Priority Updates from the Research Literature from the Family Physicians Inquiries Network

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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 of *Clostridium difficile* infection.[1]

STRENGTH OF RECOMMENDATION

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

Shen NT, Maw A, Tmanova LL, et al. Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: a systematic review with meta-regression analysis. *Gastroenterology*. 2017;152:1889-1900. e9.

ILLUSTRATIVE CASE

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.

While several systematic reviews have demonstrated efficacy for probiotics in the prevention of CDI,[4-6] guidelines from the American College of Gastroenterology and the Society for Healthcare Epidemiology of America did not incorporate a recommendation for the use of probiotics in their CDI prevention strategy.[7,8]

The PLACIDE trial studied the use of probiotics in inpatients ages ≥ 65 years receiving either oral or parenteral antibiotics and found no difference in the incidence of CDI in those who received probiotics vs those who did not.[9] Even though the PLACIDE trial was the largest, high-quality, randomized controlled trial (RCT) on the use of probiotics to prevent CDI, it had a lower incidence of CDI than was assumed in the power calculations. Additionally, previous systematic reviews did not always follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and did not focus specifically on hospitalized patients, who are at higher risk for CDI.

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

STUDY SUMMARY

Probiotics prevent CDI in hospitalized patients receiving antibiotics

This meta-analysis of 19 RCTs evaluated the efficacy of probiotics for the prevention of CDI in 6261 adult hospitalized patients taking antibiotics. All patients were ≥ 18 years (mean age 68-69 years) 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 probiotics

used were 1 or a combination of 4 strains (*Lactobacillus, Saccharomyces, Bifidobacterium, Streptococcus*). Probiotic doses ranged from 4 billion to 900 billion colony-forming u/day and were started from 1 to 7 days after first antibiotic dose. Duration of probiotic use was either fixed at between 14 and 21 days or varied based on the duration of antibiotics (extending 3-14 days after the last antibiotic dose).

Control groups received matching placebo in all trials but 2; those 2 used usual care of no probiotics as the control. Common patient exclusions were pregnancy, immune system compromise, 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 (I^2 = 0.0%; P = .56) when the data were pooled from all 19 studies (relative risk [RR] = 0.42; 95% confidence interval [CI], 0.30-0.57). The median incidence of CDI in the control groups from all studies was 4%, which yielded a number needed to treat (NNT) of 43 (95% CI, 36-58).

The researchers examined the NNT at varying incidence rates. If the incidence of CDI was 1.2%, the NNT to prevent 1 case of CDI was 144, and 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; 95% CI, 0.22-0.48), but not if they were started at 3 to 7 days (RR = 0.70; 95% CI, 0.40-1.2). 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%; P = .35).

Administration of probiotics to hospitalized patients—particularly when started within 1 to 2 days of initiating antibiotic therapy—can prevent *C diff* infections.

WHAT'S NEW

Probiotics provide added benefit if taken sooner rather than later

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

Findings do not apply to all patients; specific recommendations are lacking

Findings from this meta-analysis do not apply to patients who have an immunocompromising condition, are pregnant, have a prosthetic heart valve, have a pre-existing gastrointestinal disorder (eg, irritable bowel disease, pancreatitis), or 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

Lack of "medication" status leads to limited availability in hospitals

The largest barrier to giving probiotics to hospitalized adult patients is the availability of probiotics on local hospital formularies. Probiotics are not technically a medication; they are not regulated or approved by the US Food and Drug Administration 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 treatment of CDI. **JFP**

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