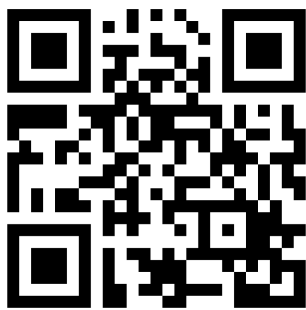


Community-acquired *Clostridium difficile* infection: an increasing public health threat

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Abstract: There has been a startling shift in the epidemiology of *Clostridium difficile* infection over the last decade worldwide, and it is now increasingly recognized as a cause of diarrhea in the community. Classically considered a hospital-acquired infection, it has now emerged in populations previously considered to be low-risk and lacking the traditional risk factors for *C. difficile* infection, such as increased age, hospitalization, and antibiotic exposure. Recent studies have demonstrated great genetic diversity for *C. difficile*, pointing toward diverse sources and a fluid genome. Environmental sources like food, water, and animals may play an important role in these infections, apart from the role symptomatic patients and asymptomatic carriers play in spore dispersal. Prospective strain typing using highly discriminatory techniques is a possible way to explore the suspected diverse sources of *C. difficile* infection in the community. Patients with community-acquired *C. difficile* infection do not necessarily have a good outcome and clinicians should be aware of factors that predict worse outcomes in order to prevent them. This article summarizes the emerging epidemiology, risk factors, and outcomes for community-acquired *C. difficile* infection.

Keywords: community acquired infection, *Clostridium difficile*, epidemiology, risk factors, outcome

Introduction

Clostridium difficile is the major cause of infectious diarrhea in hospitalized patients¹ and the primary infectious cause of pseudomembranous colitis.² Recent studies have shown increasing incidence, severity, and recurrence rates of *C. difficile* infection (CDI).³⁻⁹ It has recently surpassed methicillin-resistant *Staphylococcus aureus* as the most common hospital-acquired infection in the USA.^{10,11} However, in contrast with prior epidemiological studies, CDI is now being increasingly recognized as a cause of diarrhea in the community, especially in younger individuals and in populations lacking the traditional risk factors for CDI, such as hospitalization and antibiotic exposure.^{3,4,12-14} This review focuses on the epidemiology, increasing importance, novel risk factors, and outcomes for community-acquired CDI.

Epidemiology of community-acquired CDI

In 2007, the Infectious Diseases Society of America proposed guidelines for the classification of CDI to overcome the issue of multiple surveillance definitions.¹⁵ CDI is defined as: community-acquired if symptom onset occurs in the community or within 48 hours of admission to a hospital, after no hospitalization in the past 12 weeks; hospital-acquired if onset of symptoms occurs more than 48 hours after admission to or

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less than 4 weeks after discharge from a health care facility; or indeterminate if symptom onset occurs in the community between 4 and 12 weeks after discharge from a hospital.^{15,16} A study from the Cleveland Clinic (Cleveland, OH, USA) compared two different definitions of community-acquired CDI and showed concordance in only 71% of cases.¹⁷ Using different definitions, the percentage of community-acquired CDI varied from 10% to 37% of the total cases in another study.¹⁸ These studies have highlighted the need to use a standard definition to distinguish between hospital-acquired CDI and community-acquired CDI.

The incidence of CDI was relatively stable until the mid-to-late 1990s, after which its epidemiology changed dramatically. Since 2000, there have been several reports of an increase in the incidence and severity of CDI,^{5,7,11,19–23} with CDI being increasingly recognized in the community.^{3,13,24–28} Community-acquired CDI was likely previously underdiagnosed owing to a lack of awareness of CDI outside the hospital setting. Data from North America and Europe suggest that 20%–27% of all CDI cases are community-associated, with an incidence of 20–30 per 100,000 population.^{3,13,29,30} In a population-based US study, 41% of the 385 definite CDI cases were community-acquired; the overall incidence of community-acquired and hospital-acquired CDI increased by 5.3-fold and 19.3-fold, respectively, over the study period.¹² In both this and another study,³¹ patients with community-acquired infection were younger compared with those with hospital-acquired infection (median age 50 years versus 72 years), more likely to be female (76% versus 60%), had lower comorbidity scores, and were less likely to have severe infection (20% versus 31%).¹²

Traditional risk factors may be absent in community-acquired CDI

Community-acquired CDI has been described in populations previously considered to be at low risk, including healthy peripartum women, children and young adults, antibiotic-naïve patients, and those with no recent health care exposure.^{3,13,32,33}

Antibiotic exposure

Exposure to antimicrobial agents is recognized as the most important risk factor for CDI.³⁴ A recent study by Dial et al determined that as many as 45.7% of patients with CDI had no prior exposure to antibiotics in the 90-day period before the onset of CDI.³⁵ In another case-control study, 52% of patients had no antibiotic exposure in the 4-week time period prior to CDI onset.¹³ A population-based cohort

study from the Mayo Clinic, Rochester, MN, USA, showed that patients with community-acquired CDI were less likely to have been exposed to antibiotics when compared with those having hospital-acquired CDI (78% versus 94%).¹² A case-control study demonstrated that, although patients with community-acquired CDI were more likely to have had antibiotic exposure compared with healthy controls, 27% of cases did not receive antibiotics in the 6 months prior to infection.³⁶ A recent large epidemiological study using active surveillance showed that more than a third of patients with community-acquired CDI did not receive antibiotics in the 12 weeks prior to infection.³⁷ These results indicate that although antimicrobial use remains a risk factor for CDI in the community, it may not be as important for hospital-acquired CDI. The risk of developing community-acquired CDI may also be affected by the antimicrobial agent administered, with two recent meta-analyses indicating that exposure to clindamycin, fluoroquinolones, and beta lactams/beta lactamase inhibitors conferred much greater risk of community-acquired CDI compared with macrolides, sulfonamides, and penicillins.^{38,39}

Age

Although increasing age is a well recognized risk factor for CDI, studies have consistently shown that case patients with community-acquired CDI were younger than those with hospital-acquired CDI.^{12,40} In a population-based study from Olmsted County, MN, USA, patients with community-acquired CDI were younger than those with hospital-acquired CDI (median age 50 years versus 72 years) and more likely to be female (76% versus 60%).¹² A recent, large, population-based study with active surveillance for community-acquired CDI revealed a median patient age of 51 years.³⁷ An epidemiological study from the UK showed that almost all community-acquired CDI cases occurred in patients younger than 65 years of age.⁴¹ In contrast, almost one third of patients with community-acquired CDI in another cohort were elderly (aged >65 years), similar to findings in another investigation where almost a half of patients with community-acquired CDI were elderly.³¹ These findings suggest that although patients with community-acquired CDI are younger than those with hospital-acquired CDI, community-acquired CDI occurs among all age groups in the community. There has been increasing evidence of community-acquired CDI affecting the pediatric population, traditionally thought to be at low risk for CDI, with a population-based cohort study from the Mayo Clinic, showing a striking increase in CDI in the pediatric population over the last 20 years,

especially in the community setting and in infants,⁴² while other studies have reported an increase in pediatric CDI presenting to the outpatient setting⁴³ and the emergency room.⁴⁴ The role of asymptotically colonized infants in the spread of community-acquired CDI is discussed below.

Gastric acid suppression

The role of gastric acid suppression in CDI remains controversial. There is conflicting evidence as to whether stomach acid kills *C. difficile* spores.^{45,46} Proton pump inhibitors (PPIs) may also affect the microbiota of the stomach and the large intestine.⁴⁷ Recent data have suggested that circumventing the potentially protective effect of stomach acid, for example through the use of post-pyloric enteral feeding or the use of PPIs or histamine-2 receptor blockers, may lead to a two to three-fold increased risk of acquisition of CDI.^{25,48} Two recent meta-analyses concluded that PPI use is associated with 1.69–1.74 times the odds of CDI relative to no PPI use.^{49,50} Some other studies have shown that after controlling for important confounders, use of PPIs and histamine-2 receptor blockers was not associated with the risk of CDI,⁵¹ or adverse outcomes from CDI.⁵² Thus, it is not clear whether use of acid-suppressing drugs is an independent risk factor for CDI, although the US Food and Drug Administration has recently issued a warning that PPIs are associated with an increased risk of CDI. Hospital-acquired CDI and community-acquired CDI may differ in their relationship to PPI use owing to differences in circulating Clostridial strains and the differential antibiotic exposure in the two settings.⁵³ There was a trend toward higher PPI use in antibiotic-naïve patients with community-acquired CDI when compared with patients with community-acquired CDI and antibiotic exposure.³⁷ A retrospective review demonstrated a clinically relevant interaction between antibiotic and PPI use in hospitalized patients with CDI, with patients receiving a single antibiotic being more than five times more likely to be exposed to PPIs when compared to patients receiving five or more antibiotics.⁵⁴

Comorbid conditions

Additional potential risk factors for CDI that have been identified include a higher number of comorbid conditions, ie, chronic kidney disease, inflammatory bowel disease, immunodeficiency including human immunodeficiency virus (HIV) infection, hypoalbuminemia, malignant lesions, solid organ transplant, and use of chemotherapeutic agents.^{55–58} These patients are at increased risk of CDI not only due to their underlying disease, but also their frequent prolonged

hospitalizations and broad-spectrum antimicrobial use. As care shifts closer to the home and these patients experience more outpatient health care, it will not be surprising if we observe increasing community-acquired CDI in these patient populations.

Reduced microbial diversity in the gut is a common pathogenic pathway for inflammatory bowel disease and CDI.⁵⁹ Patients with inflammatory bowel disease, especially those with colonic involvement, have long been known to have increased CDI rates and disproportionately higher morbidity and mortality compared with CDI patients without inflammatory bowel disease.^{55,57,60,61} Multiple reasons probably account for this, including older age, medications (immunosuppressives/antibiotics), and hospitalization. In retrospective population studies of both adults and children, patients with inflammatory bowel disease and CDI were younger and more often had acquired infections as outpatients compared with patients without inflammatory bowel disease and with CDI.^{60,62,63}

Chronic kidney disease has been associated with increased risk of CDI in several studies,^{64,65} although some found increased risk only in patients undergoing dialysis.⁶⁶ Concomitant acute kidney injury predicts a worse outcome in CDI,⁶⁷ which is in line with the Infectious Diseases Society of America guidelines that the presence of acute kidney injury is a marker of CDI disease severity.¹⁶

Steroid initiation has been shown to increase CDI risk three times over other immunomodulator agents in patients with inflammatory bowel disease independent of dose and treatment duration,⁶⁸ and steroid use has been shown to increase short-term mortality in hospitalized patients with CDI.⁶⁹ High-dose corticosteroid use has also been associated with an increased risk of CDI relapse in solid organ transplant patients.⁷⁰ Data on risk of CDI with other immunomodulatory medications is more controversial, with some studies failing to find an association^{68,71} and others showing increased risk.^{60,72} *C. difficile* has been recognized as the most common cause of bacterial diarrhea in HIV patients, although rates of CDI have reduced in the HIV population after initiation of antiretroviral therapy, so not mirroring the global trend of increased CDI burden.⁷³

Several early studies have shown an increased risk of CDI in the transplant population, although infection did not seem to have a worse outcome in hematopoietic stem cell transplant patients, and most patients responded well to standard CDI therapy.^{74–77} No significant difference was found with regard to disease severity in solid organ transplant recipients and controls.⁷⁰ A recent, nested, retrospective,

case-control study demonstrated a high rate of CDI in hematopoietic stem cell transplant recipients, with prior chemotherapy, broad-spectrum antimicrobial use, and vancomycin-resistant enterococci colonization recognized as risk factors.⁷⁸ Similar risk factors were observed in a retrospective study in kidney transplant recipients.⁷⁹ The onset to CDI in autologous hematopoietic stem cell transplant recipients and kidney transplant recipients has been found to be less than a week.^{74,78,79} This supports the hypothesis that CDI is not always nosocomially acquired, even when it presents in the hospital setting, and patients may have been colonized earlier, even in the community setting.

Sources and transmission of community-acquired CDI

The primary means of transmission of CDI is believed to be from environment-to-person or person-to-person via the fecal-oral route. The organism is ingested either as the vegetative form or as spores (which survive for longer periods in the environment and are able to endure acidic stomach pH). Antimicrobial drugs alter the protective gut microbiome by decreasing bacterial diversity and create a favorable microenvironment for *C. difficile* to colonize and proliferate. Patients with diarrhea secondary to CDI shed spores into the environment and may be considered as a primary source of spreading infection.⁸⁰ Infection control guidelines strongly recommend strict isolation of these patients when inpatients, in order to limit person-to-person transmission via health care personnel or the environment.^{81–83} Despite implementation of infection control practices, there is an increasing incidence of community-acquired CDI, which suggests alternate sources of infection and modes of transmission in the community. Assorted sources may be playing a role in *C. difficile* transmission alongside symptomatic patients. Using whole genome sequencing of more than 1,200 *C. difficile* isolates from the health care and community setting, a study based in Oxfordshire, UK, demonstrated that 45% of all isolates were genetically distinct from all previously tested isolates.⁸⁴ The genetically diverse nature of these isolates suggests the existence of other important sources of infection apart from symptomatic patients. These possible novel factors are discussed below.

Novel and established risk factors

The factors responsible for the emergence of CDI in the community include increasing outpatient antibiotic prescriptions, greater use of acid-suppression medications, an increase in the proportion of asymptomatic carriers in the community

leading to an increase in person-to-person transmission, novel risk factors like food and water contamination, and the epidemic *C. difficile* strain.^{3,85–87} Higher clinician awareness of CDI as a possible explanation of diarrhea in the community probably also contributes to the increased incidence via an increase in the number of stool tests for *C. difficile* performed in patients with diarrhea.

Role of asymptomatic carriers

Colonization of healthy nonhospitalized adults is uncommon, but colonization rates among hospitalized patients are much higher, ranging from 25% to 55%.^{88,89} In the context of a *C. difficile* infection outbreak in a long-term care facility, a study from Cleveland, OH, USA, found that more than half of asymptomatic residents were fecal carriers of toxigenic *C. difficile* strains, more than a third of which were epidemic North American pulse-field type 1 (NAP1) strains. Asymptomatic carriers outnumbered CDI patients seven to one during this study. Previous CDI and recent antibiotic use were found to predict asymptomatic carriage. Skin and environmental surface contamination in asymptomatic carriers was nearly as high as in CDI patients, and spores were also recovered from the study investigators' hands. These findings suggest that asymptomatic carriers contribute significantly to CDI transmission in long-term care facilities, and may have a role in dissemination of *C. difficile* in the community as well.⁸⁸ High rates of internally acquired *C. difficile* colonization and CDI have been reported inside long-term care facilities,⁹⁰ and a recent study from Scotland showed increased CDI rates among care home residents older than 65 years of age when compared with controls residing at home.⁹¹ A case-control study identified close contact with infants under the age of 2 years as a potential risk factor for community-acquired CDI.¹³ A plausible role for infants and young children acting as reservoirs and vectors for *C. difficile* is supported by data showing that several toxigenic and nontoxigenic strains are carried by infants, although none were found to carry the hypervirulent 027 or 078 strains.^{92,93} Regular diaper changing of babies carrying *C. difficile* by mothers has been hypothesized to explain the female predilection of community-acquired CDI.⁹⁴

Role of outpatient health care exposure

Exposure to *C. difficile* in outpatient settings may provide a possible link in the chain between nosocomial CDI and community-acquired CDI. More than 80% of CDI patients discharged from hospital had an outpatient clinic visit within 12 weeks of discharge in one study,⁹⁵ and CDI patients have

been known to shed spores even after completion of therapy.⁹⁶ Health care exposure in outpatient settings (physicians' offices, emergency departments, dialysis facilities) is a potential risk factor for community-acquired CDI, with a recent large study showing that more than two thirds of patients with community-acquired CDI without inpatient hospital exposure had low-level exposure in the preceding 12 weeks.³⁷

Role of food and animals

Given the genetic diversity in *C. difficile* isolates, the isolation of *C. difficile* in food and animals, the similarities in strains isolated from animals and humans, and the absence of traditional risk factors in a large subset of patients with community-acquired CDI, there is mounting concern over food-borne and zoonotic spread of *C. difficile* in the community.^{97–99} A recent study showed that *C. difficile* spores survived the 71°C temperature recommended for cooking ground meats.¹⁰⁰ *C. difficile* carriage has also been reported in many animal species, including cattle and pigs; these may be a potential reservoir for clinically relevant strains eventually causing CDI in humans.^{101–107} There have been several recent studies identifying *C. difficile* strains in retail meat products, including beef, chicken, and pork,^{102,108,109} and similarities between strains isolated from animal feed and those reported to cause CDI in humans.^{98,99,102,105} *C. difficile* ribotype 078 was originally identified as the predominant strain in swine and cattle, and is now increasingly identified in human CDI as causing severe disease and increased mortality, especially in the community setting.¹¹⁰ Animal and human strains of ribotype 078 are almost clonal, indicating that isolates had a common ancestry and porcine to human transmission is a possibility.^{98,111} These findings are also supported by the fact that ribotype 078 was the predominant type found in retail meat as well.¹⁰⁹ However, in a recent study, the most common strain isolated was NAP1, while less than 7% of culture-positive isolates from community-acquired CDI patients were NAP7 or NAP8, which are the more common strains found in food and animals.^{37,108} There is currently no strong objective evidence to classify *C. difficile* as a food-borne or zoonotic illness. Laboratory contamination of meat samples and circulation of clonal *C. difficile* isolates among animals may contribute to the identical genotypes often seen, and strict discriminatory typing may be the only way to clarify this issue.¹¹²

Emergence of new strains

A hypervirulent *C. difficile* strain belonging to a specific type (ribotype 27/protein profile NAP1) was identified in 2005

in several CDI outbreaks all over the world, including the USA.^{5,6,113–118} It is identified by polymerase chain reaction (PCR) as ribotype 27, by pulsed-field gel electrophoresis as NAP1 and by restriction-endonuclease analysis as group BI, leading to its nomenclature as BI/NAP1 or NAP1/027.⁶ It is also classified as toxinotype III by restriction fragment length polymorphism PCR of the toxin genes. The increased virulence of this strain may be related to the production of toxin early in infection and markedly increased toxin production (16–23 times more than other strains).⁹ Asymptomatic carriage of the hypervirulent strain has been linked to transmission in long-term care facilities.⁸⁸ Although some regions are starting to see a decrease in the prevalence of this strain,^{119,120} it is likely that other epidemic strains of *C. difficile* may emerge. There has also been increased focus on PCR ribotype 078 in the past decade owing to its hypervirulence and clonal presence in pigs and humans. Community-associated disease was more common among ribotype 078-infected cases, and affected patients were younger when compared with those having the 027 strain.¹¹⁰ Recent reports have corroborated the fear that new strains are emerging with non-027 and non-078 “hypervirulent” strains causing severe infection in both the community and hospital settings.^{121,122} Newer nontypical strains now account for a majority of infections in the community setting.¹²³ The molecular epidemiology of *C. difficile* is both diverse and dynamic,¹²⁴ with some strains causing large clusters during certain periods and then becoming endemic. The genetic diversity of this organism likely contributes to it being able to establish infection and cause epidemics.

Molecular typing of community-acquired CDI isolates

Typing is an essential tool to identify and characterize *C. difficile* isolates. There are various methods currently adapted globally to type *C. difficile* isolates, including pulsed-field gel electrophoresis, PCR ribotyping, toxinotyping based on restriction fragment length polymorphism, restriction endonuclease analysis, multilocus variable-number tandem-repeat analysis, multilocus sequence typing, amplified fragment length polymorphism, and surface layer protein A gene sequence typing.¹²⁵ Different methods are used across the globe, with PCR ribotyping and pulsed-field gel electrophoresis more frequently used in Europe and North America, respectively.¹²⁶ A uniform worldwide method to type strains would be more ideal. Multilocus variable-number tandem-repeat analysis¹²⁷ and whole genome sequencing¹²⁸ both offer increased discrimination

over other typing schemes, and have reported very similar findings despite the fact that they analyzed different parts of the bacterial genome.¹²⁹

Specific *C. difficile* genotypes have been recognized to predict outcomes in CDI. Walker et al recently demonstrated that strain-specific inflammatory pathways may contribute to increased severity of illness in PCR ribotypes 027 and 078.¹³⁰ Increased toxin production was primarily thought to be responsible for their “hypervirulent” behavior.⁹ However, no single factor can fully explain the increased virulence of *C. difficile* strains, and differences in toxins, sporulation, drug resistance, and cell surface proteins all play a role.¹³¹

Typing studies have demonstrated that community-acquired CDI strains have a diverse molecular epidemiology, with similarities to and differences from hospital-acquired CDI strains.^{26,40,132} Some studies indicate that ribotype 027 is associated with community-acquired CDI more than hospital-acquired CDI and others have reported that ribotype 027 accounts for more cases of hospital-acquired CDI,^{9,123,133} whereas a large surveillance study showed that similar percentages of community-acquired CDI and hospital-acquired CDI patients were infected with the NAP1 epidemic strain.⁴⁰ NAP1/toxinotype (TOX) 3 and NAP1/TOX 5 were the most common types isolated from 89 community-acquired CDI samples in one study, whereas TOX 0 strains have historically been most common in nosocomial CDI.^{134,135}

Similarities in strain distribution in the community and hospital settings indicate that *C. difficile* may move easily from either setting to the other and common reservoirs may exist. Long-term care facilities and outpatient facilities may both be important for transfer of isolates between inpatient health care facilities and the community. Reports have also shown the preponderance of several PCR ribotypes in community-acquired CDI not often seen in the hospital epidemic setting.^{123,136} This argues against the presence of a direct link between nosocomial outbreaks and community onset cases. These results indicate that community-acquired CDI isolates have extremely diverse genomes, and multiple transmission routes and sources for infection probably exist.

Outcomes of community-acquired CDI

Recent reports indicate a significant increase in severe cases, colectomies, and deaths related to CDI.²⁰ Identifying patients who are at high risk for severe CDI early in the course of infection may direct therapy and help to improve outcomes. Severe disease in the hospital has been associated

with increasing age, presence of the hypervirulent strain, elevated white cell count, hypoalbuminemia, and elevated creatinine.^{5–9,51,137–140}

Although community-acquired CDI has generally been characterized as a mild illness, it can be associated with complications and poor outcomes, including hospitalization and severe CDI. In a study of patients with community-acquired CDI at the Mayo Clinic, 40% required hospitalization, 20% had severe infection, 4.4% had severe complicated infection, 20% had treatment failure, and 28% had recurrent CDI.¹⁴¹ Increasing age was a predictor of need for hospitalization, severe infection, severe complicated infection, and treatment failure, but not recurrence. Higher Charlson Comorbidity Index scores predicted the need for hospitalization and severe complicated infection, but not other outcomes. Patients who required hospitalization were older, had higher comorbidity scores, and had a higher incidence of severe infection than those who were treated in the community. The need for hospitalization has a tremendous impact on health care costs and patient outcomes. Hospitalization inadvertently exposes patients to other risks and avoidable complications, including venous thrombosis and other hospital-acquired infections. Therefore, patients with community-acquired CDI who are older or who have higher comorbidities, as well as those who meet the current definition of severe infection (based on white blood cell count or rising creatinine), should be monitored closely and managed more aggressively in the community to prevent poor outcomes.

Conclusion

The incidence of community-acquired CDI has increased significantly over the past decade. Utilizing only hospital data likely underestimates the burden of CDI. Community-acquired CDI accounts for a significant proportion of total CDI and is increasingly being recognized as an important health threat. Community-acquired CDI can affect younger patients lacking the traditional risk factors like antibiotic exposure, prior hospitalization, or age. The absence of these risk factors is not enough to exclude CDI, and testing for CDI must be considered in all patients with acute diarrhea.

Environmental sources like food, water, animals, and pets may play an important role in these infections, apart from the role symptomatic patients and asymptomatic carriers play in spore dispersal. Prospective strain typing is a possible way to explore the suspected diverse sources of CDI in the community and the genetic diversity of this organism. However, strain typing is not widely available, and currently treatment

recommendations do not differ according to *C. difficile* strain. Without belittling the inpatient infection control measures in place, we require additional studies to identify *C. difficile* sources in the community, and determine measures to control this infection outside the hospital. Patients with community-acquired CDI do not necessarily have a good outcome, with a large proportion requiring hospitalization. Given the additional risks and costs associated with hospitalization, clinicians should be aware of factors that predict a need for hospitalization in these patients, which might lead to more intensive therapy and monitoring.

Disclosure

The authors report no conflicts of interest in this work.

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