

Commentary

***Clostridium difficile*: the increasingly difficult pathogen**

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See related review by Gould and McDonald, <http://ccforum.com/content/12/1/203>

Abstract

The epidemiology of *Clostridium difficile* infection is changing as a result of the epidemic spread of the hypervirulent North American Pulsefield type 1 strain. Clinicians are likely to encounter this disease more frequently than ever in their practice, and should be familiar with the updates in its diagnosis and treatment.

In the present issue of *Critical Care*, Gould and McDonald [1] provide a comprehensive, up-to-date review of *Clostridium difficile* – a pathogen of increasing concern worldwide. Recognized as the main cause of antibiotic-associated diarrhea for several decades [2], *Clostridium difficile* infection (CDI) had developed a reputation more as an economic challenge than a therapeutic one. That perception has changed dramatically in recent years, after several outbreaks of unprecedented severity, with increased frequency of complications such as septic shock, toxic megacolon, colectomy, and death were reported in the United States and Canada [3,4]. This different clinical picture is attributed to the emergence of a new *C. difficile* strain, designated North American Pulsefield type 1 (NAP1). This strain's heightened virulence correlates with 20-fold greater toxin production compared with historical strains [1,2]. Intriguingly, the NAP1 strain has been found in cattle and other animals, as well as in retail ground meat [5], but food-borne transmission has not been proven.

In light of the changing epidemiology and spectrum of *C. difficile* disease, what are the implications for clinicians?

Need for early diagnosis, with increased index of suspicion in nontraditional populations

The majority of CDI still occurs in patients with well-recognized risk factors – antibiotic exposure and advanced age, hospitalization, or nursing-home residence. CDI has also

been reported, however, in patients previously considered at low risk for the disease, such as healthy patients from the community [6], postpartum women, and perhaps patients on gastric acid suppressive medications [7]. The toxin enzyme immunoassay remains the main diagnostic modality in most clinical settings [6] but is rather insensitive, necessitating the submission of at least two specimens to improve the diagnostic yield. Prompt initiation of effective therapy can be crucial, especially in light of the rapid progression to fulminant disease observed with the NAP1 strain. Empiric treatment is now recommended immediately after specimen collection for patients with severe CDI [8,9], and the disease should be suspected in patients with unexplained leukemoid reaction even in the absence of diarrhea [10].

Changing treatment concepts

Metronidazole has been historically recommended as first-line CDI therapy primarily due to its low cost, its noninferiority to vancomycin, and its lower propensity for colonization with vancomycin-resistant enterococci and staphylococci [8]. Metronidazole remains a viable option for mild to moderate disease [1,9]. Recent data from observational studies and clinical experience suggest that metronidazole's efficacy may be decreasing [11], and a switch to oral vancomycin is indicated if at least some symptomatic improvement is not observed after 1–2 days of metronidazole treatment [9]. Oral vancomycin remains the preferred treatment for severe disease – defined in a recent randomized controlled trial [12] as the presence of pseudomembranous colitis or intensive care unit hospitalization, or the presence of two or more of the following: age >60 years, temperature >38.3°C, white blood cell count >15,000 cells/mm³, albumin <2.5 mg/dl. As emphasized by Gould and McDonald in their review article [1], efforts must be directed to ensure drug delivery to the lumen of the colon in patients with decreased peristalsis and ileus [9].

CDI = *Clostridium difficile* infection; NAP1 = North American Pulsefield type 1.

Early surgical consultation

Previously CDI was rarely a surgical disease, but recent experience is demonstrating otherwise. Emergency colectomy has been noted to improve survival in severely ill patients [13]. The clinical challenge is in identifying the patients warranting colectomy and its timing. In patients with suspected severe CDI, and those with ileus or toxic megacolon, an early surgical consultation should be obtained [9,13].

Continuing challenges

Perhaps the most frustrating aspect of CDI for the patient and physician is the high relapse rate (25%), and, in some patients, the multiple recurrences after discontinuation of *C. difficile* therapy [2]. This aspect of management is particularly difficult since there are no formal treatment guidelines, and the therapeutic options currently used – such as vancomycin with long tapers or pulsed doses, fecal implants, use of probiotics, or intravenous immunoglobulin – are based on anecdotal evidence from case reports or case series [2,9].

A variety of new therapeutic agents are currently under investigation, and they are nicely summarized in the article by Gould and McDonald [1]. The research into defining the role played by the host's immune responses in determining disease outcome is particularly exciting [14], and immunomodulatory therapies with monoclonal antibodies and a *C. difficile* vaccine are currently undergoing phase 2 clinical trials [15].

Until better treatment options, with agents that remediate disease more quickly and with fewer relapses, become available, the responsibility for interrupting nosocomial *C. difficile* transmission remains literally 'in our hands,' through the proper use of hand hygiene, through consistent and early isolation of infected patients, through antibiotic stewardship, and thorough environmental cleaning.

Competing interests

The authors declare that they have no competing interests.

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