Contemporary Management of Clostridium difficile Infection

Clostridium difficile infection (CDI) is a primarily nosocomial diarrheal illness that is increasing in incidence and severity, due in part to the recently recognized hypervirulent BI/NAP1/027 epidemic strain. Infectious spores of C. difficile contaminate the hospital environment and, when ingested, bind to the colonic epithelium and cause toxin-mediated cell destruction. The spectrum of symptomatic disease ranges from mild diarrhea to fulminant pseudomembranous colitis.

Exposure to antibiotics that disrupt the colonic microflora is the most important risk factor for CDI. Clindamycin, cephalosporins, and expanded-spectrum fluoroquinolones are the agents associated with the highest risk, whereas metronidazole, vancomycin, and aminoglycosides entail the lowest risk. Other risk factors for CDI include prolonged hospitalization, older age, medical comorbidities, and the use of proton pump inhibitors.

Strategies for the management of CDI are based on the severity of disease and the degree of recurrence. Many patients now require empiric anti-C. difficile treatment, especially when they present with severe disease or are at high risk for complications.
The offending antibiotic(s) should be discontinued, if possible. Although an earlier study indicated that resolution of CDI occurred in 20% to 25% of patients who stopped all antibiotics, no recent studies supporting this approach have been conducted. Nearly all patients with CDI will require *C. difficile*-specific antibiotic therapy. Antidiarrheal medications, such as loperamide and diphenoxylate plus atropine, should be avoided because they may increase the risk for severe complications. A lactose-free diet may provide symptomatic benefit, particularly for lactose-intolerant patients.

To reduce transmission, hospitalized patients should be placed under contact isolation precautions (disposable gowns and gloves) until their diarrhea resolves. Patients, visitors, and health care workers should practice proper hand hygiene, preferably with soap and water because alcohol-based hand rubs are not sporicidal (Table 2). In general, *C. difficile*-specific antibiotics (Table 3) are administered for 10 to 14 days. Resolution of diarrhea usually occurs within 3 to 5 days of starting therapy. Truly refractory CDI is uncommon, and may be associated with continuation of the inciting antibiotic. Testing to confirm if CDI is cured is not recommended as toxins are often detected in the stool after clinical improvement. In addition, test results do not predict treatment failure or recurrence.

**Antibiotic Treatment of Mild To Moderate CDI**

Therapies for mild to moderate CDI include the following (see also Table 3):

- **Metronidazole.** When specific anti- *C. difficile* antibiotics are required, 500 mg of oral metronidazole (Flagyl, Pfizer) 3 times per day or 250 mg 4 times per day is still considered first-line therapy in most cases. Conflicting evidence exists regarding a temporal increased incidence of metronidazole treatment failure, which is associated with cephalosporin use and presence of CDI at hospital admission.

In 3 head-to-head prospective trials, the response rate for metronidazole (90%-95%) was equivalent to that for vancomycin for patients with mild to moderate CDI. Oral administered metronidazole readily achieves high concentrations in the stool of patients with diarrhea, and oral administration is superior to IV administration, although the latter is used when patients present with vomiting or ileus. Short-term use is well tolerated; however, mild nausea and a metallic taste are common, and long-term use may result in peripheral neuropathy. Metronidazole can interfere with the metabolism of warfarin; thus, the international normalized ratio should be monitored in patients receiving anticoagulant therapy. Metronidazole also is not recommended for pregnant women or young children. The addition of rifampin to metronidazole does not improve efficacy.

Tinidazole (Tindamax, Presutti Laboratories, Inc) is a longer-acting analog of metronidazole that has anti- *C. difficile* activity and is FDA-approved for several parasitic infections; however, no clinical studies for the treatment of CDI have been reported.

**Vancomycin.** Oral vancomycin (Vancocin, Viro-Pharma) is first-line therapy for patients who are pregnant and who present with severe disease. Vancomycin has potent activity against *C. difficile* and, except in rare circumstances, is not absorbed when administered orally. Oral vancomycin (125 mg 4 times per day) is equivalent to high-dose oral vancomycin (500 mg 4 times per day) for the treatment of mild to moderate CDI. Oral vancomycin is expensive and although there are concerns it may increase the risk for enteric vancomycin-resistant Enterococcus colonization, it is not clear if that risk is any greater than with metronidazole therapy. Intravenously administered vancomycin does not reach adequate levels in the stool and should not be used for
Rifaximin. Rifaximin (Xifaxan, Salix) is a poorly absorbed derivative of rifampin that is FDA-approved for the treatment of traveler’s diarrhea. In a small, uncontrolled case series, the oral administration of 200 to 400 mg of rifaximin twice per day for 2 weeks following vancomycin therapy prevented the recurrence of CDI in 7 of 8 patients; however, rifaximin resistance developed in one C. difficile isolate.  

Nitazoxanide. Nitazoxanide (Alinia, Romark) is an antiparasitic agent with anti–C. difficile activity that has been approved by the FDA for treatment of cryptosporidiosis and giardiosis. In a randomized controlled trial, the response and recurrence rates of patients who received 500 mg of nitazoxanide twice per day for 7 to 10 days were similar to those of patients given standard-dose metronidazole.  

Other agents. To date, no anti–C. difficile therapies have proved superior to metronidazole or vancomycin for the treatment of mild to moderate CDI. Fidaxomicin (OPT-80, Optimer) is an investigational minimally absorbed antibiotic that appears to be as effective as vancomycin in Phase III testing. Trials of bacitracin, teicoplanin, and fusidic acid have shown these agents to be inferior or equivalent, and none are readily available in oral formulation in the United States.

Management of Severe CDI

The incidence of severe CDI—eg, white blood cell counts greater than 15,000/mm³ or a rise in serum creatinine greater than 50%—is increasing. Severe CDI can lead to electrolyte disturbances, volume depletion with hypotension, renal dysfunction, leukocytosis, toxic megacolon, and death. Early surgical consultation is important because subtotal colectomy with ileostomy may be required for the most severe cases.  

Anecdotal and recent prospective data suggest that oral (or enteral) vancomycin should be considered first-line therapy for severe CDI. Combination therapy can be used, such as 500 mg of vancomycin administered orally or by nasogastric tube every 6 hours, metronidazole administered intravenously, and in some instances where enteral therapy is not possible, vancomycin administered via retention enema. Combination therapy is warranted if the site of infection cannot be reached by conventional therapy. Surgical consultation is warranted in these patients. One observational study suggested that the intracolonic delivery of vancomycin may reduce the need for surgical intervention. Intracolonic vancomycin should not be administered routinely to patients with mild or moderate CDI who can tolerate oral therapy.

Management of Recurrent CDI

Strategies for the management of recurrent CDI differ according to the degree of recurrence (Table 4). After an initial episode of CDI, 15% to 20% of patients have a recurrence within 60 days, and the risk increases to up to 65% in those who have had multiple prior episodes. If recurrence is due to re-exposure to antibiotics, the inciting antibiotic should be discontinued whenever possible; however, specific anti–C. difficile therapy is usually necessary. Second episodes (first recurrences) are treated with the same

### Table 3. Specific Anti–C. difficile Antimicrobial Agents

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<tr>
<th>Recommended</th>
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<tr>
<td>Metronidazole (oral or per tube)</td>
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<tr>
<td>Vancomycin (oral or per tube)</td>
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<tr>
<td><strong>Recommended for severe CDI</strong>b</td>
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<tr>
<td>Metronidazole (IV)</td>
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<tr>
<td>Vancomycin (oral or per tube)</td>
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<tr>
<td>Vancomycin (intracolonic; eg, via retention enema)</td>
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<tr>
<td><strong>Limited or no efficacy data</strong></td>
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<tr>
<td>Nitazoxanide (oral; Alinia for Oral Suspension, Römark)</td>
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<tr>
<td>Rifampin (oral, in conjunction with metronidazole or vancomycin)</td>
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<tr>
<td>Rifaximin (oral; Xifaxan, Salix)</td>
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<tr>
<td>Tinidazole (oral; Tindamax, Presutti Laboratories)</td>
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<tr>
<td><strong>Investigational drugs</strong></td>
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<tr>
<td>Fidaxomicin (formerly difimicin; OPT-80, Optimer)</td>
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<td>Tolevamer (Genzyme)</td>
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* FDA-approved for CDI.  

** Management of Recurrent Or Refractory CDI

<table>
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<th>Anti–C. difficile antibiotic management</th>
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<tr>
<td>Switch from metronidazole to vancomycin</td>
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<tr>
<td>Tapered dosing</td>
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<tr>
<td>Pulsed dosing</td>
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<tr>
<td>Rifaximin</td>
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<tr>
<td><strong>Enhancement of immunity</strong></td>
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<tr>
<td>Passive immunity</td>
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<tr>
<td>IVIG</td>
</tr>
<tr>
<td>Anti–toxin A monoclonal antibodya</td>
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<tr>
<td>Active immunity</td>
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<tr>
<td>Toxoid vaccinea</td>
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* Investigational.

CDI, C. difficile infection; IVIG, intravenous immunoglobulin
regimen as initial episodes (ie, metronidazole or vancomycin for 10-14 days). Treatment of CDI with the investigational drug fidaxomicin was associated with a lower risk for recurrence in a recent Phase III trial comparing it with oral vancomycin.

**Anti--C. difficile Therapy**

Further recurrences of CDI are most often managed with anti--C. difficile antibiotics, usually 125 to 500 mg of vancomycin, in a tapered or pulsed dosing strategy. Pulsed dosing can be used following a standard course of therapy or at the end of a taper. It usually involves the administration of a single dose every 3 days for 2 to 3 weeks. In a retrospective analysis, a lower risk for CDI recurrence was reported in patients who received pulsed or tapered vancomycin than in those who received an untapered vancomycin regimen. The addition of 600 mg of oral rifampin twice daily to an oral vancomycin regimen successfully prevented recurrence in 6 of 7 patients in an uncontrolled study.

**Other Therapies**

Prebiotics (food additives that may enhance the growth of colonic bacteria) and probiotics (microorganisms that have putative health benefits when ingested) have been studied in this setting with mixed results. Anion-binding resins such as colestipol and cholestyramine putatively bind C. difficile toxins and have little effect on the colonic flora, but are generally not recommended because efficacy is equivalent to placebo and they bind some coadministered drugs including vancomycin. The investigational nonabsorbed polymer toleramycin appeared promising in Phase II studies, but was inferior to vancomycin in Phase III testing (37% efficacy in severe disease).

**Conclusion**

The incidence and severity of CDI are increasing, partly because of outbreaks of a hypervirulent strain of C. difficile. Episodes of CDI generally respond rapidly to metronidazole or vancomycin, but recurrence remains a significant problem.

No new agents have proved superior to standard therapies, but recent trials have expanded the available options. Large, prospective trials are still needed to evaluate different dosing regimens of vancomycin for recurrent CDI, to firmly establish or disprove the efficacy of probiotics, and to test new therapies, with an emphasis on reducing recurrences. Prevention efforts should focus on reducing the unnecessary use of antibiotics. The Infectious Disease Society of America/Society for Healthcare Epidemiology in America has published guidelines on antimicrobial stewardship to assist in such efforts.

**References**


33. Miller M, Mullen K, Weiss K, et al. OPT-80 versus vancomycin in *Clostridium difficile* infection: Results of a randomized clinical trial. Abstract (751a) presented at: Digestive Disease Week; June 2, 2009; Chicago, IL.


For a long time, *Clostridium difficile* remained an “orphan” infection, with only 2 common treatment choices (metronidazole and vancomycin). Recent outbreaks of *C. difficile* infections (CDIs) in North America, Europe, and in other areas around the world have been linked to a more virulent, more refractory strain that is associated with greater disease severity. Attributable mortality estimates in Quebec indicate that the risk for death is 3-fold greater with this strain than with CDI occurring prior to 2002, making prompt recognition of cases and optimal management of infection essential for a successful therapeutic outcome. This sharp paradigm shift in CDI has prompted a renewed interest in studying treatment options as well as hope for reduced recurrence rates, a problem that plagues current treatments.

The educational review on the preceding pages provides a topical overview of CDIs that is extremely germane to pharmacists in acute care, long-term care, and outpatient-practices. It is important to know that, with guidelines forthcoming from the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (presented at the joint ICAAC/IDSA meeting in October 2008), there will be a change in treatment practice for patients with severe CDI, to obligatory oral vancomycin.

Data for this change are chiefly based on 2 recent studies demonstrating better outcomes, as explained in the educational review. Furthermore, the manner in which vancomycin is dosed always has been an issue of folklore. Studies of 125 mg every 6 hours versus 500 mg every 6 hours showed that increasing the dose had no benefit with respect to days to resolution of symptoms. In fact, the Kaplan-Meyer plots of days to symptom resolution were superimposable. Furthermore, concentrations of oral vancomycin are so great in relation to the minimum inhibitory concentration values against *C. difficile* that an increase in dose is probably never warranted. However, based on expert opinion, for some severe cases of CDI where ileus or toxic mega-colon are suspected, elevated oral doses have been suggested to perhaps increase penetration to sites of infection (colon). Rare cases of CDI in the small intestine have been noted.

The fact is, CDI no longer is an orphan disease but rather is a burgeoning area of study. This is creating a windfall of opportunity for pharmacists, regardless of practice area. There will be novel treatment options to evaluate for formularies, from drugs to bugs to immunologics. In some instances, evaluation of therapies may require that we think beyond the concept of treatment success; because vancomycin is so efficacious, newer agents are not likely to be superior. However, the ability to arrest the plague of recurrent disease, with relatively non-absorbable limited-spectrum agents, or non-toxigenic *C. difficile* strains, or immunologics, will warrant a close look. Even most bean counters likely will pay for a higher cost drug if reimbursement for care hinges on *C. difficile*; thus, a focus on prevention will prevail not only for clinicians in the trenches, but also in the minds of administrators.

Giving an organism to prevent infection by the organism is another concept that formulary committees may one day have to grapple with (as in the case of attempts to colonize patients with non-toxigenic *C. difficile*). Immunologics, possibly with purified anti-toxins A and B and vaccines, are being evaluated in clinical trials. All are going to converge on the practice of pharmacy in one manner or another.

There also is great opportunity to collaborate with infection control and environmental services colleagues, regarding overall strategies, from prevention to diagnosis to treatment and cycling back to prevention of future episodes. Antimicrobial stewardship, which is a proven approach, should be a component of any multidisciplinary approach to minimizing CDI. Throughout the United States, Canada, and certain European and Asian countries, antimicrobial stewardship programs are being developed and funded more formally. Such antimicrobial stewardship programs, which Dale Gerding, MD, has referred to as akin to “motherhood and apple pie,” have been linked to reductions in CDI in an analysis in the *Cochrane Review*.

As CDI unvels itself, so too do the opportunities for pharmacists to be involved in all aspects of this disease.

**Suggested Readings**


