Community-Acquired *C. difficile* Diarrhea Cases on the Increase

BY BRUCE JANCIN
Denver Bureau

LISBON — *Clostridium difficile*–associated diarrhea contracted in the community is an underappreciated and costly problem, Judith A. O'Brien asserted at the 12th International Congress on Infectious Diseases.

Hospital-acquired *C. difficile* diarrhea grabs all the attention. But cases that originate while patients are living at home are a growing problem, probably caused by widespread use of proton pump inhibitors and other gastric acid suppressants along with liberal prescribing of broad-spectrum antibiotics, according to Ms. O'Brien, director of cost research at the Caro Research Institute, Concord, Mass.

She presented an analysis of hospital data that included all 9.3 million discharges during 2002 in the states of California, Florida, Maryland, Massachusetts, New Jersey, and Washington. Community-acquired *C. difficile* intestinal infection was the principal diagnosis in 10,860 cases. Among those cases, 95% of affected patients were living at home prior to hospitalization; the remainder lived in nursing homes or prisons.

Community-acquired *C. difficile* diarrhea was primarily a disease of the elderly. The mean age of affected individuals was 68 years; the median age was 75.

Of 10,860 cases of community-acquired *C. difficile* diarrhea, 95% of affected patients were living at home prior to hospitalization.

Overall, 72% of all the patients who were affected patients were admitted through the emergency department.

In-hospital mortality was 4.2%. Mean and median length of stay for all patients was 6.8 and 5 days, respectively.

In Massachusetts, the only state that had reliable ICU data, 9% of the patients spent time in an ICU, with an average ICU length of stay of 7.9 days.

The mean and median cost of a hospital stay for management of *C. difficile* diarrhea was $15,800 and $9,142, respectively, or collectively roughly $217 million in inpatient costs in 2002 in the six states.

However, these figures seriously underestimate the total costs of management of community-acquired *C. difficile* diarrhea.

The reason for that is that 41% of patients who were admitted from home required postdischarge follow-up home health care services or were sent to a subacute nursing facility, rehabilitation center, or other facility, Ms. O'Brien noted at the congress, which was sponsored by the International Society for Infectious Diseases.

The study was funded by an unrestricted grant from Genzyme Corp. ■

Disinfectant Dispensers May Harbor Bacteria

LISBON — The dispensers of alcohol-based disinfectant for hand washing that are ubiquitous in hospitals and physicians' offices are often contaminated with bacteria, including potential pathogens, Dr. Kiran Mangalpally cautioned at the 12th International Congress on Infectious Diseases.

He cultured the push bars of 44 such dispensers at Mount Vernon (N.Y.) Hospital, where he is a resident in internal medicine. Thirty-five, or 80%, proved culture positive.

The push bars are activated by pressure applied by the palm or fingers, which releases a squirt of hand rinse or foam. But the disinfectant does not reach the push bar itself.

Twenty-nine of the soap dispenser push bars grew coagulase-negative staphylococci and four grew *Staphylococcus aureus*, including two that yielded methicillin-resistant *S. aureus*. Another two push bars grew nonstaphylococcal bacteria.

For comparison, Dr. Mangalpally also cultured 11 doorknobs from hospital bathrooms. Nine of the 11 proved culture positive, all of which grew only coagulase-negative staphylococci.

"This is one of those simple things we don't think about much," the physician noted in an interview at the congress, which was sponsored by the International Society for Infectious Diseases.

—Bruce Jancin

Search Goes On for Effective Therapies to Combat CDAD

BY KERRI WACHTER
Senior Writer

BETHESDA, MD. — Despite the experience from recent epidemics, the search for effective treatments for *Clostridium difficile*–associated diarrhea continues, Dr. Mark Miller said at an annual conference on antimicrobial resistance sponsored by the National Foundation for Infectious Diseases.

During the 2002-2004 epidemic of *C. difficile*–associated diarrhea (CDAD) in Quebec, spontaneous improvement was rare and serious disease developed rapidly. "Many of us remember many of the cases where they're fine today, they start getting diarrhea tonight, and tomorrow afternoon they're in the intensive care unit with hypotension and acute respiratory distress syndrome," said Dr. Miller, head of infectious diseases at Sir Mortimer B. Davis—Jewish General Hospital in Montreal.

Traditional treatment for CDAD has been to stop the offending antibiotic, which may relieve symptoms in about 20% of patients. "This is probably not true any more," Dr. Miller said.

Traditionally, oral administration of drug therapy is preferred, even if that means using a nasogastric tube. Metronidazole (250-500 mg four times daily) has been preferred over vancomycin (125-500 mg four times daily) because it is considerably cheaper, reduces the risk of vancomycin-resistant mutations, and has comparable efficacy, tolerability, and relapse rates, compared with vancomycin.

In Quebec, it is currently considered unethical to withhold specific CDAD therapy. Almost all patients are started on empiric therapy before the toxin assay comes back from the laboratory, said Dr. Miller, also a professor of microbiology/immunology at McGill University.

There also have been a few anecdotal or small series reports saying that the clinical response is slower or that the relapse rate is higher with metronidazole than with vancomycin.

According to the latest treatment algorithm developed in Quebec, serious cases of CDAD are started on vancomycin, bypassing metronidazole. Likewise, a patient who fails to improve on metronidazole is switched to vancomycin.

The use of metronidazole and vancomycin together is widespread in many institutions, but the effectiveness of the combination has not been studied. Some physicians are adding rifampin to metronidazole, and others are adding rifampin or bacitracin to vancomycin. Likewise, these combinations have not been studied. "As you start getting a number of different recipes, it means that nobody is very happy with any single recipe," Dr. Miller said.

In addition, there is a host of adjuvant nonantibiotic therapies available or in the pipeline. Dr. Miller discussed the literature on these therapies and gave his comments:

► **Probiotics.** Probiotics have been suggested as bioprophylaxis or biotherapy. However, the few studies that have been done with standardized probiotics have shown no effect on *C. difficile*. In a meta-analysis, researchers concluded that there is insufficient evidence for the routine use of probiotics to prevent or treat CDAD (CMAJ 2005;173:167-70). In addition, because a substance's intended use determines how it is regulated in the United States, many probiotic products are not standardized and are poorly quantified.

► **Prebiotics.** Last year a group in the United Kingdom described the use of oligofructose—a so-called prebiotic—for the treatment of CDAD along with conventional therapy. In the study, patients were randomized to conventional therapy alone or in conjunction with 30 days of oligofructose consumption (Clin. Gastroenterol. Hepatol. 2005;3:442-8). Patients taking oligofructose had a substantial increase in beneficial bifidobacteria in the gut. There was also a decreased relapse rate for those on oligofructose.

► **Toxin binders.** Toxin binders, such as cholestyramine and tolevamer, are another avenue of treatment under investigation. These compounds bind to toxins produced by *C. difficile*, which lead to CDAD.

Cholestyramine is indicated to help reduce serum cholesterol levels but is sometimes used off label to treat CDAD. However, small case series have not shown it to be effective. "I find that all it does is give my patients more GI symptoms of bloating and flatulence and pain. I don't find it very useful," Dr. Miller said.

Tolevamer is an investigational polymer (Genzyme Corp.) that is designed to selectively bind to *C. difficile* toxins A and B. A phase II study showed that high-dose tolevamer (6 g/day) was equivalent to oral vancomycin for curing mild to moderate CDAD. Phase III trials are underway to compare the drug with vancomycin and metronidazole.

► **Immunotherapy.** Interest in the use of intravenous immunoglobulin to treat CDAD was sparked when researchers noted that patients with multiple relapses appeared to be deficient in their immunoglobulin G (IgG) response to toxins. High-titer antitoxin A was associated with protection from and recurrence of disease (N. Eng. J. Med. 2000;342:390-7).

Several small case series using IV immunoglobulin for severe or recurrent disease have shown marked clinical responses in most patients. Dr. Miller and his colleagues are currently performing their own retrospective analysis of IV immunoglobulin use during the Quebec outbreak.

A spin-off approach is passive immunotherapy using just antibodies to *C. difficile* toxins. Studies have shown that humans produce large quantities of antitoxin IgG after immunization. Researchers at Acambis are currently investigating a vaccine with antitoxin A and antitoxin B IgG.

Researchers are also investigating animal-derived hyperimmune antitoxin products, such as a whey protein concentrate made from the milk of cows vaccinated with *C. difficile* toxoids. The product appears to help prevent CDAD relapse, based on data from a pilot study (J. Med. Microbiol. 2005;54:197-205).

► **Fecal flora restoration.** Fecal restoration is also being investigated as an effective—albeit unpleasant—therapy for CDAD. The idea is to use enemas of normal stool to restore normal fecal flora. Anecdotal and small series reports show a good response in patients with recurrent CDAD. One study also showed that it is possible to give donor stool via a nasogastric tube.

Dr. Miller disclosed that he is a consultant for and/or holds research grants from ActivBiotics Inc., Advanced Biologics, Bayer, BD's GeneOhm, Conagra Foods Inc., Genzyme Corporation, GlaxoSmithKline, Janssen-Ortho Inc., LDI[3], Optimer Pharmaceuticals Inc., and Wyeth. ■