Expert Weighs Benefits of Probiotics for Diarrhea

BY DAMIAN McNAMARA

MIAMI — Varying degrees of success and some caveats come with the use of probiotics to combat or prevent *Clostridium difficile* infection and antibiotic-associated diarrhea.

Saccharomyces boulardii, lactobacilli, and bifidobacteria are among the better-studied probiotic options for these purposes, Dr. Curtis Danskey said at the International Probiotics Association World Congress.

Many hospitalized patients do not have normal gut flora, but "if we can restore the normal intestinal flora, an effective probiotic may protect [these] patients," said Dr. Danskey, who is on the medicine faculty at Louis Stokes Cleveland VA Medical Center.

The antibiotics routinely prescribed to fight *C. difficile* also kill beneficial flora in the gut, which is where probiotic therapy might help. "There is evidence [supporting the] use of probiotics for antibiotic-associated diarrhea if you want to use them," Dr. Danskey said.

► ***Saccharomyces boulardii.*** This organism is a type of yeast and is "probably one of the most well-studied probiotics for *C. difficile*," Dr. Danskey said. In one study, patients with *C. difficile* disease experienced a significant reduction in recurrences when treated with high-dose vancomycin for 10 days followed by *S. boulardii* for 28 days, compared with a regimen of vancomycin followed by placebo (Clin. Infect. Dis. 2000;31:1012-7).

On the downside, there have been reports of fungemia associated with *S. boulardii* treatment, particularly in immunocompromised patients, Dr. Danskey said (Crit. Care 2008;12:414). There is a risk of transfer of fungemia to patients, so "I will not use it in my ICU, [but I] may use it in an outpatient setting in someone with recurrent infections."

► **Lactobacilli and bifidobacteria.** There is some rationale for use of these two probiotic species to prevent *C. difficile* infection, Dr. Danskey said. Lactobacilli, for example, can inhibit growth of *C. difficile* in vitro (J. Med. Microbiol. 2004;53:551-4). Also, reduced lactobacilli levels were found in the stool of hospitalized patients with *C. difficile* (Clin. Infect. Dis. 1997;25[suppl 2]:S189-90). "A lack of these organisms may allow *C. difficile* to grow."

Historically, the numbers have been small in many probiotic trials that did not show a reduction in *C. difficile* infection. "Up to 2005, the data were not very convincing," Dr. Danskey said.

After that, reports became more robust. For example, in one study, 135 hospitalized patients aged 50 years and older taking antibiotics were randomized to a lactobacillus preparation or placebo (BMJ 2007;335:80). A total of 12% of the probiotic group developed AAD, compared with 34% of placebo patients. In addition, no patient who took the probiotic developed a *C. difficile* infection vs. 17% of the placebo group.

The antibiotics for *C. difficile* also kill beneficial flora, which is where probiotic therapy might help.

DR. DANSKEY

"The results looked very impressive," Dr. Danskey said. However, the study received a fair amount of criticism. For example, the placebo group drank a sterile milkshake, which could have caused diarrhea, some said. Other aspects of the study that drew criticism included the highly selected patient population (only 8% of screened patients were enrolled) and the exclusion of patients taking antibiotics most likely to cause diarrhea.

"However, the 8% rate is still higher than a just-published study [of monoclonal antibodies targeted against *C. difficile* toxins] that only enrolled 3% of screened patients," Dr. Danskey said (N. Engl. J. Med. 2010;362:197-205). Also, in the 2007 lactobacillus vs. placebo study, 43 of 69 probiotic-treated patients (62%) received a high-risk antibiotic, as did 46 of the 66 placebo patients (70%), he said.

In terms of potential adverse events, there are some concerns about safety, "although we eat yogurt [with lactobacillus species] all the time," Dr. Danskey said. For example, researchers reported two cases of sepsis associated with probiotic lactobacillus strains (Pediatrics 2005; 115:178-810).

A meta-analysis of probiotics for AAD and *C. difficile* infection was published a year ago (Anaerobe 2009;15:274-80).

► **Nontoxigenic probiotics.** Normally, *C. difficile* growth and toxin production start shortly after infection in susceptible individuals. A person can be an asymptomatic carrier, but about one-third of patients develop disease, Dr. Danskey said. When this happens, *C. difficile* toxins bind to the lining of the GI tract, leading to cell death and significant inflammation. Colonoscopy and sigmoidoscopy often show pseudomembranous colitis in these patients.

Nontoxigenic probiotics that compete with *C. difficile* are in development. "Evidence suggests patients colonized with nontoxigenic strains were protected from infection with toxigenic strains," Dr. Danskey said.

Dr. Danskey receives research support from Viral Pharma (which is developing nontoxigenic probiotic strains) and the Department of Veterans Affairs. ■

Probiotic May Benefit Children With Prolonged Diarrhea

BY PATRICE WENDLING

VANCOUVER — Contrary to prior studies, *Lactobacillus* GG did not significantly affect the overall duration or severity of acute infectious diarrhea in a double-blind, randomized trial of 129 children presenting in the pediatric emergency department.

Children with longer diarrheal illness however, appeared to respond better to outpatient use of *Lactobacillus* GG (LGG), said Dr. Abigail Nixon, a pediatric fellow in training at the Jacobi Medical Center, Bronx, N.Y., at the annual meeting of the Pediatric Academic Societies.

Probiotics have been shown to decrease the duration of infectious diarrhea, although there are no U.S. studies of the use of probiotics to treat infectious diarrhea in the outpatient setting.

The study involved 129 children, aged 6 months to 6 years (mean 25.5 months), presenting to the emergency department (ED) with acute diarrhea, defined as more than two loose stools in the preceding 24 hours (mean 5.3 episodes). Patients were randomized to 10 capsules of dissolvable powder containing LGG or placebo containing inulin, a polysaccharide.

Parents administered the powder twice daily for 5 days and recorded in a home diary the number of stools. A blinded researcher called the caregiver daily for 5 days, and recorded the number of stools and the date and time of the first normal stool.

The percentage of children returning to normal stool during the study period was similar among patients randomized to LGG and those receiving placebo, at 75% and 70%, respectively, Dr. Nixon said.

There also was no significant difference in the median time to normal stool—60 hours with LGG vs. 74 hours with placebo—or in the number of diarrheal stools during the study—5.0 with LGG vs. 6.5 with placebo.

The lack of a significant benefit from LGG may be caused by the fact that children treated and discharged from the ED are in general not as ill as those who are admitted, Dr. Nixon explained, and therefore it's more difficult to document an effect of the probiotic.

The population that has very mild disease doesn't benefit from probiotics because they don't need it.

DR. NIXON

"I think there's a population of children who probably have very mild disease who don't benefit from probiotics because they don't need it; they would have gotten better on their own," she said in an interview. "I think that's why as a group as a whole, we didn't see a meaningful difference."

Still, the results support a trend for a benefit of probiotics, she added.

Among patients presenting with more than 2 days of diarrhea, a post hoc subgroup analysis revealed that a significantly higher percentage of the LGG patients returned to normal stool than did placebo-treated patients, 79% vs. 58%, respectively.

In addition, LGG patients returned to normal stool almost 24 hours earlier than did their counterparts treated with placebo (51 hours vs. 74 hours), and had half the number of diarrheal stools (3.5 vs. 7). Both differences were statistically significant.

After the researchers adjusted for age, children with more than 2 days of diarrhea treated with LGG were twice as likely to return to normal stool as were children in the placebo group.

"LGG may have a restorative effect on the intestinal flora and therefore would preferentially benefit patients presenting with prolonged diarrhea," said Dr. Nixon, who recommends probiotics, either as tablets or fortified yogurt, to her patients in the ED.

She noted that a reduction in the time to resolution of diarrhea might have important public health implications in terms of missed work, lost revenue, and school absenteeism.

Diarrhea accounts for about 1.5 million pediatric outpatient visits and more than 200,000 hospitalizations annually in the United States, Dr. Nixon said at the meeting.

An analysis of the study's secondary outcomes among the entire cohort found no difference between groups in the time for patient or parents to return to normal activity or in the need to return for medical care or hospitalization.

Session moderator Dr. Benard P. Dreyer, professor of pediatrics at New York University, wondered whether LGG might have been less effective because of the increasing rate of rotavirus vaccination in children. Dr. Nixon said the impact of rotavirus is unclear, as viral cultures were not conducted. ■

VITALS

Major Finding: Overall, 75% of patients randomized to *Lactobacillus* GG returned to normal stool, vs. 70% of those receiving placebo.

Data Source: Double-blind randomized trial of *Lactobacillus* GG in 129 children with acute infectious diarrhea.

Disclosures: Amerifit Brands Inc. provided the study product and placebo, and a small patient incentive. Dr. Nixon disclosed no conflicts of interest.