Asymptomatic *C. difficile* Triples Diarrhea Risk

VITALS

Major Finding: After adjustment for age and antibiotic use, the relative risk of diarrhea in *C. difficile*–colonized patients was more than 3-fold greater (odds ratio 3.3) than in noncolonized patients; the risk for clinical diagnosis and treatment was 10-fold greater (OR 10.1).

Data Source: A follow-up study of 320 hospitalized patients.

Disclosures: Dr. Leekha reported having nothing to disclose.

BY MIRIAM E. TUCKER

ATLANTA — Hospitalized patients who were asymptomatically colonized with toxigenic *Clostridium difficile* had a significantly greater risk of developing clinically significant *C. difficile* infection and diarrhea, compared with noncolonized patients, in a study of 320 adults admitted to one hospital.

The finding is contrary to previous reports and should be explored further, Dr. Surbhi Leekha said at the Decennial International Conference on Healthcare-Associated Infections.

"The take-home is that there may be an association between initial colonization at the time of hospitalization and the subsequent development of diarrhea, but we cannot determine based on these results whether the increased risk is a direct consequence of that colonization or whether colonization is a marker for other [factors] with that patient, such as severity of illness, immune status, or recurrent hospitalization, that in turn predispose to CDI," she concluded.

Asymptomatic colonization with *C. difficile* occurs in approximately 8%-20% of hospitalized patients, who then can serve as "reservoirs" contributing to nosocomial transmission. At least three prior studies have suggested that these patients are not at risk for symptomatic disease and may even be at lower risk, provided a "critical period" of about 1-2 weeks has passed following acquisition of the organism (Clin. Infect. Dis. 1994;18:181-7; Lancet 1990;336:97-100; Lancet 1998;351:633-6).

A previous part of the current study had enrolled 320 adults admitted to Saint Marys Hospital, Rochester, Minn., who had stool specimens tested for toxigenic *C. difficile* using polymerase chain reaction assay within 5 days of admission between March 1 and April 30, 2009. Of these patients, 30 (9.4%) were found to be colonized without symptoms. Factors associated with *C. difficile* colonization included recent hospitalization (relative risk 2.3) and chronic dialysis (RR 7.6). Dr. Leekha, of the Mayo Clinic, Rochester, reported those findings at the 2009 meeting of the Infectious Diseases Society of America.

The current follow-up was done 3-4 months after determination of *C. difficile* colonization status. Of the 320 asymptomatic patients who had a history of *C. difficile* infection (CDI), 12 were excluded. Of the remaining 308, follow-up information was obtained via telephone calls and chart reviews for 272 patients. Of those, 25 were colonized and 247 were not.

Those who were colonized were significantly more likely to have been hospitalized recently (64% vs. 36%), to be on chronic hemodialysis (12% vs. 2%), to be on proton pump inhibitors (52% vs. 37%), and to have recent corticosteroid use (32% vs. 15%). Antibiotic use and subsequent hospitalization during the follow-up period did not differ significantly between the two groups, Dr. Leekha reported.

Diarrhea developed in 32 (12%) of the 272 patients, including 7 of the 25 who were colonized (28%) and 25 of the 247 who were not (10%).

Clinical diagnosis and treatment for CDI occurred in 8 of the 272 patients (3%), including 4 of the 25 *C. difficile*–colonized patients (16%) and 4 of the 247 noncolonized patients (2%). After adjustment for age and antibiotic use, the relative risk of diarrhea for colonized patients was more than 3-fold greater (odds ratio 3.3), compared with noncolonized patients; the risk for clinical diagnosis and treatment was 10-fold greater (OR 10.1), she said.

Of the eight patients who were treated for CDI, two—one colonized, one not—did not have diarrhea and therefore would probably not have been tested for *C. difficile* in a usual clinical setting. All four of the treated noncolonized patients had used systemic antibiotics within 2 weeks of symptom onset. But interestingly, of the four treated colonized patients, one had not used antibiotics within 2 weeks and one had undergone outpatient ocular surgery and had used only ocular antibiotics. Whether those play a role in CDI is unknown, Dr. Leekha commented.

It also is not known why the findings of this study differ from those of previous studies, which had suggested a "protective effect" of colonization. Carriers were found to have had higher levels of toxin A IgG, compared with those with symptoms, which was postulated to play a role. Further elucidation of host factors is needed, she said. ■

Probiotics for *C. difficile* and Diarrhea Have Pros and Cons

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.

C. difficile can cause up to 30% of nosocomial diarrhea cases in hospitalized patients (Pol. J. Microbiol. 2005;54:111-5). In addition, antibiotic-associated diarrhea (AAD) occurs in 3%-29% of hospitalized patients and is associated with increased length of stay and costs (J. Hosp. Infect. 2003;54:202-6).

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 several 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 adjacent patients, so "I will not use it in my ICU, [but I] may use it in an outpatient setting in someone with recurrent infections," he added.

► **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 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 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). He also cited a meta-analysis of the advantages and disadvantages of probiotics for AAD and *C. difficile* infection (Anaerobe 2009;15:274-80).

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DR. DANSKEY

► **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. "This makes logical sense—they will compete with toxigenic strains in the GI system." So far, the evidence primarily comes from animal research. "It is now in phase I trials in patients and will move forward if it is shown to be effective and safe." ■

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