

Update on Emerging Infections From the Centers for Disease Control and Prevention

Commentator

Fredrick M. Abrahamian, DO

From the Department of Emergency Medicine, Olive View-University of California, Los Angeles Medical Center, Sylmar, CA.

Section Editors

David A. Talan, MD

Olive View-UCLA Medical Center, Sylmar, CA.

Gregory J. Moran, MD

Robert Pinner, MD

Centers for Disease Control and Prevention, Atlanta, GA.

Editor's note: This article is part of a regular series on emerging infections from the Centers for Disease Control and Prevention (CDC) and the EMERGENCY ID NET, an emergency department-based and CDC-collaborative surveillance network. Important infectious disease public health information with relevance to emergency physicians is reported. The goal of this series is to advance knowledge about communicable diseases in emergency medicine and foster cooperation between the front line of clinical medicine and public health agencies.

Severe *Clostridium Difficile*-Associated Disease in Populations Previously at Low Risk—Four States, 2005

[Centers for Disease Control and Prevention. Severe *Clostridium difficile*-associated disease in populations previously at low risk—four states, 2005. *MMWR Morb Mortal Wkly Rep.* 2005;54:1201-1205.]

Clostridium difficile is a spore-forming, Gram-positive bacillus that produces exotoxins that are pathogenic to humans. *C difficile*-associated disease ranges in severity from mild diarrhea to fulminant colitis and death. Antimicrobial use is the primary risk factor for development of *C difficile*-associated disease because it disrupts normal bowel flora and promotes *C difficile* overgrowth. *C difficile* typically has affected older or severely ill patients who are hospital inpatients or residents of long-term-care facilities. Recently, however, both the frequency and severity of health-care-associated *C difficile*-associated disease has increased; from 2000 to 2001, the rate of US hospital discharge diagnoses of *C difficile*-associated disease increased by 26%.¹ One possible explanation for these increases is the emergence of a previously uncommon strain of *C difficile* responsible for severe hospital outbreaks.² Although individual cases of *C difficile*-associated disease are not nationally reportable, in 2005, the Pennsylvania Department of Health and CDC received several case reports of serious *C difficile*-associated disease in otherwise healthy patients with minimal or no exposure to a health care setting. An investigation was initiated by the Philadelphia Department of Public Health,

Pennsylvania Department of Health, and CDC to determine the scope of the problem and explore a possible change in *C difficile*-associated disease epidemiology. This report summarizes the results of the investigation in Pennsylvania and 3 other states, which indicated the presence of severe *C difficile*-associated disease in healthy persons living in the community and peripartum women, 2 populations previously thought to be at low risk. The findings underscore the importance of judicious antimicrobial use, the need for community clinicians to maintain a higher index of suspicion for *C difficile*-associated disease, and the need for surveillance to better understand the changing epidemiology of *C difficile*-associated disease.

CASE REPORTS

Case 1

A woman aged 31 years who was 14 weeks pregnant with twins went to a local emergency department (ED) after 3 weeks of intermittent diarrhea, followed by 3 days of cramping and watery, black stools 4 to 5 times daily. Stools specimens tested positive for *C difficile* toxin, and the patient was admitted. Her only antimicrobial exposure during the preceding year was trimethoprim sulfamethoxazole (for a urinary tract infection) approximately 3 months before admission. She was treated with metronidazole and discharged but was readmitted the next day for 18 days with severe colitis, receiving metronidazole, cholestyramine, and oral vancomycin. She improved while receiving vancomycin and was allowed to return home. However, 4 days later she was readmitted with diarrhea and hypotension. She spontaneously aborted her fetuses. Despite aggressive treatment, including a subtotal colectomy, intubation, and inotropic medication, the patient died on the third hospital day. Histopathologic examination of the colon demonstrated megacolon with evidence of pseudomembranous colitis.

Case 2

A girl aged 10 years (unrelated and without contact with case 1) went to a children's hospital ED because of intractable diarrhea, projectile vomiting, and abdominal pain. She had not taken antimicrobials during the preceding year. Stool specimens

were positive for *C difficile* toxin. The child had been healthy until 2 weeks before the ED visit, when she became symptomatic within days of her younger brother's having a febrile diarrheal illness. The boy was not receiving antimicrobials when he became ill. His symptoms resolved within 2 to 3 days without medical treatment, but his sister had a temperature as high as 102°F (39°C), abdominal pain, and diarrhea. One week into her illness, she was examined by a clinician, who performed a rapid streptococcal antigen test on a swab from her oropharynx; the result was positive. The patient was prescribed amoxicillin but was unable to take it because of her stomach cramps and diarrhea; her symptoms worsened until she was having liquid stools up to 14 times daily. Symptoms resolved with hospital admission and the administration of intravenous fluids, electrolytes, and metronidazole.

EPIDEMIOLOGIC AND LABORATORY INVESTIGATIONS

In May and June 2005, a request for voluntary reports of peripartum *C difficile*-associated disease (ie, 4 weeks before and after delivery) was initiated by Philadelphia Department of Public Health; case definitions for peripartum *C difficile*-associated disease were developed and distributed nationally through the Epidemic Information Exchange (Epi-X) and locally through the Philadelphia Department of Public Health Health Alert Network. The New Jersey Department of Health and Senior Services also distributed the alert statewide through its Health Alert Network system. A separate request for reporting of community-associated *C difficile*-associated disease, along with a case definition, was developed and distributed in June in Philadelphia and 4 surrounding Pennsylvania counties (Bucks, Chester, Delaware, and Montgomery) through local and statewide health alert networks.

Detailed, open-ended interviews were conducted with patients who were reported by hospital personnel to state and local health departments after distribution of the notices. Medical details, such as type of antimicrobial agent and duration, were confirmed with treating clinicians whenever possible. To determine the minimum population rate and rate per antimicrobial prescription of community-associated *C difficile*-associated disease, the number of cases reported from Philadelphia and 4 surrounding counties was divided by 2004 US census population estimates for these 5 areas. The number of antimicrobial prescriptions was calculated on the basis of census estimates of the population surveyed, multiplied by national prescribing rate estimates.³ Available toxin-positive stool samples were cultured for *C difficile* with standard methods. Isolates underwent pulsed-field gel electrophoresis, toxinotyping, and detection of binary toxin and deletions in *tcdC*, a putative negative regulator of toxin production.^{2,4}

Ten peripartum and 23 community-associated *C difficile*-associated disease cases were reported from 4 states during May to June 2005, with onset dates ranging from February 26, 2003, to June 28, 2005. All but 1 of the cases occurred during 2004 to

2005. Age of nonperipartum cases ranged from 6 months to 72 years (mean 26 years; median 23 years). Peripartum cases occurred in patients from New Hampshire, New Jersey, Ohio, and Pennsylvania; because community-associated *C difficile*-associated disease surveillance was conducted only in the greater Philadelphia area, these cases were only from this area. Transmission to close contacts was evident for 4 cases: 2 were in children of *C difficile*-associated disease patients with peripartum exposures, 1 was in an adult caring for a hospitalized parent with confirmed *C difficile*-associated disease, and 1 was in an adult who visited a parent with confirmed *C difficile*-associated disease in a nursing home. One peripartum mother who transmitted *C difficile* to her child also transmitted *C difficile*-associated disease to a family friend.

Eight (24%) of 33 patients reported no exposure to antimicrobial agents within 3 months before *C difficile*-associated disease onset. Five of these were children, 3 of whom required hospitalization. Three of the 8 cases without exposure to antimicrobial agents occurred in patients who had close contact with a person with diarrheal illness; 2 of these persons had confirmed *C difficile*-associated disease. An additional 3 (9%) of 33 patients contracted *C difficile*-associated disease after receiving fewer than 3 doses of antimicrobials; 2 received only 1 dose of clindamycin for group B streptococcus prophylaxis before *C difficile*-associated disease onset. Clindamycin was the most common antimicrobial exposure noted; overall, 10 (30%) of 33 cases were in patients who reported exposure to the drug before disease onset; these 10 patients included the 2 who had fewer than 3 doses of antimicrobials. Fifteen (46%) patients required hospitalization or an ED visit. Thirteen (39%) patients had a relapse of disease and required antimicrobials.

The estimated minimum annual incidence of community-associated *C difficile*-associated disease in Philadelphia and its surrounding 4 counties during July 2004 to June 2005 was 7.6 cases per 100,000 population, with 1 case of *C difficile*-associated disease for every 5,549 outpatient antimicrobial prescriptions; this figure is based on national estimates of antimicrobial prescribing in ambulatory settings applied to the Philadelphia area. Two patient isolates were available for characterization and were compared with the recently described "epidemic strain" that has been detected as the cause of either severe hospital outbreaks or hospital-endemic cases of *C difficile*-associated disease in 6 states.² Neither shared the same toxinotype as the epidemic strain, but both were binary toxin positive; one isolate, from an Ohio peripartum *C difficile*-associated disease case, was greater than 80% related by pulsed-field gel electrophoresis to the epidemic strain, and the other, from a Philadelphia-area community-associated *C difficile*-associated disease case, had an 18-base-pair deletion in *tcdC*.

Considered in the context of recent high-morbidity, hospital-associated outbreaks in North America, Great Britain, and the Netherlands,⁵ these cases of severe *C difficile*-associated disease in populations previously thought to be at low risk might further reflect the changing epidemiology of *C difficile*-

associated disease. Certain features of *C difficile*-associated disease 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, might be changing.

C difficile exotoxins A and B cause colonic dysfunction and cell death. The epidemic strain produces 16 times more toxin A and 23 times more toxin B compared with other common strains.⁵ The increased severity of epidemic *C difficile*-associated disease might result from this level of toxin production; however, the actual role of *tcdC* deletions in increased toxin production has not been determined. *C difficile* toxinotype 0 is the historical standard type; variant toxinotypes have previously accounted for less than 20% of US hospital isolates.⁶ Although the role of this binary toxin in human disease is unknown, it was previously detected in only 6% of clinical isolates but now is found uniformly in the epidemic strain.⁶ The isolates recovered during this investigation were both variant toxinotypes and carried the gene for binary toxin; one also carried the same 18-base-pair deletion in *tcdC* as the epidemic strain.

Virulent strains, which cause more severe disease in populations at high risk, might also cause more frequent, severe disease in populations previously at low risk (eg, otherwise healthy persons with little or no exposure to health care settings or antimicrobial use). Although the minimum annual incidence cited in this report is similar to previous estimates in ambulatory populations (8 to 12 cases per 100,000 population), the community-associated *C difficile*-associated disease case definition more stringently excluded hospital-acquired *C difficile*-associated disease.^{7,8} The estimated case rate per antimicrobial prescription is twice as high as the less than 1 case per 10,000 incidence cited in these earlier studies.^{7,8} Because reporting in this investigation was voluntary, the true incidence of community-associated *C difficile*-associated disease is probably higher. Because historic surveillance data are not available, determining whether *C difficile*-associated disease rates in peripartum women are changing is not possible; however, the only available report suggests a low baseline incidence, with only 3 obstetric cases identified among 74,120 obstetrics and gynecology admissions to 1 North Carolina hospital during 1985 to 1995.⁹

The findings in this report are subject to at least 2 limitations. First, because the report describes a convenience sample, the results are subject to reporting and selection biases. Second, because this sample was collected in a limited geographic region, results might not be generalizable to other regions. Moreover, although a single national estimate for ambulatory prescribing rates was applied to this region, substantial variation in these rates might exist.

Further investigation into the scope of community-associated *C difficile*-associated disease acquisition and related risk factors is warranted. Nonetheless, the cases described in this report demonstrate the need for clinicians to consider the diagnosis of *C difficile*-associated disease in patients with severe

diarrhea even if the patients do not necessarily have traditional risk factors such as recent hospitalization or antimicrobial use. Patients should seek medical attention for diarrhea lasting longer than 3 days or accompanied by blood or high fever. The findings underscore the fact that antimicrobial exposure is not benign and that judicious antimicrobial use in all health care settings should continue to be emphasized.

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COMMENTARY

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Over the past few years, traditional nosocomial pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA) have emerged as community-associated infections among patients without traditional risk factors. The present report suggests that another typical nosocomial pathogen, *Clostridium difficile*, has also emerged as a cause of infections among individuals without health care setting exposures. Community-associated MRSA infections are due to new strains possessing previously uncommon virulence factors. Similarly, some *C difficile*-associated disease also appears to be caused by a new *C difficile* variant that produces greater amounts of exotoxin than older nosocomial strains.

The case definition for community-associated *C difficile*-associated disease in any adult or child has been proposed as the