CME

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

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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.

EPIDEMIOLOGY AND RISK FACTORS

Clostridium difficile (*C. difficile*) is a Gram-positive, spore-forming bacterium usually spread by the fecal-oral route. It is non-invasive and produces toxins A and B that cause disease, ranging from asymptomatic carriage, to mild diarrhea, to colitis, or pseudomembranous colitis. CDI is defined as the acute onset of diarrhea with documented toxigenic *C. difficile* or its toxin and no other documented cause for diarrhea (3).

Rates of CDI have been increasing since 2000, especially in the elderly with a recent hospitalization or residing in long-term care facility (LTCF). Carriage of *C. difficile* occurs in 5–15% of healthy adults, but may be as high as 84.4% in newborns and healthy infants, and up to 57% in residents in LTCF. Transmission in health-care facilities results mostly from environmental surface contamination and hand carriage by staff members and infected patients.

The two biggest risk factors are exposure to antibiotics and exposure to the organism; others are comorbid conditions,

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Table 1. Summary and strength of recommendations

Diagnostic tests

1. Only stools from patients with diarrhea should be tested for *Clostridium difficile*. (Strong recommendation, high-quality evidence)

2. Nucleic acid amplification tests (NAAT) for *C. difficile* toxin genes such as PCR are superior to toxins A + B EIA testing 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 screening algorithms with subsequent toxin A and 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)

Management of mild, moderate, and severe CDI

6. If a patient has strong a 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 insufficiently 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 four times daily 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)

Management of severe and complicated CDI

14. Supportive care should be delivered to all patients 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 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 colon and/or significant abdominal distention. (Strong recommendation, low-quality evidence)

18. Surgical consult should be obtained in 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 (renal and pulmonary); mental status changes; white blood cell count ≥50,000 cells/μl, lactate ≥5 mmol/l; or failure to improve on medical therapy after 5 days. (Strong recommendation, moderate-quality evidence)

Management of recurrent CDI (RCDI)

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 evidence)

Management of patients with CDI and co-morbid conditions

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 empiric 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)

Table 1. (continued)

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)

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)

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

30. A hospital-based infection control programs can help to decrease the incidence of CDI. (Conditional recommendation, moderate-quality 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 Protective Agency (EPA)-registered disinfectant with *C. difficile*-sporicidal label claim or 5000 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 (*Lactobacillus rhamnosus* GG and *Saccharomyces boulardii*) decrease the incidence of antibiotic associated diarrhea, there is insufficient evidence that probiotics prevent *C. difficile* infection. (Strong recommendation, low-quality evidence)

CDI, Clostridium difficile infection; CT, computerized tomography; EIA, enzyme immunoassay; IBD, inflammatory bowel disease.

gastrointestinal tract surgery, and medications that reduce gastric acid, including proton-pump inhibitors (PPIs) (7,8). More information on epidemiology is in the appendix.

MICROBIOLOGY AND DIAGNOSIS

The best standard laboratory test for diagnosis has not been clearly established. For the past 30 years, the two primary reference tests are the *C. difficile* cytotoxin neutralization assay (CCNA) and toxigenic culture (TC) (9,10). *C. difficile* culture alone is not sufficient because not all *C. difficile* strains produce toxin (9–14).

Recommendation

1. Only stools from patients with diarrhea should be tested for *C. difficile*. (Strong recommendation, high-quality evidence)

Summary of the evidence. Because *C. difficile* carriage is increased in patients on antimicrobial therapy, only diarrheal stools warrant testing (3,14). Very occasionally, a patient with ileus and complicated disease will have a formed stool (3), in which case the laboratory should be made aware of this special clinical situation. Rectal swabs can be used for PCR

and thus may be useful in timely diagnosis of patients with ileus (15).

Recommendations

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)

Summary of the evidence. Diagnostic testing for *C. difficile* has rapidly evolved in the past decade (see **Table 2**). Previously, toxin A + B EIAs were the most widely used diagnostic tests (16–18) because of ease of use and objective interpretation. However, EIA tests have substantially reduced sensitivities compared with reference standards. Moreover, toxin A immunoassays (without toxin B) miss detecting the small number of pathogenic strains that only produce toxin B (10,19). A systematic review of these tests showed that toxin A + B EIA tests had a sensitivity of 75–95%

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.

and a specificity of 83–98% compared with CCNA reference testing (18). Two major advances in the laboratory diagnosis are the use of GDH detection in stools as a means of screening for CDI and the development of NAATs such as PCR to detect toxigenic strains of *C. difficile.*

GDH is an enzyme produced by *C. difficile* in relatively large amounts compared with toxins A and B (20,21). Although GDH is sensitive, it is not as specific for CDI, because this enzyme is produced by both toxigenic and non-toxigenic organisms. Additionally, antibodies against *C. difficile* GDH may cross react with the same enzyme in other clostridial species (22). Reports and meta-analyses detail sensitivity ranging from 75% to > 90% with a negative predictive value of between 95% and 100%, although its positive predictive values have been found to be as low as 50% (18,23). The sensitivity of GDH antigen detection has led to its use as a screening test as part of CDI testing algorithms, although it should be noted that as many as 10% of patients with toxigenic organisms can be missed by this method. In this approach, GDH is the initial test, and GDH-negative specimens are reported as negative with no further testing done. GDH-positive specimens must undergo additional testing for *C. difficile* either by NAAT or by EIA testing followed by NAAT if the EIA results are discordant (24–27).

Evidence suggests that NAATs for toxigenic *C. difficile* are good stand-alone tests for toxigenic *C. difficile*. There are several Food and Drug Administration (FDA)-approved NAAT's, including PCR assays and isothermal amplification tests. PCR is an excellent confirmatory test, but data for isothermal amplification testing are not yet sufficient to recommend it.

Clinical practice guidelines have evolved over the past 3 years to suggest the following diagnostic approaches (11,28). (1) GDH screen followed by a confirmatory test in two- or three-step algorithms. (2) NAAT for toxigenic *C. difficile*, but only in patients with documented diarrhea. Their use in any other clinical setting may yield false positive test results. (3) EIA for toxin A + B lacks sensitivity compared with CCNA and TC and should not be used as a stand-alone test. More information on microbiological testing is in the appendix.

Timing of assays

Recommendations

4. Repeat testing should be discouraged. (Strong recommendation, moderate-quality evidence)
5. Testing for cure should not be done. (Strong recommendation, moderate-quality evidence)

Summary of the evidence. Several studies have shown that repeat testing after a negative test is positive in < 5% of specimens and repeat testing increases the likelihood of false positives (29–31). If repeat testing is requested, the physician should confer with the laboratory to explain the clinical rationale. There is no evidence that repeated testing can enhance the sensitivity or negative predictive values of NAATs for *C. difficile* diagnosis compared with TCs. Empiric therapy for CDI should not be discontinued or withheld in patients with a high pre-test suspicion for CDI. Studies have shown that both toxin A + B EIA and TC may remain positive for a long as 30 days in patients who have resolution of symptoms (32,33). False positive "test of cure" specimens may complicate clinical care and result in additional courses of inappropriate anti-*C. difficile* therapy.

MANAGEMENT OF MILD, MODERATE AND SEVERE CDI

We propose the following classification of disease severity (**Table 3**): mild disease is defined as CDI with diarrhea as the only symptom; moderate disease is defined as CDI with diarrhea but without additional symptoms/signs meeting the definition of severe or complicated CDI below. Severe disease is CDI that presents with or develops during the course of the disease with hypoalbuminemia (serum albumin < 3 g/dl) and either of the following: (1) a white blood cell (WBC) count ≥15,000 cells/mm³ or (2) abdominal tenderness without criteria of complicated disease. Complicated CDI is CDI that presents with or develops at least one of the following signs or symptoms: admission to intensive care unit, hypotension with or without required use of vasopressors, fever ≥38.5 °C, ileus, or significant abdominal distention, mental status changes, WBC ≥35,000 cells/mm³ or < 2,000 cells/mm³, serum lactate levels >2.2 mmol/l, or any evidence of end

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 500 mg 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 125 mg four times a day for 10 days)
Severe disease	Serum albumin <3 g/dl plus ONE of the following: WBC ≥15,000 cells/mm³, 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/mm³ or <2,000 cells/mm³ 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.

organ failure. Symptoms of ileus include acute nausea, emesis, sudden cessation of diarrhea, abdominal distention, or radiological signs consistent with disturbed intestinal transit. These criteria have not been validated but are chosen based upon comparison of clinical severity scoring indices for CDI and may have excellent negative predictive values but relatively poor positive predictive values for determining likelihood of death or need for colectomy (34). A recent analysis of several clinical scoring systems evaluated risk factors for severe CDI defined as patients requiring intensive care unit care or colectomy necessitated by CDI, or who died and whose death was attributed to CDI within 30 days after the diagnosis (35). Three independent risk factors determined by multivariate analysis were found to predict severe disease: abdominal distension, elevated WBC, and hypoalbuminemia. We propose redefining severe disease using these three criteria to guide therapy. We recommend using only an elevated WBC and hypoalbuminemia (as opposed to serum creatinine) because these values are relatively straightforward to use clinically. Furthermore, WBC and albumin values are directly linked to the pathogenesis of CDI; TcdA is a potent neutrophil chemoattractant that can result in increasing serum WBC counts. Hypoalbuminemia may correlate with severity of diarrhea because it results in a protein-losing enteropathy and albumin is considered a negative acute phase protein and a marker of inflammatory states. Our definition of complicated CDI is based upon a combination of the same multivariate analysis, findings of multiple case series, and recommendations of the IDSA/SHEA and ESCMID (4,34–46). Accurate stratification of patients based upon severity of disease using these criteria will ensure adequate and timely institution of appropriate therapy without over-treating too many patients.

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 insufficiently 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)

Summary of the evidence. A meta-analysis of 12 observational studies and randomized control trials (RCTs) showed that continued use of antimicrobials for infections other than CDI is significantly associated with an increased risk of CDI recurrence (47). A retrospective review of 246 patients treated during the years 2004–2006 also confirmed an independent association of non-CDI antimicrobial use with recurrence but only when non-CDI antimicrobials were given after CDI therapy was completed (48). In light of this consistent observational evidence, exposure to antibiotics other than those intended to treat CDI should be avoided unless absolutely indicated.

Recommendations

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)

Summary of the evidence. The two first-line antibiotics used most often to treat CDI in North America are metronidazole and

vancomycin; a third, fidaxomicin, was approved for treatment of CDI in 2011. Treatment for CDI can be initiated before laboratory confirmation for patients with a high pre-test suspicion of disease. Two older RCTs that compared vancomycin and metronidazole for treatment of CDI did not demonstrate superiority of metronidazole compared with vancomycin (33,49). However, two more recent RCTs concluded vancomycin is superior to metronidazole for patient with severe CDI (50,51). In one, 150 patients were stratified by an *ad-hoc* definition of CDI severity and then randomized to oral metronidazole or vancomycin (50). Clinical cure was defined as a negative follow-up toxin assay and absence of diarrhea on day 6 of therapy. Using this definition, 90% of patients treated with metronidazole and 98% treated with vancomycin were cured of mild CDI, but cure rates were lower in the severe disease group treated with metronidazole (76%) compared with vancomycin (97%). Although widely cited as evidence that vancomycin is superior to metronidazole for the treatment of severe CDI, this study has potential limitations, including nonstandard dose of metronidazole and using an invalidated definition of cure (a negative follow-up toxin assay) when metronidazole is known to be inferior to vancomycin for microbiological end points during CDI therapy (52). Most importantly, the definition of mild CDI in the trial included many patients who would be considered as having severe CDI by the proposed definition based on cohort studies in this treatment guideline.

Although the continued preference for metronidazole as the treatment of choice in mild-to-moderate CDI is based on equal efficacy for most patients, an additional and important reason remains cost. Oral vancomycin costs $71 to 143 per day (depending on the dosing regimen chosen) compared with metronidazole, which costs $2 per day. Although the intravenous formulation of vancomycin can be compounded by inpatient hospital pharmacies and some outpatient pharmacies at approximately half this cost, the cost difference remains substantial and can impair compliance. Another reason that vancomycin is not used in the inpatient setting is the theoretical risk of promoting acquisition of vancomycin-resistant enterococcus. However, vancomycin-resistant enterococcus has not been shown to be a valid reason to avoid use of vancomycin for treatment of CDI, as both vancomycin and metronidazole treatment for CDI have been shown to promote vancomycin-resistant enterococcus acquisition in prospective observational studies (52).

Although it is common practice to prescribe 10–14 days of treatment for CDI, treatment duration is 10 days in all the previous RCTs of both metronidazole and vancomycin. Because there is no evidence that supports longer treatment durations as more efficacious, the use of 14-day treatment courses is not recommended for the initial treatment of mild-to-moderate CDI when a treatment response has been observed by day 10. There is also no evidence to support the practice of extending anti-CDI therapy for the duration of therapy if the patient is also on a non-CDI antibiotic.

An alternate antibiotic is fidaxomicin (200 mg orally 2 times per day for 10 days) for the treatment of mild-to-moderate CDI. On the basis of two RCTs with oral vancomycin, the FDA granted approval for fidaxomicin in May 2011 (53,54). In both published phase III trials, fidaxomicin demonstrated non-inferiority to vancomycin in the modified intention-to-treat and the per-protocol analyses for clinical response at the end of therapy and at 25 days post therapy. Further *post-hoc* analyses suggested that fidaxomicin is superior to vancomycin as there were fewer recurrences at 25 days after therapy. However, this superiority was seen only with initial infections not caused by NAP1/BI/027 where fidaxomicin was associated with a 16.9 and 19.6% risk reduction for recurrence in the two trials, which translates to a number needed to treat of 5–6 patients with non-/NAP1/BI/027 CDI treated with fidaxomicin to prevent one recurrence.

There are several important limitations to these findings. First, neither trial extended to 90 days, the full extent needed to document recurrences by identical strains. Second, there is no biological plausibility to explain a strain-specific superiority of fidaxomicin; there are no differences in minimal inhibitory concentrations between NAP1/BI/027 and non-NAP1/BI/027 strains, and both vancomycin and fidaxomicin have similar spectra of activity against Gram-positive stool bacteria. Third, surveillance testing in a patient on the fidaxomicin study arm has already revealed the evolution of a *C. difficile* strain with an elevated minimal inhibitory concentration to fidaxomicin due to a mutation in RNA polymerase B. Resistance to vancomycin *in vitro* has not been observed in vancomycin trials to date. Finally, the cost of fidaxomicin is significantly higher than that of vancomycin. Given the limited data available, we urge caution in committing patients to a course of this drug before more definitive evidence of superiority in post-marketing clinical trials.

Recommendation

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)

Summary of the evidence. Previous CDI guidelines have not delineated when CDI patients should be evaluated for treatment failure once committed to a course of metronidazole for CDI or when a change from metronidazole to vancomycin or other agents is indicated. In the largest observational prospective study of metronidazole-treated CDI patients, 103 of 207 (50%) had complete responses to 9 days of therapy. Of the remaining patients, 58 (28%) had an initial response to metronidazole but developed recurrent CDI (RCDI) within 90 days. Forty-six (22%) patients had no response to metronidazole by day 9 of treatment and ultimately were switched to oral vancomycin ($n = 16$, 8%) or given prolonged metronidazole therapy ($n = 30$, 14%) at the treating physician's discretion. In all, 5 of the 16 patients (31%) switched to vancomycin and 15 of the 30 patients (50%) kept on metronidazole had a response to treatment, a non-significant difference ($P = 0.35$). Of the patients who ultimately responded to metronidazole, almost half had done so with only a 7-day course of metronidazole; the exact day upon which most patients had symptom resolution was not reported (55). Given the initial response rate to metronidazole

in this study, it is reasonable to persist with metronidazole mono-therapy for patients with mild-to-moderate CDI for at least 7 days unless signs or symptoms consistent with severe CDI or metro-nidazole intolerance develop at any point during therapy and escalating to vancomycin at standard dosing for patients who do not respond in 5–7 days or who develop signs or symptoms of severe CDI. We recommend discontinuing metronidazole because the side effects (nausea, vomiting, and taste disturbances) may be mistaken for patients with signs of ileus due to worsening CDI, and because there is insufficient evidence to support the practice of continuing metronidazole for mild-to-moderate CDI when a decision to escalate therapy to vancomycin has been made.

The use of very high doses of vancomycin (500 mg orally four times daily) was included in the IDSA/SHEA treatment guidelines for management of severe complicated CDI as defined by the treating physician (3). As a result, it has become common practice to use higher doses of vancomycin if patients are failing to respond to the standard recommended dose of 125 mg four times daily. A trial of 46 patients randomized to 500 or 125 mg of vancomycin four times daily for the initial treatment of CDI showed no difference in duration of diarrhea, relapse rate, or microbiological cure (carriage of *C. difficile* at the end of therapy) (56). Moreover, fecal levels of vancomycin in patients with CDI with this dose achieve levels that are a minimum of 10 times the minimal inhibitory concentration reported for *C. difficile* strains (57). Given the high cost of vancomycin therapy, there is insufficient evidence to support the use of doses >125 mg four times daily for patients with mild-to-moderate CDI, particularly for outpatients. Drug costs are in **Table 4**.

Recommendation

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)

Summary of the evidence. Metronidazole treatment should be avoided in pregnancy and breast feeding. First trimester exposure to metronidazole is not recommended in FDA guidelines because of concern regarding ready placental transmission and case reports describing facial anomalies following exposure. Metronidazole and its active metabolites are readily detected in breast milk and in the plasma of infants.

Recommendation

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)

Summary of the evidence. Oral vancomycin cannot reach segments of colon that are not in continuity with the gastrointestinal tract, such as the patient with an upstream ileostomy, Hartman's

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.

pouch, or colostomy. Metronidazole may also fail to treat a diverted segment of downstream colon because metronidazole is rapidly absorbed by the small intestine with only 6–15% of drug excreted in the stool. Moreover, there are data to suggest that IV metronidazole will also enter the colon lumen following secretion across the inflamed colonic mucosa, and CDI patients who respond to treatment have a dramatic fall in the fecal concentrations of the antibiotic following initiation of therapy. When CDI is documented in an excluded segment of diverted colon, administration of vancomycin by enema is recommended to guarantee that treatment will reach the affected area, using vancomycin enemas of 500 mg in 100–500 ml of normal saline every 6 h for CDI (58), volume depending on length of segment to be treated. The duration of enema therapy should continue until the patient has significant improvement.

Recommendation

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)

Summary of the evidence. The IDSA/SHEA guidelines included a C-III recommendation to "avoid [the] use of antiperistaltic agents, as they may obscure symptoms and precipitate toxic megacolon" (3). A literature review of 55 patients with CDI who were exposed to such agents found that 17 patients developed colonic dilatation and 5 died (59). All of these adverse outcomes, however, occurred in patients with CDI who initially received treatment with antiperistaltic agents alone. All 23 patients in this review who received antiperistaltic agents only in combination with CDI antimicrobial therapy survived. For patients with mild-to-moderate CDI whose antimicrobial treatment is well underway, the use of these drugs to control the most debilitating symptom of CDI should be further studied in prospective trials.

MANAGEMENT OF SEVERE AND COMPLICATED CDI

Supportive care and diagnosis

Recommendation

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)

Summary of the evidence. Diarrhea results in significant volume depletion and electrolyte abnormalities that must be corrected. One can consider pharmacological venous thromboembolism prophylaxis as these patients are at increased risk as are patients with active ulcerative colitis (60).

We also recommend the maintenance of an oral or enteral diet (but not an elemental diet) in patients who have normal bowel function as fermentable carbohydrates are crucial for microbial health and may contribute to normalizing the microbiota (61–64).

Recommendation

15. CT (computerized tomography) scanning of the abdomen and pelvis is recommended in patients with complicated CDI. (Conditional recommendation, low-quality evidence)

Summary of the evidence. Abdominal and pelvic CT scans can be used as an adjunct to determine the severity and extent of disease and can detect colon wall thickening, ascites, "megacolon", ileus, or perforation (41,65–67). We advocate its use in patients with complicated CDI if there is no immediate indication for operative intervention.

Recommendation

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)

Summary of the evidence. There are no RCTs available to guide recommendations for the choice and dosing of antibiotic therapy for the treatment of patients with severe CDI. Recommendations are extrapolated from clinical experience and data pertaining to RCDI, as well as consideration of impaired gastrointestinal motility and ileus that occurs in these patients (32). The IDSA/SHEA guidelines recommend vancomycin 500 mg orally or via enteric feeding tube four times per day and adding intravenous metronidazole (500 mg IV three times per day) if the patient has ileus or significant abdominal distention (3).

There are limited data on alternate antibiotic regimens for severely ill CDI patients. Fidaxomicin, as mentioned previously, was not inferior to vancomycin for initial cure for CDI, but no data are available on the efficacy of this drug in severe or complicated disease. Tigecycline is a novel analog of minocycline that exhibits broad antimicrobial activity against Gram-negative and Gram-positive organisms. Several published case reports suggest open-label benefit of intravenously administered tigecycline as a rescue strategy for the treatment of patients with severe CDI, in whom therapy with vancomycin and metronidazole has failed. However, further RCTs are required before we can make definitive recommendations regarding the use of tigecycline or fidaxomicin for the treatment of complicated CDI (68).

Recommendation

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)

Summary of the evidence. In patients with ileus, inability to tolerate oral or enteral feeding, or significant abdominal distention, the adjunctive use of direct installation of vancomycin into the colon is recommended as neither vancomycin or IV metronidazole will reliably reach the colon. Intravenous metronidazole must reach the luminal surface of the colon at therapeutic concentrations, which depends on biliary secretion of metronidazole into the small intestine and increased transit time, perhaps in the setting of diarrhea (69). Although oral/enteral vancomycin is not systemically absorbed, delivery to the colon and the site of CDI is impaired in the presence of adynamic ileus. Direct instillation via colonic retention enema, colonoscopy, or long rectal tube has been shown to be an effective strategy in smaller series reports (70,71). For this approach, vancomycin 500 mg in a volume of at least 500 ml four times per day is recommended. Again, a higher dosing strategy is utilized and it is given in a greater volume than that previously recommended based upon the hypothesis that larger volumes increase the likelihood that the drug will be delivered to the more proximal aspect of the colon; a volume of at least 500 ml is believed to ensure delivery to the ascending and transverse colon. Direct colonic installation of vancomycin is used in combination with intravenous metronidazole and oral/enteral vancomycin, although the dose of oral/enteral vancomycin is decreased given the addition of direct colonic delivery and potential concerns for systemic absorption with higher doses. If saline is being used as a carrier for vancomycin enemas, serum electrolytes should be closely monitored because of potential colonic electrolyte absorption and subsequent electrolyte abnormalities, most notably hyperchloremia. If hyperchloremia occurs, a carrier with a lower concentration of chloride (e.g., Ringer's Lactate) may be utilized. This combined approach and dosing strategy is based upon the rationale of ensuring effective delivery of therapeutic concentrations of antimicrobial therapy to the site of infection.

SURGERY FOR COMPLICATED CDI

Recommendation

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)

Summary of the evidence. A major challenge in the management of severe, complicated CDI is the inability to predict in which patient medical therapy will fail, and lack of consensus on the indications or timing of surgery except the very rare complication of colonic perforation. The vague term "clinical deterioration" is frequently mentioned in already critically ill patients in whom medical therapy has failed. These strategies rely on surgery as a salvage therapy, which may account for the poor outcomes associated with subtotal colectomy in complicated CDI, and mortality rates that range from 35% to 80% (38,39,41,42,65,72).

It has become evident that surgery is of benefit to patients at the advanced extreme of CDI, and early surgical consultation has been associated with improved survival. Data reviewed in several series suggest that earlier colectomy (time from presentation to surgery) was associated with a significantly decreased mortality (40,73,74). In an analysis of the literature from January 1989 to May 2009, earlier diagnosis and treatment with subtotal colectomy and end-ileostomy reduced mortality associated with fulminant CDI (75). One study demonstrated a trend toward decreased mortality rates in patients with fulminant disease who underwent colectomy compared with those who did not (42). These investigators further showed that admission of patients with complicated CDI to a surgical service was associated with a decreased mortality and a shorter mean interval from admission to operation compared with admission to a non-surgical service.

Independent risk factors for mortality in patients who underwent colectomy that have been found consistently among multiple studies include the development of shock, as determined by the need for vasopressors, and increased lactate (≥5 mmol/l), mental status changes, end organ failure, renal failure, and the need for preoperative intubation and ventilation (39,43,65,74).

The above findings suggest that early operative management before the development of shock and organ failure leads to improved survival. Currently, there is no scoring system that creates a threshold for operative management. However, the more negative prognostic signs a patient has, the earlier surgical consultation and operative management should be considered.

The established operative management of severe, complicated CDI has been subtotal colectomy with end-ileostomy. Survival of patients treated with segmental colectomy were worse than those treated with subtotal colectomy (41,76,77), likely because CDI usually involves the entire colon. Intraoperative assessment of the extent of disease is difficult based upon the external appearance of the colon from the serosal surface. Although some series have reported perforation or infarction of the colon to be common findings at the time of surgery, colonic necrosis and perforation are not inherent to the disease process (69); they likely result from the development of shock with secondary non-occlusive ischemia and the use of vasopressors or when abdominal compartment syndrome develops and compromises colonic perfusion.

Interest has developed in early operative management other than colon resection given that the colon is most often viable at this stage without perforation (78,79). A recent case-controlled series demonstrated that loop ileostomy with intraoperative colon lavage with polyethylene glycol 3350/balanced electrolyte solution and post-operative antegrade colonic vancomycin flushes via the ileostomy led to colon preservation in over 90% of patients and had significantly improved survival compared with historical controls who had undergone colectomy (19% vs. 50% mortality) (78). Over 80% of cases were performed using a minimally invasive surgical approach, and a majority of patients who were followed long term had restoration of gastrointestinal continuity. Advantages of this approach are the potential willingness to utilize this treatment earlier in the course of disease based upon potential preservation of the colon and fewer long-term adverse consequences. Further validation of this approach is required.

MANAGEMENT OF RCDI

RCDI is a therapeutic challenge because there is no uniformly effective therapy. After treatment of an initial episode of *C. difficile*, the chance of RCDI within 8 weeks is 10–20%, but when a patient has had one recurrence, rates of further recurrences increase to 40–65% (80). Recurrence can be due to the same strain or to a different strain (81). Recurrences may be due to an impaired immune response and/or alteration of the colonic microbiota. Evidence for an impaired immune response comes from small studies. In one study of hospitalized patients with CDI, those who developed RCDI had lower levels of immunoglobulin G (IgG) antibody to toxin A (82). In another, three patients who were given a vaccine to clear *C. difficile* developed an IgG response to toxin A (83).

Evidence that an altered colonic microbiota is the main factor in the pathophysiology of RCDI is growing. A study of the colonic microbiota in normal controls, individuals with one episode of CDI and patients with RCDI, showed that those with RCDI had a marked decrease in the diversity of the flora compared with the other two groups (84). Moreover, therapy that puts healthy donor stool into the stomach, small intestine, or colon of patients with RCDI (fecal microbiota transplant (FMT)) has the highest rate of success (≥90%) compared with results of other therapies (85).

Recommendation

Treatment of 1–2 CDI recurrences

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)

Summary of the evidence. Repeat courses of antibiotics, usually metronidazole or vancomycin are necessary to treat RCDI; both have similar recurrence rates. Re-treatment with a 10–14-day regimen is common. The IDSA/SHEA guidelines recommend treatment of the first recurrence using the same antibiotic that was used for the initial episode; use of vancomycin is recommended for repeated recurrences because of the risk of neuropathy with repeated administration of metronidazole (3). The use of vancomycin, 125 mg four times daily for 10 days, is preferred for any recurrence if it is severe, even if the initial episode had been treated with metronidazole. If the initial episode was treated with vancomycin, a tapered and pulsed regimen or just a pulsed regimen of vancomycin may be considered; none of these recommendations for extended vancomycin regimens have been studied in RCTs. Evidence that longer, tapered, pulsed-dosing is more effective than conventional regimens comes from evaluation of placebo-treated patients in a trial of a probiotic adjunct to antibiotic therapy in patients who already had one or more recurrences. Patients who had a standard 10–14-day course had recurrence rates of up to 54%, compared with 31% in those who had tapering regimens (gradually lowered doses) and 14% in those who had pulsed (every 2–3 day) regimens (80). There are no controlled data to support specific tapering or pulse regimens (86). We here propose a simple cost-effective regimen: a standard 10-day course of vancomycin at a dose of 125 mg given four times daily, followed by 125 mg daily pulsed every 3 days for ten doses (Scott Curry, personal communication). There is no convincing evidence of efficacy of other antibiotics, such as rifampin or rifaximin. In one study, six of seven patients responded to treatment with vancomycin and rifampin (87). In three small series, a total of 16 of 20 patients had no further recurrences when treated with 2 weeks of rifaximin after a 2-week course of vancomycin (88–90); a recently published RCT of this regimen did not find a decrease in documented CDI recurrences with rifaximin (91). Moreover, high-level resistance to rifampin is a concern and should limit its use (92).

Treatment of ≥3 CDI recurrences
Recommendation
20. If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)

Summary of the evidence. Fecal microbiota transplant (FMT) is the term used when stool is taken from a healthy individual and instilled into a sick person to cure a certain disease (85). Studies show that patients with RCDI have abnormally proportioned colon microbiota, and that reintroduction of normal bacteria via donor feces corrects this imbalance, restoring phylogenetic richness and colonization resistance.

The first documented use of FMT in the English language was a case series of four patients with pseudomembranous enterocolitis, three of whom were critically ill; fecal enemas (donated by the residents caring for the patients) were administered as an adjunct to antibiotic treatment; all four patients had resolution of symptoms within hours of FMT (93). The first documented case of confirmed RCDI treated with FMT was reported in 1983 in a 65-year-old woman who had "prompt and

complete normalization of bowel function" (94). Up until 1989, retention enemas had been the most common technique for FMT; however, alternative methods subsequently were used, including fecal infusion via nasogastric duodenal tube in 1991 (95), colonoscopy in 2000 (96), and self-administered enemas in 2010 (97). By 2011, approximately 325 cases of FMT had been reported worldwide, including approximately 75% by colonoscopy or retention enema, and 25% by nasogastric or nasoduodenal tube, or by esophagogastroduodenoscopy (98,99). Overall, mean cure rates to date are approximately 91% (99). In a recent series of 70 patients with RCDI, FMT was effective even in patients with the *C. difficile* NAP1/BI/027 strain (100). A retrospective multicenter follow-up study of RCDI patients treated with FMT demonstrated a 91% primary cure rate and a 98% secondary cure rate (101).

FMT appears to be safe, with no adverse effects or complications directly attributed to the procedure yet described in the existing literature (85,102). The potential for transmission of infectious agents is a concern, however, and a recent publication outlines rigorous screening of stool donors' blood and stool for common bacterial and viral enteropathogens (85). In one series, a standardized filtered, frozen, and then thawed preparation of stool from pre-screened universal donors showed cure rates equal to or better than those from patient-identified donors (103).

Long-term follow-up of FMT is limited. In the only such follow-up study to date, 77 patients had FMT and were followed for >3 months (3 months to >10 years). Of these 77 subjects, four developed an autoimmune disease (rheumatoid arthritis, Sjögren's syndrome, idiopathic thrombocytopenic purpura, and peripheral neuropathy) at some time after the FMT, although a clear relationship between the new disease and the FMT was not evident (101). RCTs are necessary to prove the efficacy of FMT and to determine the optimal route of administration among other variables and safety in immunosuppressed patients needs to be established. An RCT of donor feces administered by duodenal infusion with gut lavage showed significant efficacy compared to vancomycin or vancomycin with gut lavage without donor feces (104). The study was terminated early because it was deemed unethical to continue as the cure rate was 81% compared to 23% with vancomycin alone and 31% with vancomycin and gut lavage. An NIH-funded blinded RCT is underway, using FMT via colonoscopy with donor or recipient stool for transplant (Colleen Kelly, Lawrence Brandt, personal communication).

Other investigational treatments
Recommendation
21. There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCDI. (Moderate recommendation, moderate-quality evidence)

Summary of the evidence. A probiotic is a living organism that, when ingested, is beneficial to the host. Several probiotics have been tested in patients with RCDI, always as an adjunct to antibiotics. In one study, the yeast *Saccharomyces boulardii* resulted in fewer recurrences in a group of patients with RCDI (35% vs. 65%) (105); however, the study had inadequate randomization by the type of adjunct CDI antibiotic. In a later study, its efficacy was limited to the subgroup of patients treated with high doses

(2 gm/day) of vancomycin (17% vs. 50%) but not in those given metronidazole or lower doses of vancomycin in whom recurrence rates were 56–60% (32). A small trial of *Lactobacillus plantarum* 299v combined with metronidazole had recurrence rates of 35% compared with 66% in the control groups, a difference that was not statistically significant (106). Two small RCTs of *Lactobacillus rhamnosus GG* failed to show efficacy in treating RCDI (107,108). One uncontrolled study using Kefir (an over-the-counter probiotic drink) as an adjunct to antibiotics did result in decreased recurrence of *C. difficile* (109).

A meta-analysis of probiotics for the prevention of antibiotic-associated diarrhea and for the treatment of CDI concluded that *S. boulardii* was only effective for *C. difficile* disease (110); however, a Cochrane analysis concluded that there was insufficient evidence to recommend probiotics, in general, as an adjunct to antibiotics in the treatment of *C. difficile* diarrhea (111). The most recent systematic review and meta-analysis of *S. boulardii* concluded that although there is strong evidence from numerous large RCTs for efficacy in prevention of antibiotic-associated diarrhea, the evidence for efficacy in the treatment of *C. difficile* as an adjunct to antibiotics is weak and more RCTs are needed (112).

Thus, there are no strong data to support the use of probiotics for RCDI treatment, and only weak evidence of therapeutic efficacy for *S. boulardii.* There is no evidence for the use of probiotics in the treatment of initial or severe disease. Moreover, these are live organisms and they should be used cautiously, if at all, in individuals with significant immune suppression because of the possible risk of bacteremia or fungemia. There are cases of *S. boulardii* fungemia reported in patients with central venous catheters, and thus its use in an ICU or in immunocompromised patients is not recommended (113,114). There are also numerous case reports of invasive lactobacillus infections in non-immunosuppressed (mostly elderly) patients (115–117). Finally, the use of probiotics is not regulated by the Food and Drug Administration, there is no good quality control for most probiotics, and studies have shown that some probiotics contain no live organisms, or alternatively, contain organisms not on the product label (118,119). In view of the lack of efficacy data, abundant data on potential harm, high costs, and lack of biological plausibility for these non-human micro-organisms to confer colonization resistance, their use cannot be recommended.

Non-toxigenic strains of *C. difficile* have been used to treat CDI. Two patients with RCDI were given a non-toxigenic strain of *C. difficile* with resolution of symptom, but no RCTs have been done (120).

Recommendation

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)

Summary of the evidence. Evidence that resolution of diarrhea after treatment for CDI is associated with development of immune responses in the host includes a rise in anti-toxin antibodies after successful therapy (121–123), and lower levels of IgG anti-toxin A antibodies in patients with RCDI compared with those with CDI develop RCDI (82). Thus, there has been interest in immune approaches to treat both severe (refractory) and recurrent RCDI.

Publications to date on IVIG to treat RCDI in humans include six case reports and six small case series with varied patient inclusions (severe and recurrent), ages, doses of therapy used, and duration of therapy among other parameters (124,125). Many patients also received concomitant standard therapy, making interpretation of efficacy difficult. Passive immunizations with IVIG have been reported to be successful in several small series, including both children and adults. A recent review concluded that the grade of evidence is weak, given the lack of RCTs (125). One exception may be patients with hypogammaglobulinemia, which is common in patients following solid organ transplants, and may predispose to CDI. In one study, there was a fivefold increased risk of CDI in heart transplant recipients. These patients had decreased immunoglobulins and immunoglobulin therapy reduced the risk of CDI and RCDI recurrence (126). For this group of patients, IVIG may be beneficial, but more studies are needed before this can be stated definitively. IVIG has been associated with drug-induced aseptic meningitis and fluid overload states.

In a phase II clinical trial, a monoclonal antibody to toxins A and B used as an adjunct to antibiotics was shown to decrease recurrence rates in patients with CDI (7% compared with 38%); in patients with a previous episode of CDI, the recurrence rate was 7% compared with 18% in the control group ($P = 0.07$) (127). This product is only available in phase III trials. An oral anti-Clostridium whey protein from cows immunized to *C. difficile* toxoid was studied in the Netherlands. Early studies of *C. difficile* showed promise for treatment of patients with RCDI, with no further recurrences (128), but in a later study there was no significant decrease in recurrences (44% vs. 45%) (129). Further development of this product has been halted due to lack of funding.

A vaccine containing toxoids A and B has been tested in healthy volunteers (130). Given to healthy adults, the levels of IgG to toxin A were higher than levels associated with protection in other studies. Active immunization with this vaccine was used in combination with antibiotics to successfully treat three patients with RCDI (131). Several vaccines are in trials. There is no convincing evidence for efficacy of bile salt binders or whole gut lavage (132–134).

MANAGEMENT OF CDI AND CO-MORBID CONDITIONS

Several patient groups are newly recognized as either at an elevated risk for acquiring the infection or suffering adverse outcomes from CDI: patients with inflammatory bowel disease (IBD), including those with an ileostomy or an ileo-anal pouch following colectomy (135–138); patients with chronic liver disease (139,140); organ transplant recipients (solid organ and hematopoietic); patients with ongoing malignancy, particularly those undergoing chemotherapy, patients who chronically use steroids; patients with hypogammaglobulinemia and pregnant women and women in the peripartum period (141–143).

Patients with IBD

Recommendations

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)

Summary of the evidence. There has been a significant increase in the incidence of CDI in IBD patients, with recurrence in up to one-third in both children and adults (144–148).

Risk factors are pre-existing colonic inflammation, especially in ulcerative colitis, severe underlying IBD, and ongoing immunosuppression (136,149–152). Among the different therapies, the highest risk appears to be with corticosteroid use, which confer a threefold increase of CDI. Corticosteroid exposure within 2 weeks of the diagnosis of CDI was also associated with a twofold increase in mortality (153). Patients with IBD have a higher rate of colectomy and a greater mortality than either non-CDI IBD or non-IBD CDI controls (135,137,150). The clinical presentation of an IBD flare and CDI often is indistinguishable and requires a high index of suspicion for prompt detection and institution of appropriate therapy. All patients who require hospitalization because of an IBD flare, as well as ambulatory patients with risk factors for CDI (e.g., recent hospitalization, antibiotic use) or unexplained worsening of symptoms in the setting of previously quiescent disease, should be tested for *C. difficile*.

Recommendation

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)

Summary of the evidence. Management of concomitant immunosuppression in such patients is challenging, including when to treat a patient for CDI when they present with what appears to be an exacerbation of IBD. The decision to wait for a positive test to prove CDI or institute empirical therapy should be guided by severity of presentation. For mild-to-moderate cases, it is appropriate to treat for an IBD flare alone if there are no specific additional risk factors for *C. difficile*, and to treat if stool testing is positive. In patients with severe colitis, however, particularly in the presence of additional risk factors (e.g., recent health-care contact, antibiotic use, hospitalization) concomitant treatment for presumed *C. difficile* and an IBD flare may be warranted. Because it is often difficult to distinguish the effect of CDI independent from that of underlying IBD and because the data reporting worse outcomes in patients on combination immunosuppression and antibiotic therapy (153,154) have several limitations, we recommend that ongoing immunosuppression be continued at existing doses in IBD-CDI patients. One study has suggested that reducing the dose of systemic corticosteroids may help reduce the need for colectomy (149), but there are no prospective studies to confirm or refute this. Escalation of the corticosteroid dose or initiation of anti-TNF (anti-tumor necrosis factor) therapy in patients with a positive CDI probably should be avoided for 72 h after initiating therapy for CDI. In patients with severe disease, early co-management with surgeons is essential as patients with fulminant colitis may require emergent subtotal colectomy. Response to treatment should be based on clinical symptoms and signs. However, if diarrhea persists after completion of CDI treatment, a repeat *C. difficile* test may be warranted. If negative, escalation of IBD immunosuppressive therapy can be done to treat persistent disease. Although this testing recommendation appears to conflict with previous recommendations, personal experience of several authors indicates that repeat stool testing may be indicated in IBD patients.

Patients who have had a colectomy and have an ileostomy or an ileo-anal pouch remain at risk for CDI, with symptoms of increased stool frequency, or ostomy output, bleeding, or systemic features of fever, abdominal pain, and leukocytosis (155–158). Because some studies have reported high rates of adverse outcomes for CDI in such patients, it is essential to have a high index of suspicion. All patients with persistent or unexplained symptoms should be tested for *C. difficile*. Treatment of *C. difficile* pouchitis or enteritis is similar to treatment of other IBD patients.

Immunosuppressed patients

Recommendation

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)

Summary of the evidence. In patients with community-acquired CDI, 0.2% may have underlying chronic liver disease or cirrhosis (159), whereas in hospitalized patients with CDI, this rate is estimated at 2–5% (140,160). The rate of CDI in the post-transplant setting is higher with 3–11% of such patients developing CDI (161–163). Use of antibiotics or PPIs are risk factors for CDI in patients with cirrhosis, but whether such risk is greater than that in non-liver disease controls is not clear (139); severity of liver disease has not been shown consistently to be an independent risk factor (164). Recommendations for therapy are the same as for other patients.

Pregnant or peripartum women
Recommendation

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

Summary of the evidence. Although the rate of CDI among hospitalized pregnant women historically has been as low as 0.02%, a report of 10 cases of peripartum CDI with a 40% hospitalization rate and one fatality brought attention to this new potentially high-risk subgroup (141–143,165). Most of these women had a history of recent antibiotic use (9 of 10 patients in one series or hospitalization (165). Another report found recent Cesarean section appears to confer a higher risk for CDI than vaginal delivery (142). The rate of maternal and fetal mortality in patients with severe CDI remains high (30%) with 5 of 10 patients in one series developing toxic megacolon (165). A high index of suspicion, early testing, and initiation of appropriate antibiotic therapy is essential.

INFECTION CONTROL AND PREVENTION
Infection control practices
Recommendation

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

Summary of the evidence. Early detection of CDI should lead to earlier treatment and earlier introduction of infection control measures. The Association for Professionals in Infection Control and Epidemiology recommends several surveillance measures (166,167): (1) a high index of suspicion in patients with risk factors for CDI (recent or current antimicrobials, use of anti-neoplastic agents, advanced age, recent hospitalization, or residence in a LTCF, previous CDI); (2) physician advocacy for the use of the best *C. difficile* diagnostic tests with a rapid turn-around time and a high sensitivity and specificity for detection of toxigenic *C. difficile*; and (3) ensuring that appropriate staff members are informed immediately about positive *C. difficile* results, so that appropriate therapy and contact precaution measures can be initiated.

A previous report describes one institution's comprehensive efforts to control an outbreak of CDI caused by the hypervirulent strain (NAP1/BI/027) using a *C. difficile* infection control "bundle", consisting of education, increased and early case finding, expanded infection control measures, development of a *C. difficile* management team, and antimicrobial stewardship. Hospital rates of *C. difficile* decreased from 7.2 cases per/1,000 discharges during the year before institution of these measures to 4.8 cases per/1,000 discharges in the subsequent 5 years (168).

Recommendation

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)

Summary of the evidence. Patients and hospital staff who are asymptomatic carriers of *C. difficile* may contribute to horizontal spread within an institution (15,168). Antimicrobial therapy to eradicate asymptomatic carriage of *C. difficile* is not recommended. In one study, metronidazole was not effective in eliminating carriage, and while vancomycin initially cleared the organism from stools, the rate of re-colonization was high at follow up 2 months later (169) often with new strains; one asymptomatic carrier developed CDI after vancomycin treatment. Treatment of carriers also may increase the shedding of spores (170).

Recommendation

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

Summary of the evidence. Antibiotics are the biggest risk factor for CDI. Any antibiotic can cause CDI, but clindamycin, cephalosporins, and fluoroquinolones pose the greatest risk for CDI, as well as multiple antibiotics and longer duration of antibiotics. Numerous studies have shown that restriction of the most common offending antimicrobials is effective in CDI prevention (171–173). In one study, an antimicrobial stewardship program contributed to a 60% decrease in CDI incidence during an epidemic (173). During an epidemic, active monitoring of CDI, as is done for vancomycin-resistant enterococcal infections, allows identification of alarming trends and the chance for relatively early interventions. It is probably wise to monitor the incidence of CDI following any change in a formulary's antibiotic "drug of choice". Several guidelines for antibiotic stewardship programs have been published (174–176).

Recommendation

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

Summary of the evidence. The ability to culture *C. difficile* is significantly higher from the surfaces in rooms of infected patients than from the surfaces of rooms of non-infected patients (15). *C. difficile* can also be cultured from the surfaces of rooms of patients with asymptomatic CDI, albeit to a lesser degree than from the rooms of patients with symptomatic CDI. Additionally; it has been shown that the skin surfaces of patients with CDI diarrhea that resolved 2 weeks before is still contaminated with *C. difficile* that may be transferred to an examining gloved hand (177). One recommendation is to maintain contact precautions for 48 h after diarrhea ceases (178). Some institutions have implemented contact precautions for the duration of hospitalization as part of their infection control interventions for CDI (168).

Recommendation

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)

Summary of the evidence. A cohort study of nosocomial acquisition of CDI reported higher acquisition rates in double rooms than in single rooms and a significantly higher risk of acquisition after exposure to a roommate positive for *C. difficile* (15). If a private room is not possible, two patients with documented CDI can share a room.

Recommendation

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)

Summary of the evidence. Hand hygiene is a cornerstone of prevention of nosocomial infections, including *C. difficile*. Although hand carriage of most vegetative bacteria and viruses is reduced by alcohol-based hand antiseptics, such is not the case with *C. difficile* spores (179). Therefore, hand washing with soap and water is recommended. In one study, *C. difficile* was shown to persist on the hands of 14 of 16 personnel who washed with plain soap compared with 1 of 7 personnel who remained positive after washing with 4% chlorhexidine (Gluconate) antiseptic (15). Personnel who contact patients with CDI can easily contaminate their hands with *C. difficile* spores. A prospective controlled trial of vinyl glove use for handling body substances showed a significant decline in CDI rates from 7.7 per 1,000 discharges before institution of glove use to 1.5 cases per 1,000 discharges after institution of glove use ($P=0.015$) (180). Evidence that the use of gowns prevents spread of CDI is less compelling than that regarding the use of gloves, but gown use is recommended. Gowns and gloves must be removed before leaving the patient's room.

Recommendation

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)

Summary of the evidence. Several studies have shown a decrease in CDI when using disposable thermometers rather than electronic thermometers. In an RCT, the rate of CDI decreased significantly from 0.37 to 0.16 per 1,000 patients days when disposable thermometers were substituted for electric thermometers and was cost effective (181). Dedicated non-disposable equipment should be kept in the patient's room.

Recommendation

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)

Summary of the evidence. The environment is an important source of nosocomial infections (182,183). Interventions to reduce environmental contamination by *C. difficile* have decreased the incidence of infection, including a hypochlorite-based solution in a bone marrow transplant unit and ammonium compound cleaning agent in another study (184–186). The Centers for Disease Control and Prevention recommends an EPA-registered disinfectant that has a *C. difficile*-sporicidal label claim. Available chlorine concentrations should be 5,000 p.p.m. Evidence supports the use, for at least 10 min, of chlorine-containing cleaning agents with a minimum of 5,000 p.p.m. of available chlorine.

Recommendation

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)

Summary of the evidence. Several meta-analyses have shown a decrease in antibiotic-associated diarrhea with probiotics (*L. rhamnosus GG* and *S. boulardii*), but there are only limited studies to show a decrease in CDI with probiotics. One RCT showed that a yogurt drink containing *Lactobacillus casei*, *Lactobacillus bulgaricus*, and *Streptococcus thermophilus* reduced the risk of CDI in hospitalized patients for whom antibiotics were prescribed (187), but the study had small numbers of patients, excluded patients receiving high-risk antibiotics, and had a high rate of CDI in the placebo-treated patients. Another study reported that capsules containing *Lactobacillus acidophilus* CL1285 and *L. casei* LBC80R were effective in preventing both AAD and CDI in 255 hospitalized patients (188). There is insufficient evidence to support the routine use of probiotics to prevent CDI. Probiotics for RCDI are discussed in a previous section.

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APPENDIX
Definitions of CDI

Definitions
Use of standardized definitions for CDI (health-care onset-health-care facility associated (HO-HCFA), community onset-health-care facility associated (CO-HCFA), community associated (CA), or indeterminate disease (ID) will allow comparison among studies. (Strong recommendation, moderate-quality evidence)

Type of case	Definition
Health-care facility-onset health-care facility associated (HO-HCFA)	Occurs when onset of symptoms 3 days after admission to a health-care facility.
Community onset health-care facility associated (CO-HCFA)	Onset of symptoms within 4 weeks after being discharged from a health-care facility.
Community associated (CA)	Occurs when onset of symptoms occurs outside a health-care facility or <3 days after admission to a health-care facility and has not been discharged from a health-care facility in the previous 12 weeks.
Indeterminate or unknown onset (ID)	CDI develops after being discharged from a health-care facility 4–12 weeks previously.
Recurrent CDI	Episode of CDI that occurs 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode resolved.

CDI, Clostridium difficile infection.

CDI may be further defined according to the time of symptom onset and history of hospitalization (189,190): Health-care onset health-care facility-associated (HO-HCFA) CDI is defined as onset of symptoms 3 days after admission to a health-care facility. Community onset health-care facility-associated (CO-HCFA) CDI is defined as onset of symptoms within 4 weeks after being discharged from a health-care facility. Community-associated (CA) CDI occurs when a person develops CDI outside of a health-care facility or <3 days after admission in someone who has not been discharged from a health-care facility in the previous 12 weeks. If CDI develops after being discharged from a health-care facility 4–12 weeks previously, the case is considered as indeterminate disease (ID). RCDI is defined as an episode of CDI that occurs 8 weeks after the onset of a previous episode, provided the symptoms from the previous episode have resolved. Several studies performed in different geographic areas of the United States document HO-HCFA CDI to be the most frequent (53–89%) followed by CO-HCFA CDI (3–28%), CA (5–27%), and ID (5%) of cases (15,191–193). In order to ensure uniformity of data reporting and to allow comparability among studies, we recommend these definitions be used. For surveillance studies, incidence rates should be expressed as cases of CDI per 10,000 patient-days (194).

CDI prevalence/incidence. Rates of CDI have been increasing globally since 2000, a national point—prevalence of CDI from a survey in US health-care facility inpatients in 2008 was 13.1/10,000 patients (195). Almost 70% of patients were >60 years

of age, and 52.2% were 70 years. Nearly 80% had received antibiotics in the previous 30 days. Overall, 73% of cases were health-care-associated CDI. More recent surveillance data from 2010 from the Emerging Infections Program that includes 111 acute-care hospitals and 310 nursing homes and from the 711 acute-care hospitals reporting to the National Health Care Safety Network found that 97% of cases were health-care related. Of these, 75% had onset of among persons previously hospitalized (196). In a study of US trends from 2000 to 2005, the incidence of CDI in adults increased from 5.5/10,000 to 11.2/10,000 (197). In adults aged 18–44 years, the increase was only 1.3/10,000 to 2.4/10,000, but in those aged 65–84 years, the increase was from 22.4/10,000 to 49/10,000 and in those >85 years CDI it nearly doubled from 52/10,000 to 112/10,000 (197).

Carriage of *C. difficile* occurs in 5–15% of healthy adults and may be transient (198–200). Among newborns and healthy infants, carriage rates may be as high as 84.4% up to age 2 years (199,201,202). Some infants may have non-toxigenic strains. Hospitalized patients have much higher carriage rates; in a prospective study, 26% of 428 patients in a medical ward acquired *C. difficile*; 62% remained asymptomatic (15). Among the elderly, carriage rates may be higher, especially in those in LTCFs. In one study of an epidemic in a LTCF, 51% of asymptomatic carriers had toxigenic *C. difficile* (203), indicating that LTCF may be a reservoir for cases of CDI.

CA-CDI has received a great deal of attention as a potential emerging cause of outpatient diarrheal illness, but all of the studies of CDI in non-hospitalized populations have used laboratory surveillance to find cases (204–207). A recent prospective study of outpatients with diarrheal illnesses presenting to emergency rooms and outpatient clinics in the United States showed only 43/1091 (3.9%) with positive tests for *C. difficile*, of whom only 7 (0.6%) had no traditional risk factors for CDI and no co-infections (208). Within hospitals, even outbreaks of diarrhea attributed to norovirus have been initially mis-attributed to *C. difficile* because of the high carriage rate within hospital populations (209). Given these data, the pre-test suspicion for CDI in healthy outpatients without antimicrobial exposures remains low and should remain so even for outpatients with positive *C. difficile* tests.

Since 2000, an epidemic strain has emerged (NAP1/BI/027), associated with an increase in the endemic incidence and an increase in the mortality of patients in some institutions (210–214). The NAP1/BI/027 strains have a higher rate of fluoroquinolone resistance, produce 16 times more toxin A, and 23 times more toxin B *in vitro* than other *C. difficile* strains (215); and produce a binary toxin. Patients infected with this strain are reported to have lower clinical cure rates and higher rates of CDI recurrences than patients with other strains (216). However, several studies have failed to demonstrate an association between NAP1/BI/027 strains and severe disease (217–220). Moreover, non-027 ribotype strains have been associated with severe clinical outcomes in at least two studies (221,222).

Transmission. Transmission within health-care facilities largely results from horizontal transmission via environmental surface contamination, hand carriage by hospital personnel, and infected

roommates (15,217–225). In a cohort of 2,859 patients, a multi-variate analysis found that physical proximity to a patient with CDI significantly increased the risk of CDI (relative risk = 1.86, 95% confidence interval 1.06–3.28) (224). In addition to health-care facility sources, *C. difficile* is found in soil, a variety of animals and pets (e.g., cats, dogs, horses, cattle, swine), and food products, including various meats and ready-to-eat salads (226–231). In animals, some strains are species specific but others affect humans as well. The epidemic strain NAP1/BI/027 has been isolated from food and from domestic pets; however, there are no documented studies that this route of transmission has caused human illness (230,231).

Risk factors. The two biggest risk factors for CDI are exposure to antibiotics, especially broad-spectrum antibiotics and exposure to the organism, usually through admission to a health-care facility. Other factors in epidemiological studies that increase the risk of CDI include older age, gastrointestinal surgery, nasogastric tube feeding, reduced gastric acid, and concurrent disease, including inflammatory bowel disease (144,145,232–236). An impaired immune response has been implicated; a small series showed that patients with *C. difficile* in their stools who developed diarrhea had lower levels of IgG to toxin A than those who remained asymptomatic (237). Serious underlying illness and the presence of other concurrent diseases place the patient at increased risk of CDI, especially if the patient is receiving additional antibiotics for concurrent infections and has a longer hospital stay. As many risk factors for CDI are correlated, multivariate analysis provides independent risk estimates for variables that occur at the same time. Most multivariate models find advanced age, antibiotic use, co-morbidities, and longer hospital stays are independently predictive of CDI (211,214,232). Although several studies have not shown an association with proton pump inhibitors (PPIs) and CDI, many other studies have found an association (235,236). A meta-analysis of 29 studies of patients with CDI found that PPI increased the risk of CDI (pooled odds ratio = 2.15, 95% confidence interval (CI) 1.81–2.55) (234). Two recent meta-analyses confirm association and strengthen the evidence that PPI use is associated with an increased risk of CDI (7,8).

The risk factors for recurrent CDI are slightly different from those for initial CDI. In a prospective study of 209 patients with recurrent CDI, logistic regression revealed only two significant independent risk factors for CDI recurrence: increased age and a lower quality of health at enrollment (238). One meta-analysis of 12 studies totaling 1,382 patients with recurrent CDI and found risk factors for recurrent CDI that included continued use of non-*C. difficile* antibiotics (odds ratio (OR) = 4.23, 95% CI 2.1–8.5), antacids (OR = 2.1, 95% CI 1.1–4.1), and older age (OR = 1.6, 95% CI 1.1–2.4) (239). Another group developed a prediction rule with a 77% accuracy based on three risk factors: age >65 years, severe or fulminant illness, and additional antibiotic use after CDI therapy was completed (240).

Microbiological testing

There are several FDA-approved NAAT's, including PCR assay and loop-mediated isothermal amplification (LAMP). PCR is an excellent confirmatory test, but data for LAMP testing is not yet sufficient to recommend it. Currently, there are six FDA-approved NAATs available: four PCR assays, a LAMP method, and a ribonuclease-mediated isothermal amplification and chip-based detection method (83–93,241–251). Because there are few published data on the performance of one of the PCR tests, Simplexa-*C. difficile* Universal Direct Test (Quest Diagnostics, Madison, NJ), and the ribonuclease-mediated isothermal amplification and chip-based detection method test (Great Basin Corporation, Salt Lake City, UT), it is not possible to comment on their performance at this time. Meta-analysis of three commercial PCR assays, GeneOhm Cdiff Assay BD Diagnostics GeneOhm, San Diego, CA; Xpert *C. difficile* Test Cepheid, Sunnyvale, CA; and ProGastro Cd Assay Gen-Probe, San Diego, CA indicate that they have similar sensitivities of and specificities of ~90% and ~95%, respectively, compared with TC (214). A recent large study comparing widely used commercially available tests showed that PCR for toxigenic *C. difficile* and GDH testing were the most sensitive tests for detection of *C. difficile* in stool specimens compared with a composite reference method of TC or a negative culture in patients with multiple positive tests and a clinical course consistent with CDI. Additionally, the PCR test studied was more specific than GDH. Importantly, both methods were statistically more sensitive than CCNA and various toxin A + B EIAs (245).

PCR is an excellent confirmatory test for GDH compared with TC; no such data currently exist for LAMP testing (25,249,251). Amplification methods, however, do have superior sensitivity compared with GDH, toxin A + B EIA, and CCNA tests (245,248–251).