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# Prescribing an antibiotic? Pair it with probiotics

When you prescribe antibiotics, tell patients that taking probiotics for the entire course of treatment will help prevent diarrhea.

## PRACTICE CHANGER

Recommend that patients taking antibiotics also take probiotics, which have been found to be effective both for the prevention and treatment of antibiotic-associated diarrhea (AAD).<sup>1</sup>

## STRENGTH OF RECOMMENDATION

**A:** Based on a systematic review and meta-analysis of randomized controlled trials.

Hempel S, Newberry S, Maher A, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea. *JAMA*. 2012;307:1959-1969.

## ILLUSTRATIVE CASE

When you prescribe an antibiotic for a 45-year-old patient with *Helicobacter pylori*, he worries that the medication will cause diarrhea. Should you recommend that he take probiotics?

**M**ore than a third of patients taking antibiotics develop AAD,<sup>2</sup> and in 17% of cases, AAD is fatal.<sup>3,4</sup> Although the diarrhea may be the result of increased gastrointestinal (GI) motility in some cases, a disruption of the GI flora that normally acts as a barrier to infection and aids in the digestion of carbohydrates is a far more common cause.

## Morbidity and mortality are high

AAD is associated with several pathogens, including *Clostridium difficile*, *Clostridium perfringens*, *Klebsiella oxytoca*, and *Staphy-*

*lococcus aureus*,<sup>2</sup> and varies widely in severity. Pseudomembranous colitis secondary to *C difficile* is the main cause of AAD-related mortality, which more than doubled from 2002 to 2009.<sup>3,4</sup> *C difficile* infections cost the US health care system up to \$1.3 billion annually.<sup>5</sup> With such high rates of morbidity and mortality and high health care costs associated with AAD, even a small reduction in the number of cases would have a big impact.

Probiotics replenish the natural GI flora with nonpathogenic organisms. A 2006 meta-analysis of 31 randomized controlled trials (RCTs) assessing the efficacy of probiotics for both the prevention of AAD and treatment of *C difficile* found a pooled relative risk of 0.43 for AAD in the patients taking probiotics.<sup>6</sup> However, many of the studies included in that meta-analysis were small. As a result, in 2010, the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) recommended against the use of probiotics for the prevention of primary *C difficile* infection, citing a lack of high-quality evidence.<sup>7</sup>

Nonetheless, that same year, 98% of gastroenterologists surveyed expressed a belief that probiotics had a role in the treatment of GI illness.<sup>8</sup> And in 2011, the 3rd Yale Working Group on Probiotic Use published recommendations for probiotic use based on expert opinion.<sup>9</sup> The meta-analysis detailed in this PURL, which included more than 30 trials

published since the 2006 meta-analysis, addressed the efficacy of probiotics for prevention and treatment of AAD.

### STUDY SUMMARY

#### Probiotics significantly reduce AAD

Hempel et al reviewed 82 studies and pooled data from 63 RCTs (N=11,811) to identify the relative risk (RR) of AAD among patients who received probiotics during antibiotic treatment compared with those who received no probiotics or were given a placebo.<sup>1</sup> The studies encompassed a variety of antibiotics, taken alone or in combination, and several probiotics, including *Lactobacillus*, *Bifidobacterium*, *Saccharomyces*, and some combinations.

The outcome: The pooled RR for AAD in the probiotics groups was 0.58 (95% confidence interval, 0.50-0.68;  $P<.001$ ), with a number needed to treat of 13. Although the authors reported that the overall quality of the included trials was poor, a sensitivity analysis of the higher quality studies yielded similar results.

Subgroup analyses by type of probiotic and duration of antibiotic treatment were also consistent with the overall pooled RR. In subgroup analysis by age, a similar decrease in AAD was found among the youngest patients (0-17 years) and those between the ages of 17 and 65 years. Among patients older than 65 years—for whom there were just 3 studies—a nonsignificant decrease in risk was found. Twenty-three of the studies assessed adverse outcomes, and none was found.

### WHAT'S NEW

#### A reason to pair antibiotics and probiotics

This meta-analysis reached a similar conclusion as the 2006 meta-analysis: Probiotics appear to be effective in preventing and treating AAD in children and adults receiving a wide variety of antibiotics for a number of conditions. The results were also consistent with those of a new meta-analysis that looked specifically at one pathogen—and found a reduction of 66% in *C difficile*-associated

diarrhea in patients taking probiotics with their antibiotics.<sup>10</sup>

### CAVEATS

#### Limited data on the safety of probiotics exist

There was some heterogeneity among the studies in the meta-analysis by Hempel et al, and some of the studies were of poor quality. Because of this, the authors used subgroup and sensitivity analysis, which supported their initial conclusion.

Probiotics have generally been considered safe; however, there have been rare reports of sepsis and fungemia associated with probiotic use, especially in immunosuppressed patients.<sup>1</sup> Fifty-nine of the included studies did not assess adverse events, which limited the ability of this meta-analysis to assess safety.<sup>1</sup> Patients taking probiotics should be monitored for adverse effects.

### CHALLENGES TO IMPLEMENTATION

#### Lack of guidance on dosing and duration

Since probiotics are considered food supplements, health insurance will not cover the cost (which will likely be more than \$20 per month; [www.walgreens.com](http://www.walgreens.com)). No single probiotic strain has high-quality evidence; however, most of the RCTs included in the meta-analysis used combinations of *Lactobacillus* species, which are usually found in over-the-counter antidiarrheal probiotic supplements. No standard dose exists, but dose ranges in RCTs are  $10^7$  to  $10^{10}$  colony-forming units per capsule (taken one to 3 times daily);<sup>1</sup> however, product labels have variable accuracy.<sup>11</sup> The duration of treatment ranges from one to 3 weeks—or as long as the patient continues to take antibiotics.

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 Twenty-three probiotics studies assessed adverse outcomes, and none was found.

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