

C. Difficile: A Growing Threat



Richmond Sy, MD, FRCPC

Presented at Ottawa University's Internal Medicine Update for Family Physicians, Ottawa, Ontario, January 2007.

The association between *C. difficile* and antibiotic-related diarrhea has been established since the late 1970s.¹ Since that time, *C. difficile* infections have become a mainstay of acute care hospitals and nursing homes. It is the leading cause of antibiotic-associated diarrhea. The incidence of *C. difficile* has increased over the last decade. The proportion of patients with severe, recurrent or refractory disease has also increased, with an estimated mortality rate of 6% to 30%.



What is the microbiology?

C. difficile is an anaerobic gram-positive rod that is spore forming. It is 2 µm to 17 µm in length. It produces two toxins, Toxin A and Toxin B, which cause watery diarrhea. Toxin A causes fluid secretion and intestinal inflammation. Toxin B is a cytotoxin that is 10 to 1,000 times more potent than Toxin A. It is Toxin A that leads to pseudomembranous colitis. A recent epidemic strain (called strain B1, nucleosome assembly protein-1, or toxinotype III) produces increased levels of Toxins A and B (16-fold and 23-fold higher levels, respectively). This strain has been implicated in the recent outbreaks in Quebec.



What are the clinical features?

The hallmark of *C. difficile* infection is watery diarrhea associated with recent antibiotic use. Classic symptoms include diarrhea and lower abdominal cramping pain. Clinically evident bleeding is usually absent. In severe cases, systemic symptoms, such as the following, can occur:

- fever,
- nausea,
- anorexia and
- fatigue.

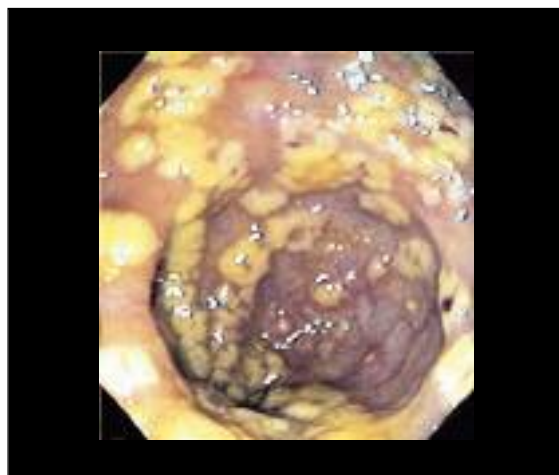


Figure 1. Pseudomembranous colitis.

On laboratory findings, a pronounced leukocytosis is often present. Ongoing diarrhea can cause hypoalbuminemia and anasarca.

Fulminant colitis is rarely reported but can lead to life-threatening situations, such as toxic megacolon, perforation and sepsis.

Q & A *How to investigate and how to diagnose?*

The endoscopic feature of pseudomembranous colitis is pathognomonic for *C. difficile* infection. The colonic mucosa is inflamed and studded with numerous adherent yellowish plaques (Figure 1). This is considered an advanced stage of the disease and is predominantly located in the rectosigmoid region and, in some instances, can be patchy.

Testing

Several tests are available to detect *C. difficile*. These include:

- anaerobic culture,
- direct toxin testing,
- detection of toxin mediated cytopathic effects on cells,
- detection of antigens and
- nucleic acid amplification techniques.

Cytotoxic assay are considered the most sensitive (92% to 100%) of all the techniques but it is time- and labour-intensive. The enzyme immunoassay kits that use monoclonal antibodies against Toxin A alone or both Toxin A and B are the most commonly-used methods to detect *C. difficile*. The enzyme immunoassay is simple, easy to use and quick. Unfortunately, the sensitivity is lower (66% to 96%) than that of the cytotoxic assay. False-negatives can occur,

Table 1
Antibiotics leading to *C. difficile* infection

Frequently

- Ampicillin
- Cephalosporins
- Clindamycin

Infrequently

- Tetracyclines
- Sulfonamides
- Macrolides
- Chloramphenicol
- Trimethoprim
- Quinolones

Rarely

- Aminoglycosides
- Metronidazole
- Bacitracin
- Vancomycin

so repeat testing is often necessary if suspicion is high.

Q & A *What are the risk factors?*

The main risk factor for *C. difficile* infection is antibiotic use. Almost all antibiotics are associated with *C. difficile* infection. The most widely implicated antibiotics are:

- clindamycin,
- cephalosporins,
- ampicillin and
- fluoroquinolones.

Tetracyclines, macrolides and sulfonamides have infrequently led to *C. difficile* infections (Table 1).

More controversially, proton pump inhibitors (PPIs) have been associated with an increased incidence of *C. difficile* infection. Gastric acid suppression may lead to impaired host defenses against invading bacteria.

Table 2

Metronidazole vs. vancomycin

	Metronidazole	Vancomycin
Dose	250 mg to 500 mg	125 mg to 500 mg
Frequency	3 to 4 times per day	3 to 4 times per day
Duration	10 to 14 days	10 to 14 days
Route	Oral or IV	Oral
Response rate	> 96%	> 96%
Cost	\$15	\$380
Disadvantage	Systemic side-effects	Encourages vancomycin resistance

Currently, studies have been inconsistent and more are required to establish the true risk of PPIs.

Additional risk factors

Other risk factors include the:

- severity of underlying illness,
- chemotherapeutic agents,
- surgery,
- older patients,
- prolonged hospital stay,
- ICU admission and
- tube feeding.

Q *What is the treatment?*

Treatment of *C. difficile* infection includes discontinuing the offending antibiotic and supportive care. Resolution of symptoms can be

Dr. Sy is an Assistant Professor, Division of Gastroenterology, Department of Medicine, University of Ottawa and a Staff Member, Ottawa Hospital, General Campus, Ottawa, Ontario.

expected in 15% to 23% of individuals without antibiotic therapy.

The addition of metronidazole is considered a first-line therapy for patients that fail to respond to conservative therapy.² Oral vancomycin is recommended as a second-line therapy for patients that fail a course of metronidazole. Oral vancomycin is a second-line therapy due to its higher costs compared to metronidazole and its concerns about potentiating vancomycin resistance. Studies comparing treatment with metronidazole and vancomycin demonstrate equal efficacy (Table 2). Vancomycin can be considered first-line therapy if the patient is:

- intolerant of metronidazole,
- pregnant,
- < 10-years-of-age, or
- critically ill.

For severe or resistant cases, IV metronidazole has been used with success. IV vancomycin is generally not recommended as fecal concentrations are suboptimal. In rare occasions, surgery may be necessary for fulminant colitis.

Q *What is the risk of relapse?*

Relapse of treated *C. difficile* can occur in 8% to 50% of cases. Risk factors for recurrence include:

- new exposure to antibiotics,
- > 65-years-of-age,
- severe underlying illness,
- low serum albumin levels,
- ICU admission, or
- prolonged hospital stay.

The rapid rate of recurrence may reflect spore germination after antibiotic treatment is completed. Treatment of recurrence often includes repeated courses of metronidazole or vancomycin. Novel strategies that include pulsed doses of antibiotics, probiotics and anion exchange resins (such as cholestyramine, immunoglobulins and fecal therapy) have been reported but controlled studies are lacking.

Q *How to prevent and control infection?*

Patients infected with *C. difficile* should be isolated in a single room, preferably with a private bathroom. Contact precautions should be implemented. Rooms should be cleaned with bleach, rectal thermometers avoided and hand-washing with soap enforced. Alcohol-based hand cleaners are not recommended because *clostridia* spores can survive alcohol. Antibiotic polices that limit clindamycin and cephalosporin abuse have been effective in reducing infection rates.

Take-home message

- *C. difficile* is the most common nosocomial infection
- First-line treatment is metronidazole
- Patients that relapse or have recurrent disease are difficult to treat
- Preventative strategies are important to decrease rates of *C. difficile* infection in hospitals

Q *Final thoughts?*

C. difficile is a significant nosocomial infection that leads to considerable morbidity and mortality. Despite increased awareness, the incidence of *C. difficile* infection is rising worldwide.

Treatment with metronidazole or vancomycin is efficacious, but resistant and recurrent cases are becoming increasingly more common.

Current management should include greater care in avoiding the overuse of antibiotics and the implementation of preventative strategies in hospitals. **Dx**

References

1. Bartlett JG: Role of *Clostridium Difficile* in Antibiotic Associated Pseudomembranous Colitis. *Gastroenterol* 1978; 75(5):778-82.
2. Fekety R: Guidelines for the Diagnosis and Management of *Clostridium Difficile*-Associated Diarrhea and Colitis. American College of Gastroenterology, Practice Parameter Committee. *Am J Gastroenterol* 1997; 92(5):739-50.