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Editorial

Unlocking the Power of Probiotics: A Comprehensive Review on Safeguarding Hospitalised Patients from Clostridium Difficle 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 difficle, 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, a 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 boulardiiand 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 difficle 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.

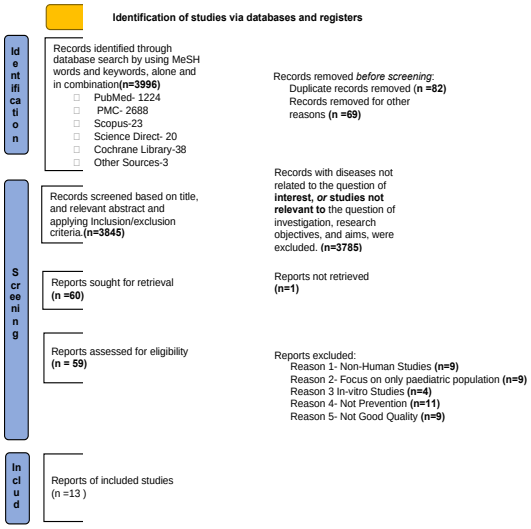

Table 1 demonstrates the quality assessment as per AHRQ Standards

First author (year)	AHRQ Standards
Allen et al. (2013)	Good Quality
Selingeret al. (2013)	Good Quality
Ehrhardtet al. (2016)	Good Quality
Johnson et al. (2012)	Good Quality
Pattani et al. (2013)	Good Quality
McFarland et al. (2015)	Good Quality
Lau et al. (2016)	Good Quality
Shen et al. (2017)	Good Quality
Goldenberg et al. (2017)	Good Quality
Agamennone et al. (2018)	Good Quality
Liao et al. (2021)	Good Quality
SylwiaDudzicz (2018)	Good Quality
Ravi Mallina (2018)	Good Quality

Type of study	Age group	Number (enrolled/completed)	Probiotic (composition)	AAD in treatment group	AAD in control group	Significant difference treatment-control	RR
randomized, placebo-controlled, double-blind	elderly (>65 y)	2981/2941	*Lactobacillus acidophilus* CUL60, *Lactobacillus acidophilus* CUL21, *Bifidobacteriumbifidum* W23, *Bifidobacteriumlactis* CUL34 - CUL20	159/1470 (10.8%)	153/1471 (10.4%)	NO	1.04
randomized, placebo-controlled, double-blind	adults (57 years average)	229/122	*Bifidobacterium breve* BB02, *Bifidobacteriumlongum* BL03, *Bifidobacteriuminfantis* BI04, *Lactobacillus acidophilus* BA05, *Lactobacillus plantarum* BP06, *Lactobacillus paracasei* BP07, *Lactobacillus delbrueckiisubspbulgaricus* BD08, *Streptococcus thermophilus* BT01	5/117 (4.3%)	10/112 (8.9%)	NO	0.48
randomized, placebo-controlled, double-blind	adults (58 years average)	477/292	*Saccharomyces cerevisiae varboulardii (S boulardii)*	16/146 (11%)	11/146 (7.5%)	NO	1.02

First Author/Year of Publication	Study Type	Results/Outcome	Conclusion
Johnson et al. 2012	Systematic review & Meta Analysis	A meta-analysis of 3 studies using the same probiotic (5×1010 CFU L. acidophilus CL1285 and L. casei LBC80R), demonstrated a statistically significant difference between those taking the probiotic and those receiving a placebo (RR 0.21, 95% CI 0.11–0.42, p 0.001). Though there was a lot of variation in the research design and prevalence of CDI, the impact estimate was quite homogeneous. A meta-analysis of the 4 studies that used S. boulardii showed a trend towards lower CDI rates in the probiotic group, but this finding was not statistically significant (RR 0.70, 95 % CI 0.29–1.69) and there were higher levels of heterogeneity in the probiotic group than in the control group (I2 17.2 percent; p = 0.30). There was a combined overall effect of lower CDI rates among antibiotic recipients receiving probiotics compared to those receiving placebo (RR 0.39, 95% CI 0.19–0.79; heterogeneity of the effect estimate: I2 = 33.9 percent ; p = 0.17), according to a meta-analysis of all seven studies.	The L. acidophilus + L. casei formulation has a consistent and substantial impact, and S. boulardii preparations had a trend towards being helpful; the combined total effect demonstrated considerable protection from CDI
Pattani et al. 2013	Systematic review & Meta Analysis	Meta-analysis shows a statistically significant reduction in the risk of AAD (RR 0.61, 95% CI 0.47 to 0.79; I2= 39%; RD –0.09, 95% CI–0.13 to –0.05; NNT to benefit 11, 95% CI 8 to 20). For CDI, the event rates were 18 (3.1%) of 572 patients in the intervention arm and 55 (10.4%) of 527 patients in the placebo arm (RR 0.37, 95% CI 0.22 To 0.61; I2= 0%; RD –0.07, 95% CI –0.11 to –0.02; NNT to benefit 14, 95% CI 9 to 50). AAD and CDI decreased regardless of whether a Lactobacillus-based or S. boulardii based formulation was employed. It was shown, however, that only combined studies of formulations based on Lactobacillus exhibited statistically significant decreases.	For the specific patient population of adult inpatients requiring antibiotics, the data highlights the advantages of probiotics for avoiding AAD and CDI. These individuals can benefit from probiotic treatment if there are no contraindications. Despite the fact that Lactobacillus-based formulations have a better track record, the research does not clearly suggest which probiotic is preferred
McFarland et al. 2015	Systematic review & Meta Analysis	According to the pooled data, there was little heterogeneity across the 23 treatment arms of probiotics and controls (I2 = 17.2%, p = 0.23), therefore the fixed-effect model was adopted. Four of the tested probiotics were significantly effective for primary CDI prevention: S. boulardii (pRR = 0.50, 95 %CI 0.29, 0.85), L. casei DN114001 (pRR = 0.05, 95%CI 0.01, 0.55), a mixture of Lactobacillus acidophilus and Bifidobacteriumbifidum (pRR = 0.41, 95% C.I. 0.21, 0.80), and the mixture of L. acidophilus and L. casei and L. rhamnosus (pRR = 0.21, 95% C.I. 0.11, 0.40). The pooled results for L. rhamnosus GG did not reach statistical significance. The pooled results indicated a moderate degree of heterogeneity (I2 = 35.4%, p = 0.17), so a fixed-effect model was used. Neither S. boulardii nor L. rhamnosus GG was significantly efficacious for secondary CDI prevention.	In the primary prevention of CDI, four distinct kinds of probiotics have been proven to be beneficial (S. boulardii, L. casei DN114001, the mixture of L. acidophilus and Bifido. bifidum and the mixture of L. acidophilus, L. casei and L. rhamnosus). A meta-analysis of secondary prevention of CDI could only be performed on two kinds of probiotics (S. boulardii and L. rhamnosus GG), however none of the pooled results approached statistical significance.
Lau et al. 2016	Systematic review & Meta Analysis	Comparatively, less than half (62/4124 [1.5%]) of patients in the probiotics group had CDI as opposed to 145/3833 [3.8%] in the placebo or no supplement group. A fixed-effects model was adopted since there was no significant heterogeneity between the trials (P=0.751, I2=0.000). The probiotics group had a substantially reduced chance of developing CDI than the control group, according to a meta-analysis. (RR =0.395; 95% CI, 0.294–0.531; P<0.001). Subgroup analysis identified Lactobacillus, Saccharomyces, or a mixture of probiotics were beneficial in reducing the incidence of CDI (RR =0.363; 95% CI, 0.225–0.585; P,0.001 for Lactobacillus; RR =0.415; 95% CI, 0.217–0.796; P=0.008 for Saccharomyces; and RR =0.418; 95% CI, 0.263–0.664; P,0.001 for mixed probiotics). Hospitalized patients were more likely to benefit from probiotic use compared to outpatients (RR =0.390; 95% CI, 0.283–0.538; P,0.001 versus RR =0.306; 95% CI, 0.013–7.470; P=0.468).	Probiotic supplementation is a helpful complement in the regular treatment of patients undergoing antibiotic medication. Since CDI and CDI have high morbidity and mortality rates, probiotic supplementation's significant reduction in CDI rates and apparent lack of significant negative side effects should encourage physicians to consider these readily available, low-cost supplements as an effective and potentially routine therapy for patients receiving antibiotics.
Shen et al. 2017	Systematic review & Meta Analysis	The risk of CDI in the control group varied from 0% to 40%, whereas the risk in the probiotic group ranged from 0% to 11%. Using a random-effects model, the overall RR was 0.42 (95% CI, 0.30_0.57; P<001). There was no indication of statistically significant impact heterogeneity across the 19 trials (I2 =0.0%; P=0.56). Because the median incidence of CDI in the 19 studies' control groups was 4%, the RR for CDI of 0.42 translates to requiring to treat 43 (95% CI, 36-58) individuals with probiotics to prevent 1 case of CDI. The number needed to treat to prevent one incidence of CDI at the 25th percentile (1.2%) was 144. The NNT for baseline incidence at the 75th percentile (7.4%) was 23. To determine CDI efficacy, the time of probiotic treatment was important. Only one research permitted probiotics to be begun seven days following antibiotics. Whereas 18/19 studies initiated probiotics within 3 days of antibiotic use	It is clear that probiotics are effective in avoiding CDI among hospitalised individuals who are receiving antibiotics, and the study illustrates the necessity of probiotic delivery in a timely fashion. More effective are probiotics administered within 2 days of the initial antibiotic.
Goldenberg et al. 2017	Systematic review & Meta Analysis	The incidence of CDI in the probiotic group was 1.5% (70/4625) compared to 4.0% (164/4147) in the placebo or no treatment control group (RR 0.40, 95% CI 0.30 to 0.52; random-effects). As a result, 42 individuals (95 percent CI 32-58) would need to be treated to prevent one	Anecdotal data of moderate quality suggests a substantial preventive benefit of probiotics (e.g. S. boulardior L. acidophilus plus L. casei at a dose of 10 to 50 billion CFUs per day)
Agamennone et al. 2018	Systematic review & Meta Analysis	Probiotics were linked to a lower rate of AAD (467/3720 [13 %]) than the control group (648/3640 [18 %]) (RR 0.66, 95 percent CI 0.64–0.67). The incidence of AAD in studies utilising probiotic dairy products was 15.2 % compared to 27.5% in the control group (RR 1.01, 95 % CI 0.95–1.07). The incidence of diarrhoea in the probiotic group was 12.2 % compared to 16.3 % in the control group in studies using dietary supplements (i.e. non-dairy products) (RR 0.64, 95 % CI 0.63–0.65).	There is enough data to provide a recommendation for using particular probiotic bacteria and the study illustrates the necessity of probiotic delivery in a timely fashion. More effective are probiotics administered within 2 days of the initial antibiotic. A high rating was given to products that include a minimum daily dose of 2×10^ CFU of the probiotic strain Lactobacillus rhamnosus GG.
Liao et al. 2021	Systematic review & Meta Analysis	Since there was a lot of variability across the included trials (P<0.1, I2 = 58% >50%), a random effect model to obtain the overall AAD rate. It was shown that when compared to placebo, probiotics lowered the incidence of AAD by 38 percent (RR, 0.62; 95% CI, 0.51-0.74)	This meta-analysis suggests that early administration of probiotics has a positive and safe effect in preventing AAD in adults.

First Author/Year of Publication	Intervention	Study Population	Study Type	Results/Outcome
Sylwia Dudzicz et al. 2018	Lactobacillus plantarum 299v	patients hospitalized in the nephrology and transplantation ward over a three year period	Retrospective Observational Study	The results suggest LP299v, is effective in reducing the incidence of CDI in patients hospitalised in the nephrology and transplantation ward and receiving immunosuppresive therapy.
Ravi Mallina et al. 2018	probiotic yoghurt drink ACTIMEL (containing L. casei, L. bulgaricus, and S. thermophilus)	patients over the age of 70 years of age treated surgically for femoral neck fractures and who received more than 3 days of antibiotics for infection of any cause	Retrospective Observational Study	The results suggest ACTIMEL is not effective in reducing the incidence of CDI in elderly inpatients with femoral neck fractures receiving antibiotics for infection of any cause.

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 substancesby 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 Bifidobacteriumbifidum 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 ab vailable, 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.

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