ACG Clinical Guideline: Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

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Abstract

Clostridium difficile infection (CDI) is a leading cause of hospital-associated gastrointestinal illness and places a high burden on our health-care system. Patients with CDI typically have extended lengths-of-stay in hospitals, and CDI is a frequent cause of large hospital outbreaks of disease. This guideline provides recommendations for the diagnosis and management of patients with CDI as well as for the prevention and control of outbreaks while supplementing previously published guidelines. New molecular diagnostic stool tests will likely replace current enzyme immunoassay tests. We suggest treatment of patients be stratified depending on whether they have mild-to-moderate, severe, or complicated disease. Therapy with metronidazole remains the choice for mild-to-moderate disease but may not be adequate for patients with severe or complicated disease. We propose a classification of disease severity to guide therapy that is useful for clinicians. We review current treatment options for patients with recurrent CDI and recommendations for the control and prevention of outbreaks of CDI.

Introduction

Clostridium difficile infection (CDI) is a leading cause of hospital-associated gastrointestinal illness and places a high burden on our health-care system, with costs of 3.2 billion dollars annually (1,2). This guideline provides recommendations for the diagnosis and management of patients with CDI as well as for the prevention and control of outbreaks. It supplements previously published Infectious Disease Society of America (IDSA)/Society of Hospital Epidemiologists of America (SHEA) and European Society of Clinical Microbiology and Infectious Diseases (ESCMID) guidelines (3,4) and an evidence-based review (5).

Each section presents the key recommendations followed by a summary of the evidence (Table 1). The GRADE system was used to grade the strength of our recommendations and the quality of the evidence (6). The strength of a recommendation is graded as "strong", when the evidence shows the benefit of the intervention or treatment clearly outweighs any risk, and as "conditional", when uncertainty exists about the risk-benefit ratio. The quality of the evidence is graded as follows: "high", if further research is unlikely to change our confidence in the estimate of the effect; "moderate", if further research is

likely to have an important impact and may change the estimate; and "low", if further research is very likely to change the estimate.

Microbiology and Diagnosis
Recommendations
1. Only stools from patients with diarrhea should be tested for *C. difficile*. (Strong recommendation, high-quality evidence)
2. Nucleic acid amplification tests (NAATs) for *C. difficile* toxin genes such as PCR are superior to toxins A + B enzyme immunoassay (EIA) as a standard diagnostic test for CDI. (Strong recommendation, moderate-quality evidence)
3. Glutamate dehydrogenase (GDH) screening tests for *C. difficile* can be used in two- or three-step algorithms with subsequent toxin A + B EIA testing, but the sensitivity of such strategies is lower than NAATs. (Strong recommendation, moderate-quality evidence)
4. Repeat testing should be discouraged. (Strong recommendation, moderate-quality evidence)
5. Testing for cure should not be done. (Strong recommendation, moderate-quality evidence)

Table 2. Diagnostic testing for *C. difficile*					
Test	**Sensitivity**	**Specificity**	**Availability**	**Expense**[a]	**Utilization**
C. difficile culture	Low	Moderate	Limited	$5–10	No diagnostic use; only toxigenic organisms cause disease
Toxigenic culture	High	High	Limited	$10–30	Reference method Epidemiologic tool Limited diagnostic use
CCNA	High	High	Limited	$15–25	Reference method Limited diagnostic use
GDH	High	Low	Widely	$5–15	Diagnostically as a screening test; must be confirmed
Toxin EIA tests	Low	High	Widely	$5–15	Must detect toxins A+B; inferior sensitivity
NAATs	High	High	Widely	$20–50	Use only in acute disease; false positives of concern
CCNA, *C. difficile* cytotoxin neutralization assay; GDH, glutamate dehydrogenase; EIA, enzyme immunoassay; NAAT, nucleic acid amplification tests.					
[a] Cost of goods; does not reflect laboratory changes.					

Management of Mild, Moderate and Severe CDI
Recommendations

6. If a patient has a strong pre-test suspicion for CDI, empiric therapy for CDI should be considered regardless of the laboratory testing result, as the negative predictive values for CDI are insuffi ciently high to exclude disease in these patients. (Strong recommendation, moderate-quality evidence)

7. Any inciting antimicrobial agent(s) should be discontinued, if possible. (Strong recommendation, high-quality evidence)

8. Patients with mild-to-moderate CDI should be treated with metronidazole 500 mg orally three times per day for 10 days. (Strong recommendation, high-quality evidence)

9. Patients with severe CDI should be treated with vancomycin 125 mg orally four times per day for 10 days. (Conditional recommendation, moderate-quality evidence)

10. Failure to respond to metronidazole therapy within 5–7 days should prompt consideration of a change in therapy to vancomycin at standard dosing. (Strong recommendation, moderate-quality evidence)

11. For mild-to-moderate CDI in patients who are intolerant/allergic to metronidazole and for pregnant/breastfeeding women, vancomycin should be used at standard dosing. (Strong recommendation, high-quality evidence)

12. In patients in whom oral antibiotics cannot reach a segment of the colon, such as with Hartman's pouch, ileostomy, or colon diversion, vancomycin therapy delivered via enema should be added to treatments above until the patient improves. (Conditional recommendation, low-quality evidence)

13. The use of anti-peristaltic agents to control diarrhea from confirmed or suspected CDI should be limited or avoided, as they may obscure symptoms and precipitate complicated disease. Use of anti-peristaltic agents in the setting of CDI must always be accompanied by medical therapy for CDI. (Strong recommendation, low-quality evidence)

Table 3. CDI severity scoring system and summary of recommended treatments			
Severity	**Criteria**	**Treatment**	**Comment**
Mild-to-moderate disease	Diarrhea plus any additional signs or symptoms not meeting severe or complicated criteria	Metronidazole 500mg orally three times a day for 10 days. If unable to take metronidazole, vancomycin 125 mg orally four times a day for 10 days	If no improvement in 5–7 days, consider change to vancomycin at standard dose (vancomycin 125mg four times a day for 10 days)
Severe disease	Serum albumin <3g/dl plus ONE of the following: WBC ≥15,000 cells/mm^3, Abdominal tenderness	Vancomycin 125 mg orally four times a day for 10 days	
Severe and complicated disease	Any of the following attributable to CDI: Admission to intensive care unit for CDI Hypotension with or without required use of vasopressors Fever ≥38.5 °C Ileus or significant abdominal distention Mental status changes WBC ≥35,000 cells/mm^3 or <2,000 cells/mm^3 Serum lactate levels >2.2 mmol/l End organ failure (mechanical ventilation, renal failure, etc.)	Vancomycin 500 mg orally four times a day and metronidazole 500 mg IV every 8 h, and vancomycin per rectum (vancomycin 500 mg in 500 ml saline as enema) four times a day	Surgical consultation suggested
Recurrent CDI	Recurrent CDI within 8 weeks of completion of therapy	Repeat metronidazole or vancomycin pulse regimen	Consider FMT after 3 recurrences

CDI, *Clostridium difficile* infection; FMT, fecal microbiota transplant; IV, intravenous; WBC, white blood cell.

Table 4. Cost of antibiotic therapy for *C. difficile* infection			
	Cost per dose	**Regimen**	**Cost per 10-day regimen**
Metronidazole 500 mg	$0.73	500 mg three times a day	$22.00
Vancomycin 125 mg pills	$17.00	125 mg four times a day	$680.00
Vancomycin 125 mg IV compounded for oral	$2.50–$10.00	125 mg four times a day	$100.00–$400.00
Fidaxomicin 200 mg	$140.00	200 mg twice a day	$2,800.00
IV, intravenous. Vancomycin IV form can be compounded for oral use as well as used for enema therapy.			

Management of Severe and Complicated CDI
Recommendations

14. Supportive care should be delivered to all patients with severe CDI and includes intravenous fluid resuscitation, electrolyte replacement, and pharmacological venous thromboembolism prophylaxis. Furthermore, in the absence of ileus or significant abdominal distention, oral or enteral feeding should be continued. (Conditional recommendation, low-quality evidence)
15. CT (computerized tomography) scanning of the abdomen and pelvis is recommended in patients with complicated CDI. (Conditional recommendation, low-quality evidence)
16. Vancomycin delivered orally (125 mg four times per day) plus intravenous metronidazole (500 mg three times a day) is the treatment of choice in patients with severe and complicated CDI who have no significant abdominal distention. (Strong recommendation, low-quality evidence)
17. Vancomycin delivered orally (500 mg four times per day) and per rectum (500 mg in a volume of 500 ml four times a day) plus intravenous metronidazole (500 mg three times a day) is the treatment of choice for patients with complicated CDI with ileus or toxic colitis and/or significant abdominal distention. (Strong recommendation, low-quality evidence)
18. Surgical consultation should be obtained on all patients with complicated CDI. Surgical therapy should be considered in patients with any one of the following attributed to CDI: hypotension requiring vasopressor therapy; clinical signs of sepsis and organ dysfunction; mental status changes; WBC count ≥ 50,000 cells/μl, lactate ≥ 5 mmol/l; or complicated CDI with failure to improve on medical therapy after 5 days. (Strong recommendation, moderate-quality evidence)

Management of RCDI
Recommendations
19. The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however, vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. (Conditional recommendation, low-quality evidence)
20. If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)
21. There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCDI. (Moderate recommendation, moderate-quality evidence)
22. No effective immunotherapy is currently available. Intravenous immune globulin (IVIG) does not have a role as sole therapy in treatment of RCDI; however, it may be helpful in patients with hypogammaglobulinemia. (Strong recommendation, low quality of evidence)

Management of CDI and Co-Morbid Conditions
Recommendations
Patients with IBD:
23. All patients with IBD hospitalized with a disease flare should undergo testing for CDI. (Strong recommendation, high-quality evidence)
24. Ambulatory patients with IBD who develop diarrhea in the setting of previously quiescent disease, or in the presence of risk factors such as recent hospitalization or antibiotic use, should be tested for CDI. (Strong recommendation, moderate-quality evidence)
25. In patients who have IBD with severe colitis, simultaneous initiation of empirical therapy directed against CDI and treatment of an IBD flare may be required while awaiting results of *C. difficile* testing. (Conditional recommendation, low-quality evidence)
26. In patients with IBD ongoing immunosuppression medications can be maintained in patients with CDI. Escalation of immunosuppression medications should be avoided in the setting of untreated CDI. (Conditional recommendation, low-quality evidence)
27. Patients with IBD who have a surgically created pouch after colectomy may develop CDI and should be tested if they have symptoms. (Strong recommendation, moderate-quality evidence)

Immunosuppressed Patients:
28. Underlying immunosuppression (including malignancy, chemotherapy, corticosteroid therapy, organ transplantation, and cirrhosis), increases the risk of CDI and such patients should be tested if they have a diarrheal illness. (Strong recommendation, moderate-quality evidence)

Pregnant or Peripartum Women:
29. Any diarrheal illness in women who are pregnant or periparturient should prompt testing for *C. difficile*. (Conditional recommendation; low-quality evidence)

Infection Control and Prevention
Recommendations

30. A hospital-based infection control program can help to decrease the incidence of CDI. (Conditional recommendation, moderate-quality of evidence)

31. Routine screening for *C. difficile* in hospitalized patients without diarrhea is not recommended and asymptomatic carriers should not be treated. (Strong recommendation, low-quality evidence)

32. Antibiotic stewardship is recommended to reduce the risk of CDI. (Strong recommendation, high-quality evidence)

33. Contact precautions for a patient with CDI should be maintained at a minimum until the resolution of diarrhea. (Strong recommendation, high quality evidence)

34. Patients with known or suspected CDI should be placed in a private room or in a room with another patient with documented CDI. (Strong recommendation, high-quality evidence)

35. Hand hygiene and barrier precautions, including gloves and gowns, should be used by all health-care workers and visitors entering the room of any patient with known or suspected CDI. (Strong recommendation, moderate-quality evidence)

36. Single-use disposable equipment should be used for prevention of CDI transmission. Non-disposable medical equipment should be dedicated to the patient's room, and other equipment should be thoroughly cleaned after use in a patient with CDI. (Strong recommendation, moderate-quality evidence)

37. Disinfection of environmental surfaces is recommended using an Environmental Protection Agency (EPA)-registered disinfectant with *C. difficile*-sporicidal label claim or 5,000 p.p.m. chlorine-containing cleaning agents in areas of potential contamination by *C. difficile*. (Strong recommendation, high-quality evidence)

38. Although there is moderate evidence that two probiotics (*L. rhamnosus* GG and *S. boulardii*) decrease the incidence of antibiotic-associated diarrhea, there is insufficient evidence that probiotics prevent CDI. (Strong recommendation, low-quality evidence)