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USE OF PROBIOTICS FOR THE MANAGEMENT OF ACUTE GASTROENTERITIS IN CHILLDREN : A SYSTEMATIC REVIEW

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Abstract

One of the illnesses that affect children the most frequently is acute gastroenteritis. There are around 500 million children throughout the world who are affected by this illness each year. The acute infectious diarrhea that occurs in affluent nations often has a moderate clinical course, and symptoms typically disappear on their own within a few days. The assessment of dehydration is the most essential part of both diagnostic and therapeutic care since it establishes the degree of AGE and is one of the criteria that is considered when deciding whether or not a patient should be admitted to the hospital. Outpatient care is appropriate for the vast majority of patients; hospitalization should only be considered for individuals who require rehydration by enteral or parenteral routes. Oral rehydration with fluids of a hypoosmolar concentration is the initial therapy of choice. Antidiarrheals such as racecadotril and diosmectite, probiotics such as Lactobacillus GG and Saccharomyces boulardii, and ondansetron, which lessens the severity of nausea and vomiting, are also beneficial. Antibiotherapy is something that should only be explored in the most dire of circumstances. Acute diarrhea is a well-known medical condition that is straightforward to cure if the patient adheres to a few basic guidelines that have been clearly outlined. There is an insufficient amount of data to support the use of probiotics in either a therapeutic or preventative capacity for the treatment of acute gastroenteritis in children.

Keyword: *Acute Gastroenteritis; Chilldren; Diarrhea; Probiotics*

INTRODUCTION

Acute gastroenteritis, often known as AGE, is an extremely prevalent and burdensome pediatric sickness that continues to be responsible for more than 500,000 fatalities in children younger than 5 years old around the world each year. The treatment options available are confined to supportive care with the goals of preventing dehydration, providing fluid replacement therapy, and reducing the negative effects of vomiting as much as possible.[1]

In spite of the lack of evidence supporting their benefit, certain guidelines advocate the consumption of probiotics; as a result, probiotics are frequently utilized as a treatment for AGE in children living in high-income nations.[2] However, in light of two recent large, multi-center, randomized controlled trials (RCTs), which failed to find any benefit associated with two probiotic formulations in children with AGE, the evidence in support of the use of probiotics has been subjected to a more stringent level of scrutiny than it previously had been.[3,4]

The importance of microbial communities in immunologic development, infection prevention, and intestinal barrier maintenance is becoming increasingly evident. These roles provide credibility to the hypothesis that probiotic (i.e., beneficial living organisms) administration can affect the human gut microbiota. Given the abundance of supportive meta-analyses, review papers, and marketing for probiotics, it is easy to comprehend why medical professionals adopt a "can't hurt, could assist" position toward these medicines.[5]

As a result, the most recent Cochrane review on the topic, as well as key groups like the American Gastroenterology Association, are now rethinking and updating their support of the use of probiotics in children who have acute infectious gastroenteritis.[3] When there is solid evidence of success in lowering the severity and duration of diarrhea symptoms, active therapy with probiotics and/or medications may be undertaken. Active treatment should be delivered early in the disease's progression for maximum efficacy.[6]

This article aims to look at research studies related to use of probiotics for the management of acute gastroenteritis in chilldren.

METHODS

Protocol

To ensure that this research was carried out in accordance with the standards that were referenced, the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines were adhered to. This was done to guarantee that the results of this investigation were accurate.

Criteria for Eligibility

This review of the literature aims to investigate the use of probiotics for the management of acute gastroenteritis in children by evaluating or analyzing previous studies on the subject. The current investigation has raised a significant issue. Researchers take part in studies that meet the following criteria: 1) To be considered for publication, publications must be written in English and focus on the efficacy of probiotics in the treatment of acute gastroenteritis in children. 2) Articles published after 2013 but prior to the time period covered by this systematic review were included in this assessment. Editorials, submissions without a DOI, previously published review articles, and entries that are substantially similar to those previously published in a journal are all examples.

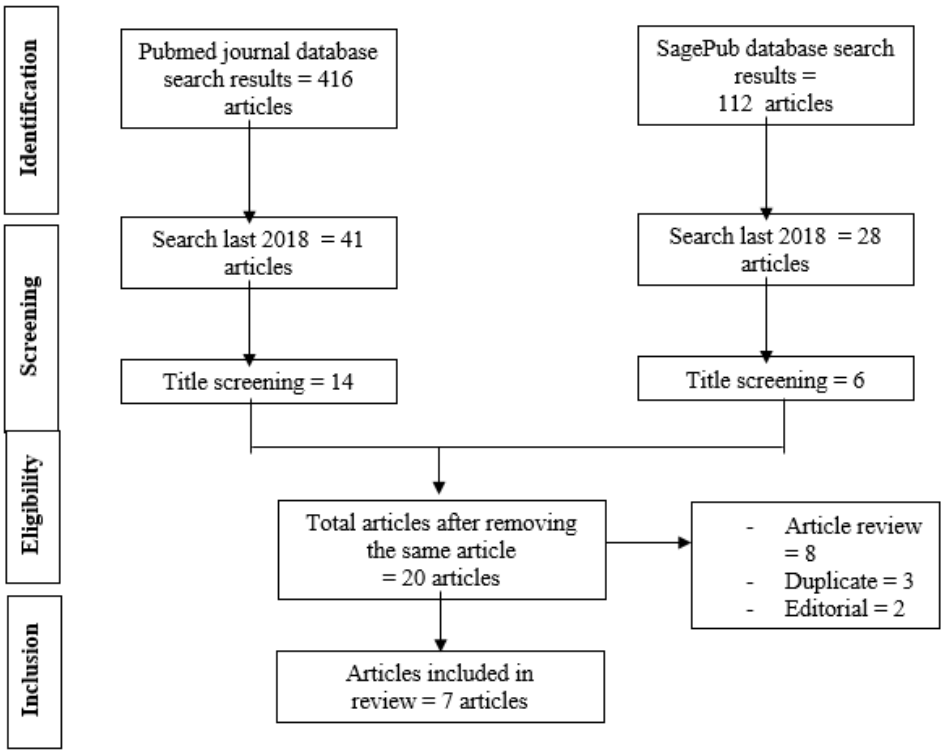

Figure 1. Article search flowchart

Search Strategy

The search for studies to be included in the systematic review was carried out from February, 5th 2023 using the PubMed and SagePub databases by inputting the words: *("probiotic s"[All Fields] OR "probiotical"[All Fields] OR "probiotics"[MeSH Terms] OR "probiotics"[All Fields] OR "probiotic"[All Fields]) AND ("acute"[All Fields] OR "acutely"[All Fields] OR "acutes"[All Fields]) AND ("gastroenteric"[All Fields] OR "gastroenteritis"[MeSH Terms] OR "gastroenteritis"[All Fields] OR "gastroenteritides"[All Fields])* is used as search keywords.

Data retrieval

The author changed the inclusion criteria after reading the titles and abstracts of previous studies. The revised criteria are detailed in the supplementary materials to this study. This revealed the problem's breadth and numerous dimensions, which require further investigation. The author arrived at this conclusion after reviewing several studies that followed a similar format. Only studies that met all inclusion criteria were considered in systematic reviews. This limited the search to material that was relevant.

Our staff rejected research proposals that did not meet our specifications. This ensured a thorough investigation. Names, authors, publication dates, locations, study activities, and parameters were discovered during this investigation. The product categories that are available are listed below. These abilities can be learned through practice. The source of this information may influence how it is presented.

Quality Assessment and Data Synthesis

Before deciding which papers to investigate further, each author conducted their own independent analysis of a separate piece of research described in the titles and abstracts of the publications. Following that, we will read all of the publications that meet the inclusion criteria and are thus appropriate for inclusion in the systematic review. Then, based on our findings, we'll decide which papers to include in the review. These criteria have been used to select the pieces of writing that will be reviewed. in order to make the process of selecting articles for evaluation as simple as possible. Which previous studies have been conducted, and what characteristics of those studies qualify them for inclusion in the review?

RESULT

First study showed development of moderate-to-severe gastroenteritis symptoms after the beginning of treatment did not differ between groups (probiotic -18.4% [162/882] vs. placebo -18.3% [162/888]; risk ratio [RR] = 1.00; 95% confidence interval [CI] = 0.87-1.16; P = 0.95); however, the placebo group was more likely to experience these symptoms than the probiotic group. There was no evidence of an interaction between baseline severity and treatment (P = 0.61) for the primary outcome or any of the secondary outcomes, including diarrhea duration (P = 0.88), maximum diarrheal episodes in a 24-hour period (P = 0.87), unscheduled healthcare visits (P = 0.21), and hospitalization (P = 0.87) respectively.[7]

Freedman, et al (2020)[8] conclude that there were no virus-specific positive effects that could be attributed to the probiotic, either in the reduction of clinical symptoms or in the clearance of viral nucleic acid from stool specimens obtained up to 28 days after enrollment. They give evidence from pathophysiology and microbiology to corroborate the clinical findings, and they come to the conclusion that our data do not support the routine administration of probiotics to children with acute gastroenteritis, independent of the virus that is causing the illness.

Schnadower, et al (2018)[9] showed there were no significant differences between the *L. rhamnosus GG* group and the placebo group in the duration of diarrhea (median, 49.7 hours in the *L. rhamnosus GG* group and 50.9 hours in the placebo group; P=0.26), duration of vomiting (median, 0 hours in both groups; P = 0.17), or day-care absenteeism (median, 2 days in both groups; P = 0.67) or in the rate of household transmission (10.6% and 14.1% in the two groups, respectively; P = 0.16). Those preschoolers who were given a 5-day course of *L. rhamnosus GG* for their acute gastroenteritis did not do any better than those who were given a placebo in terms of their recovery from the illness.

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Follow up	Species	Result
Schnadower, 2021[7]	Canada	Randomized placebo-controlled trials	1,770 children 3-48 months of age	14-days	Lactobacillus rhamnosus GG and combination probiotic: L. rhamnosus and L. helveticus	After therapy, probiotic -18.4% [162/882] and placebo -18.3% [162/888] developed moderate-to-severe gastroenteritis symptoms (risk ratio [RR] = 1.00; 95% confidence interval [CI] = 0.87-1.16; P = 0.95). The primary and secondary outcomes of diarrhea duration (P = 0.88), maximum 24-hour diarrheal episodes (P = 0.87), unplanned healthcare visits (P = 0.21), and hospitalization (P = 0.87) showed no interaction between baseline severity and therapy (P = 0.61).
Freedman, 2020[8]	Canada	Randomized Controlled Trial	886 children	28 days	L. helveticus / L. rhamnosus	The probiotic did not reduce clinical symptoms or viral nucleic acid clearance from stool specimens collected up to 28 days after enrollment. Our data do not support routine probiotic administration to children with acute gastroenteritis, independent of the virus, based on pathophysiological and microbiologic evidence.
Schnadower, 2018[9]	United State of America	Prospective, randomized, double-blind trial	971 participants	14 days	Lactobacillus rhamnosus	The duration of diarrhea, vomiting, day-care absenteeism, and household transmission were not significantly different between the L. rhamnosus GG group and the placebo group (median, 49.7 hours in the GG group and 50.9 hours in the placebo group; P=0.26).
Freedman, 2018[10]	Canada	Randomized, double-blind trial	886 children 3 to 48 months of age with gastroenteritis	14-days	Lactobacillus rhamnosus R0011 and L. helveticus R0052	There were no significant differences between the probiotic group and the placebo group in the median duration of diarrhea (52.5 hours [interquartile range, 18.3 to 95.8] and 55.5 hours [interquartile range, 20.2 to 102.3], respectively; P=0.31) or vomiting (17.7 hours [interquartile range, 0 to 58.6] and 18.7 hours [interquartile range, 0 to 51.6], P=0.18), the percentages of participants with unscheduled visits to a health care provider (30.2% and 26.6%; odds ratio, 1.19; 95% CI, 0.87 to 1.62; P=0.27), and the percentage of participants who reported an adverse event (34.8% and 38.7%; odds ratio, 0.83; 95% CI, 0.62 to 1.11; P=0.21).
Freedman, 2022[11]	Canada	Multicenter randomized, placebo controlled trials	1,565 children	14-days	L. rhamnosus R0011 / L. helveticus R0052	No differences between groups were identified for adenovirus (adjusted relative risk [aRR]: 1.42; 95% confidence interval [CI]: .62, 3.23), norovirus (aRR: 0.98; 95% CI: .56, 1.74), rotavirus (aRR: 0.86; 95% CI: .43, 1.71) or bacteria (aRR: 1.19; 95% CI: .41, 3.43). At pathogen-group and among individual pathogens there were no differences in diarrhea duration or the total number of diarrheal stools between treatment groups, regardless of intervention allocation or among probiotic sub-groups. Among adenovirus-infected children, those administered the *L. rhamnosus R0011/L. helveticus R0052* product experienced fewer diarrheal episodes (aRR: 0.65; 95% CI: .47, .90).
Freedman, 2021[12]	Canada	Multicenter, randomized, double-blinded, placebo-controlled ancillary study	886 PROGUT participants	days 0, 5, and 28	Lactobacillus rhamnosus / helveticus	When comparing measured sIgA concentrations between days 0 and 5, we found no treatment allocation effects [β: −0.24 (−0.65, 0.18); P = 0.26] or interaction between treatment and specimen collection day [β: −0.003 (−0.09, 0.09); P = 0.95]. Although stool sIgA decreased between day 5 and day 28 within both groups (P < 0.001), there were no differences between the probiotic and placebo groups in the median changes in sIgA concentrations when comparing day 0 to day 5 median (IQR) [500 (−1135, 2362) compared with 362 (−1122, 4256); P = 0.77, Cohen's d = 0.075] and day 5 to day 28 [−1035 (−3130, 499) compared with −1260 (−4437, 843); P = 0.70, Cohen's d = 0.067], respectively.

Freedman, et al (2018)[10] showed no significant differences between the probiotic group and the placebo group in the median duration of diarrhea (52.5 hours [interquartile range, 18.3 to 95.8] and 55.5 hours [interquartile range, 20.2 to 102.3], respectively; P=0.31) or vomiting (17.7 hours [interquartile range, 0 to 58.6] and 18.7 hours [interquartile range, 0 to 51.6], P=0.18), the percentages of participants with unscheduled visits to a health care provider (30.2% and 26.6%; odds ratio, 1.19; 95% CI, 0.87 to 1.62; P=0.27), and the percentage of participants who reported an adverse event (34.8% and 38.7%; odds ratio, 0.83; 95% CI, 0.62 to 1.11; P=0.21).

Other study by Freeedman, et al (2022)[11] showed no differences between groups were identified for adenovirus (adjusted relative risk [aRR]: 1.42; 95% confidence interval [CI]: .62, 3.23), norovirus (aRR: 0.98; 95% CI: .56, 1.74), rotavirus (aRR: 0.86; 95% CI: .43, 1.71) or bacteria (aRR: 1.19; 95% CI: .41, 3.43). At pathogen-group and among individual pathogens there were no differences in diarrhea duration or the total number of diarrheal stools between treatment groups, regardless of intervention allocation or among probiotic sub-groups. Among adenovirus-infected children, those administered the L. rhamnosus R0011/L. helveticus R0052 product experienced fewer diarrheal episodes (aRR: 0.65; 95% CI: .47, .90).

Freedman, et al (2021)[12] showed median stool sIgA concentrations did not differ between the probiotic and placebo groups at any of the study time points: day 0 median (IQR): 1999 (768, 4071) compared with 2198 (702, 5278) (P = 0.27, Cohen's d = 0.17); day 5: 2505 (1111, 5310) compared with 3207 (982, 7080) (P = 0.19, Cohen's d = 0.16); and day 28: 1377 (697, 2248) compared with 1779 (660, 3977) (P = 0.27, Cohen's d = 0.19), respectively.

When comparing measured sIgA concentrations between days 0 and 5, they found no treatment allocation effects [β: −0.24 (−0.65, 0.18); P = 0.26] or interaction between treatment and specimen collection day [β: −0.003 (−0.09, 0.09); P = 0.95]. Although stool sIgA decreased between day 5 and day 28 within both groups (P < 0.001), there were no differences between the probiotic and placebo groups in the median changes in sIgA concentrations when comparing day 0 to day 5 median (IQR) [500 (−1135, 2362) compared with 362 (−1122, 4256); P = 0.77, Cohen's d = 0.075] and day 5 to day 28 [−1035 (−3130, 499) compared with −1260 (−4437, 843); P = 0.70, Cohen's d = 0.067], respectively.[12]

Study on Vietnam showed placebo group had a median time from the first dose of study medication to the beginning of the first 24-hour period without diarrhea of 43 hours (inter-quartile range (IQR): 15-66 hours), while the probiotic group had a median time of 35 hours (IQR: 20-68 hours) (acceleration factor: 1.09; 95% confidence interval: 1.78-1.51; p=1.62) In addition, there was no evidence to suggest that therapy with probiotics was effective in any of the pre-defined subgroups, nor was it substantially linked with any secondary outcome.[13]

DISCUSSION

Acute gastroenteritis is one of the most common childhood infections. Every year, an estimated 500 million children worldwide suffer from the condition. The course of acute infectious diarrhea in developed countries is relatively mild; symptoms usually resolve spontaneously within a few days. Unfortunately, high mortality rates continue to be a major issue in low-income countries. Acute diarrhea is defined as a change in stools consistency to loose or liquid and/or an increase in the number of defecations to more than three per day. Fever, nausea, and vomiting are also symptoms of gastroenteritis.[3,14]

Viruses are the most common cause of AGE, with rotavirus being the most common agent. The diagnosis is based on a medical interview, which includes detailed information about the duration and characteristics of the symptoms as well as epidemiological data. The most important aspect of diagnostic and therapeutic management is the assessment of dehydration, which determines the severity of AGE and is used as one of the factors used to determine hospital admission.[3,15]

The vast majority of patients can be treated as outpatients; hospitalization should be reserved for those who require enteral or parenteral rehydration. First-line treatment is oral rehydration with hypoosmolar fluids. Probiotics (*Lactobacillus GG, Saccharomyces boulardii*), racecadotril and diosmectite as antidiarrheals, and ondansetron to reduce the intensity of nausea and vomiting are also effective. Antibiotherapy should only be considered in extreme cases. Acute diarrhea is a well-known medical problem that can be easily treated by adhering to a few simple, well-defined rules.[4,15,16]

It is becoming more and more evident that microbial communities serve vital functions in the process of immunologic development, the prevention of infection, and the maintenance of the intestinal barrier. These roles provide support to the idea that the administration of probiotics, which are defined as living organisms that are thought to benefit their host, can affect the microbiome found in the human stomach. It is easy to understand why medical professionals adopt views regarding probiotics that may be summarized as "can't hurt, might help." This is because there have been several meta-analyses and review articles written in support of probiotics, as well as marketing that promotes their use.[5]

It has been shown that taking probiotics can shorten the duration of AGE symptoms and lessen their severity. As an addition to oral rehydration salts (ORS), certain probiotic strains may be considered for use in children diagnosed with AGE. These strains include Lactobacillus rhamnosus GG, Saccharomyces boulardii, and also L reuteri DSM 17938, if they are accessible and the caretakers are in accord.[3] On other hand, data using the combination of these two characteristics in order to address the feeling that the impact of probiotics is more pronounced when introduced early in the course of an illness and when supplied to children with a more severe sickness.[7,17,18]

However, even among children with severe diarrhea that only lasted for a short period of time, we found no differences in the number of children experiencing moderate-to-severe AGE or any of our secondary outcomes across treatment groups. This was true for all of our secondary outcomes as well. Because the majority of the previous research on probiotics focused on the isolated outcomes of diarrhea frequency and duration, we decided to solely investigate these outcomes. Despite our efforts, we were unable to identify any improvements that may be ascribed to probiotic treatment.[7,9,10,17,18]

For children with AGE, Freedman observed no beneficial virus-specific clinical effects associated with the administration of a 5-day course of an *L. helveticus/L. rhamnosus* combination probiotic. Similarly, when compared to placebo, probiotic administration did not result in faster clearance of viral pathogens from stool specimens. These findings support the conclusion that in children with viral-induced AGE who present to an ED, twice-daily administration of a combined *L. rhamnosus/L. helveticus* probiotic does not reduce the severity of AGE or speed up virus clearance in stool.[8]

There have only been a few research that have looked into the possible therapeutic value of probiotics in treating norovirus infections. A randomized controlled trial (RCT) comparing L. acidophilus to a placebo was conducted on children hospitalized in Vietnam with severe diarrhea. There was no significant difference in stool viral load decrease between the intervention group and the placebo group among the 68 children who had been infected with norovirus. These findings are expanded upon by the results of our study, which included 363 individuals who were infected with the norovirus.[13]

Freedman, et al (2020)[8] found that there was no therapeutic benefit linked with the administration of probiotics in this cohort. Notably, viral load analyses were performed on 816 children who participated in the Canadian study. Among those children who were infected with rotavirus or norovirus, there was no evidence of accelerated clearance of stool viral nucleic acid associated with probiotic use up to 28 days after enrolment. This was the case even though the study was

conducted in Canada. In addition, the fecal IgA concentrations of children who were infected with rotavirus or norovirus did not differ from one another based on the medication that they received (ie, probiotic vs placebo).[8,12]

There is a paucity of data about the use of probiotics in the community for the purpose of preventing diarrhea. In a randomized clinical experiment that was carried out at a number of different sites, almost four hundred newborns were each given one of two types of infant formula: a control formula or a test formula. The test formula contained the prebiotic bovine milk oligosaccharides and the probiotic *Bifidobacterium lactis*. Sixty infants who were breastfed served as a reference group.[10,19]

Despite an increase in fecal *bifidobacteria* in infants who were given the test formula, there was no significant difference between the three groups of children in terms of the incidence of diarrhea or any other kind of illness measured throughout the first year of life.[20,21] The control group had a lower rate of diarrhea than was anticipated, which meant that the trial did not have sufficient power. In diarrhea stools, few enteropathogens were found, hence suggesting a high prevalence of non-infectious diarrhea in the research. However, an RCT using *L. reuteri* DSM 17938 in 340 children found a substantial decrease in diarrheal and respiratory illnesses over a 6-month follow-up period.[22]

CONCLUSION

There is a lack of evidence on administering probiotics to children with acute gastroenteritis, both as a treatment and for prevention.

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