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Clostridium difficile Infection Management

Evidence Based Medicine Guideline

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SUMMARY
Treatment for *Clostridium difficile* infection (CDI) is based on disease severity. Mild and severe disease is best treated with oral vancomycin or fidaxomicin. Intravenous metronidazole and rectal vancomycin are reserved for patients with fulminant CDI or who cannot take oral medications. Any patient with fulminant CDI should be evaluated by a surgeon for subtotal colectomy with end-ileostomy. Multiple recurrent episodes of CDI is effectively treated with fecal microbiota transplantation.

RECOMMENDATIONS

- **Level 1**
  - **Antimicrobial CDI treatment duration should be at least 10 days. (See Table 1)**
  - **Initial episodes of mild and severe CDI should be treated with vancomycin 125 mg PO q 6 hrs or fidaxomicin 200 mg PO q 12 hrs***
  - **Fulminant CDI is treated with vancomycin 500 mg PO q 6 hrs and metronidazole 500 mg IV q 8 hrs with rectal vancomycin added in cases of severe ileus. (See Table 1)**
  - **Recurrent CDI should preferentially be treated with fidaxomicin (or vancomycin if resource limited). (See Table 2)**
  - **Recurrent CDI may also be treated with fecal microbiota transplantation.**
  - **If surgical management is warranted for severely ill patients, a subtotal colectomy with end ileostomy is recommended.**
- **Level 2**
  - **Upon suspicion or diagnosis of CDI, the inciting antibiotic or medication should be stopped if clinically possible.**
- **Level 3**
  - **Avoid anti-peristaltic agents as they could conceal symptoms and precipitate toxic megacolon by delaying toxin excretion.**
  - **Treatment duration may be increased to 14 days for patients who respond slowly to therapy or as indicated by clinical judgment.**
  - **An alternative to colectomy is loop ileostomy with intraoperative colonic lavage (using 8 L polyethylene glycol solution) followed by vancomycin flushes (500 mg mixed with 500 mL Lactated Ringer's) q 8 hrs for 10 days.**
  - **Alternative antibiotic therapy for multiply-recurrent CDI is vancomycin 125 mg PO q 6 hrs followed by either tapered or pulsed dosing regimens for the next 3-5 weeks.**
  - **Antimicrobial treatment should be started empirically in cases where laboratory confirmation may be significantly delayed or unavailable.**
  - **No recommendation exists regarding withholding or avoiding PPIs.**

*Consider fidaxomicin in patients with at least 2 of the following: ≥ 65 years of age, severe CDI (WBC ≥15,000 or <4,000 cells/mL, or SCr ≥1.5 mg/dL), or immunocompromised state

LEVEL OF RECOMMENDATION DEFINITIONS

- **Level 1:** Usually based on Class I data or strong Class II evidence if randomized testing is inappropriate. Conversely, low quality or contradictory Class I data may be insufficient to support a Level I recommendation.
- **Level 2:** Reasonably justifiable based on available scientific evidence and strongly supported by expert opinion. Usually supported by Class II data or a preponderance of Class III evidence.
- **Level 3:** Supported by available data, but scientific evidence is lacking. Generally supported by Class III data. Useful for educational purposes and in guiding future clinical research.

INTRODUCTION

Clostridium difficile infection (CDI) is diagnosed by the presence of at least one of the following (1):

1. Signs and symptoms of CDI plus microbiological evidence of infection (toxin or toxin-producing bacteria) with no other identifiable cause
2. Pseudomembranous colitis as seen on colonoscopic examination or pathological specimens

The signs and symptoms of CDI comprise three different clinical manifestations: diarrhea, ileus, and toxic megacolon (1). Diarrhea is defined as loose or watery stool that takes the shape of the collecting receptacle at least three times in a 24-hour period, or more frequently than is normal for the patient. Ileus is characterized by vomiting, constipation or obstipation, and/or radiographic evidence of dilated bowel. This presentation of CDI is seen in less than one percent of affected patients (2). Toxic megacolon is diagnosed when the colon is more than six centimeters in transverse dimension on imaging and there are signs of a severe systemic inflammatory response.

Disease due to CDI is classified as mild, severe, or fulminant. The characteristics of each classification are summarized below.

Mild	WBC < 15 x 10^3/ul AND Cr < 1.5
Severe	WBC > 15 x 10^3/ul OR Cr ≥ 1.5
Fulminant	All above criteria and the presence of hypotension, shock, ileus or megacolon

Recurrent CDI is defined as disease that recurs within eight weeks of treatment completion and symptom resolution (3). Up to 35% of patients treated for CDI experience a recurrence, and 65% of these patients will have multiply-recurrent disease (4). It is not possible to distinguish clinically between disease due to relapse of the initial infection or that due to reinfection with a new strain of *Clostridium difficile*. Therefore, the terms recurrence and relapse are often used interchangeably.

The treatment of CDI based on clinical severity is largely based on the 2017 Infectious Disease Society of America (IDSA) guidelines and the joint 2021 update from IDSA and the Society for Healthcare Epidemiology of America (5). These publications represent consensus guidelines based on the available evidence. Both panels followed a process which included a systematic weighting of evidence using the GRADE system.

TREATMENT OF MILD CDI

Previously, two randomized controlled trials before the year 2000 had shown that metronidazole and vancomycin are equally effective in treating mild and severe cases of CDI (6-7). However, a randomized controlled trial in 2007 by Zar et al. showed that treatment with oral vancomycin was superior and decreased recurrence rates compared to metronidazole (8). A 2014 study by Johnson et al. showed that both oral metronidazole and tolevamer were inferior to oral vancomycin in the treatment of CDI (9).

In 2011, the FDA approved a new antibiotic for the treatment of CDI: fidaxomicin. Several randomized controlled trials have supported its effectiveness in patients with mild CDI (10-13). Louie et al. conducted a non-inferiority study of fidaxomicin vs. vancomycin and found comparable initial cure rates (88% vs. 86% respectively) as well as a significant reduction in recurrence at four weeks (15% vs. 25%) (10). A similar study was performed by Cornely et al. with similar results for initial cure (88% resolution with fidaxomicin vs. 87% with vancomycin) and recurrence at four weeks (13% vs. 27%) (11). Two new RCTs have been published since the 2017 guidelines were released. One study by Guery et al. found that extended dose fidaxomicin had a similar clinical cure rate compared with standard vancomycin therapy at 2 and 12 days after the end of treatment as well as a statistically significant sustained clinical cure rate at 30 days (70% with fidaxomicin vs. 59% with vancomycin) (12). Mikamo et al. perfomed a similar study and found that patients treated with fidaxomicin vs. vancomycin had no significant difference in sustained clinical cure rate at 28 days (67% and 66% respectively) (13). With the addition of these two studies, the

Infectious Disease Society of America and the Society for Healthcare Epidemiology of America published a focused update to their 2017 guidelines recommending fidaxomicin over vancomycin as the first line treatment for initial and recurrent CDI episodes due to its sustained clinical response (5). They maintain that vancomycin remains an appropriate therapy. They do, however, acknowledge that fidaxomicin is expensive and the decision to use one or the other may be based on available resources.

The acquisition cost of a course of fidaxomicin is substantially higher than that for metronidazole or vancomycin in the USA which may limit first-line use in some settings with the most significant cost drivers being extended hospitalization and rehospitalization (14). Two US-based retrospective studies have compared the cost of treating CDI with fidaxomicin vs. vancomycin. Gallagher et al. performed a retrospective study of 95 hospitalized patients treated for CDI where fidaxomicin was administered to patients with a recurrence or elevated risk factors (15). Most had moderate to severe CDI. Vancomycin was the alternative. Use of fidaxomicin significantly reduced recurrence rates and length of stay (LOS) of readmissions in comparison to vancomycin. Fidaxomicin drug costs totaled $62,112 and vancomycin drug costs were $6,646. However, due to reduction in recurrence, readmission and LOS, the hospital saved $142,507 overall in the fidaxomicin cohort. Summers et al. performed a similar study of 147 patients with severe CDI (16). Recurrence rates for fidaxomicin group were lower (7% vs. 18%), however hospitalization cost was not significantly different ($129,339 vs. $153,564). Several analytic simulation models have been performed using US pricing to determine cost effectiveness of fidaxomicin treatment over vancomycin with four (17,20-22) advocating for increased usage of fidaxomicin over vancomycin based on long-term cost savings and two (18,19) concluding that the use of fidaxomicin would not be cost effective.

TREATMENT OF SEVERE AND FULMINANT CDI WITHOUT TOXIC MEGACOLON

Oral vancomycin is the preferred therapy for severe and fulminant CDI, a recommendation that is based largely on a randomized controlled trial by Zar et al. that compared metronidazole and vancomycin and stratified patients by disease severity (8). For patients with severe CDI, vancomycin was significantly more effective than metronidazole (97% cure vs. 76%, p=0.02). The dose of vancomycin used in this study was 125 mg and no prospective studies support the use of higher dosages. One randomized controlled trial compared regimens with 125 mg and 500 mg and found similar efficacy for both (23). The results of this study were not stratified by disease severity however. Strong expert opinion favors using higher doses of oral vancomycin for more severe or recalcitrant cases of CDI as evidenced in the 2017 guidelines (5). It should be noted that higher doses of vancomycin enterally can result in detectable serum concentrations. Fidaxomicin has been used to treat severe CDI. In their RCT, Louie et al. found similar rates of clinical cure at the end of treatment for fidaxomicin and vancomycin in the treatment of severe disease (82% vs. 88%) (10). They also saw a significantly decreased rate of recurrence for fidaxomicin vs. vancomycin in treatment of severe disease (13% vs. 27%). One retrospective multicenter Veteran's Administration study published by Gentry et al. found no statistically significant difference for combined clinical failure or recurrence after treatment of severe CDI with fidaxomicin (31.9%) vs. vancomycin (25.5%) (24).

TREATMENT OF FULMINANT CDI WITH TOXIC MEGACOLON

Surgery is the best treatment for fulminant CDI in severely ill patients with shock or otherwise deteriorating clinical status. The perioperative mortality, however, is significant and can reach up to 80% in some reports. The more severe the patient's disease at the time of surgery, the higher the mortality. Other risk factors for post-operative mortality include lactate > 5 mmol/l, mental status changes, need for vasopressors, need for intubation, and other signs of end organ failure (1).

INDICATIONS FOR SURGERY
Five days of unsuccessful medical therapy
WBC > 50 x 10^3/ul
Lactate > 5 mmol/l
Sepsis
Peritonitis
Perforation
Mental status changes
Shock
Respiratory failure
Renal failure
Abdominal compartment syndrome
Unexplained clinical deterioration

The most comprehensive review to-date of surgery for CDI comes from the Eastern Association for the Surgery of Trauma (EAST) (25). A systematic review of the literature identified 32 relevant studies, none of which were randomized and only two of which were prospective. Based on this review, the current EAST practice guidelines recommend early intervention with total or subtotal colectomy. A meta-analysis of eight of the studies found that early surgery, defined as before the onset of shock, can reduce the risk of mortality by up to 50%. As it is difficult to predict when a patient will progress to shock, some authors recommend surgical evaluation after five days of medical therapy with no improvement or worsening of the

patient's clinical status (25,26). Other published indications for surgery are WBC > 50 x 10^3/ul, lactate > 5 mmol/l, sepsis, peritonitis, perforation, mental status changes, shock, respiratory failure, renal failure, abdominal compartment syndrome, or any unexplained clinical deterioration (26). Currently, there are no validated scoring systems to predict which patients will respond to medical therapy and which will ultimately require surgery.

When fulminant CDI is managed with surgery, the recommended procedure is subtotal colectomy with end ileostomy. Following a subtotal colectomy, some surgeons prescribe a seven-day course of intravenous metronidazole to treat any residual disease in the rectum (27).

Unfortunately, due to the high morbidity and mortality associated with surgery for CDI, surgical evaluation is often delayed. Less morbid procedures may encourage earlier consideration for surgery. One such procedure currently under investigation is loop ileostomy with colonic lavage (27). Although available evidence to-date is limited to case series and anecdotal data, the results have been promising. The procedure involves the creation of a loop ostomy in the terminal ileum, intraoperative antegrade lavage of the colon using a polyethylene glycol 3350/electrolyte solution (GoLytely), and post-operative antegrade colonic flushing with a vancomycin solution. Intravenous metronidazole is often administered post-operatively. The pathophysiologic basis of this procedure is three-fold. The loop ileostomy diverts the enteric stream and deprives the *Clostridium difficile* bacteria of nutrients. The intra-operative high-volume lavage mechanically reduces bacterial and toxin concentrations in the colon. The post-operative lavage and intravenous metronidazole are synergistic in eliminating remaining bacteria.

Thus far, Neal and colleagues have provided the strongest evidence of the effectiveness of loop ileostomy with colonic lavage, after treating 42 patients with complicated CDI with this procedure (28). Creation of the loop ileostomy was achieved laparoscopically in a majority of patients (35 patients, 83% percent of the cohort), while 7 patients required conversion to an open procedure. Intraoperative lavage was performed using eight liters of warmed GoLytely solution. A 24 French Malecot catheter was inserted into the distal limb of the loop ileostomy for postoperative delivery of vancomycin flushes using 500 mg in 500 ml of Lactated Ringer's solution every eight hours for ten days. Postoperatively, patients received a ten-day course of 500 mg of intravenous metronidazole every eight hours. 39 patients (93% of the cohort) were successfully treated with this procedure while three patients ultimately required a colectomy. All 39 patients had resolution of their CDI. 30-day mortality in the cohort was 19%, compared to 50% in a group of historical controls (p=0.006). Of the patients who were followed for six months afterwards, 79% had their ileostomy reversed. Among the controls, only 19% were reversed. However, recurrence of CDI after reversal of the ileostomy remains unknown. More rigorous and reproducible data with longer follow-up may eventually establish ileostomy with colonic lavage as the standard of care for surgical management of CDI.

For patients with complicated CDI who cannot or will not undergo surgery, the Infectious Disease Society of America (IDSA) recommends dual therapy with both metronidazole and vancomycin (2). Because of the likelihood of ileus or megacolon and the resultant possibility of oral medications not effectively reaching the colon, intravenous metronidazole is recommended. In addition, due to its proven efficacy for severe CDI, vancomycin is also recommended. Oral formulations of vancomycin are preferred over rectal, though both risk incomplete passage through the colon. Intravenous vancomycin is not efficacious for the treatment of CDI.

TREATMENT DURATION

The typical recommended treatment course for CDI is ten days. However, it is recognized that some patients may respond slowly to treatment and may, therefore, require a longer course of therapy. For this reason, a ten-day treatment course may be increased to fourteen days based upon the patient's response as well as the clinician's judgment (2). Guery et al. investigated extended-pulse dosed fidaxomicin administered over 27 days. This outperformed the standard 10-day course of vancomycin in terms of sustained clinical response for treatment of severe and non-severe CDI (12). No RTCs have been performed to study extended tapered or pulse-dosed vancomycin.

CONSULTING SERVICES

Consider formal Infectious Disease consultation for initial fulminant CDI and for second or subsequent recurrences of CDI.

REFERENCES

1. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: Update of the treatment guidance document for Clostridium difficile infection. Clinical Microbiology and Infection 2014; 20 Suppl 2:1-26.
2. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol 2010; 31(5):431-455.
3. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroent 2013;108(4):478-498.
4. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis 2011; 53(10):994-1002.
5. Johnson S, Lavergne V, Skinner A 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(5):e1029-e1044.
6. Teasley DG, Gerding DN, Olson MM, Peterson LR, Gebhard RL, Schwartz MJ, et al. Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhoea and colitis. Lancet 1983; 2(8358):1043-1046.
7. Wenisch C, Parschalk B, Hasenhundl M, Hirschl AM, Graninger W. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. Clin Infect Dis 1996;22(5):813-818.
8. 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(3):302-307.
9. Johnson S, Louie TJ, Gerding DN, Cornely OA, Chasan-Taber S, Fitts D, Gelone SP, Broom C, Davidson DM; Polymer Alternative for CDI Treatment (PACT) investigators. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. Clin Infect Dis 2014; 59(3):345-354.
10. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. NEJM 2011; 364(5):422-431.
11. Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, et al. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. The Lancet Infectious Diseases 2012; 12(4):281-289.
12. Guery B, Menichetti F, Anttila VJ, et al; EXTEND Clinical Study Group. Extendedpulsed 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; 18:296–307.
13. 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; 24:744–752.
14. Burton HE, Mitchell SA, Watt M. A Systematic Literature Review of Economic Evaluations of Antibiotic Treatments for Clostridium difficile Infection. Pharmacoeconomics 2017; 35(11):1123-1140.
15. Gallagher JC, Reilly JP, Navalkele B, Downham G, Haynes K, Trivedi M. Clinical and economic benefits of fidaxomicin compared to vancomycin for Clostridium difficile infection. Antimicrob Agents Chemother 2015; 59(11):7007-7010.
16. Summers BB, Yates M, Cleveland KO, Gelfand MS, Usery J. Fidaxomicin Compared With Oral Vancomycin for the Treatment of Severe Clostridium difficile-Associated Diarrhea: A Retrospective Review. Hosp Pharm 2020; 55(4):268-272.
17. Stranges PM, Hutton DW, Collins CD. Cost-effectiveness analysis evaluating fidaxomicin versus oral vancomycin for the treatment of Clostridium difficile infection in the United States. Value Health 2013; 16(2):297-304.
18. Bartsch SM, Umscheid CA, Fishman N, Lee BY. Is fidaxomicin worth the cost? An economic analysis. Clin Infect Dis 2013; 57(4):555-561.
19. Konijeti GG, Sauk J, Shrime MG, Gupta M, Ananthakrishnan AN. Cost-effectiveness of competing strategies for management of recurrent Clostridium difficile infection: a decision analysis. Clin Infect Dis 2014; 58(11):1507-1514.
20. Jiang Y, Sarpong EM, Sears P, Obi EN. Budget Impact Analysis of Fidaxomicin Versus Vancomycin for the Treatment of Clostridioides difficile Infection in the United States. Infect Dis Ther 2022; 11(1):111-126.

21. Rajasingham R, Enns EA, Khoruts A, Vaughn BP. Cost-effectiveness of Treatment Regimens for Clostridioides difficile Infection: An Evaluation of the 2018 Infectious Diseases Society of America Guidelines. Clin Infect Dis 2020; 70(5):754-762.
22. Chen J, Gong CL, Hitchcock MM, Holubar M, Deresinski S, Hay JW. Cost-effectiveness of bezlotoxumab and fidaxomicin for initial Clostridioides difficile infection. Clin Microbiol Infect 2021; 27(10):1448-1454.
23. Fekety R, Silva J, Kauffman C, Buggy B, Deery HG. Treatment of antibiotic-associated Clostridium difficile colitis with oral vancomycin: comparison of two dosage regimens. Am J Med 1989; 86(1):15-19.
24. Gentry CA, Nguyen PK, Thind S, Kurdgelashvili G, Skrepnek GH, Williams RJ 2nd. Fidaxomicin versus oral vancomycin for severe Clostridium difficile infection: a retrospective cohort study. Clin Microbiol Infect 2019; 25(8):987-993.
25. Ferrada P, Velopulos CG, Sultan S, Haut ER, Johnson E, Praba-Egge A, 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(6):1484-1493.
26. Carchman EH, Peitzman AB, Simmons RL, Zuckerbraun BS. The role of acute care surgery in the treatment of severe, complicated Clostridium difficile-associated disease. J Trauma Acute Care Surg 2012; 73(4):789-800.
27. Fagenholz PJ, de Moya MA. Acute inflammatory surgical disease. Surg Clin North Am. 2014; 94(1):1-30.
28. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. Ann Surg 2011; 254(3):423-9.