Clostridium difficile

Seeing the Problem

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Clostridium difficile is a growing problem in Canadian hospitals as the most common cause of nosocomial diarrhea and is a major source of health-care burden, morbidity and mortality. First reported in 1935 as part of an infant's normal fecal flora, this gram-positive, anaerobic bacterium has since been recognized for its protean clinical manifestations (Table 1).

The estimated annual cost of managing *C. difficile*-associated disease (CDAD) in the US is approximately $1 billion.[1] A Canadian surveillance project in 1997 found that, on average, a hospital is likely to face 10 readmissions [illegible] to CDAD, with an [illegible] $128,200 [illegible]

Robert's case

- Robert, 71, lives independently.
- He is hospitalized with community-acquired pneumonia.
- He receives cefuroxime and azithromycin for three days and is discharged on oral azithromycin after hi[illegible] improve[illegible]

[illegible]ppriate?

[illegible]s necessary?

For the answer, go to page 89.

[illegible] symptomatic [illegible]symptomatic individuals?

Healthy adults are resistant to *C. difficile* colonization because of colonic bacterial flora. Alteration in colonic flora, such as gut exposure to antibiotics, results in the loss of resistance. Therefore, as an ecological niche is created, the gastrointestinal (GI) tract becomes susceptible to *C. difficile* colonization, allowing for *C. difficile* spore germination. The most frequently implicated antibiotics leading to CDAD are the broad spectrum agents (beta lactams, such as penicillins, cephalosporins and clindamycin). However, any antibiotic can cause CDAD by altering the bowel flora. Several other

Table 1

Clinical manifestations of *C. difficile*

- Asymptomatic
- Mild watery diarrhea
- Fever
- Anorexia
- Nausea
- Abdominal discomfort
- Leukocytosis
- Pseudomembranous colitis
- Death

Table 2

Factors predisposing to CDAD

- Chemotherapy agents
- Immunosupressants
- Gastrointestinal surgery
- Nasogastric tubes
- Stool softeners
- Enemas
- Gastrointestinal stimulants
- Anti-peristaltic agents
- Antacids
- Enteral feeds
- Advancing age
- Severe co-morbid illness

CDAD: *C. difficile* associated disease

factors play a role in changing the protective effect of normal GI flora[1] (Table 2).

The next requisite criterion for clinical disease is the toxigenic colonizing strain.

How is CDAD diagnosed?

Toxin production is the basis of *C. difficile* diagnosis. The gold standard of diagnosis is the tissue culture cytotoxin assay, which detects cytotoxin (toxin B) in stool filtrate. This test has a specificity of 99% to 100% and sensitivity of 80% to 90%, but requires a facility to process tissue cultures and is more time consuming (48 hours) than the rapid four-hour enzyme immunoassays.

The enzyme immunoassay tests may detect toxin A or B from stool filtrates. These tests have less sensitivity, 65% to 85%, than the tissue culture assays, however, their specificity is 95% to 100%.

Stool culture has limited utility because of asymptomatic carriage of non-toxigenic strains and the long turn-around time for receiving results. Stool should only be submitted for *C. difficile* toxin testing when they conform to the shape of the container. Many diagnostic laboratories will not process formed stool for *C. difficile* toxin.

When a diagnosis has not been established by stool toxin analysis, and the patient is clinically unwell, the diagnosis may be aided by computed axial tomographic scanning of the abdomen, sigmoidoscopy or colonoscopy. These techniques may demonstrate pseudomembranous colitis.

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How is CDAD Treated?

Treatment should begin with the cessation of the responsible antibiotic. Cessation might not be possible, as it may impact the patients other underlying problems.

In cases of mild CDAD, discontinuation of the current antibiotics may be sufficient. In more significant cases, oral metronidazole, 500 mg, three times daily, is administered for 10 to 14 days. Oral vancomycin, 125 mg, four times daily for 10 to 14 days, is the second-line therapy, due to concern regarding selection of vancomycin-resistant enterococcus.

Other alternative therapies include teicoplanin, bacitracin or fusidic acid, however, these alternatives are rarely used in Canada. Avoidance of antiperistaltic drugs is recommended to reduce the risk of toxic megacolon, which, along with colonic perforation, is an indication for operative management. Rifampin and anion-binding resins (colestipol or cholestyramine) may be useful adjuncts. Binding resins should be administered either one hour before or four to six hours after antibiotic therapy to reduce the binding of these therapeutic agents.

Although patients may require two to three months to clear *C. difficile* carriage from their GI tract, most begin to experience an improvement in their GI symptoms within four to seven days of initiating antibiotic therapy.

The following suggestions should help minimize the spread of *C. difficile* spores in hospitals and diminish the risk of CDAD in other hospitalized patients:

- Contact precautions
- Dedicated equipment for patients with CDAD
- Single-use, disposable rectal thermometers
- Early empiric treatment of suspected cases
- Education of patients, staff and family on infection prevention and control strict handwashing
- Intensified housekeeping in affected areas, particularly using sporicidal agents

There has been an increased interest in the study of probiotics. Probiotics are indigenous nonpathogenic micro-organisms that may compete with pathogenic bacteria for specific binding sites on intestinal epithelial cells. Results of these studies have shown variation.

FAQ

1. What is the role of toxins in *C. difficile*-associated disease (CDAD)?

Toxin A, an enterotoxin, causes intestinal injury and secretion via necrosis, increased intestinal permeability and inhibition of protein synthesis. Toxin B, a cytotoxin, preferentially acts as a potent colonic toxin, with minor effects on the intact intestine. This toxin likely becomes active in the presence of intestinal wall damage.

2. Are there any antibiotics that do not contribute to CDAD?

Antibiotics, such as aminoglycosides, macrolides, sulfonamides, tetracyclines and quinolones, though considered to be less frequently associated with CDAD, may also contribute to it. Even metronidazole and vancomycin have been associated with CDAD.

3. What precautions should be taken with patients with CDAD?

Contact precautions to prevent the spread of *C. difficile* spores, attention to hand hygiene and minimizing unnecessary antibiotics are the initial step to preventing CDAD.

Robert's followup

C. difficile disease is immediately suspected and stool testing for *C. difficile* toxin is undertaken. The azithromycin is stopped and Robert is started on oral metronidazole for the next 14 days. With supportive care, his symptoms resolve and he is discharged from hospital.

One large, randomized, controlled trial demonstrated that *saccharomyces boulardii* aided in the prevention of recurrent *C. difficile*-associated colitis, though only in patients with sequential *C. difficile* infections. No beneficial effect was demonstrated on initial *C. difficile* infection. Similar benefit was observed for *lactobacillus plantarum* as well as with non-toxigenic strains of *C. difficile*.[4]

It is likely that probiotics do not cause any harm and may offer benefits to patients wishing to try them. At this time, data from well-controlled trials is lacking and probiotics cannot be recommended. Currently, immunization against *C. difficile* relapse is being studied.[5] Dx

References
1. Oldfield, EC III: Clostridium difficile-associated diarrhea: Risk factors, diagnostic methods, and treatment. Rev Gastroenterol Disord 2004; 4(4):186-95.
2. Miller MA, Hyland M, Ofner-Agostini M, et al: Morbidity, mortality, and healthcare burden of nosocomial Clostridium difficile-associated diarrhea in Canadian hospitals. Infect Control Hosp Epidemiol 2002; 23(3):137-40.
3. Jobe BA, Grasley A, Deveney KE, et al: Clostridium difficile colitis: An increasing hospital-acquired illness. Am J Surg 1995; 169(5):480-3.
4. Fedorak RN, Madsen KL: Probiotics and prebiotics in gastrointestinal disorders. Curr Opin Gastroenterol 2004; 20(2):146-55.
5. Sougioultzis S, Kyne L, Drudy D, et al: Clostridium difficile toxoid vaccine in recurrent C. difficile-associated diarrhea. Gastroenterology 2005; 128(3):764-70.

Take-home message

What is *C. difficile*?

- Gram-positive anaerobic bacterium
- Disease requires:
  - toxigenic strain
  - susceptible host

How to diagnose

- Stool sample for tissue culture cytotoxin assay (gold standard)
- Rapid enzyme immunoassay for toxin (most frequently used technique)

How to treat

- Cessation of antibiotics
- First-line therapy: Oral metronidazole, 500 mg, three times daily, 10 to 14 days
- Second line therapy: Vancomycin, 125 mg, orally, four times daily for 10 to 14 days