Probiotics for the Treatment and Prevention of Clostridium difficile Infection
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Introduction
Clostridium difficile infection (CDI) is the most common cause of healthcare-associated diarrhea, accounting for 20% to 30% of cases. CDI is defined as the presence of diarrhea (≥3 unformed stools in ≤24 hours) and either a positive stool test result or colonoscopic or histopathologic findings of pseudomembranous colitis. In 2009, CDI-related hospital stays accounted for 0.9% of all hospitalizations, with a four-fold increase in mortality compared to other hospitalized patients. In recent years, significant efforts have been made to identify interventions that decrease the incidence, severity, and recurrence of disease, including the use of biologic methods such as probiotics.

Probiotics are defined by the World Health Organization as live microorganisms that confer a health benefit on the host when administered in adequate amounts. Probiotics may contain various strains and colony-forming units (CFU) of microorganisms, but the most commonly utilized strains include lactobacilli, bifidobacteria, and the yeast Saccharomyces boulardii. Probiotics are hypothesized to be effective in the prevention and treatment of CDI through a number of mechanisms, including maintenance of normal gastrointestinal flora, secretion of antimicrobial molecules, immunomodulatory effects, and inhibition of pathogenic bacterial colonization via adhesion sites.

S. boulardii has also been shown to increase host titers of anti-toxin A IgA and secretion of a protease that hydrolyzes C. difficile toxins A and B.

Safety
Probiotics are marketed in the United States as dietary supplements and manufacturers can make health claims based on data in a healthy population, but supportive data are not evaluated by the Food and Drug Administration. Probiotics are generally regarded as safe, but the administration to patients at high risk of opportunistic infections has not been adequately studied. The PROPATRIA trial raised questions regarding the safety of probiotics after use in patients with severe acute pancreatitis was associated with a significant increase in mortality and bowel ischemia. Multiple case reports of endocarditis, bacteremia, and fungemia have been associated with probiotic supplementation. In addition, reports have suggested transmission of infection to hospitalized patients not receiving probiotics, possibly via contamination of vascular catheters among neighboring patients. Resistance determinants carried on mobile genetic elements in probiotics potentially can confer resistance to gastrointestinal pathogens.

Boyle and colleagues proposed risk factors for probiotic use, warranting caution in patients with a single major or more than one minor risk factor. Major risk factors include immunocompromise and prematurity. Minor risk factors include the presence of a central venous catheter (contraindicated with S. boulardii), impaired intestinal epithelial barrier, administration of probiotic by jejunostomy, or cardiac valvular disease (Lactobacillus probiotics only).

Probiotics for Primary Prevention of CDI
The use of probiotics for primary prevention of CDI remains controversial. Several studies have investigated this topic, but results have been conflicting due to variability in study methodology. The Infectious Diseases Society of America/Society for Hospital Epidemiology of America 2010 guidelines recommend against the use of probiotics for the primary prevention of CDI based on limited data and possible adverse effects.
In 2013, Goldenberg and colleagues published a meta-analysis of randomized controlled trials investigating the use of various probiotics for the prevention of *C. difficile*-associated diarrhea (CDAD) or CDI in adults or children receiving antibiotic therapy. The risk of CDAD was evaluated in 23 randomized controlled trials (n=4213) and was shown to be significantly reduced with probiotics (relative risk [RR] 0.36, 0.26 to 0.51). Additionally, the authors evaluated the incidence of CDI in 13 trials (n=961) and found it not significantly different between groups. The authors concluded that probiotics appeared to be effective in preventing CDAD, but the optimal probiotic product, dosage, and length of treatment, as well as related adverse events, needed to be studied further.

To further investigate the relationship between probiotics and CDAD, Allen and colleagues conducted the PLACIDE trial, a large-scale multicenter, randomized, double-blind, placebo-controlled study in elderly (≥65 years) hospitalized patients exposed to at least one antibiotic. Patients received a multistrain preparation of lactobacilli and bifidobacteria (n=1470) or placebo (n=1471) for 21 days. There was no difference between study groups in the occurrence of antibiotic-associated diarrhea or *C. difficile* diarrhea.

In 2012, Pozzoni and colleagues published a single-center, randomized, double-blind, placebo-controlled, parallel group trial in older hospitalized patients (>50 years). Patients received *S. boulardii* (n=141) or placebo (n=134) within 48 hours of beginning antibiotic therapy and continued treatment for 7 days after antibiotic cessation. *S. boulardii* was not effective in preventing antibiotic associated diarrhea or CDAD.

Although a meta-analysis evaluating multiple products and doses in varied populations demonstrated that probiotics may be effective in preventing CDAD, recent prospective studies have been unable to demonstrate similar results. The role of probiotics in the primary prevention of CDI remains unclear, and the risks and potential benefits of probiotic therapy must be evaluated on a patient-specific basis.

**Probiotics for Treatment and Secondary Prevention of CDI**

Despite highly effective antibiotics available for the treatment of CDI, the rate of recurrence has been estimated at 6% to 25% in the general population, with frequency in patients ≥65 years of age reaching 50%. Current American and European guidelines do not support the use of probiotics in the treatment of primary CDI or prevention of recurrent CDI due to lack of sufficient and compelling evidence.

McFarland and colleagues conducted a double-blind, placebo-controlled trial to evaluate the efficacy of *S. boulardii* in reducing the incidence of recurrence in patients with active CDI (initial or recurrent disease) who were receiving metronidazole or vancomycin. Patients were randomized to receive *S. boulardii* or placebo for 4 weeks. Overall, those treated with *S. boulardii* had a lower rate of CDI recurrence (adjusted RR 0.43, 0.20-0.97). This result was largely influenced by the subgroup of 60 patients (48.3%) with recurrent disease who had a reduction in recurrence from 64.7% to 34.6% (*P*=0.04). There was no significant reduction in recurrence for patients with their initial episode of CDI; however, treatment failure in this group was low overall.

Focusing on secondary prevention of CDI, Surawicz and colleagues conducted a double-blind, placebo-controlled, multicenter trial of 32 patients randomized to receive *S. boulardii* beginning on day 7 of a 10-day high-dose oral vancomycin regimen and continued for 28 days.
combined with high-dose vancomycin, those receiving S. boulardii had a significantly reduced incidence of recurrent CDI compared to patients receiving placebo (16.7% vs. 50%, \(P=0.05\)).

In 2003, Wullt et al conducted a prospective, placebo-controlled multicenter trial of 21 patients who were randomized to receive metronidazole for 10 days in combination with a fruit drink containing oats fermented with Lactobacillus plantarum 299v or placebo for an additional 28 days.\(^{19}\) The majority of patients in each group had clinical and bacteriologic cure of CDI with no difference between groups. Thirty-six percent of patients in the treatment group and 67% of patients in the placebo group had recurrence of CDAD at 70 days; however, these results did not reach statistical significance and the study was underpowered due to slow enrollment.

A meta-analysis of the trials cited and other pilot studies showed combined results favored probiotics (RR 0.59, 0.41-0.85); however, post hoc analysis contributed this effect largely to patients with recurrent CDI.\(^{20}\) A Cochrane review of the same studies concluded that there was insufficient evidence to recommend probiotics in the treatment of CDAD.\(^{21}\)

Large scale trials addressing the treatment and secondary prevention of recurrent CDI have provided varied results. Further evidence will be needed to evaluate the usefulness of probiotics, including determination of the appropriate strain, dose, and duration of therapy.

**Conclusions**

Probiotics are not recommended for the treatment or prevention of CDI based on lack of conclusive supporting evidence, as well as the risk of adverse events.\(^{1}\) While some small trials and meta-analyses have shown probiotics to be effective, large-scale trials utilizing a single dose and product in specific populations have failed to demonstrate benefit. The potential complications of bacteremia, fungemia, endocarditis, and possible mortality currently outweigh any benefit.

**References**


