Management of *Clostridium difficile* Infection

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Abstract: Since the discovery of *Clostridium difficile* infection (CDI) in the 1970s, there has been an increase in the incidence, severity, and recurrence rate of the disease. We reviewed the recent CDI literature in PubMed published before February 28, 2016 that focused on advances in therapy. Despite a large number of studies describing methods for diagnosing the disease, there is currently no definitive test that identifies this infection with certainty, which complicates therapy. Recommended therapy for CDI includes oral metronidazole for mild cases and oral vancomycin or fidaxomicin for moderate to severe cases, each given for 10 to 14 days. For infection with spore-forming *C difficile*, this length of treatment may be insufficient to lead to cure; however, continuing antibiotics for longer periods of time may unfavorably alter the microbiome, preventing recovery. Treatment with metronidazole has been associated with an increasing failure rate, and the only clear recommended form of metronidazole for treatment of CDI is the intravenous formulation for patients unable to take oral medications. For vancomycin or fidaxomicin treatment of first CDI recurrences, the drug used in the initial bout can be repeated. For second or future recurrences, vancomycin can be given in pulsed or tapered doses. New modalities of treatment, such as bacteriotherapy and immunotherapy, show promise for the treatment of recurrent CDI.

Introduction

Clostridium difficile is a Gram-positive, anaerobic, spore-forming, toxin-producing bacteria first identified as a cause of antibiotic-associated colitis by 3 investigators working with animal models in the 1970s.[1] The organism is now the most commonly identified infectious cause of antibiotic- and health care–associated diarrhea. The Centers for Disease Control and Prevention estimated that almost half a million infections of this disease occurred in the United States in 2011 and that the infection was associated with death in 29,000 people that year.[2] A recent cost estimate for hospitalized patients with primary *Clostridium difficile* infection (CDI) was $20,693, and for recurrent CDI, the estimate was $45,148.[3]

Table 1. Classification of CDI by Severity for Determining Appropriate Therapy[10,11,88]

Clinical Severity	Clinical Findings
Nonsevere illness (mild to moderate)	Must have all: Nonbloody diarrhea (passage of <6 watery stools/day), afebrile, mild abdominal pain, creatinine level <1.5 × baseline, and WBC <15,000/mm^3
Severe illness	Must have at least one: Advanced age, mental changes, serum albumin ≤2.5 g/dL, WBC >15,000/mm^3, creatinine level >1.5 × baseline, or abdominal tenderness and ileus
Severe complicated illness	Must have at least one: Hypotension/shock with serum lactate levels >2.2 mmol/L, need for ICU confinement for CDI, organ failure, or WBC ≥35,000/mm^3 or <2000/mm^3

CDI, *Clostridium difficile* infection; ICU, intensive care unit; WBC, white blood cells.

Despite advances in the treatment of CDI, there has been a steady increase in incidence, severity, mortality, and disease recurrence.[4-6] Prior antibiotic exposure is the most important risk factor for CDI, leading to disruption of the normal colonic flora, which results in reduced intestinal colonization resistance. Additional risk factors for CDI are inflammatory bowel disease, immunodeficiency, hypoalbuminemia, malignancy, organ transplant, and chemotherapy.[7-9] The high recurrence rate of CDI questions the current recommendations for therapy for first episodes of CDI.

This article discusses treatment for initial and recurrent CDI. Two medical societies have provided overviews of this topic.[10,11] The current article focuses on recent data obtained after these reports were published and includes controversial areas and recommendations for treatment.

Overview of Initial Treatment for *Clostridium difficile* Infection

The diagnosis of CDI is still challenging despite the many laboratory tests for the infection and its growing importance. There are 2 factors complicating laboratory diagnosis of CDI: colonization by *C difficile*, which is common in hospitalized patients, causes a positive test result for fecal toxin; and CDI explains less than one-fourth of antibiotic-associated diarrhea cases in the hospital setting. Both of these factors explain why many of the patients treated for CDI do not actually have the infection.

An important part of therapy is to discontinue the antibiotics that predisposed the patient to CDI. In very mild cases, this may be sufficient to reverse the disease process, requiring no CDI-directed therapy. Specific CDI treatment recommendations are influenced by 2 factors: the severity of the disease (Table 1) and the number of previous discrete bouts of CDI experienced.

Pharmacologic Treatment for the First Episode of Clostridium difficile *Infection*

Guidelines for the treatment of CDI provided by the Infectious Diseases Society of America in 2010 recommended that oral metronidazole be used for all but the more severe cases of CDI, where oral vancomycin would be preferred.[10] Based upon 2 studies showing that metronidazole was inferior to oral vancomycin for CDI,[12,13] metronidazole should be considered for treatment of only the mildest cases. Vancomycin or fidaxomicin (Dificid, Merck) is a better choice for all clinically important cases of CDI because of metronidazole's flawed pharmacokinetics for intestinal infections. Nearly all of the drug is absorbed from the small bowel, and low to absent colonic levels of the drug are seen during therapy,[14] producing lower cure rates than oral vancomycin.[12] In contrast, oral administration of vancomycin leads to high fecal drug concentrations and higher rates of recovery.[15]

Our recommended approach to treatment of the first bout of CDI experienced is provided in Table 2. We feel that the main use of metronidazole is for patients who cannot take oral anti-CDI drugs because of ileus, shock, or toxic megacolon, situations in which the intravenous route is employed. In these cases, it should be possible to also administer vancomycin as an enema.[10] Once oral drugs can be used, oral vancomycin or fidaxomicin should be initiated.

The recommended oral dose of vancomycin is 125 mg 4 times daily for 10 to 14 days. The capsule form of vancomycin is expensive (>$1000 for 10 days), but the cost can be reduced to less than $200 through the use of compounded liquid vancomycin, which is given in the same dose and has equivalent expected efficacy.[16] However, insurance companies may not pay for this form of the drug, information that should be sought before prescribing it. In patients with severe complicated CDI (Table 1), the recommended treatment is intravenous metronidazole with high-dose vancomycin 250 to 500 mg 4 times daily orally or, if oral administration is not possible, via a nasogastric tube or via an enema.

In 2011, fidaxomicin was approved by the US Food and Drug Administration for the treatment of CDI. Fidaxomicin is a macrocyclic antibiotic with little systemic absorption after oral administration,[17] which leads to high colonic concentrations of the drug.[18] CDI

Table 2. Recommended Treatment Options for the First Episode of CDI[a]

Recommended Therapy	Dose/Schedule	Comment(s)
Metronidazole	Mild CDI: 500 mg 3 times daily for 10 days (PO or IV)	• Less effective than other options for treating CDI • Only used in the mildest cases and only via IV route if the patient is unable to take oral medications
Vancomycin	Mild to severe cases: 125 mg 4 times daily for 10-14 days PO Severe complicated cases: 250-500 mg 4 times daily. Consider 500 mg of vancomycin in 100 mg normal saline per rectum every 6 hours as a retention enema in the face of ileus.	• Superior to metronidazole for moderate to severe CDI • Increases the risk of VRE[89]
Fidaxomicin	All forms of CDI: 200 mg PO twice daily for 10 days	• Lower rate of recurrence than other treatments • Less likely than vancomycin to promote acquisition of VRE[25] • More expensive than other treatments
Tigecycline	Refractory cases of CDI: 100 mg IV, then 50 mg IV twice daily	• Not approved for treatment • Can be used as rescue treatment for patients with severe CDI when treatment with vancomycin and metronidazole fails[29]
Nitazoxanide	All forms of CDI: 500 mg PO twice daily for 10 days	• Not approved for treatment • In preliminary study, as effective as metronidazole or vancomycin[31,32] • More studies are needed.
Rifaximin	All forms of CDI: 400-550 mg twice daily for 14 days	• Not approved for treatment • Has been used with tigecycline with or without vancomycin for refractory cases of CDI[36,37] • More studies are needed.
Colonic surgery (colectomy or colon bypass)	Indicated with shock, respiratory failure, lactate levels >5 mmol/L, signs of end organ damage. Associated with refractory CDI and fulminant colitis.	• Colon-sparing approach has been described in the literature to reduce mortality and preserve the colon.

[a]Initial antibiotics causing CDI should be stopped if possible, and patients should be hydrated.

CDI, *Clostridium difficile* infection; IV, intravenous; PO, oral; VRE, vancomycin-resistant enterococci.

cure rates are comparable between oral vancomycin and fidaxomicin.[19] Fidaxomicin given in a dose of 200 mg twice daily for 10 days is associated with a lower rate of recurrence compared with a 10-day course of oral vancomycin (125 mg 4 times daily) for CDI caused by non-NAP1/ribotype 027 strains.[19,20] Possible explanations for reduced recurrence rates with fidaxomicin include effective inhibition of *C difficile* toxin production,[21] inhibition of spore production,[22] and improved preservation of the intestinal bacterial microbiome during and after treatment of CDI.[23,24] Fidaxomicin was shown to be less likely than other treatments to lead to new-onset colonization by vancomycin-resistant enterococci and Candida species.[25]

Fidaxomicin is up to 3 times the cost of other anti-CDI therapy, which has prevented the drug's widespread use. Nevertheless, fidaxomicin is an appropriate first-line treatment in CDI considering the reduced rate of disease recurrence and prevention of subsequent costs of therapy and hospitalization.[26,27] The drug may actually be a less-expensive option considering all of the management costs of treating CDI with vancomycin, and fidaxomicin was shown in one study to be associated with an overall improvement in quality of life.[28]

A new anti-CDI antibiotic is tigecycline, which has been used in limited studies in critically ill patients infected with *C difficile* who have failed standard anti-CDI therapy.[29,30] Randomized, controlled trials are needed to assess the safety and efficacy of this agent and to better define the drug's role in the treatment of CDI.

Another antimicrobial agent evaluated in patients with CDI is the antiparasitic drug nitazoxanide (Alinia, Romark), which was found in a study to be as effective as metronidazole[31] or oral vancomycin as treatment for CDI.[32]

The orally administered, poorly absorbed rifamycin, rifaximin (Xifaxan, Salix), has been evaluated for treatment of CDI in preliminary studies. This agent has been shown to successfully treat patients with mild to moderate CDI who failed metronidazole treatment.[33] Rifaximin, like fidaxomicin, is less damaging to intestinal flora than other drugs[34] despite achieving very high fecal levels of the drug,[35] which is important in the prevention of CDI recurrence. Rifaximin, together with tigecycline with or without vancomycin, has been used successfully to treat refractory or fulminant CDI.[36,37]

Ramoplanin shows in vitro activity against strains of *C difficile*, including strains that have reduced susceptibilities to vancomycin and metronidazole.[38] More study is needed on this agent.

Teicoplanin, a nonabsorbed glycopeptide antibiotic,[39] requires further study to determine its usefulness in managing CDI cases. In one study, teicoplanin, at a dose of 400 mg administered orally and twice daily, compared favorably with vancomycin in terms of cure and side-effect profile.[40]

Indications for Surgery

Surgical management is indicated in patients with CDI who are not responding to medical treatment. Fulminant colitis with colonic perforation and rapidly progressive disease are also indications for surgical treatment.[41] The traditional surgical approach to CDI, subtotal or total colectomy, is associated with poor outcomes and mortality as high as 50%.[42] An alternative to colectomy in severe CDI is the creation of a diverting loop ileostomy with colonic lavage and treatment with vancomycin.[43] Another colon-sparing approach includes a loop ileostomy with intraoperative colonic lavage using warmed polyethylene glycol solution via the ileostomy with instillation of vancomycin flushes postoperatively via the ileostomy.[44]

Recurrent *Clostridium difficile* Infection

Recurrent CDI is the most common complication of the infection. In recurrent cases of CDI, the same clinical findings are seen, including diarrhea and abdominal pain together with positive *C difficile* fecal toxin testing. Recurrences are often seen within days of stopping anti-CDI antibiotics in patients with apparent clinical response to treatment. Recurrences may be seen up to 2 months after apparent recovery from a bout of CDI.[10] In such a situation, the recurrence more likely represents a new infection or reinfection. The rate of recurrence after a first bout of CDI treated with metronidazole or oral vancomycin is approximately 25%.[45] After a first recurrence, the risk of additional recurrences is at least 40%.[46] Patients with 3 or more recurrences often have one recurrence after another, leading to near-total disability and poor quality of life with limited options for therapy.

Risk factors for recurrence are older age, comorbidity, use of proton pump inhibitors,[45] continuation of the antibiotic that led to the first CDI bout, reduced diversity of the intestinal microbiota from continued exposure to antibiotics,[47] and failure to mount a serum antibody to the toxins of *C difficile*.[48,49]

Antibiotic Treatment for Recurrent Clostridium difficile *Infection*

Treatment approaches for recurrent CDI are listed in Table 3. Recommendations for the first recurrence of CDI are to stop any non-CDI antibiotics, if possible, and to take anti-CDI antibiotics. If oral vancomycin or fidaxomicin was used in the first episode of CDI, the same drug can be used again because the reason for recurrence is not the development of antimicrobial resistance by the infecting strain of *C difficile*. Metronidazole is not recommended for recurrent disease for reasons previously discussed.

In patients with a first recurrence of CDI, fidaxomicin was similar to vancomycin in achieving an initial clinical response, but the rate of subsequent recurrence was lower (19% vs 35%, respectively).[50] For the treatment of a second recurrence of CDI, a repeat 10-day course of vancomycin followed by 6 to 7 weeks of tapering or a pulse strategy[51] is recommended to inhibit the vegetative cells of *C difficile* while allowing restoration of the intestinal microbiota.[52]

Some investigators have followed standard treatment in patients with recurrent CDI with a second anti-CDI antimicrobial agent as a chaser treatment. Drugs used this way include fidaxomicin[53] and rifaximin.[54-58] A second approach to chaser therapy is to administer a probiotic after the full course of anti-CDI antibiotics. Some probiotics have immunoprotective effects on the gastrointestinal tract by increasing intestinal secretory immunoglobulin A and inhibiting production of proinflammatory cytokines (eg, interleukin-8).[59,60] *Saccharomyces boulardii* has been successfully used after anti-CDI antibiotic therapy in 2 randomized, double-blind, placebo-controlled trials.[61,62] However, the concern with the use of a probiotic such as *S boulardii* is the

Table 3. Recommended Treatment Options for Recurrent Episodes of CDI

Recommended Therapy	Comment(s)
First recurrence (can repeat use of vancomycin or fidaxomicin if used for first dose)	
Vancomycin PO 125 mg 4 times daily for 10-14 days	• Antibiotic resistance is not the reason for recurrence.
Fidaxomicin PO 200 mg twice daily for 10 days	• Lower rate for future recurrence compared with vancomycin
≥2 recurrences	
Vancomycin PO 125 mg 4 times daily for 10 days, then tapered dose: Week 1: 125 mg 4 times daily Week 2: 125 mg twice daily Week 3: 125 mg once daily Week 4: 125 mg every other day (4 doses) Weeks 5 and 6: 125 mg every 3 days (5 doses)	• Intermittent or pulse dose attempts to inhibit vegetative cells of *C difficile* while preserving colonic flora, which is important in recovery from CDI
Vancomycin PO pulse dose: 125 mg every 2 days or 500 mg every 3 days for 3 weeks	
Fidaxomicin PO 200 mg twice daily for 21 days	• Spares colonic flora and has a lower rate of recurrence compared with vancomycin • Can be used if it was not previously
Rifaximin PO 400 mg twice daily for 14 days	• Low rates of change of gut flora • Can be used as rifaximin chaser after initial treatment with oral vancomycin
Intravenous immunoglobulin (400 mg/kg)	• Can be repeated up to 3 times if needed • Evidence for value lacking
Monoclonal antibodies to *C difficile* toxin(s)	• Single infusion to be used after standard antimicrobial therapy • Not currently approved
Fecal microbiota transplantation: Stool (≥50 g) given as fresh or frozen product via colonoscopy, enema, nasogastric route, or capsules	• Attempts to restore colonic microbiota with the use of intestinal microorganisms from a healthy donor • Success rate up to 90%

CDI, *Clostridium difficile* infection; PO, oral.

risk of bloodstream invasion in immunocompromised patients,[63] hosts often seen in CDI. The fermented milk drink Kefir, with its multiple probiotics, has been used successfully as a chaser treatment after a course of vancomycin in a preliminary study of recurrent CDI.[64]

Fecal Microbiota Transplantation

Because patients with recurrent CDI have decreased diversity in their fecal microbiome, restoration of the intestinal microbiota, which can be achieved by fecal microbiota transplantation (FMT), is considered the most effective therapeutic approach to treat patients with at least 3 recurrences of CDI.[65-67] FMT has been shown to lead to normalization of the diversity of intestinal microbiota.[68] FMT was first described hundreds of years ago in China for the treatment of diarrhea and has been used for many years in treating animal disorders (in a process called rumen transfaunation).[69] FMT was successfully used in the 1950s in a small number of patients with pseudomembranous colitis.[70] In 1970, one of the authors of this article (HLD) performed a successful FMT by enema in a patient with progressive postantibiotic colitis complicated by renal failure (unpublished data). This was 8 years before the discovery of *C difficile* as the cause of the disorder.

Cure rates exceed 90% following FMT for multiple-recurrent CDI.[71-74] FMT is a cost-effective strategy for the treatment of multiple-recurrent CDI[75] if available, and it is less expensive and more effective than a prolonged course of vancomycin.[76] FMT can be delivered to the intestine by colonoscopy,[65] nasogastric route,[77] enema,[78] or capsules with frozen product.[79] Frozen product from a healthy donor is as effective as using freshly prepared product,[78] allowing more convenient product development. The increased cost and the occurrence of adverse events are limitations of colonoscopic delivery, compared

with administration by enema. Two possible advantages of colonoscopic delivery of FMT product are that insurance companies may pay for colonoscopy, making FMT less expensive in these patients, and the colonoscopist will be able to evaluate the integrity of the gut mucosa in the face of coexistent inflammatory bowel disease. The major limitation of FMT is that the procedure is not being performed in all medical centers. Comprehensive donor screening is needed to reduce the possibility of transmitting infectious agents to the recipients.[80]

Clinical trials are underway to produce a product that can have widespread availability to restore intestinal microbiota in patients with refractory bouts of CDI. Two product approaches in development include culturable gut organisms[81] and purified nonpathogenic *Clostridium* spp spores isolated from donor stools that can be administered by oral or colonic routes.

Immunologic Approaches

Another approach to the treatment of recurrent CDI is to facilitate immune responsiveness to the toxins of *C difficile*. A randomized, double-blind, placebo-controlled study using monoclonal antibodies against *C difficile* toxins significantly reduced CDI recurrence.[82] This approach is under development and is not yet available. However, a high cost of the monoclonal antibody will limit its broad use in preventing CDI recurrence. The logical indication for this preparation once licensed is the treatment of patients with multiple bouts of CDI when FMT is not available.

Intravenous immunoglobulin (IVIG) is another option that can be considered in the treatment of recurrent CDI. In case reports, IVIG was found to be associated with improvement of intestinal vascular permeability and mucosal damage in mice with experimentally induced CDI.[83] There are little data in humans with recurrent CDI to show benefit of IVIG.[84,85] Further randomized, placebo-controlled studies are needed to evaluate the cost and benefit of IVIG in recurrent CDI.

Toxoid vaccines made from *C difficile* toxins are in development to prevent CDI in high-risk populations and may reduce rates of CDI in high-risk patients.

Toxin-Binding Agents

Cholestyramine and colestipol have been shown to bind *C difficile* toxins A and B in vitro,[86] and in mild cases of CDI, an extended course of cholestyramine may have value.[87]

Conclusion

Further studies are needed to establish an accurate test to diagnose CDI to prevent treating patients colonized by *C difficile* who have diarrhea due to another cause. Treatment of CDI continues to be challenging due to the high rate of infection recurrence.

The currently recommended duration of antimicrobial therapy for primary CDI is 10 to 14 days. For anthrax, another infection by a spore-forming organism, 2 months of therapy are indicated to prevent recurrence. Thus, longer-term treatment may be needed for many patients with CDI. Clinicians face a therapeutic dilemma in that CDI cure requires the reestablishment of gut microbiota diversity but prolonged treatment with full doses of antibiotics reduces intestinal microbiota diversity and gut colonization resistance. Administering standard initial therapy for 10 days to patients with primary CDI and then also giving them low-dose antibiotics intermittently for 3 to 4 weeks may reduce rates of recurrence while allowing the microbiota to become reestablished. Alternatively, 2 or more weeks of probiotic therapy may be used after standard antibiotics in primary infection to prevent recurrence.

Regarding patients with multiple recurrences, if tapering or intermittent doses of anti-CDI antibiotics are not helpful, FMT is the best approach. This treatment, which is designed to restore intestinal microbiota, should become available in all medical centers, and commercialization of the microbiota restoration methods under development is needed.

Because of the importance of anti–*C difficile* antibody development to disease prevention and recovery, immunologic approaches are being developed to prevent CDI in high-risk patients and to treat cases of CDI to prevent recurrences. Toxoid preparations to prevent CDI are in clinical trials, and monoclonal antibodies against toxins A and B of *C difficile* are being commercialized to prevent recurrences in patients with CDI.

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