

Treatment of antibiotic-associated diarrhea caused by *Clostridium difficile*

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INTRODUCTION — *Clostridium difficile* associated disease (CDAD) is one of the most common hospital-acquired (nosocomial) infections, and is an increasingly frequent cause of morbidity and mortality among elderly hospitalized patients. *C. difficile* colonizes the human intestinal tract after the normal gut flora has been altered by antibiotic therapy and is the causative organism of antibiotic-associated pseudomembranous colitis.

The treatment of CDAD, including initial management, management of relapse, and management of severe disease, will be reviewed here [1]. The pathophysiology, epidemiology, clinical manifestations, and diagnosis are discussed separately. (See "[Epidemiology, microbiology, and pathophysiology of *Clostridium difficile* infection](#)" and "[Clinical manifestations and diagnosis of *Clostridium difficile* infection](#)".)

GENERAL MANAGEMENT PRINCIPLES — An important initial step in the treatment of CDAD is cessation of the inciting antibiotic as soon as possible. If ongoing antibiotics are essential for treatment of the primary infection, it may be prudent, if possible, to select antibiotic therapy that is less frequently implicated in antibiotic-associated diarrhea, such as aminoglycosides, sulfonamides, macrolides, [vancomycin](#), or [tetracycline](#).

Management must also include implementation of infection control policies. Patients with suspected or proven *C. difficile* infection should be placed on contact precautions, and healthcare workers should wash hands before and after patient contact. Hand hygiene with soap and water is recommended over alcohol-based hand sanitizers, since *C. difficile* spores are resistant to killing by alcohol. (See "[Prevention and control of *Clostridium difficile* in hospital and institutional settings](#)".)

In addition, antimotility agents such as [loperamide](#) and opiates have traditionally been avoided in CDAD, but the evidence that they cause harm is equivocal [2,3]. Supportive care with attention to correction of fluid losses and electrolyte imbalances is also important. Patients may have regular diet as tolerated, unless surgery or other procedure is planned.

INDICATIONS FOR TREATMENT — Patients with typical manifestations of *C. difficile* (eg, diarrhea, abdominal pain or nausea and vomiting) and a positive diagnostic assay should receive antibiotics for treatment for *C. difficile* [4]. Empiric therapy is appropriate pending results of diagnostic testing if the clinical suspicion is high. Treatment of *C. difficile* is not indicated in patients who have a positive toxin assay but are asymptomatic. (See "[Clinical manifestations and diagnosis of *Clostridium difficile* infection](#)", section on 'Diagnosis'.)

INITIAL THERAPY FOR NON-SEVERE DISEASE — Standard therapy for CDAD consists of oral [metronidazole](#) or oral [vancomycin](#) [5]. Formal guidelines published in the 1990s advocate metronidazole

over vancomycin as first-line therapy [6-9]. Reasons include the lower cost of metronidazole relative to vancomycin and the comparable clinical effectiveness in non-severe disease. In addition, use of metronidazole has also been favored over vancomycin to limit the spread of vancomycin-resistant enterococci (VRE), although subsequent data has suggested that the risk of bowel VRE colonization is equivalent with these drugs [10,11].

Several randomized trials have demonstrated equivalent efficacy of [metronidazole](#) and [vancomycin](#) for the treatment of non-severe CDAD [12-14]. As an example, a prospective, randomized double-blind trial included 81 patients with mild CDAD; metronidazole and vancomycin produced similar rates of clinical cure (90 versus 98 percent) [12].

Observational study of *C. difficile* disease in Canada during 1991 to 2003 preliminarily suggested that patients treated with [metronidazole](#) for an initial episode of CDAD may be at increased risk for relapse [15,16]. However, review of the data through 2006 demonstrated a similar trend in the frequency of recurrences for both metronidazole and [vancomycin](#), suggesting that the rise in recurrence rate during 2003-2004 for patients treated with either drug may have corresponded to reinfection during a period when in-hospital exposure to *C. difficile* spores was very high [17,18].

Limitations of [metronidazole](#) include dose-dependent peripheral neuropathy and side effects of nausea and metallic taste. Although the above studies are limited because of their observational methodologies, the findings raise the possibility that metronidazole may be less effective than oral [vancomycin](#) [19]. Nevertheless, metronidazole remains the initial therapy of choice for non-severe CDAD pending further study. The treatment of severe disease is discussed below. (See '[Management of severe disease](#)' below.)

Antibiotic dosing — [Metronidazole](#) should be used for initial treatment of non-severe CDAD. The recommended regimen is 500 mg three times daily or 250 mg four times daily for 14 days. As discussed below, intravenous metronidazole at a dose of 500 mg every eight hours may also be used for treatment of CDAD in patients in whom oral therapy is not feasible. Fecal concentrations in the therapeutic range are achievable with this regimen because of the drug's biliary excretion and increased exudation across the intestinal mucosa during CDAD [20].

If oral [vancomycin](#) is used, the recommended dose is 125 mg four times daily. Oral vancomycin is not absorbed systemically and achieves predictably high levels in the colon. Dosing regimens of 125 mg four times daily and 500 mg four times daily are equally effective for the treatment of CDAD ([graph 1](#)) [21]. Intravenous vancomycin has no effect on *C. difficile* colitis since the antibiotic is not excreted appreciably into the colon.

Duration of therapy — The recommended duration of initial antibiotic therapy for non-severe *C. difficile* diarrhea is 14 days. Patients with an underlying infection requiring prolonged duration of antibiotics should continue CDAD treatment throughout the antibiotic course plus one additional week after its completion.

Repeat stool toxin assays are NOT warranted following treatment. Up to 50 percent of patients have positive stool assays for as long as six weeks after the completion of therapy [21].

NON-SEVERE RELAPSE — Relapse is defined by complete abatement of CDAD symptoms while on appropriate therapy, followed by subsequent reappearance of diarrhea and other symptoms after treatment has been stopped. Relapse should be distinguished from persistent diarrhea without resolution during initial therapy, which should prompt an evaluation for other causes. In the absence of an alternative diagnosis, such patients should be considered to have refractory illness.

Relapse of CDAD should also be distinguished from reinfection with the same or a different strain of *C. difficile* [22-24]. Studies using molecular methods have shown that up to one-half of recurrent

episodes are reinfections rather than relapses of infection with the original strain [25,26].

Relapse occurs in 10 to 25 percent of cases treated with [metronidazole](#) or [vancomycin](#), and patients may experience several episodes of relapsing colitis [9,13,27-30]. Most relapses occur within one to two weeks after discontinuing antibiotic therapy, although relapses rarely can occur as late as two to three months. Relapse tends to occur in the setting of mild disease; patients with fulminant colitis tend to manifest with severe symptoms during the initial episode of infection. This may be related to variability in host immune response to *C. difficile* infection. (See "[Epidemiology, microbiology, and pathophysiology of Clostridium difficile infection](#)".)

Risk factors for relapse include prolonged antibiotic use, prolonged hospitalization, age >65 years, diverticulosis, comorbid medical conditions and severe illness [28,31-33]. Patients with at least one episode of recurrent *C. difficile* have a 50 to 65 percent chance of additional episodes [34].

Pathophysiology — The mechanism of relapsed CDAD following initial infection is not fully understood. It may be due to persistent spores from the initial infection. *C. difficile* spores in colonic diverticula, for example, may escape mechanical clearance by peristalsis and may have limited exposure to antibiotic levels in the lumen [28].

Impairment of the host immune response to *C. difficile* toxins may also be an important mechanism for relapse. Asymptomatic carriers of *C. difficile* tend to have high serum antibody levels against toxin A [35], while patients with relapsing *C. difficile* diarrhea tend to have lower anti-toxin antibody levels than patients with a single, brief episode of diarrhea [31,36-38].

Antibiotic resistance does not appear to be a factor in relapse. However, treatment with [metronidazole](#) or [vancomycin](#) for an initial episode of CDAD may alter the colonic microenvironment (with regard to flora or other factors), potentially increasing susceptibility to relapse or subsequent reinfection. (See '[Metronidazole failure](#)' below.)

Management of initial relapse — The signs and symptoms of relapse are similar to those in the initial episode, usually without progression in severity [39]. Because a positive stool toxin assay does not exclude asymptomatic carriage, other causes for diarrhea should be considered, including other infections, inflammatory bowel disease, or irritable bowel syndrome. Colonoscopy should be considered in atypical cases to evaluate for evidence of CDAD and to exclude other etiologies.

There does not appear to be an association between the treatment agent given for first relapse ([metronidazole](#) or [vancomycin](#)) and the risk of subsequent relapse [32,40]. Failure to respond to metronidazole should not be interpreted as evidence of a metronidazole-resistant organism. (See '[Metronidazole failure](#)' below.)

Patients with mild symptoms of relapse who are otherwise well may be managed conservatively, without antibiotic therapy. If symptoms are persistent or if the patient is elderly or has other underlying comorbidities, initial relapse following therapy for CDAD should be treated with [metronidazole](#). The decision to administer [vancomycin](#) as treatment for first relapse should be based upon the presence of markers of severe disease at the time of first recurrence, rather than on previous drug exposure. ([table 1](#)) and (see '[Management of severe disease](#)' below).

Management of subsequent relapse — Patients with one relapse have a substantial risk of further episodes of *C. difficile* diarrhea after the second course of antibiotic therapy is discontinued. In one study, for example, patients with one or more previous relapses had a subsequent relapse rate of 65 percent following standard therapy with [metronidazole](#) or [vancomycin](#) [30].

If the patient relapses after a second course of [metronidazole](#) or [vancomycin](#), other causes for the patient's symptoms should also be considered. A positive stool cytotoxin assay is not diagnostic, since

it does not exclude asymptomatic carriage.

There are no rigorous studies of management for multiple relapses of CDAD. Patients with multiple relapses may benefit from tapering dose and intermittent antibiotic therapy with or without the use of probiotics.

Intermittent antibiotic therapy — The use of intermittent antibiotic therapy is based upon a theory that *C. difficile* relapse may be due to the presence of persistent spores that survive antibiotic therapy. Intermittent therapy may allow the spores to germinate on the days when no antibiotics are administered. Once the spores have converted to the fully functional vegetative, toxin-producing forms, they are susceptible to killing when the antibiotics are readministered. (See "[Epidemiology, microbiology, and pathophysiology of Clostridium difficile infection](#)".)

Intermittent antibiotics can be administered as a pulsed or tapered regimen. A pulsed regimen consists of the same drug dose administered every few days; a tapered regimen consists of a stepwise decrease in dose over a period of time. Prolonged antibiotic therapy, with or without intermittent dosing, may also be important for definitive treatment.

Intermittent and prolonged [vancomycin](#) regimens have been evaluated in observational studies [[28,40](#)]. In one study of 163 CDAD cases, for example, 29 patients were treated with a vancomycin tapered regimen and seven were treated with a vancomycin pulse regimen; relapse rates were 31 and 14 percent, respectively [[40](#)].

Probiotics — Studies of probiotics are inconclusive regarding treatment benefit. The supporting data are presented separately. (See "[Clostridium difficile and probiotics](#)" and "[Probiotics for gastrointestinal diseases](#)", section on 'Antibiotic-associated diarrhea'.)

Rifaximin — A small case series has suggested that sequential therapy with [vancomycin](#) followed by [rifaximin](#) may be effective for the treatment of recurrent CDAD [[41](#)]. Eight women with recurrent CDAD received a two week course of rifaximin when they were asymptomatic, immediately after completing their last course of vancomycin. Seven of the eight had no further recurrence of infection.

We suggest management of a second relapse with intermittent and tapering antibiotic therapy with or without probiotics as outlined in Table 1 ([table 1](#)). We suggest management of subsequent relapses with [vancomycin](#) followed by [rifaximin](#).

However, exposure to rifamycins before the development of CDAD is a risk factor for [rifampin](#) resistant *C. difficile* infection. In such cases, the use of [rifaximin](#) for treatment of CDAD may be limited [[42](#)].

[[43](#)]

SEVERE DISEASE

Definition — Patients with acute *C. difficile* infection may develop signs of systemic toxicity with or without profuse diarrhea warranting admission to an intensive care unit or emergency surgery. These more severe manifestations occur more frequently in the setting of initial *C. difficile* infection than with relapse.

There is no consensus definition for severe CDAD, nor is there agreement as to the most important clinical indicators that should be used to differentiate severity [[12,16,44](#)]. The following illustrate some definitions that have been described in the literature:

- Clinicians in the setting of the Quebec outbreak identified a white blood cell count >20,000 cells/microL and an elevated serum creatinine as potential indicators of complicated disease [[16](#)]. Significantly elevated white blood cell counts in the absence of any other positive cultures should raise

a suspicion for *C. difficile* infection.

- As part of a randomized trial comparing [metronidazole](#) to [vancomycin](#), a scoring system was devised to identify patients with severe infection [12]. One point each was given for age >60 years, temperature >38.3°C, serum albumin <2.5 mg/dL (25 g/L), or peripheral white blood cell count >15,000 cells/microL within 48 hours of enrollment. Two points were given for endoscopic evidence of pseudomembranous colitis or treatment in the intensive care unit. Patients with two or more points were considered to have severe disease.
- In a phase 3 trial of tolevamer versus [vancomycin](#) and [metronidazole](#), severe disease was defined as ≥10 bowel movements per day, a peripheral white blood cell count ≥20,000 cells/microL or severe abdominal pain [45].

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 criteria mentioned above.

Incidence — Severe disease is more common during the initial CDAD episode. Data on the incidence are limited, especially given the lack of a consensus definition. The risk of complications during first CDAD recurrence in the Quebec outbreak caused by the hypervirulent NAP1 strain was 11 percent [32]. Complications included shock, need for colectomy, megacolon, perforation, or death within 30 days. Older age, high leukocyte count, and acute renal failure were strongly associated with a complicated course.

MANAGEMENT OF SEVERE DISEASE — Patients with severe CDAD (by clinician judgment) should receive antibiotic therapy, supportive care, and close monitoring. Surgery should be considered if the patient's clinical status fails to improve. 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 [27]. (See "[Toxic megacolon](#)" and '[Surgery](#)' below.)

Antibiotics — Guidelines published in the 1990s recommended oral [metronidazole](#) over oral [vancomycin](#) as first-line therapy for both mild and severe CDAD [6-9]. This recommendation was based upon studies showing equivalent cure rates, although there was no stratification according to disease severity, the sample sizes were small, and the studies were performed before the appearance of hypervirulent isolates [13,14].

The major pharmacologic advantage of [vancomycin](#) over [metronidazole](#) is that it is not absorbed, so maximal quantities of vancomycin can act intracolonicly at the local site of toxin production. The major advantage of metronidazole over vancomycin is that the cost of metronidazole is substantially lower. With respect to in vitro activity, risk of relapse, and potential for emergence of vancomycin resistant enterococci, the drugs appear to be relatively similar [10,18,46-48].

Oral [vancomycin](#) is the preferred therapy for severe or refractory cases [12,32,45,49]. This issue was directly addressed in a prospective, randomized double-blind trial that included 69 patients with severe CDAD as defined above [12]. The cure rate was significantly higher with vancomycin (97 versus 76 percent with [metronidazole](#)). (See '[Definition](#)' above.)

Although the data are limited, clinical practice is shifting toward using oral [vancomycin](#) as initial therapy for severe CDAD [50]. Some have endorsed vancomycin as the preferred therapy for moderate or severe disease caused by the epidemic strain; others favor its use for all patients with severe and/or complicated disease [18,46,51].

Oral antibiotics — Oral [vancomycin](#) (125 mg four times daily) or oral [metronidazole](#) (500 mg three times daily or 250 mg four times daily for 14 days) should be initiated promptly for severely ill patients. Some data suggest that levels achieved with higher dosing of vancomycin (500 mg four times daily)

may be equivalent to levels with standard dosing [21]. Nevertheless, many clinicians favor higher dosing for severe disease although there is no supportive evidence.

Intravenous antibiotics — Severely ill patients with ileus may have markedly delayed passage of oral antibiotics from the stomach to the colon. These individuals may benefit from the addition of intravenous [metronidazole](#) at a dose of 500 mg every eight hours. Fecal concentrations in the therapeutic range are achieved with this regimen because of biliary and intestinal excretion of the drug [20]. In contrast, intravenous [vancomycin](#) has no effect on *C. difficile* colitis since vancomycin is not excreted into the colon.

Intracolonic antibiotics — Intracolonic [vancomycin](#) (vancomycin enema) may be an effective adjunctive therapy for patients who cannot tolerate oral preparation, although data are limited [52-54]. In a case series of nine patients with refractory symptoms, toxic megacolon, or fulminant colitis, rectal vancomycin was administered in addition to standard antibiotics [52]. Rectal vancomycin (0.5 to 1 g dissolved in one to two liters of isotonic saline) was given as a single 60 minute retention enema every 4 to 12 hours. Eight patients had complete resolution of symptoms and one patient died from multisystem organ failure.

Thus, intracolonic [vancomycin](#) may be effective adjunctive therapy for CDAD in selected patients. It may be especially useful in the setting of profound ileus that impairs the distal delivery of orally administered drugs.

Antibiotic recommendation — Patients with severe disease should be treated with high dose oral [vancomycin](#) (500 mg four times daily) together with intravenous [metronidazole](#) (500 mg every eight hours). Intracolonic vancomycin may be considered in patients with profound ileus.

The standard duration of antibiotic therapy for *C. difficile* diarrhea is 10 to 14 days; the antibiotic course should be tailored to clinical circumstances for patients with severe disease. Those with an underlying infection requiring prolonged duration of antibiotics should continue CDAD treatment throughout the antibiotic course plus one additional week after its completion.

Surgery — Some severely ill patients with CDAD require emergency colectomy because of toxic megacolon-associated ileus, perforation or impending perforation, necrotizing colitis or rapidly progressive and/or refractory septicemia [55]. Although the optimal timing of surgery remains uncertain, it is fairly clear that the appropriate surgical intervention for CDAD is subtotal colectomy (removal of the entire colon without removal of the rectum) with ileostomy [43].

Timing of surgery — Literature written prior to the emergence of the hypervirulent strain suggested surgery for CDAD patients with severe disease unresponsive to medical therapy within 48 hours, bowel perforation, or multiorgan system failure [56]. However, in the setting of CDAD due to the hypervirulent strain, some patients progressed from severe disease to death in less than 48 hours. Furthermore, some patients with severe disease cannot receive enteral therapy due to ileus or severe nausea and vomiting.

Data from the Canadian outbreak with the hypervirulent strain have been used to try to standardize criteria for surgical intervention. In a retrospective review, colectomy was most beneficial for immunocompetent patients aged ≥ 65 years with a white blood cell count $\geq 20,000$ cells/microL and/or a plasma lactate between 2.2 and 4.9 meq/L [57].

We favor early surgery for patients with the above criteria. In addition, surgical intervention is advisable in the setting of peritoneal signs, severe ileus, or toxic megacolon.

Subtotal colectomy — Patients undergoing emergency surgical intervention for CDAD should be managed with subtotal colectomy and ileostomy [57-60]. In a retrospective review of 14 patients who

underwent surgery for severe CDAD, nine patients survived, of whom eight had subtotal colectomy and one had a right hemicolectomy [58]. Four of the five patients who died had undergone left hemicolectomy.

Primary anastomosis is not feasible acutely due to the pancolitis associated with severe disease. However, after colonic inflammation has subsided, closure of the ileostomy and ileorectal anastomosis can be created.

METRONIDAZOLE FAILURE — The reasons for [metronidazole](#) failure are poorly understood [61]. Stool metronidazole concentrations in patients receiving the drug orally are higher in watery stools at the beginning of CDAD treatment than in semiformal stools a few days later [20]. Thus, stool metronidazole levels decrease as colonic inflammation subsides. In contrast, oral [vancomycin](#) maintains high stool concentrations (1000 to 3000 mcg/mL throughout the course of therapy) [20,62].

Given these observations, even a modest increase in an organism's minimum inhibitory concentration for [metronidazole](#) might lead to insufficient stool levels after a few days of treatment. Although some metronidazole resistance in *C. difficile* has been described [63-67], resistance rates are low and do not appear to be increasing in the setting of the rising rates of treatment failure [29,68-70].

Risk factors associated with [metronidazole](#) failure include recent cephalosporin use, *C. difficile* on admission and transfer from another hospital [71].

ALTERNATIVE THERAPIES — Other therapeutic options for CDAD are being developed, and drugs used for other infections are being studied as alternatives to [metronidazole](#) and [vancomycin](#) [72].

Probiotics — Studies of probiotics are inconclusive regarding benefit. The data are presented separately. (See "[Clostridium difficile and probiotics](#)".)

Alternative antibiotics — A meta-analysis of 12 studies (total of 1157 participants) evaluated eight different antibiotics for the treatment of CDAD: [vancomycin](#), [metronidazole](#), [fusidic acid](#), [nitazoxanide](#), teicoplanin, [rifampin](#), [rifaximin](#), and [bacitracin](#) [4]. In paired comparisons, no single antibiotic was clearly superior to others. Combination therapy has been tried without success [73].

[Nitazoxanide](#) may be as effective as [vancomycin](#) (as suggested by a randomized trial of 50 CDAD patients) although the small sample precluded conclusions about noninferiority of nitazoxanide to vancomycin [74].

Teicoplanin may be at least as effective as [vancomycin](#) or [metronidazole](#), although it is costly and is not available in the United States [13,75].

Anion-binding resins — The importance of toxin production in the pathophysiology of *C. difficile* diarrhea prompted consideration of anion-binding resins as a possible alternative to antimicrobial therapy [76]. An advantage of resin therapy is that the bowel floras are not altered, as occurs with [vancomycin](#) or [metronidazole](#). This may allow more rapid reconstitution of the normal colonic flora.

The anion-binding resins [colestipol](#) and [cholestyramine](#) are not effective as primary therapy for *C. difficile* colitis [77,78], although they may be beneficial as adjunctive therapy for relapsing infection [79]. In a series of 11 patients with relapsing CDAD, the administration of colestipol with tapered [vancomycin](#) led to sustained resolution in all patients [79].

Tolvamer is a novel *C. difficile* toxin binding resin developed specifically for CDAD [45,80]. Preliminary study suggests promising results, although it is not yet FDA approved or commercially available.

Anion-exchange resins bind [vancomycin](#) as well as toxins; thus, the resin must be taken at least two or three hours apart from the vancomycin [76]. Suggested regimens are [colestipol](#) (5 g every 12

hours) or [cholestyramine](#) (4 g three or four times daily) for one to two weeks, usually with vancomycin.

Intravenous immunoglobulin — Intravenous immunoglobulin (IVIG) contains *C. difficile* antitoxin 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 CDAD [[36,81,82](#)], a retrospective review of 18 patients who received IVIG demonstrated no significant difference in clinical outcomes compared with 18 matched control cases [[83](#)].

Fecal bacteriotherapy — Fecal bacteriotherapy may be considered for patients with severe and recurrent CDAD. (See "[Fecal bacteriotherapy in the treatment of recurrent *Clostridium difficile* infection](#)".)

INFORMATION FOR PATIENTS — Educational materials on this topic are available for patients. (See "[Patient information: Antibiotic-associated diarrhea \(*Clostridium difficile*\)](#)".) We encourage you to print or e-mail this topic review, or to refer patients to our public web site, www.uptodate.com/patients, which includes this and other topics.

SUMMARY AND RECOMMENDATIONS

- The initial step in the treatment of CDAD is cessation of the inciting antibiotic as soon as possible. (See '[General management principles](#)' above.)
- Infection control practices must be implemented, including contact precautions and hand hygiene. Hand hygiene must include soap and water, as alcohol based agents do not kill *C. difficile* spores. (See '[General management principles](#)' above.)
- We suggest oral [metronidazole](#) for initial treatment of non-severe CDAD (**Grade 2B**). (See '[Initial therapy for non-severe disease](#)' above.)
- We suggest oral [metronidazole](#) for treatment of a non-severe initial relapse of CDAD (**Grade 2C**). (See '[Management of initial relapse](#)' above.)
- We suggest intermittent and tapering [vancomycin](#) therapy with probiotics for treatment of non-severe second relapse of CDAD ([table 1](#)) (**Grade 2C**). (See '[Management of subsequent relapse](#)' above.)
- We suggest [vancomycin](#) therapy followed by [rifaximin](#) for treatment of non-severe subsequent relapse of CDAD ([table 1](#)) (**Grade 2C**). (See '[Management of subsequent relapse](#)' above.)
- We recommend oral [vancomycin](#) for treatment of severe disease (**Grade 1B**). In critically ill patients, in addition to oral vancomycin we suggest treatment with intravenous [metronidazole](#) (**Grade 2C**). Given the lack of efficacy data for adding intravenous metronidazole, some experts prefer to treat with oral vancomycin alone. (See '[Antibiotics](#)' above and '[Definition](#)' above.)
- We suggest intracolonic [vancomycin](#) for treatment of severe disease in patients with profound ileus (**Grade 2C**). (See '[Management of severe disease](#)' above, section on Antibiotics).
- We recommend urgent surgical evaluation for patients ≥ 65 years of age with a white blood cell count $\geq 20,000$ cells/microL and/or a plasma lactate between 2.2 and 4.9 meq/L. In addition, surgical

intervention is advisable in the setting of peritoneal signs, severe ileus, or toxic megacolon. (See ['Management of severe disease'](#) above, section on Surgery).

- For patients undergoing surgery, we recommend subtotal colectomy with ileostomy ([Grade 1C](#)). (See ['Management of severe disease'](#) above, section on Surgery).
- Potential alternative therapies requiring further investigation prior to routine use include new antibiotic agents, binding resins, intravenous immunoglobulin, and fecal bacteriotherapy. (See ['Alternative therapies'](#) above.)

[[84,85](#)]

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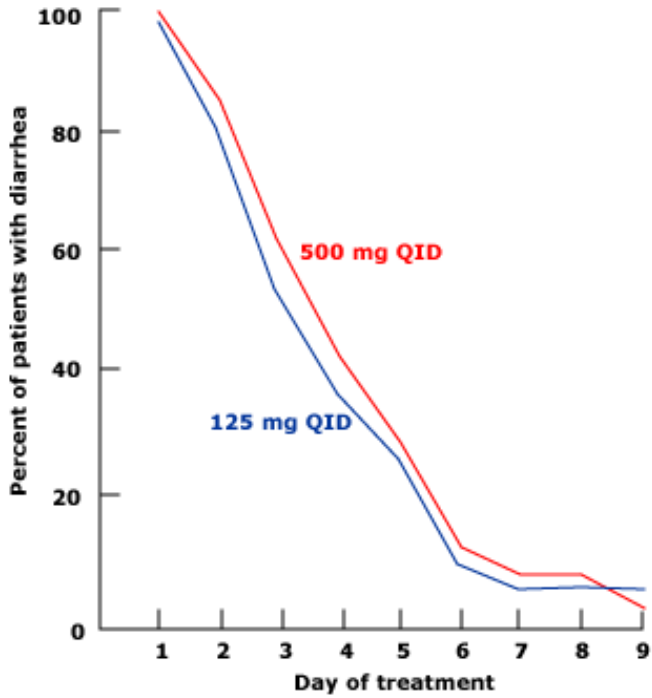
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GRAPHICS

High and low dose oral vancomycin are equally effective in acute *C. difficile* colitis



Disappearance of diarrhea was identical in patients with acute clostridium difficile colitis who received either high (500 mg four times daily, red line) or low (125 mg four times daily, blue line) dose oral vancomycin for 10 days.

Redrawn from Fekety, R, Silva, J, Kaufman, C, et al. Am J Med 1989; 86: 15.

Treatment of non-severe Clostridium difficile associated diarrhea**Initial episode**

Preferred: metronidazole (500 mg orally three times daily or 250 mg four times daily) for 10 to 14 days

Alternative: vancomycin (125 mg orally four times daily) for 10 to 14 days

First relapse

Confirm diagnosis (see text)

If symptoms are mild, conservative management may be appropriate

If antibiotics are needed, repeat treatment as in initial episode above

Second relapse^[1]

Confirm diagnosis (see text)

Tapering and pulsed oral vancomycin:

125 mg orally four times daily for 7 days

125 mg orally twice daily for 7 days

125 mg orally once for 7 days

125 mg orally every other day for 7 days

125 mg orally every 3 days for 14 days

A three week course of probiotics (eg, *Saccharomyces boulardii* 500 mg orally twice daily) may be used. The probiotics may be overlapped with the final week of the taper and continued for two additional weeks in the absence of antibiotics.

Subsequent relapse^[2]

Confirm diagnosis (see text)

Vancomycin 125 mg orally four times daily for 14 days, followed by

Rifaximin 400 mg twice daily for 14 days

Data from:

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

2. 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.