The Challenges Posed by Reemerging *Clostridium difficile* Infection

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There have been recent, marked increases in the incidence and severity of *Clostridium difficile*–associated disease (CDAD). These may be attributable to the emergence of a hypervirulent strain of *C. difficile* that produces increased levels of toxins A and B, as well as an extra toxin known as “binary toxin.” This previously uncommon strain has become epidemic, coincident with its development of increased resistance to fluoroquinolones, the use of which is increasingly associated with CDAD outbreaks. Although not necessarily related to this epidemic strain, unusually severe CDAD has been reported in populations that had previously been thought to be at low risk, including peripartum women and healthy persons living in the community. Challenges posed by the changing epidemiology of CDAD are compounded by current limitations in diagnostic testing, treatment, and infection control. Overcoming these challenges and limitations will require a concerted effort from a variety of sources, including an ongoing partnership between infectious disease clinicians and public health professionals.

BACKGROUND

*Clostridium difficile*, a gram-positive, spore-forming, toxin-producing bacillus, was first described in 1935 as a component of the intestinal flora in healthy newborn infants. The role of *C. difficile* in human disease was not appreciated until the 1970s, when it was identified as the causative agent of pseudomembranous colitis [1]. Additional studies demonstrated that *C. difficile*–associated disease (CDAD) encompasses a range of disease severity from colitis (which, in many cases, manifests only as diarrhea) to toxic megacolon (which can result in sepsis and even death). *C. difficile* is the most commonly identified cause of antibiotic-associated diarrhea, accounting for 15%–25% of cases [2]. A typical presentation involves an older patient with frequent, loose, watery stools who has been recently treated with a course of antimicrobials while hospitalized for a chronic medical condition. Because most patients experience no complications [3], many clinicians have, in the past, viewed CDAD as more of a nuisance or a side effect of antimicrobial use, rather than focusing on it as a disease entity. Regardless, the financial burden of the disease has always been significant. One study in the 1990s revealed that, even though CDAD had a low attributable mortality rate (i.e., <2%), it was costing US hospitals $1 billion annually to treat [4].

CHANGING EPIDEMIOLOGY IN HEALTH CARE SETTINGS

Despite this history of CDAD as a relatively mild—albeit costly—health care–associated infection, there have been alarming increases in both the incidence and severity of this disease over the past several years. An analysis of US hospital discharge data revealed that CDAD rates increased abruptly beginning in 2001, with a doubling of national rates from 2000 through 2003 [5]. This increase was most prominent for patients aged >64 years, among whom the rates are highest (figure 1), and it occurred in all geographic regions.

Regional outbreaks of more-severe disease, resulting in increased deaths and in colectomies performed to avert death, date back to the year 2000. The earliest report was in Pittsburgh, Pennsylvania [6]; other outbreaks soon followed in Quebec, Canada [7], and the Centers for Disease Control and Prevention (CDC) initially began hearing about outbreaks of severe CDAD from hospitals in the mid-Atlantic and southeastern United States [8]. On the basis of data from Quebec, the attributable mortality rate for CDAD increased to 6.9% [7].
EMERGENCE OF AN EPIDEMIC STRAIN

Growing evidence suggests the emergence of a hypervirulent, epidemic strain as an important factor in the recent increases in CDAD incidence and severity. In both Quebec hospitals and hospitals in multiple locations in the United States, a previously uncommon strain of _C. difficile_ was found to be the epidemic strain and to be responsible for multiple, near-simultaneous outbreaks of hospital infection [7, 8]. Not only has this strain been identified in 24 states (as of March 2007), it has also been identified as causing outbreaks in the United Kingdom and in parts of continental Europe, suggesting it is now a global epidemic strain [9]. It is characterized as North American Pulsed Field Type 1 (NAP1), restriction enzyme analysis type “BI,” and PCR ribotype 027 [8, 10]. NAP1/BI/027 can also be characterized via restriction enzyme analysis of the toxin and surrounding regulatory genes as “toxinotype III,” a previously uncommon toxontype; historically, >80% of hospital strains were toxinotype 0 [11].

In addition to the large clostridial toxins A and B, which are the main recognized virulence factors of _C. difficile_, NAP1/BI/027 possesses an extra toxin known as binary toxin. This toxin, which is related to the iota-toxin found in _Clostridium perfringens_, was first discovered in _C. difficile_ in 1988 [12] and, until recently, was found in ≈6% of isolates recovered from hospitalized patients [11]. Although studies are underway, the role of binary toxin in human CDAD remains unknown [13]. In addition, NAP1/BI/027 possesses an 18–base pair deletion [7, 8] and a frameshift mutation leading to a premature stop codon [14] in _tdIC_, a putative negative regulator of toxin A and B production. This may be important, because NAP1/BI/027 has been shown to produce ~16-fold more toxin A and 23-fold more toxin B in vitro [10]. Whether it is binary toxin, increased toxin A and B production, or other unidentified virulence factors that are responsible, NAP1/BI/027 does appear to produce more-severe disease than other strains [7, 15].

Increased virulence alone, however, does not explain how a previously uncommon strain has recently become epidemic; historic isolates of NAP1/BI/027 from nearly 25 years ago possess the same binary toxin genes and deletions in _tdIC_ as contemporary isolates [8]. One factor that has changed is an increase in resistance to fluoroquinolones. Not only are contemporary isolates of NAP1/BI/027 more resistant to fluoroquinolones than are historic isolates of this same strain, they are also more resistant than contemporary, nonepidemic strain isolates [8, 16]. The concept of a particular _C. difficile_ strain becoming an epidemic strain on the basis of a selective advantage afforded by increased resistance to a particular antimicrobial was previously observed in the late 1980s and early 1990s with the highly clindamycin-resistant “J” strain [17].

DISEASE IN PREVIOUSLY LOW-RISK POPULATIONS

In addition to disease in health care settings, _C. difficile_ can cause disease in healthy individuals. In 2005, the CDC reported the occurrence of severe CDAD in several peripartum women and persons living in the community [18]. Although severe peripartum disease is still uncommon, the CDC is aware of cases of CDAD in this population that have resulted in colectomy or death. Previous reports of community-associated CDAD (CA-CDAD) from the United States suggested that CA-CDAD was very uncommon [19]; however, studies performed in Sweden 5–10 years ago suggested that as many as 1 in 5 cases of CDAD may be CA-CDAD [20]. In addition, some patients with CA-CDAD may not have a history of recent antimicrobial use [18, 21], which, if confirmed, could change our understanding of _C. difficile_ as a human pathogen. Thus far, there is little information about the strains responsible for CA-CDAD or the sources of these strains.

EMERGING RISK FACTORS

Antimicrobial therapy is the most widely recognized risk factor for CDAD; these drugs are thought to act through the disruption of the normal bowel flora, providing a niche for _C. difficile_ to multiply and elaborate toxins. Although virtually all antimicrobial agents have been implicated in the development of CDAD, some recent studies of CDAD caused by the current NAP1/BI/027 strain have found that fluoroquinolones were the antimicrobials most closely associated with disease [6, 22]. In addition, increased duration of antimicrobial therapy, the use of broad-spectrum antimicrobials, and the use of multiple agents all contribute to the incidence of CDAD [23]. Another recently described risk factor that remains controversial is the use of stomach acid–suppressing medications, such as proton pump inhibitors. Although some reports have refuted the role...
of these drugs [24, 25], others have suggested that proton pump inhibitors are particularly important in CA-CDAD and contribute to an apparent increase in the rate of CDAD among patients without precedent antimicrobial use [21, 26].

New exposure to *C. difficile*, especially in the hospital setting, where both the environment and the hands of health care workers easily become contaminated with spores from other patients, also plays an important role in the spread of disease. Unlike other multidrug-resistant organisms, the risk of developing CDAD is decreased, rather than increased, in hospitalized patients who are already colonized with *C. difficile* [27]. This may be due to a boosting in serum antitoxin antibody levels observed in these patients [28]. However, protection is also observed in both humans and animal models when colonization occurs with nontoxigenic strains [27, 29], suggesting there may be a role for the colonizing strain to occupy a microbial niche in the large intestine and to protect against superinfection with a new toxigenic strain. Regardless of the mechanism of protection, it is the patient who is newly exposed to *C. difficile*, rather than the patient who is already colonized with *C. difficile*, who is at increased risk of developing CDAD during an inpatient stay at a health care facility.

**DIAGNOSTIC CHALLENGES**

Clinicians should maintain a high level of suspicion regarding any patient who is receiving or who has recently received antimicrobials and who presents with diarrhea. Because of the emergence of CA-CDAD, clinicians should also consider the disease in patients from the community who present with several days of diarrhea, even without a history of antimicrobial exposure, provided that diagnostic tests for other bacterial and protozoan pathogens are also performed and that the results are negative. In addition, *C. difficile* testing in the absence of diarrhea may be appropriate in certain circumstances in which an intestinal ileus is suspected.

Although the tissue cytotoxic assay is considered to be the gold standard, this test requires technical expertise, and it takes at least 48 h before results are available. As a result, most clinical laboratories use EIAs, which are much easier to perform and which can provide results in as little as 2 h. However, the sensitivity of EIAs is lower (range, 60%–95%). Although specificity has not been traditionally viewed as a major issue with either the tissue cytotoxic assay or EIAs, it is possible that, if these tests are used in populations in which the prevalence is relatively low (e.g., patients without precedent antimicrobial use), their positive predictive value will be unacceptably low. Additional studies are needed to improve our understanding of the limitations of current, commonly used assays and to improve testing paradigms.

An approach that is still used in some European laboratories but that has been abandoned in virtually all US hospital laboratories is the use of anaerobic culture for the *C. difficile* organism. Although the test is extremely sensitive [30], it fell out of favor because of the high level of work involved, the slow turnaround time, and the inability to differentiate toxin-producing strains from non–toxin-producing strains. This last limitation has been addressed in some laboratories by performing a “toxigenic culture,” in which an EIA is used to determine whether a *C. difficile* isolate recovered from culture is a toxin-producing strain. At least 1 report suggests that a toxigenic culture may be significantly more sensitive than EIAs and tissue cytotoxic assays that directly use stool specimens [31]. In addition, at present, the only way to determine what strains are affecting patients in a hospital or region is to perform stool culture; the shift by laboratories away from culture has made it more difficult to understand the changing epidemiology of *C. difficile*.

**TREATMENT CHALLENGES**

For the first several years after *C. difficile* was recognized as a cause of antibiotic-associated diarrhea, oral vancomycin was considered to be the treatment of choice. By the early 1980s, results of studies suggested that oral metronidazole was therapeutically equivalent to oral vancomycin in the treatment of CDAD [32, 33]. The main attractions of metronidazole were that it was less expensive than vancomycin and that some experts thought that it was less likely to promote the spread of vancomycin-resistant enterococci. Although not approved by the US Food and Drug Administration for this indication, oral metronidazole became the drug of choice for initial CDAD therapy, with the caveat that oral vancomycin should be used in patients with the most severe forms of disease [34].

Recently, however, the initial treatment of CDAD has come under renewed scrutiny as failure rates for metronidazole used as initial therapy have been reported to be in the range of 16%–38% [35, 36]; these are much higher than metronidazole failure rates of ~7% that were reported in the 1990s [37]. Although there are no reports from North America of in vitro resistance to metronidazole, there is ongoing debate regarding the appropriate first-line therapy for *C. difficile* infection. Because most cases of CDAD are still mild, metronidazole would appear to still be appropriate for the initial treatment of most patients; what is unresolved is where in the continuum of “moderate-to-severe” disease should oral vancomycin become the preferred agent, and what are the most important clinical indicators (e.g., WBC count, abdominal tenderness, and elevated serum creatinine level) that should be used to differentiate severity?

It is disconcerting that, after 30 years of dealing with CDAD, we remain limited to 2 medications (i.e., oral vancomycin and
metronidazole) for treatment. Fortunately, there are now a handful of agents being developed as new therapies for CDAD. Tovecamer, a \textit{C. difficile} toxin-binding resin, is the agent farthest along in the approval process among the agents that are being developed specifically for CDAD [38]. Other agents, such as rifaximin [39] and nitazoxanide [40], are already approved for other gastrointestinal infections and are currently being investigated as potential therapies for CDAD. Novel agents in earlier phases of development include monoclonal antibodies directed at toxins A and B [41] and a \textit{C. difficile} vaccine [42].

Another treatment challenge is recurrent CDAD, which occurs in \( \sim 20\% \) of cases after initial successful therapy. Although recurrence can develop up to 2 months after the completion of therapy, most recurrences occur within the first 30 days, and at least one-half of all recurrences represent reinfection (i.e., with a new infecting strain) rather than relapse. Several risk factors for recurrence have been identified, including advanced age, increased elevation of the WBC count during initial illness, and antimicrobial use in the interim between initial treatment and the recurrence. Along with recent evidence of increased clinical failures with metronidazole, there is evidence suggesting an increased number of recurrences. Overall, the most important risk factor for recurrence is recurrence itself; patients with at least 1 episode of recurrent CDAD have a 50\%–65\% chance of experiencing additional episodes [43].

Patients who develop multiple recurrences may be especially difficult to treat. One of the most common therapeutic techniques is to attempt a tapering of the vancomycin dose over the next 2 months, with decreasing doses or pulsed doses at the end of that taper. This highlights the problem with using an antimicrobial to treat a disease originally caused by the use of an antimicrobial: a patient’s lower intestinal flora remains disturbed after discontinuing use of the antimicrobial directed at CDAD; it is at this point that CDAD is most likely to recur. Whether dosage tapering or pulsed dosing allows some restoration of normal flora while still suppressing \textit{C. difficile} is unknown, but it does appear to have some efficacy in preventing recurrence. Although many have hoped that a specific probiotic could help fill the microbial void in the large intestine, either during or after antimicrobial therapy, few data support the use of these probiotics in the treatment of either initial or recurrent CDAD [44]. However, human stool transplants, either via enema or feeding tube, have shown some promise in treating patients with multiple recurrences of CDAD and for whom a variety of other regimens have failed [45].

**PREVENTION CHALLENGES**

Because inpatient health care facilities remain at the epicenter of \textit{C. difficile} transmission, there are several strategies that infection-control programs should use to prevent patient-to-patient transmission of \textit{C. difficile}. First, contact precautions should be used for all patients with known CDAD [46]; these should include placement of the patient in a single room while he or she has diarrhea, with a bathroom used solely by that patient; alternatively, patients with CDAD may share the same room and bathroom (i.e., patient cohorting), provided that each is transferred out of the room once diarrhea ceases. In addition, gloves should be used by health care workers for all patient contact.

Because alcohol does not eradicate \textit{C. difficile} spores, there has been concern that widespread use of alcohol-based hand sanitizers for health care worker hand hygiene has had a role in recent increases in CDAD rates. However, there are data from a number of health care facilities demonstrating that overall CDAD rates tend to either decrease or remain the same after the introduction and increased use of alcohol-based sanitizers as the primary mode of hand hygiene in the care of all patients, including those with CDAD [47]. Nonetheless, if a health care facility is experiencing an outbreak of CDAD, it is prudent for health care workers to wash their hands with soap and water rather than using an alcohol-based hand sanitizer after glove removal [48].

Because \textit{C. difficile} spores have the ability to survive on dry surfaces for several months, special attention needs to be given to environmental cleaning of care areas that accommodate patients with CDAD. At present, the only available products that are reliably sporicidal contain at least 5000 parts per million of sodium hypochlorite. This translates into a 1:10 dilution of household bleach that must be prepared fresh daily and that can be quite caustic and damage the surfaces of hospital equipment. Despite these drawbacks, use of such a solution should be considered for environmental cleaning of rooms and bathrooms used by patients with CDAD, especially in a facility that is experiencing an outbreak.

Finally, major attention should be paid to controlling antimicrobial use. Targeted restriction of a particular antimicrobial agent or class of agents, such as clindamycin or third-generation cephalosporins, has led to control of individual hospital outbreaks or to reduced CDAD rates across hospitals [17, 49–50]. This was evident in the control of several outbreaks caused by the highly clindamycin-resistant J strain: clindamycin restrictions were followed by rapid reductions in CDAD cases [17]. Some have attempted, with varied success, individual restrictions or of formulary substitutions for fluoroquinolones during outbreaks caused by NAP1/BI/027 [22, 51]. However, it appears that fluoroquinolone resistance in NAP1/BI/027 strain is a class effect that is not limited to the newer 8-methoxyfluoroquinolones but that also results in higher MICs to all currently available fluoroquinolones [8, 16]. Thus, if any fluoroquinolone...
restriction is going to contribute to control, it is likely to be restriction or reduced use of all fluoroquinolones.

**FUTURE DIRECTIONS**

With the spread of NAP1/BI/027 throughout almost one-half of all US states, as well as much of Canada and western Europe, it is likely that rates of CDAD and associated morbidity and mortality will continue to increase before we see improvement. To reduce this morbidity and mortality, we will need advances in available treatments, therapeutic management strategies, and diagnostics. There will undoubtedly be new challenges presented by this organism as we improve our understanding of disease in previously low-risk populations and learn how *Clostridium difficile* is transmitted in the community. To meet these challenges, it is clear that there will be an ongoing need for a coordinated and concerted effort on the part of clinicians, infection-control professionals, researchers, members of industry, and public health officials.

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**References**