



***Clostridium difficile*-Associated Diarrhea**

Diarrhea associated with antibiotic use is often mild and self-limiting, but it can also be a very serious condition. Recent outbreaks of *Clostridium difficile* infections in Canadian hospitals have focused attention on this organism. This article attempts to explain the potential causes of antibiotic-associated diarrhea (AAD) and to provide some information about *C. difficile* associated diarrhea (CDAD) in particular.

Antibiotic-Associated Diarrhea (AAD) vs *Clostridium difficile*-Associated Diarrhea (CDAD)

Diarrhea can occur after a course of any antibiotic as a result of drug specific mechanisms or disruption of normal colonic flora. Examples of drug specific mechanisms include: erythromycin acts as a motilin-receptor agonist and clavulanate appears to stimulate small bowel motility. Rarely, penicillins may cause a segmental colitis.¹ Many cases of AAD may actually be caused by agents other than antibiotics. Laxatives, antacids, contrast agents, products containing lactose or sorbitol, NSAIDs, antiarrhythmic drugs, or cholinergic agents can all cause diarrhea.²

Disruption of normal colonic flora allows for overgrowth of pathogenic organisms. *Staphylococcus aureus*, *Clostridium perfringens*, *Salmonella*, *E. coli* and possibly *Candida albicans* have all been found to overgrow when the normal flora has been disturbed.² *C. difficile* is the most common pathogenic organism accounting for 20% of cases of AAD.² *C. difficile* is also the most serious cause, as it is responsible for >95 % of cases of pseudomembranous colitis.²

AAD is usually moderate in severity. Less severe diarrhea may be treated symptomatically paying particular attention to hydration status.¹ More severe diarrhea may require discontinuation of the offending antibiotic. Diarrhea usually resolves upon antibiotic discontinuation.² If antibiotic therapy is required, switching to an antibiotic that causes diarrhea less commonly may be warranted.¹ Sulfonamides, tetracyclines, aminoglycosides and metronidazole are possible alternatives.^{1,2} AAD is common in patients with a previous history of diarrhea with antibiotic therapy² and occurs in the community and institutional settings.

C. difficile is a spore forming, gram-positive anaerobic bacillus that produces two toxins; toxin A, (an enterotoxin) and toxin B (a cytotoxin).^{3,4} These spores are found in the feces, survive on surfaces and are transmitted by ingestion to a new host. After ingestion, the spores germinate in the colon and form vegetative bacilli capable of growth and toxin production.⁵ *C. difficile* may be transmitted and infect without prior antibiotic use. It is possible to carry *C. difficile* asymptotically. Approximately 3% of people in the community and 20 –30% of hospitalized patients are colonized.^{3,6} Up to 50% of infants may be carriers and are usually asymptomatic.⁷

Although clindamycin, second and third generation cephalosporins, and many penicillins have been implicated, *C. difficile* infection may be caused by any antibiotic,^{2,5} including, though rarely, the drugs used to treat CDAD metronidazole and vancomycin.⁵ There has been an increase in the incidence of CDAD associated with fluoroquinolone use.⁸ Presenting symptoms may include high fever, nausea, marked abdominal pain, hypotension, hypoalbuminemia, severe sepsis, and/or evidence of colitis.⁵ Lab tests may show elevated white blood cell counts, low albumin levels, and the presence of white blood cells in the feces.² In severe cases the patient may present with a toxic megacolon, in which case little or no diarrhea may be seen.³ CDAD may present up to 2 months after antibiotic use.⁵ Elderly, immunocompromised and/or patients who have had a long stay in a healthcare setting are most prone to CDAD.^{4,9} It has been postulated that CDAD is associated with proton pump inhibitor use¹⁰, though this has been

challenged and requires further investigation.¹¹

Diagnosis of CDAD

Several tests can be used for diagnosis. Cytotoxin assay using tissue culture is the gold standard. However, turn-around time is long.^{2,5} Most labs use enzyme immunoassays (EIA) to detect toxin A, toxin B, or both. EIA is less sensitive than cytoxin assays but results are available more quickly.^{2,5} If the tests are negative, but clinical suspicion is high, testing should be repeated and empirical treatment may be instituted.⁵

Treatment

Goals of treatment are to reestablish the normal flora and to reduce the burden of *C. difficile* toxin. If possible discontinue or change the precipitating antibiotic. Almost ¼ of cases will resolve within 2 to 3 days after discontinuation of the offending antibiotic.^{4,12} Probiotics or yogurt cultures have been given to promote recolonization with normal colonic flora and have shown variable results.^{5,6,12,13,14} Anti-peristaltics should be avoided in CDAD, as they may promote retention of toxin.^{3,12}

Most cases will require treatment with antibiotics, but this does increase the chance of relapse.² Metronidazole is the most commonly used agent, dosed at 250mg po QID or 500 mg po TID for 10 days.^{1,2,3,6,15} Vancomycin is also used in doses of 125 mg po QID x 10 days.^{1,5,15} Vancomycin is not preferred, as it is much more costly and there are concerns about the emergence of Vancomycin-Resistant Enterococci (VRE).^{2,15} Vancomycin may be necessary in cases of metronidazole intolerance.^{2,15} The use of metronidazole in pregnancy, especially the first trimester, is controversial. The majority of data suggests metronidazole poses no significant structural risk to the fetus though there are concerns about the potential of carcinogenicity. Treatment options should be discussed among the pregnant patient and her health care professionals.¹⁶

Response to treatment is rapid, with resolution of fever within 24 hours, and resolution of diarrhea in 4 to 5 days.² Diarrhea that persists >7 days may be considered a treatment failure.¹⁵ In treatment failure with metronidazole, vancomycin should be instituted at the above mentioned dose. Alternatively, the physician may consider other possible explanations for the diarrhea.¹⁵ It is important to assess for ileus or toxic megacolon, since these conditions may prevent the drug from reaching the target site.²

Multiple Relapses

Relapses may occur in up to 25 % of cases.² The diarrheal symptoms usually recur within 3 to 21 days after drug therapy is discontinued. Relapses are thought to be from reinfection or from germination of spores within the colon.⁵ The first relapses should be treated with the original agent.^{2,10,17} Several regimens have been proposed to treat multiple relapses including pulse dosing of vancomycin, cholestyramine, and probiotic therapy (such as *Saccharomyces boulardii*).² New treatments being developed to treat multiple relapses and to prevent initial infections include vaccines,¹⁷ toxin binders,¹⁸ immunoglobulins¹⁵ and monoclonal antibodies.¹⁵

C. difficile Outbreaks

Recent outbreaks of *C. difficile* have been associated with higher mortality rates than in the past.⁹ Investigators have also found a higher incidence of CDAD unresponsive to metronidazole.⁹ While resistance to metronidazole would be a plausible explanation, metronidazole susceptibility in treatment failure and treatment success has been shown to be similar.^{19,20} Proposed explanations for the reduced responsiveness to metronidazole include the increase of older, sicker patients and increased use of broad spectrum antibiotics.²⁰ The idea of more virulent strains of *C. difficile* is controversial.^{9,21} Nonetheless, alternative treatments to metronidazole need to be developed.²² A management strategy that requires no Rx&D resources is to reduce unnecessary antibiotic use.

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