



# *Clostridioides difficile* infection in adults: Treatment and prevention

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## INTRODUCTION

*Clostridioides difficile* infection (CDI) is one of the most common hospital-acquired (nosocomial) infections and is an increasingly frequent cause of morbidity and mortality among older adult hospitalized patients [1-3]. CDI is also increasingly diagnosed in younger patients and in the community. *C. difficile* colonizes the human intestinal tract after the normal gut flora has been disrupted (frequently in association with antibiotic therapy) and is the causative organism of antibiotic-associated colitis including pseudomembranous colitis.

The treatment of CDI in adults, including management of initial disease, recurrent disease, severe disease, and fulminant disease (previously referred to as severe, complicated CDI) will be reviewed here [4].

Issues related to surgical management of CDI are discussed separately. (See "[Surgical management of \*Clostridioides difficile\* colitis in adults](#)".)

The epidemiology, pathophysiology, clinical manifestations, and diagnosis of CDI in adults are discussed separately. (See "[Clostridioides difficile infection in adults: Epidemiology, microbiology, and pathophysiology](#)" and "[Clostridioides difficile infection in adults: Clinical manifestations and diagnosis](#)".)

Issues related to prevention of CDI in individual patients are discussed here; issues related to prevention of CDI in health care and community settings are discussed separately. (See

["Clostridioides difficile infection: Prevention and control".](#))

Issues related to CDI in children are discussed separately. (See ["Clostridioides difficile infection in children: Clinical features and diagnosis"](#) and ["Clostridioides difficile infection in children: Treatment and outcome"](#) and ["Clostridioides difficile infection in children: Microbiology, pathogenesis, and epidemiology"](#).)

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## GENERAL PRINCIPLES

**Infection control** — Patients with suspected or proven CDI should be placed on contact precautions, and health care workers should wash hands before and after patient contact. Hand hygiene with soap and water may be more effective than alcohol-based hand sanitizers in removing *C. difficile* spores, since *C. difficile* spores are resistant to killing by alcohol. Therefore, use of soap and water is favored over (or in addition to) alcohol-based hand sanitization, although thus far, no studies have demonstrated superiority of soap and water in infection control [2,3]. (See ["Clostridioides difficile infection: Prevention and control"](#).)

**Discontinue inciting antibiotic agent(s)** — An important initial step in the treatment of CDI is discontinuation of the inciting antibiotic agent(s) as soon as possible [2,3]. Treatment with concomitant antibiotics (ie, antibiotics other than those given to treat CDI) is associated with prolongation of diarrhea, increased likelihood of treatment failure, and increased risk of recurrent CDI [5-7]. If ongoing antibiotics are essential for treatment of the primary infection, if possible, it may be prudent to select antibiotic agents that are less frequently implicated in antibiotic-associated CDI ( [table 1](#)).

**Management of fluids, nutrition, and diarrhea** — Supportive care with attention to correction of fluid losses and electrolyte imbalances is important.

Patients may have regular, low-residue diet as tolerated (to reduce stool frequency and volume). Since the diarrhea is due to a colonic process, instituting measures such as a lactose-free diet is not required.

Antimotility agents (eg, [loperamide](#), [diphenoxylate-atropine](#)) have traditionally been avoided in CDI, but the evidence that they cause harm is equivocal [3,8,9]. We reserve use of these agents for patients in whom there is difficulty keeping up with fluid losses, in the absence of ileus or colonic distention.

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## MANAGEMENT

## Clinical approach

**Assessing disease severity** — Patients with acute CDI may develop signs of systemic toxicity with or without profuse diarrhea warranting admission to a hospital or an intensive care unit or consideration for emergency surgery. There is no consensus definition for severe or fulminant CDI nor is there agreement as to the most important clinical indicators that should be used to differentiate severity; prospectively validated severity scores for CDI are needed [2,3,10-15].

Proposed criteria for disease severity (based on expert opinion) include [2]:

- Nonfulminant disease:
  - Nonsevere CDI – White blood cell count  $\leq 15,000$  cells/microL and serum creatinine  $< 1.5$  mg/dL
  - Severe CDI – White blood cell count  $> 15,000$  cells/microL and/or serum creatinine  $\geq 1.5$  mg/dL
- Fulminant colitis (previously referred to as severe, complicated CDI) – Hypotension or shock, ileus, or megacolon

For the purposes of the treatment decisions in the following discussion, determination of disease severity is left to clinician judgment and may include any or all of the above criteria. Age  $\geq 65$  years confers increased risk for severe CDI; this and other risk factors are discussed further separately. (See "[Clostridioides difficile infection in adults: Epidemiology, microbiology, and pathophysiology](#)", section on 'Risk factors'.)

**Indications for treatment** — Treatment is warranted for patients with typical manifestations of CDI (acute diarrhea [ $\geq 3$  loose stools in 24 hours] with no obvious alternative explanation) and a positive diagnostic laboratory assay [16,17].

In addition, empiric treatment is reasonable in the setting of very high clinical suspicion for CDI (particularly for patients with symptoms of severe or fulminant colitis), pending results of diagnostic testing [3]. (See "[Clostridioides difficile infection in adults: Clinical manifestations and diagnosis](#)".)

Treatment is not indicated in patients who have a positive diagnostic laboratory assay but do not have diarrhea or other CDI disease manifestations, as asymptomatic carriage is common.

**When to admit to the hospital** — All patients with fulminant CDI should be admitted immediately to the hospital for stabilization, intravenous hydration, and antibiotic

administration. Most patients with mild CDI can be managed in the outpatient setting. However, hospitalization should be considered in patients with severe CDI or in any patient who is frail, shows signs and symptoms of dehydration (eg, low blood pressure, orthostasis, poor urinary output), or who have poor social support and may not be able to call for help if symptoms worsen.

## Nonfulminant disease

### Initial episode

#### Nonsevere disease

- **Clinical approach**

- **Regimen selection** – For patients with an initial episode of nonsevere CDI, appropriate treatment regimens include either oral [fidaxomicin](#) or oral [vancomycin](#); we favor fidaxomicin over vancomycin given a small benefit with respect to recurrence rates, in accordance with 2021 Infectious Diseases Society of America (IDSA) guidelines ([table 2](#)) [1]. Patients at greater risk for recurrence (ie, age >65 years, compromised immunity, severe CDI, or ribotype 027/078/244 infections) may be more likely to benefit from fidaxomicin; however, these subgroups have not been studied prospectively in randomized trials. (See '[Cost considerations](#)' below.)

[Metronidazole](#) is an alternative but less effective agent for treatment of nonsevere CDI if oral [vancomycin](#) and oral [fidaxomicin](#) are not available; however, it should be avoided in patients who are frail, age >65 years, or who develop CDI in association with inflammatory bowel disease [1,18-20]. Intravenous vancomycin is not effective for treatment of CDI since the drug is not excreted appreciably into the colon during short-term systemic administration.

- **Duration of treatment** – The duration of initial antibiotic therapy for treatment of nonsevere CDI is 10 days [2]. Patients with CDI in the setting of another underlying infection requiring prolonged duration of antibiotic therapy are at increased risk for recurrent CDI [7]. In such cases, we typically continue CDI treatment throughout the antibiotic course plus an additional tail of one week after its completion [21,22]. (See '[Prevention](#)' below.)
- **Follow up** – In patients who are recovering or whose symptoms have resolved, repeat stool assays are **not** warranted during or following treatment, as up to 50 percent of

patients have positive stool assays for as long as six weeks after the completion of therapy [23,24].

- **Evidence summary** – The above approach is supported by four randomized trials including 1673 patients with CDI treated with [fidaxomicin](#) or [vancomycin](#) [25-28]; in one of the studies, patients in the fidaxomicin arm received an extended-pulsed regimen rather than a standard regimen [27]. In a pooled analysis of these studies, initial clinical cure was comparable between the groups (risk ratio 1.00, 95% CI 0.96-1.04); clinical cure at four weeks following completion of therapy was observed more frequently among patients treated with fidaxomicin (risk ratio 1.16, 95% CI 1.09-1.24) [1]. There was no difference in mortality (risk ratio 0.90, 95% CI 0.66-1.23) or drug-related adverse events.

Similarly, in an earlier 2017 meta-analysis of 22 randomized trials including 3215 patients with nonsevere CDI treated with oral [vancomycin](#), oral [fidaxomicin](#), and oral [metronidazole](#); for achieving symptomatic cure, fidaxomicin was modestly more effective than vancomycin (71 versus 61 percent; relative risk 1.17, 95% CI 1.04-1.31) [17].

For patients infected with non-NAP1 strains, treatment with [fidaxomicin](#) has been associated with lower CDI recurrence rate [25,29,30]. However, no difference in recurrence rates has been observed among patients infected with NAP1 strains [25]. (See "[Clostridioides difficile infection in adults: Epidemiology, microbiology, and pathophysiology](#)", section on 'PCR ribotype 027 strain'.)

- **Effect on microbiome** – Thus far, minimal alteration of the microbiome has been observed with [fidaxomicin](#) [31,32]. The risk of bowel colonization with vancomycin-resistant enterococci associated with [vancomycin](#) and [metronidazole](#) use is comparable and likely higher than with fidaxomicin use [33-36].
- **Metronidazole failure** – Use of [metronidazole](#) has been associated with higher rates of treatment failure in observational and retrospective studies [37,38]. The reasons for metronidazole failure are poorly understood [39,40]. One factor may be that stool drug levels in patients taking oral metronidazole (which is well absorbed) decrease as colonic inflammation subsides, whereas stool drug levels in patients taking oral [vancomycin](#) or [fidaxomicin](#) (which are poorly absorbed or not absorbed) remain high throughout the course of therapy [41,42]. Age >65 years may be another factor associated with risk for metronidazole failure [43].

**Severe disease** — Management of severe disease (see '[Assessing disease severity](#)' above) consists of antibiotic therapy, supportive care, and close monitoring; in addition, patients

should be assessed for surgical indications. Further study is warranted to better determine the role of fecal microbiota transplantation (FMT) in treatment of severe CDI.

- **Antibiotic therapy**

- **Regimen selection** – For patients with an initial episode of severe CDI, we suggest oral [fidaxomicin](#) over oral [vancomycin](#), in accordance with 2021 IDSA guidelines ( [table 2](#)) [1]. Fidaxomicin cost considerations are discussed below. (See '[Cost considerations](#)' below.)

Both [fidaxomicin](#) and [vancomycin](#) may be administered with standard dosing or in an extended-pulsed regimen, as summarized in the table [44,45]. Given lack of data, we do not favor use of [tigecycline](#) for treatment of *C. difficile* colitis.

- **Monitoring during treatment** – In patients with mucosal disruption due to severe or fulminant colitis, systemic absorption of enteral [vancomycin](#) can occur; this consideration is particularly important for patients with renal insufficiency (creatinine clearance <10 mL/minute) [2,46,47]. We favor monitoring serum vancomycin levels for patients with renal failure who have severe colitis and require a prolonged course (>10 days) of enteral vancomycin therapy.

**Duration of treatment** – The standard duration of antibiotic therapy (with either [vancomycin](#) or [fidaxomicin](#)) for an initial CDI episode is 10 days; however, the duration of the antibiotic course should be individualized for patients with severe disease depending on response to therapy and clinical course. Patients with an underlying infection requiring prolonged antibiotic administration should continue CDI treatment throughout the antibiotic course plus one additional week after its completion. (See '[Prevention](#)' below.)

- **Evidence summary** – The above approach is supported indirectly by data from studies of patient with nonsevere disease, as summarized above. (See '[Nonsevere disease](#)' above.)

Studies in patients with severe disease are more limited than in patients with mild to moderate disease but support the use of [fidaxomicin](#) or [vancomycin](#) over [metronidazole](#) for severe CDI [10,48,49]. Metronidazole is not recommended for severe CDI.

The treatment outcomes achieved with standard dosing of [vancomycin](#) (125 mg four times daily) are likely equivalent to those achieved with higher dosing (500 mg four

times daily) [23].

Data on the comparative efficacy of [fidaxomicin](#) and [vancomycin](#) in severe disease are limited. In one retrospective study including more than 850 patients with severe CDI treated with fidaxomicin or vancomycin, clinical outcomes were similar (combined clinical failure or recurrence 32 versus 26 percent) and mortality (11 versus 12 percent at 30 days) [50].

- **Role of fecal transplant** – FMT has been used in patients with severe and fulminant colitis as an alternative to colectomy and has been associated with reductions in mortality in retrospective and observational studies; however, prospective randomized studies comparing FMT with colectomy are needed to determine whether there is a role for routine use of FMT in treatment of severe and fulminant CDI [2,3,51-53].

In a retrospective study including 111 hospitalized patients with CDI (of whom 66 underwent FMT), use of FMT was associated with improved survival among patients with severe disease (odds ratio [OR] 0.08, 95% CI 0.016-0.34) [54]. In a cohort study including 57 patients with severe or fulminant CDI treated with FMT, the cure rate among 19 patients with severe CDI was 100 percent; cure rates among 33 patients with fulminant CDI were 87 percent [55]. Similarly, in a retrospective study including 48 patients hospitalized in the ICU with severe or fulminant CDI, use of FMT was associated with a mortality benefit over standard of care (OR 0.23, 95% CI 0.06-0.97) [56]. In another study including 199 patients with severe or fulminant CDI, implementation of an FMT program was associated with a reduction in mortality rate (10.2 to 4.4 percent) and colectomy rate (6.8 to 2.7 percent) [57].

FMT instillations should be administered via colonoscope, since a larger volume of stool can be instilled into the colon than via oral capsule administration [58]. In addition, the possibility of a concomitant atonic colon or ileus may prevent orally administered fecal material from reaching the colon. Multiple stool infusions may be more effective than a single infusion [58,59]. Issues related to FMT are discussed further separately. (See "[Fecal microbiota transplantation for treatment of \*Clostridioides difficile\* infection](#)".)

- **Surgery** - Early surgical consultation is warranted for patients with CDI who meet one or more of the following clinical indicators that have been associated with poor prognosis ( [table 3](#)) [60-65]:
  - Hypotension
  - Fever  $\geq 38.5^{\circ}\text{C}$
  - Ileus or significant abdominal distention
  - Peritonitis or significant abdominal tenderness



- Altered mental status
- White blood cell count  $\geq 20,000$  cells/microL
- Serum lactate levels  $> 2.2$  mmol/L
- Admission to intensive care unit
- End organ failure (eg, requiring mechanical ventilation, renal failure)
- Failure to improve after three to five days of maximal medical therapy

Toxic megacolon should be suspected if the patient develops abdominal distention with diminution of diarrhea; this may reflect paralytic ileus resulting from loss of colonic muscular tone [66]. (See "[Toxic megacolon](#)".)

Earlier surgical consultation facilitates timely operative management if a patient's clinical course worsens. Several studies have demonstrated or implied that in patients who undergo surgery for *C. difficile* colitis, timely surgical management improves outcomes [60-63]. Early surgical consultation for severe or complicated CDI has been advocated by multiple society guidelines [3,64,67-69].

Issues related to surgical management of CDI are discussed further separately. (See "[Surgical management of Clostridioides difficile colitis in adults](#)".)

**Recurrent episode** — Recurrent CDI is defined by resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms, usually within two months of discontinuing treatment [2]. Approach to recurrent CDI caused by relapse or by reinfection are the same. (See "[Clostridioides difficile infection in adults: Clinical manifestations and diagnosis](#)", section on 'Recurrent disease'.)

The approach to antibiotic management of nonfulminant recurrent CDI is the same regardless of severity, but varies depending on the number of recurrences, as discussed below ( [table 2](#)).

For patients with a recurrent episode of CDI that is severe, considerations regarding surgery and FMT are as discussed above. (See '[Severe disease](#)' above.)

**First recurrence** — Management of a first CDI recurrence consists of antibiotic therapy. In addition, for patients with prior CDI within the last six months, we suggest adjunctive use of [bezlotoxumab](#) (if available and cost considerations allow for its use), in accordance with 2021 IDSA guidelines ( [table 2](#)) [1] (see '[Cost considerations](#)' below). The use of commercially available [fecal microbiota encapsulated spores](#) (Vowst; oral capsules) and the use of a rectal suspension (Rebyota) have also been approved by the US Food and Drug Administration to prevent further recurrences in patients with at least one recurrence of CDI [70,71]. However, they are not widely available yet, and we await more data comparing them to conventional FMT



and bezlotoxumab before adopting their use. (See "[Fecal microbiota transplantation for treatment of \*Clostridioides difficile\* infection](#)", section on 'FMT products'.)

- **Antibiotic treatment**

- **Regimen and duration** – For patients with a first recurrence of CDI, we favor [fidaxomicin](#) over [vancomycin](#), in accordance with 2021 IDSA guidelines [1]. Cost considerations are discussed below. (See '[Cost considerations](#)' below.)

These agents may be administered with standard dosing or in an extended-pulsed regimen, as summarized in the table ( [table 2](#)). The rationale for use of a pulsed regimen is based on the hypothesis that this approach may facilitate a gradual return of the normal colonic microbiome and/or allow treatment of vegetative *C. difficile* released by persistent fecal spores.

The duration of antibiotic therapy depends on the regimen selected, as summarized in the table ( [table 2](#)). For patients with CDI in the setting of another underlying infection requiring prolonged duration of antibiotic therapy, we typically continue CDI treatment throughout the antibiotic course plus an additional tail of one week after its completion [21,22]. (See '[Prevention](#)' below.)

- **Evidence summary**

- **Fidaxomicin** – Use of [fidaxomicin](#) for treatment of recurrent CDI is supported by subgroup analysis from three randomized trials including 253 patients with recurrent CDI treated with fidaxomicin or [vancomycin](#) [25-27,29]. In a pooled subgroup analysis, initial clinical cure was comparable between the groups (risk ratio 1.03, 95% CI 0.94-1.14); clinical cure at 30 days following completion of therapy was observed more frequently among patients treated with fidaxomicin (risk ratio 1.27, 95% CI 1.05-1.54) [1]. There was no difference in mortality (risk ratio 0.81, 95% CI 0.20-3.38) or drug-related adverse events.

Use of extended-pulsed [fidaxomicin](#) dosing is supported by a randomized trial including 364 patients hospitalized with CDI who were randomly assigned to receive extended-pulsed fidaxomicin (200 mg oral tablets, twice daily on days 1 to 5, then once daily on alternate days on days 7 to 25) or [vancomycin](#) (125 mg oral capsules, four times daily for 10 days) [27]. Clinical cure at 30 days following completion of therapy was observed more frequently among patients treated with extended-pulsed fidaxomicin (70 versus 59 percent; odds ratio 1.62, 95% CI 1.04-2.54). Recurrent CDI rates were 2 percent in patients receiving extended-pulsed

fidaxomicin and 17 percent in those treated with vancomycin. In a separate investigation, tapered-pulsed fidaxomicin was used to treat 46 patients who had failed prior treatment by tapered-pulsed vancomycin [72]. Sustained clinical response rates at 30 and 90 days were 74 percent and 61 percent, respectively.

- **Pulse-tapered oral vancomycin** – Use of pulse-tapered oral [vancomycin](#) for treatment of recurrent CDI is supported by small retrospective studies [24,73-76]. In one nonrandomized study of 163 patients with recurrent CDI, 29 patients were treated with a vancomycin-tapered regimen and 7 were treated with a vancomycin-pulsed regimen; recurrence rates were 31 and 14 percent, respectively, compared with a recurrence rate of 45 percent for other regimens [24]. In another study, 12 patients with recurrent CDI were treated with a vancomycin-tapered regimen; the recurrence rate was 41 percent [74].

- **Use of bezlotoxumab** – [Bezlotoxumab](#), a humanized monoclonal antibody that binds to C. difficile toxin B, received US Food and Drug Administration approval in 2016 [77]. Bezlotoxumab is given as a one-time infusion, during administration of a standard treatment regimen ( [table 2](#)); it should be used with caution in patients with congestive heart failure.

In two randomized trials including more than 2500 patients with CDI, administration of [bezlotoxumab](#) together with standard treatment was associated with a lower rate of recurrent CDI than standard treatment alone (17 versus 28 percent in the first trial; similar findings in the second trial) [78]. Most patients received treatment with [vancomycin](#); if [fidaxomicin](#) is used for treatment of initial or recurrent CDI, the utility of bezlotoxumab is currently unknown. Addition of bezlotoxumab was associated with a reduction in CDI recurrence at 12 weeks (risk ratio 0.62, 95% CI 0.51-0.75) and reduction in hospital readmission at 30 days (risk ratio 0.46, 95% CI 0.29-0.71), but no reduction in mortality was observed [1].

In a post-hoc subgroup analysis including patients with one or two episodes of CDI within the last six months, the pooled risk difference with [bezlotoxumab](#) was -17.4 percent (95% CI -27.5 to -7.3) [1,79]. Most participants (76 percent) had  $\geq 1$  risk factor; these included age  $\geq 65$  years, history of severe CDI, immunocompromise, and infection with ribotype 027/078/244. In the setting of at least three risk factors for CDI recurrence, bezlotoxumab reduced the recurrence risk by approximately 25 percent; in the setting of one or two risk factors for recurrence or  $\geq 1$  prior episodes of recurrent CDI, bezlotoxumab reduced the recurrence risk by approximately 15 percent. In the absence of risk factors for recurrence, bezlotoxumab provided no additional benefit over antibiotic therapy alone.

**Second or subsequent recurrence** — Management of a second CDI recurrence consists of antibiotic therapy. In addition, for patients with prior CDI within the last six months, we suggest adjunctive use of [bezlotoxumab](#), in accordance with 2021 IDSA guidelines [1]. Cost considerations are discussed below. (See '[Cost considerations](#)' below.)

For patients who have received appropriate antibiotic treatment for at least three CDI episodes (ie, initial episode plus two recurrences), who subsequently present with a fourth or further episode (third or subsequent recurrence), we favor FMT in regions where available [1,2]. However, some favor FMT for patients who have received antibiotic treatment for at least two CDI episodes (ie, initial episode plus one recurrence) [3]. Pending referral for FMT, we treat with antibiotic therapy ( [table 2](#)). (See "[Fecal microbiota transplantation for treatment of \*Clostridioides difficile\* infection](#)".)

For patients with a third or subsequent CDI recurrence who are unable to undergo FMT, management consists of antibiotic therapy (in addition to adjunctive use of [bezlotoxumab](#) for patients with prior CDI within the last six months) [1]. Following completion of a treatment regimen, we favor use of suppressive oral [vancomycin](#) in some circumstances [3]. Cost considerations are discussed below. (See '[Cost considerations](#)' below.)

- **Antibiotic treatment**

- **Regimen and duration** – For patients with a second or subsequent CDI recurrence, we favor a fidaxomicin-based regimen over a vancomycin-based regimen, in accordance with 2021 IDSA guidelines ( [table 2](#)) [1]. Cost considerations are discussed below. (See '[Cost considerations](#)' below.)

The duration of antibiotic therapy depends on the regimen selected, as summarized in the table ( [table 2](#)). For patients with CDI in the setting of another underlying infection requiring prolonged duration of antibiotic therapy, we typically continue CDI treatment throughout the antibiotic course plus an additional tail of one week after its completion [21,22]. (See '[Prevention](#)' below.)

- **Evidence summary** – Data supporting use of [fidaxomicin](#) and [vancomycin](#) for treatment of recurrent CDI are described above. (See '[First recurrence](#)' above.)

Use of [vancomycin](#) followed by [rifaximin](#) has been evaluated in two small studies [80,81]. In one series, eight women with recurrent CDI received a two-week course of rifaximin when they were asymptomatic, immediately after completing their last course of vancomycin. Seven patients had no further recurrence of infection [80].

- **Use of bezlotoxumab** – Data supporting use of [bezlotoxumab](#) for treatment of recurrent CDI are described above. (See '[First recurrence](#)' above.)

- **Fecal transplantation (FMT)**

- **Approach** – FMT consists of administering stool microbiota into the intestinal tract of a patient with recurrent CDI. The use of commercially available [fecal microbiota encapsulated spores](#) (Vowst; oral capsules) and the use of a [fecal microbiota rectal suspension](#) (Rebyota) have been approved by the US Food and Drug Administration to prevent further recurrences in patients with at least one recurrence of CDI [70,71]. However, they are not widely available yet, and we await more data comparing them to conventional FMT and [bezlotoxumab](#) before adopting their use (see "[Fecal microbiota transplantation for treatment of \*Clostridioides difficile\* infection](#)", section on '[FMT products](#)'). We avoid FMT in immunocompromised patients and patients with inflammatory bowel disease [58].

Risks associated with FMT include procedural complications and transmission of infection. Issues related to pretreatment evaluation and administration of FMT are discussed separately. (See "[Fecal microbiota transplantation for treatment of \*Clostridioides difficile\* infection](#)", section on '[Adverse events and complications](#)'.)

Given higher failure rates with traditional oral FMT administration compared with colonoscopy, for patients who have undergone oral FMT administration and present with CDI recurrence within eight weeks, we suggest repeat FMT with colonoscopy [3]. For patients with further recurrence despite two FMTs or who are not candidates for FMT, we administer an antibiotic treatment regimen ( [table 2](#)) followed by suppressive oral [vancomycin](#) (125 mg orally once daily) to reduce the risk of further recurrence [3]. (See "[Fecal microbiota transplantation for treatment of \*Clostridioides difficile\* infection](#)", section on '[Delivery routes and efficacy](#)'.)

- **Evidence summary** – The efficacy of FMT for management of recurrent CDI has been evaluated in randomized controlled and open-label trials; cure rates range from 70 to 90 percent within a follow-up period ranging from 10 to 18 weeks [74,82-86]. In one meta-analysis of 320 participants from six randomized trials comparing FMT with placebo or antibiotics, the weighted pooled cure rate was higher for FMT compared with the control (77 versus 40 percent; RR 1.92, 95% CI 1.36-2.71) [87]. Another meta-analysis of randomized trials showed similar findings (68 cure rate for FMT versus 44 percent cure rate for the comparator) [88].

- **Use of suppressive vancomycin**

- **Approach** – For patients who are not FMT candidates, we suggest use of suppressive oral [vancomycin](#) following completion of antibiotic treatment [3]; patients most likely to benefit are those at greatest risk for CDI recurrence (eg patients ≥65 years, patients with history of severe CDI, or immunosuppressed patients).

In such cases, we administer [vancomycin](#) (125 mg orally once daily) for six to eight weeks with close follow-up. Some patients continue to experience loose stools at this dose; in such cases, twice daily or three-times daily dosing is reasonable. Suppressive vancomycin may be continued indefinitely for patients in whom recurrent CDI may be life threatening.

- **Evidence summary** – This approach is supported by a small retrospective study including 20 patients with recurrent CDI who were not FMT candidates or who relapsed after FMT [89]. Patients were treated with oral [vancomycin](#) for a minimum of eight weeks; during 200 patient-months of follow-up, one case of relapse occurred; among those who stopped suppressive vancomycin, 31 percent relapsed within six weeks.

[Fidaxomicin](#) might be useful for long-term suppressive use; thus far, data are not available.

**Cost considerations** — In the setting of cost constraints, we prioritize use of [fidaxomicin](#), [bezlotoxumab](#), and suppressive oral [vancomycin](#) for patients at greatest risk for CDI recurrence (eg age ≥65 years, history of severe CDI, or immunosuppression) [1]. In the United States, there is an increasing acceptance among commercial and governmental payers to pay for the cost of fidaxomicin [90]. Detailed discussion of cost considerations for each agent is out of the scope of this topic. (See "[Clostridioides difficile infection in adults: Epidemiology, microbiology, and pathophysiology](#)", section on 'Risk factors'.)

**Fulminant colitis** — Management of fulminant colitis (see '[Assessing disease severity](#)' above) consists of antibiotic therapy, supportive care, and close monitoring; in addition, patients should be assessed for surgical indications. Some favor FMT in some circumstances.

**Antibiotic therapy** — The approach to antibiotic therapy depends on whether concomitant ileus is present.

**Absence of ileus** — For treatment of patients with fulminant colitis but without ileus, we suggest oral (or per nasogastric tube) [vancomycin](#) (500 mg four times daily) plus parenteral [metronidazole](#) (500 mg every 8 hours) ( [table 2](#)) [2,3,13,91].

We do not use [fidaxomicin](#) or [bezlotoxumab](#) in fulminant disease given lack of evidence and experience with these agents in these settings.

There are no data comparing [vancomycin](#) dosing; in this life-threatening situation with concern about intestinal motility and delivery to the site of infection, higher doses of vancomycin are conventional [1].

The rationale for use of parenteral [metronidazole](#) is that there may be delayed passage of oral [vancomycin](#) from the stomach to the colon. Therapeutic stool metronidazole concentrations can be achieved with intravenous metronidazole because of biliary and intestinal excretion of the drug [41,92,93]. Use of parenteral metronidazole is supported by a retrospective study including 88 critically ill patients (of whom 44 received parenteral metronidazole in addition to oral vancomycin, and the remainder received oral vancomycin monotherapy); a lower mortality rate was observed among those who received dual therapy (36 versus 16 percent) [92]. However, in a subsequent retrospective study including 525 patients with fulminant CDI, there was no association between dual therapy and death, colectomy within 90 days, or CDI recurrence [94].

### **With concomitant ileus**

- **Clinical approach** - For patients with concomitant ileus (or another condition preventing oral [vancomycin](#) from reaching the colon), the approach to antibiotic therapy is the same as for patients with no concomitant ileus, as discussed in the preceding section. (See '[Absence of ileus](#)' above.)

Additional considerations include addition of [vancomycin](#) (administered rectally) or FMT (administered retrograde via enema or antegrade via loop colostomy). However, these interventions are associated with risk of colonic perforation; therefore, they should be restricted to patients who are unresponsive to standard therapy and the procedure should be performed by personnel with appropriate expertise [3,95-97]:

- If FMT is available, we suggest its use rectally or via loop colostomy over rectal [vancomycin](#) given greater likelihood of benefit. (See '[Role of fecal transplant](#)' below.)
- If rectal [vancomycin](#) is given, it is administered in addition to oral vancomycin (since it can be difficult to determine whether ileus is partial or complete) [3,95-97].

The optimal dosing of rectal [vancomycin](#) has not been established by clinical trials, and case descriptions vary widely. It is often given as a retention enema (500 mg in 100 mL of normal [saline](#); retained for as long as possible and readministered every six hours). As discussed for severe disease above, the duration of therapy is generally at least 10 days



but should be individualized to the clinical course; if recovery is delayed, the duration can be extended to 14 days.

- **Monitoring during treatment** - In patients with mucosal disruption due to severe or fulminant colitis, systemic absorption of enteral [vancomycin](#) can occur; this consideration is particularly important for patients with renal insufficiency (creatinine clearance <10 mL/minute) [2,46,47]. We favor monitoring serum vancomycin levels for patients with renal failure who have severe or fulminant colitis and require a prolonged course (>10 days) of enteral vancomycin therapy. Intravenous vancomycin has no effect on *C. difficile* colitis since vancomycin is not excreted into the colon.
- **Evidence summary**
  - **Oral vancomycin** – Data supporting use of oral [vancomycin](#) for fulminant colitis is based on evidence in severe disease. (See '[Severe disease](#)' above.)
  - **Rectal vancomycin** – Reports in the literature of the use of rectal [vancomycin](#) for CDI are limited [2,95,96,98,99]. In one case series including nine patients with refractory symptoms, toxic megacolon, or fulminant colitis, rectal vancomycin was administered in addition to standard antibiotics; eight patients had complete resolution of symptoms and one patient died from multisystem organ failure [95].
  - **Parenteral metronidazole** – Data supporting use of parenteral [metronidazole](#) for fulminant colitis are described above. (See '[Absence of ileus](#)' above.)

**Role of fecal transplant** — The circumstances in which FMT is most likely to be beneficial are uncertain; data on use of FMT for management of fulminant CDI are limited to retrospective and observational studies. (See '[Second or subsequent recurrence](#)' above.)

Among patients with fulminant disease, situations in which we consider FMT include [58]:

- Patients with recurrent infection that is fulminant.
- Patients with fulminant disease and concomitant ileus (or another condition preventing oral [vancomycin](#) from reaching the colon); in such cases, we favor FMT (administered rectally or via loop colostomy) in addition to antibiotic therapy. (See '[Antibiotic therapy](#)' above.)
- Patients with fulminant disease not improving after three to five days of medical therapy.



For patients with fulminant disease, we favor administration of FMT in a reduced volume via enema (100 mL every six hours) ( [table 2](#)). Issues related to FMT are discussed further separately. (See "[Fecal microbiota transplantation for treatment of \*Clostridioides difficile\* infection](#)".)

**Surgery** — Considerations regarding surgery for patients with fulminant colitis are the same as those for patients with severe disease, as discussed above ( [table 3](#)). (See '[Severe disease](#)' above.)

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## ALTERNATIVE THERAPIES

Other therapeutic options for CDI are discussed below; based on available data, none warrants routine use for management of CDI [[100](#)].

- **Probiotics** – We do not favor adjunctive administration of probiotics for treatment of CDI, in agreement with society guidelines [[3](#)]. Limitations of the available data include differences in probiotic formulations studied, duration of probiotic administration, definitions of CDI, duration of study follow-up, and inclusion of patients not typically considered at high risk for CDI [[101-103](#)].
- **Alternative antibiotics** – A meta-analysis of 22 studies including more than 3200 participants evaluated several alternative antibiotics for treatment of CDI, including [fusidic acid](#), [nitazoxanide](#), teicoplanin, [rifampin](#), [rifaximin](#), [bacitracin](#), cadazolid, LFF517, and surotomycin; no single agent was clearly superior [[17](#)]. Combination therapy has been tried without success [[104](#)]. Nitazoxanide may be as effective as [vancomycin](#) (as suggested by a randomized trial of 50 CDI patients), although the small sample precluded conclusions about noninferiority of nitazoxanide to vancomycin [[105](#)]. Teicoplanin may be at least as effective as vancomycin or [metronidazole](#), although it is costly and is not available in the United States [[106,107](#)].

Ridinilazole is an investigational antimicrobial agent restricted to the gastrointestinal tract. In a phase 3 randomized, double-blinded trial that included over 700 adults with CDI, oral ridinilazole (200 mg twice a day for 10 days) achieved a similar sustained clinical response rate (defined as clinical cure at the end of treatment and no recurrence within 30 days) as [vancomycin](#) (73 versus 71 percent) and a lower rate of recurrent CDI (8 versus 17 percent, 95% CI -14% to -4.5%) [[108](#)]. It is unknown how ridinilazole compares to [fidaxomicin](#).

- **Intravenous immune globulin (IVIG)** – IVIG contains anti-*C. difficile* antibodies and has been used in some patients with relapsing or severe *C. difficile* colitis. Although there are

case reports suggesting IVIG may be a useful addition to antibiotic therapy for refractory CDI [109-111], a retrospective review of 18 patients who received IVIG demonstrated no significant difference in clinical outcomes compared with 18 matched control cases [112].

- **Anion-binding resins** – Tolevamer is a *C. difficile* toxin-binding resin developed specifically for CDI [113]. Preliminary studies with tolevamer showed promising results, although subsequent large trials have found it to be inferior to both [vancomycin](#) and [metronidazole](#) as primary therapy for CDI [48]. Similarly, the anion-binding resins [colestipol](#) and [cholestyramine](#) are not effective as primary therapy for *C. difficile* colitis [114,115].

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## PREVENTION

Issues related to prevention of CDI in individual patients are discussed below; issues related to prevention of CDI in health care and community settings are discussed separately. (See "[Clostridioides difficile](#) infection: Prevention and control".)

**Primary prevention** — Strategies for preventing an initial episode of CDI include:

- Minimizing antibiotic use (see "[Clostridioides difficile](#) infection: Prevention and control", section on 'Antibiotic stewardship' and "[Clostridioides difficile](#) infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'Antibiotic use')
- Avoiding gastric acid suppression (see "[Clostridioides difficile](#) infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'Gastric acid suppression')

Primary prophylaxis with oral [vancomycin](#) may be of benefit in patients at high risk for CDI. In a randomized open-label trial of 100 hospitalized patients determined to be at high risk for a first episode of CDI (age ≥60 years who had received systemic antibiotics during a prior hospitalization within 30 days and were receiving antibiotics during the current hospitalization), vancomycin (125 mg daily) reduced the rate of CDI during the hospitalization compared with no prophylaxis (zero versus six cases) [116]. Two patients in the no-prophylaxis group developed recurrent CDI after discharge from the hospital; no cases occurred after discharge in the vancomycin prophylaxis group. No new vancomycin-resistant *Enterococcus* colonization was found in those patients receiving prophylaxis. Larger prospective studies are warranted prior to determining the role of primary prophylaxis in CDI.

In patients undergoing hematopoietic cell transplantation with concomitant antibiotic administration, prophylaxis (with oral [vancomycin](#) or [fidaxomicin](#)) may also be useful for prevention of CDI [117,118]; further study is needed.

In addition, vaccination is an area of investigation for prevention of CDI. Several studies have shown that the host humoral immune response to *C. difficile* toxins A and B influences the clinical course of CDI as well as the risk of relapse [109,119-123].

We do not favor administration of probiotics for prevention of CDI, in agreement with society guidelines [2,3]. There are multiple studies of various probiotics for CDI prevention; the data are highly inconsistent [102,103,124-130]. An important flaw of the meta-analyses is that they erroneously refer to "probiotics" as a single entity; however, no single probiotic agent has shown reliable or reproducible efficacy for prevention of CDI (even *Saccharomyces boulardii* or *Lactobacillus* GG, which are the best studied).

**Secondary prevention** — Strategies for preventing a recurrent episode of CDI include those summarized above for preventing an initial episode of CDI.

Additional strategies include:

- **Use of secondary prophylaxis during concomitant antibiotic use** – For patients at increased risk for recurrence (patients  $\geq 65$  years of age or patients with significant immunocompromise who were hospitalized for severe CDI within the past three months) who require ongoing treatment with systemic antibiotics, we administer oral *vancomycin* (125 mg orally once daily) for the duration of antibiotic treatment plus an additional tail of one week [3]. *Metronidazole* should not be used for secondary prophylaxis because of its dose-dependent association with peripheral neuropathy. Data on *fidaxomicin* use in secondary prophylaxis are not yet available.

This approach is supported by a retrospective study including 172 patients with at least two prior CDI episodes subsequently started on other antibiotics, prophylactic oral *vancomycin* was associated with a lower likelihood of yet another recurrence (54 versus 70 percent); prophylaxis made no difference in recurrence rates among 379 patients with only one prior CDI episode [21]. In a subsequent retrospective study of over 750 patients who had at least one prior episode of CDI and received courses of systemic antibiotics, prophylactic oral *vancomycin* was not associated with an overall difference in recurrences of CDI [131]. However, among the subset of patients with only one prior episode of CDI, relapses were less frequent at 90 days with prophylactic *vancomycin*. Hence, data on the utility of oral *vancomycin* in reducing CDI recurrence in patients on systemic antibiotic therapy are conflicting.

- **Gastrointestinal colonization by nontoxigenic *C. difficile* strains** – Gastrointestinal colonization by nontoxigenic *C. difficile* strains has been shown to prevent CDI with exposure to a toxigenic strain [132-134]; further study of this approach is needed. In a

randomized trial including 173 patients who recovered following treatment of CDI with [metronidazole](#) or [vancomycin](#), administration of nontoxigenic *C. difficile* strain M3 was associated with a lower rate of recurrent CDI (recurrence rate 11 versus 30 percent; odds ratio 0.28, 95% CI 0.11-0.69; p = 0.006) [[134](#)].

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## SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "[Society guideline links: \*Clostridioides difficile\* infection](#)".)

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## INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5<sup>th</sup> to 6<sup>th</sup> grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10<sup>th</sup> to 12<sup>th</sup> grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or email these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "[Patient education: \*C. difficile\* infection \(The Basics\)](#)")
  - Beyond the Basics topic (see "[Patient education: Antibiotic-associated diarrhea caused by \*Clostridioides difficile\* \(Beyond the Basics\)](#)")
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## SUMMARY AND RECOMMENDATIONS

- **General principles** – General principles in the treatment of *Clostridioides difficile* infection (CDI) include discontinuation of the inciting antibiotic agent(s), and implementation of infection control practices including contact precautions and hand hygiene. Use of soap

and water may be more effective than alcohol-based hand sanitizers in removing *C. difficile* spores, which are resistant to killing by alcohol. (See '[General principles](#)' above.)

- **Assessing disease severity** – There are no consensus definitions for severe CDI. Determination of disease severity may include the following criteria (see '[Assessing disease severity](#)' above):

- Nonfulminant disease:
  - Nonsevere CDI – White blood cell count  $\leq 15,000$  cells/microL and serum creatinine  $< 1.5$  mg/dL
  - Severe CDI – White blood cell count  $> 15,000$  cells/microL and/or serum creatinine  $\geq 1.5$  mg/dL
- Fulminant colitis – Hypotension or shock, ileus, or megacolon

- **Nonfulminant disease**

- **Initial episode** – For patients with an initial episode of CDI (regardless of severity), we suggest [fidaxomicin](#) over [vancomycin](#) ( [table 2](#)) (**Grade 2C**), given a small benefit with respect to recurrence rates. Patients with severe CDI also warrant assessment for surgical indications ( [table 3](#)). (See '[Initial episode](#)' above.)
- **Recurrent episodes** – Recurrent CDI is defined by resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms within two months of discontinuing treatment. The management approach varies depending on the number of recurrences (see '[Recurrent episode](#)' above):
  - For patients with a first or second CDI recurrence, we suggest a fidaxomicin-based regimen over a vancomycin-based regimen (**Grade 2C**). These agents may be administered with standard dosing or in an extended-pulsed regimen ( [table 2](#)). In addition, for patients with prior CDI within the last six months, we suggest adjunctive use of [bezlotoxumab](#) (**Grade 2C**). (See '[First recurrence](#)' above and '[Second or subsequent recurrence](#)' above.)
  - For patients with a third or subsequent CDI recurrence, we suggest fecal microbiota transplantation (FMT) in settings where available (**Grade 2B**). For patients who are not FMT candidates, treatment consists of medical management as for second recurrence ( [table 2](#)); following completion of treatment, we suggest use of suppressive oral [vancomycin](#) (**Grade 2C**). (See '[Second or](#)

subsequent recurrence' above and "[Fecal microbiota transplantation for treatment of \*Clostridioides difficile\* infection](#)".)

- **Cost considerations** – In the setting of cost constraints, we prioritize use of [fidaxomicin](#), [bezlotoxumab](#), and suppressive oral [vancomycin](#) for patients at greatest risk for recurrent CDI (eg age  $\geq 65$  years, history of severe CDI, or immunosuppression). (See '[Cost considerations](#)' above.)
- **Fulminant colitis** – Management of fulminant colitis consists of antibiotic therapy and assessment for surgical indications ( [table 3](#)); further study of the role of FMT in treatment of fulminant CDI is needed. For treatment of fulminant colitis, we suggest oral [vancomycin](#) plus parenteral [metronidazole](#) ( [table 2](#)) (**Grade 2C**).

In the setting of ileus, we suggest addition of FMT (administered via enema), rather than rectal [vancomycin](#) (**Grade 2C**). However, given risk of colonic perforation, this approach should be restricted to patients who are not responsive to standard antibiotic therapy and performed only by personnel with appropriate expertise. (See '[Fulminant colitis](#)' above.)

- **Prevention**

- For patients at increased risk for recurrent CDI (age  $\geq 65$  years, history of severe CDI, or immunosuppression) who require ongoing treatment with systemic antibiotics, we suggest secondary prophylaxis with oral [vancomycin](#) (**Grade 2C**). (See '[Secondary prevention](#)' above.)
- We suggest not using probiotics for treatment or prevention of CDI (**Grade 2C**). (See '[Alternative therapies](#)' above and '[Prevention](#)' above.)

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## Antimicrobial agents that may induce *Clostridioides difficile* diarrhea and colitis

Frequently associated	Occasionally associated	Rarely associated
<ul style="list-style-type: none"> <li>▪ Fluoroquinolones</li> <li>▪ Clindamycin</li> <li>▪ Penicillins and combinations (broad spectrum)</li> <li>▪ Cephalosporins (2<sup>nd</sup>/3<sup>rd</sup>/4<sup>th</sup> generation)*</li> <li>▪ Carbapenems</li> </ul>	<ul style="list-style-type: none"> <li>▪ Macrolides</li> <li>▪ Penicillins (narrow spectrum)</li> <li>▪ Cephalosporins (1<sup>st</sup> generation)</li> <li>▪ Trimethoprim-sulfamethoxazole</li> <li>▪ Sulfonamides</li> </ul>	<ul style="list-style-type: none"> <li>▪ Aminoglycosides</li> <li>▪ Tetracyclines</li> <li>▪ Tigecycline</li> <li>▪ Chloramphenicol</li> <li>▪ Metronidazole</li> <li>▪ Vancomycin</li> <li>▪ Nitrofurantoin</li> </ul>

\* Use of 1 to 2 doses of a first-generation cephalosporin for surgical antibiotic prophylaxis does not confer significant risk for *C. difficile* infection.

Data from:

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## Treatment of *Clostridioides difficile* infection (CDI) in adults

Clinical condition	Treatment
<b>Nonfulminant disease</b>	
<b>Initial episode (nonsevere or severe disease)</b>	Management of an initial CDI episode consists of treatment with an antibiotic regimen.
<p><b>Nonsevere disease</b> is supported by the following clinical data: White blood cell count <math>\leq 15,000</math> cells/mL and serum creatinine level <math>&lt; 1.5</math> mg/dL</p> <p><b>Severe disease*</b> is supported by the following clinical data: White blood cell count <math>&gt; 15,000</math> cells/mL and/or serum creatinine level <math>\geq 1.5</math> mg/dL</p>	<p><b>Antibiotic regimens:</b></p> <ul style="list-style-type: none"> <li>▪ Fidaxomicin<sup>¶</sup> 200 mg orally twice daily for 10 days</li> <li>▪ Vancomycin<sup>Δ</sup> 125 mg orally 4 times daily for 10 days</li> <li>▪ For nonsevere disease, alternative regimen if above agents are unavailable: <ul style="list-style-type: none"> <li>• Metronidazole<sup>◇</sup> 500 mg orally 3 times daily for 10 to 14 days</li> </ul> </li> </ul>
<b>Recurrent episode<sup>§</sup></b>	Management of a recurrent CDI episode consists of treatment with an antibiotic regimen, in addition to adjunctive bezlotoxumab <sup>¶</sup> if feasible.
<b>First recurrence</b>	<p><b>Antibiotic regimens:</b></p> <ul style="list-style-type: none"> <li>▪ Fidaxomicin<sup>¶</sup> <ul style="list-style-type: none"> <li>• 200 mg orally twice daily for 10 days, <b>OR</b></li> <li>• 200 mg orally twice daily for 5 days, followed by once every other day for 20 days</li> </ul> </li> <li>▪ Vancomycin<sup>Δ</sup> in a tapered and pulsed regimen, for example: <ul style="list-style-type: none"> <li>• 125 mg orally 4 times daily for 10 to 14 days, then</li> <li>• 125 mg orally 2 times daily for 7 days, then</li> <li>• 125 mg orally once daily for 7 days, then</li> <li>• 125 mg orally every 2 to 3 days for 2 to 8 weeks</li> </ul> </li> <li>▪ Vancomycin<sup>Δ</sup> 125 mg orally 4 times daily for 10 days</li> </ul> <p><b>Adjunctive treatment:</b> Bezlotoxumab<sup>¶</sup> 10 mg/kg intravenously, given once during administration of standard antibiotic regimen.</p>
<b>Second or subsequent recurrence</b>	<p><b>Antibiotic regimens:</b></p> <ul style="list-style-type: none"> <li>▪ Fidaxomicin<sup>¶</sup> <ul style="list-style-type: none"> <li>• 200 mg orally twice daily for 10 days, <b>OR</b></li> </ul> </li> </ul>

	<ul style="list-style-type: none"> <li>• 200 mg orally twice daily for 5 days, followed by once every other day for 20 days</li> <li>▪ Vancomycin<sup>Δ</sup> in a tapered and pulsed regimen (example as above)</li> <li>▪ Vancomycin<sup>Δ</sup> followed by rifaximin: <ul style="list-style-type: none"> <li>• Vancomycin 125 mg orally 4 times daily by mouth for 10 days, then</li> <li>• Rifaximin 400 mg orally 3 times daily for 20 days</li> </ul> </li> </ul> <p><b>Adjunctive treatment:</b> Bezlotoxumab<sup>¶</sup> 10 mg/kg intravenously, given once during administration of standard antibiotic regimen.</p> <p><b>Role of fecal microbiota transplantation (FMT):</b> For patients who have received appropriate antibiotic treatment for at least 3 CDI episodes (ie, initial episode plus 2 recurrences), who subsequently present with a fourth or further CDI episode (third or subsequent recurrence), we favor FMT in regions where available<sup>‡</sup>. Pending referral for FMT, we treat with an antibiotic regimen as outlined above.</p>
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## Fulminant disease

<p><b>Fulminant disease*</b> is supported by the following clinical data: Hypotension or shock, ileus, megacolon</p>	<ul style="list-style-type: none"> <li>▪ Absence of ileus: Enteric vancomycin plus parenteral metronidazole<sup>‡</sup>: <ul style="list-style-type: none"> <li>• Vancomycin<sup>Δ</sup> 500 mg orally or via nasogastric tube 4 times daily, <b>AND</b></li> <li>• Metronidazole 500 mg intravenously every 8 hours</li> </ul> </li> <li>▪ If ileus is present, additional considerations include: <ul style="list-style-type: none"> <li>• FMT (administered rectally)** <b>OR</b></li> <li>• Rectal vancomycin (administered as a retention enema 500 mg in 100 mL normal saline per rectum; retained for as long as possible and readministered every 6 hours)<sup>¶¶</sup></li> </ul> </li> </ul>
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The standard course of treatment for an initial episode of CDI is 10 days. Some patients, particularly those treated with metronidazole or with severe disease, may have a delayed response; in such circumstances, treatment may be extended to 14 days. For patients with inflammatory bowel disease, an extended duration of 14 days is also appropriate. If continuation of antibiotic(s) for a primary infection is essential, we continue CDI treatment for one week after completion of other antibiotics.

\* The criteria proposed for defining severe or fulminant CDI are based on expert opinion and may need to be reviewed upon publication of prospectively validated severity scores for patients with CDI. Patients with severe or fulminant CDI also warrant assessment for surgical indications; refer to UpToDate topic on treatment of CDI for further discussion.

¶ For patients with nonfulminant disease, we suggest a fidaxomicin-based regimen over a vancomycin-based regimen. In addition, for patients with nonfulminant recurrent disease and prior CDI in the last 6 months, we suggest adjunctive bezlotoxumab. Use of fidaxomicin or bezlotoxumab have each been associated with a small benefit with respect to CDI recurrence rates (10 to 15% decrease). In the setting of cost constraints, we prioritize use of these agents for patients at greatest risk for CDI recurrence (age

≥65 years, severe CDI, or immunosuppression). Vancomycin remains an acceptable agent for treatment of initial and recurrent CDI.

Δ Systemic absorption of enteral vancomycin can occur in patients with mucosal disruption due to severe or fulminant colitis; this consideration is particularly important for patients with kidney insufficiency (creatinine clearance <10 mL/minute). Therefore, monitoring serum vancomycin levels is warranted for patients with kidney failure who have severe or fulminant colitis and require a prolonged course (>10 days) of enteral vancomycin therapy.

◇ Metronidazole should be avoided in patients who are frail, age >65 years, or who develop CDI in association with inflammatory bowel disease. Caution is also warranted during pregnancy and lactation.

§ The approach to antibiotic management of nonfulminant recurrent CDI is the same regardless of severity, but varies depending on the number of recurrences, as outlined above. For patients with a recurrent episode of CDI that is severe, refer to UpToDate topic on treatment of CDI for further discussion.

¥ The bezlotoxumab [prescribing information](#) in the United States warns that in patients with a history of congestive heart failure, the drug should be reserved for use when the benefit outweighs the risk, given reports of increased heart failure exacerbations and associated deaths in such patients. In addition, data for use of bezlotoxumab combined with fidaxomicin are limited.

‡ In contrast to the above approach, some favor FMT for patients who have received antibiotic treatment for at least 2 CDI episodes (ie, initial episode plus one recurrence), who subsequently present with a third or further CDI episode (second or subsequent recurrence)<sup>[1]</sup>.

† Continue dosing for 10 days. If recovery is delayed, treatment can be extended to 14 days.

\*\* In the setting of ileus, we favor FMT over rectal vancomycin. However, such procedures are associated with risk of colonic perforation; therefore, they should be restricted to patients who are not responsive to standard therapy, and the procedure should be performed by personnel with appropriate expertise. Refer to the UpToDate topic on FMT for discussion of safety, efficacy, and delivery protocols.

¶¶ Rectal vancomycin may be administered as a retention enema, either in addition to oral vancomycin (if the ileus is partial) or in place of oral vancomycin (if the ileus is complete). Given potential risk of colonic perforation in setting of CDI, rectal vancomycin instillation should be performed by personnel with appropriate expertise.

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*Adapted from: Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis 2021; 24:ciab549. By permission of Oxford University Press on behalf of IDSA and SHEA. Copyright © 2021. Available at: <https://www.idsociety.org/practice-guideline/clostridioides-difficile-2021-focused-update/>. OUP and the IDSA are not responsible or in any way liable for the accuracy of the adaptation. The Licensee is solely responsible for the adaptation in this publication.*

*Reference:*

1. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol 2021; 116:1124.



## Indications for surgical consultation in the management of CDI

<b>Any one of the following:</b>
▪ Hypotension with or without required use of vasopressors
▪ Fever $\geq 38.5^{\circ}\text{C}$
▪ Ileus or significant abdominal distention
▪ Peritonitis or significant abdominal tenderness
▪ Mental status changes
▪ WBC $\geq 20,000$ cells/mL
▪ Serum lactate levels $>2.2$ mmol/L
▪ Admission to intensive care unit for CDI
▪ End organ failure (mechanical ventilation, renal failure, etc.)
▪ Failure to improve after three to five days of maximal medical therapy

CDI: *Clostridioides* (formerly *Clostridium*) *difficile* infection; WBC: white blood cell.

## Contributor Disclosures

**Ciarán P Kelly, MD** Equity Ownership/Stock Options: Cour Pharmaceuticals [Celiac disease]. Grant/Research/Clinical Trial Support: Merck [C difficile infection]; Milky Way Life Sciences [C difficile infection, Celiac disease]; Pfizer [C. difficile infection]; Takeda [Celiac disease]. Consultant/Advisory Boards: AnaptysBio [Celiac disease]; Cour Pharmaceuticals [Celiac disease]; Facile Therapeutics [C difficile infection]; Ferring [C difficile infection]; Finch [C difficile infection]; GSK [Celiac disease]; Immunic [Celiac disease]; Merck [C difficile infection, celiac disease]; Milky Way Life Sciences [C difficile infection, Celiac disease]; Pfizer [C difficile infection, Celiac disease]; Recursion [C difficile infection]; RVAC Medicines [C difficile infection]; Seres Therapeutics [C difficile infection]; Summit [C difficile infection]; Takeda [Celiac disease]; Xencor [Celiac disease]. All of the relevant financial relationships listed have been mitigated. **J Thomas Lamont, MD** Equity Ownership/Stock Options: Allurion [Weight loss]. Consultant/Advisory Boards: Teledoc [Gastrointestinal diseases]. All of the relevant financial relationships listed have been mitigated. **Johan S Bakken, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Stephen B Calderwood, MD** Consultant/Advisory Boards: Day Zero Diagnostics [Whole genome sequencing for microbial identification and determination of antimicrobial susceptibility]. All of the relevant financial relationships listed have been mitigated. **Milana Bogorodskaya, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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