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# The role of probiotics in antibiotic-associated diarrhea, acute diarrhea and functional constipation in children

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## Abstract

### Introduction and purpose

Interest in intestinal microbiota and its influence on human health has persisted for many years. Caring for intestinal microbiota is often associated with taking a probiotic, especially during antibiotic therapies. Probiotics are widely used by parents of children, as well as by heathcare professionals. Because of their long history of presence on the market and the many studies conducted on probiotics, they have become an evident addition to the treatment of gastrointestinal disorders. The aim of this review is to emphasize what are the current recommendations for the use of probiotics in children in antibiotic-associated diarrhea, acute diarrhea and functional constipation, determine what the safety of their use is, what to look for when choosing a product and what are the current trends in research on the effectiveness of probiotics.

## Material and methods

For this review, we used the literature available in PubMed and Google Scholar using the following keywords: “probiotics”, “probiotics in pediatrics”, “gut microbiota”, “acute gastroenteritis”, “antibiotic-associated diarrhea in children”, “functional constipation”.

## Brief description of the state of knowledge

Probiotics are often used in pediatrics despite their uncertain effectiveness. At the same time, there is a focus on the quality, purity and appropriate dosage of preparations available on the market. In addition, probiotics as a dietary supplement can, like any substance, cause side effects. Therefore, extra precaution must be taken when administering a preparation or refraining from administering a probiotic to children with immune disorders.There have been a significant number of studies in which the use of probiotics provides a clinically insignificant benefit or is comparable to the use of placebo. The benefit of their use mostly in antibiotic-associated diarrhea in children is difficult to determine because of the lack of routine test of the etiology of diarrhea after antibiotic therapy, which may not actually be related to antibiotic intake.

## Conclusion

It is important to consider the associated advantages and disadvantages of introducing probiotics into the treatment of a pediatric patient, including financial ones. Probiotics may be considered during antibiotic therapy in children if a broad-spectrum antibiotic is being used, the duration of therapy is prolonged, or there are other risk factors for antibiotic-associated diarrhea in children. In acute gastroenteritis, probiotics can be considered; however, their effectiveness is limited. Probiotics should not be used in the treatment of functional constipation. It is preferable to use probiotics in the form of a medicine because such products are subjected to more stringent requirements before being brought to market. The efficacy of probiotics is both strain-specific and disease-specific.

**Key words:** probiotics, probiotics in pediatrics, gut microbiota, acute gastroenteritis, antibiotic-associated diarrhea in children, functional constipation.

## Gut microbiota and probiotics

The human digestive system is inhabited by approximately $10^{13}$ bacteria, forming an ecosystem that evolves alongside the host's life [1]. The activity of such a significant number of cells influences human health both directly and indirectly by affecting host cells. Bioactive molecules produced by the gut microbiota interfere with human biochemical pathways, causing changes at the immune system level, regulating energy homeostasis, and reducing the likelihood of colonization by pathogenic strains [2].

The concept of improving health and immunity by influencing gut microbiota is a significant topic for patients and physicians, as well as for pharmaceutical companies, food producers, and cosmetics manufacturers [3-5]. This makes it necessary to approach such products with caution and consider whether their application will yield the expected results. Labels indicating the presence of probiotics make a product more attractive to consumers [6]. Most probiotics on the market are available as food additives or dietary supplements rather than as medications. By definition, a medication is intended to prevent or treat diseases, improve, or modify physiological functions. In contrast, dietary supplements exhibit a nutritional or other physiological effect, with the active substance provided at a nutritional dose [7]. As a result, the effects of specific probiotic-containing products are sometimes not scientifically proven.

The definition of a probiotic itself is "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [8]. Many conditions must be met for probiotics to be effective. Their efficacy depends on the dose and duration of therapy, which varies between strains. Recommendations from the product manufacturer may differ from those in scientific guidelines. These recommendations should be based on scientific studies [7]. A sufficient amount of live microorganisms must be present at the time of use. Therefore, both the expiration date and proper storage conditions are crucial.

In research, the most evidence for the beneficial effects of probiotics has been described in the infectious gastroenteritis, prevention of antibiotic-associated, Clostridioides difficile-associated and nosocomial diarrhea [9].

One of the most common applications of probiotics is in gastrointestinal disorders [10]. In pediatrics, they are used, among other purposes, in the prevention of antibiotic-associated diarrhea, as adjunct therapy in acute diarrhea, and in functional gastrointestinal disorders.

**Probiotics in Antibiotic-Associated Diarrhoea**

The effect of antibiotics consists of killing or preventing the growth of bacteria that cause infections. However, at the same time they affect the normal gut microbiota, causing dysbiosis. By reducing the biodiversity of the gut microbiota, antibiotics increase the risk of colonization by resistant bacterial strains, most prominently Clostridioides difficile, which may lead to diarrhoea. At the same time, antibacterial substances that act directly on the intestinal mucosa can cause damage [10]. The frequency of this side effect ranges from 15-35%, depending on the antibiotic used. Typically, testing to identify the etiological factor is not performed [11-13]. Antibiotic-associated diarrhoea (AAD) is defined as "3 or more loose or watery stools per day in a 24-hour period, caused either by C. difficile or of otherwise unexplained etiology, after testing for common, predefined diarrheal pathogens" [14,15]. The cause of the diarrhoea cannot be: infections, food poisoning, use of laxatives, or chronic gastrointestinal diseases. AAD is a mild and self-limiting side effect of antibiotic therapy but especially in young children can lead to rapid dehydration and electrolyte imbalances. Furthermore, diarrhoea itself and accelerated gastrointestinal passage reduce the effectiveness of the used antibiotics[16].

The definition of AAD may vary across published studies. It is important to note that not all diarrhoea occurring after antibiotic therapy is caused by the therapy itself. A distinction must be made between AAD and diarrhoea occurring during antibiotic therapy. This creates difficulties in estimating the effectiveness of probiotics in preventing AAD versus preventing diarrhoea regardless of its etiology [14].

The protective effect of probiotics against AAD is through the production of bactericidal acids and peptides. Additionally, by adhering to intestinal epithelial cells, probiotics compete with pathogenic strains for binding space [12]. They also influence the integrity of intestinal epithelial cells and improve intestinal immune responses [10]. Studies indicate that probiotics coadministered with antibiotics moderately reduce the risk of diarrhoea and that higher doses of probiotics are more effective than lower ones [17].

In a randomized clinical trial by J. Łukasik et al. [14], a multispecies probiotic did not significantly reduce the risk of AAD when analyzed according to the most stringent definition. However, the group receiving probiotics had an overall lower risk of diarrhoea regardless of etiology during and up to seven days after completing antibiotic therapy and less frequently required intravenous hydration. The authors point out that the common causes of diarrhoea during hospitalization, such as norovirus and rotavirus, are not directly related to prior antibiotic therapy [14]. Current recommendations suggest the possibility of administering probiotics together with antibiotic therapy to prevent AAD in cases where the type of antibiotic used,

duration of treatment, patient age, coexisting diseases, or a history of AAD indicate an increased risk of AAD [18].

A rare but very hazardous form of AAD is pseudomembranous colitis caused by C. difficile. It develops in children with additional risk factors for AAD i.e. cystic fibrosis, inflammatory bowel disease, malignancy [9]. Moderate-quality evidence suggests that probiotics reduce the risk of C. difficile infection. However, it is important to be aware of the careful use of antibiotics in children with chronic diseases [19].

**Probiotics in Acute Diarrhea**

Acute diarrhea in children is usually self-limiting and its primary treatment includes oral rehydration or, in cases of severe dehydration, intravenous rehydration [20].

Probiotics can be used in the treatment of acute diarrhea in children alongside oral rehydration therapy. With an increasing amount of research on the efficacy of probiotics, it appears that they are less effective than initially believed. Currently, it is thought that adding probiotics to treatment reduces the duration of diarrhea by less than one day [19-22].

In children, common etiological agents of acute diarrhea are viruses such as Norovirus, Adenovirus, and Rotavirus. The mechanism by which probiotics potentially exert their effects on viral infections includes influencing the virus replication cycle by competing with the pathogen for attachment space on intestinal epithelial cells, producing antiviral molecules, or stimulating epithelial cells to synthesize such molecules. Additionally, probiotic bacteria can bind viruses, promoting their excretion [23].

According to the ESPGHAN and ASPGHAN recommendations from 2014 [21], the use of specific strains such as Lactobacillus GG (low-quality evidence; strong recommendation) and Saccharomyces boulardii (low-quality evidence; strong recommendation) could be considered. However, in the latest ESPGHAN recommendations from 2020, the recommendations for these strains have been downgraded to weak [18]. Other strains approved by ESPGHAN include Lactobacillus reuteri and a combination of Lactobacillus helveticus and Lactobacillus rhamnosus. By contrast, in North America, the use of probiotics for acute infectious gastroenteritis is not recommended. This is primarily because most studies on the efficacy of probiotics have been conducted outside North America [24].

In a randomized study by K. Chen et al. (2023) [25], the authors evaluated the efficacy of treating acute diarrhea with a specific strain, Bifidobacterium animalis subsp. Lactis XLTG11. They analyzed samples before and after probiotic administration to assess the composition of the gut microbiota. The study indicated that administering Lactis XLTG11 led to a reduction in

the duration of diarrhea, faster improvement in stool consistency, and beneficial changes in the composition of the gut microbiota [25].

Research has also explored the efficacy of other bacterial strains not included in European recommendations. For instance, Bacillus clausii, due to its ability to form endospores, which are more resistant to gastric acid and bile, has attracted the interest of researchers [26]. However, there is currently insufficient evidence supporting the efficacy of this strain in the treatment of acute diarrhea in children [18,27].

A particular type of acute diarrhea is nosocomial diarrhea. By definition, it is diarrhea occurring 48h after the patient's admission to the hospital or within 48h of discharge [18]. Nosocomial infections are a compound issue because, on the one hand, they are negative from the patient's point of view due to the health costs incurred, prolonged hospital stay and possible worsened treatment outcomes, but at the same time they affect the health care system by increasing the cost of hospitalization [28]. There is a trial from 2016 confirming the effectiveness of the Lactobacillus GG strain in reducing the risk of nosocomial diarrhea. However, the trial examined the efficacy of the probiotic in combination with zinc, vitamin B and C. The results may be difficult to interpret with regard to the efficacy of the probiotic itself [29]. According to the recommendations, it is reasonable to consider the administration of a probiotic for the prevention of nosocomial diarrhea in children, selecting L. rhamnosus GG, bearing in mind the moderate quality of evidence [28].

**Probiotics in Functional Constipation**

Another potential application of probiotics is in the treatment of functional constipation in children. Functional constipation is a clinical diagnosis based on history and physical examination after excluding organic causes of symptoms [30].

Functional constipation is a relatively common issue during childhood. Contributing factors may include an inadequate, low-fiber diet, insufficient fluid intake and low physical activity. Experiencing pain during defecation can lead to prolonged stool retention, which in turn exacerbates the symptoms [31]. Stool retained in the rectum becomes harder and drier due to extended period of water absorption by the rectal mucosa [32]. The clinical presentation of the disorder depends on various factors such as age, developmental stage, intellectual capacity, and stress exposure [31].

Certain species and strains of probiotic bacteria may influence intestinal motility and secretion, thereby affecting stool consistency and frequency [33]. Although this theory has been confirmed in animal models, there are too few well-designed, high-quality randomized

controlled trials providing sufficient evidence of the positive effects of probiotics in treating functional constipation in children. Some reviews have demonstrated statistically significant differences in outcomes of constipation treatment with probiotics [34]. However, they are not currently included in the latest ESPGHAN recommendations [18].

**Safety of Probiotics**

The safety of providing the recommended bacterial strains to immunocompetent children in the study is high [35]. Symptoms including bloating, nausea, diarrhea may occur due to the osmotic properties of the product and are more common at higher doses [36]. Severe side effects of probiotics described in case reports are infections caused by the administered probiotic bacteria, including sepsis, conditions caused by contamination of the product or toxins produced by the bacteria. Nevertheless, the cases described included children with an incriminating medical history. [37]. Additionally, the limited research on the risks of probiotics may be due to the difficulty of growing probiotic bacteria on standard culture media. This contributes to the underreporting of side effects, such as severe infections linked to probiotics. In a review by D'Agostin et al. [38], case reports of pediatric patients who developed invasive infections related to probiotic use were analyzed. The review highlighted the need to carefully assess the use of probiotics in high-risk patients. These groups include premature infants, patients with intravenous catheters, and those with pre-existing intestinal diseases such as short bowel syndrome, enteral/parenteral nutrition, abdominal surgery, intestinal inflammation, and diarrhea. The latter two risk factors are particularly relevant as acute infectious gastroenteritis is also a common reason for prescribing probiotics. This paradox can be explained by the increased translocation of pathogens through damaged intestinal mucosa. Immunocompromised states further elevate the risk [38,37].

Probiotics are widely used despite uncertain efficacy, moderate evidence, and weak grades of recommendation [18]. The probiotic market continues to grow rapidly worldwide, leading to increased consumption. The belief in the safety of probiotics stems from their long-standing presence in the market and numerous publications. They have become a natural adjunct in the treatment of many conditions without considering whether they provide any benefit [38].

It is important to acknowledge that along with the potential benefits, there are also risks of adverse effects associated with probiotics [39]. One risk lies in the difficulty of ensuring the safety of specific products. Most probiotics available on the market are sold as dietary supplements, which are subject to fewer requirements before marketing than medicinal products or medications. Manufacturers are usually not obligated to demonstrate safety and purity before

distribution. This may result in discrepancies between the actual contents of a dietary supplement and what is stated on the product label [7,38].To ensure safer and more effective use of probiotics, stricter conditions for their market approval are necessary. These should include requirements for product purity and alignment of packaging information with actual content. Furthermore, standardized protocols for safety outcomes in clinical trials are needed to ensure comprehensive and transparent data collection. This would allow for the development of more detailed guidelines for the clinical use of probiotics [40]. Currently, there are plenty of contradictory findings regarding bacteria within a single genus. Different species or strains of Lactobacillus (now Lacticaseibacillus) or all Bacillus or all Bifidobacterium have shown different effectiveness [41]. For greater safety in the use of probiotics, it is important to determine precisely which strain of bacteria is responsible for the beneficial effect of the therapy. This can prevent the administration of other unnecessary strains, reducing the risk of side effects.

**Summary**

Probiotics have demonstrated some benefit in the treatment of gastrointestinal diseases in children. In accordance with the progression of studies, results have been less promising than previously thought. The reduced confidence is a result of large differences in RCTs and a lack of specific recommendations. However, developing consistent evidence on the effects of probiotics is difficult due to discrepancies in effectiveness across studies due to the multiplicity of strains, different dosage or duration of therapy. Definitions of the given conditions treated with probiotics also vary. It appears that probiotics, like other medicinal products, should be used with caution and only when indicated.

When administering a probiotic to children, it is very important to check that this is in compliance with current guidelines and that the child is not at risk of developing severe infections due to probiotics. There are only a few indications for using a probiotic, so it should not be included routinely. The use of probiotics is relatively safe with precautions. In addition, it is important to pay attention to which strain of bacteria is most effective in a given individual. It is also important to assess whether the recommended strain of probiotic bacteria in the amount stated on the label is actually in the product, in light of changes in the taxonomic classification of bacterial strains, as the correct dose is essential for full efficacy.

The human microbiome has been a subject of interest for many years. Developing methods for studying the different genomes present in a test sample make it possible to identify the presence of specific bacterial species. This allows us to confirm that the administered probiotic bacteria

are indeed present in the intestinal microbiota, thereby minimizing the risk of misinterpreting the test results received. It is possible that more studies on the effect of a particular strain of bacteria are needed to increase the effectiveness of probiotics. Despite the many published trials of probiotic effects in children, it is not possible to develop specific treatment strategies due to the heterogeneity of results and the high risk of bias. More well-designed, dedicated-dose response studies research is needed on the effectiveness of the probiotic depending on the strain. Among the conditions described in this review, only AAD and acute diarrhea have recommendations for probiotic use with specific requirements.

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