Pseudomembranous colitis: An update

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HS Brar, CM Surawicz. Pseudomembranous colitis: An update. Can J Gastroenterol 2000;14(1):51-56. *Clostridium difficile* is the most common nosocomial infection of the gastrointestinal tract. Most cases are associated with antibiotic therapy that alters the fecal flora, allowing overgrowth of C *difficile* with production of its toxins. Diagnosis is made by detection of the organism or toxin in the stools. A variety of different tests can be used, but none is perfect. A stool culture can be positive in someone without diarrhea, ie, a carrier. While the cytotoxin is the gold standard, it is expensive, and there is a delay before results are available. Thus, many laboratories use the enzyme-linked immunoassay tests to detect toxin of C *difficile* because they are a more rapid screen. Depending on the specific test used, they can detect toxin A, toxin B or occasionally both. Sensitivity and specificity rates vary. First line therapy for C *difficile* disease should be metronidazole 250 mg qid for 10 days. Vancomycin should be reserved for severe cases where metronidazole has failed or where metronidazole cannot be tolerated or is contraindicated. Recurrent C *difficile* disease is a particularly vexing clinical problem. A variety of biotherapeutic approaches have been used. Retreatment with antibiotics is almost always necessary. In addition, the nonpathogenic yeast *Saccharomyces boulardii* has been showed to be of benefit as an adjunct in preventing further recurrences.

Key Words: Clostridium difficile; *Enzyme-linked immunoassay; Pseudomembranous colitis*

Colite pseudo-membraneuse : une mise à jour

RÉSUMÉ : *Clostridium difficile* est l'infection nosocomiale la plus courante du tractus intestinal. La plupart des cas sont associés à une antibiothérapie qui altère la flore intestinale, permettant la prolifération de C. *difficile* avec libération de toxines. Le diagnostic est posé par dépistage de l'organisme ou de ses toxines dans les selles. On peut utiliser différents tests mais aucun d'entre eux n'est parfait. Une culture des selles peut être positive chez un sujet sans diarrhée, c'est à dire, un sujet porteur. La recherche de cytotoxines constitue le test de référence mais ce dernier est coûteux, et un certain délai est nécessaire pour obtenir les résultats. C'est pourquoi de nombreux laboratoires font appel aux dosages par une technique immuno-enzymatique pour déceler la toxine de C. *difficile* parce qu'elle constitue une méthode de dépistage plus rapide. Selon le test spécifique utilisé, il est possible de déceler la toxine A, la toxine B et quelquefois les deux à la fois. Les taux de sensibilité et de spécificité varient. Le traitement de première ligne pour la maladie causée par C. *difficile* devrait être du métronidazole à raison de 250 mg quatre fois par jour pendant 10 jours. On devrait réserver la vancomycine pour les cas sévères résistants au métronidazole ou en cas d'intolérance ou de contre-indication au métronidazole. La récurrence de la maladie à C. *difficile* est un problème clinique particulièrement contrariant. Une variété d'approches biothérapeutiques ont été utilisées mais une deuxième antibiothérapie est presque toujours nécessaire. De plus, la levure non pathogène *Saccharomyces boulardii* s'est révélée bénéfique comme traitement adjuvant pour prévenir d'autres récidives de la maladie.

Clostridium difficile is the most common nosocomial infection of the gastrointestinal tract. Epidemics have been documented in hospitals as well as in nursing homes and rehabilitation centres (1). The association of C *difficile* disease with antibiotic therapy is well recognized, and many newer broad spectrum antibiotics may predispose patients to its acquisition. C *difficile* can cause diarrhea in previously healthy individuals who are given antibiotics in an outpatient setting. This article focuses on the diagnosis and therapy for C *difficile*-associated disease, as well as on illness complicated by ileus, toxic megacolon or recurrences.

PATHOGENESIS

Pseudomembranous colitis (PMC) occurs when changes in fecal flora allow the overgrowth of C *difficile* with production of its toxins A and B. This usually occurs in the setting of an-

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TABLE 1
Detection of *Clostridium difficile* toxins

Method	Sensitivity	Specificity
Cytopathic effect toxin B	Gold standard	Gold standard
Enzyme-linked immunoassay toxin A	85%	100%
Polymerase chain reaction of stool	83%	100%

tibiotic use, when colonization resistance is altered by changes in fecal flora. Colonization resistance is the term coined by Van der Waaij et al (2) in 1971 to describe the protective role of the indigenous enteric flora, preventing colonization by microorganisms that are pathogens or potential pathogens. Anaerobic bacteria appear to be crucial in maintaining colonization resistance. For example, in mice given broad spectrum antibiotics, the fecal flora is altered but is re-established only if anaerobes are given orally. The mechanisms of colonization resistance are not known but are probably multiple, such as the ability of some bacteria to inactivate beta-lactam antibiotics or other antibiotics. Patients who receive tube feeding are also more likely to acquire C *difficile* independent of antibiotic use (3).

C *difficile* has been identified from various sources in the environment (including spores in the soil and water). In hospitals, the patient with PMC is the most important reservoir. Impaired colonization resistance permits C *difficile* spores to germinate in the human gut. Gut mucus may serve as a chemoattractant (4). C *difficile* has been shown to produce several enzymes that may mediate tissue degradation. Among these, hyaluronidase, chondroitin-4-sulphatase and collagenase have all been studied extensively. In addition, C *difficile*'s toxins, enterotoxin (toxin A) and cytotoxin (toxin B), have been studied. Both toxins produce vascular permeability and hemorrhage, but only toxin A leads to fluid accumulation. However, toxin B is reported to be more harmful to colonic epithelium in vitro (5). Both toxins may catalyze glucosylation of threonine at position 37 on the GTP-binding protein Rho. This may lead to change from F-actin to G-actin in cells, thus accounting for the cell rounding seen in tissue culture (6). In general, strains that produce more toxin and are more adherent are more virulent.

DIAGNOSIS

Clinical clues: C *difficile*-associated diarrhea should be suspected in anyone who develops diarrhea during antibiotic therapy. Diarrhea can even occur up to eight weeks after the end of a course of antibiotics. It is more common after oral antibiotics, and has even been reported as a complication of single dose cephalosporin given preoperatively (7). The diagnosis is made by detection of C *difficile* and/or one of its toxins in the stool. Colitis should be suspected when there is fever, abdominal pain and diarrhea with gross or occult blood in the stools (8). White blood cells may be present in the stools but are not a reliable indicator of colitis. They can be absent even when stools are positive for toxins. A recent prospective analysis of factors predicting a positive C *difficile* toxin in the stool indicated usefulness of the following predictive parameters: cephalosporin use, prolonged hospital stay, onset of diarrhea six or more days after receiving antibiotics, fecal leucocytes in the stool and presence of semiformed stool (6). A study to identify patients with a very low likelihood of C *difficile*-associated diarrhea found that patients without a history of antibiotic use or significant diarrhea or abdominal pain were unlikely to have a positive C *difficile* toxin assay (9).

Stool tests: A good review of diagnostic tests has been published recently by Brazier (10).

C difficile *cytotoxin (toxin B):* The gold standard in diagnosis is the presence of C *difficile* cytotoxin (toxin B) in the stools (Table 1). This is present in 95% to 100% of cases of PMC. The test is performed using tissue culture; the test is positive when cells show cytopathic rounding – an effect of the cytotoxin. The test takes at least 24 to 48 h. The test can be falsely negative if the stool specimen has been improperly stored or if toxin levels are too low to be detected. C *difficile* cytotoxin is degraded at room temperature; therefore, if the stool must be stored, it should be kept refrigerated at 4°C until tested. Strains that produce only toxin A are uncommon but can also explain the false negative toxin. Overall, the specificity is 95% to 99% and sensitivity is 70% to 100%. The cost of toxin is $36.00 in laboratories in Seattle, Washington.

C difficile *culture:* The role of C *difficile* culture is controversial because it detects asymptomatic carriers. Certainly there are patients with diarrhea who have C *difficile* in the stool but do not have toxin. When their diarrhea responds to therapy that eradicates C *difficile*, this entity is called 'C *difficile*-positive toxin-negative diarrhea' (11). Obviously it can only be diagnosed with culture. For this reason, C *difficile* culture is advocated in cases where diagnosis is uncertain, in evaluating some cases of chronic diarrhea or when empirical therapy has failed. As with the cytotoxin, there is a 24 to 48 h delay in receiving results. The cost of culture is $24.50 in our hospital's microbiology laboratory.

Enzyme-linked immunoassay* C difficile *toxin assays: The first enzyme-linked immunoassay test for detection of C *difficile* toxins in stools was developed by Yolken et al (12) in 1981. Many clinical laboratories use one of several enzyme-linked immunoassays to detect toxins A, B or both. Reports of sensitivity of 85% and specificity of 100% have been reported (13-16). These tests are used as a rapid screen; a false negative test does not always exclude disease, and clinical judgement is still important. At the Harborview Medical Centre, Seattle, Washington, the C *difficile* antigen test used costs $27.00.

Latex agglutination test: The latex agglutination assay is a rapid test to detect a C *difficile* protein. It does not detect the enterotoxin, but rather a protein that can be positive due to other bacteria such as other clostridial strains (17). It is used as initial rapid screen, but results must be interpreted with caution because false positive results may range from 1% to 30%; sensitivity ranges from 68% to 90%.

Other stool tests: Molecular methods such as polymerase

TABLE 2
Antibiotic therapy for *Clostridium difficile* disease

Antibiotic	Dose	Cost for 10-day course (US$)	Side effects
Metronidazole	250 mg qid	25–30	Nausea, vomiting, diarrhea, metallic taste, 'antabuse' effect, peripheral neuropathy (irreversible)
Vancomycin	125 mg qid	300	Rash (rare)
Bacitracin	25,000 U qid	150	Bitter taste
Fusidic acid	0.5–1.5 g/day	Not Available in United States	
Teicoplanin	100 mg bid	Not available in United States	

chain reaction are described in the literature (18) as having a sensitivity of 83% and a specificity of 100% when applied to stool. The sensitivity and specificity of 100% are reported with polymerase chain reaction methods applied to C *difficile* cultures (19). However, these methods are limited by cost and general lack of availability outside a research setting. The test may be useful for evaluating epidemics.

Endoscopy: When an immediate diagnosis is necessary, flexible sigmoidoscopy or colonoscopy can be used to visualize the colonic mucosa. Typical pseudomembranes are creamy white or yellow plaques adherent to the mucosa. These are usually seen in the distal colon within the reach of a flexible sigmoidoscope. Occasionally, they can be limited to the right colon (10% to 20% of cases), so full colonoscopy can be considered in cases where the diagnosis is strongly suspected but the left colon looks normal.

THERAPY FOR C *DIFFICILE* DISEASE

Initial therapy: Initial evaluation should assess hydration and severity of illness. The diagnosis rests on stool examination, but because results may not be available for 24 to 48 h, empirical therapy may sometimes be necessary. It is reasonable to treat for C *difficile* in anyone who develops diarrhea in the hospital, in some cases of chronic diarrhea, when symptoms worsen or progress, when colitis is present or in anyone who has a history of prior C *difficile* infection.

Antibiotics: The two most commonly used antibiotics to treat C *difficile* disease are metronidazole and vancomycin (Table 2). The recommended oral doses are metronidazole 250 mg qid or vancomycin 125 to 500 mg qid for 10 days. The lower dose of vancomycin (125 mg qid) is as effective as the higher dose (500 mg qid) in mild to moderate disease and is significantly less costly (20). Vancomycin was the first agent used to treat PMC (21,22). Vancomycin is not absorbed from the gastrointestinal tract; thus, side effects are uncommon. Rash has been reported.

Metronidazole is absorbed from the gastrointestinal tract. Side effects include nausea, vomiting, peripheral neuropathy, a metallic taste in the mouth and an 'antabuse-like' effect requiring patients to abstain from drinking alcohol. Although C *difficile* resistance is rare, cases of PMC have been reported in association with metronidazole.

Clinical trials indicate that the two drugs are equivalent for the treatment of mild disease (23). Metronidazole should be used as the first line choice for C *difficile* disease. Vancomycin use must be restricted to lessen the risk of development of vancomycin-resistant organisms such as *Enterococci* species. In addition, metronidazole is more cost effective. We favour the use of vancomycin when there is no response or poor response to metronidazole in patients with colitis or when metronidazole cannot be given, as in early pregnancy.

Other antibiotics are also effective for C *difficile* disease. Oral bacitracin has been given at 80,000 U/day. However, it is expensive, and its use is limited by an unpalatable taste (24). In one study it was less effective than vancomycin (25). Fusidic acid has also been used to treat C *difficile* (26); it is not available in the United States. The glycopeptide antibiotic teicoplanin, given 100 mg twice a day for 10 days was shown to be equivalent in efficacy to vancomycin 500 mg qid (27,28). It may soon be available in the United States. Other glycopeptides under investigation include eremomycin (studied in hamsters) and ramoplanin.

Nonantimicrobial therapy: The use of antidiarrheals in PMC is controversial, but there is suggestive evidence that they should be avoided. Agents such as diphenoxylate hydrochloride or loperamide decrease diarrhea, but the decreased transit may lengthen the duration of illness and lead to complications (29).

The bile salt-binding resin cholestyramine has been used; this agent causes constipation and may be helpful in decreasing diarrhea. The rationale for these bile salt-binding agents came from the notion that the resin might also bind toxin, though this has not been supported by laboratory evaluation. In addition, resin binding of antibiotics would decrease their efficacy. Thus, we do not recommend their use in most cases.

Clinical response: The diarrhea usually improves in one to four days, with resolution by two weeks. Recurrence of diarrhea occurs in 12% to 24% of cases and is difficult to treat as further recurrences become even more likely (see 'Recurrent C *difficile*').

Treatment when ileus or toxic colon is present: The patient with PMC who has an associated ileus or toxic colon or megacolon presents a therapeutic dilemma because it is difficult to deliver the oral antibiotics to the colon. Therapy should include intravenous metronidazole, which penetrates intestinal tissue. The dose is 500 mg every 6 to 8 h (30). Some feel that intravenous vancomycin may have no role because failure may occur (31-33). We, however, favour the advice of Fekety and Shah (34), who recommended the use of

parenteral vancomycin as well as metronidazole. This is such a desperate clinical situation that all measures should be tried to reverse the disease process. Vancomycin can be given by nasogastric tube or rectally as enemas. The senior author has had experience using a colonoscope to decompress a dilated colon, and then placing a decompression tube to relieve distension as well as to deliver vancomycin. On rare occasions, a surgical cecostomy may be necessary to decompress the colon and deliver vancomycin to the colonic lumen. In these critically ill patients, serial clinical evaluation is important to look for signs that urgent surgery may be needed. Mortality from fulminant toxic colitis or perforation is very high.

Indications for surgery: The main indication for surgery is worsening clinical condition despite adequate therapy. Clinical clues are organ failure, peritonitis (suggesting perforation) and progressive colitis. Progressive disease can be documented by abdominal computed tomography scan; a very thick colon wall and the presence of ascites are poor prognostic signs. In one surgical series, patients with a worse prognosis were older, had an ileus, history of recent antibiotics, and ascites or very thick colon wall on computed tomography scan (35).

The procedure of choice is subtotal colectomy because segmental resection of colitis often leads to reoperation to remove remaining diseased bowel (36). The key to avoiding this grim situation is early diagnosis and therapy. The rectal stump should be irrigated postoperatively with vancomycin because *C difficile* persists there after surgery.

Recurrent *C difficile*: Most patients respond to treatment with resolution of diarrhea, but 20% of patients relapse; these patients are even more likely to have continued relapses. This is a challenging clinical problem. The pathophysiology is not known; it is likely due to altered fecal flora, allowing continued overgrowth of *C difficile*. In one study, fingerprints of *C difficile* isolates showed that over half of patients with recurrences had the same strain (37). In other cases, a new strain can cause the recurrence.

There are three basic therapeutic approaches to relapsing *C difficile* colitis: antibiotics, binding resins and ecological approaches.

Antibiotics: Most patients need repeated courses of antibiotics, usually metronidazole or vancomycin. The same or an alternate antibiotic is repeated or vancomycin is given in tapered or pulsed doses, or longer (several weeks) courses are given. Pulsing makes the most sense because it allows spores (which are resistant to antibiotics) to germinate and be killed by the antibiotic when it is given again.

Binding resins: While binding resins are reported to bind the toxin, their efficacy has never been proven. They can be nonspecifically constipating. We do not recommend their use, but if given they should be timed in such a way as not to bind the antibiotics, such as cholestyramine or colestipol.

Ecological approaches: Ecological approaches are the most sensible because they promote normalization of the fecal flora, which should then inhibit overgrowth of *C difficile* (a) *Saccharomyces boulardii*. We have been treating patients with *S boulardii* as a part of a research protocol. *S boulardii* is a nonpathogenic yeast with an unusual optimum growth temperature of 37°C. The yeast was originally isolated from the lychee fruit in Southeast Asia in the 1920s after observations of folkloric use as an antidiarrheal agent. Animal studies using the hamster model of clindamycin colitis showed a significant decrease in mortality when animals were treated with *S boulardii* compared with placebo (38). When *S boulardii* was used to treat relapse in the same animal model, it was also highly efficacious (39). When used as an adjunct to antibiotic therapy in first infections with *C difficile* disease, it had no benefit over placebo in recurrent disease. However it was significantly more effective than placebo as an adjunct to antibiotic therapy in the treatment of recurrent *C difficile* disease in those who had already had one or more recurrence (40).

It is not known how *S boulardii* exerts its prophylactic or therapeutic effects. It does have antagonistic properties against several pathogens in vitro and in vivo in animal models. Other mechanisms of action include activation of *C difficile* toxin or its receptor in vitro (41), stimulation of immunoglobulin A in rat small intestine (42) and normalization of fecal flora. Importantly, it resists the effect of antibiotics. Other advantages include the ease of oral administration and lack of side effects because the yeast is not absorbed.

***Nontoxigenic strains of* C difficile:** Two cases of *C difficile* were successfully treated with oral administration of nontoxogenic strains of *C difficile* (43). About one-quarter of *C difficile* isolates do not produce toxin and thus do not cause disease. This approach may be associated with a decrease in relapsing PMC, although only a small number of individuals have been treated.

Rectal bacteriotherapy: Rectal bacteriotherapy has been reported to treat relapsing PMC. Specifically, fecal enemas have been given to patients, using rectal infusion of homologus feces donated from healthy donors, such as relatives (44). However, this is not advisable because it is impossible to assure the safety of homologus feces and other pathogens may be introduced inadvertently.

Somewhat more aesthetically appealing, however, is the use of rectal installation of mixtures of anaerobes that may result in the clearing of *C difficile*. Five patients with relapsing PMC were treated with rectal instillation of 10 different facultatively anaerobic and aerobic bacteria, with prompt clearing of *C difficile* and its toxin from the stool (45). An additional patient in this study was treated with an enema of fresh feces from a healthy relative. The study showed that *Bacteriodes* species had been absent during the patient's illness and was present after recovery, suggesting that colonization with *Bacteriodes* species appears to be especially important in maintaining normal bowel function and strengthening the resistance to gastrointestinal infections. The ability of the *Bacteriodes* species to aid in restoration of intestinal homeostasis may be related to its production of beta-lactamase, as previously described.

Lactobacillus GG: *Lactobacillus* GG is a species with unusual characteristics. It is resistant to gastric acid and to bile, and

survives in the human gastrointestinal tract for four to seven days. In a published letter (46), five patients with relapsing C *difficile* (two to five prior relapses) had no further relapses after oral therapy with *Lactobacillus* GG. A recent presentation did not show any efficacy of *Lactobacillus* GG in a patient with recurrent C *difficile* disease (47).

PROGNOSIS

Recent evaluation of prognostic criteria revealed a worse prognosis with a low albumin (less than 25 g/L), a fall in albumin greater than 11 g/L, more than three antibiotics and persistent toxin in the stools seven days or longer after therapy (48). There was no correlation with sex, age, length of hospital stay, past illness or recurrent C *difficile* infection.

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