Current Treatment Options for Severe *Clostridium difficile*–associated Disease

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Abstract: A notable trend toward severe *Clostridium difficile* colitis and poor outcomes has emerged since recognition of the hypervirulent *C. difficile* NAP1/027 strain. This trend has increased the emphasis on appropriate treatment regimens in refractory cases of *C. difficile* infection. In mild-to-moderate cases, oral metronidazole remains adequate first-line therapy, but in the absence of a good clinical response, switching to vancomycin may be necessary. Oral vancomycin should be used as initial therapy in severely ill patients or patients who cannot tolerate metronidazole. Rectal administration of vancomycin may be used as adjunctive therapy for severely ill patients. Patients with an ileus who cannot tolerate oral medications may improve with adjunct intravenous metronidazole and/or rectal vancomycin. Early surgical consultation should be requested, as some patients will require emergent colectomy. The shifting landscape of *C. difficile* infection has undermined our complacency regarding this long-recognized disease.

Keywords
Clostridium difficile, refractory *Clostridium difficile*–associated disease, vancomycin

Effective treatment of *Clostridium difficile* infection that does not respond to standard first-line therapy is of vital importance to current clinical practice. The emergence in 2000–2001 of a hypervirulent strain called NAP1/027 or BI/NAP1, as well as the general aging of the population and ubiquitous antibiotic overuse, has coincided with a marked increase in both nosocomial infection rates and poor clinical outcomes. Moreover, in 2005, the Centers for Disease Control reported several cases of severe community-acquired *C. difficile*–associated disease (CDAD), which included a subset of patients without prior antibiotic exposure.[1] Muto and colleagues recognized a remarkable increase in severe cases starting in 2000 at a Pittsburgh teaching hospital, in which the average annual incidence of nosocomial CDAD was noted to increase by 250% between 1999 and 2001.[2] The proportion of severe cases increased from 5.6% in 1999 to 9.3% in 2001. Over a 16-month period beginning in January 2000, 37 severe cases of CDAD were diagnosed, and 26 of these cases required colectomy. Pépin and associates described a much larger epidemic in Quebec beginning in 2002, in which a cumulative 1-year attributable mortality of 16.7% was observed for patients with nosocomial

C. difficile colitis, as well as a 6.7-day increase in length of stay, compared with case-matched controls.[3] A particularly striking increase was noted in patients older than 65 years of age, in whom the incidence of CDAD rose from 102 cases to 866.6 cases per 100,000 between 1991 and 2003.[4] Recent reports also document increased rates and worsening severity in patients with inflammatory bowel disease (IBD),[5,6] with more patients requiring colectomy, particularly those with ulcerative colitis. A recent paper analyzed an extensive database of IBD patients and found a 4-fold increase in mortality in patients with *C. difficile* infection.[7]

Antibiotic Risk Factors

Cephalosporin and clindamycin usage have long been recognized as risk factors for *C. difficile* colitis, but until recently, fluoroquinolones had not been considered a significant risk. In 2000, Muto and associates noted a spike in fluoroquinolone use in a Pittsburgh hospital that predated the increase of severe CDAD cases by 9 months. A comparison of the 12-month period beginning in March of 1998 with the one beginning in March of 1999 demonstrated that use of fluoroquinolones rose from 217 daily doses to 275 daily doses per 1,000 patient-days.[2] This coincided with the emergence of a hypervirulent strain, BI/NAP1/027, which had been identified as early as 1984. This strain produces a binary toxin of unknown significance and has an 18 bp deletion in a gene that regulates toxin production. This mutation allows for increased production of toxins A and B in vitro, which may explain why it appears to cause more severe disease. Prior to 2001, BI/NAP1/027 isolates were resistant to clindamycin and levofloxacin (levaquin, Ortho-McNeil). The strain has since acquired resistance to gatifloxacin and moxifloxacin.[8] In some hospitals, formulary changes to these drugs have predated epidemics.

Diagnostic Examinations

Diagnosis of CDAD is usually confirmed by detection of toxins A and/or B in stools or culture, though the latter does not confirm toxin production. Enzyme immunoassay (EIA) examinations have largely replaced cytotoxin tissue culture assay for toxin B, though their sensitivity and specificity are not as good. False-negative examinations are an important concern for clinicians. Some EIA examinations can detect both toxin A and B; others test only for toxin A and a common clostridial antigen that acts as surrogate marker for the presence of clostridia. As these examinations test for toxin A alone, they do not detect the 2–3% of strains that produce only toxin B. Thus, confirmation for toxin B via examinations such as toxin B assay or polymerase chain reaction is necessary when the EIA for toxin A is negative but the common clostridial antigen is positive. In short, clinical judgment is still very important in diagnosis.

Treatment of Mild-to-Moderate *Clostridium difficile*–associated Disease

The two most common drugs used to treat *C. difficile* are metronidazole (500 mg PO TID) and vancomycin (125 mg PO QID) for 10–14 days. The standard first-line therapy in both the inpatient and outpatient settings remains oral metronidazole, unless there are contraindications to the medicine such as first trimester of pregnancy or inability to tolerate it. For severe disease, initial therapy with vancomycin is now recommended (Table 1). In all patients with CDAD, inciting antibiotics should be discontinued, if possible, or changed to a regimen with a narrower spectrum. Antimotility agents should not be used, even in mild cases.

Most patients respond in several days. In one study of patients with mild-to-moderate disease, symptoms resolved in an average of 3.0 days with vancomycin and 4.6 days with metronidazole.[9]

In the past, response rates to both drugs have been 95% or better. However, several recent reports have noted higher failure rates with metronidazole.[10-12] Prior to 2004, metronidazole failure rates were 0–6%; since 2004, reported rates have ranged from 16% to 38%. In a prospective observational study published in 2005, Musher and associates examined treatment outcomes in all patients treated for *C. difficile* over an 8-month period at one Veterans Affairs (VA) hospital.[10] During this time, oral vancomycin usage was restricted by hospital policy and was not prescribed as initial therapy for CDAD. Of 207 patients, 46 (22%) had persistent symptoms after 10 days of treatment with at least 1.5 g daily of oral metronidazole, a finding that contrasted sharply with a 1994 study from a different VA, in which 97% of 632 patients responded to metronidazole.[11] This decreased response to metronidazole likely reflects increased severity of disease. Thus, given the increasingly virulent nature of *C. difficile* infections, particularly in the nosocomial environment, an argument can be made to presume treatment failure after 3 days of metronidazole if there is no decrease in diarrhea or abdominal discomfort, and a switch to oral vancomycin should be considered. In a 2005 editorial, Gerding recommends that the switch to vancomycin also be considered in patients whose leukocytosis worsens during therapy.[13]

Modifiable practices that may decrease initial treatment failures include avoiding the use of antimotility agents and discontinuing the causative antibiotic, if possible.

Table 1. Guidelines for Treatment of Mild, Severe, and Complicated *Clostridium difficile*–associated Disease (CDAD)

	Criteria	Treatment
Mild–moderate CDAD		Metronidazole 500 mg TID × 10–14 days
Severe CDAD	WBC >15,000 cells/μL or >50% rise in serum creatinine	Vancomycin 125 mg PO QID × 10–14 days
Complicated CDAD	Hypotension, ileus, toxic megacolon, need for intensive care unit admission or colectomy, colonic perforation, lack of response to therapy	Vancomycin 500 mg QID orally (if able to tolerate oral medication) or per nasogastric tube and/or metronidazole 500–750 mg IV every 8 hrs If complete ileus, IV metronidazole as above plus vancomycin enemas (500 mg 100 mL normal saline every 6 hr via rectal foley) Early surgical consultation Early colectomy before lactate ≥5 mmol/L

Adapted from Cohen SH[16] with permission.

IV=intravenous; WBC=white blood cell count

Treatment of Severe *Clostridium difficile*–associated Disease

Of patients with *C. difficile* infection, 3–8% develop fulminant colitis.[14] Markers of disease severity include ileus, renal insufficiency, colon wall thickening on computed tomography imaging, and endoscopic visualization of pseudomembranes, as well as the usual signs of septic physiology: fever, significant leukocytosis, hypotension requiring fluid resuscitation, and tachypnea. These markers may portend toxic megacolon, imminent intestinal perforation, or fulminant colitis, and they may predict a significantly higher risk of colectomy or death. Empiric therapy should be started for ill patients as soon as *C. difficile* is suspected, to avoid any delay related to obtaining the results of stool or equivocal examinations. As stool examinations are imperfect, clinical judgment is still vital.

Importantly, oral metronidazole monotherapy is not an appropriate initial treatment for patients at highest risk, in particular, those who present with significant predictors of disease severity or are of advanced age and have worrisome comorbidities. In a recent prospective controlled study by Zar and associates, patients were randomized to vancomycin or metronidazole for 10 days and stratified into mild and severe disease subgroups by clinical risk factors.[15] Severe disease was defined as being in an intensive care unit (ICU), the presence of pseudomembranes upon endoscopic examination, or the existence of 2 or more of the following factors: 60 or more years of age, fever of more than 38.3° C, albumin of less than 2.5 mg/dL, or white blood cell count of more than 15,000/μL within 48 hours of admission. Among patients with mild disease, clinical cure was achieved in 90% of patients receiving metronidazole and 98% of patients receiving vancomycin (P=.36). However, in patients with severe disease, metronidazole response rates were 76% compared with 97% for vancomycin (P=.02). Pépin and colleagues observed an overall 79% decrease in progression to severe complicated CDAD in patients initially treated with vancomycin rather than metronidazole, giving further evidence for vancomycin's role when patients do not respond to metronidazole.[4] Thus, vancomycin is now recommended for initial therapy of severe disease.[16] Although the standard regimen for vancomycin is 125 mg orally four times daily, in our experience, some severely ill patients require higher doses of 250 mg or even 500 mg orally four times daily. Given the rather poor enteric absorption of vancomycin, an increase in toxicity would not be anticipated. We have also seen severely ill patients require longer courses of antibiotics, sometimes up to 3–4 weeks, which may be given safely as long as they continue to improve. In the VA study by Musher and colleagues, 30 of the 46 patients who still had symptoms after 10 days of metronidazole therapy were treated with a prolonged course. Symptom resolution was achieved in only half of these patients with metronidazole alone.[10] Of course, in such patients the need for colectomy versus a longer course of medical therapy must be seriously considered, but as long as the patients continue to improve, even if slowly, the latter may be reasonable.

In such ill patients, adjunct therapies such as intravenous (IV) metronidazole may be helpful. The efficacy of IV metronidazole has not been definitively demonstrated,

but at least one retrospective study examined its use as monotherapy in 10 patients with CDAD.[17] A majority of these patients experienced resolution, and none developed fulminant colitis or toxicity such as peripheral neuropathy. Another adjunctive therapy is the rectal administration of vancomycin. Apisarnthanarak and colleagues reviewed the use of intracolonic vancomycin in 9 patients at an academic medical center between 1998 and 2001.[18] All these patients were noted to have significant comorbidities such as congestive heart failure, active malignancy, or advanced age, and the median leukocyte count was 24,000/μL. Although 5 of the patients received surgical consultation, none of the patients required colectomy, and 8 of the 9 patients achieved clinical cure. The interval of administration varied among patients and ranged from 4 to 12 hours. For such enemas, an IV solution of vancomycin can be used (0.5–1 g of vancomycin dissolved in 100 mL of normal saline inserted via rectal foley every 6 hours). Rectal administration appears to be a potentially useful adjunct in patients with ileus, though therapy by this method alone should not be expected to exert much effect proximal to the splenic flexure. Shetler and associates described a case series in which 4 of 7 patients with severe *C. difficile* colitis experienced resolution of their pseudomembranous colitis after treatment with adjunctive intracolonic vancomycin via a decompression tube placed during colonoscopy.[19] This method is not commonly used, most likely due to concerns regarding the potential for colonic perforation.

In the fall of 2007, Cohen presented new Infectious Diseases Society of America guidelines, soon to be published, for treatment of severe and complicated CDAD (Table 1).[16] Severe CDAD is defined as patients having a white blood cell count greater than 15,000 cells/μL and/or a 50% rise in serum creatinine. In these patients, the guidelines recommend initial therapy with vancomycin 125 mg four times daily. Complicated CDAD is defined as the presence of one or more of the following factors: hypotension, ileus, toxic megacolon, need for ICU admission or colectomy, or colonic perforation. In these patients, if complete ileus is not present, the guidelines recommend vancomycin 500 mg four times a day orally or per nasogastric tube and/or IV metronidazole 500–750 mg every 8 hours. For patients with a complete ileus, the recommendations include IV metronidazole and rectal vancomycin (500 mg in 100 mL of normal saline every 6 hours via rectal Foley tube). This stepwise treatment approach will be helpful for clinicians caring for patients with severe CDAD.

Although studies are lacking, the consensus is that antimotility agents should not be used for CDAD, even if the CDAD is mild in severity. Continuation of the inciting antibiotic may also contribute to treatment failures. An observational study by Modena and colleagues demonstrated that in a small series of patients prescribed metronidazole for symptomatic CDAD, cure was achieved in 100% of patients (10 of 10) whose causative antibiotics were stopped, but in only 59% of patients (10 of 17) in whom antibiotics were continued (P=.02).[20]

Treatment failure is likely multifactorial and largely due to increasing disease severity and patient comorbidities. Even vancomycin monotherapy may no longer be sufficient in the deteriorating patient. A study conducted by Pépin and Valiquette suggests that the clinical superiority of vancomycin was lost after the emergence of NAP1/027 in Quebec in 2003. Between 1991 and 2002, patients who were treated initially with vancomycin rather than metronidazole had significantly lower rates of progression to severe CDAD (adjusted odds ratio, 0.21; 95% confidence interval, 0.05–0.99; P=.048); however, from 2003 to 2006, initial vancomycin treatment no longer demonstrated this advantage over metronidazole therapy (adjusted odds ratio, 0.90; 95% confidence interval, 0.53–1.55; P=.71).[21]

Lack of response to therapy does not appear to result from *C. difficile* resistance to the treating antibiotic. Although one study from Spain suggested that drug resistance was a contributing factor,[22] this pattern of antibiotic resistance has not been verified in the United States. With severe disease that does not respond to therapy, urgent surgical intervention is of critical importance.

Role of Surgery

In patients with refractory or fulminant colitis, total or subtotal colectomy with end ileostomy is life-saving, and an understanding of appropriate surgical consultation is essential.[14] Total colectomy includes resection of the sigmoid and preserves the rectum and pelvic tissue planes.[23] A study by Lamontagne and colleagues utilized retrospective analysis to determine which patients might benefit most from surgical intervention.[24] During an epidemic period, 165 patients with CDAD were admitted to the ICU of two Quebec hospitals, and 38 of these patients ultimately underwent colectomy. The researchers evaluated both patients with CDAD requiring ICU placement and ICU patients whose CDAD was severe enough by itself to require critical care. The primary indications for surgery were perforation, shock resistant to pressor therapy, toxic megacolon, and failure to respond to medical therapy. The mortality rate in patients undergoing colectomy was 34% compared with 58% in patients managed medically (P=.02). Patients with advanced age (>75 years), chronic immunosuppression, high lactate levels (≥5 mmol/L), or severe leukocytosis (≥50,000/μL) were at highest risk of subsequent mortality, but even after adjusting for these

variables, colectomy reduced the odds of death by 78%. It is clear that some patients fare better with early intervention prior to the onset of severe multi-organ failure and concomitant severe lactic acidosis. Survival benefit could not be demonstrated for patients who were less than 65 years of age or patients with a normal lactate level or a peak white blood cell count of less than 20,000/μL, though the authors cautioned that this finding may have been limited by the size of the study. Ultimately, surgery may confer the greatest benefit upon patients over 65 years of age, as well as patients whose lactate levels or white blood cell counts are continuing to rise despite therapy.

Other Antibiotics

Several other antibiotics are being studied in the treatment of CDAD. One is nitazoxanide, a nitrothiazolide antibiotic. Musher and associates published a prospective double-blinded study in 2006 comparing metronidazole and nitazoxanide as initial therapy and concluded that nitazoxanide was as effective as metronidazole.[25] Of note, this initial study excluded ICU patients and those with hemodynamic instability, IBD, advanced liver disease, or renal disease. The same group of researchers recently published an open-label study of nitazoxanide in patients who had failed metronidazole therapy. Twenty-eight patients who had experienced no improvement in symptoms after 14 days of metronidazole (mean duration of treatment, 22.4 days) were prescribed 10 days of 500 mg of nitazoxanide twice daily. Twenty patients (71%) experienced rapid resolution of symptoms, but 6 of these patients later experienced disease recurrence.[26] Nitazoxanide may have an emerging role in stable patients who do not improve with metronidazole. Although nitazoxanide is relatively expensive, it still costs less than vancomycin; in 2006, the average wholesale price of a 10-day course of nitazoxanide was approximately $240.[27]

Teicoplanin was suggested by a 2007 Cochrane Report to be the best choice for treatment, given evidence of its significant advantage over vancomycin for bacteriologic cure and its borderline superior effectiveness as a symptomatic cure.[28] However, teicoplanin remains unavailable in the United States and is reputed to be of great cost as well.

Rifampin and its poorly absorbed analog rifaximin (Xifaxan, Salix) have been of particular interest, given their excellent in-vitro activity against *C. difficile*. The data have been inconsistent thus far but unconvincing overall. In 2004, Nomura and associates reported successful treatment of an elderly patient with fulminant colitis.[29] The patient had persistent and severe symptoms despite 10 days of oral metronidazole and vancomycin and discontinuation of the causative antibiotics. He was not considered a surgical candidate due to the severity of his underlying recurrent non-Hodgkin lymphoma. The patient was subsequently started on oral rifampin 600 mg twice daily, and resolution of both fever and diarrhea was noted within several days. However, a prospective randomized study published in 2006 compared metronidazole and rifampin combination therapy with metronidazole alone and found no significant difference in time to symptom resolution, though there was a significant increase in mortality in the metronidazole plus rifampin group.[30] It should be noted that this study excluded patients with ileus and toxic megacolon, and it was halted early due to study futility. There have been more promising reports of rifaximin therapy following completion of vancomycin therapy for recurrent disease, and this therapy may be more appropriate in the setting of multiple recurrences of colitis rather than severe acute disease.[31]

Nonantibiotic Therapies

Several case reports have noted the use of IV immunoglobulin (IVIG) to induce passive immunity and achieve cure in patients with severe persistent colitis or recurrent disease.[32] A retrospective case series conducted by McPherson and associates reported resolution in 6 of 8 patients with severe pseudomembranous colitis or megacolon detected upon imaging who had failed standard therapy (median, 10 days of metronidazole and 11 days of vancomycin).[33] None of the 14 patients observed in the study experienced side effects attributable to IVIG infusion. Another, more detailed, analysis was undertaken by Juang and colleagues, who retrospectively evaluated a population of patients with severe CDAD during an epidemic period between July 2001 and July 2003.[34] During this period, 79 patients were identified with severe CDAD, 18 of whom were treated with IVIG. Pair-matching was utilized, and no significant difference was discovered in the number of colectomies or deaths with or without IVIG administration. Thus, this therapy lacks proven efficacy.

A single case report describes the use of steroids in a pediatric case of refractory CDAD.[35] As steroids have been successfully used for IBD, questions have arisen regarding the potential role of steroids in the inflammatory diarrhea of *C. difficile*. A 5-year-old boy received amoxicillin clavulanate for sinusitis and developed bloody diarrhea, which was positive for *C. difficile* toxin. Imaging demonstrated an ileus, and the patient was started on IV metronidazole and oral vancomycin. The patient continued to have 10–15 bloody stools daily despite 2 weeks of therapy, and a flexible sigmoidoscopy confirmed pseudomembranous disease. The patient was subsequently given IV methylprednisolone (1 mg/kg twice daily), and

the diarrhea resolved within 24 hours. After 3 days, the therapy was switched to oral prednisone, followed by a month-long taper. These results are isolated but intriguing, though they have not been reported in adult patients. In IBD patients on steroids or other immunosuppressants, a trend toward more severe cases of *C. difficile* colitis has been noted, suggesting that immunosuppression may be detrimental in these patients. Furthermore, it remains vital that trials of aggressive and maximal medical therapy do not forestall surgical evaluation.

Summary

Appropriate measures for a clinically deteriorating patient include the addition of vancomycin to metronidazole, surgical evaluation, and consideration of IV metronidazole and intracolonic vancomycin, particularly in cases complicated by ileus. Once again, assessing whether the causative antibiotic can be discontinued is of critical importance. Antimotility agents should not be used. With severe disease, initial therapy is recommended with vancomycin 125 mg orally every 6 hours. If patients do not respond, vancomycin can be increased to 2 g daily and the addition of IV metronidazole and/or vancomycin enemas can be considered, as well as early surgical consultation. Serial abdominal examinations and measurements of white blood cell counts, albumin, creatinine, and lactate are good markers to follow, in addition to the overall clinical condition. Early colectomy can be life-saving.

Confidence in the first-line therapies for *C. difficile* colitis has eroded, and our longstanding complacency about CDAD lies firmly in the past. The marked trend toward refractory and severe disease, poor outcomes, and increased recurrences has led to increased involvement of gastroenterologists in nosocomial cases and underscores the need for better therapies as well as attention to prevention.

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