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Community-associated *Clostridium difficile* infection: How real is it?

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Abstract

Community-associated *Clostridium difficile* infection (CA-CDI) represents 32% of all CDI cases based on U.S. population-based data. The current epidemic strain, NAP1, is the most prevalent strain causing these infections. Although complications, recurrence and death are uncommon, one-fourth of the CA-CDI patients are hospitalized within 7 days after the diagnosis.

Keywords

Community-associated; *Clostridium difficile* infection; Surveillance

In the early 2000s, a previously uncommon *Clostridium difficile* strain designated restriction endonuclease analysis type BI, North American pulsed-field gel electrophoresis type 1 (NAP1), PCR ribotype 027 (i.e., BI/NAP1/027) was found to be causing outbreaks in Canada, United States, and Europe [1–3]. Since then, increases in incidence and severity of *C. difficile* infection (CDI) among hospitalized patients have been documented [3–5], and in at least one US region [6], *C. difficile* is now the most common cause of healthcare-associated infections. In addition to its emergence as an important healthcare-acquired pathogen, *C. difficile* has also been increasingly reported among individuals in the community who were traditionally considered to be at low risk, such as healthy peripartum women, children and persons with minimal or no recent exposure to healthcare settings [7].

In response to these changes in *C. difficile* epidemiology, the Centers for Disease Control and Prevention (CDC) launched an active, population-based surveillance for CDI in 2009 through the Emerging Infections Program (EIP). The objectives and methods of this surveillance have been described elsewhere [8]. Briefly, one of the objectives of the EIP CDI surveillance is to describe the epidemiology of community-associated CDI (CA-CDI). In order to do that, EIP epidemiologists in each participating site investigate all positive

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Potential conflicts of interest

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C. difficile toxin or molecular assays from clinical, reference and commercial laboratories serving the catchment area. A case for the surveillance is defined as a positive *C. difficile* stool specimen in a resident of surveillance area aged 1 year or older who did not have a positive test in the previous 8 weeks. Medical records are reviewed to collect information on symptoms, co-infections, outcomes and recent healthcare exposures. Based on location of stool collection and healthcare exposures in the 12 weeks prior to specimen collection, cases are classified as community-associated (CA) if a positive specimen was collected as an outpatient or within 3 days of an acute care admission in a patient without documentation of an overnight stay in a healthcare-facility in the 12 weeks prior to stool collection; or healthcare-associated (HA) if positive specimen was collected more than 3 days after hospital admission, any time during nursing-home stay, or in a patient with documented overnight stay in a healthcare-facility in the 12 weeks prior to stool collection. As part of this surveillance, cultures are obtained from a convenience sample of positive *C. difficile* stool specimens, and recovered *C. difficile* isolates are sent to CDC laboratory for molecular characterization.

In 2010, CDI surveillance was conducted in eight diverse US geographic areas including: San Francisco County, CA; the five county Denver metropolitan area, CO; New Haven/ Waterbury Area, CT; the eight county Atlanta metropolitan area, GA; Benton, Morrison, Stearns, and Todd Counties, MN; Monroe County, NY; Klamath County, OR; and Davidson County, TN. Seven of these eight surveillance sites contributed a full calendar year of data, while one site contributed 7 months of data.

A total of 10,342 CDI cases were identified across participating sites. Of those, 3269 (32%) were community-associated. The median age of CA-CDI cases was 52 years (range: 1–93years), and 61% were female. Over one-fourth of the cases (27%) were hospitalized within the 7 days after positive *C. difficile* stool collection. Admission to the intensive care unit within the 7 days after stool collection, colectomy and death was uncommon: 2%, 0.3%, and 0.9% of cases, respectively. The recurrence rate was 9%; recurrences occurred a median of 26 days (range 14–56 days) after the incident *C. difficile* positive stool specimen. Co-infections with other enteric pathogens were documented in 8 patients; 6 with *Salmonella* sp. and 2 with *Shigella* sp. Of the female patients with CA-CDI, 1% was in the peripartum period.

Of the 588 CA-CDI isolates submitted to CDC, the most common pulsed-field gel electrophoresis (PFGE) type was NAP1 (138; 23.5%), followed by NAP11 (67; 11.4%), and NAP4 (63, 10.7%). A large proportion of isolates did not fall under any of the known PFGE types and were classified as unnamed (Table 1).

The proportion of all CDI cases classified as CA-CDI, 32%, is higher than the 20%–27% that have been previously reported in Canada and in one region of the United States using a similar definition [9,10]. A possible reason for this may be the inclusion of large outpatient/ commercial laboratories in the surveillance. The incidence of CA-CDI is estimated to range between 20 and 40 per 100,000 population based on studies conducted prior to the introduction of molecular diagnostics for *C. difficile* [11,12]. Since 2009, the U.S. Food and Drug Administration (FDA) has approved five nucleic acid amplification tests (NAAT)

for CDI diagnosis [13]. NAAT is known to have a higher sensitivity compared to enzyme immunoassay. Based on a recent meta-analysis, the overall sensitivity of NAAT was 90% (95% CI 88%–91%) compared to toxigenic culture or cell culture cytotoxicity neutralization assay [14]. The adoption of more sensitive testing for CDI diagnosis by clinical and commercial laboratories will likely increase CDI rates overall, including CA-CDI rates.

Reports of CDI among peripartum women from 4 US states called attention to the risk of disease among this patient group [7]. Based on our data, the peripartum cases represented only a small proportion, 1%, of all CA-CDI cases among women suggesting that CDI among this group is still relatively uncommon.

The recurrence rate for CA-CDI (9%) in our data is lower than the 22% recurrence rate reported for healthcare-associated CDI (HA-CDI) cases by other investigators [15] and the 18% recurrence rate we found among HA-CDI cases. This may be related to several factors such as: 1) fewer exposures among CA-CDI cases to *C. difficile*-provocative antibiotics and to inpatient healthcare settings after the CDI diagnosis, which are known to be associated with increased risk of recurrent disease. Based on our data, CA-CDI cases who were hospitalized within the 7 days after positive *C. difficile* stool collection had a recurrence rate of 11% compared to 8% among those CA-CDI cases who were not admitted after the diagnosis reinforcing the hypothesis that inpatient healthcare exposure plays a role in recurrence rate; and 2) younger age among CA-CDI cases (median age of 52 years, compared to 74 years for HA-CDI cases).

Risk factors for CA-CDI have not been well explored. Although antibiotics are known to be the major drivers of CDI [16], there have been reports of CA-CDI among persons without antibiotic exposure [9,17]. This raised concerns about other potential risk factors for CDI in the community. The use of acid-suppressive agents, particularly proton pump inhibitors (PPI), has been associated with an increased risk of CA-CDI in some studies [18,19]. The mechanism by which PPI increases the risk of CDI is not fully understood, and no data are currently available suggesting that PPI stewardship will decrease CA-CDI rates.

The isolation of *C. difficile* in retail meat has led many investigators to suspect potential food borne transmission of this pathogen. Previous reports have shown a prevalence of 2%–11% of *C. difficile* in retail meats [20–22]. However, a recent study done across 9 US diverse geographic locations found no *C. difficile* in the 1755 retail meat products cultured [23]. *C. difficile* has also been isolated from the environment in outpatient clinics [24]and daycare centers [25], suggesting that the environment may play a role in disease transmission in the community. Finally, exposure to household members with CDI and children aged less than 2 years, a group that is known to be highly colonized with *C. difficile*, have been associated with an increased risk of *C. difficile* in the community [11,26]. Although these potential sources of *C. difficile* in the community have been described, they have not been fully evaluated, and epidemiologic correlation between these sources and CDI is still lacking.

In conclusion, community-associated CDI is real and it represents one-third of all CDI cases. The current epidemic strain, NAP1, is the most prevalent strain causing these infections.

Although complications, recurrence and death are uncommon, one-fourth of the patients with CA-CDI are hospitalized within 7 days after the diagnosis. Studies looking at risk factors and sources of CDI in the community are needed to inform prevention strategies.

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Table 1

Pulsed-field gel electrophoresis (PFGE) type among community-associated *C. difficile* infection ($N = 588$).

PFGE type	*N* (%)
NAP1	138 (23.5)
NAP2	16 (2.8)
NAP3	4 (0.7)
NAP4	63 (10.7)
NAP5	7 (1.2)
NAP6	38 (6.5)
NAP7	20 (3.4)
NAP8	2 (0.3)
NAP9	22 (3.8)
NAP10	12 (2.0)
NAP11	67 (11.4)
NAP12	16 (2.8)
Unnamed	183 (31.1)