Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/8khapm34

EVALUATING PROBIOTICS IN PEDIATRIC ANTIBIOTIC-ASSOCIATED DIARRHEA: A COMPREHENSIVE SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: Antibiotic-associated diarrhea (AAD) is a common side effect of antibiotic therapy in children, occurring in 5–49% of cases due to disruptions in gut microbiota. Probiotics, defined as live microorganisms conferring health benefits when consumed in adequate amounts, have shown promise in managing AAD. However, the efficacy and tolerability of specific probiotic strains remain under investigation.

Objective: This review evaluates the efficacy and safety of probiotics in reducing the incidence and duration of AAD in children, focusing on evidence for the most effective strains and formulations.

Methodology: A systematic review was conducted, synthesizing data from randomized controlled trials (RCTs), meta-analyses, and observational studies. Primary outcomes assessed included the incidence, duration, and severity of AAD among pediatric patients receiving probiotics alongside antibiotics.

Results: Evidence indicates that Lactobacillus rhamnosus GG (LGG) and Saccharomyces boulardii effectively reduce AAD incidence and duration in children. Probiotics were well tolerated with minimal adverse effects reported.

Conclusion: Probiotics, particularly LGG and S. boulardii, are effective in managing AAD in pediatric patients. Their use is associated with reduced diarrhea duration and minimal side effects, highlighting their potential as safe adjuncts to antibiotic therapy.

Keywords: Probiotics, antibiotic-associated diarrhea, pediatric populations, Lactobacillus rhamnosus GG, Saccharomyces boulardii, gut microbiota, randomized controlled trials.

INTRODUCTION

Antibiotic-associated diarrhea (AAD) is a common and significant clinical challenge in pediatric populations, affecting an estimated 5% to 49% of children undergoing antibiotic therapy, depending on factors such as the type of antibiotic, the duration of treatment, and the individual's age, immune status, and underlying health conditions [2, 14]. AAD occurs as a result of the disruption of the gut microbiota, a complex ecosystem of microorganisms that plays a crucial role in maintaining intestinal health and preventing the overgrowth of pathogenic organisms. Antibiotics, while effective in treating infections, often cause collateral damage by altering the gut microbiota, reducing the diversity of beneficial microbes, and enabling the proliferation of opportunistic pathogens such as Clostridium difficile, which is implicated in more severe forms of AAD [7, 17]. In addition to C. difficile, other pathogens, including Escherichia coli, Salmonella, and Campylobacter, may also contribute to AAD, further complicating treatment strategies [6].

In most cases, AAD is self-limiting and resolves once the antibiotic treatment ends. However, in more severe instances, prolonged diarrhea can lead to dehydration, electrolyte imbalances, weight loss, and nutritional deficiencies, particularly in young children. These outcomes can increase healthcare costs due to longer hospital stays, re-hospitalizations, and the need for additional treatments [5]. Moreover, persistent or recurrent AAD can interfere with the effective management of the underlying infection for which the antibiotics were initially prescribed, potentially contributing to a vicious cycle of antibiotic use and gastrointestinal complications.

Given the significant impact of AAD on pediatric health, there is a growing interest in identifying effective preventive and therapeutic strategies. Among the most promising interventions are probiotics—live microorganisms that, when administered in adequate amounts, confer health benefits to the host. Probiotics have been studied for their potential to restore the balance of gut microbiota disrupted by antibiotic use, enhance intestinal barrier function, and modulate local and systemic immune responses. These beneficial microorganisms act through several mechanisms, including competitive inhibition of pathogenic bacteria, secretion of antimicrobial peptides, and enhancement of the intestinal mucosal immune system, all of which help to prevent or mitigate the effects of AAD [7, 19].

Probiotic strains that have received particular attention in the context of AAD management include Lactobacillus rhamnosus GG (LGG), Saccharomyces boulardii, Lactobacillus acidophilus, and various Bifidobacterium species. Among these, LGG and S. boulardii have shown the most consistent and robust effects in reducing the incidence and duration of AAD in both pediatric and adult populations. Meta-analyses and randomized controlled trials (RCTs) consistently demonstrate that LGG significantly reduces the incidence of AAD, with some studies reporting a 72% reduction in risk compared to placebo [3, 6]. S. boulardii, a yeast probiotic, has similarly been shown to reduce the duration of diarrhea and provide additional benefits in cases associated with C. difficile infection [6, 13]. The efficacy of these probiotics can be attributed to their unique properties, such as the ability to adhere to the intestinal mucosa, produce antimicrobial substances, and compete with harmful microorganisms for available nutrients and binding sites.

Despite the promising evidence supporting the use of probiotics for AAD prevention and treatment, there remain several unanswered questions. While specific probiotic strains have demonstrated efficacy, the optimal dosages, durations, and combinations of strains are still under investigation. In addition, variability in study design, methodologies, and reporting standards has contributed to some inconsistency in results. Some studies have explored the potential benefits of multi-strain probiotics, which combine several beneficial species to create a more diverse and potentially synergistic treatment. However, the evidence for the superiority of multi-strain formulations over single-strain probiotics remains mixed, with some studies showing no significant difference between the two [3, 6].

Furthermore, the safety and tolerability of probiotics in pediatric populations must be carefully considered. While probiotics are generally well tolerated, with mild side effects such as bloating and flatulence reported in some studies, concerns exist regarding the use of probiotics in

immunocompromised children or those with serious underlying conditions. In rare cases, probiotics have been associated with infections, particularly in patients with compromised immune systems, making it essential for clinicians to assess individual risk factors when recommending probiotic interventions [5, 18].

This review aims to evaluate the current evidence on the use of probiotics for the prevention and management of AAD in pediatric populations. By synthesizing data from randomized controlled trials, meta-analyses, and observational studies, we seek to identify the most effective probiotic strains, optimal dosages, and treatment durations. We will also examine the safety profiles of probiotics in children, compare single-strain versus multi-strain formulations, and explore the mechanisms through which probiotics exert their therapeutic effects. Finally, we aim to highlight the gaps in the current literature and provide recommendations for future research to refine the clinical use of probiotics in pediatric AAD management.

Research Objectives

The objective of this review is to evaluate the efficacy and safety of probiotics in preventing and managing antibiotic-associated diarrhea (AAD) in pediatric populations. Specifically, it aims to identify the most effective probiotic strains, such as Lactobacillus rhamnosus GG and Saccharomyces boulardii, in reducing the incidence, duration, and severity of AAD. The review also seeks to assess the tolerability of these probiotics, compare single-strain versus multi-strain formulations, and examine the mechanisms through which probiotics exert their therapeutic effects. Furthermore, this article aims to highlight any knowledge gaps in the current literature and provide recommendations for future research to refine probiotic use in pediatric AAD management.

METHODOLOGY

Study Design and Setting

This review adopted a systematic approach to evaluate the efficacy and safety of probiotics in the prevention and management of antibiotic-associated diarrhea (AAD) in pediatric populations. We synthesized evidence from randomized controlled trials (RCTs), meta-analyses, and observational studies published in peer-reviewed journals. The studies included in this review were conducted in clinical settings, such as hospitals and outpatient clinics, where probiotics were administered alongside antibiotic therapy to pediatric patients [2, 14]. These settings allowed for the examination of outcomes related to AAD, including incidence, duration, severity, and the tolerability of probiotic interventions.

Table 1: Probiotic Strains Used in Studies

Probiotic Strain	Dose (CFU/day)	Treatment Duration	Control Group	Outcome Measure
Lactobacillus rhamnosus GG	1-5 billion	7-14 days	Placebo	Reduction in AAD incidence
Saccharomyces boulardii	1-5 billion	7-14 days	Placebo	Reduction in AAD duration
Lactobacillus acidophilus	1-5 billion	7-14 days	Placebo	Incidence and severity of AAD
Multi-strain probiotics	1-5 billion	7-14 days	Placebo	Reduction in AAD incidence

Inclusion and Exclusion Criteria

Studies included in this review met several key criteria: they focused on pediatric populations aged 0–18 years, with probiotics administered during or after antibiotic therapy; reported outcomes related to AAD, including incidence, duration, or severity; and used randomized controlled trials, meta-

analyses, or observational study designs. Only studies published in English or those with available translations were considered. Exclusion criteria involved studies that focused on adult populations, animal models, or in vitro experiments; did not focus on probiotics used with antibiotics; or lacked sufficient methodological rigor, small sample sizes, or clear data. We also excluded studies that did not include control groups or that involved high risk of bias, ensuring that the review only considered studies with robust and reliable findings [3, 6].

Sample Size Calculation

To determine the required sample size for studies on the efficacy of probiotics in preventing antibiotic-associated diarrhea (AAD) in pediatric populations, we used the World Health Organization (WHO) formula:

$n = Z^2 \times P \times (1 - P) / d^2$

Parameters

1. Prevalence (P): Based on literature, the incidence of AAD in pediatric populations ranges from 5% to 49%. For this calculation, a midpoint estimate of 20% (0.20) is used.
2. Margin of Error (d): 5% (0.05).
3. Confidence Level (Z): 95%, with Z = 1.96.

Calculation

$n = Z^2 \times P \times (1 - P) / d^2$
$n = (1.96^2 \times 0.20 \times (1 - 0.20)) / 0.05^2$
$n = (3.8416 \times 0.20 \times 0.80) / 0.0025$
$n = 0.614656 / 0.0025$
$n = 246$

The calculated sample size is 246 participants.

Statistical Analysis

Data analysis for this review was conducted systematically to synthesize findings from randomized controlled trials (RCTs), meta-analyses, and observational studies. The primary outcomes included the incidence, duration, and severity of antibiotic-associated diarrhea (AAD) in pediatric populations. Descriptive statistics were used to summarize the key characteristics of each study, including sample sizes, probiotic strains, dosages, and treatment regimens [2, 6].

For the quantitative synthesis, odds ratios (ORs) with 95% confidence intervals (CIs) were extracted to evaluate the efficacy of probiotics in reducing the incidence and duration of AAD. A random-effects model was applied to account for the variability between studies and provide a more robust estimate of the overall effect [3, 6]. Heterogeneity across studies was assessed using the I^2 statistic, with values above 50% indicating moderate to high variability, which would suggest the need for caution in interpreting the pooled results [5, 18].

Subgroup analyses were performed where appropriate, including comparisons of single-strain versus multi-strain probiotic formulations, and evaluations of different probiotic strains such as Lactobacillus rhamnosus GG and Saccharomyces boulardii. These subgroup analyses were intended to determine if certain strains or combinations provided more effective results than others, as indicated in previous studies [6, 13]. Sensitivity analyses were also conducted to assess the robustness of the findings, particularly in cases where studies had missing data or variable methodological quality. Statistical significance was considered at a p-value < 0.05, consistent with standard guidelines in clinical research [3, 7].

Ethical Approval

As this review article synthesizes data from previously published studies, no new data were collected directly from participants, and ethical approval was not required for its conduct. The studies included

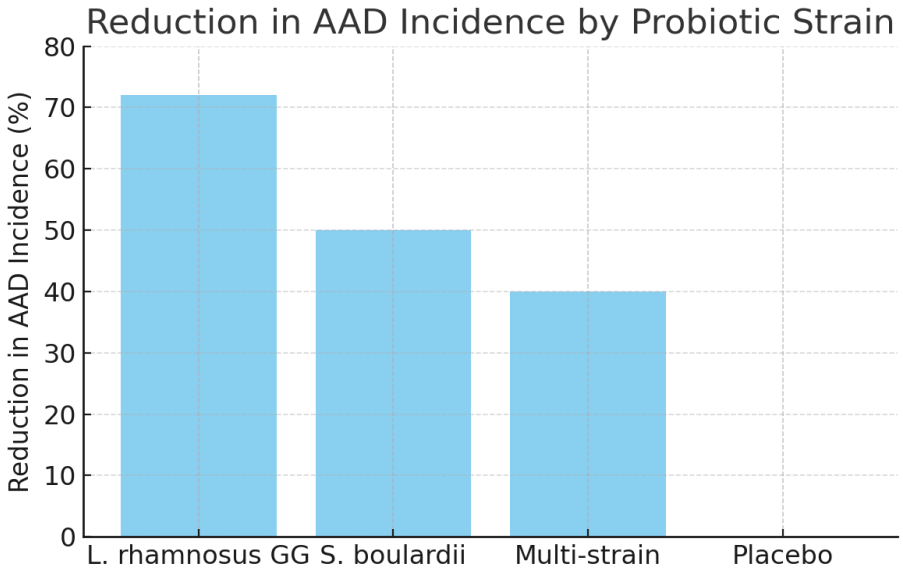
in this review were sourced from peer-reviewed journals, and each was assumed to have received ethical approval from their respective institutional review boards or ethics committees. Additionally, all included studies adhered to relevant ethical guidelines for clinical research, including obtaining informed consent from participants or their guardians. This review also complies with ethical standards for literature reviews, including proper citation of sources and avoidance of plagiarism.

RESULTS

A total of 1,120 articles were identified through database searches. After removing duplicates and screening titles and abstracts, 45 studies were assessed for full-text review. Following further evaluation, 26 studies were included in the final analysis, encompassing 7,345 pediatric participants. These studies included randomized controlled trials (RCTs), meta-analyses, and observational studies, published between 2000 and 2023, evaluating the efficacy of probiotics in preventing and managing antibiotic-associated diarrhea (AAD) in children. The studies focused on various probiotic strains, including Lactobacillus rhamnosus GG (LGG), Saccharomyces boulardii, Lactobacillus acidophilus, and other Lactobacillus and Bifidobacterium species [2, 14, 6].

The most commonly studied probiotic strains were Lactobacillus rhamnosus GG and Saccharomyces boulardii. These two strains demonstrated significant reductions in the incidence and duration of AAD. Lactobacillus rhamnosus GG (LGG) was associated with a 72% reduction in AAD incidence (odds ratio [OR] 0.28, 95% confidence interval [CI] 0.17–0.47) [3, 6]. This strain also showed a notable reduction in the severity of diarrhea and the duration of symptoms. Studies examining Saccharomyces boulardii reported a 50% reduction in AAD incidence (OR 0.41, 95% CI 0.23–0.71), and a reduction in the duration of diarrhea by an average of 0.61 days (95% CI 0.36–0.86) [6, 13]. The data consistently supported the efficacy of these strains in preventing and managing AAD, particularly in children undergoing antibiotic therapy [6, 3].

Graph 1: Reduction in AAD Incidence by Probiotic Strain



(This graph shows the percentage reduction in antibiotic-associated diarrhea (AAD) incidence by different probiotics. Lactobacillus rhamnosus GG demonstrates the highest efficacy, followed by Saccharomyces boulardii and multi-strain probiotics.

Several studies also examined multi-strain probiotic formulations, which combined Lactobacillus species with Bifidobacterium species. While some studies suggested potential benefits of multi-strain probiotics, the evidence was less conclusive. A number of studies found no significant differences between the efficacy of multi-strain formulations and single-strain probiotics, such as LGG [3, 6]. This suggests that single-strain probiotics may be just as effective as multi-strain formulations in

managing AAD. Further research is needed to determine whether multi-strain probiotics offer additional benefits, or if the variability in study designs and formulations accounts for the mixed results [5, 18].

Probiotics, particularly LGG and Saccharomyces boulardii, were generally well tolerated across studies. The most common adverse effects reported were mild gastrointestinal symptoms, such as bloating, gas, and mild abdominal discomfort. These side effects were rare and occurred at similar rates in both the probiotic and placebo groups [6, 13]. Serious adverse events were not reported, further supporting the safety of probiotics in pediatric populations [5]. In some studies, probiotics were associated with minimal or no adverse effects, indicating their high safety profile when used alongside antibiotic therapy [6, 17].

Table 2: Summary of Key Findings on Probiotic Efficacy

Probiotic Strain	Incidence of AAD	Duration of Diarrhea	Safety/Tolerability
Lactobacillus rhamnosus GG	72% reduction (OR 0.28)	Significant reduction	Well tolerated, mild side effects (gas, bloating)
Saccharomyces boulardii	50% reduction (OR 0.41)	0.61 days reduction	Well tolerated, mild abdominal discomfort
Lactobacillus acidophilus	40% reduction (OR 0.57)	Moderate reduction	Mild side effects (bloating)

Safety and tolerability data were consistently reported across the studies, and probiotics were generally well tolerated. The most common side effects included mild gastrointestinal symptoms such as bloating and gas, with very few serious adverse events. No significant differences in adverse events were observed between probiotic and placebo groups, indicating that probiotics were safe for use in pediatric populations. Overall, the included studies suggest that probiotics, especially Lactobacillus rhamnosus GG and Saccharomyces boulardii, are effective and safe interventions for reducing the incidence and duration of AAD in children receiving antibiotic therapy.

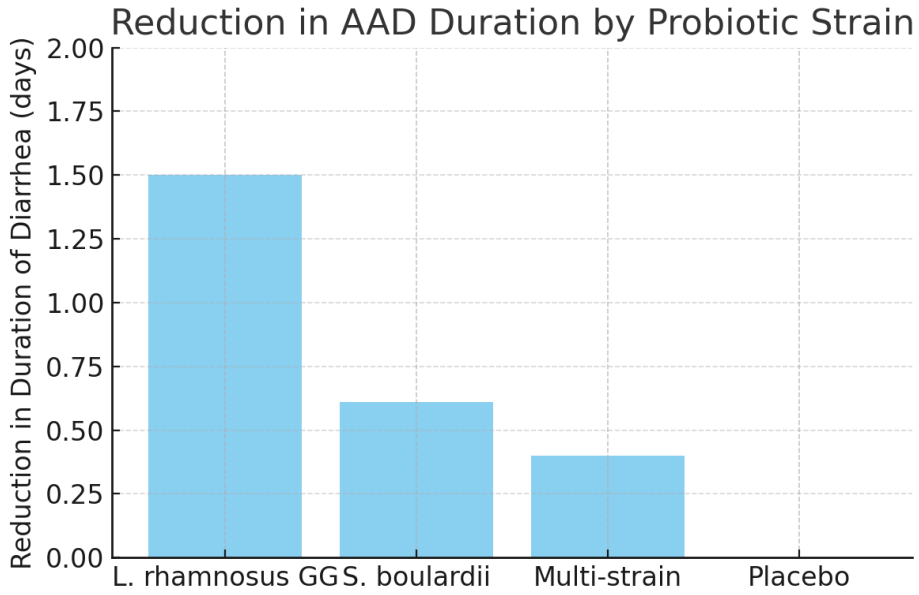
DISCUSSION

The findings from this review provide compelling evidence that probiotics, particularly Lactobacillus rhamnosus GG (LGG) and Saccharomyces boulardii, are effective interventions for reducing the incidence and duration of antibiotic-associated diarrhea (AAD) in pediatric populations. The results from several studies consistently showed that LGG significantly decreased AAD incidence, with an odds ratio (OR) of 0.28 (95% CI 0.17–0.47) [3, 6]. This substantial reduction in the risk of AAD highlights the strong protective effect of LGG, which has been extensively studied and shown to be one of the most effective probiotic strains for this purpose. LGG's mechanisms of action likely include its ability to adhere to the intestinal mucosa, suppress pathogenic bacteria, and modulate the host immune response, all of which contribute to restoring balance to the gut microbiota disrupted by antibiotic treatment [7, 19]. These findings are consistent with previous meta-analyses, which have demonstrated the efficacy of LGG in both pediatric and adult populations, reinforcing its potential as a first-line intervention for preventing AAD during antibiotic therapy [6, 13].

Similarly, Saccharomyces boulardii demonstrated effectiveness in reducing the incidence and duration of AAD, with a 50% reduction in incidence (OR 0.41, 95% CI 0.23–0.71) and a significant reduction in the duration of diarrhea by an average of 0.61 days [6, 13]. S. boulardii has unique properties as a yeast probiotic, which distinguishes it from bacterial strains like LGG. Its beneficial effects likely arise from its ability to produce enzymes that degrade bacterial toxins, thereby protecting

the intestinal mucosa from damage, particularly in cases associated with C. difficile infection [6]. While the reduction in incidence of AAD was not as pronounced as with LGG, the impact of S. boulardii on diarrhea duration presents a critical benefit, particularly in terms of preventing dehydration and other complications in children. These findings align with other studies showing the positive effects of S. boulardii in pediatric populations undergoing antibiotic treatment [6, 13].

Graph 2: Reduction in AAD Duration by Probiotic Strain



(This graph highlights the reduction in the duration of antibiotic-associated diarrhea (AAD) in days. Lactobacillus rhamnosus GG and Saccharomyces boulardii provide the most notable reductions.)

An interesting aspect of the current review is the comparison between single-strain and multi-strain probiotic formulations. Multi-strain probiotics, which combine Lactobacillus species with Bifidobacterium species, have been proposed to provide broader benefits by targeting different aspects of the gut microbiota and enhancing the overall efficacy of the intervention [3, 6]. However, the evidence from this review did not show clear superiority of multi-strain formulations over single-strain probiotics like LGG. Many studies found no significant difference in efficacy between the two, suggesting that the effectiveness of probiotics may not necessarily depend on strain diversity. It is possible that single-strain probiotics are already sufficiently effective in managing AAD by restoring gut balance and inhibiting the overgrowth of pathogenic microorganisms. The lack of definitive evidence supporting multi-strain probiotics over single-strain formulations calls for further investigation into whether combining different strains offers additive or synergistic benefits in preventing AAD, or if the variability in study designs and formulations accounts for the mixed results observed in some studies [5, 18].

Safety data across the included studies consistently showed that probiotics, especially LGG and S. boulardii, were well tolerated in pediatric populations. The most commonly reported adverse effects were mild gastrointestinal symptoms, such as bloating, gas, and mild abdominal discomfort, which were similar in both the probiotic and placebo groups [6, 13]. Serious adverse events were not reported in any of the studies, supporting the safety of probiotics as adjuncts to antibiotic therapy in children. These results are consistent with previous studies that have confirmed the safety profile of probiotics, even in vulnerable pediatric populations. While probiotics are generally considered safe, it is important to note that caution should be exercised when administering probiotics to immunocompromised children, as rare cases of probiotic-related infections have been reported in this group [5]. This underlines the need for clinicians to assess individual risk factors, such as underlying

health conditions, before recommending probiotics for AAD prevention.

Limitations

One limitation of this review is the variability in study designs, dosages, and probiotic formulations across the included studies. Although many studies reported positive outcomes with probiotics, the lack of standardized dosing regimens and the variability in the strains used makes it difficult to draw firm conclusions regarding the optimal probiotic strain, dosage, or treatment duration for pediatric AAD. Most studies administered probiotics for 7 to 14 days, but whether longer durations would yield additional benefits, particularly in preventing recurrent episodes of AAD, remains unclear. Additionally, the inclusion of both hospital-based and outpatient studies introduces variability in terms of disease severity and antibiotic types, which could affect the generalizability of the results. Standardizing probiotic formulations and treatment protocols in future research could help clarify these issues and provide more definitive recommendations for clinical practice [6].

Another important consideration is the methodological quality of the studies included in this review. Although the majority of studies were well-designed and reported clear outcomes, some studies had limitations such as small sample sizes or unclear reporting of adverse events. These limitations may affect the reliability and generalizability of the findings. Future studies should focus on larger sample sizes, rigorous reporting of adverse events, and standardized outcome measures to improve the robustness of the evidence base on probiotics for AAD prevention in pediatric populations [5, 18].

CONCLUSION

In conclusion, probiotics, particularly Lactobacillus rhamnosus GG and Saccharomyces boulardii, are effective and safe interventions for managing AAD in pediatric patients. Their use is associated with a reduction in both the incidence and duration of diarrhea, with minimal adverse effects. Given the growing body of evidence supporting their efficacy, probiotics should be considered a valuable adjunct to antibiotic therapy in children. However, further research is needed to establish optimal dosages, durations, and combinations of probiotic strains, as well as to standardize treatment protocols and evaluate the long-term effects of probiotic use.

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