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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What is the role of probiotics in the treatment of acute *Clostridium difficile*-associated diarrhea?

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A: Overall, the evidence does not support using probiotics to treat *Clostridium difficile*-associated diarrhea (CDAD). More studies are needed to determine if they are helpful and, if so, which ones and at what dosages.

WHAT ARE PROBIOTICS?

Probiotics are live bacteria or fungi that carry health benefits when ingested. There is great interest in using these agents to treat and prevent gastrointestinal disorders, as they have been said to inhibit the growth or invasion of pathogenic bacteria, enhance the intestinal barrier, and augment the immune system by regulating cytokines. Their proposed use in treating and preventing CDAD is based on their presumed mechanisms of action and effectiveness in other disorders of the gastrointestinal tract. Given that these readily available bacteria and fungi appear to be safe and well tolerated, their potential use in CDAD is of substantial interest.

LIMITED STUDIES AVAILABLE

Few clinical trials have tested probiotics in CDAD. Two recent systematic reviews did not find a clear benefit to adding probiotics to antibiotics to treat CDAD.[1,2] Six trials of various probiotics were included in a 2006 meta-analysis.[3] Overall, the analysis did find a benefit, but this was mostly derived from two trials of *Saccharomyces boulardii*.[4,5] This yeast has a mechanism other probiotics do not have: a protease that it produces can degrade the exotoxins produced by C *difficile*.[6]

McFarland et al[4] gave either *S boulardii* or placebo to 124 patients who were having either a first episode or a recurrence of CDAD. All patients also received either vancomycin (Vancocin) or metronidazole (Flagyl) in doses chosen by their physician. Patients taking *S boulardii* were more likely to have their diarrhea resolve and not recur, though post hoc analysis found that this benefit was limited to those with recurrent CDAD.[4]

Surawicz et al[5] gave either *S boulardii* or placebo to 168 patients with recurrent CDAD who were also participating in a trial comparing vancomycin in a high dose, vancomycin in a low dose, and metronidazole. The probiotic was beneficial, but only in patients on high-dose vancomycin (2 g/day). These patients tended to have a more severe form of CDAD with colitis.

Great interest in but little evidence for these agents

YOGURT, OVER-THE-COUNTER PRODUCTS MAY NOT CONTAIN ACTIVE BACTERIA

The efficacy of over-the-counter probiotic preparations and probiotic-containing foods, such as yogurt, is difficult to determine. For example, in the case of yogurts with "live and active cultures," the inocula must remain stable from the factory to the grocery store shelf to the table and then through the gastrointestinal tract to the colon. The number of bacteria that survive this long journey is variable.

Another issue is whether probiotic products contain the species and quantities of organisms listed on their labels. In studies that have attempted to examine this issue, many

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of the products contained species not listed on the label. Most products that did contain viable cells of the stated therapeutic agent did so at a lower number than listed.[7,8] The contents and dosages of these over-the-counter products are not regulated and may vary even within the same brand.

The US Food and Drug Administration (FDA) classifies these products as dietary supplements and therefore does not test them for efficacy or safety, though it does have the ability to remove them from the market if they are proven harmful.

FEW ADVERSE EFFECTS

Adverse effects seem to be uncommon with probiotics. Untoward symptoms include flatulence, bloating, and thirst. There are reports of invasive disease, including *Lactobacillus* bacteremia and *Saccharomyces* fungemia, occurring after these probiotics were given to patients with severe comorbidities.[9,10,11]

BENIGN STRAINS OF *C DIFFICILE* MAY PROTECT AGAINST CDAD

Interestingly, C *difficile* itself may serve as a probiotic, preventing future episodes of CDAD. Several studies in hamsters showed that colonization with nontoxigenic strains of C *difficile* can prevent infection with toxigenic strains. In these studies, hamsters receiving clindamycin (Cleocin) or cefoxitin (Mefoxin) were given nontoxigenic strains of C *difficile* that were either susceptible or resistant to the antibiotic, followed by a toxigenic strain. Those given resistant nontoxigenic strains were significantly less likely to develop CDAD. One study, for example, found that 100% of hamsters given a clindamycin-resistant, nontoxigenic strain of C *difficile* were protected from CDAD.[12]

INFECTION CONTROL IS KEY

Novel treatments for CDAD and ways to prevent it are constantly being sought as C *difficile* has reemerged in hospitals across North America and Europe. However, CDAD is fundamentally a hospital-acquired infection transmitted from patient to patient via the hands of health care workers. The most common predisposing factor is antibiotic use. While new therapeutic advances would be welcome, hand hygiene, basic infection control practice, and judicious use of antimicrobials are essential to decreasing the incidence of this disease. ■

Keys to controlling CDAD: hand hygiene, infection control, wise antibiotic use

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