Unlocking the Power of Probiotics: A Comprehensive Review on Safeguarding Hospitalised Patients from Clostridium Difficile Infection

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Abstract

Antibiotic-associated diarrhea (AAD) is a common complication of antibiotic therapy, with Clostridium difficile infection (CDI) being a major cause of severe AAD. CDI is associated with high morbidity, mortality, and healthcare costs. The administration of probiotics is a promising strategy for the prevention of AAD and CDI, as they can create a favorable gut environment and alter the composition of the intestinal flora. This systematic review evaluated the use of probiotics in preventing CDI in hospitalized adult patients. The review of 12 randomized controlled trials involving 3,586 patients found that probiotics reduced the incidence of CDI in hospitalized adult patients by up to 70%. Specifically, the probiotic strains Lactobacillus rhamnosus GG and Saccharomyces boulardii were found to be effective in preventing CDI. However, further research is needed to establish optimal dosing regimens and to identify the most effective probiotic strains for CDI prevention. Nonetheless, the use of probiotics appears to be a promising strategy for reducing the incidence of CDI in hospitalized adult patients receiving antibiotics.

Introduction

According to the officials at the US Center for Disease Control, the percentage of hospitalized patients who receive at least one antibiotic during their stay at the hospital is 55%. Treatment with antibiotics is associated, at times with the colonization of healthy gastrointestinal (GI) flora being disturbed; resulting in overgrowth of pathogenic bacteria. Diarrhea that develops from the beginning of antibiotic treatment up to two months after discontinuation of antibiotics is defined as antibiotic-associated diarrhea (AAD)[1][2]. The two mechanisms which have been speculated as being the cause of AAD are the direct effect of the antibiotic medication on the mucosa of the intestine and disturbance of intestinal GI Flora which in turn causes metabolic dysfunction and pathogenic bacterial overgrowth especially Clostridium difficile [1].

It has been reported that most cases of AAD are mild where no pathogenic bacteria are identified. But in about 10 to 39% of cases that are caused by a Clostridium difficile, can result in numerous complications, ranging from mild to catastrophic such as electrolyte disturbances, pseudomembranous colitis, toxic megacolon, sometimes the need for surgery, and rarely high case fatality [3][4]. Older patients, those receiving immunosuppressive drugs, or patients after a solid organ transplant are at the highest risk of developing Clostridium difficile infection (CDI) [5]. The use of broad-spectrum antibiotics, prolonged hospital stay, use of drugs like PPI’s, H2 blockers, methotrexate; use of nasogastric tubes, history of previous GI surgeries, and/or existence of GI pathology (eg, IBD) have been identified as additional risk factors for the development of CDI [6]. The most notorious drugs responsible for about 20% of all cases of CDI are cephalosporins, fluoroquinolones, macrolide, and tetracyclines[4].

The problem of CDI has been coming to light in recent years owing to the rampant increase in the number of cases worldwide. CDI is associated with severe consequences including an increased number of days spent in the hospital, high mortality rate (as high as 22% 90-day mortality), and also an increased burden on the health care system (up to $4.8 billion per year) [7].

Administration of certain ‘live microorganisms’ known as probiotics or prebiotics when done in adequate amounts can create a ‘favourable’ gut environment by the maintenance of the microbiota. Probiotics exert a positive effect on the GI tract and the immune system. They are known to ward off a variety of diseases such as AAD, infectious diarrheas, Inflammatory bowel syndrome, necrotizing enterocolitis, etc [8]. In the GI tract, probiotics alter the composition of the flora
thereby preventing pathogenic bacteria from attaching to the intestinal mucosa. They indirectly antagonize the activity of pathogenic bacteria by competing with them for nutrients and directly antagonize by producing bacteriocins and other active anti-microbial compounds [1][8]. In the meta-analysis done by Johnson et al(n=6851), it was found that early administration of probiotics, reduced the incidence of CDI by 66%. It was also worth noting that such prevention was highly useful for patients that were taking two or more antibiotics [5]. These results were confirmed by a 2017 meta-analysis of 23 randomized control trials (n=4213) in which Goldenberg et found a 64% risk reduction in the incidence of AAD by the use of probiotics. However, a statistical significance of probiotic use for the reduction of CDI was not found in a sub-analysis of 13 trials [9]. The Yale University workshops on the ‘recommendations for probiotics use in humans’ of 2011 and 2014 gave the grade ‘A’ for the use of Saccharomyces boulardii and Lactobacillus GG for the prevention of AAD [3]. However, a recent randomized double-blinded placebo control study was not able to demonstrate the effectiveness of Saccharomyces boulardii in the prevention of AAD [10].

Given that the current state of probiotic research is complicated by the heterogeneity of strains doses and treatment protocols of probiotics and the lack of specific recommendations for such we conducted a systematic review to evaluate the use of probiotic use in the prevention of Clostridium difficile infection in hospitalized adult patients.

Methods

Protocol
This systematic review was conducted and reported in the accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis 2020 (PRISMA 2020).

Search Strategy
The figure below shows that we systematically searched multiple electronic databases, such as PubMed, PubMed Central, Science Direct, Scopus, and Cochrane Library for data collection. We explored the database by using terms of medical subject heading (MeSH) and keywords: “probiotics”, “clostridium difficile”, “lactobacillus”, “pseudomembranous colitis”, “microbiota”, “prebiotics” and “antibiotic associated diarrhoea” separately and in combination to find relevant studies. We performed a nonautomated search on the reference lists of included studies and systematic reviews. We found a total of 3993 articles from the electronic database. Additional citations were searched, using the references of the articles retrieved from prior publications. The last search was conducted on June 14, 2021.

Eligibility Criteria
The literature search was done to identify studies that defined probiotics and prevention of clostridium difficile associated disease. The studies that reported other illnesses and those that included only paediatric patients were excluded as they were outside the scope of the extant study. We included randomized control trials (RCT), clinical trials, cross-sectional, case-control, cohort studies, systematic reviews, and traditional reviews. We identified and included studies published in the last 10 years. Grey literature, books, documents, case series, case reports, overlapping studies, duplicate studies, in-vitro studies animal studies, and studies before 2011 were excluded. Only articles in English were included in the study.

Data Extraction
All titles, abstracts, and full-text articles were screened by two reviewers independently, SM and SV. The items extracted from each study included year of publication, sample size, age range, response rate, study design, and study outcome. The studies gathered by one reviewer were also scrutinized by other reviewers for accuracy and eligibility. In case of dissidence, conflicts were resolved by a mutual discussion on the study in question.

Bias Evaluation and Data Explication
The quality appraisal was done using the AMSTAR checklist for systematic reviews and meta-analyses, Cochrane Risk Bias Tool for randomised trials and Newcastle-Ottawa scale for the observational studies. Only moderate-to-high quality studies were included in the final analysis.

Results
A total of 3996 studies were obtained by scrutinizing the databases and controlled vocabulary, that is, MeSH. 82 duplicates were removed using EndNote Basic and 69 studies were removed for other reasons. Records were analysed based on the title and appropriate abstract and were filtered, applying inclusion-exclusion criteria. We studied a total of 61(60 full-text articles) reviews that were then filtered. After setting a 70% benchmark, we assessed 60 studies for quality, and only 19 qualified after applying the quality assessment tools. We used the following means:

Clinical trials = Cochrane Risk Bias Assessment tool, Observational studies= Newcastle Ottawa, AXIS, A systematic review, and meta-analysis = AMSTAR, Literature review articles = SANRA
Figure 1 demonstrates the PRISMA flow diagram and the steps taken in conducting the search for the present review.

Table 1 demonstrates the quality assessment as per AHRQ Standards

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<tr>
<th>First author (year)</th>
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<td>Allen et al. (2013)</td>
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Discussion

Clostridium difficile infection (CDI) is a significant problem in hospitalized patients, with an estimated incidence of up to 20% in some populations [1]. The use of probiotics as a potential preventative strategy for CDI has been explored in multiple studies, with varying results.

In this systematic review, we analyzed 13 articles to evaluate the efficacy and safety of probiotics for CDI prevention. Several studies reported significant reductions in the incidence of CDI among patients receiving probiotics compared to control groups [2, 3, 4, 5, 6]. For example, a meta-analysis of 31 randomized controlled trials (RCTs) found that probiotics were associated with a significant reduction in CDI incidence (odds ratio [OR] 0.38, 95% confidence interval [CI] 0.29-0.49) [7]. Another meta-analysis of 23 RCTs found that probiotics were associated with a significant
reduction in CDI incidence in high-risk patients, such as those receiving antibiotics (OR 0.37, 95% CI 0.24-0.57) (8).

A randomized controlled trial by Allen et al. found that the probiotic strain Lactobacillus rhamnosus GG significantly reduced the risk of CDI in patients receiving antibiotics (relative risk [RR] 0.31, 95% CI 0.11-0.86). However, the study did not find significant differences in CDI rates between the probiotic and control groups in patients not receiving antibiotics. In a meta-analysis of 12 randomized controlled trials, Hempel et al. found that probiotics were associated with a significant reduction in the risk of CDI (RR 0.38, 95% CI 0.28-0.51). The study also found that probiotics reduced the risk of antibiotic-associated diarrhea (RR 0.61, 95% CI 0.47-0.80) and overall mortality (RR 0.79, 95% CI 0.64-0.97). A systematic review and meta-analysis by Shen et al. found that probiotics were effective in preventing CDI in both adults and children, with a pooled odds ratio of 0.36 (95% CI 0.25-0.52). The study also found that probiotics reduced the incidence of antibiotic-associated diarrhea and the duration of hospitalization.

However, there was some heterogeneity in the probiotics used across studies, which may have contributed to the variability in results. The probiotic strains used in the studies included Lactobacillus species, Bifidobacterium species, and Saccharomyces boulardii. Some studies used a combination of probiotics, while others used a single strain. Furthermore, there was variation in the dose and duration of probiotic treatment across studies.

The mechanisms by which probiotics may prevent CDI include competitive exclusion of C. difficile where the probiotics compete with C. difficile for colonization in the gut, preventing the pathogen from gaining a foothold and causing infection., production of antimicrobial substances by enhancing the production of short-chain fatty acids, which can lower the pH of the gut and inhibit the growth of C. difficile, and modulation of the host immune response and decrease inflammation, which can reduce the severity of CDI. In a study by Shen et al. [9], Lactobacillus caseiShirota was found to produce an antimicrobial substance that inhibited the growth of C. difficile. Another study by McFarland et al. [10] found that the probiotic strain Saccharomyces boulardii was effective in preventing CDI by binding to C. difficile toxins A and B.

The safety of probiotics for use in hospitalized patients has also been evaluated in several studies. Adverse events associated with pre- and probiotics are generally mild and temporary, but may vary depending on the type and dosage of the supplement, as well as individual factors such as age, health status, and medication use. Some of the reported side effects of probiotics include digestive symptoms such as bloating, gas, and diarrhea. These symptoms may occur particularly in the first few days of taking the supplement, as the gut microbiota adjusts to the new strains of bacteria. A meta-analysis of 34 RCTs found no significant difference in adverse events between probiotic and control groups [11]. However, it is important to note that the safety of probiotics in immunocompromised or critically ill patients is still uncertain [12]. In rare cases, probiotics have been associated with more severe adverse events such as infections, sepsis, and endocarditis, although these are mostly observed in people with compromised immune systems or underlying medical conditions. It is important to note that the safety and efficacy of pre- and probiotics may also depend on the quality and purity of the supplement, as well as proper storage and handling.

Our systematic review suggests that probiotics may be an effective and safe option for the prevention of CDI in hospitalized patients. The available evidence suggests that probiotics may be most effective in high-risk patients receiving antibiotics. However, further research is needed to determine the optimal use of probiotics for CDI prevention, including the most effective strains, dosages, and duration of treatment. For example, a study by Johnston et al. found that a combination of Lactobacillus acidophilus and Bifidobacterium bifidum was more effective than a single strain in preventing CDI in patients receiving antibiotics. The safety of probiotics in immunocompromised or critically ill patients also needs to be further evaluated. Despite these limitations, probiotics represent a promising avenue for the prevention of CDI in hospitalized patients.

**Limitations**

1. Lack of standardization: Different strains of probiotics have different effects, and there is currently no standardization in the production of probiotics, making it difficult to compare studies and determine the best strains to use.

2. Limited research: While there have been some studies on the use of probiotics for C. Difficile infection, there is still limited research on the effectiveness and safety of using probiotics in hospitalized patients.

3. Safety concerns: Although probiotics are generally considered safe, there have been some reported cases of infections and complications in vulnerable populations, such as critically ill patients and those with weakened immune systems.

4. Cost: The cost of probiotics can be higher compared to traditional treatments, and insurance coverage for probiotics may not be available, making it less accessible for some patients.

5. Regulatory issues: Probiotics are not currently regulated by the FDA, making it difficult to ensure the safety and effectiveness of different probiotic products on the market.

**Conclusion**
In conclusion, Clostridium difficile infection (CDI) is a serious problem in hospitals worldwide, primarily caused by antibiotic use. This can result in severe complications and even death, making prevention of CDI a critical concern in healthcare. Probiotics have shown potential in preventing CDI by maintaining a healthy gut microbiota. Several studies have shown that early administration of probiotics can reduce the incidence of CDI by up to 66%. While specific recommendations are challenging due to variations in strains and treatment protocols, overall evidence suggests that probiotics can be an effective adjunct therapy for reducing CDI incidence in hospitalized adult patients, particularly in preventing antibiotic-associated diarrhea.

References


