		

Safety
During the second visit, possible side effects (nausea, vomiting, skin rash, etc.) were monitored. They were evaluated as mild, moderate, severe, life-threatening, for which the side effects evaluation scale was used [23].

Results and discussion
We presented effectiveness of treatment by assessing diarrhea frequency, fever and degree of dehydration in the study and control group at admission and after treatment.
The mean stool frequency (in points) at admission to the clinic was 1.6 in the study group and 1.51 in the control group; the fever score in the study group was 1.25 and 1.18 in the control group; the dehydration score at the time of admission to the clinic was 1.46 in the study group and 1.2 in the control group. Baseline characteristics did not differ significantly between study and control groups (Fig 1).

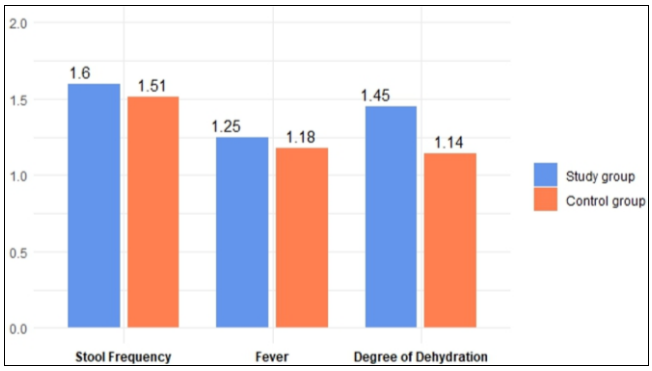

Fig 1: Diarrhea frequency, fever and degree of dehydration at admission in the study and control group (average score)

Frequency of diarrhea

In the study group in total, the frequency of bowel movements at the time of admission to the clinic was 1.60, and after treatment was 0.38 The results reveal a statistically significant decrease in bowel movement frequency from the pre-treatment period (mean = 1.60) to the post-treatment period (mean = 0.38) within the study group ($p<0.001$, underscoring the effectiveness of the treatment intervention.

In the subgroup of individuals with non-infectious gastroenteritis and colitis (K52.9), the frequency of diarrhea reduced statistically significantly from 1.55 at the time of admission to 0.40 after treatment ($p<0.001$), indicating the substantial impact of the treatment intervention.

In the subset of individuals with Antibiotic-associated diarrhea (K52.1), the frequency of diarrhea demonstrated a statistically significant decrease from 1.56 at the time of admission to 0.33 after treatment ($p<0.001$), this suggests that the treatment was effective in reducing the frequency of diarrhea.

In the group of people diagnosed with an unspecified viral intestinal infection (A08.4), the frequency of diarrhea decreased significantly from 1.65 before treatment to 0.38 after treatment ($p <0.001$). These results demonstrate the effectiveness of the treatment in significantly reducing the frequency of diarrhea in people with this type of viral intestinal infection.

Frequency of diarrhea at admission and after treatment in a study group is shown on Fig 2. In general, prescription of the probiotics mixture was significantly effective to reduce frequency of diarrhea after 5 days of treatment in study group in total, as well as in patients with Noninfectious gastroenteritis and colitis, unspecified, Antibiotic-associated diarrhea and viral intestinal infection, unspecified.

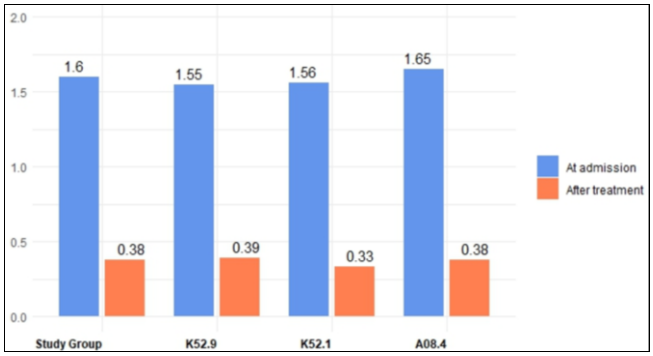

Fig 2: Frequency of stool at admission and after treatment in the study group in total and in the patients with specific diagnoses (average score)

In the control group, there was a significant decrease in bowel movement frequency from 1.51 at admission to 0.88 after treatment ($p<0.001$). This finding suggests that the treatment had a significant effect on reducing the frequency of bowel movements in the control group.

In a control group of people with non-infectious gastroenteritis and colitis (K52.9), the frequency of diarrhea decreased from 1.5 at the time of admission to the clinic to 0.75 after treatment. However, the change observed did not reach statistical significance, as indicated by a $p=0.3711$. Therefore, the effectiveness of the treatment in reducing the frequency of diarrhea in this subgroup remains inconclusive based on the current statistical analysis.

In the control group of individuals diagnosed with antibiotic-associated diarrhea (K52.1), the frequency of diarrhea decreased from 1.4 at the time of admission to 0.8 after treatment. This change was statistically significant ($p=0.01966$). These findings suggest that the treatment effectively reduced the frequency of diarrhea among individuals with antibiotic-associated diarrhea.

In the control group of individuals diagnosed with an unspecified viral intestinal infection (A08.4), the frequency of diarrhea significantly decreased ($p<0.001$) from 1.55 at the time of clinic admission to 0.93 after treatment. This implies that the treatment has significantly reduced the frequency of diarrhea in individuals with viral intestinal infection within the control group.

The frequency of diarrhea at admission and after treatment in a control group is shown on Fig 3. In conclusion, the treatment had a significant impact on reducing bowel movement frequency in the control group as an entire. While the efficacy remains inconclusive for individuals with non-infectious gastroenteritis and colitis, the treatment demonstrated effectiveness in reducing diarrhea frequency among those with antibiotic-associated diarrhea and unspecified viral intestinal infection within the control group.

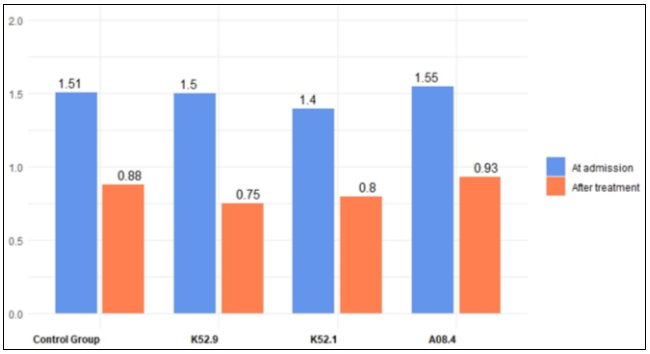

Fig 3: Frequency of stool at admission and after treatment in the control group in total and in the patients with specific diagnoses (average score)

Fever

According to the study group, the fever score significantly ($p<0.001$) decreased from 1.25 at admission to the clinic to 0.17 after treatment, indicating a highly significant and positive effect of the treatment.

In the subgroup of individuals with non-infectious gastroenteritis and colitis, the fever score at admission was 0.93, and after treatment significantly decreased to 0.11 ($p<0.001$). This indicates that the treatment had a highly

significant impact on reducing fever symptoms in this particular group.

In the subgroup of individuals with antibiotic-associated diarrhea, the fever score was 1.01 at admission, significantly decreasing to 0.16 after treatment ($p<0.001$). This noteworthy reduction in fever score indicates a highly significant and positive effect of the treatment in alleviating fever symptoms in individuals with antibiotic-associated diarrhea within this subgroup.

Fever scores decreased significantly from 1.48 at admission to 0.21 after treatment in the subset of individuals with unspecified viral intestinal infection ($p<0.001$). There was a significant and positive reduction in fever symptoms in this specific subgroup as a result of treatment.

As can be seen in Fig 4, the fever score significantly decreased after treatment in the entire study group and in all other three groups as well.

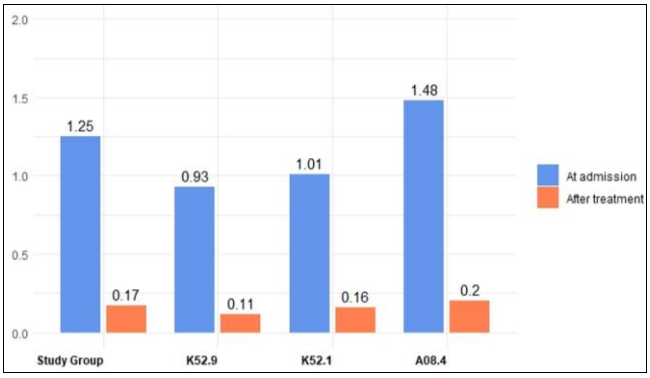

Fig 4: Fever at admission and after treatment, study group (average score)

In the control group, the fever score at admission to the clinic was 1.18, showing a statistically significant decrease to 0.79 after treatment ($p=0.01196$). This indicates that the treatment in the control group had a notable effect in reducing fever symptoms.

In the subset of individuals with non-infectious gastroenteritis and colitis, the fever score at admission was 0.75, with a subsequent decrease to 0.25 after treatment. However, this observation did not reach statistical significance ($p=0.3458$), which indicates that the treatment's effect on fever symptoms remains inconclusive.

In the subgroup of individuals experiencing antibiotic-associated diarrhea, the fever score upon clinic admission was 1.6, significantly ($p=0.01966$) decreasing to 1.0 after treatment. The result demonstrates the treatment's effectiveness in reducing fever symptoms within this specific subgroup.

In the subset of individuals with unspecified viral intestinal infection, the fever score at admission to clinic was 1.1, with a subsequent decrease to 0.79 after treatment. However, this observed change did not show statistical significance (p-value=0.1692), suggesting that the impact of the treatment on fever symptoms within this specific subgroup is inconclusive based on the current statistical analysis.

As can be seen in Fig 5 the control group showed a significant reduction in fever symptoms after treatment, whereas the impact of the treatment in the non-infectious gastroenteritis and colitis subgroup remains inconclusive. In individuals with antibiotic-associated diarrhea, the treatment effectively reduced fever, but its impact in the unspecified viral intestinal infection subgroup was inconclusive based on the current analysis.

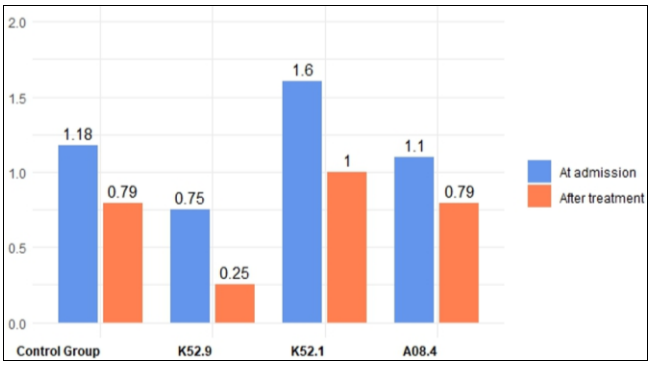

Fig 5: Fever at admission and after treatment, control group (average score)

Dehydration

In the entire study group, the dehydration score at admission was 1.45, significantly decreasing to 0.03 after treatment ($p<0.001$). This indicates a highly significant and positive impact of the treatment in alleviating dehydration.

In the subgroup of individuals with non-infectious gastroenteritis and colitis, the dehydration score was 1.32 at admission, significantly decreasing to 0.02 after treatment ($p<0.001$). As a result, we can conclude that the treatment significantly reduces the severity of dehydration in this specific subgroup of patients.

In the subset of individuals experiencing antibiotic-associated diarrhea, the dehydration score registered 1.32 at admission, demonstrating a significant reduction to 0.05 post-treatment ($p<0.001$). This substantial decrease underscores the highly significant and beneficial influence of the treatment in mitigating dehydration within this particular subgroup.

In the subset of individuals with unspecified viral intestinal infection, the dehydration score at admission - 1.63, significantly decreased to 0.03 after treatment ($p<0.001$). This substantial reduction indicates a highly significant and positive impact of the treatment in alleviating dehydration within this specific subgroup.

As a summary, the dehydration score significantly decreased in all groups after the five-day course of treatment with probiotics mixture (Fig 6).

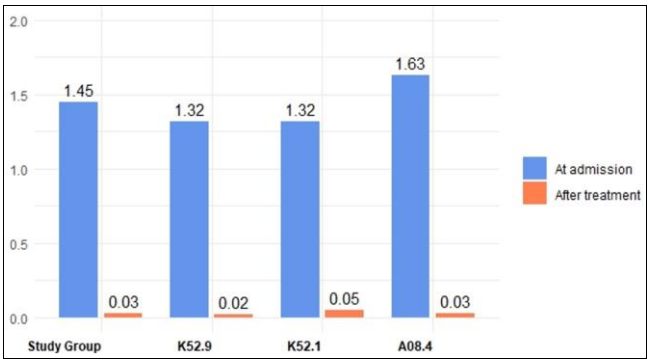

Fig 6: Degree of dehydration at admission and after treatment, study group (average score)

In the entire control group, the dehydration score on the first day was 1.14, significantly decreasing to 0.05 after treatment ($p<0.001$). This substantial reduction underscores

the highly significant and positive impact of the treatment in alleviating dehydration within the control group.

In the subgroup of individuals with non-infectious gastroenteritis and colitis, the dehydration score at the time of admission to the clinic was 1.5, and after treatment, it reached 0 (p=0.1489). However, the observed change did not achieve statistical significance, suggesting that the effectiveness of the treatment on dehydration in this specific subgroup remains inconclusive based on the current statistical analysis.

In the subset of individuals with antibiotic-associated diarrhea, the dehydration score at admission to the clinic 1.4 significantly (p = 0.01073) reached to 0 after treatment. This observed change was statistically significant, indicating that the treatment effectively mitigated dehydration in this specific subgroup.

In the subset of individuals with unspecified viral intestinal infection, the dehydration score at admission was 1, significantly decreasing to 0.07 after treatment (p = 0.0005441). This significant reduction underscores the positive impact of the treatment in alleviating dehydration within this specific subgroup.

As can be seen in Fig 7, the five-day course of standard treatment in the control group demonstrated a highly significant reduction in dehydration, while results in the non-infectious gastroenteritis and colitis subgroup were inconclusive. However, in individuals with antibiotic-associated diarrhea, the treatment significantly mitigated dehydration, and a similar positive impact was observed in those with unspecified viral intestinal infection.

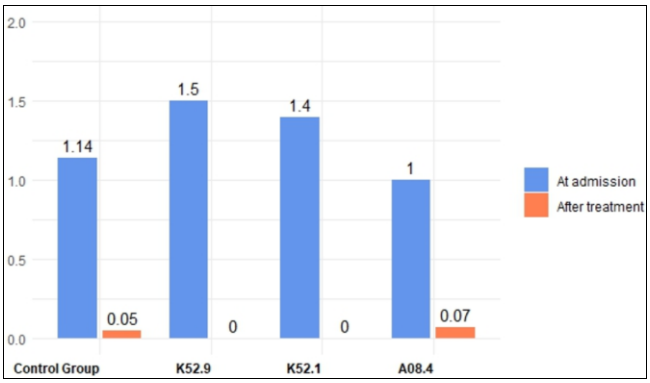

Fig 7: Degree of dehydration at admission and after treatment, control group (average score)

Safety

The study of the safety profile showed that none of the children in the study group had to stop treatment due to adverse side effects, and no side effects of the probiotics were detected.

Discussion

The incidence of gastroenteritis has decreased significantly in developing countries due to improved hygiene and the use of the rotavirus vaccine. However, thousands of children still die from gastroenteritis, most of them in poor countries. Management of gastroenteritis is simple, inexpensive and effective, and is largely the same worldwide. Universal guidelines for gastroenteritis include simple interventions early in the course of the disease, such as rehydration, continued oral feeding, and anti-infectives, as well as probiotics, in certain clinical settings [24].

The role of probiotics in the modulation of the intestinal microbiota due to the disturbance of the intestinal microbiota developed after dysbiosis has been established. Despite the lack of data on changes in the gut microbiome in acute bacterial or viral gastroenteritis, probiotics have been shown to reduce the number of diarrheal episodes, improve disease course and symptoms [25, 26].

In an open, observational, parallel, non-randomized, prospective, multicenter study, was assessed the effectiveness and safety of a 5-day course of Active flora duo *(Saccharomyces boulardii* and *Lactobacillus rhamnosus*) in various infectious and functional disorders of the gastrointestinal tract (Viral intestinal infection, unspecified, Antibiotic-associated diarrhea, Non-infectious gastroenteritis and colitis) in children.

A study of 704 children confirmed the effectiveness of a combination of *Saccharomyces boulardii* and *Lactobacillus rhamnosus* in reducing the frequency of diarrhea, fever, and degree of rehydration in all three diagnoses compared to a control group.

International guidelines recommend the use of 4 probiotics (*S boulardii* CNCM I-745, or *L rhamnosus* GG, or *L reuteri* DSM17938 or a 2-strain mixture of *L rhamnosus* 19070 and *L reuteri* DSM12246), along with ORS and zinc (if deficient), there is a strong recommendation against L helveticus R0052 and L rhamnosus R0011 (moderate certainty of evidence) and a weak recommendation against Bacillus clausii strains O/C, SIN, N/R, and T (very low certainty of evidence [27].

Li *et al* conducted a network meta-analysis of 21 different types of probiotics (84 studies) and concluded *Lactobacillus reuteri, Bifidobacterium, Saccharomycesboulardii, Lactob callus species (spp.)* plus *Bifidobacterium spp*. Plus *Saccharomyces spp*., and *Bacillus spp.* Plus *Enterococcus spp*. plus *Clostridium spp*. significantly reduced the duration of diarrhea when compared with placebo. *Saccharomyces* and *Lactobacillus reuteri* significantly reduced the risk of diarrhea lasting ≥2 days when compared with placebo or no treatment, with moderate evidence. Among all probiotics, *Saccharomyces boulardii* may be the most effective in reducing both duration of diarrhea (compared with placebo) and risk of diarrhea lasting ≥2 days (compared with placebo or no treatment) [28].

But in the Cochrane review is concluded, that probiotics probably make little or no difference to the number of people who have diarrhea lasting 48 hours or longer, and there is an uncertainty whether probiotics reduce the duration of diarrhoea [29].

Regarding antibiotic-associated diarrhea, a recent (2023) overview of systematic reviews of probiotics, in which a total of 20 systematic reviews were included, showed that high doses (5-40 billion CFUs per day) of probiotics had a significant effect in the prevention of AAD, but it is too early to conclude the effectiveness and safety of other probiotic drugs for AAD in children, except for *Lacticaseibacillus rhamnosus* and *Saccharomyces boulardii*. Current evidence shows that probiotics effectively prevent and treat AAD in children, and the effect of probiotics on pediatric AAD may be a potential dose-response effect. However, the conclusion should be treated with caution due to deficiencies in the methodological, reporting, and evidence quality of the included systematic reviews [16].

Conclusion

A 5-day course of Active Flora Duo (*Saccharomyces boulardii* and *Lactobacillus rhamnosus*) is effective and safe for various infectious and functional disorders of the gastrointestinal tract (intestinal viral and other specified etiology infections, antibiotic-associated diarrhea, non-infectious gastroenteritis and colitis) in children.

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