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Wolters Kluwer

Clostridioides (formerly Clostridium) difficile infection in adults: Treatment and prevention

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Literature review current through: Mar 2021. | **This topic last updated:** Feb 24, 2021.

INTRODUCTION

Clostridioides (formerly *Clostridium*) *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]. 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 [2].

Issues related to surgical management of CDI are discussed separately. (See "Surgical management of Clostridioides (formerly Clostridium) difficile colitis in adults".)

The epidemiology, pathophysiology, clinical manifestations, and diagnosis of CDI in adults are discussed separately. (See "Clostridioides (formerly Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology" and "Clostridioides (formerly Clostridium) 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 (formerly Clostridium) difficile infection: Prevention and control".)

Issues related to CDI in children are discussed separately. (See "Clostridioides (formerly Clostridium) difficile infection in children: Clinical features and diagnosis" and "Clostridioides (formerly Clostridium) difficile infection in children: Treatment and outcome" and "Clostridioides (formerly Clostridium) 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 [1]. (See "Clostridioides (formerly Clostridium) 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 [1]. 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 [3-5]. 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 [6-8]. 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 [1,8-14].

Proposed criteria for disease severity (based on expert opinion) include [1]:

- 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 (formerly Clostridium) 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 [15,16].

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 [8]. (See "Clostridioides (formerly Clostridium) 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.

Nonfulminant disease — The approach to management of nonfulminant disease (see 'Assessing disease severity' above) varies depending on disease severity and whether the

patient presents with an initial episode or a recurrent episode.

Initial episode

Nonsevere disease — Management of nonsevere CDI (see 'Assessing disease severity' above) consists of antibiotic therapy. Appropriate antibiotics include oral vancomycin or oral fidaxomicin; dosing is summarized in the table (table 2) :

- Oral vancomycin is bacteriostatic against *C. difficile* and achieves predictably high levels in the colon [17]. Intravenous vancomycin is not effective for *C. difficile* colitis since, during the course of short-term administration, the antibiotic is not excreted appreciably into the colon.

- Fidaxomicin is bactericidal against *C. difficile* and is not absorbed systemically; it has been associated with a lower recurrence rate than oral vancomycin but is more costly [1,5,18].

- Metronidazole is bacteriostatic against *C. difficile*; it is an alternative agent if oral vancomycin and oral fidaxomicin are not available [1]. Metronidazole should be avoided in patients who are very old or infirm or who develop CDI in association with inflammatory bowel disease [19-21].

The duration of initial antibiotic therapy for nonsevere CDI is 10 days [1]. Patients with CDI in the setting of another underlying infection requiring prolonged duration of antibiotic therapy are at increased risk for recurrent CDI [5]. In such cases, we typically continue CDI treatment throughout the antibiotic course plus an additional tail of one week after its completion [22,23]. (See 'Prevention' below.)

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 [17,24].

The above approach is supported by a meta-analysis including 22 randomized trials of 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) [16]. In a randomized trial including more than 600 patients treated with vancomycin or fidaxomicin, initial symptomatic response rates after treatment with fidaxomicin were similar to those after treatment with vancomycin (88 versus 86 percent) [25]. In another randomized trial including 259 patients with nonsevere CDI treated with oral vancomycin and 278 patients treated with metronidazole, symptomatic

response rates after treatment with metronidazole were inferior to those after treatment with vancomycin (73 versus 81 percent; p = 0.02) [26].

The CDI recurrence rate has been observed to be lower among patients with non-NAP1 strains treated with fidaxomicin than patients treated with vancomycin (15 versus 25 percent in one study) [25,27,28]. However, no difference in recurrence rates has been observed among patients infected with NAP1 strains [25]. (See "Clostridioides (formerly Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'NAP1/BI/027 strain'.)

Thus far, minimal alteration of the microbiome has been observed with fidaxomicin [29,30]. The risk of bowel colonization with vancomycin-resistant enterococci (VRE) associated with vancomycin and metronidazole use is comparable [31-33].

Use of metronidazole has been associated with higher rates of treatment failure [34,35]. In one retrospective study including 845 patients with CDI treated with metronidazole, the probability of recurrence within 60 days increased from 20 to 47 percent between 1991 to 2002 and 2003 to 2004 [35]. In one prospective observational study including 207 patients with CDI treated with metronidazole, half were cured, 22 percent continued to have symptoms for ≥10 days despite treatment, and 28 percent responded initially but had a recurrence within 90 days [34].

The reasons for metronidazole failure are poorly understood [36,37]. Age may be an important factor associated with metronidazole failure. In a retrospective study of 3656 veterans with a first episode of mild CDI treated with metronidazole, age ≤65 years was associated with higher odds of success (1.63 times higher, 95% CI 1.29-2.06) than in those >65 years [38]. When comparing metronidazole with vancomycin for treatment in patients ≤65 years of age, rates of failure, CDI recurrence, and all-cause mortality were similar.

Another contributing factor for metronidazole failure 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 [39,40]. Rarely, metronidazole tolerance in *C. difficile* has been described; however, clinical resistance rates do not appear to be increasing, even in the setting of the rising rates of treatment failure [41-49]. Hence, prior exposure to metronidazole is not likely to further decrease the efficacy of metronidazole for the treatment of CDI.

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 early treatment of severe CDI.

Antibiotic therapy — For treatment of severely ill patients, we suggest oral vancomycin (125 mg four times daily) or fidaxomicin (200 mg twice daily) (table 2). For patients with severe disease treated with oral vancomycin who do not demonstrate clinical improvement after three to five days, adding fidaxomicin to oral vancomycin is reasonable, although data supporting this approach are lacking.

The standard duration of antibiotic therapy (with either vancomycin or fidaxomicin) for *C. difficile* diarrhea 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.)

Studies in patients with severe disease are more limited than in patients with mild to moderate disease, but support the use of vancomycin over metronidazole for severe CDI. In a randomized trial, vancomycin resulted in a higher initial clinical response rate (both clinical and microbiologic) than metronidazole among 69 patients with severe CDI (97 versus 76 percent) [9,26,50]. In one retrospective cohort study of over 47,000 patients with CDI, among the 3130 patients with severe disease, vancomycin was associated with a reduced 30-day mortality compared with metronidazole [50]. Oral vancomycin also has the pharmacologic advantage of not being absorbed so that maximal concentrations of the drug can act locally at the site of infection. Metronidazole and vancomycin appear to be relatively similar with respect to in vitro activity and potential for emergence of VRE [31,51-54].

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) [17].

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) [1,55,56]. 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. Intravenous vancomycin has no effect on *C. difficile* colitis since vancomycin is not excreted into the colon.

Data on the comparative efficacy of fidaxomicin are more limited in severe disease, but there is no clear evidence that either vancomycin or fidaxomicin is superior. In a retrospective study of patients with severe CDI, fidaxomicin (n = 213) and vancomycin (n = 639) were associated with largely similar clinical outcomes (combined clinical failure or recurrence 32 versus 26 percent) and mortality (11 versus 12 percent at 30 days) [57].

Intravenous tigecycline has been used in a small number of patients with severe CDI that was refractory to standard therapy [58,59]. Given the lack of data, we do not favor use of tigecycline for treatment of *C. difficile* colitis.

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 [1,60-62].

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) [63]. 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 22 patients with fulminant CDI were 87 percent [64]. 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) [65]. 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) [66].

FMT instillations should be administered via colonoscope, since as 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 the fecal material from reaching the colon. Multiple stool infusions may be more effective than a single infusion [67]. Issues related to FMT are discussed further separately. (See "Fecal microbiota transplantation for treatment of Clostridioides (formerly Clostridium) 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) [68-73]:

- 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 [74]. (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 [68-71]. Early surgical consultation for severe or complicated CDI has been advocated by multiple society guidelines [8,72,75-77].

Issues related to surgical management of CDI are discussed further separately. (See "Surgical management of Clostridioides (formerly Clostridium) 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 [1]. (See "Clostridioides (formerly Clostridium) 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 — For patients with a first recurrence of CDI who were initially treated with oral vancomycin, regimens include oral vancomycin (administered in a pulse-tapered fashion) or oral fidaxomicin (table 2) [1]. For patients with a first recurrence of CDI who were treated with fidaxomicin or metronidazole for the initial episode, treatment with oral vancomycin is appropriate [1].

Administration of vancomycin in a pulse-tapered fashion over several weeks may be effective for management of recurrent CDI. It has been postulated that this form of intermittent antibiotic therapy may facilitate a gradual return of the normal colonic microflora. A tapered oral vancomycin regimen consists of a stepwise decrease in dose over a period of time; an approach is summarized in the table (table 2).

Data on intermittent and tapered vancomycin regimens are limited [24,78-81]. 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 [79].

Use of secondary prophylaxis during concomitant antibiotic use may be useful for prevention of recurrent infection; this is discussed further below. (See 'Prevention' below.)

Second recurrence — There are no rigorous studies evaluating the approach to management for patients with more than one episode of recurrent CDI. Regimens include oral vancomycin (administered in a pulse-tapered fashion), oral fidaxomicin, or oral vancomycin followed by oral rifaximin (table 2).

Issues related to administration of vancomycin in a pulse-tapered fashion regimen are discussed above. (See 'First recurrence' above.)

Sequential therapy with vancomycin followed by rifaximin may be effective for the treatment of recurrent CDI (table 2). This approach has been evaluated in two small studies [82,83]. 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 [82].

Exposure to rifamycins prior to the development of CDI and repeated courses of rifaximin are risk factors for rifampin-resistant CDI [84]. Therefore, we would not use rifaximin for patients who have received it during a prior CDI episode or who had exposure to rifamycins prior to developing CDI.

Use of secondary prophylaxis during concomitant antibiotic use may be useful for prevention of recurrent infection; this is discussed further below. (See 'Secondary prevention' below.)

Third or subsequent recurrence — For patients with multiple recurrences of CDI who have received appropriate antibiotic treatment for at least three CDI episodes (ie, initial episode plus two recurrences), we favor FMT in regions where expertise is available. (See 'Role of fecal transplant' below.)

FMT consists of instillation of processed stool collected from one or more healthy donors into the intestinal tract of a patient with recurrent CDI. Pretreatment evaluation for and administration of FMT is discussed further separately. (See "Fecal microbiota transplantation for

treatment of Clostridioides (formerly Clostridium) difficile infection", section on 'Clinical approach'.)

FMT appears to be safe with generally self-limited mild to moderate adverse events [1,85-88]. 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 [79,85,89-92]. 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 [93]. 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) [92].

Additional details related to FMT are discussed separately. (See "Fecal microbiota transplantation for treatment of Clostridioides (formerly Clostridium) difficile infection", section on 'Safety and efficacy'.)

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 fecal transplant 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) [1,8,12,94].

Data regarding the benefit of parenteral metronidazole are limited. Its use 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) [95]. However, in a subsequent retrospective study including 2114 patients (of whom 993 received dual therapy), there was no association between dual therapy and death, colectomy within 90 days, or CDI recurrence [96].

With concomitant ileus — 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 via enema). 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 [8,97-99]:

- If FMT is available, we suggest its use 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) [8,97-99]. The optimal dosing of intracolonic vancomycin has not been established by clinical trials, and case descriptions vary widely; rectal vancomycin 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, duration of therapy is generally at least 10 days but should be individualized to the clinical course. If recovery is delayed, treatment can be extended to 14 days.

Additional considerations — 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) [1,55,56]. 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.

Data on the optimal treatment of patients with fulminant disease are limited. The preference for oral (or enteric) vancomycin is based on evidence in severe (but not fulminant disease) presented above (see 'Severe disease' above). We do not use fidaxomicin in fulminant disease because of lack of evidence and experience with this agent in this setting.

The rationale for the addition of intravenous metronidazole is that there may be delayed passage of oral antibiotics from the stomach to the colon. Fecal metronidazole concentrations in the therapeutic range can be achieved with intravenous metronidazole because of biliary and intestinal excretion of the drug. However, it is uncertain whether intravenous metronidazole alone is as effective as oral vancomycin therapy [39,95,100-102].

Reports in the literature of the use of rectal vancomycin for CDI are limited [1,97,98,103,104]. 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 [97].

Role of fecal transplant — The circumstances in which FMT is likeliest to be beneficial are uncertain; data on use of FMT for management of fulminant CDI are limited to retrospective and observational studies. (See 'Role of fecal transplant' 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) 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 (formerly Clostridium) 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 'Surgery' above.)

ALTERNATIVE THERAPIES

Other therapeutic options for CDI are discussed below; based on available data, none warrants routine use for management of CDI [105].

- Probiotics – We do not favor adjunctive administration of probiotics for treatment of CDI, in agreement with society guidelines [8]. 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 [106-108].
- 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 [16]. Combination therapy has been tried without success [109]. 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 [110]. Teicoplanin may be at least as effective as vancomycin or metronidazole, although it is costly and is not available in the United States [111,112].

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) [113].

- 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 [114-116], a retrospective review of 18 patients who received IVIG demonstrated no significant difference in clinical outcomes compared with 18 matched control cases [117].

- Anion-binding resins – The importance of toxin production in the pathophysiology of *C. difficile* diarrhea has prompted consideration of anion-binding resins as a possible alternative to antimicrobial therapy [118]. Tolevamer is a *C. difficile* toxin-binding resin developed specifically for CDI [119,120]. 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 [26,119]. Similarly, the anion-binding resins colestipol and cholestyramine are not effective as primary therapy for *C. difficile* colitis [121,122].

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 (formerly Clostridium) difficile infection: Prevention and control".)

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

- Minimizing antibiotic use (see "Clostridioides (formerly Clostridium) difficile infection: Prevention and control", section on 'Antibiotic stewardship' and "Clostridioides (formerly

Clostridium) difficile infection in adults: Epidemiology, microbiology, and pathophysiology", section on 'Antibiotic use')

- Avoiding gastric acid suppression (see "Clostridioides (formerly Clostridium) 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 placebo (zero versus six cases) [123]. Two patients in the placebo 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 [124,125]; 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 [114,126-130].

We do not favor administration of probiotics for prevention of CDI, in agreement with society guidelines [1,8]. There are multiple studies of various probiotics for CDI prevention; the data are highly inconsistent [107,108,131-137]. 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 *Saccharaomyces 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 – In patients with a recent history of CDI (in the preceding 12 months) who require systemic antibiotic therapy,

secondary prophylaxis with oral vancomycin may reduce the likelihood of CDI recurrence, although data are mixed [22,23]. The optimal dose of oral vancomycin for secondary prophylaxis is uncertain; reasonable regimens may consist of standard dosing (125 mg orally four times daily) or reduced dosing (125 to 250 mg once or twice daily) [23]. We typically administer oral vancomycin (125 mg orally once daily) for the duration of the antibiotic treatment course plus an additional tail of one week. Metronidazole should not be used for secondary prophylaxis because of its dose-dependent association with peripheral neuropathy.

Prospective, randomized study of secondary prophylaxis for prevention of CDI is needed [1]. In one retrospective study including 172 patients with at least two prior CDI episodes subsequently started on other antibiotics, prophylaxis with oral vancomycin (125 mg orally four times daily) 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 [22]. 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 [138]. 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 is conflicting.

- Monoclonal antibodies – In a study of patients treated with standard of care antibiotics for CDI, higher endogenous antibody titers against toxin B, but not toxin A, were associated with lower subsequent recurrence rates [139]. Similarly, adjunctive use of monoclonal antibodies against *C. difficile* toxin may also reduce the recurrence rate of CDI [130,140,141]. Bezlotoxumab (a monoclonal antibody that binds to *C. difficile* toxin B) received US Food and Drug Administration approval in 2016 for secondary prevention of CDI in patients at high risk for recurrence (including patients >65 years of age and those with a prior history of CDI) [142]. In two randomized trials including more than 2500 patients, use of bezlotoxumab together with standard oral antibiotic therapy was associated with a lower rate of recurrent infection than oral antibiotic therapy alone (17 versus 28 percent in the first trial; findings were similar in the second trial) [140]. The response to bezlotoxumab did not appear to vary by the antibiotic used to treat CDI (metronidazole, vancomycin, fidaxomicin), although the study was not designed to evaluate this question. The addition of actoxumab (a monoclonal antibody that binds to *C. difficile* toxin A) did not improve efficacy. There remain a number of unresolved issues to guide placement of bezlotoxumab in perspective with other approaches to treatment of CDI (including fecal microbiota

transplant); these include identifying which patients are most likely to benefit as well as cost-effectiveness analyses.

- 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 [143-145]. 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) [145].

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 (formerly Clostridium) 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: Antibiotic-associated diarrhea (C. difficile infection) (The Basics)")
- Beyond the Basics topic (see "Patient education: Antibiotic-associated diarrhea caused by Clostridioides (formerly Clostridium) difficile (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- The initial step in the treatment of *Clostridioides* (formerly *Clostridium*) *difficile* infection (CDI) is cessation of the inciting antibiotic as soon as possible. Infection control practices must be implemented, including contact precautions and hand hygiene. 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. (See 'General principles' above.)

- There is no consensus definition for severe or fulminant CDI. Determination of disease severity is left to clinician judgment and may include any or all of the following criteria (based on expert opinion) (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 (previously referred to as severe, complicated CDI) – Hypotension or shock, ileus, or megacolon

- The approach to management of nonfulminant disease varies depending on disease severity and whether the patient presents with an initial episode or a recurrent episode. (See 'Nonfulminant disease' above.)

  - Initial episode:

    - Management of nonsevere CDI consists of antibiotic therapy. For initial treatment of nonsevere CDI, we suggest oral vancomycin or fidaxomicin (**Grade 2B**). Both are more effective than metronidazole. Dosing is summarized in the table (table 2). The duration of therapy is 10 days. In patients who are recovering or whose symptoms have resolved, repeat stool assays are not warranted during or following treatment. (See 'Nonsevere disease' above.)

    - Management of severe CDI consists of antibiotic therapy and assessment for surgical indications (table 3). For treatment of severe CDI, we recommend oral vancomycin rather than metronidazole (**Grade 1B**). Fidaxomicin is a reasonable

alternative to vancomycin, although data are somewhat limited in this setting. Dosing is summarized in the table (table 2). The standard duration of therapy is 10 days; however, the duration should be individualized depending on clinical course (See 'Severe disease' above.)

- 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. The approach to antibiotic management of nonfulminant recurrent CDI varies depending on the number of recurrences and the agent(s) used previously (table 2) (see 'Recurrent episode' above):

  - For patients with a first or second recurrent CDI episode treated with vancomycin for the initial episode, we suggest treatment pulse-tapered oral vancomycin or oral fidaxomicin (**Grade 2C**). Fidaxomicin is associated with a lower recurrence rate than standard vancomycin therapy, but vancomycin is less expensive. For patients with a first recurrent CDI episode treated with fidaxomicin or metronidazole for the initial episode, we treat with standard oral vancomycin. (See 'First recurrence' above.)

  - For patients with frequently recurring CDI (≥3 recurrences), we suggest fecal microbiota transplantation (FMT) in settings where available (**Grade 2B**). (See 'Third or subsequent recurrence' above and "Fecal microbiota transplantation for treatment of Clostridioides (formerly Clostridium) difficile infection".)

  For patients with recurrent CDI that is severe, management consists of antibiotic therapy (as outlined above) and assessment for surgical indications (table 3); further study of the role of FMT in treatment of severe CDI is needed. (See 'Recurrent episode' above.)

- 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 antibiotic 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) (**Grade 2C**), rather than rectal vancomycin. However, because of the risk of colonic perforation, such procedures 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.)

- For patients with a recent history of CDI who require systemic antibiotic therapy, 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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Topic 2698 Version 96.0

GRAPHICS

Antimicrobial agents that may induce *Clostridioides* (formerly *Clostridium*) *difficile* diarrhea and colitis

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

* 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.*
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Graphic 55479 Version 10.0

Antibiotic regimens for the treatment of *Clostridioides* (formerly *Clostridium*) *difficile* infection in adults

Clinical condition	Treatment*
Nonfulminant disease	
Initial infection	
Nonsevere disease Supportive clinical data: White blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL	▪ Vancomycin 125 mg orally 4 times daily for 10 days, **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days ▪ If above agents are unavailable: Metronidazole[¶] 500 mg orally 3 times daily for 10 days
Severe disease[Δ] Supportive clinical data: White blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL	▪ Vancomycin[◊] 125 mg orally 4 times daily for 10 days, **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days
Recurrent infection (Nonsevere or severe disease)	
First recurrence	▪ If vancomycin was used for the initial episode: • Vancomycin pulsed-tapered regimen: ○ 125 mg orally 4 times daily for 10 to 14 days, then ○ 125 mg orally twice daily for 7 days, then ○ 125 mg orally once daily for 7 days, then ○ 125 mg orally every 2 or 3 days for 2 to 8 weeks, **OR** • Fidaxomicin 200 mg orally twice daily for 10 days ▪ If fidaxomicin or metronidazole was used for the initial episode: Vancomycin 125 mg orally 4 times daily for 10 days
Second or subsequent recurrence	▪ Vancomycin pulsed-tapered regimen (outlined above), **OR** ▪ Fidaxomicin 200 mg orally twice daily for 10 days, **OR** ▪ Vancomycin followed by rifaximin: • Vancomycin 125 mg orally 4 times per day for 10 days, then • Rifaximin 400 mg 3 times daily for 20 days, **OR** ▪ FMT[§]
Fulminant disease[Δ] (Previously referred to as severe, complicated *C. difficile* infection) Supportive clinical data: Hypotension or shock, ileus, megacolon	
Initial episode	▪ Enteric vancomycin plus parenteral metronidazole[¥]: • Vancomycin[◊] 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)[†] • 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)**
Recurrent episode	▪ Antibiotics as for initial fulminant episode above ▪ Some favor FMT in the context of a first or second recurrence that presents as a fulminant episode

CDI: *Clostridioides* (formerly *Clostridium*) *difficile* infection; FMT: fecal microbiota transplantation.

* Randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment; in such circumstances, extending treatment duration to 14 days is reasonable.

¶ Metronidazole should be avoided in patients who are very elderly or infirm or who develop CDI in association with inflammatory bowel disease.

Δ 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.

◊ 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 renal insufficiency (creatinine clearance <10 mL/minute). Therefore, monitoring serum vancomycin levels is warranted for patients with renal failure who have severe or fulminant colitis and require a prolonged course (>10 days) of enteral vancomycin therapy.

§ Where available, FMT is the preferred management approach for patients with third or subsequent recurrence. Appropriate antibiotic treatment for at least two recurrences (ie, three CDI episodes) should be attempted prior to offering FMT.

¥ 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 administration protocols. Given potential risk of perforation in the setting of CDI, a reduced volume enema (100 mL per rectum every 6 hours) may be used.

** 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).

Adapted from: 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(7):987-994. By permission of Oxford University Press on behalf of IDSA and SHEA. Copyright © 2018. Available at: https://www.idsociety.org/practice-guideline/clostridium-difficile/.

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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

Ciarán P Kelly, MD Equity Ownership/Stock Options: Cour Pharmaceuticals [Celiac disease]; Glutenostics [Celiac disease diagnostic]. Grant/Research/Clinical Trial Support: Aptalis [Celiac disease]; Merck [C difficile infection]; National Institutes of Health [C difficile]. Consultant/Advisory Boards: Artugen [C difficile infection]; Cour Pharmaceuticals [Celiac disease]; Finch [C difficile infection]; Glutenostics [Celiac disease diagnostic]; Innovate [Celiac disease]; J&J Jannsen [Celiac disease]; Kanyos [Celiac disease]; Matrivax [C difficile infection]; Merck [C difficile infection, celiac disease]; Seres Therapeutics [C difficile infection]; Summit [C difficile infection]; Takeda [Celiac disease]; Teravance [Celiac disease]; Vedanta [C difficile infection]. **J Thomas Lamont, MD** Nothing to disclose **Johan S Bakken, MD, PhD** Nothing to disclose **Stephen B Calderwood, MD** Equity Ownership: Pulmatrix [Infectious diseases]. Consultant/Advisory Boards: Day Zero Diagnostics [Whole genome sequencing for microbial identification and determination of antimicrobial susceptibility]. **Elinor L Baron, MD, DTMH** Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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