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Probiotics as Support for Antibiotic Therapy: Benefits and Risks

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ABSTRACT

Antibiotic therapy, while essential for treating bacterial infections, is often accompanied by adverse effects, including disruption of the gut microbiota and the development of antibiotic-associated diarrhea (AAD). Probiotics, live microorganisms that confer health benefits when administered in adequate amounts, have been proposed as a supportive treatment during antibiotic therapy to mitigate these side effects. This review explores the potential benefits and risks of using probiotics alongside antibiotics, with a focus on their role in maintaining or restoring the balance of the gastrointestinal microbiota, preventing dysbiosis, and reducing the incidence of AAD. Studies have shown that probiotics may also exert direct or indirect antimicrobial effects, enhancing the efficacy of antibiotic therapy and potentially aiding in the eradication of pathogens such as *Helicobacter pylori*. However, the efficacy of probiotics varies depending on the strain used, the type of antibiotic administered, and the patient's health status. Despite promising results, the use of probiotics is not without risks, such as the potential for infections in immunocompromised individuals. This paper discusses the mechanisms through which probiotics exert their effects, reviews the latest clinical evidence, and highlights the need for further research to better understand their optimal use in conjunction with antibiotic therapy.

Introduction: Antibiotic therapy, while effective in combating bacterial infections, can disrupt the gut microbiota, often leading to antibiotic-associated diarrhea (AAD). In this context, probiotics have been explored as potential adjuncts to alleviate these adverse effects.

Research indicates that using probiotics during antibiotic treatment may reduce the risk of AAD. For instance, a meta-analysis by Szajewska and Kołodziejczyk found that probiotics decrease the likelihood of AAD in adults, with higher doses being more effective than lower ones. [1]

However, the efficacy of probiotics in protecting the diversity of the gut microbiome during antibiotic therapy remains controversial. A systematic review and meta-analysis conducted by Matuskova et al. suggest that probiotic supplementation does not significantly prevent the reduction of gut microbiota diversity caused by antibiotics. [2]

Moreover, concerns about the safety of probiotics have been raised, particularly regarding the potential transfer of antibiotic resistance genes. A systematic review by Zhang et al. highlights the need for further research to evaluate the risks associated with the spread of antibiotic resistance through probiotic strains. [3]

Therefore, while probiotics may offer certain benefits as adjuncts to antibiotic therapy, it is essential to carefully consider the associated risks and conduct further studies to fully understand their impact on patient health.

Aim of study: The aim of this study is to evaluate the role of probiotics as adjuncts to antibiotic therapy, particularly in mitigating the adverse effects associated with antibiotic use, such as antibiotic-associated diarrhea (AAD) and disturbances in the gut microbiota. Specifically, this study seeks to assess the efficacy of probiotic supplementation in maintaining gut microbiome diversity during antibiotic treatment and its potential to reduce the incidence and severity of AAD. Additionally, the study aims to examine the safety concerns surrounding the use of probiotics, including the risk of antibiotic resistance gene transfer, and to provide insights into the optimal strains and dosages for maximizing the benefits of probiotics in clinical practice. Through a comprehensive review of the current literature, this study aims to contribute to a better understanding of the therapeutic potential and limitations of probiotics in supporting gut health during antibiotic therapy.

Keywords: Probiotics, Antibiotics, Gastrointestinal microbiome

Probiotics

What is it?

The concept of "probiotic" originates from the Greek language, meaning "for life." Since its initial introduction by Lilley and Stillwell in 1965, it was understood as a substance secreted by one microorganism to promote the growth of another. The term emerged as a counterpart to "antibiotic," and its original interpretation seemed straightforward. However, over time, its meaning evolved. In 1971, Sperti employed the term to describe tissue extracts that supported microbial growth. Another shift occurred in 1974 when Parker associated probiotics with intestinal flora, defining them as "organisms and substances that promote the maintenance of microbiological equilibrium in the intestines." To refine this definition further, Fuller in 1989 characterized probiotics as "live microbial feed supplements that positively affect the host by enhancing the intestinal microbial balance." [4,6]. Currently, probiotics are defined as live microorganisms which, when administered in appropriate quantities, confer specific health benefits to the host, including the improvement of intestinal microbial balance, bolstering of the immune system, and support for metabolic health. This evolution of the definition reflects the growing importance of scientific research in understanding their mechanisms of action [5,7].

How do probiotics work?

The human gastrointestinal tract, with its extensive surface area of approximately 150–200 m², represents an extraordinarily complex ecosystem that facilitates the adhesion and colonization of microorganisms. This vast surface is the result of structural adaptations, including circular folds, villi, and microvilli, which significantly enhance its absorptive capacity [8]. Gastrointestinal disorders frequently stem from imbalances or disruptions within the gut microbiota, as revealed through research into probiotic mechanisms. Consequently, probiotics are defined as live cultures of microorganisms that restore microbial balance, support intestinal health, and counteract associated dysfunctions. Contemporary studies continue to validate the efficacy of both viable and non-viable microbial cultures in promoting gastrointestinal well-being [9]. Although probiotic microorganisms are widely recognized for their health benefits, the precise mechanisms underpinning their effects remain incompletely understood. Beyond their technical characteristics, attributes that promote and sustain health are crucial criteria for selecting appropriate strains [10]. The functionality of probiotics relies on their capacity to maintain microbiota equilibrium and interact with the host. Probiotics compete with pathogens for adhesion sites within the gut, thereby reducing pathogenic colonization. Additionally, they produce antimicrobial compounds that inhibit pathogen growth, while supporting the integrity

of the intestinal barrier to minimize permeability and shield against the translocation of harmful substances [10,11].

Probiotic Bacteria

In probiotic preparations, microorganisms commonly used belong to genera such as *Lactobacillus*, *Bifidobacterium*, *Streptococcus*, and *Lactococcus*, as well as certain strains of fungi. Foods that primarily contain lactic acid bacteria include fermented dairy products, cheeses, fruit juices, wine, and meat products like sausages. Probiotic preparations can consist of both single and mixed cultures of live microorganisms [12]. According to Fuller, probiotics are live microorganisms added to food that support the host's health by improving intestinal microflora balance. To be effective, they must originate from humans, survive the challenging conditions of the gastrointestinal tract (such as low pH and digestive enzymes), function in the large intestine, adhere to intestinal epithelial cells, and provide clear health benefits. Additionally, they need to maintain their stability and viability both during storage and under unfavorable environmental conditions, such as low pH, digestive enzymes, or other factors inhibiting growth or adhesion [4,5].

Potential risks and limitations of using probiotics

The safety and risk of adverse effects associated with probiotics depend not only on the strain but also on the product's components. A report from the World Health Organization (WHO) and the Food and Agriculture Organization (FAO) published in 2002 indicates that probiotics can potentially lead to systemic infections, adverse metabolic effects, and excessive immune system stimulation in susceptible individuals [13]. Species such as *Lactobacillus*, *Bifidobacterium*, and *Lactococcus* are classified by the FDA as "Generally Recognized as Safe" (GRAS), whereas others, such as *Streptococcus* and *Enterococcus*, do not possess this status despite their use as probiotics. The safety assessment of probiotic strains takes into account their origin, antibiotic resistance, and non-pathogenicity, as well as their infectivity, toxicity, and the risk of excessive immune system stimulation [14].

Systemic Infections

Bacterial strains present in probiotics may penetrate through a compromised intestinal barrier, potentially leading to endocarditis and bacteremia, which can consequently result in multi-organ failure and sepsis. It has also been observed that bacteria from probiotic formulations can cause dental caries, urinary tract infections, meningitis, and splenic abscesses [14]. A study was conducted to evaluate the safety of probiotics in critically ill patients, particularly those with acute pancreatitis. The results indicated that although the incidence of infectious

complications was similar between the probiotic and placebo groups, mortality was significantly higher in the probiotic group (16% vs. 6%). Additionally, there were more reported cases of bowel ischemia and signs of intestinal damage. Despite probiotics reducing overall bacterial translocation, there was an increase in translocation in patients with organ dysfunction. The cause of bowel ischemia in this study population was hypothesized to be due to increased oxygen demand in the intestinal mucosa under conditions of reduced blood flow. Another hypothesis suggested that probiotics might have triggered a severe inflammatory response in the small intestine, leading to decreased blood flow in the capillaries. This suggests that probiotics may be beneficial for moderately ill patients but potentially harmful for those in critical condition. [13,15]

Adverse Metabolic Actions

Probiotic bacteria may increase the risk of cholestasis and colorectal cancer due to their production of bile salt hydrolase (BSH). This enzyme facilitates the dehydroxylation of bile salts, which can accumulate in the organism and be converted into harmful secondary bile acids (<https://pmc.ncbi.nlm.nih.gov/articles/PMC7256845/>). D-lactic acidosis has been documented in five patients, one of whom presented with short bowel syndrome [13].

Intestinal microbiota can also modulate drug toxicity. One example of this mechanism is glucuronidation—a process in which glucuronic acid, through the action of the enzyme UDP-glucuronosyltransferase, conjugates with a drug to form soluble glucuronides. Certain anaerobic bacteria produce the enzyme β -glucuronidase, which hydrolyzes these conjugated compounds. Such hydrolysis may lead to increased recirculation of toxins, hormones, and drugs within the enterohepatic circulation, thereby contributing to the formation of local carcinogenic factors. Excessive β -glucuronidase activity may elevate the risk of colorectal cancer, although a certain level of this enzyme is essential for the recirculation of compounds such as vitamin D, thyroid hormones, and estrogens. [16]

Excessive Stimulation of the Immune System

Probiotic strains can induce alterations in the immune system, leading to increased sensitivity of the organism to vaccines and allergens, which may consequently result in adverse effects. Probiotics influence both cellular and humoral immune responses, as well as stimulate cytokine production. Certain components of bacterial cell walls can elicit symptoms such as fever or arthritis [14,17]. Whether probiotics exert protective or detrimental effects, and whether they stimulate or suppress the immune system, depends on the interplay between microbiological signals, the host genotype, and environmental factors [15].

Gene Transfer

The use of probiotics carries certain risks, including the potential transfer of antibiotic resistance genes between probiotics and other gut microbiota as well as pathogens. Some probiotic strains, such as species of *Lactobacillus*, are naturally resistant to various classes of antibiotics, including aminoglycosides, monobactams, and fluoroquinolones [14]. Furthermore, lactic acid bacteria may harbor plasmids containing genes responsible for resistance to tetracycline, erythromycin, chloramphenicol, lincosamides, macrolides, streptomycin, and streptogramins. Currently, these observations are theoretical due to the lack of clinical studies that could validate them. [13].

Additionally, the transfer of the vancomycin resistance gene, *vanA*, from *Enterococcus* to *Lactobacillus acidophilus* has been documented in an animal model, providing evidence for the possibility of in vivo transfer [15].

The levels of antibiotic resistance gene transfer from probiotics to other gut bacteria represent a scientifically confirmed threat that warrants attention from both researchers and regulatory bodies. The assessment of this risk should adopt both genotypic and phenotypic approaches, analyzing gene mobility, expression, and clinical significance. Even low transmissibility, such as through transformation from dead cells, can have significant consequences. Special caution should be exercised regarding antibiotic resistance genes deemed critical by the WHO. A review of older probiotic strains and their alignment with current safety standards is essential [16].

The Use of Probiotics During Antibiotic Therapy

The use of probiotics during antibiotic treatment has a beneficial effect on both the digestive and immune systems, helping to reduce the risk of complications associated with antibiotics. One of the most common issues is antibiotic-associated diarrhea (AAD), particularly following the use of broad-spectrum antibiotics. The main goal of probiotic therapy is to restore gut microbiota, strengthen the natural barrier, and reduce the risk of pathogenic and harmful microorganism overgrowth. The articles reviewed below focus on evaluating the effectiveness of probiotics and providing recommendations for their use.

The review article “Probiotics for the Prevention of Antibiotic-Associated Diarrhea” by Kira Kopacz and Sangita Phadtare explores the use of probiotics in the prevention of AAD. The authors discuss both the pathophysiological basis of this condition and clinical data on the effectiveness of various probiotic strains.

The aim of the article is to present the current state of knowledge regarding probiotics as a preventive measure against AAD, explain their mechanisms of action, identify the most effective strains, and discuss safety and practical application, along with clinical guidelines. The authors note that AAD can affect up to 30% of patients and is caused by disruption of the intestinal microbiota, weakening of colonization resistance, and overgrowth of pathogens such as *Clostridioides difficile*. Probiotics exert a protective effect through several mechanisms: they enhance intestinal immunity by increasing IgA production and activating macrophages, support the regeneration of the intestinal epithelial barrier, and regulate the microbial composition. They also improve water absorption and inhibit pathogen colonization by competing for adhesion sites and producing bactericidal substances.

Randomized trials and meta-analyses indicate that probiotics can reduce the risk of AAD by approximately 51%. The most thoroughly studied and effective strains include *Lactobacillus rhamnosus* GG, *Saccharomyces boulardii*, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, *Bacillus subtilis*, and *Streptococcus faecium*. Probiotics also show potential in preventing infections and recurrences of *C. difficile*-associated diarrhea, particularly in hospitalized and elderly patients.

While probiotics are generally considered safe, the authors highlight the risk of side effects, especially in immunocompromised patients. These may include systemic fungal infections with *Saccharomyces cerevisiae* or sepsis from certain *Bifidobacterium* strains. Therefore, the choice of strain, proper dosage (typically $\geq 10^9$ CFU/day), and simultaneous initiation with antibiotic treatment are crucial.

The article also notes the lack of globally consistent guidelines for the use of probiotics in AAD prevention. For instance, the American Gastroenterological Association (AGA) supports specific strains for this use, while the American College of Gastroenterology (ACG) advises against their use in *C. difficile* infections. In Canada, strains like *L. rhamnosus* GG and *S. boulardii* are recommended for children.

The authors conclude that probiotics may be an affordable, accessible, and potentially effective method to prevent AAD, but further research is needed on dosage, long-term safety, and optimal strain selection for different patient groups. They also emphasize the need for standardized quality control of probiotic supplements, proper labeling, and education for healthcare providers and patients [18].

The article “A Complementary Medicine Approach to Augmenting Antibiotic Therapy: Current Practices in the Use of Probiotics During Antibiotic Therapy” by Nicholas A. Kerny and Tony

L. Brown examines the use of probiotics during antibiotic treatment as a method to reduce side effects such as AAD, *C. difficile* infections (CDI), and *Candida* overgrowth.

This article aims to review clinical practices related to probiotics during antibiotic therapy and provide practical recommendations for dosage and timing. Probiotics may reduce the risk of AAD by up to 42%. Despite growing interest, there is still a lack of standardized protocols for combining probiotics with antibiotics. It is generally recommended to take probiotics 2–6 hours after the antibiotic and to continue their use for 7–10 days after finishing the antibiotic course. However, no specific strains or doses have been universally established, complicating the creation of standard guidelines.

The authors also point out the issues related to the lack of regulation of probiotics as drugs (e.g., no FDA oversight) and the varying quality of products. In immunocompromised patients, probiotics may cause adverse effects. Moreover, the lack of reimbursement and pharmaceutical documentation makes it difficult to monitor actual probiotic use.

In conclusion, probiotics may serve as a valuable support in antibiotic therapy, particularly for preventing AAD and fungal infections. However, more research and formal guidelines are needed to ensure their widespread, safe, and effective use [19].

Benefits of Probiotics During Antibiotic Therapy

Probiotics are live microorganisms that, when administered in adequate amounts, provide a health benefit to the host. One of the conditions for which probiotics have been widely recommended is antibiotic-associated diarrhea (AAD), a frequent adverse effect of antibiotic therapy. The aggregated evidence suggests that probiotics may be effective in reducing the incidence of AAD. However, further research is required to identify the specific probiotics with the greatest therapeutic efficacy and to determine their effectiveness in different patient populations and in conjunction with various antibiotics. [20]

Probiotics may help maintain or restore gut microbiota homeostasis during or following antibiotic treatment through several mechanisms. These include competitive exclusion for receptor binding sites and nutrients, inhibition of pathogen adherence to epithelial and mucosal surfaces, modulation of colonic pH to favor nonpathogenic bacterial species, enhancement of immune responses, and the production of antimicrobial substances. [21]

Antibiotics are frequently utilized in the eradication therapy of *Helicobacter pylori* (*H. pylori*) infections. However, the increasing prevalence of antibiotic resistance and the associated adverse effects have led to a significant decline in the success rates of eradication treatments. Recent research suggests that probiotic supplementation may offer promising potential in this

context. Probiotics have been shown to help restore the balance of the gastrointestinal microbiota, which may be disrupted by antibiotic therapy, thereby preventing dysbiosis. Additionally, emerging evidence indicates that probiotics may exert direct or indirect inhibitory effects on *H. pylori*, thereby contributing to the success of eradication therapy. Consequently, probiotics may play a beneficial role in improving outcomes of *H. pylori* eradication. [22]

Conclusions

In light of current evidence, the use of probiotics as adjuncts to antibiotic therapy appears to offer clinically significant benefits, particularly in the prevention of antibiotic-associated diarrhea and *Clostridioides difficile* infections. Probiotics contribute to the restoration of intestinal homeostasis disrupted by antibiotics through modulation of the gut microbiota, reinforcement of mucosal barrier integrity, and immunomodulatory activity. However, their administration is not devoid of risk, especially in immunocompromised individuals, critically ill patients, or those with compromised intestinal perfusion. Reports of bacteremia, D-lactic acidosis, and bacterial translocation across damaged intestinal epithelium underscore the necessity for careful clinical evaluation and patient-specific therapeutic decisions. Furthermore, the potential for horizontal transfer of antibiotic resistance genes from probiotic strains to commensal or pathogenic gut flora constitutes a significant concern from both epidemiological and therapeutic perspectives. Despite promising results from clinical trials, there remains a lack of standardized guidelines regarding optimal probiotic strains, dosages, and duration of use, limiting the routine implementation of probiotics in clinical practice. Therefore, further high-quality randomized controlled trials and translational research are essential to establish precise recommendations and ensure both the safety and efficacy of probiotic supplementation in the context of antibiotic treatment.

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