

## CLINICAL/NARRATIVE REVIEW

# *C. difficile* Infection: Changing Epidemiology and Management Paradigms

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The incidence of *Clostridium difficile* infection (CDI) has been rising in hospitals, long-term care facilities, and within the community. Cases have been more severe with more complications, deaths, and higher healthcare-associated costs. With the emergence of a hypervirulent strain of *C. difficile* and the increasing prevalence of community-acquired CDI among healthy patients without traditional risk factors, the epidemiology of *C. difficile* has been evolving. This changing epidemiology requires a change in management. Taking into account new risk factors for CDI and growing subpopulations of affected individuals, diagnostic, treatment, and prevention approaches need to be adjusted.

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## INTRODUCTION

The incidence of *Clostridium difficile* has been rising steadily over the past two decades with subsequent increases in mortality, prolonged hospital stays with higher level care, and a substantial rise in healthcare costs.<sup>1,2</sup> In fact, not only is *C. difficile* infection (CDI) the most common cause of hospital-acquired diarrhea, it has replaced methicillin-resistant *Staphylococcus aureus* as the most common hospital-acquired infection overall.<sup>2–4</sup>

*C. difficile* is a gram-positive, rod-shaped, spore-forming anaerobe with the ability to produce enterotoxin A and cytotoxin B (linked to the *tcdA* and *tcdB* genes, respectively), which are responsible for its virulence. Toxin B activates monocyte cytotoxin release and is significantly more potent than enterotoxin A, which causes local tissue injury.<sup>5</sup> *C. difficile* is known to cause disease through release of these two toxins. Clinically, there is a wide spectrum of *C. difficile* presentations ranging from asymptomatic carriage to severe, life threatening, fulminant colitis, and toxic megacolon.<sup>6–8</sup>

Traditionally, *C. difficile* strains unable to produce one or both of these toxins were considered as non-pathogenic; however, there is now evidence that some strains may also produce a binary toxin transcribed from the *ctdA* and *ctdB* genes.<sup>9</sup> The significance of this binary toxin on the pathogenicity of *C. difficile* is unknown. The BI/NAP1/027 strain produces this toxin as well as markedly increased levels of Toxin A and Toxin B, which may contribute to its hypervirulence.<sup>10</sup> This new development may explain the rising incidence and severity of CDI.

## CHANGING EPIDEMIOLOGY

While *C. difficile* has been linked to disease since at least the 1970s, it was not until 2000 that the incidence and severity of

CDI has shown a steady rise.<sup>4</sup> This has continued to the current time.

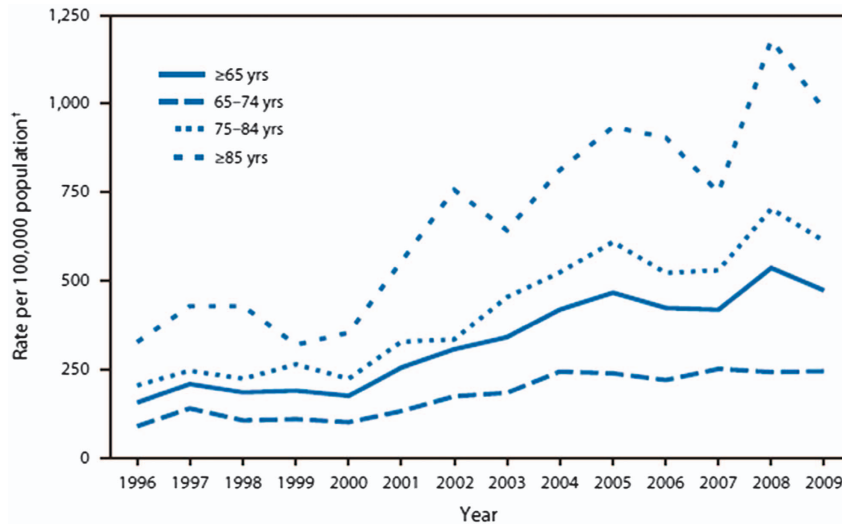
The greatest increase in cases has been seen in hospital settings. From the 1990s to 2000, CDI rates remained relatively stable across all age groups as shown in Figure 1. Since then, the incidence of CDI has increased from approximately 30–40 cases per 100,000 population in the mid 1990s to 84 cases per 100,000 population in 2005.<sup>4</sup> McDonald *et al.* describe an increase in CDI from 264,000 cases in 1996 to 978,000 cases in 2003.<sup>4</sup> Similarly, the US Agency for Healthcare Research and Quality's Healthcare Cost and Utilization Project identifies 24,200 hospital stays for patients with a principal CDI diagnosis (85,700 for CDI among all-listed diagnoses) in 1993 compared with 110,600 hospital stays in 2009 for a primary CDI diagnosis (336,600 for CDI among all-listed diagnoses).<sup>11</sup> Although this database is a limited, nationwide sample of inpatient hospital stays, it illustrates a four-fold increase in the number of hospitalizations over a 16-year time period. CDI was associated with at least 1% of all hospital stays in 2009.<sup>11</sup>

Using patient discharge data, similar trends are seen. Nationally, among adult, non-maternal hospital discharges, there were 7.4 per 1,000 hospitalizations for CDI in 2003 compared with 13.5 per 1,000 in 2012.<sup>12</sup> Surveillance efforts have also demonstrated increased morbidity and mortality among CDI patients. Death certificates with enterocolitis due to *C. difficile* as the primary cause of death increased from 793 in 1999 to 7,483 in 2008; the age-adjusted death rate rose 15%.<sup>13</sup> Similar trends in CDI incidence have been seen in Canada and throughout Europe.<sup>14–16</sup>

## CHANGING POPULATIONS AT RISK

Several subpopulations are disproportionately affected by *C. difficile* and have higher associated morbidity and mortality.

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**Figure 1** Rates of *Clostridium difficile* infection among hospitalized patients aged  $\geq 65$  years, by age group—National Hospital Discharge Survey, United States, 1996–2009 (from Centers for Disease Control and Prevention. *Morb Mortal Wkly Rep (MMWR)* 2011;60(34):1171.

**Table 1** Risk factors for *Clostridium difficile* infection

Antibiotic exposure
Older age (65 or older)
Prior, lengthy hospitalization or long-term care facility exposure
Comorbidities: malignancy, cystic fibrosis, inflammatory bowel disease, diabetes mellitus, cirrhosis, chronic kidney disease, immunodeficiency, solid organ or hematopoietic stem cell transplantation
Other medication exposure: chemotherapy, immunosuppressants, proton pump inhibitors
Prior gastrointestinal surgery
Consumption of processed meats
Presence of gastrostomy or jejunostomy tube

Adapted from refs. 1, 17, and 34.

These include the elderly, immunocompromised individuals (including patients receiving chemotherapy or following solid organ transplantation), patients with inflammatory bowel disease (IBD), and patients with significant co-morbidities beyond CDI. Table 1 lists the various risk factors for CDI.

While the elderly have always been at increased risk of developing CDI, much of the rise in hospital-acquired cases has been seen in patients over the age of 65. In fact, the rate of CDI discharge diagnoses was seven-fold higher in patients  $\geq 65$  years compared with patients aged 45–64 years ( $P < 0.001$ ).<sup>4</sup> Patients with CDI were nearly 20 years older (67.9 years vs. 48.1 years) and patients  $\geq 85$  years had the highest rate (1,089 per 100,000 population), compared with only 11 per 100,000 for patients under 18 years old.<sup>11</sup> In 2008, *C. difficile* ranked as the 18th leading cause of death among persons aged  $\geq 65$ ; 93% of *C. difficile*-associated deaths occurred in persons aged  $\geq 65$ .<sup>13</sup> As the US population continues to age, it is not unexpected that CDI rates among

persons  $\geq 65$  years old will continue to rise.<sup>4,17</sup> Moreover, comparing 2000 with 2003, a greater number of hospitalized patients with a CDI discharge diagnosis were transferred to a long-term care facility.<sup>4</sup> Various potential explanations for this rise among the elderly have been proposed, including residence at long-term care facilities, increased use of antibiotics and proton pump inhibitors, and decreased host defenses.<sup>4,18</sup>

Patients with IBD are also at increased risk of developing CDI. In this population, CDI prevalence was 1.7% compared with 0.4% of the general population. Among IBD patients, those with ulcerative colitis had a higher CDI incidence (2.8%) compared with Crohn's disease patients (1.0%).<sup>19</sup> Therefore, any IBD patient presenting with flare symptoms should be tested for *C. difficile* toxin to rule out disease. It remains unclear whether this higher CDI prevalence is related to increased antibiotic exposure, more frequent contact with healthcare settings, or an immunocompromised state.<sup>2</sup>

Multiple theories have been proposed to explain the overall rise in CDI—hospitalized patients are often older and sicker, there is increased use of broader spectrum antibiotics (e.g., fluoroquinolones resulting in resistance patterns), and inadequate prevention measures in healthcare settings.<sup>2,4,17,18</sup> It is not known if the widespread use of waterless, alcohol-based hand gels contributes to the nosocomial spread of *C. difficile*, although several studies have shown no increase in CDI with increased use of these hand gels in lieu of handwashing.<sup>20,21</sup> There is also increased testing among patients who present with diarrhea.

## EMERGENCE OF COMMUNITY STRAINS

Despite the rise in CDI-related hospitalizations worldwide, the population affected appears to have evolved since 2000. Historically, CDI has been associated with antibiotic use, although there is a growing number of patients who present with diarrheal symptoms and are diagnosed with CDI without

**Table 2** CDI classification and symptom onset

Disease classification	Symptom onset
HCF onset, HCF-associated CDI	> 48 h after admission but before discharge from an HCF
Community-associated CDI	Community onset or within 48 h of HCF admission, if symptom onset was > 12 weeks after last HCF discharge
Community onset, HCF-associated CDI	Community onset or within 48 h of HCF admission, if symptom onset was ≤ 4 weeks after last HCF discharge
Indeterminate CDI	Does not meet criteria for above disease classifications
Unknown CDI	Lack of available data; unable to classify

CDI, *Clostridium difficile* infection; HCF, healthcare facility. Adapted from refs. 5 and 24.

any prior antimicrobial exposure.<sup>22,23</sup> These are frequently healthy adults without significant medical comorbidity. Therefore, it has become reality that prior antibiotic exposure can no longer be assumed. Furthermore, it is hypothesized that there is an emergence of community strains of *C. difficile*. To better characterize CDI by exposure setting and timing, disease classifications have been established as described in Table 2.<sup>5,24</sup>

Although CDI-related discharges started to stabilize in 2009, overall CDI rates have continued to rise.<sup>11</sup> This finding is mostly attributable to community acquisition diagnosed in outpatient care settings. It is estimated that community-acquired CDI may now account for up to 40% of CDI cases.<sup>3</sup> These patients tend to be younger and healthier without recent hospitalization, antibiotic exposure or co-morbidities.<sup>3,25</sup>

The mode of transmission within the community remains unclear. Exposure to *C. difficile* is through the fecal–oral route followed by an incubation period that may lead to infection, colonization, or complete clearance. Otten *et al.* suggest that exposure does not necessarily dictate disease—some persons become colonized, others develop clinical disease, some may develop disease with clearance, and some persons may have relapse.<sup>26</sup> The determinants of which category a person falls into are unclear. For those persons who develop disease, infection may be cleared as vegetative cells and spores are eradicated, but infection may recur.

There are four proposed sources of *C. difficile* exposure within the community—person–person contact, animal–person contact, food contamination, and environment–person contact.<sup>26</sup> Since infected persons shed *C. difficile*, person–person transmission is the most reasonable hypothesis for community-level acquisition; this mode of transmission has been clearly demonstrated in hospital settings.<sup>27</sup> Situations have also been identified by which employees carry spores home exposing family members to *C. difficile* (e.g., healthcare workers, daycare centers, and veterinary clinics). Animals also shed *C. difficile*, including dogs, cats, horses, and calves, which should be considered as a potential mode of transmission in agricultural settings.<sup>26</sup> Various studies have identified *C. difficile* in food products, including ground meat and water, although there is no clear evidence of disease transmission.<sup>28–30</sup> Finally, environmental surfaces may become contaminated which is a common concern in healthcare settings, but extends to the community.<sup>26,27</sup> This lack of a clear understanding of how community-acquired CDI is transmitted illustrates the need for a multidisciplinary approach including improved home cleaning practices and

hand hygiene at the hospital and community level; the impact on food safety practices and animal exposure is less defined.

A major factor in the development of community-acquired CDI was the identification of the hypervirulent, toxigenic strain, BI/NAP1/O27.<sup>5</sup> Spiking between 2002 and 2006 as an international epidemic, this new strain has resulted in more severe clinical presentations requiring longer hospitalizations and resultant rises in healthcare costs. In particular, this strain has been linked to severe cases of CDI, especially among the elderly. This is likely related to 16 times greater toxin A production and 23 times greater toxin B production with high rates of fluoroquinolone resistance.<sup>31</sup> The strain was initially identified following outbreaks in Canada, the United States, and Europe.<sup>32,33</sup> Since then, there have been other strains, such as PCR ribotypes 001, 018, 078, and 106 which have had associated outbreaks.<sup>34</sup>

There has also been a rise of proton pump inhibitors therapy among outpatients. There is increasing epidemiologic evidence that the long-term use of proton pump inhibitors may increase the risk of CDI, but perhaps not recurrent CDI (RCDI).<sup>35,36</sup> The mechanisms for this are not known, but may be related to a higher gastric pH decreasing colonization resistance.<sup>34</sup>

## CHANGING MANAGEMENT

While the *C. difficile* organism and the populations it targets have both been evolving over the past 20 years, science has not stalled. There has been the development of new diagnostic testing strategies for *C. difficile*. In the 1990s, immunoassays were the primary diagnostic modality; however, current testing approaches have been modified to include more sensitive and specific molecular tests, such as polymerase chain reaction (PCR) that allows for earlier detection and more rapid treatment. This nucleic acid amplification test is more sensitive than toxin enzyme immunoassay tests and *C. difficile* culture and more specific than glutamate dehydrogenase testing; it is also widely available and has become the test of choice for rapid diagnosis of CDI.<sup>1</sup> Despite the increased cost of PCR compared with immunoassays, it is a more cost-effective testing choice as it offers earlier detection, increased accuracy, and allows for more rapid treatment; it also allows for isolation of CDI patients and prevents further spread of infection.<sup>6</sup> Despite this, one challenge with PCR is the risk of overdiagnosis, particularly in asymptomatic carriers who may be less likely to spread spores and contribute to the infection burden.<sup>37–40</sup> Additionally, this improved, highly sensitive, and specific test may explain some of the increased identification of cases and

**Table 3** Treatment for *C. difficile* infection

CDI	Clinical presentation	Regimen	Considerations
Mild–moderate	Diarrhea No signs of severe or complicated disease	Metronidazole 500 mg p.o. t.i.d. × 10 days <sup>a</sup> Alternative: Fidaxomicin 200 mg p.o. b.i.d. × 10 days	Avoid in pregnancy or with breast-feeding. Change to vancomycin if no response within 72 h
Severe	Albumin < 3 g/dl Abdominal distention WBC > 15,000	Vancomycin 125 mg p.o. q.i.d. × 10 days <sup>a</sup>	Increase to 250–500 mg p.o. q.i.d. if poor response
Complicated	Fever Significant leukocytosis (> 35,000) or leukopenia < 2,000) Hypoalbuminemia Abdominal distention +/- ileus +/- shock with hypotension or evidence of end-organ failure +/- elevation in serum lactate (> 2.2 mmol/l) or C-reactive protein	Metronidazole 500 mg IV t.i.d. and vancomycin 500 mg p.o. q.i.d. +/- vancomycin enemas 500 mg p.r. q.i.d.	Includes patients with ileus, recent abdominal surgery, or inability to take p.o. These patients should be admitted to the intensive care unit. Consider surgery consult to consider surgical approaches to treatment
Recurrent	CDI episode within 8 weeks of previous episode	1st recurrence: repeat metronidazole, vancomycin, or fidaxomicin 2nd recurrence: pulsed vancomycin regimen: 125 mg q.i.d. × 10 days, then 125 mg daily every 3 days × 10 doses	Consider FMT after 3 recurrences

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplantation; IV, intravenous; RCT, randomized control trial; WBC, white blood cell. Adapted from refs. 1 and 6.

<sup>a</sup>Recent guidelines recommend a 10-day course of therapy for treatment of mild-to-moderate CDI; this is also the length of therapy in the RCT of these drugs.<sup>1</sup> If the patient is not clinically improved, then therapy can be extended or changed.

explain the rise in CDI prevalence. Since widespread use of *C. difficile* PCR may also pick up asymptomatic carriers, testing is only indicated in symptomatic patients.

As CDI has emerged as a common hospital-acquired infection and has become increasingly more prevalent in the community, the approach to reduction of risk factors and management has become more challenging requiring more creative solutions.

Traditionally, metronidazole and vancomycin have been the mainstays of CDI treatment with the newer antibiotic, fidaxomicin, as an alternative. Patients treated with fidaxomicin had lower recurrence rates of CDI compared with vancomycin in clinical trials; however, its use has been limited somewhat by its high cost. Treatment regimens are often dictated by disease severity as detailed in Table 3.<sup>1</sup>

Despite effective treatment options for primary CDI, recurrence rates are 10–20%, with rates up to 40–65% after a first recurrence.<sup>41</sup> With recurrence, treatment is often more challenging and clinical presentations may be more severe. A first recurrence can be treated with the same initial antibiotic (i.e., vancomycin, metronidazole, or fidaxomicin), unless the recurrence is severe in which case vancomycin is indicated. There is interest in fidaxomicin as a treatment for RCDI since recurrence rates for primary CDI were lower than for vancomycin, but the drug has not been studied for RCDI specifically. Other regimens include the use of the adjunct probiotic, *Saccharomyces boulardii* and intravenous immune globulin.<sup>42,43</sup> There is ongoing research into a monoclonal antibody to toxins A and B to treat recurrences and several vaccines are in development as well.<sup>44–46</sup>

Furthermore, as research into the intestinal microbiome continues to progress, we are learning more about the complex, interdependent ecosystem responsible for food digestion,

immune system activation, and protection from invasive bacteria, also known as colonization resistance.<sup>47</sup> Research on the microbiome continues to grow, particularly over the past several years. *C. difficile* is a prime example where altered microbiota contribute to disease; therefore, strategies to restore the intestinal microbiome may be effective as a treatment modality. Given the high rates of CDI recurrence and lack of uniformly successful therapy, there has been growing interest in fecal microbiota transplantation (FMT). FMT is a treatment that directly alters—and restores—the gut microbiome. FMT is the delivery of stool from a healthy donor into the colon of a patient with RCDI, either by the upper gastrointestinal route, such as nasoduodenal infusion or into the colon by enema or colonoscopy. Meta-analyses of the hundreds of published cases and series show an efficacy of 90% and a landmark randomized control trial showed efficacy in RCDI patients given stool by the nasoduodenal route compared with vancomycin therapy; a more recent randomized control trial also shows colonoscopic infusion to be more effective than vancomycin.<sup>48–51</sup> FMT with colonoscopic delivery has been demonstrated to be a cost-effective intervention for RCDI compared with oral vancomycin.<sup>52</sup>

While treatment of CDI is an important area for ongoing research, prevention efforts also need to be enhanced to counteract the growing epidemic, both for the individual patient and in interrupting transmission.

There is interest in the role of probiotics for prevention. While there is good evidence for two probiotics that prevent antibiotic-associated diarrhea (*Lactobacillus rhamnosus* GG and *S. boulardii*), there is less evidence that they prevent CDI.<sup>53</sup> A meta-analysis concluded that there was moderate efficacy for probiotics in prevention of CDI, but this combined studies of many different probiotics or mixtures of probiotics in varied clinical settings.<sup>54</sup> Moreover, a large randomized

control trial of *Lactobacillus* spp. and *Bifidobacter* spp. in elderly inpatients showed no efficacy in the prevention of CDI.<sup>55</sup> Probiotics have a good safety profile (although they should not be given to immune compromised patients for risk of bloodstream infections), but the data at this time are insufficient to recommend a specific product and which patient populations might benefit the most.

In healthcare settings, prevention measures include private hospital rooms for CDI patients, dedicated hospital equipment (e.g., stethoscopes), personal protective equipment (e.g., gowns and gloves), and availability of sinks with soap for handwashing or alcohol hand gels. There also needs to be thoughtful use of antibiotics to prevent development of resistance patterns.

Although preventive efforts have traditionally been a focus in hospital settings with comprehensive environmental cleaning with sodium hypochlorite (bleach), this thinking should be expanded to community settings.<sup>56</sup> Affected patients should disinfect their home with a water/bleach (9:1 ratio of water to bleach) combination to ensure eradication of *C. difficile* spores and to help limit community transmission.

*C. difficile* infection prevalence is increasing for various reasons as discussed above. As a result, we need to refocus our prevention and management strategies. The future is promising, however, with ongoing research and development of better testing modalities, more effective medications, novel therapies including monoclonal antibodies and vaccines, and success with old therapies, such as FMT. We have implemented effective prevention strategies in the hospital setting to limit the spread of infection. As community-acquired CDI has emerged, we need to extend these strategies to the household.

## Study Highlights

### WHAT IS CURRENT KNOWLEDGE

- ✓ *Clostridium difficile* infection (CDI) incidence is rising, including in the community setting.
- ✓ There are more complications, deaths, and healthcare-associated costs associated with CDI.

### WHAT IS NEW HERE

- ✓ There are new risk factors with specific subpopulations at risk.
- ✓ Changing epidemiology requires new management and treatment paradigms.

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