prompt initiation of specific CDI treatment has become the standard. Empirical treatment is appropriate if CDI is strongly suspected on clinical grounds. General treatment guidelines include hydration and the avoidance of antiperistaltic agents and opiates, which may mask symptoms and possibly worsen disease. Nevertheless, antiperistaltic agents have been used safely with vancomycin or metronidazole for mild to moderate CDI.

Oral administration of vancomycin, fidaxomicin, or metronidazole is recommended for CDI treatment. IV vancomycin is ineffective for CDI, and fidaxomicin is available only for oral administration; when IV metronidazole is administered, fecal bactericidal drug concentrations are achieved during acute diarrhea; however, in the presence of adynamic ileus, IV metronidazole treatment of CDI has failed. Two large clinical trials comparing vancomycin and fidaxomicin indicated comparable resolution of diarrhea (~90% of patients) as well as significantly reduced rates of recurrent CDI with fidaxomicin from rates with vancomycin. In previous randomized trials, diarrhea response rates to oral therapy with vancomycin or metronidazole were ≥94%, but four observational studies found that response rates for metronidazole had declined to 62–78%. Although the mean time to resolution of diarrhea is 2–4 days, the response to metronidazole may be much slower. Treatment should not be deemed a failure until a drug has been given for at least 6 days. On the basis of data for shorter courses of vancomycin and the results of two large-scale clinical trials, it is recommended that vancomycin, fidaxomicin, and metronidazole be given for at least 10 days. Metronidazole is not approved for CDI by the U.S. Food and Drug Administration (FDA), but most patients with mild to moderate illness respond to 500 mg given by mouth three times a day for 10 days; extension of the treatment period may be needed for slow responders. In addition to the reports of increases in metronidazole failures, a prospective, randomized, double-blind, placebo-controlled study has demonstrated the superiority of vancomycin over metronidazole for treatment of severe CDI. The severity assessment score in that study included age as well as laboratory parameters (elevated temperature, low albumin level, or elevated WBC count), documentation of PMC by endoscopy, and treatment of CDI in the intensive care unit. Although a validated severity score is not available, it is important to initiate treatment with oral vancomycin for patients who appear seriously ill, particularly if they have a high WBC count (>15,000/μL) or a creatinine level that is ≥1.5 times higher than the premorbid value **(Table 161-2)**. In addition, a randomized blinded trial compared a toxin-binding polymer, tolevamer, with two antibiotic regimens for treatment of CDI and showed that vancomycin was superior to metronidazole for all patients regardless of severity. Small randomized trials of nitazoxanide, bacitracin, rifaximin, and fusidic acid for treatment of CDI have been conducted. These drugs have not been extensively studied, shown to be superior, or approved by the FDA for CDI, but they provide potential alternatives to vancomycin, fidaxomicin, and metronidazole.

RECURRENT CDI

Overall, ~15–30% of successfully treated patients experience recurrences of CDI, either as relapses caused by the original organism or as reinfections following treatment. Rates of CDI recurrence are significantly lower among patients treated with fidaxomicin rather than vancomycin. Rates of recurrence are comparable with vancomycin and metronidazole. Recurrence rates are higher among patients ≥65 years old, those who continue to take antibiotics while being treated for CDI, and those who remain in the hospital after the initial episode of CDI. Patients who have a first recurrence of CDI have a high rate of second recurrence (33–65%). In the first recurrence, re-treatment with metronidazole is comparable to treatment with vancomycin (Table 161-2), and fidaxomicin is superior to vancomycin in reducing the risk of further recurrences in patients who have had one recurrence. Recurrent CDI, once thought to be relatively mild, has now been documented to pose a significant (11%) risk of serious complications (shock, megacolon, perforation, colectomy, or death within 30 days). There is no standard treatment for multiple recurrences, but long or repeated metronidazole courses should be avoided because of potential neurotoxicity. The use of vancomycin in tapering doses or with pulse dosing every other day for 2–8 weeks may be the most practical approach to treatment of patients with multiple recurrences. Other approaches include the administration of vancomycin followed by the yeast *Saccharomyces boulardii*; the administration of vancomycin followed by a fecal microbiota transplant given via nasoduodenal tube, colonoscope, or enema; and the intentional colonization of the patient with a nontoxigenic

TABLE 161-2 RECOMMENDATIONS FOR THE TREATMENT OF *CLOSTRIDIUM DIFFICILE* INFECTION (CDI)[a]

Clinical Setting	Treatment(s)	Comments
Initial episode, mild to moderate	Metronidazole (500 mg tid × 10–14 d)	Vancomycin (125 mg qid × 10–14 d) may be more effective than metronidazole. Fidaxomicin (200 mg bid × 10 d) is another alternative.
Initial episode, severe	Vancomycin (125 mg qid × 10–14 d)	Indicators of severe disease may include leukocytosis (≥15,000 white blood cells/μL) and a creatinine level ≥1.5 times the premorbid value. Fidaxomicin is an alternative.
Initial episode, severe complicated or fulminant	Vancomycin (500 mg PO or via nasogastric tube) ***plus*** metronidazole (500 mg IV q8h) ***plus consider*** Rectal instillation of vancomycin (500 mg in 100 mL of normal saline as a retention enema q6–8h)	Severe complicated or fulminant CDI is defined as severe CDI with the addition of hypotension, shock, ileus, or toxic megacolon. The duration of treatment may need to be >2 weeks and is dictated by response. Consider using tigecycline (50 mg IV q12h after a 100-mg loading dose) in place of metronidazole.
First recurrence	Same as for initial episode	Adjust treatment if severity of CDI has changed with recurrence. Consider fidaxomicin, which significantly decreases the likelihood of additional recurrences.
Second recurrence	Vancomycin in taper/pulse regimen	Typical taper/pulse regimen: 125 mg qid × 10–14 d, then bid × 1 week, then daily × 1 week, then q2–3d for 2–8 weeks.
Multiple recurrences	Consider the following options: • Repeat vancomycin taper/pulse • Vancomycin (500 mg qid × 10 d) plus *Saccharomyces boulardii* (500 mg bid × 28 d) • Vancomycin (125 mg qid × 10–14 d); then stop vancomycin and start rifaximin (400 mg bid × 2 weeks) • Nitazoxanide (500 mg bid × 10 d) • Fecal microbiota transplantation • IV immunoglobulin (400 mg/kg)	The only controlled studies that included patients with one or more recurrent CDI episodes were with vancomycin and *S. boulardii*, which showed borderline significance compared with vancomycin plus placebo, and fecal microbiota transplantation, which was highly significant compared with a high-dose course of vancomycin. (The vancomycin taper was not compared.)

[a]All agents are given orally unless otherwise specified.