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Probiotics in *Clostridium difficile* Infection

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Abstract

Clostridium difficile infection (CDI) is one of the most prevalent nosocomial infections. A dramatic increase in the incidence and severity of CDI has been noted in the past decade. Current recommendations suggest metronidazole as first-line therapy in mild to moderately severe CDI and oral vancomycin in individuals with severe CDI, or when metronidazole fails or is contradicted. Alterations of the colonic microbiota, usually caused by antimicrobial therapy, seem to play a critical role in CDI pathogenesis. Probiotics are live microorganisms that confer a health benefit to the host, and have been used in CDI. Although a wide variety of probiotics have been studied, the exact role of probiotics in preventing and treating CDI is not clear. In this study, we reviewed the current literature and recommendations on the most commonly studied protiotic agents (*Saccharomyces boulardii,* Lactobacillus species, and probiotic mixtures) used to prevent or treat CDI. Lactobacillus-containing probiotic mixtures and *S. boulardii* may be effective in the prevention of CDI in high-risk antibiotic recipients but this finding is based on small, individual studies, and further, larger, well-controlled studies are needed to confirm preliminary positive findings and to better delineate the efficacy of probiotics in CDI prevention or treatment.

Keywords

probiotics; *Clostridium difficile* infection; *Saccharomyces boulardii*

CLOSTRIDIUM DIFFICILE INFECTION

Clostridium difficile is a spore-forming, anaerobic, Gram-positive bacterium that causes gastrointestinal infection with diarrhea and colitis. *C. difficile* infection (CDI) is most prevalent in hospitals and nursing homes where patients frequently receive antibiotics, and represents one of the most common nosocomial infections. There has been a marked increase in the incidence and severity of CDI during the past decade. Recent studies report that nosocomial CDI substantially increases the cost of hospitalizations due largely to a 3-day to 4-day prolongation of hospital stay. As a result inpatient hospital costs of CDI total $1

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to $3 billion per annum in the United States.[1–3] The clinical outcomes of CDI range from asymptomatic carriage to mild diarrhea to fulminant, often fatal, pseudomembranous colitis.

Recurrent CDI is one of the most challenging aspects of the disease. Approximately 25% of patients treated for CDI with metronidazole or vancomycin experience recurrent symptoms, typically within 4 weeks of completing antibiotic therapy. Metronidazole is currently recommended as first-line therapy in mild to moderately severe CDI.[4–10] There are recent data to support the use of oral vancomycin as first-line treatment in individuals with severe CDI.[11] Oral vancomycin is also used in less severe disease if metronidazole therapy fails or is contraindicated. Owing to increasing incidence, rising death rates, and frequent recurrences, there is a substantial need for more effective approaches to CDI prevention and therapy. In this study, we will review the available data and recommendations on using probiotics to prevent or treat CDI.

COLONIZATION RESISTANCE AND CDI

A large and diverse community of microorganisms colonizes the gastrointestinal tract. However, recent studies indicate that, a limited number of ecosystems develop in humans each with a defined and balanced repertoire of inhabitants.[12] Colonization resistance is recognized as a mechanism whereby the intestinal microflora protects itself against incursion by new, potentially harmful microorganisms. Alterations of the microbiota of the human gastrointestinal tract have been recognized in several disease states including antibiotic-associated diarrhea (AAD) and inflammatory bowel disease.[13,14] It is believed that healthy adults are protected from *C. difficile* colonization and disease primarily by the colonization resistance conferred by their normal bacterial flora. A disturbed colonic microflora leads to a loss of colonization resistance and hence becomes vulnerable to CDI and CDI recurrences.[15,16] The classic example of the importance of colonization resistance to *C. difficile* is the very high rates of colonization in healthy neonates before their gut flora is established.[17] Antibiotic therapy, inflammatory bowel disease with colitis, cytotoxic chemotherapy, and bowel cleansing for colonoscopy or for bowel surgery can all change the endogenous microflora and allow *C. difficile* to colonize and proliferate. Recent studies on microbiome using 16S rRNA-encoding gene sequences demonstrate that there are reproducible patterns of community dynamics within the gut microflora after antibiotic treatment in mice.[18] Human studies have shown that fecal microflora from patients with recurrent CDI was greatly altered, and characterized by markedly decreased diversity compared with control individuals and to patients with just a single episode of CDI.[15] Based on the clear importance of colonization resistance in CDI, prophylactic and therapeutic approaches employing preservation and restoration of the gut microbiota are promising strategies to reduce the growing burden of disease caused by CDI.

PROBIOTIC AGENTS IN CDI

Probiotics are live microorganisms that, when administered in adequate dosage, confer a health benefit to the host. Russian scientist and Nobel Laureate Eli Metchnikoff made the original observations of the positive role played by certain bacteria. He suggested that it may be possible to modify the gut flora, replace harmful microbes with useful microbes, and

thereby improve health. A wide variety of probiotics have been tested and used to prevent or treat CDI.[19,20] The best studied probiotic agents in CDI are *Saccharomyces boulardii*, Lactobacillus GG (LGG) and other lactobacilli, and probiotic mixtures.

S. BOULARDII

The probiotic yeast *S. boulardii* is usually marketed in a lyophilized form and is therefore often referred to as *S. boulardii* lyo. *S. boulardii* is very closely related to *Saccharomyces cerveciae*, which is commonly known as brewer's or baker's yeast. In 1923, Henri Boulard, a French pharmacist and scientist, isolated this yeast from lychee and mangosteen fruit after he observed that natives of South-east Asia chewed on the skins of these fruits to lessen the symptoms of cholera. *S. boulardii* grows at an unusually high temperature of 37°C and is generally nonpathogenic and noninvasive.

Studies in *Vibrio cholerae* infection revealed that the water and electrolyte hypersecretion caused by cholera toxin can be reduced by *S. boulardii*. It is hypothesized that a protease secreted by *S. boulardii* can inhibit stimulation of adenylate cyclase by cholera toxin in enterocytes lining the intestinal tract. This decreases the production of cyclic adenosine monophosphate and secretion of chloride and fluid in response to cholera toxin.[21] Multiple mechanisms of action have been described for *S. boulardii* effects in CDI include reducing intestinal permeability, increasing intestinal sIgA responses, preventing activation of nuclear factor kappa B and mitogen-activated protein kinase signaling pathways, inhibiting production of proinflammatory cytokines such as interleukin-8, and reducing *C. difficile* toxin effects by protease degradation, and by decreasing toxin receptor binding.[22–26]

Two randomized control trials (RCTs) have examined the efficacy of *S. boulardii* in prevention and management of simple antibiotic-associated diarrhea (AAD) and of CDI. McFarland et al[27] reported in 1994 that 500mg of *S. boulardii*, given twice daily for 4 weeks during and after antibiotic treatment for CDI yielded an overall CDI recurrence rate of 26.3% comparing to a 44.8% CDI recurrence rate in the placebo group (P=0.05). A previous history of CDI substantially influenced the results. The efficacy of *S boulardii* was significant in patients with recurrent CDI (recurrence rate 34.6%, compared with 64.7% in placebo; P=0.04), but not in patients with initial CDI (recurrence rate 19.3% compared with 24.2% in placebo; P=0.86). Conversely, in a follow-on study published in 2000, Surawicz et al[28] reported CDI recurrence rates in patients receiving standard antibiotic therapy for CDI for 10 days either with 1 g/d of *S. boulardii* for 28 days or placebo. The CDI recurrence rate in subjects receiving *S. boulardii* (43.3%) was not significant as compared to subjects who received placebo (47.4%). In a post hoc analysis, an almost statistically significant decrease in CDI recurrences was found only in subjects treated with high-dose vancomycin (2 g/d) and *S. boulardii* (16.7% vs. 50.0% for high-dose vancomycin plus placebo; P=0.05). Thus, *S. boulardii* does not seem to be effective in primary prevention of CDI in antibiotic recipients. Whether or not it can be effective in preventing recurrence in patient with CDI is unclear and additional studies are needed to address this unresolved question.

LACTOBACILLUS SPECIES

Lactobacillus species including LGG have also been studied in several RCTs for prevention of CDI. LGG is a substrain of *Lactobacillus rhamnosus* isolated from the intestinal tract of an healthy human by Drs Sherwood Gorbach and Barry Goldin in 1983. LGG is believed to be capable of surviving gastric acidity and small intestinal bile acids and of colonizing the human digestive tract to exert its probiotic effects.[29] LGG has been shown to excrete biosurfactants, organic acids including lactic acid, bacteriocins, and hydrogen peroxide to inhibit colonization and growth of pathogens. LGG has shown beneficial effects in the prevention and treatment of diarrhea of various etiologies in children and in adults. In 1987, Gorbach et al[30] published the first case series of 5 patients with multiple recurrences of CDI who were treated successfully with LGG in an open-label study. In another open-label, uncontrolled study, Biller et al[31] reported that 4 children with multiple recurrences of CDI had resolution of their infection after 2 weeks of LGG administration. Conversely, in a small placebo-controlled trial published in 2005 by Lawrence et al[32] found no benefit for LGG in rates of recurrent CDI after 39 days of follow-up.

Wullt et al[33] conducted a small scale, double-blind, placebo-controlled trial of *Lactobacillus plantarum* 299v for the treatment of recurrent CDI. Four of 11 subjects (36.4%) who received metronidazole with *Lactobacillus plantarum* 299v, and 6 of 9 subjects (66.7%) treated with metronidazole and placebo had recurrence of CDI. However, the efficacy of *L. plantarum* cannot be evaluated from this study due to the small sample size.[33]

PROBIOTIC MIXTURES

A variety of probiotic mixtures have been studied in the treatment and prevention of ADD and CDI and 2 recent randomized controlled trials indicated efficacy for certain probiotic mixtures in preventing CDI.

Hickson et al[34] studied the probiotic mixture of *Lactobacillus casei* DN-114 001 (*Lactobacillus casei imunitass*), *Saccharomyces thermophilus,* and *Lactobacillus bulgaricus* in a probiotic drink (Actimel, Danone, France). After screening 1760 hospital inpatients, 135 were recruited and randomized to receive 100 g of the probiotic twice daily during and for 1 week after antibiotic therapy. The placebo group received a sterile milkshake. The primary outcome of this study was the occurrence of ADD, a secondary outcome was CDI defined as diarrhea with *C. difficile* toxin in the stool. Seven of 57 (12%) of the probiotic group developed ADD compared with 19/56 (34%) in the placebo group (P=0.007). Logistic regression to control for other factors gave an odds ratio of 0.25 (95% confidence interval, 0.07–0.85) for use of the probiotic, with low albumin and sodium also being associated with an increased risk of diarrhea. The absolute risk reduction was 21.6% (6.6% to 36.5%), and the number needed to treat was 5 (range, 3 to 15). No subject in the probiotic group and 9/53 (17%) in the placebo group developed CDI (P=0.001). Thus, in this study, a probiotic mixture had significant benefit in reducing AAD and completely prevented CDI. Despite the dramatically positive results, this study has been criticized for its very selective inclusion and exclusion criteria that disqualified “high risk” patients and for insufficient blinding to treatment because of evident differences between the 2 treatment agents.[35] The study results

are remarkable both for the very high incidence of CDI in the placebo group (17%) and the absolute efficacy of the probiotic drink in CDI prevention. Therefore, an additional RCT is needed to confirm the reproducibility and generalizability of these very encouraging initial findings.

Another randomized, double-blind, placebo-controlled dose-ranging study was recently published by Gao et al.[36] A total of 255 adult inpatients were randomized to 3 groups: 2 probiotic capsules per day, 1 probiotic capsule, and 1 placebo capsule per day, or 2 placebo capsules per day. Each probiotic capsule contained 50 billion colony forming units of a mixture of *Lactobacillus acidophilus* and *Lactobacillus casei*. Probiotic use began within 36 hours of initial antibiotic administration, continued for 5 days after the last antibiotic dose, and patients were followed for an additional 21 days. Higher dose probiotic use had a lower AAD incidence compared with lower dose probiotic (15.5% vs. 28.2%, P=0.02). Each probiotic group had a lower AAD incidence than placebo (44.1%, $P \leq 0.001$ for higher dose probiotic and P=0.02 for lower dose probiotic). In patients who acquired AAD and those taking the probiotic had a shorter duration of symptoms. There was also a reduction in CDI incidence from 23.8% in the placebo group to 1.2% in the higher dose probiotic group (P=0.002 vs. placebo) and 9.4% in the lower dose probiotic group (P=0.03 vs. placebo). As in the Hickson study,[35] the study results are remarkable both for the very high incidence of CDI in the placebo group (23.8%) and the dramatic efficacy of the higher dose probiotic capsules in CDI prevention. Once again an additional, ideally multi-center, RCT is needed to confirm these fascinating findings.

SAFETY OF PROBIOTICS

Although there are case reports of LGG bacteremia,[37–39] LGG mitral valve endocarditis,[40] LGG liver abscess,[41] and >30 reported cases of *S. boulardii* fungemia (some in neighboring patients),[42–47] complications from probiotic use are considered rare. Given the above complications, it is recommended to avoid the use of live probiotic microorganisms in patients with major risk factors for sepsis including the severely immunocompromised and premature infants.[48,37] The presence of a central vein catheter, an impaired intestinal barrier, administration of a probiotic through a J-tube, concomitant administration of a broad-spectrum antibiotic that does not cover the probiotic, using probiotics with high mucosal adhesion, and the presence of cardiac valvular disease (LLG only) have been proposed as minor risk factors.[37]

META-ANALYSES OF PROBIOTIC THERAPY FOR CDI

Several systematic reviews have examined data from studies on the use of probiotics to prevent CDI. In 2006, McFarland[49] reported her analyses of probiotics for the prevention of AAD and CDI. The inclusion criteria for her study required that studies be randomized, controlled, blinded, and published in peer-reviewed journals. Of 940 citations that referred to probiotics and CDI, only 6 RCTs met the inclusion criteria. The numbers of patients in the studies were generally small (median 25; range 15 to 138). Of the 6 RCTs, 5-treated patients with established CDI and the probiotic was combined with standard antibiotic therapy (either vancomycin or metronidazole). Among the above 6 trials, only 1, using *S. boulardii*

showed a significant reduction in CDI recurrences in the probiotic-treated group compared with the placebo group (as discussed above).[27] However, a subsequent *S. boulardii* trial showed no overall benefit in preventing CDI recurrences.[28] The remaining 4 RCTs did not reject the null hypotheses of no difference between probiotics and placebo in prevention of CDI recurrences.

In 2008, the Cochrane collaboration[50] published a review on the use of probiotics for the management of CDI in adults. The inclusion criteria included randomized, prospective studies using probiotics alone, or in conjunction with conventional antibiotics for the treatment of documented CDI. The main outcome measures were resolution of diarrhea and negative stool *C. difficile* cytotoxin assay or culture. Secondary outcomes included recurrence of CDI with diarrhea, mortality, length of hospital stay, and adverse events. The initial screening of the literature yielded 6 studies that met the inclusion criteria. However, in contrast to the McFarland study presented above, 2 studies were subsequently excluded. One study was excluded because the primary study outcome was the concentration of *S. boulardii* in stool specimens and this was considered not clinically relevant.[51] A second study was excluded because it was published only in abstract form and lacked details on methodology and had incomplete data. Therfore, only 4 RCTs were included in the final review. These 4 publications reported on the use of probiotics in conjunction with conventional antibiotic therapy (oral vancomycin or metronidazole) for the treatment of CDI and for prevention of recurrence in adults. The authors of this review concluded that the 4 studies were small in size and had methodological problems. There was a statistically significant benefit for the probiotic *S. boulardii* used in combination with antibiotics in the McFarland et al[27] study of 1994 for secondary prevention of CDI (as described above). But this result was countered by the absence of an overall benefit for the same agent in a subsequent similar study.[28] Neither of the other 2 studies showed a significant benefit. The conclusions of the Cochrane collaboration's review were that there was no evidence to support the use of probiotics alone in the treatment of CDI and that there was insufficient evidence to recommend probiotic therapy as an adjunct to antibiotic therapy for CDI or to prevent recurrence.

Two other groups performed systemic reviews of randomized controlled trials to assess the effectiveness of probiotic therapy in CDI.[52,53] Both found that heterogeneity in the study methods, in the dose and type of probiotics used and in the criteria for diagnosing CDI, made it difficult to synthesize information on the role of probiotics in CDI treatment or prevention. Tung et al[54] reviewed the effectiveness of *S. boulardii* in the prevention of primary and recurrent CDI. They concluded that *S. boulardii* may be effective for secondary prevention in some specific patient populations.

Therfore, 3 of 5 systematic reviews found no convincing evidence for the efficacy of probiotics in CDI treatment or prevention. Two found that *S. boulardii* may be effective in secondary prevention of CDI. These differing conclusions are based mainly on different interpretations of just 1 study. All reviewers agreed that the first of 2 RCTs using *S. boulardii* showed benefit in secondary prevention of CDI (see above).[27] The second *S. boulardii* study has been interpreted as showing no benefit (based on overall CDI recurrence rates) or possible benefit (P=0.05) based on a post hoc subgroup analysis (as described above).[28]

It should be noted that 2 recent studies using probiotic mixtures to prevent AAD and CDI were not included in these systematic reviews.[34,36] Both studies are discussed above.

NONTOXIGENIC C. DIFFICILE

Pathogenic strains of *C. difficile* release toxin A and toxin B, the major known virulence factors for CDI. Nontoxinogenic strains are also prevalent and can be cultured from asymptomatic patients especially during and after antibiotic therapy. These nontoxinogenic strains lack a "pathogenicity locus" of 5 genes that encode for and regulate the production and release of toxins A and B. Studies in a hamster model of CDI show that colonization with nontoxinogenic *C. difficile* can prevent infection by toxinogenic strains and thereby protect against CDI.[55] In 1987, Seal et al[56] reported that the administration of a nontoxinogenic strain of *C. difficile* to patients with multiple recurrences of CDI was effective in preventing further recurrence of disease. Studies are currently underway to use a well-characterized strain of nontoxinogenic *C. difficile* as a targeted probiotic for primary and secondary prevention of CDI in high-risk individuals such as antibiotic-treated hospital patients. One interesting facet of this approach is that spores of nontoxinogenic *C. difficile* will quickly be disseminated in the environment of treated subjects leading to a "herd treatment" effect that will inevitably expand far beyond the individuals opting for treatment. This may be beneficial if a prophylactic effect is achieved after exposure to small concentrations of the spores from the environment. However, it also raises ethical and regulatory issues concerning the mass treatment of subjects who did not provide informed consent.

CLINICAL PRACTICE GUIDELINES

The current clinical practice guidelines for CDI in adults updated by the Society of Healthcare Epidemiology of America and the Infectious Diseases Society of America in 2010 state that administration of currently available probiotics is not recommended to prevent primary CDI, as there are limited data to support this approach and there is a potential risk of bloodstream infection (C-III).[57] Similarly, the recent European guidelines[58] on treatment of CDI state that there is insufficient evidence to recommend the addition of protiobics to antibiotics because the studies investigated on probiotics and CDI had significant concerns including small numbers, nonrandomized allocations of antibiotics to which the probiotics were added, and lack of homogeneity among study groups.

SUMMARY

The role of probiotics for treatment and prevention of CDI remains controversial. There are no substantial data to support probiotic use for treatment of CDI in adults. Probiotic mixtures and *S. boulardii* may be effective in prevention of CDI in high-risk antibiotic recipients,[27,34,36,59] but this finding is based on small, individual, studies of different probiotic agents and further well-controlled studies are needed to confirm preliminary positive findings. High-lighting the need for confirmatory studies 1 RCT showed a significant benefit for *S. boulardii* in protecting against a second or subsequent recurrence of CDI.[27] However, a subsequent *S. bouladii* RCT did not demonstrate any overall benefit.[28]

Therefore, defined probiotic mixtures or *S. boulardii* may be effective in CDI prevention but additional well-controlled studies are needed to determine whether significant and reproducible efficacy exists. In the absence of such data, and taking into account the costs and risks associated with probiotic use, currently there is no sufficient evidence to recommend probiotic therapy for CDI prevention. These conclusions are in keeping recent United States and European guidelines on CDI management.[57–58]

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