Antibiotics May Spur Nastier Strains of *C. difficile*

Editorial authors urge better stewardship in using cephalosporins, clindamycin, and fluoroquinolones.

BY MIRIAM E. TUCKER
Senior Writer

Fluoroquinolone use may be driving the emergence of newer and more virulent strains of *Clostridium difficile,* Dr. John G. Bartlett and Dr. Trish M. Perl said in an editorial accompanying two simultaneous reports in the New England Journal of Medicine.

"Particularly important is antibiotic stewardship with restraint in the use of epidemiologically implicated antimicrobial agents, usually second- and third-generation cephalosporins, clindamycin, or fluoroquinolones, or a combination of the three," said Dr. Bartlett and Dr. Perl of Johns Hopkins University, Baltimore (N. Engl. J. Med. 2005;353:2503-5).

Several recent studies have documented a rise in the number and severity of *C. difficile*–associated disease cases in the United States and elsewhere. Now two new reports of detailed microbial analysis suggest that a more virulent strain of *C. difficile* is causing epidemic disease at selected locations and is associated with more frequent and more severe disease.

In one study, 187 isolates were collected from eight health care facilities in six states in which outbreaks of *C. difficile*–associated enteric disease had occurred between 2000 and 2003. In five of the facilities (two located in Maine and one each in Georgia, New Jersey, and Pennsylvania), one particular epidemic strain accounted for 50% or more of the isolates.

Among 29 of those isolates selected for further genetic testing, 25 were related by 90% or more, and all were more than 80% related. In contrast, very few of the other strains were more than 80% related, Dr. L. Clifford McDonald of the Centers for Disease Control and Prevention, Atlanta, and associates reported (N. Engl. J. Med. 2005;353:2433-41).

Two new reports of detailed microbial analysis suggest that a more virulent strain of *C. difficile* is causing epidemic disease in some locations.

All 24 of the epidemic strain isolates that were tested for susceptibility were resistant to levofloxacin, gatifloxacin, and moxifloxacin, while 19 of the 24 (79%) were also resistant to clindamycin. In contrast, among 24 other *C. difficile* strains, 23 (96%) were resistant to levofloxacin, 19 (79%) to clindamycin, and just 10 each (42%) to gatifloxacin and moxifloxacin.

Even though resistance to clindamycin and levofloxacin was common among all the strains, the minimum inhibitory concentrations were higher for those of the epidemic strain. "The increasing use of fluoroquinolones in U.S. health care facilities may have provided a selective advantage for this epidemic strain and promoted its widespread emergence," said Dr. McDonald and associates.

In the other study, Dr. Vivian G. Loo of McGill University and associates prospectively identified a total of 1,703 patients with 1,719 episodes that met the case definition for nosocomial *C. difficile*–associated diarrhea at 12 Canadian hospitals from January to June of 2004. The overall incidence was 23 per 1,000 admissions, a rate nearly four times greater than the 6/1,000 found in a 1997 survey of 18 Canadian institutions.

Among the 422 patients who died within 30 days of diagnosis of *C. difficile*–associated diarrhea, the disease was attributed to be the cause of death in 117, or 6.9% of the total 1,703 patients. In contrast, the attributable mortality rate was just 1.5% in the 1997 survey, Dr. Loo and her associates noted (N. Engl. J. Med. 2005;353:2442-9).

A total of 237 patients were compared with 237 hospitalized patients who did not have *C. difficile*–associated diarrhea, matched for age, sex, and Charlson (comorbidity) index. The case patients were significantly more likely than controls to have been exposed to antibiotics (79% vs. 60%) and enteral feeding (19% vs. 12%). Exposure to fluoroquinolones was a significant independent risk factor for *C. difficile*–associated diarrhea (odds ratio 3.9), as was cephalosporin exposure (OR 3.8).

Results of pulsed-gel electrophoresis in 157 of the isolates indicated that 82% had an identical pattern, known as a "pulsovar," that was universally resistant to fluoroquinolones. Of those 129 patients, 16% had severe *C. difficile*–associated diarrhea, compared with just 7% of 28 patients whose isolates had other pulsovars.

Polymerase chain reaction revealed that 84% of the 157 isolates possessed genes encoding for two major toxins associated with *C. difficile* virulence, as well as a partial deletion of a gene that downregulates those toxin genes. Among those 132 patients, 17% had severe *C. difficile*–associated diarrhea, compared with 0 of the 25 patients who had none of those genes.

In addition to more judicious antimicrobial use, control of *C. difficile*–associated disease also hinges on better recognition of cases and optimal disease management, Dr. Bartlett and Dr. Perl said. ■

C. difficile *Seen in Patients Lacking Usual Risk Factors*

BY MIRIAM E. TUCKER
Senior Writer

The diagnosis of *Clostridium difficile*–associated disease should be considered in patients with severe diarrhea, even if they don't have traditional risk factors such as recent hospitalization or antimicrobial use, the Centers for Disease Control and Prevention advised.

During May and June 2005, a total of 10 peripartum and 23 *C. difficile*–associated disease (CDAD) cases from previously healthy individuals in the community were voluntarily reported from four U.S. states following a request from the CDC. The findings suggest that the epidemiology of the disease might be changing to include features that have been uncommon in the past, such as close-contact transmission, high recurrence rate, young patient age, bloody diarrhea, and lack of antimicrobial exposure, the CDC warned (MMWR 2005;54:1201-5).

All but 1 of the 33 cases occurred during 2004-2005. Hospitalization was required for 15 (46%), and relapses occurred in 13 (39%). Transmission to close contacts was evident in four cases. Eight of the 33 patients (24%)—including 5 children—reported no exposure to antimicrobial agents within 3 months prior to CDAD onset. Of those eight, two reported close contact with a person who had diarrheal illness.

Clindamycin was the most common antimicrobial exposure noted prior to CDAD, representing 10 (33%) of the 33 cases. These included two patients who had taken just one dose for group B streptococcal prophylaxis before CDAD onset.

Among the cases was a 31-year-old woman who was 14 weeks pregnant with twins whose only antimicrobial exposure during the previous year had been trimethoprim-sulfamethoxazole for a urinary tract infection 3 months before she developed severe diarrhea. Despite treatment with metronidazole, cholestyramine, and oral vancomycin, she spontaneously aborted her fetuses and died 3 days later, even after receiving subtotal colectomy, intubation, and inotropic medication.

Another case was a 10-year-old girl who had not taken antimicrobials in the previous year. She had been completely healthy until 2 weeks before developing intractable diarrhea, projectile vomiting, and abdominal pain. Her symptoms eventually resolved after she received intravenous fluids, electrolytes, and metronidazole in the hospital. ■

Nationwide Study Confirms Sharp Rise in *C. difficile* Colitis

BY BETSY BATES
Los Angeles Bureau

SAN FRANCISCO — A sharp uptick in the prevalence and severity of *Clostridium difficile* colitis among hospital patients nationwide suggests that the trend extends beyond documented cases in focused regions of the United States and Canada, Dr. Rocco Ricciardi said at the annual clinical congress of the American College of Surgeons.

Analysis of national hospital data indicates "a significant change in the epidemiology of *C. difficile* colitis, which is likely secondary to a more virulent pathogen or less effective therapies," Dr. Ricciardi said.

C. difficile, a gram-positive, spore-forming bacterium, was first described in 1935. Its emergence as an important cause of severe colitis can be traced to the increased use of antibiotics, which disrupt the normal flora of the colon and permit it to flourish.

Dr. Ricciardi, a colorectal surgeon on the faculty of the University of Minnesota, examined inpatient data from the Nationwide Inpatient Sample, a discharge database of approximately 7 million hospital stays per year in 1,000 hospitals in more than 30 states.

He found nearly 300,000 cases of *C. difficile* colitis documented in inpatient charts during the study period (1993-2003). Of those, *C. difficile* colitis was the primary diagnosis in 69,373 cases. The average age of the patients was 67, and 59% were females. Most patients (64%) were white.

The prevalence rose dramatically not only for primary cases of *C. difficile* colitis—when the condition was the major reason for hospitalization—but also for patients with a secondary diagnosis of the disease.

The findings were both statistically and clinically significant. They reflect trends seen in smaller studies from Pittsburgh and Portland, Ore., and the province of Quebec.

The case fatality rate in patients with any diagnosis of *C. difficile* on their charts was 7.8% in 1993, rising to 9.3% in 2003, with the sharpest increase seen from 2001 to 2003, Dr. Ricciardi said.

The *C. difficile*–associated mortality rate per 100,000 discharges rose from 20 to greater than 50 during the 11-year period.

The colectomy rate per 1,000 patients with a primary or secondary diagnosis of *C. difficile* increased from just over 1 in 1993 to 3.4 in 2003. The curve made a sharp upward turn between 2000 and 2003.

Logistic regression analysis showed that the prevalence, case/fatality rate, and colectomy rate rose even after adjustment for age, gender, race, payer type, and comorbidity.

Discussant Dr. Karen E. Deveney, professor of surgery at Oregon Health Sciences University in Portland, hailed the investigation as an important confirmation in a population study of trends seen in her city and other regions.

"I am struck by the similarity between this study and previous publications. All seem to agree that *C. difficile* is increasing in prevalence and severity," she said. ■