New *C. difficile* Strains Traced to Antibiotic Use

Fluoroquinolone use may be involved in the development of the newer, more virulent strains.

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).

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 her 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 between January and 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.

Control of *C. difficile*–associated disease also hinges on better recognition of cases and optimal disease management, Dr. Bartlett and Dr. Perl said. ■

Young Patient Age Is a New *C. difficile* Risk Factor

BY MIRIAM E. TUCKER
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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 onset of 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, the CDC noted.

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.

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 brother also had a febrile diarrheal illness but recovered within 2-3 days without treatment. The girl's symptoms eventually resolved after she received intravenous fluids, electrolytes, and metronidazole in the hospital.

Pneumococcal Parapneumonic Empyema Up in Some Areas

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — The incidence of pediatric pneumococcal parapneumonic empyema doubled in Utah and surrounding areas since introduction of the pneumococcal conjugate vaccine, Carrie L. Byington, M.D., said in a poster presentation at the annual meeting of the Infectious Diseases Society of America.

Serotypes of *Streptococcus pneumoniae* not covered by the vaccine caused most of the recent cases.

The activity of bacterial serotypes varies by geographical region. In the past decade, Utah has had one of the highest rates of pneumococcal parapneumonic empyema (PPE) in children due to *S. pneumoniae* serotype 1, which the vaccine does not cover, said Dr. Byington of the University of Utah, Salt Lake City, and her associates.

A search of the Intermountain Health Care data warehouse found 776 cases of pediatric PPE between March 1996 and June 2005, 62% of which were treated at Primary Children's Medical Center, Salt Lake City.

In the period 1996-2000, before introduction of 7-valent pneumococcal conjugate vaccine (PCV7 or Prevnar), the center saw 38 cases per year, compared with 72 cases annually between 2001 and 2004, a significant difference.

Among 295 cases of culture-confirmed invasive pneumococcal disease in children at the center, 74 were PPE, representing 18% of invasive pneumococcal disease in the prevaccine years and 32% since the vaccine.

The investigators retrieved and serotyped pleural and fluid isolates of *S. pneumoniae* from the 74 cases.

The proportion of PPE due to serotypes covered in the vaccine decreased from 37% (9 of 24 cases) in the prevaccine era to 14% (7 of 50 cases) in more recent years.

Serotype 1 was the most common cause of PPE due to nonvaccine serotypes in both time periods, but disease due to other nonvaccine serotypes has become more common.

Serotype 1 caused 11 (46%) of 24 PPE cases in the earlier period and 17 (34%) of 50 cases since the vaccine, she said.

Other nonvaccine serotypes caused only four cases (16%) of PPE in the prevaccine years but 26 cases (52%) of PPE in the postvaccine years.

The pneumococcal vaccine may need to be broadened to cover some of these serotypes, Dr. Byington suggested in an interview.

Clinical records for the 74 PPE cases reported concomitant bacteremia in 28 children, lung abscesses in 3, and peritonitis in 1 child.

Four children developed hemolytic uremic syndrome, and 38 required intensive care, primarily to manage respiratory failure or following surgical decortication.

Four children died, two of them from PPE due to a nonvaccine serotype. ■