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".)

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.

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 ≤15,000 cells/mL and serum creatinine <1.5 mg/dL
  - Severe CDI – White blood cell count >15,000 cells/mL and/or serum creatinine ≥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 ≥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 [≥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 o*f 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. 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]. 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) [59-64]:

  - Hypotension
  - Fever ≥38.5°C

- Ileus or significant abdominal distention
- Peritonitis or significant abdominal tenderness
- Altered mental status
- White blood cell count ≥20,000 cells/mL
- 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 [65]. (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 [59-62]. Early surgical consultation for severe or complicated CDI has been advocated by multiple society guidelines [3,63,66-68].

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 [69,70]. However, they are not widely available yet, and we await more data comparing them to other sources of 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 [71]. 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 [24,72-75]. 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 [73].

- **Use of bezlotoxumab** – Bezlotoxumab, a humanized monoclonal antibody that binds to C. difficile toxin B, received US Food and Drug Administration approval in 2016 [76]. 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) [77]. 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) [1,78]. Most participants (76 percent) had ≥1 risk factor; these included age ≥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 ≥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 [79,80]. 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 [79].

- **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 instillation of processed donor stool 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 also been approved by the US Food and Drug Administration to prevent further recurrences in patients with at least one recurrence of CDI [69,70]. However, they are not widely available yet, and we await more data comparing them to other sources of 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.

    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 [73,81-85]. In one meta-analysis of randomized trials comparing FMT with placebo or antibiotics, the weighted pooled cure rate was 68 for FMT versus 44 percent for the comparator [86]. Similarly, in a randomized trial of 64 patients with recurrent CDI that was not included in the meta-analysis, resolution of infection occurred more frequently among patients

treated with oral vancomycin for 4 to 10 days followed by FMT (92 percent) than among patients treated with 10 days of oral vancomycin alone (19 percent) or fidaxomicin alone (42 percent) [85].

- **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 [87]. 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 [88]. 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) [2,3,13,89].

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 [41,90,91]. 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) [90]. 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 [92].

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 [3,93-95]:

  - 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) [3,93-95].

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 [2,93,94,96,97]. 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 [93].

  - **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:

- 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.)

ALTERNATIVE THERAPIES

Other therapeutic options for CDI are discussed below; based on available data, none warrants routine use for management of CDI [98].

- **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 [99-101].

- **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 [102]. 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 [103]. Teicoplanin may be at least as effective as vancomycin or metronidazole, although it is costly and is not available in the United States [104,105].

  Ridinilazole is an investigational antimicrobial agent restricted to the gastrointestinal tract. In a phase 2 randomized trial including 100 adults with CDI, oral ridinilazole (200 mg every 12 hours for 10 days) achieved a sustained clinical response rate (defined as clinical cure at the end of treatment and no recurrence within 30 days) of 66.7 percent compared with 42.4 percent for oral vancomycin (125 mg every 6 hours for 10 days) [106].

- **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 [107-109], a retrospective review of 18 patients who received IVIG demonstrated no significant difference in clinical outcomes compared with 18 matched control cases [110].

- **Anion-binding resins** – Tolevamer is a *C. difficile* toxin-binding resin developed specifically for CDI [111]. 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 [112,113].

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) [114]. 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 [115,116]; 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 [107,117-121].

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 [100,101,122-128]. 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 ≥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 [129]. 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 [130-132]; 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) [132].

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".)

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 5th to 6th 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 10th to 12th 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)")

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 ≤15,000 cells/mL and serum creatinine <1.5 mg/dL

    - Severe CDI – White blood cell count >15,000 cells/mL and/or serum creatinine ≥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 ≥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 ≥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.)

REFERENCES

1. 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; 73:e1029.

2. McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018; 66:e1.
3. 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.
4. Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of Clostridium difficile in adults: a systematic review. JAMA 2015; 313:398.
5. Kelly CP, LaMont JT. Clostridium difficile--more difficult than ever. N Engl J Med 2008; 359:1932.
6. Hu MY, Katchar K, Kyne L, et al. Prospective derivation and validation of a clinical prediction rule for recurrent Clostridium difficile infection. Gastroenterology 2009; 136:1206.
7. Mullane KM, Miller MA, Weiss K, et al. Efficacy of fidaxomicin versus vancomycin as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections. Clin Infect Dis 2011; 53:440.
8. Wilcox MH, Howe R. Diarrhoea caused by Clostridium difficile: response time for treatment with metronidazole and vancomycin. J Antimicrob Chemother 1995; 36:673.
9. Koo HL, Koo DC, Musher DM, DuPont HL. Antimotility agents for the treatment of Clostridium difficile diarrhea and colitis. Clin Infect Dis 2009; 48:598.
10. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis 2007; 45:302.
11. Pépin J, Valiquette L, Alary ME, et al. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ 2004; 171:466.
12. Rubin MS, Bodenstein LE, Kent KC. Severe Clostridium difficile colitis. Dis Colon Rectum 1995; 38:350.
13. Debast SB, Bauer MP, Kuijper EJ, European Society of Clinical Microbiology and Infectious Diseases. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect 2014; 20 Suppl 2:1.
14. Bauer MP, Hensgens MP, Miller MA, et al. Renal failure and leukocytosis are predictors of a complicated course of Clostridium difficile infection if measured on day of diagnosis. Clin Infect Dis 2012; 55 Suppl 2:S149.

15. Miller MA, Louie T, Mullane K, et al. Derivation and validation of a simple clinical bedside score (ATLAS) for Clostridium difficile infection which predicts response to therapy. BMC Infect Dis 2013; 13:148.
16. Drekonja DM, Butler M, MacDonald R, et al. Comparative effectiveness of Clostridium difficile treatments: a systematic review. Ann Intern Med 2011; 155:839.
17. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. Cochrane Database Syst Rev 2017; 3:CD004610.
18. Horton HA, Dezfoli S, Berel D, et al. Antibiotics for Treatment of Clostridium difficile Infection in Hospitalized Patients with Inflammatory Bowel Disease. Antimicrob Agents Chemother 2014; 58:5054.
19. Khanna S, Shin A, Kelly CP. Management of Clostridium difficile Infection in Inflammatory Bowel Disease: Expert Review from the Clinical Practice Updates Committee of the AGA Institute. Clin Gastroenterol Hepatol 2017; 15:166.
20. Nguyen LH, Örtqvist AK, Cao Y, et al. Antibiotic use and the development of inflammatory bowel disease: a national case-control study in Sweden. Lancet Gastroenterol Hepatol 2020; 5:986.
21. Carignan A, Poulin S, Martin P, et al. Efficacy of Secondary Prophylaxis With Vancomycin for Preventing Recurrent Clostridium difficile Infections. Am J Gastroenterol 2016; 111:1834.
22. Van Hise NW, Bryant AM, Hennessey EK, et al. Efficacy of Oral Vancomycin in Preventing Recurrent Clostridium difficile Infection in Patients Treated With Systemic Antimicrobial Agents. Clin Infect Dis 2016; 63:651.
23. Fekety R, Silva J, Kauffman C, et al. Treatment of antibiotic-associated Clostridium difficile colitis with oral vancomycin: comparison of two dosage regimens. Am J Med 1989; 86:15.
24. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol 2002; 97:1769.
25. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med 2011; 364:422.
26. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis 2012; 12:281.
27. Guery B, Menichetti F, Anttila VJ, et al. Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. Lancet Infect Dis 2018; 18:296.

28. Mikamo H, Tateda K, Yanagihara K, et al. Efficacy and safety of fidaxomicin for the treatment of Clostridioides (Clostridium) difficile infection in a randomized, double-blind, comparative Phase III study in Japan. J Infect Chemother 2018; 24:744.
29. Cornely OA, Miller MA, Louie TJ, et al. Treatment of first recurrence of Clostridium difficile infection: fidaxomicin versus vancomycin. Clin Infect Dis 2012; 55 Suppl 2:S154.
30. Eyre DW, Babakhani F, Griffiths D, et al. Whole-genome sequencing demonstrates that fidaxomicin is superior to vancomycin for preventing reinfection and relapse of infection with Clostridium difficile. J Infect Dis 2014; 209:1446.
31. Tannock GW, Munro K, Taylor C, et al. A new macrocyclic antibiotic, fidaxomicin (OPT-80), causes less alteration to the bowel microbiota of Clostridium difficile-infected patients than does vancomycin. Microbiology 2010; 156:3354.
32. Deshpande A, Hurless K, Cadnum JL, et al. Effect of Fidaxomicin versus Vancomycin on Susceptibility to Intestinal Colonization with Vancomycin-Resistant Enterococci and Klebsiella pneumoniae in Mice. Antimicrob Agents Chemother 2016; 60:3988.
33. Carmeli Y, Eliopoulos GM, Samore MH. Antecedent treatment with different antibiotic agents as a risk factor for vancomycin-resistant Enterococcus. Emerg Infect Dis 2002; 8:802.
34. Al-Nassir WN, Sethi AK, Li Y, et al. Both oral metronidazole and oral vancomycin promote persistent overgrowth of vancomycin-resistant enterococci during treatment of Clostridium difficile-associated disease. Antimicrob Agents Chemother 2008; 52:2403.
35. Stevens VW, Khader K, Echevarria K, et al. Use of Oral Vancomycin for Clostridioides difficile Infection and the Risk of Vancomycin-Resistant Enterococci. Clin Infect Dis 2020; 71:645.
36. Nerandzic MM, Mullane K, Miller MA, et al. Reduced acquisition and overgrowth of vancomycin-resistant enterococci and Candida species in patients treated with fidaxomicin versus vancomycin for Clostridium difficile infection. Clin Infect Dis 2012; 55 Suppl 2:S121.
37. Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of Clostridium difficile colitis with metronidazole. Clin Infect Dis 2005; 40:1586.
38. Pepin J, Alary ME, Valiquette L, et al. Increasing risk of relapse after treatment of Clostridium difficile colitis in Quebec, Canada. Clin Infect Dis 2005; 40:1591.
39. Gerding DN. Metronidazole for Clostridium difficile-associated disease: is it okay for Mom? Clin Infect Dis 2005; 40:1598.
40. Hu MY, Maroo S, Kyne L, et al. A prospective study of risk factors and historical trends in metronidazole failure for Clostridium difficile infection. Clin Gastroenterol Hepatol 2008; 6:1354.

41. Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to Clostridium difficile. Gut 1986; 27:1169.
42. Johnson S, Homann SR, Bettin KM, et al. Treatment of asymptomatic Clostridium difficile carriers (fecal excretors) with vancomycin or metronidazole. A randomized, placebo-controlled trial. Ann Intern Med 1992; 117:297.
43. Appaneal HJ, Caffrey AR, LaPlante KL. What Is the Role for Metronidazole in the Treatment of Clostridium difficile Infection? Results From a National Cohort Study of Veterans With Initial Mild Disease. Clin Infect Dis 2019; 69:1288.
44. Herpers BL, Vlaminckx B, Burkhardt O, et al. Intravenous tigecycline as adjunctive or alternative therapy for severe refractory Clostridium difficile infection. Clin Infect Dis 2009; 48:1732.
45. LaSalvia MT, Branch-Elliman W, Snyder GM, et al. Does Adjunctive Tigecycline Improve Outcomes in Severe-Complicated, Nonoperative Clostridium difficile Infection? Open Forum Infect Dis 2017; 4:ofw264.
46. Pettit NN, DePestel DD, Fohl AL, et al. Risk factors for systemic vancomycin exposure following administration of oral vancomycin for the treatment of Clostridium difficile infection. Pharmacotherapy 2015; 35:119.
47. Matzke GR, Halstenson CE, Olson PL, et al. Systemic absorption of oral vancomycin in patients with renal insufficiency and antibiotic-associated colitis. Am J Kidney Dis 1987; 9:422.
48. Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clin Infect Dis 2014; 59:345.
49. Stevens VW, Nelson RE, Schwab-Daugherty EM, et al. Comparative Effectiveness of Vancomycin and Metronidazole for the Prevention of Recurrence and Death in Patients With Clostridium difficile Infection. JAMA Intern Med 2017; 177:546.
50. Gentry CA, Nguyen PK, Thind S, et al. Fidaxomicin versus oral vancomycin for severe Clostridium difficile infection: a retrospective cohort study. Clin Microbiol Infect 2019; 25:987.
51. Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut 2017; 66:569.
52. Allegretti JR, Kassam Z, Osman M, et al. The 5D framework: a clinical primer for fecal microbiota transplantation to treat Clostridium difficile infection. Gastrointest Endosc 2018; 87:18.

53. Kelly CR, Yen EF, Grinspan AM, et al. Fecal Microbiota Transplantation Is Highly Effective in Real-World Practice: Initial Results From the FMT National Registry. Gastroenterology 2021; 160:183.

54. Hocquart M, Lagier JC, Cassir N, et al. Early Fecal Microbiota Transplantation Improves Survival in Severe Clostridium difficile Infections. Clin Infect Dis 2018; 66:645.

55. Fischer M, Sipe B, Cheng YW, et al. Fecal microbiota transplant in severe and severe-complicated Clostridium difficile: A promising treatment approach. Gut Microbes 2017; 8:289.

56. Tixier EN, Verheyen E, Ungaro RC, Grinspan AM. Faecal microbiota transplant decreases mortality in severe and fulminant Clostridioides difficile infection in critically ill patients. Aliment Pharmacol Ther 2019; 50:1094.

57. Cheng YW, Phelps E, Nemes S, et al. Fecal Microbiota Transplant Decreases Mortality in Patients with Refractory Severe or Fulminant Clostridioides difficile Infection. Clin Gastroenterol Hepatol 2020; 18:2234.

58. Ianiro G, Masucci L, Quaranta G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy plus vancomycin for the treatment of severe refractory Clostridium difficile infection-single versus multiple infusions. Aliment Pharmacol Ther 2018; 48:152.

59. van der Wilden GM, Velmahos GC, Chang Y, et al. Effects of a New Hospital-Wide Surgical Consultation Protocol in Patients with Clostridium difficile Colitis. Surg Infect (Larchmt) 2017; 18:563.

60. Sailhamer EA, Carson K, Chang Y, et al. Fulminant Clostridium difficile colitis: patterns of care and predictors of mortality. Arch Surg 2009; 144:433.

61. Bhangu A, Nepogodiev D, Gupta A, et al. Systematic review and meta-analysis of outcomes following emergency surgery for Clostridium difficile colitis. Br J Surg 2012; 99:1501.

62. Hall JF, Berger D. Outcome of colectomy for Clostridium difficile colitis: a plea for early surgical management. Am J Surg 2008; 196:384.

63. Ferrada P, Velopulos CG, Sultan S, et al. Timing and type of surgical treatment of Clostridium difficile-associated disease: a practice management guideline from the Eastern Association for the Surgery of Trauma. J Trauma Acute Care Surg 2014; 76:1484.

64. Lamontagne F, Labbé AC, Haeck O, et al. Impact of emergency colectomy on survival of patients with fulminant Clostridium difficile colitis during an epidemic caused by a hypervirulent strain. Ann Surg 2007; 245:267.

65. Kelly CP, Pothoulakis C, LaMont JT. Clostridium difficile colitis. N Engl J Med 1994; 330:257.

66. Sartelli M, Malangoni MA, Abu-Zidan FM, et al. WSES guidelines for management of Clostridium difficile infection in surgical patients. World J Emerg Surg 2015; 10:38.

67. Napolitano LM, Edmiston CE Jr. Clostridium difficile disease: Diagnosis, pathogenesis, and treatment update. Surgery 2017; 162:325.

68. Steele SR, McCormick J, Melton GB, et al. Practice parameters for the management of Clostridium difficile infection. Dis Colon Rectum 2015; 58:10.

69. Rebyota. United States Food and Drug Administration label. https://www.fda.gov/media/163587/download (Accessed on March 09, 2023).

70. US Food and Drug Administration. Vowst. https://www.fda.gov/media/167579/download (Accessed on May 11, 2023).

71. Skinner AM, Tan X, Sirbu BD, et al. A Tapered-pulsed Fidaxomicin Regimen Following Treatment in Patients With Multiple Clostridioides difficile Infection Recurrences. Clin Infect Dis 2021; 73:1107.

72. Tedesco FJ, Gordon D, Fortson WC. Approach to patients with multiple relapses of antibiotic-associated pseudomembranous colitis. Am J Gastroenterol 1985; 80:867.

73. Hota SS, Sales V, Tomlinson G, et al. Oral Vancomycin Followed by Fecal Transplantation Versus Tapering Oral Vancomycin Treatment for Recurrent Clostridium difficile Infection: An Open-Label, Randomized Controlled Trial. Clin Infect Dis 2017; 64:265.

74. Sirbu BD, Soriano MM, Manzo C, et al. Vancomycin Taper and Pulse Regimen With Careful Follow-up for Patients With Recurrent Clostridium difficile Infection. Clin Infect Dis 2017; 65:1396.

75. Bakken JS. Staggered and tapered antibiotic withdrawal with administration of kefir for recurrent Clostridium difficile infection. Clin Infect Dis 2014; 59:858.

76. Johnson S, Gerding DN. Bezlotoxumab. Clin Infect Dis 2019; 68:699.

77. Wilcox MH, Gerding DN, Poxton IR, et al. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection. N Engl J Med 2017; 376:305.

78. Gerding DN, Kelly CP, Rahav G, et al. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection in Patients at Increased Risk for Recurrence. Clin Infect Dis 2018; 67:649.

79. Johnson S, Schriever C, Galang M, et al. Interruption of recurrent Clostridium difficile-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. Clin Infect Dis 2007; 44:846.

80. Garey KW, Ghantoji SS, Shah DN, et al. A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with Clostridium difficile infection. J Antimicrob Chemother 2011; 66:2850.

81. van Nood E, Vrieze A, Nieuwdorp M, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 2013; 368:407.
82. Lee CH, Steiner T, Petrof EO, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA 2016; 315:142.
83. Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol 2013; 108:500.
84. Drekonja D, Reich J, Gezahegn S, et al. Fecal Microbiota Transplantation for Clostridium difficile Infection: A Systematic Review. Ann Intern Med 2015; 162:630.
85. Hvas CL, Dahl Jørgensen SM, Jørgensen SP, et al. Fecal Microbiota Transplantation Is Superior to Fidaxomicin for Treatment of Recurrent Clostridium difficile Infection. Gastroenterology 2019; 156:1324.
86. Tariq R, Pardi DS, Bartlett MG, Khanna S. Low Cure Rates in Controlled Trials of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection: A Systematic Review and Meta-analysis. Clin Infect Dis 2019; 68:1351.
87. Zhang K, Beckett P, Abouanaser S, et al. Prolonged oral vancomycin for secondary prophylaxis of relapsing Clostridium difficile infection. BMC Infect Dis 2019; 19:51.
88. Fang N, Ha D, Dong K, et al. Successful Fidaxomicin Hospital Discharges of Adult Patients With Clostridioides difficile Infections Post-2021 Guidelines: Are Economic Barriers Finally Coming Down? Clin Infect Dis 2022; 75:519.
89. Shane AL, Mody RK, Crump JA, et al. 2017 Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. Clin Infect Dis 2017; 65:e45.
90. Rokas KE, Johnson JW, Beardsley JR, et al. The Addition of Intravenous Metronidazole to Oral Vancomycin is Associated With Improved Mortality in Critically Ill Patients With Clostridium difficile Infection. Clin Infect Dis 2015; 61:934.
91. Friedenberg F, Fernandez A, Kaul V, et al. Intravenous metronidazole for the treatment of Clostridium difficile colitis. Dis Colon Rectum 2001; 44:1176.
92. Wang Y, Schluger A, Li J, et al. Does Addition of Intravenous Metronidazole to Oral Vancomycin Improve Outcomes in Clostridioides difficile Infection? Clin Infect Dis 2020; 71:2414.
93. Apisarnthanarak A, Razavi B, Mundy LM. Adjunctive intracolonic vancomycin for severe Clostridium difficile colitis: case series and review of the literature. Clin Infect Dis 2002; 35:690.

94. Shetler K, Nieuwenhuis R, Wren SM, Triadafilopoulos G. Decompressive colonoscopy with intracolonic vancomycin administration for the treatment of severe pseudomembranous colitis. Surg Endosc 2001; 15:653.

95. Nathanson DR, Sheahan M, Chao L, Wallack MK. Intracolonic use of vancomycin for treatment of clostridium difficile colitis in a patient with a diverted colon: report of a case. Dis Colon Rectum 2001; 44:1871.

96. Halsey J. Current and future treatment modalities for Clostridium difficile-associated disease. Am J Health Syst Pharm 2008; 65:705.

97. Apisarnthanarak A, Khoury H, Reinus WR, et al. Severe Clostridium difficile colitis: the role of intracolonic vancomycin? Am J Med 2002; 112:328.

98. Treatment of Clostridium difficile-associated disease (CDAD). Med Lett Drugs Ther 2006; 48:89.

99. Pillai A, Nelson R. Probiotics for treatment of Clostridium difficile-associated colitis in adults. Cochrane Database Syst Rev 2008; :CD004611.

100. Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. JAMA 2012; 307:1959.

101. Ritchie ML, Romanuk TN. A meta-analysis of probiotic efficacy for gastrointestinal diseases. PLoS One 2012; 7:e34938.

102. Lagrotteria D, Holmes S, Smieja M, et al. Prospective, randomized inpatient study of oral metronidazole versus oral metronidazole and rifampin for treatment of primary episode of Clostridium difficile-associated diarrhea. Clin Infect Dis 2006; 43:547.

103. Musher DM, Logan N, Bressler AM, et al. Nitazoxanide versus vancomycin in Clostridium difficile infection: a randomized, double-blind study. Clin Infect Dis 2009; 48:e41.

104. Wenisch C, Parschalk B, Hasenhündl M, et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. Clin Infect Dis 1996; 22:813.

105. de Lalla F, Nicolin R, Rinaldi E, et al. Prospective study of oral teicoplanin versus oral vancomycin for therapy of pseudomembranous colitis and Clostridium difficile-associated diarrhea. Antimicrob Agents Chemother 1992; 36:2192.

106. Vickers RJ, Tillotson GS, Nathan R, et al. Efficacy and safety of ridinilazole compared with vancomycin for the treatment of Clostridium difficile infection: a phase 2, randomised, double-blind, active-controlled, non-inferiority study. Lancet Infect Dis 2017; 17:735.

107. Leung DY, Kelly CP, Boguniewicz M, et al. Treatment with intravenously administered gamma globulin of chronic relapsing colitis induced by Clostridium difficile toxin. J Pediatr

1991; 118:633.

108. Salcedo J, Keates S, Pothoulakis C, et al. Intravenous immunoglobulin therapy for severe Clostridium difficile colitis. Gut 1997; 41:366.
109. Warny M, Denie C, Delmée M, Lefebvre C. Gamma globulin administration in relapsing Clostridium difficile-induced pseudomembranous colitis with a defective antibody response to toxin A. Acta Clin Belg 1995; 50:36.
110. Juang P, Skledar SJ, Zgheib NK, et al. Clinical outcomes of intravenous immune globulin in severe clostridium difficile-associated diarrhea. Am J Infect Control 2007; 35:131.
111. Louie TJ, Peppe J, Watt CK, et al. Tolevamer, a novel nonantibiotic polymer, compared with vancomycin in the treatment of mild to moderately severe Clostridium difficile-associated diarrhea. Clin Infect Dis 2006; 43:411.
112. Mogg GA, Arabi Y, Youngs D, et al. Therapeutic trials of antibiotic associated colitis. Scand J Infect Dis Suppl 1980; :41.
113. Kreutzer EW, Milligan FD. Treatment of antibiotic-associated pseudomembranous colitis with cholestyramine resin. Johns Hopkins Med J 1978; 143:67.
114. Johnson SW, Brown SV, Priest DH. Effectiveness of Oral Vancomycin for Prevention of Healthcare Facility-Onset Clostridioides difficile Infection in Targeted Patients During Systemic Antibiotic Exposure. Clin Infect Dis 2020; 71:1133.
115. Mullane KM, Winston DJ, Nooka A, et al. A Randomized, Placebo-controlled Trial of Fidaxomicin for Prophylaxis of Clostridium difficile-associated Diarrhea in Adults Undergoing Hematopoietic Stem Cell Transplantation. Clin Infect Dis 2019; 68:196.
116. Ganetsky A, Han JH, Hughes ME, et al. Oral Vancomycin Prophylaxis Is Highly Effective in Preventing Clostridium difficile Infection in Allogeneic Hematopoietic Cell Transplant Recipients. Clin Infect Dis 2019; 68:2003.
117. Warny M, Vaerman JP, Avesani V, Delmée M. Human antibody response to Clostridium difficile toxin A in relation to clinical course of infection. Infect Immun 1994; 62:384.
118. Aboudola S, Kotloff KL, Kyne L, et al. Clostridium difficile vaccine and serum immunoglobulin G antibody response to toxin A. Infect Immun 2003; 71:1608.
119. Kotloff KL, Wasserman SS, Losonsky GA, et al. Safety and immunogenicity of increasing doses of a Clostridium difficile toxoid vaccine administered to healthy adults. Infect Immun 2001; 69:988.
120. Sougioultzis S, Kyne L, Drudy D, et al. Clostridium difficile toxoid vaccine in recurrent C. difficile-associated diarrhea. Gastroenterology 2005; 128:764.

121. Lowy I, Molrine DC, Leav BA, et al. Treatment with monoclonal antibodies against Clostridium difficile toxins. N Engl J Med 2010; 362:197.

122. Lau CS, Chamberlain RS. Probiotics are effective at preventing Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Int J Gen Med 2016; 9:27.

123. Johnston BC, Ma SS, Goldenberg JZ, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Ann Intern Med 2012; 157:878.

124. Shen NT, Maw A, Tmanova LL, et al. Timely Use of Probiotics in Hospitalized Adults Prevents Clostridium difficile Infection: A Systematic Review With Meta-Regression Analysis. Gastroenterology 2017.

125. Sinclair A, Xie X, Saab L, Dendukuri N. Lactobacillus probiotics in the prevention of diarrhea associated with Clostridium difficile: a systematic review and Bayesian hierarchical meta-analysis. CMAJ Open 2016; 4:E706.

126. Szajewska H, Kołodziej M. Systematic review with meta-analysis: Saccharomyces boulardii in the prevention of antibiotic-associated diarrhoea. Aliment Pharmacol Ther 2015; 42:793.

127. Goldenberg JZ, Yap C, Lytvyn L, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev 2017; 12:CD006095.

128. Johnston BC, Lytvyn L, Lo CK, et al. Microbial Preparations (Probiotics) for the Prevention of Clostridium difficile Infection in Adults and Children: An Individual Patient Data Meta-analysis of 6,851 Participants. Infect Control Hosp Epidemiol 2018; 39:771.

129. Caroff DA, Menchaca JT, Zhang Z, et al. Oral vancomycin prophylaxis during systemic antibiotic exposure to prevent Clostridiodes difficile infection relapses. Infect Control Hosp Epidemiol 2019; 40:662.

130. Shim JK, Johnson S, Samore MH, et al. Primary symptomless colonisation by Clostridium difficile and decreased risk of subsequent diarrhoea. Lancet 1998; 351:633.

131. Villano SA, Seiberling M, Tatarowicz W, et al. Evaluation of an oral suspension of VP20621, spores of nontoxigenic Clostridium difficile strain M3, in healthy subjects. Antimicrob Agents Chemother 2012; 56:5224.

132. Gerding DN, Meyer T, Lee C, et al. Administration of spores of nontoxigenic Clostridium difficile strain M3 for prevention of recurrent C. difficile infection: a randomized clinical trial. JAMA 2015; 313:1719.

Topic 2698 Version 107.0

GRAPHICS

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

Frequently associated	Occasionally associated	Rarely associated
▪ Fluoroquinolones ▪ Clindamycin ▪ Penicillins and combinations (broad spectrum) ▪ Cephalosporins (2nd/3rd/4th generation)* ▪ Carbapenems	▪ Macrolides ▪ Penicillins (narrow spectrum) ▪ Cephalosporins (1st generation) ▪ Trimethoprim-sulfamethoxazole ▪ Sulfonamides	▪ Aminoglycosides ▪ Tetracyclines ▪ Tigecycline ▪ Chloramphenicol ▪ Metronidazole ▪ Vancomycin ▪ Nitrofurantoin

* 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:

1. *McDonald LC, Gerding DN, Johnson S, et al. Clinical Practice Guidelines for Clostridium difficile Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018; 66:987.*
2. *Slimings C, Riley TV. Antibiotics and healthcare facility-associated Clostridioides difficile infection: systematic review and meta-analysis: 2020 update. J Antimicrob Chemother 2021:dkab091.*
3. *Vardakas KZ, Trigkidis KK, Boukouvala E, Falagas ME. Clostridium difficile infection following systemic antibiotic administration in randomised controlled trials: a systematic review and meta-analysis. Int J Antimicrob Agents 2016; 48:1.*
4. *Ge IY, Fevrier HB, Conell C, et al. Reducing risk of Clostridium difficile infection and overall use of antibiotic in the outpatient treatment of urinary tract infection. Ther Adv Urol 2018; 10:10.*

Graphic 55479 Version 14.0

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

Clinical condition	Treatment
Nonfulminant disease	
Initial episode (nonsevere or severe disease)	Management of an initial CDI episode consists of treatment with an antibiotic regimen.
Nonsevere disease is supported by the following clinical data: White blood cell count ≤15,000 cells/mL and serum creatinine level <1.5 mg/dL **Severe disease*** is supported by the following clinical data: White blood cell count >15,000 cells/mL and/or serum creatinine level ≥1.5 mg/dL	**Antibiotic regimens:** ▪ Fidaxomicin[¶] 200 mg orally twice daily for 10 days ▪ Vancomycin[Δ] 125 mg orally 4 times daily for 10 days ▪ For nonsevere disease, alternative regimen if above agents are unavailable: • Metronidazole[◇] 500 mg orally 3 times daily for 10 to 14 days
Recurrent episode[§]	Management of a recurrent CDI episode consists of treatment with an antibiotic regimen, in addition to adjunctive bezlotoxumab[¶] if feasible.
First recurrence	**Antibiotic regimens:** ▪ Fidaxomicin[¶] • 200 mg orally twice daily for 10 days, **OR** • 200 mg orally twice daily for 5 days, followed by once every other day for 20 days ▪ Vancomycin[Δ] in a tapered and pulsed regimen, for example: • 125 mg orally 4 times daily for 10 to 14 days, then • 125 mg orally 2 times daily for 7 days, then • 125 mg orally once daily for 7 days, then • 125 mg orally every 2 to 3 days for 2 to 8 weeks ▪ Vancomycin[Δ] 125 mg orally 4 times daily for 10 days **Adjunctive treatment:** Bezlotoxumab[¶ ¥] 10 mg/kg intravenously, given once during administration of standard antibiotic regimen.
Second or subsequent recurrence	**Antibiotic regimens:** ▪ Fidaxomicin[¶] • 200 mg orally twice daily for 10 days, **OR**

	• 200 mg orally twice daily for 5 days, followed by once every other day for 20 days ▪ Vancomycin[Δ] in a tapered and pulsed regimen (example as above) ▪ Vancomycin[Δ] followed by rifaximin: • Vancomycin 125 mg orally 4 times daily by mouth for 10 days, then • Rifaximin 400 mg orally 3 times daily for 20 days **Adjunctive treatment:** Bezlotoxumab[¶ ¥] 10 mg/kg intravenously, given once during administration of standard antibiotic regimen. **Role of fecal microbiota transplantation (FMT):** 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[‡]. Pending referral for FMT, we treat with an antibiotic regimen as outlined above.
Fulminant disease	
Fulminant disease* is supported by the following clinical data: Hypotension or shock, ileus, megacolon	▪ Absence of ileus: Enteric vancomycin plus parenteral metronidazole[†]: • Vancomycin[Δ] 500 mg orally or via nasogastric tube 4 times daily, **AND** • Metronidazole 500 mg intravenously every 8 hours ▪ If ileus is present, additional considerations include: • FMT (administered rectally)** **OR** • 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)[¶¶]

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.

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* 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)[1].

† 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.

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.*

Graphic 53273 Version 44.0

Indications for surgical consultation in the management of CDI

Any one of the following:
▪ Hypotension with or without required use of vasopressors
▪ Fever ≥38.5°C
▪ Ileus or significant abdominal distention
▪ Peritonitis or significant abdominal tenderness
▪ Mental status changes
▪ WBC ≥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.

Graphic 119207 Version 3.0

Contributor Disclosures

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