

Do Probiotics Reduce *C diff* Risk in Hospitalized Patients?

A systematic review and meta-analysis says, “Yes,” but that doesn’t necessarily mean they will start appearing on hospital formularies.

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PRACTICE CHANGER

Start probiotics within 1 to 2 days of starting antibiotics in hospitalized patients to reduce the risk for *Clostridium difficile* infection.¹

STRENGTH OF RECOMMENDATION

A: Based on a meta-analysis of randomized controlled trials.

A 68-year-old woman is admitted to the hospital with a diagnosis of community-acquired pneumonia. Should you add probiotics to her antibiotic regimen to prevent infection with *Clostridium difficile*?

Clostridium difficile infection (CDI) leads to significant morbidity, mortality, and treatment failures. In 2011, it culminated in a cost of \$4.8 billion and 29,000 deaths.^{2,3} Risk factors for infection include antibiotic use, hospitalization, older age, and medical comorbidities.² Probiotics have been proposed as one way to prevent CDI.

Several systematic reviews have demonstrated efficacy for probiotics in the prevention of CDI, although not all of them followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines or focused specifically on hospitalized patients, who are at increased risk.⁴⁻⁶ The largest high-quality randomized controlled trial (RCT) on the use of probiotics to prevent CDI, the PLACIDE trial, found no difference in CDI incidence between inpatients (ages 65 and older) who did and those who did not receive probiotics in addition to their oral or parenteral antibiotics; however, this trial had a lower incidence of CDI than was assumed in the power calculations.⁷ Guidelines from the American College of Gastroenterology and the Society for Healthcare Epidemiology of

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America do not include a recommendation for the use of probiotics in CDI prevention.^{8,9}

Given the conflicting and poor-quality evidence and lack of recommendations, an additional systematic review and meta-analysis was performed, following PRISMA guidelines and focusing on studies conducted only in hospitalized adults.

STUDY SUMMARY

Probiotics prevent CDI in this population

This meta-analysis of 19 RCTs evaluated the efficacy of probiotics for the prevention of CDI in 6261 hospitalized adults taking antibiotics. All patients were 18 or older (mean age, 68-69) and received antibiotics orally, intravenously, or via both routes, for any medical indication.

Trials were included if the intervention was for CDI prevention and if the probiotic strains used were *Lactobacillus*, *Saccharomyces*, *Bifidobacterium*, or *Streptococcus* (alone or in combination). Probiotic doses ranged from 4 billion to 900 billion colony-forming U/d and were started from 1 to 7 days after the first antibiotic dose. Duration of probiotic use was either fixed at 14 to 21 days or varied based on the duration of antibiotics (extending 3-14 d after the last antibiotic dose).

Control groups received matching placebo in all but 2 trials; those 2 used usual care of no probiotics as the control. Exclusion criteria included pregnancy, immunocompromise, intensive care, a prosthetic heart valve, and pre-existing gastrointestinal disorders.

The risk for CDI was lower in the probiotic group (range 0%-11%) than in the control group (0%-40%), with no heterogeneity when the data from all 19 studies were pooled (relative risk [RR], 0.42). The median incidence of CDI in the control groups from all studies was 4%, which yielded a number needed to treat (NNT) of 43.

The researchers examined the NNT at varying incidence rates. If the CDI incidence was 1.2%, the NNT

to prevent 1 case of CDI was 144; if the incidence was 7.4%, the NNT was 23. Compared with control groups, there was a significant reduction in CDI if probiotics were started within 1 to 2 days of antibiotic initiation (RR, 0.32), but not if they were started at 3 to 7 days (RR, 0.70). There was no significant difference in adverse events (ie, cramping, nausea, fever, soft stools, flatulence, taste disturbance) between probiotic and control groups (14% vs 16%).

WHAT'S NEW

Added benefit if probiotics taken sooner

This high-quality meta-analysis shows that administration of probiotics to hospitalized patients—particularly when started within 1 to 2 days of initiating antibiotic therapy—can prevent CDI.

CAVEATS

Limited applicability, lack of recommendations

Findings from this meta-analysis do not apply to patients who are pregnant; who have an immunocompromising condition, a prosthetic heart valve, or a pre-existing gastrointestinal disorder (eg, irritable bowel disease, pancreatitis); or who require intensive care. In addition, specific recommendations as to the optimal probiotic species, dose, formulation, and duration of use cannot be made based on this meta-analysis. Lastly, findings from this study do not apply to patients treated with antibiotics in the ambulatory care setting.

CHALLENGES TO IMPLEMENTATION

Limited availability in hospitals

The largest barrier to giving probiotics to hospitalized adults is their availability on local hospital formular-

ies. Probiotics are not technically a medication; they are not regulated or FDA-approved, and thus, insurance coverage and availability for inpatient use are limited. Lastly, US cost-effectiveness data are lacking, although such data would likely be favorable, given the high costs associated with treating CDI. **CR**

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