Clostridium difficile-associated diarrhea – The new scourge of the health care facility

JM Conly MD FRCPC

Clostridium difficile had its name coined because of the difficulty in its isolation. It was first isolated and described in the mid-1930s and later identified as the etiological agent of pseudomembranous colitis. The organism, which has been isolated from soil, sand, hay and animal dung, is a Gram-positive, spore forming, anaerobic bacillus which produces toxin-mediated diarrhea or pseudomembranous colitis. The organism is now well recognized as the major (if not the only) and most important cause of infectious diarrhea occurring in hospitalized patients in developed countries (1). After colonizing the gastrointestinal tract of humans, the organism causes a wide array of manifestations, ranging from asymptomatic colonization to severe diarrhea, pseudomembranous colitis, toxic megacolon, intestinal perforation and death from secondary sepsis. Two recent publications, one by the Society of Healthcare Epidemiology of America (2) and the other by the American College of Gastroenterology (3), have provided detailed information regarding definitions, diagnosis, management (3) and control strategies for *C difficile*, and have proven to be useful guidelines for healthcare professionals. However, despite the large amount of data regarding *C difficile* and its associated diseases, it is troubling that its frequency still continues to increase. It is timely to review new developments in the pathogenesis and epidemiology of *C difficile*-associated diarrhea (CDAD) and explore the reasons for its apparent increase in the Canadian healthcare setting.

It was previously thought that *C difficile* was acquired after some period of hospitalization, resulting in asymptomatic colonization by *C difficile*. The disease developed after antimicrobials were administered that altered the normal colonic flora, allowing the rapid growth of toxin producing strains of *C difficile*. However, it is now hypothesized that hospitalized

patients are intermittently exposed to *C difficile* throughout their hospitalization but do not acquire *C difficile* until after receiving antimicrobials; they then develop disease after a brief incubation period (4-6). Recent data from several longitudinal studies suggest that colonized patients are actually at decreased risk for developing symptomatic disease (7). The studies followed 618 noncolonized patients for over 1000 observation weeks and 192 colonized patients for 282 observation weeks. The studies differentiated between those with primary asymptomatic colonization and those who remained culture positive after the resolution of CDAD. It is thought that additional factors related to host immunity or the type and timing of antimicrobial exposure are necessary for *C difficile* disease to occur. The antibiotics most commonly implicated in *C difficile* colitis are the third-generation cephalosporin group – ampicillin, amoxicillin and clindamycin. The antimicrobials least likely to be associated with *C difficile* colitis include parenterally administered aminoglycosides and vancomycin, sulphonamides, and antimicrobial agents that lack antibacterial activity (ie, some antifungal, antiviral and antiparasitic antimicrobials). Among the broad spectrum agents, the third-generation cephalosporins, trovafloxacin (Trovan, Pfizer Canada Inc, Kirkland, Quebec), possibly ciprofloxacin (Cipro, Bayer Healthcare Division, Toronto, Ontario) and clindamycin (Dalacin C, Pharmacia & Upjohn, Mississauga, Ontario) appear to have been implicated most frequently (8-10). For unknown reasons, other broad spectrum agents such as ticarcillin-clavulanate (Timentin, SmithKline Beecham, Oakville, Ontario) and piperacillin-tazobactam (Tazocin, St-Laurent, Quebec) have been less frequently implicated. However, virtually all antibiotics have been associated with *C difficile* colitis.

University Health Network, University of Toronto, Toronto, Ontario

Correspondence: Dr John Conly, Department of Medicine, Division of Infectious Diseases, Suite 13-118 Norman Urquhart Wing,

Toronto General Hospital, University Health Network, 200 Elizabeth Street, Toronto, Ontario M5G 2C4. Telephone 416-340-4858, fax 416-340-5047, e-mail john.conly@uhn.on.ca

C. difficile colonization of the colon occurs in approximately 2% to 3% of healthy adults. The incidence of community-acquired CDAD (11) is extremely low (7.7/100,000 person years). The principal reservoirs for *C. difficile* are the hospitalized patient and the hospital environment, with the risk of acquiring the organism increasing in direct proportion to the length of hospital stay. The rate of acquisition has been reported to be 13% for individuals hospitalized one to two weeks, increasing to as high as 50% for those hospitalized more than four weeks (12). A recent study conducted through the Canadian Nosocomial Infection Surveillance Program examined the period prevalence, morbidity and health care burden of CDAD in 19 Canadian hospitals and found a prevalence of 5.86/1000 admissions (95% CI 3.4 to 8.4) and 66.3/100,000 patient days (95% CI 37.5 to 95.1). The vast majority of cases (93%) developed during the patients' original hospitalization. The overall mortality during the surveillance period of those diagnosed with CDAD was 15.2%, and 9.7% of the deaths (1.5% of the total) were considered to be directly attributable to CDAD (13). The costs for readmission alone for nosocomial CDAD per year per site was estimated to be \$128,200.

There is a suggestion that nosocomial CDAD rates are increasing in several countries, including England and Wales where a sixfold increase in rates was noted between 1990 and 1993. In the United States, rates have increased up to fivefold between the late 1980s and the mid-1990s (14,15) in at least two studies which have addressed trends over time. Rates seem to be increasing in Canada, but more data are required to corroborate whether this perception is accurate. There is an interesting dichotomy, whereby declining admission rates and shorter hospital stays have resulted in less likelihood that patients will acquire CDAD, but the increase in the burden and severity of illness and the greater likelihood of receipt of antimicrobials place this smaller group of patients at potentially greater risk of acquiring CDAD. With increasing broad spectrum antimicrobial use (8,16) considered as a significant factor in the increasing rates of CDAD and with some evidence suggesting an association between bed closures and increasing nursing workload (17) with the nosocomial transmission of CDAD and vancomycin-resistant enterococci (VRE), it is interesting to speculate whether the current restructuring in the Canadian health care sector is indirectly responsible for CDAD in Canadian health care facilities. This is an area that requires further study.

Carriage rates of up to 70% have been reported in children under the age of one year, but by two years of age the 'normal' colonic flora is established and the frequency of colonization decreases to the rate of healthy adults (2). Healthy children younger than one year of age are the only population in which *C. difficile* and its toxins are frequently detected in the stool in the absence of clinical symptoms. One suggestion advanced to explain this observation is that the infant's gut lacks receptors to the toxin.

Most strains of *C. difficile* produce toxins A and B, which are the toxins thought to be responsible for disease. Toxin A interferes with the cytoskeletons of intestinal epithelial cells and causes neutrophilic infiltration and severe mucosal damage in

intestinal loop assays. Both toxins A and B have been cloned and sequenced, and their binding sites to the GTP-binding protein Rho identified (18). The toxins subsequently alter the cell's cytoskeleton by disrupting F-actin microfilaments. Although toxin B is 1000 times more potent in tissue culture assays than toxin A, it has no activity in rodent intestinal loop assays. For this reason, many investigators have attributed human pseudomembranous colitis to toxin A, but recent data suggest that both toxins A and B may contribute to human disease (18). It is of interest to note that the appearance of CDAD due to toxin A-negative (by ELISA), toxin B-positive strains of *C. difficile* have been reported recently in both the United States and Canada (19, 20). The latter strain, reported from Winnipeg, appears to have a defective toxin A gene (21).

The gold standard for the diagnosis of *C. difficile* colitis is the tissue culture assay, with toxin neutralization demonstrated by the addition of antitoxin to *C. difficile* or *Clostridium sordellii*. However, this assay is not offered by most clinical laboratories. The most frequently used test are the enzyme immunoassays, the majority of which are based on the detection of toxin A. The test is highly specific, but because of a reduced sensitivity, more than a single stool should be assayed. Only 10% to 20% of patients with mild antibiotic-associated diarrhea will have a positive toxin assay for *C. difficile*, whereas up to 95% to 100% of patients with pseudomembranous colitis will have a positive assay. A high degree of clinical suspicion is required to detect ELISA toxin A-negative CDAD (19). Other testing methodologies, including cell culture or ELISAs that detect toxin A or B, are required.

In most cases of mild to moderate diarrhea, symptoms will stop when the offending antimicrobial is withdrawn. When colitis is severe, either oral metronidazole 250 mg three times/day for 10 days or oral vancomycin 125 mg four times/day for 10 days is usually effective. Relapses occur in about 20% to 25% of patients, and the patients usually respond to another course of therapy. A few patients experience multiple relapses, making management more difficult. The treatments for CDAD have recently been reviewed (2,3), including the exciting prospect of bioprophylaxis using *Saccharomyces boulardii* as a lyophilized, live product to prevent recurrences (22). In addition to the appropriate stewardship of antimicrobials, perhaps these and other biological approaches will offer a solution for what is becoming the new scourge of the modern health care facility.

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