The Challenge of *Clostridium difficile* Infection

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***Clostridium difficile* infection is a major problem in the United States, resulting in significant morbidity, mortality, and financial costs to the health care system. This commentary provides an update regarding the epidemiology, diagnosis, current recommended management, and challenges surrounding *C. difficile* infection.**

Our understanding of the pathogenesis and treatment of *Clostridium difficile* infection (CDI) has grown since *C. difficile* was first described as the causative agent of antibiotic-associated diarrhea in 1978 [1]. Despite these advances, CDI has become increasingly prevalent and more resistant to standard treatments since 2000 [2].

Epidemiology and Clinical Importance

From 2000 to 2010, the incidence of CDI increased from 4.5 CDI discharges per 1,000 adult discharges in 2000, to 8.2 CDI discharges per 1,000 adult discharges in 2010 [3]. A recently published analysis estimated that there were approximately 453,000 newly diagnosed CDI cases in the United States in 2011, which led to 29,000 deaths [4]. The risk factors for the development of CDI are summarized in Table 1. The most important risk factor is the recent use of antibiotics [5]. In addition, it is now recognized that CDI can be acquired in the community, and this problem is on the rise [6].

C. difficile is a gram-positive, spore-forming bacteria that is spread via fecal-oral transmission. It produces 2 exotoxins, toxin A (*TcdA*) and toxin B (*TcdB*), that are responsible for its virulence. The increase in severity and resistance to standard therapy has been attributed to a new strain of *C. difficile* known as BI/NAP1/027 [7]. The increased virulence of this strain is thought to be due to increased production of toxins A and B, the presence of a 3rd toxin (binary toxin), and increased resistance to fluoroquinolone antibiotics [8].

The Centers for Disease Control and Prevention (CDC) has recognized the tremendous cost of hospital-acquired infections in the United States, and the overall financial impact of CDI on health care is substantial [9]. Hospitalized patients who develop CDI have 50% higher costs on average compared to those who do not develop CDI [10]. Although cost estimates vary, one review suggested that CDI may have resulted in as much as $4.8 billion in health care costs in 2008 [11]. This figure was for acute care facilities in the United States, and it did not include costs related to the additional time spent and/or treatment of the disease in long-term care facilities.

The human and financial burden of CDI has not been lost on the Centers for Medicare & Medicaid Services (CMS). Based on a provision of the Patient Protection and Affordable Care Act, future financial incentives to facilities will be based on their achievement of quality measures as part of CMS's value-based purchasing program. CMS has identified CDI as one of these priority targets for quality improvement over the next several years [12]. Under this program, CDI will be used in combination with other quality measures to determine whether facilities will receive reductions or increases in payments based upon their calculated performance scores.

Diagnosis of CDI

The diagnosis of CDI is based on a combination of clinical and laboratory findings. Guidelines were published by the American College of Gastroenterology (ACG) in 2013 [13] and by the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) in 2010 [14]. An update of the 2010 IDSA/SHEA guidelines will be released in spring 2016. In patients with

TABLE 1.
Risk Factors for the Development of *Clostridium difficile* Infection

Recent use of antibiotics
Exposure to *C. difficile organism*
Advanced age
Severe illness
Use of multiple antibiotics
Recent or prolonged hospitalization
Use of a proton pump inhibitor
History of gastrointestinal tract surgery
Enteral feeding
Obesity
Chemotherapy

Source: Loo VG, et al. [5]

Electronically published May 6, 2016.

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N C Med J. 2016;77(3):206-210.
0029-2259/2016/77313

appropriate risk factors, the diagnosis of CDI requires meeting both of the following criteria: the presence of diarrhea and/or radiographic evidence of ileus or toxic megacolon; and a positive stool test result for toxigenic *C. difficile* or its toxins, or colonoscopic/histopathologic evidence of pseudomembranous colitis [15].

Testing strategies for CDI vary depending on the clinical scenario. Stool culture is generally not used due to its high cost, the need for specialized equipment, and diagnostic delays [13, 14]. For patients with clinically significant diarrhea, the preferred method is stool testing using enzyme immunoassay (EIA) screening to look for glutamate dehydrogenase (GDH) antigen and for toxins A and B. A positive result for the diagnosis of CDI is accepted if EIA tests are positive for both GDH antigen and toxin A or B. A negative result to rule out CDI is accepted if both EIA tests are negative. Confirmatory polymerase chain reaction (PCR) testing may be used if the EIA results are discordant (eg, positive for GDH antigen but negative for toxin) [16].

Molecular tests such as PCR identify toxin genes regardless of toxin production and therefore are unable to differentiate between CDI and *C. difficile* colonization. A recent study showed that patients with a positive PCR test result and a negative toxin EIA test result had outcomes that were comparable to patients without *C. difficile* by either method [17]. The authors concluded that exclusive reliance on molecular tests for CDI diagnosis—without tests for toxins or host response—is likely to result in overdiagnosis, overtreatment, and increased health care costs. Repeat testing during the same episode of diarrhea or to verify cure should not be performed, as this is unlikely to yield a clinically significant result [14].

Endoscopy is indicated when the diagnosis of CDI is in doubt and alternative diagnoses are being considered [18]. The finding of pseudomembranes on endoscopy is highly suggestive but not pathognomonic for CDI. Other conditions that can lead to pseudomembrane formation include collagenous colitis, glutaraldehyde exposure, various infectious colitides, inflammatory bowel disease, ischemia, and medications (eg, nonsteroidal anti-inflammatory drugs) [19]. Additionally, CDI may be present in the absence of pseudomembranes in early or partially treated infections [20].

Recommended Treatment Guidelines

Patients diagnosed with CDI should be treated with antibiotic therapy, with the choice of drug depending on the severity of the disease. Table 2 summarizes the classification of disease severity and treatment options based on guidelines published by the ACG and by IDSA/SHEA [13, 14]. Fidaxomicin, which has been shown to be noninferior to vancomycin, may also be used as an initial treatment for mild to severe disease, although high cost is an issue [21].

Prevention

Efforts at prevention of CDI have been hampered by the spore-forming nature of the bacteria and by the ubiquitous

TABLE 2.
Summary of Guidelines for Medical Treatment of *Clostridium difficile* Infection (CDI)

Severity	Criteria	Treatment	Comment
Mild to moderate disease	Diarrhea without criteria meeting severe or complicated disease	Metronidazole 500 mg orally 3 times per day for 10–14 days or vancomycin 125 mg orally 4 times per day for 10–14 days if intolerant to metronidazole	If no improvement after 5–7 days, consider change from metronidazole to vancomycin 125 mg 4 times per day for 10 days
Severe disease	Serum albumin < 3 g/dL in addition to either: - WBC ≥ 15,000 cells/mm^3 - Abdominal tenderness Serum creatinine ≥ 1.5 times premorbid level	Vancomycin 125 mg orally 4 times per day for 10–14 days	
Severe complicated disease	Severe with: - Hypotension/shock - Ileus - Fever ≥ 38.5°C - Mental status changes - Serum lactate level > 2.2 mmol/L - End organ failure (mechanical ventilation or renal failure)	Vancomycin 500 mg orally 4 times per day and metronidazole 500 mg IV every 8 hours; if ileus is present, consider adding vancomycin 500 mg in 500 mL saline as enema 4 times daily.	Surgical consultation recommended
First recurrence	Recurrent CDI within 8 weeks of completion of therapy	Repeat metronidazole or vancomycin	
Second recurrence		Vancomycin in tapered and/or pulsed regimen: - 125 mg 4 times per day for 10–14 days - 125 mg 2 times per day for 7 days - 125 mg daily for 7 days - 125 mg every 2–3 days for 2–8 weeks	Consider fecal microbiota transplant after 3rd recurrence

Note. IV, intravenous; WBC, white blood cell.
Sources: Surawicz CM, et al [13] and Cohen SH, et al [14].

use of broad-spectrum antibiotics. *C. difficile* colonizes the colon in approximately 5% of nonhospitalized individuals and in 20% of hospitalized patients [22]. The spores can survive on surfaces for months and are very resistant to degradation. Alcohol and alcohol-based hand rubs do not destroy the bacteria in the health care setting. Spores are likely transferred to patients from contaminated equipment, hospital surfaces, and the hands or clothing of health care providers.

Although vaccination has been shown to be feasible [23, 24], there is currently no effective vaccine against *C. difficile* toxins. Therefore, the recommendations for CDI prevention relate to antimicrobial stewardship, hand hygiene, glove use, and surface disinfection [14]. In the event of an outbreak, several strategies have been successfully employed: isolation, use of protective gloves and gowns, hand washing with soap and water, and the use of disposable hospital equipment (when feasible) [25]. Antibiotic restriction has been shown to decrease the rates of CDI in hospital environments, but this approach requires great commitment on the part of hospital physicians and other administrative personnel to implement and continue successfully [26, 27].

To date, there has not been a uniform method for completely eliminating the spore form of the bacteria in hospital environments. Cleaning agents that contain hypochlorite, quaternary ammonium, and hydrogen peroxide vapor have been utilized to reduce the level of contamination of *C. difficile*, but only the chlorine-containing products and vaporized hydrogen peroxide effectively destroy the spores [28, 29]. Effective cleaning of hospital rooms is critical, but this can be laborious and training intensive. The use of automated, ultraviolet radiation devices may help in this regard [30, 31]. There are few data in the literature regarding the efficacy of enhanced education of hospital housekeeping staff in decreasing CDI rates, although one study did demonstrate reduced rates of *C. difficile* surface contamination with improved education [32].

The use of probiotics for prevention of CDI has also been examined in several trials, but the evidence for their use is equivocal at best [33].

Treatment of Recurrent Disease

One of the more vexing issues related to CDI is the recurrence of disease. This is probably related to the fact that standard treatment with vancomycin or metronidazole eradicates the *C. difficile* bacteria but does not restore the patient's native colonic microbiome. After initial successful treatment of CDI, recurrence rates can approach 25% [34]. Of those patients treated for a 2nd or 3rd time, the recurrence rate is in the neighborhood of 40%–50% [34]. Several strategies to treat recurrent disease have been employed, but there is no uniformly successful regimen. Pulsed or tapering vancomycin regimens have been utilized most often, but such treatment still results in high recurrence rates [13, 14]. The use of fidaxomicin appears to lessen recurrence rates, but not below 20% [35]. Monoclonal antibodies have been developed against *C. difficile* toxins and show promise [36], but they are not yet commercially available.

With these difficulties in mind, fecal microbiota transplantation (FMT) has been revisited. Interestingly, the first report of this treatment method occurred in 1958, well before *C. difficile* was recognized as the offending bacteria responsible for pseudomembranous colitis [37]. By restoring normal colonic microflora, FMT capitalizes on the fact that an altered patient microbiome is generally needed for the development of CDI. In 2013, the US Food and Drug Administration (FDA) ruled that FMT was a biologic product and a "drug" under their definition, thereby requiring clinicians to submit an investigational new drug (IND) application in order to administer this therapy [38]. The IND process is burdensome and requires a fair amount of regulatory infrastructure for implementation, which would not be available to smaller institutions, groups, or individual physicians. Thus, the IND requirement could significantly limit the availability of FMT for many patients. With this in mind, and after discussions with the appropriate stakeholders, the FDA decided that it would not enforce the IND requirement but would still require informed consent [39].

Based on recommendations from an expert working group [40], the appropriate indications for FMT include recurrent or relapsing CDI (3 or more episodes with failure to respond to a vancomycin taper and/or use of fidaxomicin, or 2 episodes requiring hospitalization), moderate CDI with no response to standard therapy, and possibly severe CDI with no response to standard therapy after 48 hours. Although there are slight variations in technique, the FMT method has several common requirements as outlined in Table 3. For a more detailed discussion of this treatment, readers should refer to the comprehensive review by Kelly and colleagues [41].

TABLE 3.
Methodology for Fecal Microbiota Transplantation

Donor selection	Eligible donors include spouse, partner, 1st-degree relative, household contact, friend, or universal donor. Donors are excluded for recent antibiotic use, high-risk behavior, or significant gastrointestinal disease.
Donor screening (minimal requirements)	Blood should be screened for hepatitis A, B, and C; for HIV 1 and 2; and for syphilis. Stool should be screened for *Clostridium difficile* toxin B, ova, and parasites and should be cultured for enteric pathogens. Also consider testing for giardia, cryptosporidium, isospora, cyclospora, rotovirus, listeria, vibrio, norovirus, and *Escherichia coli o157*.
Stool preparation	Fresh samples should be used within 2–6 hours; stool is homogenized in water or saline by hand or blender and filtered.
Method of administration	Recipient should be off of antibiotics for 2–3 days; installation is by nasogastric tube, upper endoscopy, colonoscopy, flexible sigmoidoscopy, or enema.

Source: Kelly CR, et al [41].

The vast majority of the data regarding FMT are contained in case series and case reports, with only 2 randomized controlled trials available to date. Drekonja and coauthors nicely summarized the available data in a systematic review in 2015 [42]. While comprehensive long-term data are not available, the technique appears relatively safe. In terms of efficacy, success rates of 60%–83% have been reported if FMT is delivered via the upper gastrointestinal tract, versus rates of 73%–100% if FMT is delivered via colonoscopy.

Inherent in the use of fresh stool specimens from donors are problems related to the time involved for the screening process and the need to use the specimen within a relatively narrow window of time. Because of these issues, the feasibility of using frozen stool samples from prescreened donors has been explored. Youngster and colleagues recently published an open-label pilot study in which 14 patients were given capsule-based FMT [43]. The results were quite promising, with an overall response rate of 90%, and only 4 patients needed retreatment. No significant adverse events were noted.

Fulminant Disease

Fulminant CDI can lead to severe complications including toxic megacolon, perforation, necrotizing colitis, or refractory disease with multiorgan system failure. In such cases, surgical intervention is required. Total or subtotal colectomy has traditionally been performed for treatment of these patients, although mortality rates can approach 50%–60% in immunosuppressed patients, older individuals, and patients who show signs of septic shock or respiratory failure [44, 45]. Prompt surgical intervention when indicated may result in lower mortality rates [44].

Because of the morbidity associated with total colectomy, the Pittsburg Protocol has been suggested as an alternative; in this procedure, only a diverting loop ileostomy is created, with subsequent colonic lavage using a vancomycin solution [46]. The initial study of 42 patients treated with this protocol showed a reduction in mortality compared to historical controls who underwent colectomy (19% versus 50%) [46]. Further studies will be needed to validate these findings.

Conclusion

CDI will remain a major health issue for the foreseeable future, and the increased attention it is receiving on a national level is justified. While the challenges of prevention and optimal treatment of both recurrent and fulminant disease remain, researchers and clinicians have clearly taken some positive steps. Refinement of the FMT technique and ongoing Phase III vaccine trials [47], which are scheduled to be completed by the end of 2017, hold promise for the future. NCMJ

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Acknowledgments

The authors would like to thank Ms. Nancy Frazier for her help in preparation of the manuscript.

Potential conflicts of interest. D.C.O. and M.W.S. have no relevant conflicts of interest.

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