# *Clostridium difficile*: The evolving story

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In September 2007, the Public Health Agency of Canada (PHAC) announced its intention to develop a plan by January 2008 to reduce the number of infections occurring in the nation's hospitals (1). This comes at a time when the Safer Healthcare Now! campaign is exploring how it can build on efforts already underway in hospitals to decrease the transmission of antimicrobial-resistant organisms (S Paton, PHAC, personal communication). While methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci are the pathogens that usually come to mind when considering antimicrobial-resistant organisms, *Clostridium difficile* is also foremost in the minds of health care workers and patients when health care-acquired pathogens are mentioned. The concern over *C difficile* is supported by recurring stories in the public press of outbreaks of *C difficile* attributed to poor hygiene in hospitals (2,3), and scientific literature that suggests the emergence of a more contagious and virulent form of this pathogen in both hospital and community settings (4-6). It is instructive to consider how *C difficile* has evolved over the past 30 years, even since our last review of this topic in 2000 (7).

Canadians play a part in both the old and recent history of *C difficile*-associated disease (CDAD). John Bartlett (8), in a commentary accompanying the re-publication of his sentinel paper linking clindamycin-associated colitis to *C difficile*, noted that the first published report of pseudomembranous colitis was in a young patient of Sir William Osler. It is sobering to learn that this was a lethal event occurring in the postoperative period. Despite its recognition more than 100 years ago, it remained an unusual infection until the antibiotic era (9). Anecdotal observation of a number of cases of antibiotic-associated colitis following clindamycin therapy led Tedesco et al (10) to pursue its etiology, which was originally attributed to *S aureus*, more rigorously. These investigators prospectively followed 200 patients treated with clindamycin (10). They found that 10% of patients developed pseudomembranous colitis detected by endoscopy, and none had *S aureus* isolated from stool (8). Bartlett speculated that, in retrospect, this 10% risk of CDAD with clindamycin may best be explained by an outbreak in Tedesco's hospital (8), a phenomenon well known with CDAD. Whatever the reason for this relatively frequent occurrence in association with clindamycin, it stimulated further investigation into the etiology of antibiotic-associated colitis.

As noted above, among the investigators were John Bartlett and his colleagues, who performed experiments that indicated that clindamycin-associated colitis in hamsters was due to a clindamycin-resistant, toxin-producing strain of *Clostridium*, later to be identified as *C difficile* (11). Over the next several years, the epidemiology, clinical manifestations, diagnosis and treatment of CDAD were elucidated (12,13). Through the 1990s, it is probably fair to say that while physicians looked forward to improved therapies for *C difficile*, there was only minimal scientific interest in the biology of *C difficile*.

It has been commonly accepted that *C difficile* is the major cause of hospital-acquired infectious diarrhea in the developed world (9,12,13). Over six weeks in 1997, the Canadian Nosocomial Infection Surveillance Program (CNISP) conducted prospective surveillance for nosocomial CDAD in 19 health care facilities across Canada (14). In this study, 269 patients (13% of inpatients with diarrhea) had nosocomial *C difficile*, for an overall rate of 66.3 cases/100,000 patient-days (95% CI 37.5 to 95.1) and 5.9 cases/1000 patient admissions (95% CI 3.4 to 8.4). The National Nosocomial Infection Surveillance (NNIS) Program in the United States gathered nosocomial CDAD rates between 1987 and 2001 (15). Overall, hospital rates were 13.0 cases/10,000 discharges in teaching hospitals and 5.1 cases/10,000 patient-days in intensive care units (ICUs). While the CNISP and the NNIS data are not comparable due to different study methodologies, they provide baseline rates for the two countries, from which comparisons can be made. In the NNIS study, CDAD rates increased significantly over time in the ICUs of hospitals that had more than 500 beds, and hospital-wide in hospitals with fewer than 250 beds (15). Other observations from the CNISP study were that the median length of time from admission to onset of symptoms was 15 days; in addition, 21 patients (8%) had complications of their CDAD and 41 patients (15%) who died were less likely to have received CDAD treatment compared with those who survived (OR 3.12; $P<0.05$) (14). However, none of the patients in the CNISP study underwent colectomy.

While there were suggestions that CDAD rates were increasing somewhat over time (15), this phenomenon certainly became more apparent in the early part of this decade. Investigators in Quebec were among the first to report a dramatic increase in both the occurrence and severity of CDAD (16). Their initial suspicion of a problem was prompted

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by the anecdotal observation of an increase in the number of patients with fulminant CDAD who required emergency colectomies. In a population-based study (16) that included both hospital and community cases, they found that the incidence of CDAD increased from 35.6 cases/100,000 population in 1991 to 156.3 cases/100,000 population in 2003, with most of the increase accounted for by those older than 65 years of age and occurring between 2002 and 2003. The authors also found that the case-fatality rate and the proportion of complicated cases more than doubled, with most of the increase occurring in 2003 (16).

Similar observations were made in the United States (US), both in population-based studies (5,17) and individual health care facilities (18,19). The CDC examined data from the National Hospital Discharge Survey between 1996 and 2003, for which CDAD was listed as any diagnosis (17). The CDC calculated that the CDAD rate increased from 31 cases/100,000 population in 1996 to 61 cases/100,000 population in 2003, with a significant increase between 2000 and 2003, and the rate was several fold higher in those older than 65 years of age than in younger persons (17). They found that the overall rates of CDAD were similar in both medium- and large-sized hospitals. A different population-based study (5), including data from 1000 hospitals in 35 states, found that *C difficile* colitis rates increased from 261 cases/100,000 discharges in 1993 to 546 cases/100,000 discharges in 2003 ($P<0.001$), a 109% increase (5).

At the same time that an increased CDAD rate was noted, there were observations that more patients were experiencing poor outcomes, in terms of both morbidity and mortality. The Quebec investigators found that the proportion of complicated CDAD cases increased from 7.1% in 1991/1992 to 18.2% in 2003 ($P<0.001$), and that the proportion of patients who died within 30 days of diagnosis increased from 4.7% to 13.8% ($P<0.001$) during the same time frame (16). Investigators in the US found that the *C difficile* colitis case-fatality rate increased from 7.84% in 1993 to 9.26% in 2003 ($P<0.001$), with the colectomy rate ranging between 1.8 cases/1000 patients and 6.4 cases/1000 patients ($P<0.001$) between 1993 and 2003 (5). At an institutional level, hospitals have reported outbreaks of CDAD with increased mortality and colectomy rates (18,19). Kenneally et al (20) found that the 30-day crude mortality rate among patients with CDAD in their ICUs was 36.7%, although the attributable mortality rate was estimated to be considerably less, at 6.1%. From November 1, 2004, until May 1, 2005, the CNISP repeated its survey of CDAD rates in selected Canadian hospitals. Compared with 1997, there were 34 participating sites and 1493 patients with health care-associated CDAD. The incidence rate was 6.4 cases/10,000 patient-days, ranging from 3.9 cases/10,000 patient-days in Atlantic Canada to 11.9 cases/10,000 patient-days in Quebec, and from 2.2 cases/1000 admissions in Alberta to 11.1 cases/1000 admissions in Quebec. Although the overall mortality rate (15.9%) was similar to the 1997 survey, it varied from 22.6% in Quebec to 9.1% in Alberta, with a case-fatality rate of 1.1% to 1.5% attributed to CDAD in Alberta, Saskatchewan, Manitoba, and Atlantic Canada, and 14.8% in Quebec. Twelve patients (1%) underwent colectomy compared with none in 1997 (D Gravel, PHAC, personal communication).

Although these studies represent only a very small number of those in the literature regarding CDAD, they reflect the changing epidemiology of CDAD over the past decade. The evidence suggests both a higher rate of CDAD and more severe disease (5,16,18-20), as well as community CDAD, often in the absence of antibiotic exposure (21). This had led to speculation (8,17) as to the reason for this change. Some of the hypotheses have included altered hosts or host factors, altered environments and/or altered pathogen; the usual hypotheses considered when the epidemiology of any disease undergoes change.

A number of host factors are known to increase the risk of CDAD, including older age and hospitalization (12,16,17). Patients with CDAD have been in hospital longer before their disease onset than control patients without CDAD (15,22,23). The increasing prevalence and severity of CDAD are unlikely related to an older population of hospitalized patients, given that the case-fatality and colectomy rates for CDAD all increased over time, even after adjusting for comorbidities for all age groups (5). It is curious to consider whether there is an inherently greater risk of acquiring CDAD in hospital now compared with past years. Dubberke et al (24) recently demonstrated that the presence of concurrently admitted patients with CDAD on the same ward increases patients risk of developing CDAD, suggesting that *C difficile* colonization pressure might be a risk factor. This is not surprising given the role of colonization pressure as a factor contributing to vancomycin-resistant enterococci transmission (25), and a prior epidemiological study (26) that suggested an increased risk of CDAD if the patient's roommate also had CDAD.

One other host factor speculated to have contributed to the outbreak of CDAD has been the increased use of proton pump inhibitors (PPIs) and $H_2$-receptor antagonists. The theory is that the lack of gastric acid that comes from the use of these medications diminishes the ability to destroy the *C difficile* spores. In one study (27) that linked pharmacy (inpatients who received a PPI) and laboratory (inpatients with cytotoxin-positive stool) databases, for which a case-control comparison was performed, use of PPIs was an independent risk for CDAD. The authors defined PPI use as receiving one of these drugs for at least three days before diarrhea developed. Muto et al (18) also found that $H_2$ blockers (OR 2.0; 95% CI 1.1 to 3.5) and PPIs (OR 2.4; 95% CI 1.3 to 4.4) increased the risk of CDAD, but the association was weak. Other investigators in Quebec were unable to demonstrate that PPIs increased the risk for CDAD in hospitalized patients (4). In the inpatient setting, the role of PPIs in the occurrence of CDAD is not conclusively demonstrated. In another study (21) linking prescription and physician databases in the United Kingdom, acid-suppressive therapy with either a PPI or an $H_2$-receptor antagonist was found to increase the risk of community-acquired CDAD. In this study, CDAD was identified as any patient who received a prescription for oral vancomycin. Hence, the study may have involved a selected group of patients. It remains to be seen whether acid-suppressive therapy is in fact a risk factor for CDAD, and whether that risk applies to both hospital and community settings.

The major risk factor for CDAD is receiving an antimicrobial, and it is recognized that almost every antibiotic has this potential. Interest has also focused on whether changing patterns of antimicrobial use have somehow contributed to the increased incidence, especially since fluoroquinolone resistance in the outbreak strain (4,28), and fluoroquinolones as a specific risk factor for CDAD in case-control studies (4,18,28,29) have been repeatedly demonstrated, particularly for the newer

broad-spectrum ones. To explore this at an institutional level, Weiss et al (30) compared antibiotic consumption (as defined daily doses/1000 hospital-days) in five Quebec institutions between 2001 and 2004 (30). Three institutions experienced a CDAD outbreak and two did not. Although they found no correlation between the type and amount of antibiotics used at the institution level and the magnitude of the outbreak, further research is needed to confirm this observation. Until then, fluoroquinolones have to be acknowledged as an independent risk factor for CDAD.

Having looked at host and environmental factors, the pathogen must also be considered. *C difficile* strains that are responsible for human disease produce two exotoxins, toxins A and B (13). Toxin A is an enterotoxin and toxin B a cytotoxin, and full damage requires the action of both (13). There are rare strains, also disease-producing, that contain one or the other toxin (13). The genetic elements encoding for toxins A and B, as well as their regulatory enzymes, are located in an area of the microorganism known as the pathogenicity locus (31). It seemed logical to wonder whether strains associated with more severe disease produced more and/or different toxins. Warny et al (32) examined this hypothesis by comparing epidemic and nonepidemic strains. They characterized the Quebec outbreak strain and found that it carried a gene (*cdtB*) encoding for a binary toxin and an 18-base pair deletion in a down-regulatory gene, *tcd*C (32). They also found that peak median toxin A and B concentrations were 16 and 23 times higher, respectively, in the outbreak strains compared with the nonoutbreak strains (32).

Other investigators in Canada and the US have examined the outbreak strains, performing both molecular studies and antimicrobial susceptibility testing. They have confirmed that these isolates are predominantly of one group – toxinotype III, restriction-endonuclease group B1 and North American pulsed-field gel electrophoresis (NAP) type 1, or B1/NAP1 (4,22,33). This strain was uncommon in historical databases, but when present, was positive for binary toxin and contained the *tcd*C deletion, demonstrating the presence of the genetic elements for this strain a number of years ago (33). The current BI/NAPI strains were more likely to be resistant to gatifloxacin and moxifloxacin than non-B1/NAPI strains examined (100% versus 42%, P<0.001) and than the historical (100% versus 0%, P<0.001) isolates (33). In terms of clinical correlation, Loo et al (4) found that severe CDAD was more commonly seen in patients with isolates having both binary toxin genes and a partial deletion of the *tcd*C gene than in those with isolates not exhibiting this genotype (16.7% versus 0%; P=0.03). However, it should be noted that not all investigators have correlated more severe disease with the outbreak strain (33) and a variety of *tcd*C mutations exist (34), all of which may play a role in pathogenesis. The role of binary toxin is even more debated. Thus, while hyperproduction of toxins A and B appears to be a factor in the more severe disease seen, the exact mechanism of this hyperproduction has yet to be fully elucidated.

Whatever the mechanism of disease, the evidence seems to be mounting regarding more severe CDAD. In the Quebec outbreak, the attributable mortality has been calculated at 16.7% (95% CI 8.6% to 25.2%), and the excess length of stay is 10.7 days, on average (35). Therefore, it is important that clinicians remain vigilant to the presence of CDAD and initiate prompt investigation and therapy. In particular, it is important to be suspicious of CDAD in patients with elevated white blood cell counts (36) and/or unexplained leukocytosis (37). While computed tomography imaging may be helpful diagnostically, it does not predict the need for surgical treatment (38).

Seeing more patients with poor outcomes has led us to question whether metronidazole should remain the first-line treatment for CDAD. A randomized controlled trial (39) of metronidazole (42 evaluable patients), 250 mg orally, compared with vancomycin (52 evaluable patients), 500 mg orally, both four times daily, showed similar efficacy and relapse rates. It is argued that this study was insufficiently powered to detect an important difference between the two agents. Another small study (40) confirmed the similar efficacy of metronidazole 500 mg and vancomycin 500 mg, both three times daily. A later study (41) demonstrated equal efficacy of 125 mg and 500 mg of vancomycin, although in another small study of 46 hospitalized patients with insufficient power to reach a firm conclusion. A more recent study (42) has shown that there is no benefit to adding rifampin to metronidazole to treat the first episode of CDAD. Therefore, metronidazole has been the first-line treatment for CDAD given apparent equal efficacy to vancomycin, good tolerability and low cost.

However, in their case-control study, Pépin et al (16) found that patients initially given oral vancomycin therapy had a 79% lower risk of progression to complicated CDAD than patients initially treated with metronidazole (OR 0.2; 95% CI 0.06 to 0.8). Metronidazole resistance was not demonstrated by Loo et al (4), and does not explain the poorer response seen in the Quebec cohort. While it is important to remember that this is not a randomized controlled trial, combined with evidence that the response to metronidazole is slow (43,44), some clinicians began recommending that vancomycin be considered as the initial treatment of choice in patients with several CDAD as characterized by a total white blood cell count greater than 20,000 cells/mm$^3$, admittance to critical care, new elevation in creatinine levels, toxic megacolon or septic shock (31). This is now supported by a randomized controlled trial (45) that suggested that metronidazole and vancomycin are equally effective for the treatment of mild CDAD, but vancomycin is superior for patients with severe disease. Relapse rates (up to 15%) were similar for vancomycin- and metronidazole-treated patients (45). In some patients with fulminant CDAD, emergency colectomy improves survival (46) and warrants consideration. Clearly, more effective therapies are needed, and several are under investigation.

In the end, however, prevention is far better than cure. This requires a two-pronged approach. Studies have clearly shown a decrease in nosocomial CDAD with restricting the use of clindamycin (47,48) and implementation of an antimicrobial stewardship program (49). Glove use for all patient care was shown to interrupt *C difficile* transmission (50). A little advertised result of the Quebec study was the drop in CDAD rate from 22.5 cases/1000 admissions to 12.4 cases/1000 admissions with introduction of major infection control measures (4). Questions have arisen over the usefulness of alcohol-based hand rinses when caring for patients with CDAD and whether they may even have contributed to the outbreaks. Boyce et al (51) did not have an increased incidence of CDAD with increasing use of alcohol-based hand rubs at their hospital, and noted that others have made the same observation. While this does not

speak to the best agent to use in the day-to-day care of patients with CDAD to reduce cross-transmission, it is important to note that there are no prospective randomized clinical trials to date to indicate that alcohol-based hand rubs should not be used, especially in the absence of an institutional outbreak. While we would not discourage hand washing with soap and water or chlorhexidine when caring for a patient with CDAD, hand hygiene with any product is better than no hand hygiene at all. If the alcohol-based hand rub is more accessible, by all means use it!

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