What have we learned about antimicrobial use and the risks for *Clostridium difficile*-associated diarrhoea?

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*Clostridium difficile* is recognized as a major cause of antibiotic-associated diarrhoea and colitis. Antimicrobial agents have been repeatedly recognized as a causative risk for *C. difficile*-associated diarrhoea (CDAD) and more recently fluoroquinolones have been particularly implicated. Unfortunately, not all reports of antimicrobial associations with CDAD have excluded variables other than antimicrobial use. Prevention of CDAD usually involves infection control interventions and antimicrobial restriction policies may not be fully substantiated by currently available data; however, antimicrobial drug restriction seems prudent in outbreak situations.

Keywords: antibiotics, hospital-acquired CDAD, anaerobes

Introduction

*Clostridium difficile* is an anaerobic Gram-positive spore-forming bacillus. It persists for an extended duration in the environment and may colonize humans without clinical disease. As an opportunistic pathogen, *C. difficile* is the major cause of antibiotic-associated diarrhoea and colitis.1 The prevalence and epidemiology of *C. difficile*-associated colitis is global. The incidence varies considerably but is increasing worldwide due to broad-spectrum antimicrobial use.2 Oldfield3 estimated that annually in the USA, there were an estimated 3 million cases of *C. difficile*-associated diarrhoea (CDAD) costing ∼1 billion dollars in healthcare expenses. CDAD is a recognized cause of hospital-acquired infectious diarrhoea; however, many cases of hospital-acquired diarrhoea do not have an established aetiology. Patel4 indicated that the financial consequences of CDAD are considerable and in the UK in 2005, CDAD is thought to have cost the National Health Service £200 million and resulted in the need for 1 million extra bed-days. Risk factors associated with hospital-acquired *C. difficile*-associated colitis include: antimicrobial use; advanced age (>65 years); laxative use; proton pump inhibitors; anti-neoplastic chemotherapeutic use; renal insufficiency; gastrointestinal surgery/procedures; severity of underlying disease; nasogastric intubation; gastric acid suppressants; duration of hospital stay; duration of antibiotic course; multiple antibiotics; and prolonged hospital stay.4–8

*C. difficile* is estimated to colonize 3% of healthy adults and 15% to 25% of hospitalized patients.9–12 The incidence of CDAD ranges from 1 to 30 cases per 1000 hospital discharges.13 Raveh et al.14 commented that for *C. difficile* to colonize the gut of a normal individual, the resident normal flora must be altered.15 Anaerobic gut flora are thought to be crucial to ‘colonization resistance’; however, the precise components involved have not yet been clearly defined.

Raveh et al.14 evaluated the risk factors for *C. difficile* toxin-positive nosocomial diarrhoea. They compared parameters from over 530 patients of whom 17% had positive toxin tests and 83% negative toxin tests. Patients who were toxin positive: were older (*P* < 0.001), more often from nursing homes (*P* < 0.05), had higher leucocyte counts (*P* < 0.001), higher blood urea nitrogen (*P* < 0.01), lower serum albumin (*P* < 0.01), more often received diuretics (*P* < 0.01) and received clindamycin (*P* < 0.05). By logistic regression analysis, previous antibiotic-associated diarrhoea was the most significant risk factor for toxin-positive diarrhoea (*P* < 0.001) followed by clindamycin therapy (*P* < 0.005), diuretics (*P* < 0.005) and older age (*P* < 0.05). Macrolides (*P* < 0.05) were also shown to contribute to the development of hospital-acquired diarrhoea.
Pathogenesis

Elliott et al. indicated that disruptions of normal colonic flora appear to be essential to the pathogenesis of C. difficile infection. Colonization resistance is the term for the mechanism by which indigenous flora controls colonization by C. difficile. As such, colonization resistance may be compromised by antimicrobial compounds, illness or by therapeutic procedures.

The pathogenesis of infections with C. difficile clearly begins with the ingestion of either vegetative organisms or with spores. Spores are non-vegetative forms that persist in the environment for extended periods and are difficult to eradicate. Spores survive gastric acidity, germinate in the colon to vegetative organisms and toxin-producing strains subsequently produce toxin. Toxins A and B lead to tumour necrosis factor production, pro-inflammatory interleukins and increased vascular permeability. This results in colitis, pseudomembrane formation and watery diarrhoea. Toxic megacolon, colon peritonitis and pseudomembranous colitis. According to Poutanen and Simor, severe cases of toxic megacolon may be associated with mortality rates of 24% to 38%. The factors impacting patients being asymptotically colonized may include:

- organism virulence,
- degree of disruption to the host’s normal flora,
- host factors (i.e. immune response)

Two studies, published several years ago, suggested that IgG antibody against toxin A was more commonly seen in asymptomatic carriers than those with CDAD (P < 0.001) and that high IgM antibody levels to surface layer proteins of C. difficile were associated with protection against recurrent CDAD.

Antimicrobial use and CDAD

Antimicrobial use and the association with CDAD remains a significant issue and Oldfield indicated it was more commonly associated with ampicillin, clindamycin and cephalosporins.

Akbar et al. reported on a case of pseudomembranous colitis 3 months after the start of rifampicin therapy for tuberculosis abdominal lymphadenopathy and suggested that clinicians should be aware of this serious complication of rifampicin therapy.

According to data reviewed and summarized by Elliott and Tedesco, they showed the association between clindamycin and pseudomembranous colitis and this agent was the highest risk agent in the 1970s; a subsequent decline in use reduced attributable risk. Throughout the 1980–1990s, third-generation cephalosporins were associated with the highest relative risk and continue as a significant risk today.

The role of fluoroquinolone use and the risks for CDAD have been a significant issue and Oldfield indicated it was more commonly associated with ampicillin, clindamycin and cephalosporins.

Yam and Smith commented on the selection of antimicrobial compounds for orthopaedic patients and the increasing incidence of C. difficile infections. They suggested that prolonged therapy with broad-spectrum antimicrobials results in unavoidable collateral damage. The primary culprits for C. difficile infection were clindamycin, cephalosporins and extended-spectrum penicillin.

Biller et al. reported on moxifloxacin therapy as a risk factor for C. difficile-associated disease during an outbreak at an acute care, non-teaching, community hospital in central Pennsylvania. The outbreak began after a hospital formulary substitution from levofloxacin to moxifloxacin for the treatment of respiratory tract infections. By univariate analysis, the following were identified as significant risk factors in C. difficile cases (n = 50) versus controls (n = 100): deficiency anaemia (P = 0.021), fluid and electrolyte disorders (P = 0.04), uncontrolled diabetes (P = 0.02), hospitalization within 6 months of admission (P < 0.001), moxifloxacin use (P = 0.004) and type II histamine antagonistic or proton pump inhibitor use showing a tendency towards significance (P = 0.06). By multivariate analysis, hospitalization within the previous 6 months (P < 0.001), moxifloxacin exposure (P = 0.01) and uncontrolled diabetes (P = 0.02) were independently associated with CDAD.
while the use of any cephalosporin, fluoroquinolone, macrolide or penicillin or the use of cefazolin, ciprofloxacin, clindamycin, ceftriaxone, levofloxacin or vancomycin were identified as risks. Specific histories of drug use in the 20 patients receiving moxifloxacin were not given—particularly in the period leading up to the outbreak. The authors indicated that switching from moxifloxacin to levofloxacin failed to control the outbreak and that this may relate to increased levofloxacin use during the intervention period. Indeed, all antimicrobial use increased in the pre-outbreak period (just over 800 DDD/1000 to ~1100 DDD/1000 patient days—estimated from graph) with intermittent fluctuations. The increase in the monthly CDAD rates between January and February 2005 was preceded by a spike in overall antimicrobial use from September–October 2004 to November–December 2004 (~1000 DDD/1000 to ~1300 DDD/1000 patient days). The precise role of any fluoroquinolone in this outbreak remains unclear and further data evaluations—if available—may be necessary to resolve this point. The authors in conclusion noted that further research was necessary to determine the role of specific antimicrobial intervention in controlling outbreaks. The authors also noted that ‘recommended enhanced infection control measures’ should be implemented during outbreaks.5,38 Finally, Biller et al.37 suggested that an assessment of ‘all antimicrobial exposures’ among CDAD patients and reviews of specific antimicrobial classes may be useful to reduce unnecessary use. Muto et al.39 reported that exposure to levofloxacin was an independent risk factor for CDAD and appeared to contribute substantially to an outbreak at a teaching hospital and that restriction in levofloxacin use (and other implicated antimicrobials—i.e. clindamycin) may be necessary to control the outbreak.

Recently, Dhalla et al.31 asked ‘Are broad-spectrum fluoroquinolones more likely to cause *Clostridium difficile*-associated disease?’ To address this question, the authors utilized a population-based case-controlled study of outpatients prescribed fluoroquinolones—the first such study conducted. Over a 3 year period, 96 individuals hospitalized with CDAD within 1 month of outpatient treatment with a fluoroquinolone were compared with 941 matched controls that had received fluoroquinolone therapy but were not hospitalized. No statistically significant increased risk of CDAD was seen among patients prescribed gatifloxacin or moxifloxacin when compared with levofloxacin. The authors concluded that this large population-based investigation of outpatients prescribed fluoroquinolones showed that there was no increased risk of CDAD in patients receiving gatifloxacin or moxifloxacin when compared with levofloxacin. In a discussion of their findings, the authors noted that their results differed from those of Loo et al.34 that reported gatifloxacin and moxifloxacin were collectively almost six times more likely than levofloxacin to be associated with CDAD. Dhalla et al.31 argued that a single, predominately clonal outbreak was in no way the same observation as a 3 year population-based outpatient study. Dhalla et al.31 noted that the study of Gaynes et al.30 reporting an increased risk of CDAD with gatifloxacin use, was uncontrolled and prone to multiple temporally confounding influences.

McDonald et al.40 reported on an epidemic, toxin gene variant strain of *C. difficile*. In this study, 187 *C. difficile* isolates were collected from eight healthcare facilities in six states where outbreaks (2000–2003) of CDAD were reported. This same strain was associated with outbreaks in Canada and Europe.34,41 Bacterial strains were analysed by pulsed-field gel electrophoresis (PFGE), restriction-endonuclease analysis (REA) and toxinotyping. Isolates belong to the REA group B1 had the same PFGE type (NAP1) and were identified in specimens from patients from all eight facilities; this strain accounted for at least half of the isolates from 5/8 facilities. The strains were toxinotype III, were positive for the binary toxin CDT and contained an 18 bp tcdC deletion. Resistance to gatifloxacin and moxifloxacin was more common in current B1/NAP1 isolates than in non-B1/NAP1 isolates (100% versus 42%, *P < 0.001*). Comparison of current B1/NAP1 isolates with historic B1/NAP1 isolates showed the current but more of the historic strains to be resistant to gatifloxacin and moxifloxacin (*P < 0.001*). The authors concluded that this previously uncommon *C. difficile* strain with variations in toxin genes is more resistant to fluoroquinolones and has emerged as a cause of geographically dispersed outbreaks of CDAD.

In a summary of healthcare facilities reporting outbreaks with the B1/NAP1 strain, McDonald et al.40 reported outbreak dates from 2000 to 2003 in Georgia, Maine, Illinois, New Jersey, Oregon and Pennsylvania where the percentage of B1/NAP1 strains ranged from 10% to 75% of all *C. difficile* strains tested. It has been suggested that the increased rate and severity of *C. difficile*-associated disease could be related to the emergence of this epidemic strain with increased virulence, antimicrobial resistance or both.

More severe disease has been reported with the B1/NAP1 strain, but not in all cases. Characteristics included higher white cell counts and more severe disease necessitating colectomy. From the Pennsylvania outbreak, investigators were unable to find a significant association between the occurrence of severe CDAD and infection with the outbreak strains (*P = 0.23*).42 McDonald et al.40 suggested that factors such as underlying host susceptibility, prevailing practices of the use of antimicrobial agents or approaches to the treatment of CDAD may have important roles in the causation of severe disease. The authors also suggest that the impact of restriction of antimicrobial agents on the spread of this strain is unknown and that restriction of fluoroquinolones would be difficult given their role in the treatment of many infectious diseases; reconsideration of fluoroquinolone use or development of innovative control measures may be necessary if the epidemics continue to spread.

From the outbreak in Quebec, Canada, in 2003–04, significant independent risk factors for infection with this strain were exposure to fluoroquinolones or cephalosporins. Case patients were more likely than controls to have the following: exposure to antibiotics (cephalosporins, clindamycin and fluoroquinolones) (79.3% versus 59.3%, *P = 0.04*) and enteral feeding (18.6% versus 11.8%, *P = 0.004*). In discussing the limitations of the study, Loo et al.34 suggested that outcome measures at 30 days from first diagnosis might result in underestimates of rates of attributable mortality, colectomy and intensive care related to the condition. Neither severity of illness nor the presence of co-existing conditions at admission were assessed. Antibiotic use in hospitalized patients was only assessed for 6 weeks prior to CDAD diagnosis and isolates were not available from all patients.

**Prevention of CDAD**

Oldfield3 suggested that to prevent CDAD, education and better compliance with isolation, use of gloves and hand washing were necessary. Control appears to be based on initiation or
reinforcement of infection control practices rather than drug restrictions. Accordingly, efforts to prevent CDAD include education, better compliance with isolation, use of gloves and hand washing.\(^3\) McFarland \textit{et al.} \(^4\) showed that 20\textasciitilde34 hospital staff members caring for patients with CDAD had \textit{C. difficile} on their hands. As well, environmental contamination is considered to be an important factor for nosocomial infection.\(^3\)\(^4\) Kuiper \textit{et al.} \(^4\) commented that ‘hospital hygiene/infection control department plays a central role in the prevention of nosocomial infections and thus a major role in the prevention of CDAD by ensuring adequate isolation of affected patients, institution of precautions and formulation of practice guidelines’. Appropriate and adequate cleaning of the hospital environment is important for prevention of CDAD, especially as Kuiper \textit{et al.}\(^4\) indicated that 30\% to 60\% of sites in hospital wards were contaminated with \textit{C. difficile} spores. Kuiper \textit{et al.}\(^5\) also indicated that up to 50\% of all antibiotic usage in hospitals is inappropriate; however, proof of this was not provided. Reducing antimicrobial use arguably would reduce antimicrobial-resistant organisms—a desirable goal. Clearly, hand decontamination through proper hand washing and glove utilization may impact on controlling \textit{C. difficile} transmission within healthcare environments.

**Conclusions**

What do we now know about CDAD? Ingestion of vegetative organisms or spores is important for pathogenesis; however, only patients with identified risks have CDAD. These organisms are acquired from the environment and from healthcare providers. Clearly, CDAD is an important infectious complication associated with antimicrobial therapy of both inpatients and outpatients and is associated with substantial morbidity and mortality. As summarized, many predisposing factors contribute to ‘at risk’ patients. Antimicrobial therapy and the risks for CDAD is a ‘hot’ topic and most recently, fluoroquinolone use is being closely scrutinized. Thomas \textit{et al.}\(^4\) conducted a systematic review of antimicrobial use and CDAD and reported that 41 of 48 studies that found an increased risk of CDAD with antimicrobial exposure had major weaknesses. The two studies that had ‘less serious threats to validity’ were by McFarland \textit{et al.}\(^4\) and Chang and Nelson.\(^4\) The report of McFarland \textit{et al.}\(^4\) found an increased risk for CDAD after cephalosporin exposure for up to 1 week and penicillin exposure for up to 2 weeks. Chang and Nelson\(^4\) provided precise estimates of the effect of clindamycin and increased numbers of antibiotics adjusted for age, length of stay and proximity to patients with CDAD’, however, adjustments for co-morbidities were not done. Thomas \textit{et al.}\(^4\) concluded that despite a large number of published studies supporting the association of various antimicrobial agents with hospital-acquired CDAD, well-designed epidemiological studies are lacking.

Inappropriate antimicrobial use is of concern, but not easily fixed as empirical use is common, based on clinical impressions and often without decision-influencing data such as the results of laboratory investigations. As with all pharmaceutical products, use is based on a ‘risk\textasciitildebenefit’ ratio and if the perceived or known benefit is such that the product is utilized, risks associated with the product use are accepted as part of the patient management. While CDAD is recognized as a potential risk following antimicrobial exposure, so is the potential for secondary infection (nosocomial?) with drug-resistant organisms, fungal infections and drug-associated side effects.

There remains little doubt that antimicrobial use increases the risks for CDAD and that certain compounds or classes of compounds are potentially associated with an increased risk. However, the exact role (risk) of each compound or class remains unresolved due to a lack of well-designed prospective studies. Ongoing investigation and outbreak reports may further resolve this point. Antimicrobials and the risks for CDAD remain very topical and undoubtedly there is more to follow with well-designed prospective studies. Until such time and likely after the completion of well designed and controlled studies, the role of infection control initiatives cannot be overstated.

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**References**

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