Antibiotics 'Cleared' In Quebec Outbreak

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WASHINGTON — Quebec's massive outbreak of *Clostridium difficile*–associated diarrhea does not appear to have been associated with any specific antibiotic use pattern. Rather, poor infection control practices were likely to blame.

The *C. difficile*–associated outbreak appeared to be caused by poor infection control practices, an analysis from four Canadian hospitals found.

That conclusion, from an analysis of four Canadian hospitals headed by Dr. Karl A. Weiss and his associates at Maisonneuve-Rosemont Hospital, Montreal, was reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

The outbreak of *C. difficile*–associated diarrhea (CDAD), which occurred in 2002-2004 at several Quebec hospitals, was caused by a new strain of *C. difficile* found to be more virulent than those previously seen (N. Engl. J. Med. 2005;353:2442-9).

Although antibiotic usage has been strongly associated with the occurrence of CDAD, the circumstances of this outbreak were at odds with that explanation: No increase in CDAD cases was seen in any province other than Quebec, which actually has the lowest per capita antibiotic consumption of all the Canadian provinces (68 prescriptions per 100 inhabitants per year, compared with the national average of 79/100).

The investigators analyzed antibiotic use data for the time periods 1999-2001, 2002, and 2003 from two hospitals that were affected by the new *C. difficile* strain outbreak and two that were not. In one of the affected hospitals, the number of CD diagnoses per 1,000 population rose from 9 in 1999-2001 to 14 in 2002 to 33 in 2003. In contrast, rates in one of the unaffected hospitals remained stable, from 5/1,000 in 1999-2001 to 4 in 2002 to 5.5 in 2003.

Comparing affected with unaffected hospitals, there was no significant relation between number of CDAD cases per 1,000 admissions and daily consumption of cephalosporins, carbapenems, β-lactams/β-lactamase inhibitors, fluoroquinolones, or intravenous clindamycin. There was no significant protective effect from any antibiotic class, Dr. Weiss and his associates said at the meeting sponsored by the American Society for Microbiology.

Proper antibiotic use is key to controlling the emergence of resistant organisms, but in the case of CDAD antibiotics appear to be acting mainly as triggering agents in patients who acquire the new strain during their hospital stay.

Instead, the Quebec outbreak appeared to be mostly caused by poor infection control practices. The situation improved markedly in 2004-2005 following substantial investment by the provincial government and implementation of stringent infection control measures such as environmental cleaning with bleach, contact precautions, early detection of cases, and handwashing with soap and water. ■

Ventilation Is Risk Factor for CDAD

WASHINGTON — Mechanical ventilation significantly increases the risk that a hospitalized patient will develop *Clostridium difficile*–associated diarrhea, Dr. Chad A. Spangler and Dr. George F. Risi reported in a poster at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

This novel finding "has the potential to support new, additional prevention and control strategies in high-risk patient populations," said Dr. Spangler and Dr. Risi, of St. Patrick Hospital, Missoula, Mont.

The incidence of *C. difficile*–associated diarrhea (CDAD) rose from 1.6 to 8.0 cases per 1,000 discharges between 2001 and 2004 at the investigators' 200-bed hospital, with most cases occurring in the intensive care unit. There was no change in the rate of CDAD cases between 2003 and 2004 despite a reduction in the use of both antipseudomonal penicillins and fluoroquinolones during that period.

Among 3,247 patients who received antibiotics and had a length of stay greater than 3 days between January 2004 and March 2005, a total of 19% required ventilation. Of those 614, CDAD developed in 47 (7.6%). With the ventilated population excluded, the infection rate was just 1.2%. The odds ratio for infection was 6.6 among those who were ventilated, compared with those who were not, the investigators reported at the meeting, which was sponsored by the American Society for Microbiology.

Other significant risk factors for CDAD included ICU stay (odds ratio 5.9); use of either proton pump inhibitor or H_2 blocker antacids (2.7); and exposure to carbapenems (4.9), third-generation cephalosporins (4.0), or antipseudomonal penicillins (4.5). Patients requiring more than 2 days on the mechanical ventilator were 11 times more likely to develop CDAD than were those requiring less ventilation, they reported.

Probiotics May Prevent Deadly Diarrhea

WASHINGTON — In hospitalized patients taking antibiotics, coadministration of the probiotic *Saccharomyces boulardii* can reduce costs and shorten hospital stay by about 3 days, and may even save lives, Allyson L. Rovetto and her associates reported in a poster at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Antibiotic-associated diarrhea (AAD) occurs in up to 30% of all hospitalized patients given antibiotics. *Clostridium difficile*–associated diarrhea (CDAD) is both the most common and the most severe manifestation of the problem, with potential complications including colitis, ileitis, toxic megacolon, and death. A recent conservative estimate of the cost of CDAD—not including physicians' costs or posthospital care costs—was $1.1 billion per year in the United States, noted Ms. Rovetto and her associates, of Mount Sinai School of Medicine, New York.

Growing evidence suggests that probiotics such as the live, nonpathogenic yeast *S. boulardii* may be effective in preventing AAD and recurrent CDAD, although that organism is linked to increased risk for fungemia, which may also lead to severe complications and death (Clin. Infect. Dis. 2005;40:1625-34).

In a study funded in part by the National Center for Complementary and Alternative Medicine of the National Institutes of Health, the investigators used data from published literature to perform a cost-effectiveness analysis of administering vs. not administering *S. boulardii* along with antibiotics to hospitalized patients.

The probability of CDAD was estimated to be 2% among those given the probiotic along with antibiotics vs. 5% given antibiotics alone. The increase in hospital cost per patient with CDAD was $4,129, and the probability of CDAD complications was 3%. The cost of *S. boulardii* treatment is approximately $20. No firm estimates of the rate of fungemia due to *S. boulardii* are available, although it appears to be increasing.

Compared with antibiotics alone, treatment with antibiotics plus the probiotic yielded a cost saving of $81.60 per patient in addition to shortening hospital stays by about 3 days.

Patients older than 65 and those with hospital stays longer than 2 weeks stand to benefit the most. The analysis revealed that even if the protective effect of *S. boulardii* were halved, it would remain the preferred strategy. In fact, the only way the probiotic's benefit would be offset is if the incidence of fungemia exceeded 2 per 100 patients, "which seems highly unlikely," they remarked.

The meeting was sponsored by the American Society for Microbiology.

Oral Vaccine Effective Against Severe Travelers' Diarrhea

WASHINGTON — An experimental oral vaccine appears safe and effective in reducing the incidence and severity of travelers' diarrhea in adults, A. Louis Bourgeois, Ph.D., reported at the annual Interscience Conference on Antimicrobial Agents and Chemotherapy.

Travelers' diarrhea (TD) occurs in more than 30% of people who travel to developing countries. The new vaccine, under development by Sweden-based SBL Vaccines, is designed to protect against both the colonization factors and the two toxins produced by enterotoxigenic *Escherichia coli* (ETEC), which is responsible for 20%-50% of all TD cases and is also a common cause of morbidity and mortality among children who live in the developing world, said Dr. Bourgeois of Johns Hopkins University, Baltimore.

A total of 1,406 healthy volunteers aged 18 years and older—most of whom were going to study Spanish in either Guatemala or Mexico—were randomly assigned to receive either the oral vaccine or placebo.

Two doses were administered 2 weeks apart by the subject at home, with the second dose taken about 1 week prior to travel. The subjects kept symptom diary cards prior to and during the 2-4 weeks of travel and provided stool samples during twice weekly office visits at the travel site.

Overall, the vaccine did not prevent TD (defined as five or more watery stools plus gastrointestinal symptoms) caused by ETEC that contained only a vaccine antigen; 1.1% of 705 vaccine recipients were affected, versus 0.71% of the 701 placebo subjects. There was a trend toward prevention of cases in which the subject had three or more watery stools per 24 hours plus moderate to severe symptoms that caused a change in daily activity (0.57% vs. 1.43%), although this did not quite reach statistical significance.

However, a major difference in TD rates was seen between the subjects with and without vaccine "takes," defined as a serum IgA antibody titer of 1,358 or greater to the B-subunit of the cholera enterotoxin component of the vaccine.

Compared with the placebo group, the vaccine recipients who had "takes" had 63% vaccine efficacy against ETEC TD with any degree of gastrointestinal symptoms, 84% efficacy against ETEC TD with GI symptoms plus a change in daily activity, and 100% efficacy against ETEC TD with moderate to severe GI symptoms plus a change in activity. Severity of ETEC illness in vaccine "takes" was reduced, compared with placebo recipients, even when the ETEC strain did not match with the vaccine, Dr. Bourgeois noted.

Future formulations of this vaccine will need to produce better immunity, but "clearly this is a concept that deserves further evaluation," he said. ■