in the clinic

Clostridium difficile Infection

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CME Objective: To review current evidence for the prevention, diagnosis, and treatment of *Clostridium difficile* infection

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Antibiotic-associated diarrhea was described in the 1950s. By 1978, *Clostridium difficile* had been established as the most common cause of infection, accounting for 15% to 25% of cases (1). The reported incidence and severity as measured by total mortality and colectomy rates rose steadily from 1993 to 2003 (2). A national survey in 2008 of 648 U.S. hospitals reported an overall *C. difficile* prevalence of 13.1 per 1000 inpatients (3). In the past decade, a strain with increased virulence has been described in relation to outbreaks in Canada, the United States, and Europe. This strain, designated NAP1/BI/027, produces a binary toxin not previously associated with *C. difficile* and produces substantially (15- to 20-fold) more toxin A and B than other strains. This strain is associated with more severe disease and mortality rates of 7% or more. It also seems to be more readily transmissible, and has been associated with community-acquired disease in persons with no established risk factors, including peripartum women and children. It is very resistant to fluoroquinolones, and emergence is believed to have been fostered by extensive use of these drugs in health care settings and in the community (4–6). This emergence of a hypervirulent form of *C. difficile* should prompt increased caution in prescribing fluoroquinolones in addition to those agents previously identified as frequent triggers of *C. difficile* diarrhea.

Prevention

How does a patient acquire *C. difficile* infection?

Colonization with *C. difficile* occurs through the fecal–oral route, usually by person-to-person transmission. Contaminated fomites and the hands of health care workers are another source of transmission (7).

A prospective 11-month study of C. difficile *transmission in hospitalized patients showed that 21% of patients who initially had negative test results acquired the organism during admission;* C. difficile *was cultured from environmental surfaces in 49% of hospital rooms of symptomatic patients and from the hands of 59% of the health care workers caring for these patients (8).*

Although the risk for *C. difficile* infection is greatly increased for persons who are hospitalized compared with those in the community, the infection still causes an estimated 8 to 12 cases per 100 000 in the outpatient population (5). Isolation of the organism from hamburger and the gastrointestinal tracts of farm animals has been reported and may account for some acquisition in the community, although exposure to persons with health care–associated colonization or disease is assumed to be the usual source (9, 10). The organism forms hardy spores that survive the acid environment of the stomach. Asymptomatic colonization may occur in 20% or more of patients in acute care hospitals, and increasing length of stay correlates with a greater likelihood of acquisition. From 4% to 20% of long-term care residents carry the organism (11). Colonization rates in the community are estimated at about 2% to 8% (12). Once colonization is established, certain factors favor development of symptomatic disease. Antibiotic disruption of the microbial balance of the gut is the most common, and longer courses and use of multiple antibiotics increase the risk for disease. Clindamycin, cephalosporins, penicillins, and recently fluoroquinolones are frequently cited triggers, but almost all antibiotics carry some risk (13, 14).

Chemotherapeutic agents may have the same effect (15). Some data suggest that the use of proton-pump inhibitors or histamine-2 blockers may play a role in some

1. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of *Clostridium difficile* infection. Clin Infect Dis. 2008;46 Suppl 1:S12-8. [PMID: 18177217]
2. Ricciardi R, Rothenberger DA, Madoff RD, et al. Increasing prevalence and severity of *Clostridium difficile* colitis in hospitalized patients in the United States. Arch Surg. 2007;142:624-31; discussion 631. [PMID: 17638799]
3. Jarvis WR, Schlosser J, Jarvis AA, et al. National point prevalence of *Clostridium difficile* in US health care facility inpatients, 2008. Am J Infect Control. 2009;37:263-70. [PMID: 19278754]
4. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005;353:2442-9. [PMID: 16322602]

patients, but reports are contradictory (16, 17). Other physical manipulations of the gastrointestinal tract, such as surgery, enemas, stool softeners, and even tube-feeding, have been identified in some studies as contributing factors (18–20). Specific immune defects, such as neutropenia or advanced HIV infection, may play a role in the development of disease. Finally, factors associated with general debility, such as advanced age or severe underlying disease, have been associated with increased risk, especially when multiple factors coexist (21).

What can clinicians do to reduce the likelihood of their patients developing *C. difficile* infection?

The primary means of prevention are to limit the use and type of antibiotics and to adhere to infection-control measures. The latter includes the use of appropriate environmental cleaning methods and solutions, but because those measures generally are not within the purview of individual clinicians, they are not discussed here.

Physicians should participate in antibiotic stewardship programs (designed in conjunction with microbiologists, pharmacists, infection-control specialists, and hospital administrators) to limit unnecessary antibiotic administration, aid in the selection of agents that carry a lower risk of *C. difficile* disease whenever possible, and ensure that duration of antibiotic therapy is minimized to the extent appropriate for the infection being treated. Many strategies have been used, from restrictive and nonrestrictive protocols for the use of high-risk drugs to routine review of current cases with feedback to attending physicians.

Several large, prospective studies have confirmed that the introduction of such antibiotic use policies was associated with statistically significant reductions in C. difficile *infection in both endemic and epidemic settings (22, 23).*

A prospective controlled, interrupted time-series study of the geriatric service of a large teaching hospital evaluated the rates of C. difficile *infection over 2 periods of 21 months, before and after institution of a feedback antibiotic prescription protocol to promote use of narrow-spectrum antibiotics when appropriate. During the study period, 6129 patients were admitted. After the institution of the antibiotic policy,* C. difficile *infection decreased significantly (incidence rate ratio, 0.35;* P = *0.009) (22).*

Because of the increasing frequency of community-acquired *C. difficile* in persons with no known risk factors, prescriptions for outpatients also should be carefully considered with regard to the antimicrobial spectrum and the relative frequency of association with *C. difficile* diarrhea.

Hospitalized patients with *C. difficile* infection should be assigned to private rooms or placed with other similarly infected patients until diarrhea has resolved. Routine infection-control procedures include strict hand hygiene between patient examinations and contact precautions, including use of gloves and gowns for any contact with patients who have *C. difficile* infection or with their bodily fluids. Conventional handwashing with soap and water should be strictly adhered to in outbreaks or after caring for a patient known or suspected to have *C. difficile* infection, rather than using alcohol-based hand rubs, which do not eliminate *C. difficile* spores.

No published trials have been designed specifically to study the protective effect of gowns, but *C. difficile* has been cultured from the uniforms of hospital workers. The use of disposable gowns is recommended on that basis (24, 25).

A prospective controlled trial examined the incidence of C. difficile *infection on 3 similar hospital wards to evaluate the efficacy*

5. Centers for Disease Control and Prevention (CDC). Severe *Clostridium difficile*-associated disease in populations previously at low risk—four states, 2005. MMWR Morb Mortal Wkly Rep. 2005;54:1201-5. [PMID: 16319813]
6. Centers for Disease Control and Prevention (CDC). Surveillance for community-associated *Clostridium difficile*—Connecticut, 2006. MMWR Morb Mortal Wkly Rep. 2008;57:340-3. [PMID: 18385641]
7. Fekety R, Kim KH, Brown D, et al. Epidemiology of antibiotic-associated colitis; isolation of *Clostridium difficile* from the hospital environment. Am J Med. 1981;70:906-8. [PMID: 7211925]
8. McFarland LV, Mulligan ME, Kwok RY, et al. Nosocomial acquisition of *Clostridium difficile* infection. N Engl J Med. 1989;320:204-10. [PMID: 2911306]
9. Rodriguez-Palacios A, Staempfli HR, Duffield T, et al. *Clostridium difficile* in retail ground meat, Canada. Emerg Infect Dis. 2007;13:485-7. [PMID: 17552108]
10. Yaeger MJ, Kinyon JM, Glenn Songer J. A prospective, case control study evaluating the association between *Clostridium difficile* toxins in the colon of neonatal swine and gross and microscopic lesions. J Vet Diagn Invest. 2007;19:52-9. [PMID: 17459832]
11. SHEA Long-Term-Care Committee. *Clostridium difficile* in long-term-care facilities for the elderly. Infect Control Hosp Epidemiol. 2002;23:696-703. [PMID: 12452300]
12. Thielman NM, Wilson KH. Antibiotic-associated colitis. In: Mandell GL, Bennett JE, Dolin R, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, seventh edition. Philadelphia: Churchill Livingstone; 2010:1375-87.

of vinyl gloves in preventing nosocomial transmission of C. difficile *on 1 of the 3 wards. The use of vinyl gloves was associated with a statistically significant reduction in symptomatic* C. difficile *infection and asymptomatic colonization (26).*

The spores of *C. difficile* are highly resistant to alcohol, and at least 1 study has shown that conventional handwashing with soap and water is superior to the use of alcohol-based hand rubs for removing *C. difficile* (27). It has been postulated that use of alcohol-based rubs may actually promote nosocomial transmission of this organism. However, several studies have failed to show an increase in the rate of *C. difficile* associated with use of alcohol-based hand gels (28, 29). Although these studies were designed to investigate whether alcohol-based hand rubs were associated with an increase in *C. difficile* infection, no decrease was noted despite more frequent hand hygiene.

Prevention... Nosocomial transmission of *C. difficile* can be prevented by thorough hand hygiene, especially with soap and water, between all patient contacts and by careful adherence to contact precautions in the care of infected persons. Judicious use of antibiotics through stewardship protocols may prevent symptomatic disease in colonized patients.

CLINICAL BOTTOM LINE

Diagnosis

What history, signs, and symptoms should raise suspicion of *C. difficile* infection?

Patients should be asked about the known risk factors for *C difficile* diarrhea (Box).

Patients commonly develop antibiotic-related diarrhea with *C. difficile* during or shortly after receiving antibiotics (30), but the symptoms can occur up to several months after completing these drugs. In patients who have been hospitalized for at least 3 days, *C. difficile* is by far the most common enteric pathogen (31).

Consider *C. difficile* infection in patients who have diarrhea or abdominal pain, especially when they have a recognized risk factor. Nausea, vomiting, and fever are often but not always present. Physical findings are variable, depending on the length and severity of disease. Signs of dehydration may be present. The abdomen may be tender, and in severe cases, peritoneal signs may be present. Ileus or toxic megacolon may result in abdominal distention (Table 1).

Risk Factors for *C. difficile* Diarrhea

- Antibiotic use: Clindamycin, cephalosporins, penicillins, and fluoroquinolones implicated most frequently, but all antibiotics have been associated. Risk increases with duration and number of antibiotics
- Antineoplastic agents
- Hospital or nursing home care; outpatient disease without previous hospital or nursing home exposure is becoming more common
- Advanced age
- Underlying disease: Malignant conditions, renal failure, generalized debility
- Gastrointestinal manipulation: Surgery, tube-feeding, enemas; use of proton-pump inhibitors, and histamine-2 blockers may also be associated

What diagnostic tests should clinicians perform when they suspect *C. difficile* infection?

Enzyme immunoassays designed to detect toxin in submitted stool specimens are the most widely used in clinical laboratories. They

13. Owens RC Jr, Donskey CJ, Gaynes RP, et al. Antimicrobial-associated risk factors for *Clostridium difficile* infection. Clin Infect Dis. 2008;46 Suppl 1:S19-31. [PMID: 18177218]
14. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. Infect Control Hosp Epidemiol. 2005;26:273-80. [PMID: 15796280]
15. Anand A, Glatt AE. *Clostridium difficile* infection associated with antineoplastic chemotherapy: a review. Clin Infect Dis. 1993;17:109-13. [PMID: 8353229]
16. Shah S, Lewis A, Leopold D, et al. Gastric acid suppression does not promote clostridial diarrhoea in the elderly. QJM. 2000;93:175-81. [PMID: 10751237]

Table 1. Clinical Features and Complications of *Clostridium difficile* Infection

Spectrum of Disease	*Diarrhea*	*Other Symptoms*	*Physical Examination*	*Colonoscopic and Other Findings*
Asymptomatic carrier	None	None	Normal	Normal
Simple antibiotic-associated diarrhea	Mild	Systemic symptoms usually absent	Usually normal	Normal
Early colitis	Profuse	Nausea, anorexia	Low-grade fever, with or without mild abdominal tenderness	Nonspecific patchy erythema
Pseudomembranous colitis	Profuse	Nausea, malaise, abdominal discomfort	Fever (sometimes high), abdominal tenderness, distention	Pseudomembranes (raised yellow plaques), leucocytosis (may be $\geq 50 \times 10^9$ cells/L, with left shift)
Fulminant colitis	Usually profuse and severe, may be absent in ileus or toxic megacolon	Nausea, abdominal discomfort or pain	Toxic appearance, fever (often high), abdominal distention, tenderness, and peritoneal signs	Endoscopy contraindicated in severely ill patients; leukemoid reaction common; radiographic studies may show colonic dilatation, mucosal thickening, perforation

provide results rapidly, with sensitivity and specificity of 65% to 85% and greater than 90%, respectively. Some commercially available kits test only for toxin A, and because some *C. difficile* strains produce only toxin B, such tests carry an increased likelihood of false-negative results.

Cytotoxin assay is the clinical reference standard for the diagnosis of *C. difficile* infection, with a sensitivity of 94% to 100% and specificity of 97%; however, it takes 24 to 48 hours and requires a tissue culture laboratory, which is not available in most hospitals. Culture is more sensitive than toxin assays but requires 48 hours or more for incubation, plus further testing to confirm that the isolate produces toxin. Culture and molecular typing of isolates are important in the epidemiologic study of outbreaks.

A report of 10 522 samples tested for C. difficile *over 7 years showed that although 10% were positive by culture, only 4.4% were positive by cytotoxin tests (32).*

Latex agglutination assays for glutamate dehydrogenase are not adequately sensitive. Enzyme-linked immunosorbent assays (ELISAs) for this enzyme have been developed and are very sensitive but not specific. Some authorities recommend their use for rapid screening as part of a 2-step test that includes confirmatory toxin testing (25).

Polymerase chain reaction (PCR) testing for *C. difficile* has been found in preliminary studies to be rapid and accurate and may emerge as the test of choice in routine diagnosis.

An observational validation study of PCR to diagnose C. difficile *diarrhea reported these sensitivities: culture, 100%; PCR, 93%; cell culture cytotoxin assay, 76%; and ELISA for toxins A and B, 73% (33).*

Because the tests designed to detect toxin carry a measurable risk for false-negative results, repeated testing on different stool specimens may be necessary. But clinical decisions about treatment should be based on the patient's risk factors and other clinical and laboratory data (25). In their overview of the performance and role of various tests for *C. difficile*, Peterson and Robicsek recommended using tests with higher sensitivity, avoiding testing for *C. difficile* for a single episode of diarrhea, and paying greater attention to key aspects of the patient's history (34) (Table 2).

Another test with diagnostic value is direct inspection via

17. Dial S, Delaney JA, Barkun AN, et al. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. JAMA. 2005;294:2989-95. [PMID: 16414946]
18. McFarland LV, Surawicz CM, Stamm WE. Risk factors for *Clostridium difficile* carriage and *C. difficile*-associated diarrhea in a cohort of hospitalized patients. J Infect Dis. 1990;162:678-84. [PMID: 2387993]
19. Thibault A, Miller MA, Gaese C. Risk factors for the development of *Clostridium difficile*-associated diarrhea during a hospital outbreak. Infect Control Hosp Epidemiol. 1991;12:345-8. [PMID: 2071877]
20. Bliss DZ, Johnson S, Savik K, et al. Acquisition of *Clostridium difficile* and *Clostridium difficile*-associated diarrhea in hospitalized patients receiving tube feeding. Ann Intern Med. 1998;129:1012-9. [PMID: 9867755]
21. Kyne L, Sougioultzis S, McFarland LV, et al. Underlying disease severity as a major risk factor for nosocomial *Clostridium difficile* diarrhea. Infect Control Hosp Epidemiol. 2002;23:653-9. [PMID: 12452292]

Table 2. Stool Tests for *Clostridium difficile*

Test	*Detects*	*Advantages*	*Disadvantages*
Cytotoxin assay	Toxin B	Standard, highly sensitive and specific	Requires tissue culture facility
Toxin enzyme immunoassay	Toxin A or A and B	Fast (2–6 h), easy to perform, high specificity	Not as sensitive as the cytotoxin assay
Glutamate dehydrogenase enzyme immunoassay	Bacterial enzyme (glutamate dehydrogenase)	Fast, inexpensive, easy to perform	Poor specificity
Culture	Toxigenic and nontoxigenic *C. difficile*	Sensitive, allows strain typing in epidemics	Requires anaerobic culture; not specific for toxin-producing bacteria; takes 2–5 d

sigmoidoscopy or colonoscopy. Characteristic raised yellow mucosal plaques, or "pseudomembranes," are highly suggestive of *C. difficile*–associated diarrhea. Unprepared flexible sigmoidoscopy is often adequate and has been shown to be an effective means of establishing the diagnosis in many cases in which toxin tests were negative (35). However, sigmoidoscopy may miss cases that could be detected by colonoscopy, because of more proximal disease, as reported in at least 2 small prospective studies using flexible sigmoidoscopy for diagnosis (36, 37). Conversely, many cases diagnosed by toxin testing or other methods do not have pseudomembranes, which may be a marker of severe disease.

Other tests that may provide supporting evidence for the diagnosis and are of value in assessing severity of disease and complications include complete blood count, creatinine, lactate level, and computed tomography of the abdomen (Table 3).

Table 3. Laboratory and Other Studies for *Clostridium difficile*–Associated Diarrhea

Test	*Sensitivity, %*	*Specificity, %*	*Comments*
Complete blood count, $\times 10^9$ cells/L			Patients with severe *C. difficile* infection may have leucocytosis >50 $\times 10^9$ cells/L
Blood urea nitrogen and creatinine			Severe disease may cause dehydration, end-organ dysfuntion
Cytotoxin assay	94 to 100	97	Uses tissue culture; not readily available in hospital laboratories; takes 24-48 h
Enzyme-linked immunosorbent assay	65 to 85	95 to 100	Widely available, rapid turnaround
Culture	100	100*	Culture requires several days
Plain abdominal films			May show thickened mucosa; dilated colon, which suggests toxic megacolon; or perforation (free air)
Computed tomography			May show thickened mucosa; dilated colon, which suggests toxic megacolon; or perforation (free air)
Lower endoscopy for *C. difficile*			May reveal pseudomembranes; highly suspicious for *C. difficile*

** If toxin production is verified by separate testing.*

22. Fowler S, Webber A, Cooper BS, et al. Successful use of feedback to improve antibiotic prescribing and reduce *Clostridium difficile* infection: a controlled interrupted time series. J Antimicrob Chemother. 2007;59:990-5. [PMID: 17387117]
23. Valiquette L, Cossette B, Garant MP, et al. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. Clin Infect Dis. 2007;45 Suppl 2:S112-21. [PMID: 17683015]
24. Perry C, Marshall R, Jones E. Bacterial contamination of uniforms. J Hosp Infect. 2001;48:238-41. [PMID: 11439013]
25. Society for Healthcare Epidemiology of America. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31:431-55. [PMID: 20307191]
26. Johnson S, Gerding DN, Olson MM, et al. Prospective, controlled study of vinyl glove use to interrupt *Clostridium difficile* nosocomial transmission. Am J Med. 1990;88:137-40. [PMID: 2301439]
27. Oughton MT, Loo VG, Dendukuri N, et al. Hand hygiene with soap and water is superior to alcohol rub and antiseptic wipes for removal of *Clostridium difficile*. Infect Control Hosp Epidemiol. 2009;30:939-44. [PMID: 19715426]
28. Gordin FM, Schultz ME, Huber RA, et al. Reduction in nosocomial transmission of drug-resistant bacteria after introduction of an alcohol-based handrub. Infect Control Hosp Epidemiol. 2005;26:650-3. [PMID: 16092747]

A high leukocyte count (>20 × 10^9 cells/L) or elevated creatinine (176.8 μmol/L [>2.0 mg/dL]) were associated with a 30-day mortality of 25.5% in a retrospective study of 1721 patients with documented C. difficile *infection at 1 hospital over 12 years (38).*

Indeed, a high leukocyte count may be a diagnostic clue to the presence of *C. difficile* infection.

A retrospective review of 70 patients with diarrhea, 35 of whom had positive stool test results for C. difficile*, revealed a mean leukocyte count in those patients of 15.8 × 10^9 cells/L versus 7.7 × 10^9 cells/L in those who had negative* C. difficile *test results (P < 0.01), and a prospective study of 60 patients with unexplained leucocytosis (>15 × 10^9 cells/L) showed positive results on* C. difficile *ELISA tests in 58% compared with 12% in a control group of hospitalized patients with normal leukocyte counts (39, 40). A retrospective observational cohort study of patients who required intensive care for* C. difficile *infection showed a lactate level of 5 mmol/L or more to be an independent predictor of 30-day mortality (41).*

Patients with *C. difficile* infection may have findings suggestive of colitis, such as mucosal thickening, on abdominal imaging (42). Complications, such as toxic megacolon or perforation, may be detected.

What other diseases should clinicians consider when they suspect *C. difficile* infection?

Other infectious and noninfectious causes should be considered in patients with diarrhea and a work-up that is negative for *C. difficile*. Other infectious causes include *Salmonella, Shigella, Campylobacter*, Shiga-toxin–producing strains of *Escherichia coli*, and in immunocompromised persons, cytomegalovirus, *Cryptosporidia*, or other opportunistic organisms. These are unusual in patients who develop diarrhea in the hospital. Intestinal obstruction, ischemic bowel, inflammatory bowel disease, gastrointestinal malignant conditions, and noninfectious forms of drug-associated diarrhea should also be considered in the differential diagnosis.

When should clinicians refer patients with suspected *C. difficile* infection to subspecialists?

Referral or consultation for further evaluation should be sought when the diagnosis is uncertain. Lower endoscopy by a gastroenterologist may provide a diagnosis when stool studies are negative or when a diagnosis is needed more rapidly than available laboratory support can provide.

Diagnosis... A variety of tests are available to detect *C. difficile* in the stool; endoscopy can also be used to make the diagnosis in many cases. Other laboratory and imaging studies are useful in supporting the diagnosis and in determining the presence of complications or indicators of poor outcome that require hospitalization and aggressive treatment.

CLINICAL BOTTOM LINE

Treatment

When is discontinuation of antibiotics alone sufficient to treat *C. difficile* infection?

Discontinuing antibiotic therapy should be considered in all patients with *C. difficile* infection if doing so will not jeopardize recovery from the condition for which the antibiotics were prescribed. Patients with mild diarrhea who have normal or nearly normal leukocyte counts and normal creatinine levels, and are not otherwise at risk for severe disease or complications, may be observed for a few days to determine whether they respond to that measure alone.

29. Rupp ME, Fitzgerald T, Puumala S, et al. Prospective, controlled, cross-over trial of alcohol-based hand gel in critical care units . Infect Control Hosp Epidemiol. 2008;29:8-15. [PMID: 18171181]
30. Dial S, Kezouh A, Dascal A, et al. Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection. CMAJ. 2008;179:767-72. [PMID: 18838451]
31. National *Clostridium difficile* Standards Group. Report to the Department of Health. J Hosp Infect. 2004;56 Suppl 1:1-38. [PMID: 15129935]
32. Delmée M, Van Broeck J, Simon A, et al. Laboratory diagnosis of *Clostridium difficile*-associated diarrhoea: a plea for culture. J Med Microbiol. 2005;54:187-91. [PMID: 15673515]
33. Peterson LR, Manson RU, Paule SM, et al. Detection of toxigenic *Clostridium difficile* in stool samples by real-time polymerase chain reaction for the diagnosis of *C. difficile*-associated diarrhea. Clin Infect Dis. 2007;45:1152-60. [PMID: 17918076]
34. Peterson LR, Robicsek A. Does my patient have *Clostridium difficile* infection? Ann Intern Med. 2009;151:176-9. [PMID: 19652187]
35. Johal SS, Hammond J, Solomon K, et al. *Clostridium difficile* associated diarrhoea in hospitalised patients: onset in the community and hospital and role of flexible sigmoidoscopy. Gut. 2004;53:673-7. [PMID: 15082585]
36. Tedesco FJ, Corless JK, Brownstein RE. Rectal sparing in antibiotic-associated pseudomembranous colitis: a prospective study. Gastroenterology. 1982;83:1259-60. [PMID: 7129030]
37. Seppälä K, Hjelt L, Sipponen P. Colonoscopy in the diagnosis of antibiotic-associated colitis. A prospective study. Scand J Gastroenterol. 1981;16:465-8. [PMID: 7323683]

In a 10-year prospective study of 908 patients with documented C. difficile *diarrhea, 135 patients (15%) responded to cessation of antibiotics alone (43).*

Which supportive measures should be used to treat *C. difficile* infection?

When antibiotics cannot be discontinued, substitution with alternative agents that are less likely to exacerbate *C. difficile* should be considered (Table 4). Fluid and electrolyte imbalances should be corrected. Antiperistaltic agents should be avoided, because they prevent both distribution of the therapeutic antibiotic within the gut and expulsion of the toxin.

Which drugs should be used to treat *C. difficile* infection?

Metronidazole and vancomycin are the mainstays of therapy in the United States (Table 5). Oral metronidazole is usually recommended for treatment of mild to moderate disease; the usual dose for adults is 500 mg 3 times daily for 10 to 14 days. For patients who cannot toerate metronidazole or for those with severe disease, vancomycin is the drug of choice. Severe disease has been variously defined, but minimum criteria cited in 1 guideline are a leukocyte count of 15 000/mm^3 or more or a creatinine level 1.5 times baseline or higher; preexisting renal failure is also widely considered to be a risk factor (24, 45). Another definition, which rests on a point system, is shown in the Box.

In cases of severe disease, the dose and route of administration are adjusted on the basis of severity and factors that alter drug delivery. For those with moderately severe disease, the recommended dose of vancomycin is 125 mg given orally or by nasogastric tube 4 times daily for 10 to 14 days. In patients with immediately life-threatening conditions or in whom ileus or other factors may prevent adquate distribution through the gut lumen, expert consensus advocates a higher dose of vancomycin—500 mg 4 times daily. Doses may be given by rectal instillation instead of or in addition to the oral doses. Intravenous metronidazole, 500 mg every 8 hours, is often added as well (25).

The choice and duration of antibiotic is also influenced by whether

Severe *Clostridium difficile* Infection

Two or more points based on the following:

- Temperature >38.3°C (1 point)
- Age >60 y (1 point)
- Albumin <0.025 g/L (1 point)
- Leukocyte count >15 × 10^9 cells/L (1 point)
- Pseudomembranous colitis (2 points)
- Intensive care unit (2 points)

Table 4. Antibiotics Associated With *Clostridium difficile* Infection*

Frequently	*Infrequently*	*Rarely*
Ampicillin plus clavulanic acid, amoxicillin	Ampicillin	Vancomycin
Second- or third-generation cephalosporins	Sulfonamides with or without trimethoprim	Penicillin or antistaphlococcal penicillin
Clindamycin	Erythromycin	First-generation cephalosporin
Fluoroquinolones	Aminoglycosides	
Antipseudomonal penicillin	Metronidazole	
	Tetracycline	

* ***Owens RC Jr, Donskey CJ, Gaynes RP, et al.*** *Antimicrobial-associated risk factors for* Clostridium difficile *infection. Clin Infect Dis. 2008;46 Suppl 1:S19-31. [PMID: 18177218]*

38. Pépin J, Valiquette L, Alary ME, et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004;171:466-72. [PMID: 15337727]
39. Bulusu M, Narayan S, Shetler K, et al. Leucocytosis as a harbinger and surrogate marker of *Clostridium difficile* infection in hospitalized patients with diarrhea. Am J Gastroenterol. 2000;95:3137-41. [PMID: 11095331]
40. Wanahita A, Goldsmith EA, Marino BJ, et al. *Clostridium difficile* infection in patients with unexplained leucocytosis. Am J Med. 2003;115:543-6. [PMID: 14599633]
41. Lamontagne F, Labbé AC, Haeck O, et al. Impact of emergency colectomy on survival of patients with fulminant *Clostridium difficile* colitis during an epidemic caused by a hypervirulent strain. Ann Surg. 2007;245:267-72. [PMID: 17245181]

Table 5. Drug Treatment for CDAD*

Agent	*Dose*	*Side Effects*	*Benefits and Notes*
Metronidazole	500 mg PO, 3 times daily for 10 to 14 d	Rarely causes CDAD. CNS side effects of seizures and peripheral neuropathy most worrisome. Possible disulfiram-like reaction with alcohol. Dysgeusia.	Preferred first-line therapy for mild or moderate initial episode or first recurrence. Cost-effective, efficacious. Reserve IV form for patients who cannot tolerate PO.
Vancomycin	125 mg PO 4 times daily for 10 to 14 d	Rarely causes CDAD. May lead to vancomycin-resistant enterococcus, renal toxicity, and ototoxicity.	Preferred for severe initial episode, such as fulminant colitis, or in immunocompromised patients or for multiple recurrences, in a tapered or pulsed regimen.
Vancomycin with metronidazole	Vancomycin, 500 mg 4 times per day PO or by nasogastric tube. Metronidazole, 500 mg IV every 8 h; for ileus, consider adding vancomycin by rectal instillation	Same as vancomycin or metronidazole alone.	Complicated severe initial episode, such as hypotension or shock with ileus or megacolon.
Bacitracin	25 000 IU PO 4 times daily for 7-14 d	Rarely causes CDAD. May cause nephrotoxicity and CNS toxicity, GI upset, and malabsorption.	Inferior to metronidazole and vancomycin. Has been granted orphan drug status for treatment of CDAD. Limited clinical evidence.
Cholestyramine	4 g PO 3-4 times daily	Constipation.	Adjuvant therapy in multiple relapses. Not used as monotherapy. Can bind vancomycin, so give several hours after. Limited evidence.
Colestipol	5 g PO every 12 h		Adjuvant therapy in multiple relapses. Not used as monotherapy. Can bind vancomycin, so give several hours after. Limited evidence.
Probiotics	$>10^{10}$ organisms per day for 4 wk	Rare. Blood stream infection in immunocompromised patients.	Adjuvant therapy. Not used as monotherapy. May restore natural defense mechanisms. Limited evidence.

CDAD = Clostridium difficile*–associated diarrhea; CNS = central nervous system; GI = gastrointestinal; IV = intravenous; PO = orally.*

**http://pier.acponline.org/physicians/diseases/d320/tables/d320-tables.html. McFarland LV. Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of* Clostridium difficile *disease. Am J Gastroenterol. 2006;101:812-22. [PMID: 16635227]*

the patient is being treated for the initial episode or for a recurrence (see below and Figure).

Vancomycin is more expensive than metronidazole, and its use in some settings has been discouraged because of the widespread emergence of vancomycin-resistant enterococci. However, its pharmacokinetic properties make it superior to metronidazole in severe *C. difficile* disease. Orally administered vancomycin is not well absorbed from the gastrointestinal tract, and therefore luminal drug levels are very high—well above the susceptibility breakpoint for all strains of *C. difficile* tested so far. Metronidazole, on the other hand, is well absorbed from the gastrointestinal tract, and luminal concentrations tend to decrease as mucosal inflammation improves, possibly permitting relapse before cure is complete (25, 46).

42. Ash L, Baker ME, O'-Malley CM Jr, et al. Colonic abnormalities on CT in adult hospitalized patients with *Clostridium difficile* colitis: prevalence and significance of findings. AJR Am J Roentgenol. 2006;186:1393-400. [PMID: 16632736]
43. Olson MM, Shanholtzer CJ, Lee JT Jr, et al. Ten years of prospective *Clostridium difficile*-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982-1991. Infect Control Hosp Epidemiol. 1994;15:371-81. [PMID: 7632199]
44. Zar FA, Bakkanagari SR, Moorthi KM, et al. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007;45:302-7. [PMID: 17599306]
45. Pépin J, Routhier S, Gagnon S, et al. Management and outcomes of a first recurrence of *Clostridium difficile*-associated disease in Quebec, Canada. Clin Infect Dis. 2006;42:758-64. [PMID: 16477549]
46. Bolton RP, Culshaw MA. Faecal metronidazole concentrations during oral and intravenous therapy for antibiotic associated colitis due to *Clostridium difficile*. Gut. 1986;27:1169-72. [PMID: 3781329]

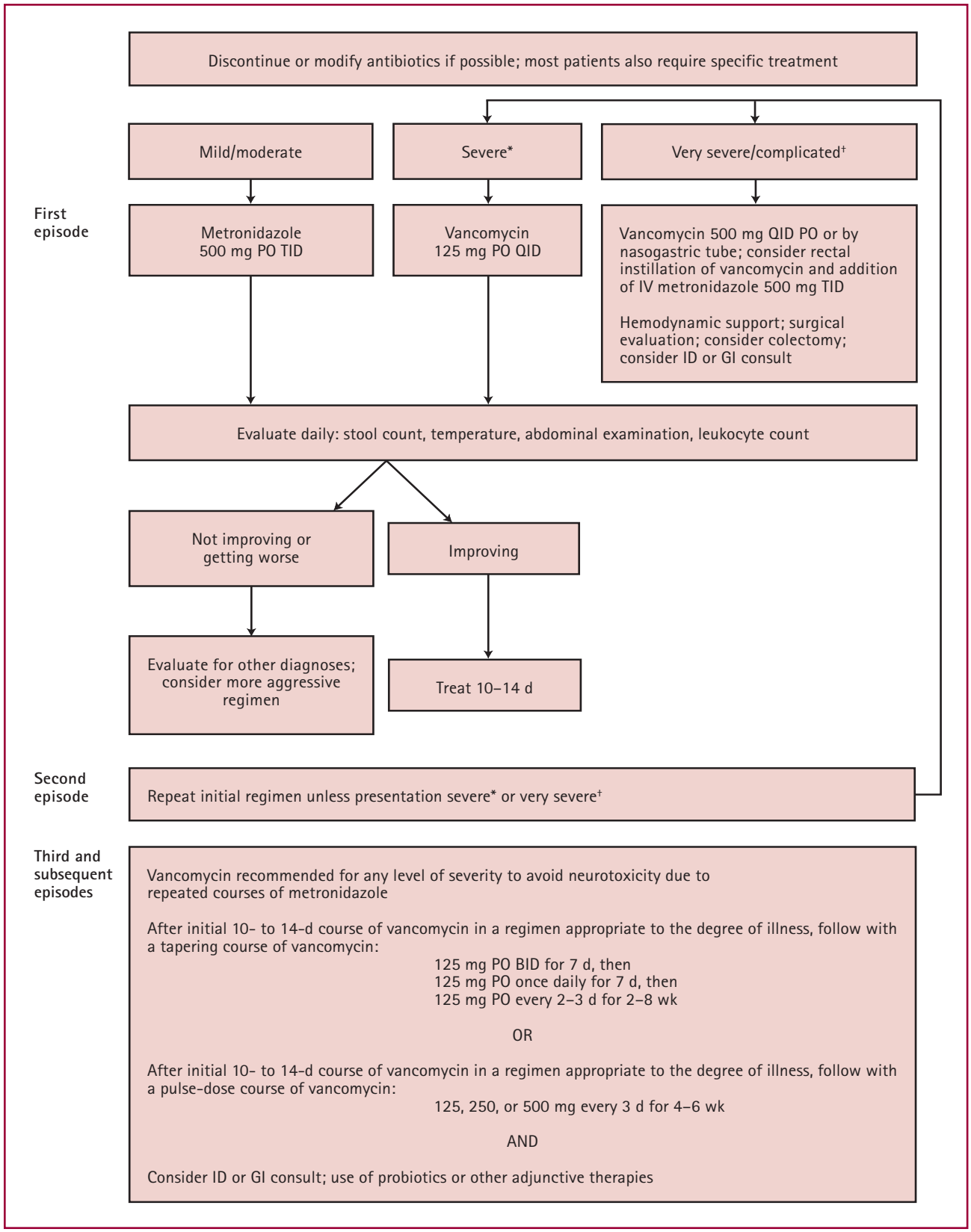

Figure. Treatment strategies for *Clostridium difficile* diarrhea. GI = gastrointestinal; ID = infectious disease; IV = intravenous; PO = oral; QID = four times daily; TID = three times daily.

*Leukocyte count ≥ 15 x 10^9 cells/L or creatinine level ≥ 1.5 times baseline.
†Associated with significant ileus, toxic megacolon, hypertension, or shock.

Two early, prospective, randomized, controlled trials (RCTs) found that vancomycin and metronidazole have equivalent efficacy in the treatment of patients with C. difficile*–associated diarrhea (47, 48).*

A systematic review of RCTs of antibiotics for use in *C. difficile* infection also noted no differences between metronidazole and vancomycin, among others (49). However, recent observational reports and some studies have raised the possibility that, at least in severe disease, metronidazole may not be effective as often or as promptly as vancomycin (50–52).

A prospective RCT compared vancomycin with metronidazole for the treatment of C. difficile*–associated diarrhea in patients with either mild or severe disease. The 2 drugs were found to be equivalent in mild disease, but in severe disease, vancomycin was superior, resulting in a cure rate of 97% versus 76% with metronidazole (*P = 0.02*) (44).*

When data from a large study comparing metronidazole, vancomycin, and tolevamer (an anionic polymer resin) were stratified according to disease severity, vancomycin was associated with significantly better clinical outcomes in patients with severe disease, with similar but nonsignificant trends in mild and moderate disease (53, 54)

Most of the work comparing vancomycin with metronidazole was done before the emergence of the hypervirulent NAP1/BI/027 strain, although at present there is no indication that the in vitro antibiotic susceptibility pattern of this strain differs from others (25).

Teicoplanin, a glycopeptide similar to vancomycin, has been found to be equivalent or perhaps superior to vancomycin, but it is not available in the United States (49). Nitazoxanide, bacitracin, fusidic acid, rifampin, and rifaximin are some of the other antibiotics that have been studied, but data on these agents are limited. Toxin-binding anion-exchange resins, such as cholestyramine, colestipol, and tolevamer, have not been consistently shown to be effective, but again, data are limited. If these agents are used, administration must be timed to minimize inactivation of vancomycin.

How should clinicians monitor patients who have *C. difficile* infection?

Patients should be followed for clinical evidence of improvement, including, where applicable, resolution of fever, reduction in stool frequency and improved consistency, normalization of abdominal examination, rehydration as indicated by physical examination and laboratory variables, and resolution of leucocytosis. Repeated stool testing is not needed in patients whose symptoms have resolved and is discouraged because treatment of asymptomatic carriers is not indicated (25). On the other hand, patients who do not respond or who relapse should be retested and, under some circumstances, may require work-up for alternative or concurrent diagnosis.

Should probiotics be used to treat *C. difficile* infection?

Numerous formulations of probiotics have been proposed to treat *C. difficile* colitis on the premise that these normally nonpathogenic yeasts and bacteria may repopulate the gastrointestinal tract and limit growth of *C. difficile*, but data are inconclusive.

A systematic review found only 4 studies of acceptable size and quality, and of those, 1 showed a statistically significant reduction in the rate of relapse in patients treated with Saccharomyces boulardii *in addition to vancomycin. The authors concluded that evidence is insufficient to recommend the use of probiotics, and guidelines written by a panel of experts warn of* S. boulardii *fungemia in immunocompromised patients (25, 55).*

47. Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhoea and colitis. Lancet. 1983;2:1043-6. [PMID: 6138597]
48. Wenisch C, Parschalk B, Hasenhündl M, et al. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of *Clostridium difficile*-associated diarrhea. Clin Infect Dis. 1996;22:813-8. [PMID: 8722937]
49. Nelson R. Antibiotic treatment for *Clostridium difficile*-associated diarrhea in adults. Cochrane Database Syst Rev. 2007:CD004610. [PMID: 17636768]
50. Musher DM, Aslam S, Logan N, et al. Relatively poor outcome after treatment of *Clostridium difficile* colitis with metronidazole. Clin Infect Dis. 2005;40:1586-90. [PMID: 15889354]
51. Belmares J, Gerding DN, Parada JP, et al. Outcome of metronidazole therapy for *Clostridium difficile* disease and correlation with a scoring system. J Infect. 2007;55:495-501. [PMID: 17983659]
52. Al-Nassir WN, Sethi AK, Nerandzic MM, et al. Comparison of clinical and microbiological response to treatment of *Clostridium difficile*-associated disease with metronidazole and vancomycin. Clin Infect Dis. 2008;47:56-62. [PMID: 18491964]
53. Bartlett JG. The case for vancomycin as the preferred drug for treatment of *Clostridium difficile* infection. Clin Infect Dis. 2008;46:1489-92. [PMID: 18419480]
54. Louie T. Results of a phase III trial comparing tolevamer, vancomycin and metronidazole in *Clostridium difficile*-associated diarrhea (CDAD) [Abstract]. Program and abstracts of the 47th Interscience Conference on Antimicrobial Agents and Chemotherapy (Washington DC). Herndon, VA: ASM Press; 2007. Abstract no. K-4259.

Should fecal transplants be used to treat *C. difficile* infection?

Fecal transplantation has been proposed as a way of recolonizing the gastrointestinal tract with normal flora to restore a microbial milieu unfavorable to *C. difficile* toxin production.

Successful treatment of refractory infection by instillation of stool from normal donors has been reported in individual cases and small case series by several investigators (56–58).

Such measures carry obvious concerns about the possibility of introducing other unrecognized pathogens.

What should be done when the patient does not respond to initial treatment?

Patients who do not improve or who relapse after initial improvement should be reevaluated clinically to assess whether *C. difficile* is still the correct diagnosis or whether an alternate explanation for lack of improvement should be sought (for example, in hospitalized patients, persistent fever and leucocytosis may be due to a superimposed nosocomial infection, persistent diarrhea may by due to supplemental enteral feedings). In patients who do not improve on medication, it is also important to ensure that the medication is being delivered effectively to the site of infection (for example, severe ileus may prevent orally administered vancomycin from getting to the colon). In patients who do not improve after 48 to 72 hours while receiving metronidazole alone, a switch to vancomycin should be considered; in patients already receiving vancomycin, the dose and delivery should be maximized, and addition of intravenous metronidazole should be considered.

What are the indications for obtaining a consultation for a patient with *C. difficile* infection?

Consultation with a gastroenterologist or infectious disease specialist (or both) should be considered for patients who respond slowly or relapse. Management changes may be guided by endoscopy and may include manipulation of current antibiotic therapy. Surgical consultation is essential if there is evidence of perforation and should be strongly considered in patients with toxic megacolon. It may also be of value in other patients with severe illness in whom medical therapy has failed.

When should patients with suspected *C. difficile* infection be hospitalized?

Patients should be hospitalized for severe disease, complications, or in other circumstances in which outpatient treatment is inadequate to meet the patient's treatment or monitoring needs. Dehydration and inability to tolerate oral medication are indications for admission. Any patient with signs of peritonitis, toxic megacolon, the sepsis syndrome, or other complications should be hospitalized. Consideration should be given to admitting patients with other indicators of severe disease (elevated creatinine, leukemoid reaction, advanced age).

When should patients with *C. difficile* infection be admitted to an intensive care unit?

Admission to intensive care is necessary for patients with severe disease and an unstable clinical condition, such as septic shock, toxic megacolon, peritonitis, or severe dehydration with hypotension or end-organ dysfunction.

When should total colectomy be considered in a patient with *C. difficile* infection?

Colectomy is required in patients with colonic perforation. It may also be of benefit in patients with toxic megacolon or septic shock due to *C. difficile* disease, especially those with an elevated lactate level. In addition, colectomy may be useful in a patient without toxic megacolon in whom all medical therapies have failed.

55. Pillai A, Nelson R. Probiotics for treatment of *Clostridium difficile*-associated colitis in adults. Cochrane Database Syst Rev. 2008:CD004611. [PMID: 18254055]
56. Schwan A, Sjölin S, Trottestam U, et al. Relapsing *Clostridium difficile* enterocolitis cured by rectal infusion of normal faeces. Scand J Infect Dis. 1984;16:211-5. [PMID: 6740251]
57. Gustafsson A, Lund-Tønnesen S, Berstad A, et al. Faecal short-chain fatty acids in patients with antibiotic-associated diarrhoea, before and after faecal enema treatment. Scand J Gastroenterol. 1998;33:721-7. [PMID: 9712236]
58. Aas J, Gessert CE, Bakken JS. Recurrent *Clostridium difficile* colitis: case series involving 18 patients treated with donor stool administered via a nasogastric tube. Clin Infect Dis. 2003;36:580-5. [PMID: 12594638]
59. Koss K, Clark MA, Sanders DS, et al. The outcome of surgery in fulminant *Clostridium difficile* colitis. Colorectal Dis. 2006;8:149-54. [PMID: 16412077]
60. Tedesco FJ, Gordon D, Fortson WC. Approach to patients with multiple relapses of antibiotic-associated pseudomembranous colitis. Am J Gastroenterol. 1985;80:867-8. [PMID: 4050760]
61. Siegel JD, Rhinehart E, Jackson M, et al. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. Accessed at www.cdc.gov/hicpac/2007ip/2007isolationprecautions.html on 18 August 2010.

Two recent retrospective studies analyzed the effect of colectomy in patients with severe infection due to C. difficile. *The first study of 14 patients included 10 patients with systemic toxicity and peritonitis, 3 patients with progressive dilatation of the colon, and 1 patient with toxic megacolon and perforation. Overall mortality was 35.7%, but total colectomy was associated with a mortality rate of 11.1% (1 of 9 patients) (59). The other larger study of 165 patients with* C. difficile *colitis requiring intensive care (leucocytosis of ≥50 × 10^9 cells/L; lactate ≥5 mmol/L; age ≥75 y; immunosuppression; or shock requiring vasopressors) showed a significant survival advantage to colectomy (adjusted odds ratio, 0.22 [95% CI, 0.07 to 0.67]; P = 0.008) (41).*

What should be done for patients with recurrent disease?

Patients who develop recurrent symptoms after apparent response to initial treatment may have relapsed or developed infection due to a different strain; for practical purposes, the difference cannot be readily determined with the clinical tools available. Therefore, for the first recurrence, expert guidelines recommend retreatment with the same course of therapy used for the initial presentation if that course is consistent with the patient's current presentation (25). On the other hand, if a patient with mild disease treated initially with metronidazole develops recurrent disease associated with indicators of severity (for example, a leukemoid reaction and dehydration), treatment should be adjusted accordingly (Figure).

Recurrences after a second course of metronidazole should not be treated again with that drug because of the possibility of cumulative neurotoxicity (25). Patients who have had more than 1 relapse or recurrence can be treated with a prolonged course of vancomycin tapered at intervals or by a regimen of intermittent or "pulse" doses. This recommendation is based on a small observational study and a consensus based on the clinical experience of experts (25).

A case series of 22 patients with several relapses of pseudomembranous colitis reported 2 to 12 months (mean, 6 months) free of disease after a tapering dose of oral vancomycin for 21 days followed by pulse doses for 21 days (60).

Treatment... Use either metronidazole or vancomycin for mild disease; use vancomycin for more severe conditions. Patients with ileus or with very severe disease may benefit from rectal instillation of vancomycin and intravenous metronidazole in addition to oral vancomycin. Multiple recurrences may require longer treatment with a tapered dose regimen.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend for preventing, diagnosing, and treating *C. difficile* infection?

The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) have published Clinical Practice Guidelines for *C. difficile* Infection in Adults (25). The Healthcare Infection Control Practices Advisory Committee of the CDC publishes periodic guidelines on infection control (61).

What other tools are available to help clinicians manage *C. difficile* infection?

The Centers for Disease Control and Prevention Web site has information on *C. difficile* for clinicians and patients (www.cdc.gov/ncidod/dhqp/id_CdiffFAQ).

in the clinic

Tool Kit

Clostridium difficile Infection

PIER Modules

www.pier.acponline.org

Access the PIER modules on *Clostridium difficile* infection. PIER modules provide evidence-based, updated information on current diagnosis and treatment in an electronic format designed for rapid access at the point of care.

Patient Information

www.annals.org/intheclinic/toolkit-cdifficile.html

Access the Patient Information material that appears on the following page for duplication and distribution to patients.

www.cdc.gov/ncidod/dhqp/id_CdiffFAQ_general.html

www.cdc.gov/ncidod/dhqp/pdf/guidelines/Cdiff_tagged.pdf

Access general information and a FAQs handout on *C. difficile* from the U.S. Centers for Disease Control and Prevention.

www.cks.nhs.uk/patient_information_leaflet/clostridium_difficile

Access patient information on *C. difficile* from the British National Health Service.

www.mayoclinic.com/health/c-difficile/DS00736

Information about *C. difficile* colitis from the Mayo Clinic.

Clinical Guidelines

www.journals.uchicago.edu/doi/abs/10.1086/651706?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%3dncbi.nlm.nih.gov

The Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) updated clinical practice guidelines for *C. difficile* infection in adults in 2010.

www.cdc.gov/hicpac/2007IP/2007isolationPrecautions.html

The Healthcare Infection Control Practices Advisory Committee of the CDC published a guideline on infection control in 2007.

www.acg.gi.org/physicians/guidelines/CdifficileDiarrhea.pdf

The American College of Gastroenterology, Practice Parameters Committee published guidelines for the diagnosis and management of *C. difficile*-associated diarrhea and colitis in 1997.

Diagnostic Tests and Criteria

www.annals.org/content/151/3/176.full

Access the Improving Patient Care article published in 2009 in *Annals of Internal Medicine*: Does My Patient Have *Clostridium difficile* Infection?

Quality Measures

Dubberke ER, Gerding DN, Classen D, et al. Strategies to prevent clostridium difficile infections in acute care hospitals. Infect Control Hosp Epidemiol. 2008;29 Suppl 1:S81-92. [PMID: 18840091]

Strategies to prevent *C. difficile* infections in acute-care hospitals from the Infectious Diseases Society of America–Medical Specialty Society and the Society for Healthcare Epidemiology of America–Professional Association.

THINGS YOU SHOULD KNOW ABOUT *C. DIFFICILE* INFECTION

In the Clinic
Annals of Internal Medicine

What is *Clostridium difficile* infection and how is it spread?

- *C. difficile* (often called *C. diff.*). is a bacterium that can cause mild to severe diarrhea and other symptoms.
- The bacteria are typically spread when people touch surfaces or other persons contaminated with trace amounts of stool and then touch their mouth or nose.
- Workers in health care settings can accidentally spread the bacteria directly to patients or contaminate surfaces that patients touch.

What are symptoms of *C. difficile* infection?

- The main symptom is having at least 3 watery bowel movements daily for 2 days or more.
- Other symptoms include fever, nausea, and abdominal pain.
- *C. difficile* infection can lead to colitis, severe intestinal problems, and sepsis. In rare cases, it can be fatal.

Who gets *C. difficile* infection?

- The infection usually occurs in people who are hospitalized or in nursing homes, and a long length of stay increases the risk.
- Taking antibiotics changes the normal balance of bacteria in the gut, allowing *C. difficile* to multiply and produce toxins. The diarrhea usually occurs during or just after taking antibiotics but can occur up to 3 months later.
- Other risk factors include gastrointestinal surgery or a serious underlying illness.
- Elderly people and people who have a weakened immune system, such as those who are receiving chemotherapy or who have HIV, are also at increased risk.

How do you know if it is *C. difficile*?

- When diarrhea and nausea are severe or persistent along with fever or abdominal pain, it suggests *C. difficile* infection.
- When doctors think a person might have *C. difficile*, they will order stool tests that see if it is the cause.

How is it treated?

- If you are taking an antibiotic, your doctor may tell you to stop taking it. Some patients may need no other treatment.
- Patients often require a different antibiotic to treat *C. difficile*.
- In the most severe cases, surgery may be needed to remove the infected part of the intestines.

For More Information

ACP®
American College of Physicians
Internal Medicine | *Doctors for Adults*

http://digestive.niddk.nih.gov/ddiseases/pubs/diarrhea/
National Institute of Diabetes and Digestive and Kidney Diseases information on what causes diarrhea.

www.nlm.nih.gov/medlineplus/clostridiumdifficileinfections.html#cat69
www.nlm.nih.gov/medlineplus/ency/article/003590.htm
Information from the National Library of Medicine's MEDLINE Plus on *C. difficile* and on what to expect if you need tested for it.

Patient Information

CME Questions

MKSAP
MEDICAL KNOWLEDGE Self-Assessment Program

1. A 68-year-old man is diagnosed with *Clostridium difficile* infection 5 days after elective hip replacement surgery. This hospital has recently reported a high incidence of *C. difficile* infections. The patient was in a 2-bed hospital room.

   In addition to bleach for enhanced room cleaning, which of the following "bundled" measures would be most effective in preventing the spread of *C. difficile* in this hospital setting?

   A. Airborne precautions and alcohol hand sanitizer
   B. Airborne precautions and soap and water for hand hygiene
   C. Barrier precautions and alcohol hand sanitizer
   D. Barrier precautions and soap and water for hand hygiene
   E. Droplet precautions and soap and water for hand hygiene

2. An 80-year-old woman is evaluated for diarrhea characterized by 6 to 8 bowel movements per day with abdominal pain. She was hospitalized 2 months ago for pneumonia complicated by *C. difficile* infection (CDI) treated with a course of metronidazole. One month after discharge, she developed a urinary tract infection and was given ciprofloxacin; CDI was again diagnosed 5 days later and treated with a course of metronidazole.

   On physical examination, the patient is afebrile, blood pressure is 130/78 mm Hg, and pulse rate is 90/min. Abdominal examination reveals hyperactive bowel sounds with mild diffuse tenderness.

   The leukocyte count is 18.9×10^9 cells/L. The results of *C. difficile* toxin assay are positive.

   A course of which of the following is the most appropriate treatment?

   A. Intravenous vancomycin
   B. Oral metronidazole followed by tapering doses of metronidazole
   C. Oral vancomycin followed by tapering doses of metronidazole
   D. Oral vancomycin followed by tapering doses of vancomycin

3. A 74-year-old woman is evaluated in the emergency department with a 2-day history of diarrhea characterized by 10 bowel movements daily, with worsening abdominal pain and fever. Today, she has had no bowel movements but does have an increasingly distended abdomen. Five weeks ago, the patient was hospitalized with necrotizing fasciitis of the right thigh, for which she had debridement, received nafcillin and clindamycin therapy, and was discharged after 2 weeks. On discharge, she was prescribed a 2-week course of nafcillin, which she completed 1 week ago.

   On physical examination, the patient is awake but disoriented. Temperature is 38.6°C (101.5°F), blood pressure is 90/55 mm Hg, pulse rate is 122/min, and respiration rate is 24/min. The abdomen is distended and tender to palpation, and bowel sounds are absent.

   Laboratory studies indicate a leukocyte count of 32.5×10^9 cells/L, serum albumin level of 25 g/L (2.5 g/dL), and a serum creatinine level of 221 µmol/L (2.5 mg/dL). Stool, blood, and urine samples are obtained for culture, and she is admitted to the intensive care unit.

   Which is the most appropriate treatment?

   A. Intravenous metronidazole and oral vancomycin
   B. Intravenous vancomycin
   C. Oral metronidazole
   D. Oral metronidazole and oral vancomycin
   E. Oral vancomycin

4. A 32-year-old man is evaluated in the emergency department for a 5-day history of worsening crampy abdominal pain and 8 to 10 loose bowel movements a day. The patient has a 5-year history of ulcerative colitis treated with azathioprine and topical mesalamine; before this episode, he had 1 or 2 bowel movements of well-formed stool a day. The patient had sinusitis recently, which resolved with antibiotic therapy. He has otherwise been healthy and has not traveled recently, had contact with sick persons, or been noncompliant with medication.

   On physical examination, the temperature is 38.3°C (101°F), the blood pressure is 130/76 mm Hg sitting and 105/60 mm Hg standing, the pulse rate is 90/min sitting and 120/min standing, and the respiration rate is 18/min. The abdomen is diffusely tender without rebound or guarding. Laboratory studies reveal hemoglobin levels of 123 g/L, leukocyte count of 28×10^9 cells/L with 15% band forms, and platelet count of 234×10^9 cells/L. Intravenous fluids are started, and stool studies are obtained.

   Which is the most appropriate treatment for presumed *C. difficile* infection?

   A. Increase dose of azathioprine
   B. Start oral vancomycin
   C. Start oral mesalamine
   D. Small-bowel radiographic series

Questions are largely from the ACP's Medical Knowledge Self-Assessment Program (MKSAP, accessed at http://www.acponline.org/products_services/mksap/15/?pr31). Go to www.annals.org/intheclinic/ to obtain up to 1.5 CME credits, to view explanations for correct answers, or to purchase the complete MKSAP program.