C. difficile *Infection Surveillance Moves Up Priority List*

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — Both health care–associated and community-acquired infections caused by the exotoxin-producing bacillus *Clostridium difficile* continue to increase, Dr. L. Clifford McDonald said during a meeting on emerging clostridial disease sponsored by the Centers for Disease Control and Prevention.

Better surveillance for *C. difficile*–associated disease (CDAD)—which can range in severity from mild diarrhea to fulminant colitis and death—has become a priority for the CDC.

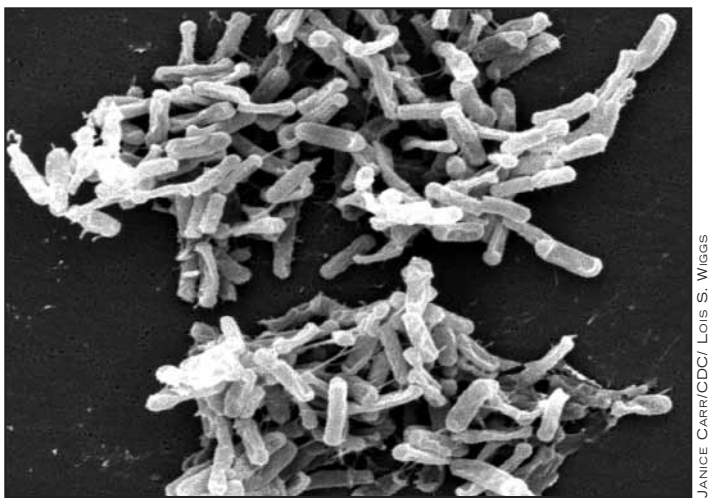
The meeting, also sponsored by the Food and Drug Administration and the National Institute of Allergy and Infectious Diseases, was convened to develop a research agenda for studying both *C. difficile* and the related anaerobic bacterium *Clostridium sordellii*, which has been linked to complications following medical abortions (see related story).

The CDC plans to issue a formal statement saying that all health care facilities should conduct some type of surveillance for CDAD, a recommendation the agency has already made informally through its Web site and public presentations. The CDC is also using established networks, such as the Emerging Infections Programs' FoodNet project, and various pilot studies and state-based epidemiologic investigations to isolate CDAD cases that arise in the community, including human infections that have also appeared in food-producing animals and strains seen in pregnant women, said Dr. McDonald, a medical epidemiologist at the CDC's Division of Healthcare Quality Promotion.

Hospital discharges for which CDAD was listed as any diagnosis doubled between 2000 and 2003 (Emerg. Infect. Dis. 2006;12:409-15). And in the latest yearly update of an ongoing survey, CDAD rates rose by another 25% from 2003 to 2004, from 61 per 100,000 population (178,000 total discharges) to 75 per 100,000 (211,000 discharges). Rates have been highest among adults aged 65 years and older.

Although most CDAD cases are still thought to arise in health care facilities, recent reports of community-associated cases—including some without recent antimicrobial use—have prompted concern that the problem may be underrecognized. At present, *C. difficile* cases are not nationally reportable.

Last December, the CDC reported a total of 33 cases of community-acquired CDAD in four U.S. states, including 10 infections among pregnant women and 8 in patients who did not have recent antimicrobial use (MMWR 2005;54:1201-5).



JANICE CARR/CDC/ LOIS S. WIGGS

All health care facilities should look for CDAD; this micrograph shows gram-positive *C. difficile* bacteria from a stool culture.

More recently, the CDC found that community-associated CDAD is increasing among patients seeking care at the Atlanta Veterans Affairs Medical Center. As of March 2006, about 30% of all CDAD cases there have occurred in outpatients, compared with about 10% in 2003. Of 61 outpatients with CDAD seen at the VA during 2003-2006, 50 had not been hospitalized in the previous 3 months and 19 had not received antimicrobials in the prior 30 days, Dr. McDonald reported.

Use of proton-pump inhibitors (PPIs) appeared to increase the risk; the CDAD patients without antimicrobial exposure were more likely to have been exposed to PPIs than were those with antimicrobial exposure (65% vs. 12%), he said.

Following the report of the 10 CDAD cases among pregnant women, the CDC conducted a survey of 405 infectious disease clinicians. Of those, 17 reported having personally seen such cases and another 23 were aware of such cases in their community. Of the 48 cases reported by the survey respondents, 14 of the infections occurred prior to delivery, 20% of the women developed recurrent disease, and three developed toxic megacolon. There was one fetal loss and one maternal death. It is unknown whether any of these cases were among those previously reported.

The infection is also emerging in food-producing animals, with recent outbreaks among neonatal pigs, dairy calves, and beef. Recently, the CDC has investigated seven cases of human CDAD in seven different states; in these patients, the strains appeared genetically similar on pulsed field gel electrophoresis to the epidemic animal strains, which has not been found in the past. ■

Infections Linked to Mifepristone Spur Debate on Proper Use

BY MIRIAM E. TUCKER
Senior Writer

ATLANTA — While the precise nature of the link between medical abortion and fatal toxic shock–like syndrome remains a mystery, the handful of case reports have prompted a difference in opinion about how such procedures should be carried out.

Activists have responded to the reports by calling for a removal of mifepristone (Mifeprex) from the U.S. market. Planned Parenthood, in contrast, has not stopped using mifepristone but has called for an end to the use of intravaginal misoprostol following oral mifepristone. This regimen is not approved by the Food and Drug Administration but is widely used and was associated with all five of the reported fatal *Clostridium sordellii* infections following medical abortion in the United States and Canada.

For its part, the American College of Obstetricians and Gynecologists will review the final report of the FDA panel before issuing any statements, Dr. Kevin Ault said in an interview.

Five cases of fatal *C. sordellii* infection have been reported against a background of approximately 560,000 medical abortions a year. "None of it is common. Clearly there are cases related to pregnancy that have nothing to do with pregnancy termination, and then there is the smaller group of nonpregnant cases. It's hard to find cause and effect here," Dr. Ault said in an interview following a 1-day meeting on emerging clostridial disease sponsored by the Centers for Disease Control and Prevention that he attended on behalf of ACOG.

At the meeting, researchers discussed the latest information in order to draft a research agenda for *C. sordellii* and *C. difficile*, another emerging infection associated with toxin-mediated sepsis that has also affected pregnant women.

Dr. Marc Fischer, a medical epidemiologist at the CDC, summarized the published literature to date on infections involving *C. sordellii*, a gram-positive anaerobic bacillus that resides in soil and colonizes the gastrointestinal and/or genital tracts of healthy humans. In various case reports and series, the organism has been identified in cases of pneumonia, endocarditis, arthritis, peritonitis, corneal ulcer, and bacteremia, and in wound infections among patients with necrotizing fasciitis, tissue allograft infections, neonatal omphalitis, postpartum endometritis, and episiotomy infections.

Between 1977 and 2001, *C. sordellii* genital tract infections and toxic shock–like syndrome were reported in 10 women, among whom the preceding events were childbirth (8) and medical abortion (1), reported from Canada in 2001. Another four cases were identified between 2003 and 2005, all involving women who had undergone medical abortions using the common "off-label" regimen of 200 mg oral mifepristone followed by 800 mcg vaginal misoprostol, said Dr. Fischer, who was the lead author of the published report of those four cases (N. Engl. J. Med. 2005;353:2352-60).

The four recent cases were all previously healthy women from California who developed symptoms including tachycardia, hypotension, vomiting or diarrhea, and abdominal pain within 5 days of taking mifepristone. Clinical laboratory findings in three of the patients included leukemoid reaction in all three, hemoconcentration in two, and thrombocytopenia in two. All died within a day of hospitalization. The clinical and pathologic findings in these cases were similar to those of the 10 previously reported cases, Dr. Fischer said.

Dr. L. Clifford McDonald, also of the CDC, reported that three additional cases of fatal toxic shock–like syndrome following medical abortion are currently under investigation by the CDC. Each of these differs in various ways from the previous five: One, in a woman who had taken oral mifepristone followed by vaginal misoprostol, was associated with *C. perfringens*, not *C. sordellii*. A second case, also of *C. perfringens*, involved the use of misoprostol with the cervical dilator Laminaria, not mifepristone. The third, although initially reported as being associated with a medical abortion, could not be confirmed as such. Moreover, investigation has shown pathologic findings consistent with appendicitis, serositis, and pneumonia, he noted.

Meanwhile, there have been three reported cases of toxic shock–like syndrome following spontaneous abortion, all involving *C. sordellii*. One of these patients was coinfected with *C. perfringens*. Another patient, in whom the *C. sordellii* did not possess the genes encoding the lethal toxin, was the only one who survived.

Several speakers offered hypotheses as to the mechanism for the lethal infections. Dr. James A. McGregor, of the obstetrics and gynecology department at Keck School of Medicine, Los Angeles, noted that mifepristone is a potent inhibitor of both progesterone and glucocorticoid receptors. As such, mifepristone may impair host immune responses and predispose women to lethal infections caused by toxigenic *C. sordellii* and other pathogens that exist normally in low numbers in the reproductive tracts of many women (Contraception 2005;72:393).

Given that there are data to suggest that early pregnancy can be terminated medically using only vaginal misoprostol without mifepristone (Contraception 2004;70:121-6), this might be considered as a possible primary prevention strategy, Dr. McGregor said.

Alternatively, medical abortions could be limited to the FDA-approved regimen of 600 mg oral mifepristone followed within 2 days by 400 mcg oral misoprostol, as Planned Parenthood has done, he suggested.

Dr. Ault advised that physicians present patients with the risks and benefits of all of the medical and surgical termination options and obtain informed consent. ■