Treatment selection for *Clostridium difficile* infection (CDI) has become more complex despite the lack of new FDA-approved treatments. The challenge of managing these patients is due, in part, to the growing prevalence and severity of the disease. Fortunately, algorithms based on the severity of illness can help clinicians choose among currently available medications. And several investigational agents show promise for reducing the high rate of CDI recurrence.

The changing epidemiology of CDI is well established in the literature. Recent surveys of US and international infectious diseases specialists indicate increased incidence of CDI over the past 5 years. Discharge data from nonfederal US hospitals showed a 2- to 3-fold increase in ICD-9 coded discharge diagnoses since 2001. Since that time, multiple outbreaks of an unusually virulent and difficult-to-treat strain of *C. difficile* have been reported in the United States, Canada, and several European countries. This particular epidemic strain of *C. difficile* belongs to toxinotype III, group BI, according to restriction-endonuclease analysis, NAP1 by pulsed-field gel electrophoresis, and ribotype 027 by polymerase chain reaction ribotyping. BI/NAP1 strains all have been shown to harbor certain putative virulence characteristics (eg, increased toxin production, an additional “binary” toxin, spore formation capacity, and high-level resistance to fluoroquinolone antibiotics). Typical clinical isolates of *C. difficile* belong to toxinotype 0. When compared with toxinotype 0 strains, BI/NAP1 strains produce between 16 and 23 times the in vitro levels of the large clostridial toxins A and B, which may be related to the mutations in the tcdC gene that is a putative negative regulator of toxin A and B production.

**Treatment of *C. difficile* Infection**

**Basic Treatment**

Because antibiotic use is a major contributing factor in CDI, when possible, discontinuation of the offending antimicrobial should be the first step in managing the disease. This intervention alone was proven to be sufficient to resolve CDI symptoms in 20% to 25% of patients within 48 to 72 hours; but with the increasing rapid clinical deterioration in some patients, delay in specific CDI treatment is not recommended except for the mildest of symptoms. Antiperistaltic and opiate agents should be avoided, although this recommendation recently was challenged.

Since the advent of the BI/NAP1/027 strain, therapy has evolved toward treatment selection based on...
TREATMENT OF FIRST- AND SECOND-EPISODE CDI

Metronidazole, vancomycin, teicoplanin, fusidic acid, bacitracin, nitazoxanide (Alinia, Romark Laboratories), and rifaximin (Xifaxan, Salix Pharmaceuticals) have demonstrated efficacy in randomized comparative trials for treatment of CDI.17,21-29

Oral vancomycin (125 mg 4 times daily for 10-14 days) and oral metronidazole (250 mg 4 times daily or 500 mg 3 times daily for 10-14 days) have been most widely used, but only vancomycin is FDA-approved.17,28,30-32 Contrary to earlier randomized controlled trials (RCTs), 2 observational studies of metronidazole suggest that it is no longer as effective as it once was in the treatment of CDI.17,28,33-35

If a patient develops a second episode of CDI after successful treatment of the first episode, retreatment with the same drug is recommended.30,36 A study conducted in Canada during an outbreak period involving BI/NAP1/027 strains of C. difficile concluded that first and second episodes responded similarly, regardless of whether metronidazole or vancomycin was administered.36 However, if the second episode was severe, vancomycin was the preferred treatment.

RECURRENT CDI (≥3 EPISODES)

Most recurrences of CDI occur within 7 to 14 days of the completion of therapy, suggesting relapse rather than reinfection.37 The infection recurs in approximately 15% to 30% of patients who have had a single episode, and in 33% to 60% of patients who have had more than 2 previous episodes.38,39,41-43

Multiple recurrences of CDI are frustrating to both the patient and the clinician. This is an area of high priority for therapeutic research studies.41-43

Contributing factors to recurrent disease include advanced patient age, continued receipt of antimicrobials, continued stay in a health care environment, and underlying high severity of illness.36 Also important is poor host immune antibody response to toxin A in an

Figure 1: Treatment recommendations for first or second episode of Clostridium difficile infection within 6 months.

CDI, Clostridium difficile infection; GI, gastrointestinal; ID, infectious disease; IVIG, intravenous immunoglobulin; NG, nasogastric; PO, orally; WBC, white blood cell

*Clinicians should track the number and description of patients’ bowel movements per day to gauge clinical response. In some cases in which patients are slowly improving, therapy may be continued longer than 10 days. It is important to avoid unnecessarily long treatments that further disrupt the commensal flora.

Adapted from reference 20.

disease severity. Figures 1 and 2 are treatment algorithms created in response to higher incidences of severe CDI that were often, but not exclusively, associated with BI/NAP1/027.20 Therapy for CDI can be divided into usual therapy for those patients presenting with first or second episodes (Figure 1), patients with recurrent disease (ie, ≥3 episodes; Figure 2), and those with very severe or fulminant disease. Oral, rather than IV, vancomycin should be administered for CDI treatment. Vancomycin also may be administered via retention enema in the presence of ileus. Oral metronidazole is preferred; however, the IV form of the drug also is effective.
increasingly aging patient population. Recurrence appears primarily to result from host immune failure, as there is no evidence that drug resistance to either of the primary treatments for CDI is a contributing factor. Controlled trials of recurrent CDI are lacking. Only a single prospective, RCT (high-dose vancomycin alone vs high-dose vancomycin plus the probiotic *Saccharomyces boulardii*) has shown a significant trend toward reduced recurrent CDI \( (P=0.051) \). Descriptive studies of vancomycin, “tapered” or “pulsed-dosed” treatment, sequential vancomycin followed by rifaximin, intravenous immunoglobulin (IVIG), the addition of rifampin to vancomycin, and donor fecal transplants all have been published—with the latter demonstrating the highest efficacy. In a study by McFarland et al, vancomycin treatment followed by tapered or pulsed-dose vancomycin resulted in significantly reduced recurrences when compared with intermediate-dose vancomycin treatment alone \( (P<0.05) \), but not when compared with high- or low-dose vancomycin alone. Tedesco and colleagues also studied vancomycin-tapered regimens in 22 patients. The regimen consisted of 500 mg per day during week 1; 250 mg per day during week 2; 125 mg per day during week 3; and pulsed-dosed vancomycin 125 mg every 3 days during weeks 4 to 6. Although these observational studies suggest that tapered and pulsed-dose vancomycin regimens may be effective in reducing recurrences, no randomized prospective studies have been performed.

Probiotics also have been evaluated in several forms among a heterogeneous population of patients, with or without concurrent treatment with an active therapy for CDI, and have employed a wide variety of study methodologies. To date, with the exception of the trend toward reduced recurrence with *S. boulardii* plus vancomycin, there has been no evidence of benefit. A systematic review of probiotic efficacy indicated that the current literature does not support the use of probiotics for treatment of CDI. Moreover, recent studies demonstrate that the so-called nonpathogenic strains of various fungi and bacteria used in the currently marketed probiotics have caused numerous cases of bactemias resulting from *Lactobacillus* spp., and fungemias.
caused by *S. boulardii*, in both immunocompetent and immunocompromised hosts.49-52

Other biotherapeutic approaches tested in open trials include treatment with rectal infusions of feces from normal hosts and infusion of a bacteria mixture that simulated normal flora.53-55 A recent review of the 8 nonrandomized reports of instillation of feces or fecal bacteria was optimistic, with very high rates of resolution of recurrence.56 Aas and colleagues also reported excellent results in 15 of 16 patients administered donor feces via a nasogastric tube.37 Despite the esthetic concerns, fecal replacement therapy has been associated with the greatest likelihood for success in multiple recurrences of CDI.

Anion-exchange resins such as cholestyramine and colestipol appear to be ineffective.57-59 The only placebo-controlled trial that has evaluated anion-exchange resins clinically was conducted using colestipol, which was determined to be comparable with placebo in terms of treating CDI.60 Although IVIG may benefit a subgroup of patients with multiple recurrences of *C. difficile* diarrhea, it is unproven overall.61-65 The most promising response rates from 2 trials were 6 of 14 and 3 of 5 patients, respectively, who experienced no further recurrence.64,65

More recent regimens include sequential vancomycin (until symptoms resolve), followed by rifaximin 400 to 800 mg per day for 2 weeks, which resulted in cessation of recurrent CDI in 7 of 8 patients who experienced 4 to 5 previous recurrences.66 Caution is emphasized with this approach as a single patient developed high-level rifaximin resistance during therapy, although the patient remained asymptomatic. Use of rifaximin is considered “off-label” because it is not FDA-approved for the treatment of CDI.

Two recent trials reported in abstract form show reduced recurrence rates with primary treatment of CDI. The results may prove useful to clinicians when faced with multiple recurrences. The first trial was a prospective, randomized double-blind study that compared use of a nonabsorbed macrocyclic antibiotic—fidaxomicin—with vancomycin. Results demonstrated a 92.1% response rate for fidaxomicin compared with an 89.8% response for vancomycin (P=NS). However, the recurrence rate for fidaxomicin was significantly lower than that for vancomycin (13.1% vs 24.0%, respectively; P=0.004).67

The second trial studied a different approach to the problem of recurrence. Two monoclonal antibodies directed against toxins A and B were administered via IV as an adjunct to metronidazole or vancomycin at the time of diagnosis and compared for recurrence with an IV placebo. The CDI recurrence rate for patients who received monoclonal antibodies was 6.9% versus 25% in the placebo group (P=0.0004).68

**Careful Treatment Monitoring**

Clinicians should examine patients being treated for CDI on a daily basis. The exam should include white blood cell (WBC) count, temperature, abdominal examination, number of bowel movements, and overall clinical status.

Patients should show some symptomatic improvement within 1 or 2 days after initiation of therapy, with a mean time-to-diarrhea resolution of 3 to 6 days, as shown in randomized treatment trials. Patients who fail to improve in the first 2 to 4 days of treatment with metronidazole, or whose status becomes worse at any point during therapy, should be switched to oral vancomycin. The usual treatment period is 10 days; however, some patients receiving metronidazole may have a delayed response to treatment compared with those treated with vancomycin; longer treatment with metronidazole may be necessary in select cases.69

After resolution of symptoms, testing stool for *C. difficile* or its toxins as a “test of cure” for CDI is not recommended because of continued shedding of the organism or toxin for weeks after treatment.30,38,70

**Severe or Fulminant CDI**

The BI/NAP1/027 strain has been associated with greater CDI severity in some, but not all, studies.71-73 If severe CDI is suspected after patient history and physical examination are obtained, then radiographic imaging studies—usually a computed tomography (CT) scan of the abdomen and pelvis—to determine presence of ileus, obstruction, perforation, toxic megacolon, colonic thickening, or ascites should be performed.72,73 Surgical consultation is indicated when megacolon, perforation, or colonic thickening are found as colectomy, which is potentially lifesaving, may be indicated.74 Additional criteria for severe, complicated or fulminant CDI include signs of sepsis, hypotension, and a WBC count greater than 50,000 mm³ (a WBC of >15,000 or 20,000 mm³ is indicative of severe disease).

For severe or fulminant CDI in which the gastrointestinal (GI) tract is functioning, oral vancomycin is the preferred medical therapy. A randomized study by Zar et al demonstrated a significantly improved outcome in patients with severe CDI treated with vancomycin rather than with metronidazole.75

If the GI tract is not functioning as a result of ileus or obstruction, reliable concentrations of oral nonabsorbed drug to the colon site of infection may be compromised. Fecal concentrations of metronidazole are similar when metronidazole is given orally or via IV in the setting of diarrhea; in the absence of diarrhea, however, levels of metronidazole in the stool after oral intake are virtually undetectable because of small bowel absorption.75 Anecdotally, IV metronidazole therapy for *C. difficile* diarrhea appears effective.76-77 A retrospective review of 10 patients who received at least 2 days of IV metronidazole as initial therapy for acute CDI—when oral therapy was not possible—showed symptomatic improvement in most patients.78 A randomized, prospective study is needed, but any metronidazole therapy alone may be inferior to vancomycin in patients with severe disease.79
In the absence of controlled trial data for patients with severe CDI and ileus, additional methods for delivering effective antimicrobial concentrations at the infection site have been used. Oral vancomycin should be given. In addition, IV metronidazole should be added and additional vancomycin may be administered via rectal enema. Nitazoxanide, a thiazolide antibiotic approved for the treatment of intestinal parasites, is comparable with vancomycin in both response and recurrence rate. Fidaxomicin has shown promise by achieving noninferiority when compared with vancomycin in the first Phase III CDI clinical trial for response rate. Fidaxomicin or metronidazole—found recurrence rates in treated patients to be 6.9% compared with 25% in the placebo group (P=0.0004). In humans, preliminary trials of a parenteral vaccine containing toxins A and B are ongoing and have shown that the product is safe and induces vigorous serum antibody responses in healthy adults. Three patients who required continuous treatment with vancomycin for the management of recurrent CDI were administered the vaccine. All 3 were able to discontinue vancomycin and large increases in serum immunoglobulin G antibodies to toxin A (3- to 4-fold) and toxin B (20- to 52-fold) were found in 2 of 3 patients.

### Conclusion

Although the efficacy of metronidazole may be declining, it continues to be effective for the initial treatment of mild to moderate CDI and for treatment of the first recurrence of CDI if the patient is not seriously ill. However, careful daily observation of patients is recommended to ensure clinical improvement. Vancomycin is recommended as initial therapy for severe or fulminant CDI.

The treatment of multiple recurrences of CDI is a continuing challenge. Use of tapered or pulsed-dose vancomycin, and vancomycin followed sequentially by rifaximin are modestly successful. Fidaxomicin has demonstrated lower recurrence rates in an initial Phase III trial, and a number of nonantibiotic treatments—including monoclonal antibodies—show definitive reduction in rates of recurrence. A vaccine is under active development. Fecal transplants have proved to be highly effective, although concerning from an aesthetic and safety standpoint. The effectiveness of probiotics must still be proven. Novel nonantibiotic approaches remain an attractive option for future therapy and prevention.

### Experimental Approaches to Management

After 25 years with no new treatments, clinical trials for several new CDI products are ongoing (Table). A number of antibiotics such as fidaxomicin (which is experimental) and nitazoxanide and rifaximin, both of which are available on the US market for other indications, are currently in Phase III clinical trials for CDI. Fidaxomicin has shown promise by achieving noninferiority when compared with vancomycin in the first Phase III CDI clinical trial for response rate. Fidaxomicin also showed a significantly reduced recurrence rate of 13.3% compared with 24% for vancomycin (P=0.004). Nitazoxanide, a thiazolide antibiotic approved for the treatment of intestinal parasites, is comparable with vancomycin and metronidazole in vitro and in hamsters. Small human trials have shown that nitazoxanide is comparable to both metronidazole and vancomycin in both response and recurrence rate. Rifaximin, a rifamycin derivative related to rifampin, is available in the United States for treatment of traveler’s diarrhea and is currently in Phase III clinical trials for treatment of CDI. Several of these agents have demonstrated reduction in the incidence of recurrence in the hamster model of CDI.

Nonantibiotic or “out-of-the-box” approaches to CDI treatment and prevention are particularly attractive as they avoid the continued suppression of normal bacterial flora by CDI antibiotics. One such approach, the anion-exchange resin tolevamer, showed promise in a Phase II trial against vancomycin. In the study, tolevamer (6 g/d) was found to be noninferior to vancomycin (500 mg/d), based on time to resolution of diarrhea (P=0.02). There was also a trend toward a lower recurrence rate with tolevamer.

Active and passive immunity against C. difficile toxins may be the ultimate protection strategy for CDI infection. Results of a Phase II clinical study for use of IV-administered monoclonal antibodies directed against toxins A and B—in combination with either vancomycin or metronidazole—found recurrence rates in treated patients to be 6.9% compared with 25% in the placebo group (P=0.0004). In humans, preliminary trials of a parenteral vaccine containing toxins A and B are ongoing and have shown that the product is safe and induces vigorous serum antibody responses in healthy adults. Three patients who required continuous treatment with vancomycin for the management of recurrent CDI were administered the vaccine. All 3 were able to discontinue vancomycin and large increases in serum immunoglobulin G antibodies to toxin A (3- to 4-fold) and toxin B (20- to 52-fold) were found in 2 of 3 patients.

### Table. Investigational Therapies for CDI

<table>
<thead>
<tr>
<th>Company</th>
<th>Product Name (Type)</th>
<th>Patient Response</th>
<th>Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimer</td>
<td>Fidaxomicin (OPT-80) (abx)</td>
<td>244/265 patients</td>
<td>Phase III</td>
</tr>
<tr>
<td>Salix</td>
<td>Rifaximin (abx)</td>
<td>9/10 patients</td>
<td>Phase III</td>
</tr>
<tr>
<td>Romark</td>
<td>Nitazoxanide (abx)</td>
<td>68/79 patients</td>
<td>Phase III</td>
</tr>
<tr>
<td>Merck, Medarex, and Massachusetts Biological Labs</td>
<td>Monoclonal antibody</td>
<td>6.9% vs 25% recurrent CDI</td>
<td>Phase II</td>
</tr>
<tr>
<td>Acambis</td>
<td>C. difficile vaccine</td>
<td>Unknown</td>
<td>Phase II</td>
</tr>
</tbody>
</table>

abx, antibiotic; CDI, Clostridium difficile; OPT-80, Optimed ABX-0085; abx, antibiotic. 
* Data from a hamster model showing reduced recurrence.
References


