Current State of *Clostridium difficile* Treatment Options

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Recent reports of reduced response to standard therapies for *Clostridium difficile* infection (CDI) and the risk for recurrent CDI that is common with all currently available treatment agents have posed a significant challenge to clinicians. Current recommendations include metronidazole for treatment of mild to moderate CDI and vancomycin for severe CDI. Results from small clinical trials suggest that nitazoxanide and teicoplanin may be alternative options to standard therapies, whereas rifaximin has demonstrated success in uncontrolled trials for the management of multiple recurrences. Anecdotal reports have also suggested that tigecycline might be useful as an adjunctive agent for the treatment of severe complicated CDI. Reports of resistance will likely limit the clinical use of fusidic acid and bacitracin and, possibly, rifaximin if resistance to this agent becomes widespread. Treatment of patients with multiple CDI recurrences and those with severe complicated CDI is based on limited clinical evidence, and new treatments or strategies are needed.

Ten to 20 years ago, there was little interest in developing new treatment agents for *Clostridium difficile* infection (CDI) because CDI in most patients responded to metronidazole or vancomycin therapy, recurrent disease was common but more easily managed, and severe complicated cases of CDI were infrequent [1]. During the past decade, the epidemiology and clinical picture of CDI have changed dramatically and the limitations of current treatment options have become more apparent. Before the approval of fidaxomicin earlier this year, oral vancomycin was the only agent approved for the treatment of CDI in the United States by the Food and Drug Administration. Multiple dosing requirements, cost, relative efficacy, risk for recurrence, development of resistance, and adverse reactions limit other treatment options (Table 1). Here, we review the currently available CDI treatment agents with emphasis on their limitations and the general approach to managing recurrent CDI and severe complicated CDI.

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CURRENTLY AVAILABLE TREATMENT OPTIONS

Vancomycin

Oral vancomycin has remained a highly effective treatment agent for CDI and is the preferred comparison antibiotic for treatment trials of new therapeutic agents [2]. The agent is not absorbed, and the concentrations of vancomycin in milligrams per gram of feces that are achieved vastly exceed the minimum inhibitory concentration (MIC) for *C. difficile* by multiple folds [3]. Although vancomycin is highly effective for initial cure, a recurrence rate of 20% has been demonstrated repeatedly [2]. Perhaps for this reason, clinicians are often tempted to increase the dose of vancomycin or extend the length of treatment for the subsequent episode. Neither of these strategies has been tested, and with data showing high fecal concentrations of vancomycin achieved by the 125 mg dose [3], there is little justification for this approach. Vancomycin treatment delays recovery of the indigenous fecal microbiota [4],

Table 1. Limitations of Available Agents Prior to May 2010 for the Treatment of *Clostridium difficile* Infection

Agent/Dose	Cost[a]/Total Treatment Course	Relative Efficacy	Recurrence Risk	Resistance in Clinical Isolates	Adverse Events	Other Comments
Vancomycin: FDA approved for CDI						
Dose: 125 mg po qid × 10 d or "taper/pulse" for recurrence: 125 mg po qid × 10–14 d, then 125 mg po bid per d × 1 wk, then 125 mg po once daily × 1 wk, then 125 mg po every 2 or 3 d for 2–8 wk	$$$$/$$$$	+++	++	Not reported	Not absorbed so systemic symptoms unlikely, nausea	Potential for resistance induction in other clinically important pathogens
Metronidazole: not approved for CDI						
Dose: 500 mg po tid × 10 d or 250 mg po qid × 10 d	$/$	++	++	Increased MICs noted in some studies	Neuropathy, nausea, abnormal taste in mouth	Increasing reports of treatment failures & slow response, less effective in severe CDI
Nitazoxanide: not approved for CDI						
Dose: 500 mg po bid × 10 d	$$	++	++	Not reported	Abdominal pain, diarrhea, nausea	Limited clinical trial data, similar recurrence rate compared with metronidazole
Rifaximin: not approved for CDI						
Dose: 400 mg po tid × 10 d or chaser regimen[b] 400 mg po bid × 14 d	$$$/$$$	++	+?	Potential for development of high-level resistance	Not absorbed, headache, abdominal pain, nausea, flatulence	Used primarily as post–vancomycin treatment in patients with multiple recurrences
Tigecycline: not approved for CDI						
Dose: 50 mg IV every 12 h × 10 d	$$$$	++?	?	Not reported	Nausea, vomiting, diarrhea	Limited case reports of treatment success and failures
Bacitracin: not approved for CDI						
Dose: 25 000 units po qid × 10 d	$$	+	+++	Increasing resistance noted	Minimal absorbed, poor taste	Limited efficacy secondary to resistance
Fusidic acid: not approved for CDI						
Dose: 250 mg po tid × 10 d	N/A in US	++	++	Reported to develop in vivo resistance	Nausea, vomiting, epigastric pain, anorexia	Concern about use as a single agent
Teicoplanin: not approved for CDI						
Dose: 400 mg po bid × 10 d	N/A in US	+++	++	Not reported	Not absorbed so systemic symptoms unlikely	Similar results to vancomycin

Abbreviations: +, lowest; ++, intermediate; +++, highest; ?, unknown; $, $0–$100; $$, $101–$500; $$$, $501–$1000; $$$$, >$1000; bid, twice daily; CDI, *Clostridium difficile* infection; FDA, US Food and Drug Administration; IV, intravenous; MIC, minimum inhibitory concentration; N/A, not available; po, oral; qid, 4 times a day; tid, 3 times a day; US, United States.

[a] All prices are estimated in US dollars as quoted from www.drugstore.com (accessed 16 September 2011) or approximated hospital pharmacy pricing (tigecycline, bacitracin).

[b] Chaser regimen is given after a standard course of oral vancomycin (the price is reflective of the rifaximin cost only).

and germination of residual spores after cessation of treatment likely contributes to symptomatic CDI recurrences. A more practical approach to managing multiple recurrences is to taper (eg, decrease frequency to twice daily, then once daily), then pulse (every other day to every third day) the vancomycin therapy after a 10- to 14-day regimen of 125 mg 4 times daily when the patient's symptoms have resolved or significantly improved [5]. Other limitations of this treatment include cost (which can be offset by using the intravenous formulation given orally in place of vancomycin capsules) and also the potential for promoting overgrowth or colonization of other clinically important pathogens that reside in the intestine (eg, *Enterococcus* and *Staphylococcus* species). An ideal agent for treatment of CDI theoretically would not be the same agent used for the systemic treatment of other pathogens and would not engender resistance to those pathogens.

Metronidazole

Oral metronidazole has been widely used as first-line treatment of CDI in the United States since 1994, when the Hospital Infection Control Practices Advisory Committee recommendations from the Centers for Disease Control and Prevention were published and cautioned against the use of oral vancomycin because of concern for potential resistance in enterococci [6]. Although this agent is still effective for the treatment of mild to moderate CDI, multiple recent reports show increased failure rates and slower time to symptom resolution [7]. In addition, oral metronidazole was shown to be inferior to vancomycin for treatment of severe CDI in 2 recent randomized comparative trials [8, 9] but was not significantly different in another trial [10]. The recent Society for Healthcare Epidemiology of America (SHEA)/Infectious Diseases Society of America (IDSA) guidelines give interim recommendations for determination of severity based on white blood cell count and serum creatinine level [11]; however, a validated severity score is still needed [12]. Metronidazole is highly absorbed, and fecal concentrations are nil in asymptomatic *C. difficile* carriers, with only modest levels achieved in patients with diarrhea [3]. Therefore, metronidazole is not the ideal agent for use in a disease that is limited to infection in the colon. In addition, there are some reports of clinical isolates with moderately increased metronidazole MICs [13]. Because it is effective in mild to moderate CDI [8] and is relatively inexpensive, oral metronidazole is still widely used.

Nitazoxanide

Nitazoxanide is a thiazolide compound that has antiparasitic activity in vivo and activity against numerous gram-positive and gram-negative anaerobic bacteria in vitro [14]. In small clinical CDI treatment studies comparing nitazoxanide with metronidazole and vancomycin, it had shown similar response rates to both the comparative drugs [15, 16]. The small size of these studies does not permit conclusions about noninferiority or superiority to metronidazole or vancomycin [16]. In another study of patients given a 10-day course of nitazoxanide after their CDI failed to respond to 14 days of metronidazole therapy, clinical cure was achieved in 54%, but relapse and failure occurred in 20% and 26% of patients, respectively (although 3 failures and 1 recurrence responded to a second course of nitazoxanide) [17]. Larger studies comparing the efficacy of nitazoxanide with that of standard therapies are needed to help define its place in the management of CDI and to test its noninferiority to currently available agents.

Rifaximin

Rifaximin is a nonabsorbed antibiotic that appears to be somewhat flora sparing. Although highly active against most strains of *C. difficile*, rifaximin is subject to the problems of other rifamycins, whereby a critical amino acid substitution in the β-subunit of the bacterial RNA polymerase leads to high-level resistance [18, 19]. Rifaximin has been used as a post-vancomycin treatment (ie, chaser) for the treatment of patients with multiple recurrences for whom previous treatment strategies failed [20–22]. Seventy-nine percent of patients from 1 center with an extended follow-up had no further recurrence after treatment with a rifaximin chaser [21, 22]. In a recent pilot study of the role of rifaximin in patients with disease unresponsive to metronidazole, 64% of the intention-to-treat population had stool cultures negative for *C. difficile* at the end of the study, and cultures remained negative for all patients at the 56-day follow-up [23]. Data from these uncontrolled and relatively small studies suggest that rifaximin may have a role in the treatment of patients with multiple recurrences or those for whom other treatments have failed, but the possibility of resistance should warrant caution, particularly in those who previously have been treated with rifampin and rifaximin.

Tigecycline

Tigecycline has a broad spectrum of activity, including many gram-positive and -negative aerobic and anaerobic bacteria [24]. Recent evidence suggests that tigecycline does not promote the growth of *C. difficile* nor its toxin production in either the human gut model or mouse model [25, 26]. There are limited case reports about the success of tigecycline in patients with severe intractable CDI for whom previous standard treatments had failed [27, 28]. Until further larger comparative studies become available, the exact role of tigecycline in CDI will remain unclear and anecdotal.

Bacitracin

Bacitracin is a polypeptide antibiotic with activity against mainly gram-positive organisms. Early studies comparing

bacitracin with vancomycin showed that both were similar in the control of symptoms, but bacitracin was inferior in the clearance of *C. difficile* from feces [29]. Two recent susceptibility studies of 276 clinical isolates showed that 100% of isolates had high-level resistance with an MIC >128 μg/mL [30, 31]. In the larger of these 2 studies, 69% of the typed isolates were found to be the North American pulsed-field gel electrophoresis type 1 (NAP1) strain [30]. With these recent reports of high-level resistance and known outbreaks with the NAP1 strain occurring worldwide, bacitracin may have limited clinical efficacy in the current management of CDI.

Fusidic Acid

Fusidic acid had been used primarily for the management of bone and soft-tissue infections due to *Staphylococcus aureus* [32]. Early studies have shown that, when used against other standard therapies for CDI, the cure rates were 83%–93% and the recurrence rate was 28% [33, 34]. In a comparison trial with metronidazole, the development of resistance to fusidic acid occurred in more than half the treatment group that had a positive culture result at follow-up [32]. This finding raises the concern for selection of resistant isolates during treatment. As is the case with *S. aureus* infections, single-drug management with fusidic acid for the treatment of CDI may not be ideal [32]. Oral fusidic acid is not available for use in the United States.

Teicoplanin

Teicoplanin is a glycopeptide antibiotic shown to have activity against gram-positive anaerobes, including *C. difficile*. In a prospective study of teicoplanin and vancomycin, clinical cure and recurrence rates were similar in both groups [35]. In a subsequent study, cures in the teicoplanin group were 100% in patients with endoscopically confirmed pseudomembranous colitis [33]. It had significantly lower rates of relapse, compared with fusidic acid, and lower rates of persistence of cytotoxin at the end of therapy, compared with fusidic acid and metronidazole [33]. Although teicoplanin appears to have acceptable cure rates and similar recurrence rates, it also appears to be efficacious in the management of severe CDI [33]. Teicoplanin is not currently available in the United States for clinical use.

MANAGING SPECIAL SITUATIONS

Multiple Recurrences

Management of recurrent CDI is poorly studied, and the recently published SHEA/IDSA clinical practice guidelines for CDI give recommendations for recurrent CDI that are based on relatively poor quality of evidence [11]. General recommendations include (1) treatment of the first recurrence with the same agent used initially but stratified by disease severity with the understanding that resistance to metronidazole and vancomycin has not been shown to be clinically relevant, (2) avoiding prolonged or repeated courses of metronidazole because of the risk for neurotoxicity, and (3) treatment of multiple recurrences with vancomycin with use of a taper and pulsed regimen.

In addition to tapered and pulsed vancomycin regimens, other management strategies for multiple CDI recurrences that have been reported in uncontrolled case series and appear to be useful include standard therapy followed by *Saccharomyces boulardii*, standard therapy followed by rifaximin, switching to nitazoxanide, intravenous immunoglobulin, and fecal transplantation [5]. There are a limited number of randomized treatment studies of recurrent CDI, but they include standard therapy followed by probiotics (*S. boulardii*, *Lactobacillus plantarum* 299v, and *Lactobacillus* GG) and a comparison of colostral immune whey versus metronidazole for 14 days [36]. The only randomized intervention result that approached significance was high-dose vancomycin therapy (500 mg 4 times daily) for 10 days followed by *S. boulardii*, 2×10^{10} colony-forming units per day for 4 weeks, compared with high-dose vancomycin alone [37]. There was no difference in recurrence rates between *S. boulardii* and placebo when given with low-dose vancomycin (125 mg 4 times daily) or metronidazole (1 g/day) or when all treatment groups were combined [37]. The recently completed phase 3 studies of fidaxomicin versus vancomycin treatment for CDI were stratified by initial CDI infection and first recurrent CDI episode. Results of the secondary analysis in which patients with first CDI recurrences were randomly assigned to fidaxomicin or vancomycin treatment should provide additional evidence for recurrent CDI treatment options [38].

Severe Complicated CDI

Severe complicated CDI refers to severe disease complicated by hypotension, shock, ileus, or megacolon, and management in this context is based on very limited data [11]. In general, recommendations are to give vancomycin orally and per rectum if ileus is present, using higher doses of vancomycin (2 g/day) with consideration for the addition of intravenous metronidazole. In addition, the recommendations are to consider colectomy, preferably before serum lactate level increases to 5 mmol/L or white blood cell count reaches 50 000 cells/mL [39]. The evidence supporting the mentioned recommendations is particularly weak, including the use of the higher dose of vancomycin. Other anecdotal interventions in this context include the use of intravenous immunoglobulin and substitution of tigecycline for intravenous metronidazole [28, 40]. Additional basic research is needed to understand the pathophysiology of severe complicated CDI to identify effective therapies. If *C. difficile* toxins reach the systemic circulation and contribute

to this manifestation, a potential intervention might be the administration of monoclonal antibodies against toxins A and B [41] or the use of hyperimmune intravenous immunoglobulin if they become available.

In summary, treatment of CDI has relied primarily on metronidazole and vancomycin for the past 30 years. Although these and other agents will still have a role in treatment of patients with CDI, limitations of these agents have stimulated the development of newer therapies. It is hoped that the recently approved agent fidaxomicin and other agents that are still in development will improve the treatment of patients with CDI.

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