Treatment of *Clostridium difficile* Infection

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Recent outbreaks of *Clostridium difficile* infection (CDI) in North America have been due to a more virulent, possibly more resistant strain that causes more-severe disease, making prompt recognition of cases and optimal management of infection essential for a successful therapeutic outcome. Treatment algorithms are presented to help guide the management of patients with CDI. Metronidazole has been recommended as initial therapy since the late 1990s and continues to be the first choice for all but seriously ill patients and those with complicated or fulminant infections or multiple recurrences of CDI, for whom vancomycin is recommended. Other options for recurrent CDI, such as probiotics and currently available anion-exchange resins, have limited efficacy and are potentially harmful. Intravenous immunoglobulin may benefit patients with refractory, recrurent, or severe disease, but no controlled data are available. Two antimicrobials available in the United States for other indications, nitazoxanide and rifaximin, have been used successfully for CDI treatment but, like metronidazole, lack United States Food and Drug Administration approval for this indication. Experimental treatments currently in clinical development include a toxin-binding polymer, tolevamer; 2 poorly absorbed antimicrobials, OPT-80 (formerly known as Difimicin) and ramoplanin; monoclonal antibodies; and a *C. difficile* vaccine.

*Clostridium difficile* infection (CDI) is increasing in incidence and, in all likelihood, severity [1–4]. In a recent national survey of infectious disease specialists, 40% reported perceiving an increase in the incidence of CDI during the past 1 or 2 years [5], and discharge data from nongovernmental US hospitals showed a 26% increase in the percentage of patients with a diagnosis of CDI from 2000 to 2001 [6]. Since 2001, several outbreaks of infection due to an unusually virulent and possibly resistant strain of *C. difficile* have been reported in the United States, Canada, and several countries in Europe [7–13].

**BACKGROUND**

*Characteristics of the epidemic strain of C. difficile.* Because of the complexity of the organism and some of the inherent limitations unique to each typing method used to identify *C. difficile* strains, several genotyping methods have been used to distinguish the various clinical isolates of *C. difficile*. The BI/NAP1 epidemic strain of *C. difficile* belongs to toxinotype III (in contrast to typical clinical isolates of *C. difficile*, which belong to toxinotype 0) and is characterized as group BI (by restriction-endonuclease analysis), North American PFGE type 1 (by PFGE), and ribotype 027 (by PCR ribotyping) [7, 14]. Analyses of clinical isolates of *C. difficile* obtained from institutions recently experiencing outbreaks have revealed that the BI/NAP1 strain accounted for 10%–82% of the isolates collected [7, 10]. BI/NAP1 strains have all been shown to harbor certain putative virulence-associated characteristics (e.g., increased toxin production, an additional “binary” toxin, hypersporulation capacity, and high-level resistance to fluoroquinolone antibiotics). BI/NAP1 strains produce in vitro levels of the large clostridial toxins A and B that are 16–23 times the levels produced by toxinotype 0 strains [14]. The noted increase in toxin production may occur secondary to an 18-bp deletion or, more likely, to a 1-bp deletion resulting in a frame...
shift in the tcdC gene, which is presumed to be a negative regulator of toxin production [7, 15, 16]. BI/NAP1 also has an increased sporation capacity that may facilitate its spread through environmental contamination [17] and has acquired fluoroquinolone-resistance determinants [7].

**Need for early diagnosis and treatment.** The reporting of more rapidly progressive severe (or fulminant) disease in concert with the appearance of a previously uncommon and more virulent strain of *C. difficile* has modified the “rules of engagement” for treating CDI, emphasizing prompt clinical recognition, timely treatment, and implementation of infection control measures, including thorough environmental cleaning critical to the overall management of CDI [3, 12]. All clinicians, infection-control personnel, and nursing staff need to be alerted to the signs and symptoms of CDI such that timely intervention can be initiated [3]. Because nurses are likely to detect patients with diarrhea 1–2 days sooner than physicians, nurses’ involvement in initiating orders for *C. difficile* toxin testing and infection control precautions may facilitate the recognition of *C. difficile* and minimize its spread [18].

**GENERAL CONSIDERATIONS**

**Initial steps.** The first step in treating a patient with documented or suspected CDI is to discontinue treatment with the offending antimicrobial when possible. In the past, this strategy was sufficient for resolution of CDI symptoms in 20%–25% of patients within 48–72 h; however, with the increased incidence of fulminant CDI and the rapid clinical deterioration of some patients, delaying treatment specific for CDI is no longer advised, except perhaps for the mildest of illnesses [19]. If it is not possible to stop underlying antimicrobial treatment, an antibiotic that is less likely to promote CDI (e.g., a macrolide, sulfamethoxazole, an aminoglycoside, or intravenous vancomycin) may be substituted; however, there are no controlled studies that support this strategy [20]. Antiperistaltic and opiate agents should be avoided [21].

The choice of initial antibiotic therapy for CDI depends on the severity of disease. Figures 1 and 2 are examples of treatment algorithms created since the identification of BI/NAP1 [23]. Different regimens are used to treat first or second episodes of CDI (figure 1), recurrent CDI (i.e., ≥3 episodes) (figure 2), and very severe or fulminant CDI. In addition, special circumstances may guide treatment choices, such as whether the gastrointestinal tract is functioning. In discussing treatments, it must be understood that intravenous vancomycin is not an option; in this article, most references to vancomycin therapy involve vancomycin administered orally or via a retention enema. The oral route is preferred for metronidazole therapy unless special circumstances exist.

**First and second episodes.** Metronidazole, vancomycin, teicoplanin, fusidic acid, bacitracin, and drugs such as nitazoxanide and higher-dose tolevamer (which were shown to be effective in smaller studies of newer potential therapies for CDI) have been demonstrated to be efficacious in randomized comparative trials of CDI treatment [19, 24–32]. The agents most studied and with the longest history of use for the treatment of CDI are oral vancomycin (125 mg 4 times per day for 10–14 days) and oral metronidazole (250 mg 4 times per day or 500 mg 3 times per day for 10–14 days), with vancomycin being the only treatment approved by the US Food and Drug Administration (FDA) [33, 34].

Historically, metronidazole has for several reasons been used as first-line therapy for most cases of CDI. Metronidazole costs less than oral vancomycin, and small, prospective, randomized trials demonstrated that the 2 agents are equally effective [19, 31]. Use of metronidazole for treatment of CDI has been advocated in previously published guidelines and in a recent Cochrane review of randomized controlled trials [33, 35]. Two observational studies of metronidazole suggested that its efficacy is no longer as great as that suggested by the randomized controlled trials (table 1) [19, 31, 36–38].

Another recent study compared rifampin-metronidazole combination therapy with metronidazole monotherapy for first-episode cases of CDI [27]. In this study, Lagrotteria et al. [27] demonstrated that outcomes for patients who received combination therapy (i.e., rifampin-metronidazole) were not better than those for patients who received metronidazole monotherapy. These findings, may, in part, have been due to the emergence of rifampin resistance. As a result of recent comparative studies of newer potential treatment options (e.g., nitazoxanide and tolevamer), the efficacies of metronidazole therapy and vancomycin therapy have been reevaluated [28, 38]. In these studies, metronidazole and vancomycin were demonstrated to be noninferior (metronidazole vs. nitazoxanide and vancomycin vs. high-dose tolevamer) or superior (vancomycin vs. low-dose tolevamer) to the newer agents [28, 38]. Although these recent studies involved relatively small numbers of patients, and although severely ill patients were excluded from participation, the studies provided some insight into the efficacy of these established treatment options relative to that of the newer agents.

If a patient develops a second episode of CDI after successful treatment of the first episode, treatment with the same drug used to treat the first episode is recommended [33, 39]. A recent study conducted in Canada during an outbreak involving the BI/NAP1 strain of *C. difficile* concluded that first and second episodes of CDI responded similarly, regardless of whether metronidazole or vancomycin was chosen as therapy [39]. However, the investigators noted that complication rates associated with recurrence were greater than previously observed, regardless of which treatment was chosen for the second episode [39]. Excutating circumstances may exist in some cases, prompting
the use of an alternative agent for treatment of a second episode of CDI [39]. For example, vancomycin therapy is preferred if markers for severe CDI are present (such as hypotension or a WBC count of >15,000 cells/mm³), and alternative routes of therapy should be considered if the functionality of the gastrointestinal tract is affected (as in patients with ileus or toxic megacolon).

**Recurrent (i.e., ≥3) episodes.** Most recurrences of CDI occur within 7–14 days after the completion of therapy, suggesting relapse rather than reinfection (figure 2) [40]. CDI recurs in 15%–35% of patients who have had 1 previous episode and in 33%–65% of patients who have had ≥2 previous episodes [31, 36, 41–44]. In some patients, episodes continually recur for years, resulting in continuous receipt of vancomycin therapy [44–46]. This is frustrating to both the patient and the clinician and is an area of high priority for therapeutic research studies.

Contributing factors to recurrent CDI include continued exposure to organisms either through reinfection (from a contaminated environment or because of poor hand hygiene) or relapsing CDI from an endogenous source (i.e., *C. difficile* spores in the gastrointestinal tract) [39]. Most important, however, appears to be poor host immune response (i.e., the inability to mount an adequate anti–toxin A IgM and/or IgG antibody response), a probable function of an increasingly aged patient population [47]. It is likely that a vicious cycle is created when the actual antimicrobial treatments that are prescribed (vancomycin or metronidazole) have a significant impact on disrupting colonization protection of the normal colonic flora, leaving the patient vulnerable to the next recurrent episode. To date, there is no evidence that resistance to either of the primary therapies for CDI contributes to clinical failures or to relapsing infection [48].
Figure 2. Treatment recommendations for the third and subsequent episodes of *Clostridium difficile* infection (CDI) occurring ≤6 months after the previous episode. Strongly consider discontinuing non-CDI antibiotic therapy as soon as possible to allow reestablishment of the normal intestinal flora. IVIG, intravenous immunoglobulin; Mtz, metronidazole; PPI, proton-pump inhibitor; Rfx, rifaximin; Van, vancomycin. *Clinicians should be cognizant of the type and number of bowel movements per day, to gauge clinical response. In some cases, when patients are slowly improving, therapy may be continued for >10 days. It is important to avoid unnecessarily long treatment durations, to prevent further disruption of the commensal intestinal flora. Adapted from the following article with permission from Pharmacotherapy: Owens RC. *Clostridium difficile*–associated disease: an emerging threat to patient safety: insights from the Society of Infectious Diseases Pharmacists. Pharmacotherapy 2006; 26:299–311.

Uncontrolled studies and anecdotal articles ranging from case reports to larger descriptive case series abound on how to manage patients with recurrent CDI. However, only 1 prospective, randomized, controlled trial described a treatment regimen (i.e., high-dose vancomycin plus *Saccharomyces boulardii*) that showed a significant trend toward reduced recurrent CDI (P = .051) [49]. First-line therapy for recurrent infection typically involves treatment with vancomycin rather than with metronidazole, in part because of the adverse effects (e.g., peripheral neuropathy) resulting from long-term exposure to metronidazole [50]. Descriptive studies have been published that evaluated treatment with high-dose vancomycin, "tapered" or "pulsed-dose" vancomycin, sequential vancomycin followed by rifaximin, intravenous immunoglobulin (IVIG), rifampin concomitant with vancomycin, and infused donor stool. Several types of probiotic therapy have also been evaluated with or without concurrent receipt of active CDI therapy in a heterogeneous population of patients, using a wide variety of study methods.

In one of the larger studies, McFarland et al. [46] evaluated a cohort of 163 patients with recurrent CDI, all of whom were from the placebo arm of the study of vancomycin plus *S. boulardii* described above [49]. The mean number of previous CDI episodes in this group was 3.2 (range, 1–14 episodes), and the median duration of symptoms was 113 days (range, 20 days to 4 years). A variety of nonrandomized regimens were administered to these patients, including treatment with a high (2 g/day), intermediate (1 g/day), or low (500 mg/day) total daily dose of vancomycin for 10 days, treatment with vancomycin followed by tapered doses for a mean of 21 days, or treatment with vancomycin (or no treatment) immediately followed by pulsed-dose vancomycin therapy (i.e., one 125-mg,
Table 1. Comparison of prospective, randomized trials with more-recent observational trials of metronidazole (Mtz) for treatment of Clostridium difficile infection (CDI).

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. of patients who responded to Mtz/total no. evaluated (%)</th>
<th>No. of patients with CDI relapse/no. who initially responded to Mtz (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Teasley et al. [19]</td>
<td>Prospective, randomized</td>
<td>40/42 (95)</td>
<td>2/39 (5) by day 21</td>
</tr>
<tr>
<td>Wenisch et al. [31]</td>
<td>Prospective, randomized</td>
<td>29/31 (94)</td>
<td>5/29 (17) by day 30</td>
</tr>
<tr>
<td>Pépin et al. [36]</td>
<td>During 1991–2002</td>
<td>622/688 (90)</td>
<td>96/622 (15) by day 60</td>
</tr>
<tr>
<td></td>
<td>During 2003–2004</td>
<td>323/438 (74)</td>
<td>109/223 (34) by day 60</td>
</tr>
<tr>
<td>Mushet et al. [38]</td>
<td>Observational</td>
<td>161/207 (78)</td>
<td>13/161 (8) by day 21; 47/161 (29) by day 90</td>
</tr>
</tbody>
</table>

NOTE. These studies are reviewed in [37].

* The number of days indicates the time after completion of treatment.

b The study population consisted of patients who may have been infected with an epidemic strain of C. difficile.

250-mg, or 500-mg dose every 3 days) for a mean of 27 days. A high total daily dose of vancomycin was slightly more effective than the traditional (i.e., low) total daily dose in terms of reduced recurrence rates, but the intermediate dose of vancomycin was the poorest performing vancomycin regimen. Vancomycin treatment followed by tapered or pulsed vancomycin therapy resulted in significantly fewer recurrences of CDI than did intermediate-dose vancomycin treatment alone (P < .05), but the differences between the tapered and pulsed regimens and the high-dose and low-dose regimens alone were not significant. Tedesco et al. [51] also studied tapered regimens of vancomycin in 22 patients. The regimen consisted of 500 mg/day during week one, 250 mg/day during week two, 125 mg/day during week three, and a pulsed dose of 125 mg every 3 days during weeks 4–6. Data from these observational studies indicate that tapered and pulsed-dose vancomycin regimens seem to be effective in reducing recurrences, but randomized prospective studies of these regimens have never been done.

Pulsed and tapered regimens of metronidazole therapy were also studied, but too few patients were evaluated to draw any conclusions [46]. It has been assumed that treatment with vancomycin or metronidazole is only effective against vegetative forms (not spore forms) of C. difficile. It is theorized that, if a period of waning antimicrobial exposure is created in the gastrointestinal tract, spores will germinate, rendering them susceptible to subsequent intermittent doses. However, this implies that spores can sense waning antimicrobial levels before they germinate. An equally plausible alternative theory is that tapered and pulsed dosing are sufficient to suppress C. difficile growth while allowing the flora to recover.

Buggy et al. [52] evaluated combination therapy with oral vancomycin (125 mg 4 times per day) and oral rifampin (600 mg 2 times per day) given for 7 days in a small number of patients. Further anecdotal experience has supported the efficacy of this approach, but the intolerability of a high-dose rifampin regimen, which is common, and the potential for drug interactions and emerging resistance are limiting factors of the overall usefulness of this combination regimen.

Cholestyramine, an anion-exchange binding resin, has also been subjectively reported as useful for treating recurrent CDI [53–55]. However, the efficacy of anion-exchange binding resins in the treatment of primary C. difficile diarrhea was negligible when evaluated under more-rigorous conditions. The only placebo-controlled trial that evaluated the toxin-binding capability of anion-exchange resins was conducted using colestipol, which was found to be comparable to placebo in terms of treating CDI and reducing fecal excretion of C. difficile toxins [56]. Animal models have confirmed that the toxin-binding affinity of cholestyramine is lower than that of other toxin-binding compounds [57]. Cholestyramine does, however, bind to a variety of drugs [58], including vancomycin, resulting in a reduction of biologic activity in stool [59]. Given the lack of efficacy data that support cholestyramine use, as well as the potential for deleterious effects when cholestyramine is combined with oral treatments for CDI, cholestyramine and colestipol use is not recommended.

IVIG may also benefit a subgroup of patients with multiple recurrences of C. difficile diarrhea [60–62]. In 2 of the studies, patients had low levels of serum anti-toxin A IgG [61, 62], and the patient in the third study had selective IgG1 deficiency [60]. The largest study published to date of IVIG was a retrospective, observational evaluation of 14 patients [63]. Six patients responded clinically to IVIG, and no relapse occurred during the period reported. The doses ranged from 150 to 400 mg/kg (1 patient received a second dose). The median response time was 10 days. In another study, treatment for 3 of 5 patients with recurrent CDI who received an IVIG dose of 300–500 mg/kg (most patients received 400 mg/kg) was considered successful, with resolution occurring within 11 days [64]. IVIG may provide a therapeutic option for patients with severe and/or relapsing CDI when no other therapeutic options are available. Unfortunately, marginal efficacy, lack of data regarding the op-
C. difficile patient was reported to have a recurrent episode and received vancomycin until symptoms resolved, at which time a 2-week regimen of vancomycin was immediately started. In this small sample, 7 of 8 patients allowed by a course of vancomycin was successful in terminating multiple recurrences of C. difficile colitis in 2 young children [67]. A more recent report combined Golytely lavage with administration of donated feces directly through a colonoscope to all segments of the colon [68]. The theoretic advantage of this refinement over previous fecal-infusion strategies was a more thorough reduction of the resident flora and recolonization of the entire colon. Finally, withholding of treatment, combined with careful observation, has also been advocated for select patients, but this option should be used with great caution to avoid severe complications of recurrent CDI [33].

Recently, 8 female patients aged 43–88 years who had had 4–8 previous episodes of CDI and had received treatment for 79–372 days were given an unconventional regimen of vancomycin followed by rifaximin [69]. A variety of treatment strategies had been attempted for these patients, including combinations of standard therapy (metronidazole or vancomycin) and rifampin, probiotics, and tapered or pulsed vancomycin regimens. Although diarrhea would cease for a period, symptoms would invariably return (mean diarrhea-free interval, 10.5 days; [range, 1–59 days]). These patients were treated with vancomycin until symptoms resolved, at which time a 2-week regimen of rifaximin (400–800 mg daily divided into 2–3 doses) was immediately started. In this small sample, 7 of 8 patients remained symptom free (follow-up range, 51–431 days). One patient was reported to have a recurrent episode and received a second 2-week course of rifaximin; she remained symptom free during a 9-month follow-up period. However, the rifaximin MIC for C. difficile isolates recovered after therapy (>256 µg/mL) was much higher than the MIC for isolates recovered before therapy (0.0078 µg/mL), although the patient remained asymptomatic. The findings from this case series suggest a promising solution to a very frustrating clinical problem facing many clinicians today; however, it should be noted that this use of rifaximin is considered to be off-label (rifaximin is not approved by the FDA for the treatment of CDI) and that resistance was clearly documented after rifaximin use.

Of the biotherapeutic strategies, treatment with the yeast S. boulardii is the best studied. In the initial report involving 13 patients with multiple recurrences CDI who received vancomycin for 10 days and S. boulardii for 28 days, 11 patients had no further recurrences [70]. A subsequent randomized, placebo-controlled study showed that S. boulardii in combination with standard therapy was more effective than standard therapy alone in preventing recurrences in patients who had a history of more than 1 C. difficile diarrhea episode [71]. A more recent, prospective, randomized study, in which the standard therapy and therapeutic dose were stratified, showed a substantial decrease in recurrent episodes in the study arm treated with high-dose vancomycin (2 g/day) and S. boulardii, compared with high-dose vancomycin and placebo [49]. Neither low-dose vancomycin nor metronidazole with or without S. boulardii was effective.

Data on regimens containing Lactobacillus organisms or S. boulardii for the treatment of recurrent CDI are poor and conflicting. The best study supporting the use of S. boulardii [71] has not resulted in FDA approval [72]. A recent meta-analysis suggested that probiotics are effective; nevertheless, because of the heterogeneity of study methods and patient populations, it is not scientifically possible to conduct a meta-analysis of findings in the probiotic literature. For related reasons, critical examination by Beckly et al. [73] of an earlier meta-analysis of probiotic use [74] cast doubt on the efficacy of these agents for treating CDI. A systematic review of probiotic efficacy indicated that findings from the current literature do not support the use of probiotics for CDI [75]. Moreover, the literature is evolving to demonstrate that the so-called nonpathogenic strains of the various fungi and bacteria used in the currently marketed probiotics have caused numerous cases of bacteremia due to Lactobacillus species and fungemia due to S. boulardii in immunocompetent hosts and immunocompromised hosts [76–79].

Other, nonantimicrobial, biotherapeutic approaches tested in open trials include treatment with rectal infusion of feces obtained from healthy hosts [80, 81] and infusion of a mixture of bacteria that simulated the normal intestinal flora [82]. A recent review of the 8 reports on infusion of feces or fecal bacteria was optimistic, indicating a good cure rate without recurrence for most patients [83]. More recently, Aas et al. [40] reported excellent results in 15 of 16 patients who received donor stool via a nasogastric tube. Despite the aesthetic concerns of this approach and the potential concern for transmission of other infectious agents, stool-infusion therapy has been associated with the greatest likelihood of success among therapies studied for treatment of recurrent CDI. An additional novel approach that was partially successful in 2 patients involved oral introduction of a harmless, nontoxic strain of C. difficile [84].

Monitoring therapeutic response. The WBC count, temperature, findings of abdominal examination, number of bowel movements, and overall clinical status of patients with CDI who are being treated should be evaluated daily. Historically, patients should show some symptomatic improvement within 1 or 2 days after the initiation of therapy, with a mean time to diarrhea resolution of 3–6 days, as shown in earlier randomized treatment trials. Anecdotal reports suggest that symptoms for patients infected with BI/NAP1 strains may take longer...
to improve than symptoms for patients infected with other \textit{C. difficile} strains. Although this finding has not been formally studied, if true it could be a reflection of the substantial increase in toxin production in vitro associated with BI/NAP1 strains. Patients who demonstrate improvement during initial metronidazole therapy, as evidenced by a decreased number of bowel movements per day and improvement in WBC count, fever, and abdominal findings, should continue to receive this regimen. Treatment for patients whose condition does not improve during the first 1–2 days of treatment or worsens at any point during therapy should be switched to oral vancomycin. Additional consultation with the infectious diseases, gastroenterology, and/or surgery services may be warranted to examine the need for alternative treatment options, an alternate route of therapy, and/or surgical intervention. The usual duration of treatment is 10 days for a patient who is responding to therapy. One study noted that the mean metronidazole response time was 1.6 days slower than that for vancomycin and that longer treatment with metronidazole may be necessary in select cases [85]. However, to allow for the reconstitution of the commensal microbiota and avoid complications of therapy, for most patients it is preferable not to extend therapy for longer than necessary. After resolution of symptoms, testing stool for \textit{C. difficile} or its toxins as a test of cure for CDI is not recommended, because patients may shed the organism or toxin for several weeks after the cessation of treatment [33, 41, 86].

\textbf{TREATMENT OF SEVERE OR FULMINANT CDI}

The BI/NAP1 strain has been associated with greater infection severity, as mentioned above [7, 12, 13, 36, 87]. If severe CDI is suspected after obtaining the patient’s history and performing a physical examination, then radiographic imaging studies—usually a CT scan of the abdomen and pelvis—are indicated to determine whether ileus, obstruction, perforation, toxic megacolon, colonic-wall thickening, and ascites are present [88, 89]. When any of these conditions are present—particularly toxic megacolon, perforation, or colonic-wall thickening—early surgical consultation is indicated, because colectomy can be a life-saving procedure [90]. Additional criteria for severe CDI may include signs of sepsis, hypotension, a WBC count that is markedly high (i.e., >50,000 cells/µL) or low (i.e., <2000 cells/µL), and increased bandemia (>20% of WBCs), in the absence of other obvious causes. For patients with severe or fulminant infection whose gastrointestinal tract is functioning, oral vancomycin is the preferred therapy. A recent prospective, double-blind, randomized clinical study indicated that the clinical cure rate for vancomycin in patients with severe CDI was significantly better than that for metronidazole (97\% vs. 76\%; \textit{P}<.02) [22]. Monitoring for signs of response to therapy (e.g., recording or measuring the number of bowel movements per day, the consistency of stool, the WBC count, the presence of fever, and the blood pressure and performing abdominal examination) must be done daily because severe CDI is life threatening, and appropriate therapeutic decisions, particularly whether to perform a colectomy, need to be made promptly.

Optimal medical treatment of fulminant infection for patients with compromised gastrointestinal tract function remains unknown. For these patients, delivery of reliable concentrations of orally administered drug to the site of infection cannot be assured. Colonic concentrations of vancomycin are negligible following intravenous administration, and there is little support for this therapeutic option. Fecal concentrations of metronidazole, however, are similar whether metronidazole is given orally or intravenously to patients with diarrhea [91]. In the absence of diarrhea, stool levels of metronidazole after oral intake are virtually undetectable because of absorption in the small bowel [91]. Anecdotal experience supports the use of intravenous metronidazole for treatment of \textit{C. difficile} diarrhea [91–93]. A retrospective review of 10 patients who received intravenous metronidazole for at least 2 days as the initial therapy for acute CDI when oral therapy was not possible showed that, in the majority of patients, symptoms improved without subsequent complications that required surgical intervention [94]. A randomized, prospective study of intravenous metronidazole was needed, but this treatment alone may be inadequate in patients with severe CDI, especially if adynamic ileus is present [95].

Therefore, in patients with severe manifestations of CDI, other methods to ensure effective antimicrobial concentrations at the site of infection should also be undertaken. For example, oral vancomycin should be given in addition to intravenous metronidazole. When severe adynamic ileus is suspected, intraluminal vancomycin should be considered. This can be accomplished by delivery via a long catheter in the small intestine [96], direct intracolonic instillation [88], or rectal delivery through an enema [88, 97, 90]. At one institution, a successful treatment strategy for 6 patients with severe ileus included oral vancomycin administered by nasogastric tube, vancomycin administered to colon via a retention enema, and intravenous metronidazole [88]. If these approaches are unsuccessful and the patient’s clinical condition deteriorates, colectomy is the only life-saving alternative [98].

\textbf{EXPERIMENTAL TREATMENTS}

After 25 years with no new drugs introduced for treatment of CDI, several new therapies are in clinical trials (table 2). The anion-exchange resin televamer has been shown to be non-inferior to vancomycin in a phase 2 trial [28]. In addition, a number of antibiotics are in various stages of development. Nitazoxanide, a thiazolide antibiotic being marketed in the United States for the treatment of intestinal parasites [99],
shows activity comparable to that of vancomycin and metronidazole in vitro and in hamsters [100]. The first human trial showed that nitazoxanide is at least as effective as metronidazole and might be useful for patients who do not respond to metronidazole therapy, cannot take metronidazole, or have repeated recurrences; however, nitazoxanide does not have an FDA-approved indication for CDI treatment [30, 72]. Other new antibiotics in the early stages of development include ramoplanin, a nonabsorbable inhibitor of cell wall synthesis; tia- cumicin B complex (OPT-80 [formerly known as Difimicin]; Optimer), a new macrocycle agent that is poorly absorbed; rifalazil and rifaximin, new rifamycin derivatives related to rifampin and rifabutin; and tinidazole, a 5-nitroimidazole similar to metronidazole [101–104]. All of these agents have shown good activity in vitro against *C. difficile* [101–104, 107], and several have been demonstrated to reduce the incidence of CDI recurrence in the hamster model (table 2). In addition, ramoplanin and rifalazil are effective in hamsters [103, 108].

Passive immunity against *C. difficile* toxins may protect against infection. Gnotobiotic mice passively immunized with monoclonal antibodies against *C. difficile* toxin A were protected against experimental *C. difficile* colitis [109], and antibodies against toxins A and B prevented infectious morbidity and mortality in hamsters [110]. Currently, a commercially available monoclonal antibody is under development for treatment of CDI in the hamster model (table 2). In addition, ramoplanin and rifalazil are effective in hamsters [103, 108].

### CONCLUSIONS

Since *C. difficile* was recognized as the cause of CDI in the late 1970s, metronidazole and vancomycin have been the primary treatment options. To minimize the emergence of vancomycin-resistant enterococci and staphylococci and to contain costs, vancomycin use in hospitals has been limited to patients who do not respond to metronidazole, have serious or fulminant CDI, or have multiple recurrences of CDI. Although the efficacy of metronidazole may be decreasing, it continues to be effective as initial therapy and as treatment of the first recurrent episode for the majority of patients who have mild-to-moderate infection; however, careful daily observation of patients is recommended to ensure that they are clinically improving during therapy. Vancomycin continues to be recommended as initial therapy for severe or fulminant CDI, a recommendation now supported by data from a randomized clinical study.

The treatment of multiple recurrences of CDI is challenging. In addition to use of vancomycin in high doses or in tapered or pulsed doses, newer experimental antibiotics may be associated with lower recurrence rates. Moreover, a number of patients who received IVIG, and controls were not adequately matched with cases. More studies will be needed to assess the efficacy of this approach. In humans, preliminary trials of a parenteral vaccine containing toxoids A and B have shown that the product is safe and induces vigorous serum antitoxin A responses in healthy adults [112, 113]. Three patients who required continuous vancomycin therapy for treatment of recurrent CDI received *C. difficile* toxoid vaccine, and all were able to discontinue vancomycin therapy [114]. Serum levels of IgG antibodies against toxins A and B increased by 4-fold and 20-fold, respectively, in one patient and by 3-fold and 52-fold, respectively, in another patient after initiation of the vaccination regimen.
antibiotic treatments, including a new experimental polymer that binds to toxins A and B, a vaccine, and monoclonal antibodies, are under development in clinical trials and appear promising. The efficacy of probiotic therapy remains to be proven, but stool-infusion therapy is highly effective albeit concerning with respect to aesthetics and safety. The ultimate efficacy of these novel approaches remains to be determined, but they provide optimistic opportunities for future therapy.

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