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- Level 1 studies, which meet all of the evidence criteria for that study type;
- Level 2 studies, which meet at least one of the evidence criteria for that study type; or
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1. Prevention

Ensure that antibiotics are used appropriately and that routine infection-control measures are in place to prevent *C. difficile* infection.

1.1 Limit the type and use of antibiotics to decrease the likelihood of outbreaks of CDAD.

Recommendations

- In hospitals, establish an antibiotic stewardship program:
  - With multidisciplinary participation (microbiologists, pharmacists, infection-control specialists, hospital administrators, and physicians)
  - That limits the use of unnecessary antibiotic administration
  - That promotes appropriate antibiotic use
  - That recommends antibiotics with lower risk for CDAD when appropriate
- Limit the use of unnecessary antibiotics in the outpatient setting.

Evidence

- A 2013 guideline from the American College of Gastroenterology on the management of *C. difficile* infections recommended infection-control measures including contact precautions, a private room for patients with CDAD, antibiotic stewardship programs, hand hygiene, gloves and gowns, single-use disposable equipment, and proper disinfection of contaminated surfaces (1).
- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults recommended that hospitals implement an antibiotic stewardship program and that clinicians limit patients' exposure to antibiotics (2).
- A 2014 systematic review of the association between CDAD and antibiotics in hospitalized patients included 13 case-control studies and 1 cohort study with nearly 16,000 total participants. The highest risk was seen with third-generation cephalosporins (OR, 3.20 [CI, 1.80 to 5.71]), followed by clindamycin (OR, 2.86 [CI, 2.04 to 4.02]), second-generation cephalosporins (OR, 2.23 [CI, 1.47 to 3.37]), and fourth-generation cephalosporins (OR, 2.14 [CI, 1.30 to 3.52]) (3).
- A 2013 systematic review of the association between antibiotic use and community-acquired CDAD included eight studies with more than 30,000 participants. Overall, exposure to antibiotics was associated with CDAD (OR, 6.91 [CI, 4.17 to 11.44]). The greatest risk was seen with clindamycin (OR, 20.43 [CI, 8.50 to 49.09]), followed by fluoroquinolones (OR, 5.65 [CI, 4.38 to 7.28]) and cephalosporins (OR, 4.47 [CI, 1.60 to 12.50]). Tetracyclines were not associated with CDAD (OR, 0.91 [CI, 0.57 to 1.45]), and trimethoprim-sulfamethoxazole was associated with a small increase in risk (OR, 1.84 [CI, 1.48 to 2.29]) (4).
- A 2013 systematic review of the association between CDAD and the use of different antibiotics in the community included seven studies. Compared with no antibiotic exposure, clindamycin (OR, 16.80 [CI, 7.48 to 37.76]), fluoroquinolones (OR, 5.50 [CI, 4.26 to 7.11]), and cephalosporins, carbapenems, and monobactams (OR, 5.68 [CI, 2.12 to 15.23]) were most strongly associated with CDAD. Tetracyclines did not increase the risk for CDAD; macrolides, penicillins, and sulfonamides/trimethoprim were associated with lower risk (5).
- A 2010 systematic review of measures to prevent CDAD included 38 mostly observational studies. There was little evidence that alcohol-based hand cleansers decreased rates of CDAD; 1 study supported the use of gloves and none addressed the use of gowns or patient isolation and cohorting. There was evidence that disposable thermometers reduced CDAD and mixed evidence
on environmental decontamination. There was strong evidence supporting the restriction of antibiotics, particularly clindamycin, and insufficient evidence to support the treatment of asymptomatic carriers or the use of probiotics (6).

- A prospective cohort study evaluated the impact of restricting the use of clindamycin in a hospital on rates of CDAD. Rates of CDAD declined after the intervention (3.33 vs. 11.5 cases/month, P<0.001) (7).

- A prospective pre-post study evaluated the impact of a “narrow spectrum” antibiotic policy, with reinforcement by physician audit and feedback, on antibiotic use and rates of CDAD in a teaching hospital. There was a decrease in the use of broad-spectrum antibiotics and an increase in the use of narrow-spectrum antibiotics after the intervention, with a reduction in the incidence of CDAD (RR, 0.35 [CI, 0.17 to 0.73]) (8).

- A prospective cohort study evaluated the impact of an infection-control policy emphasizing hand washing and limiting the use of clindamycin on rates of CDAD in a geriatric ward of a London hospital. After implementation of the policy, the rates of CDAD declined from 3.35/100 admissions to 1.94/100 admissions (P<0.05) (9).

- A 2008 narrative review described methods for controlling CDAD in hospital settings (10).

Rationale
- Antibiotic exposure and disruption of commensal gut flora by broad-specific antibiotics are key factors in the development of CDAD.

Comments
- When appropriate, the outpatient use of tetracyclines, sulfonamides, and macrolides instead of other higher-risk antibiotics may decrease the incidence of community-acquired CDAD.

1.2 Institute routine infection control measures including hand hygiene and universal precautions to prevent CDAD.

Recommendations
- Adhere to strict hand-hygiene procedures between patient exams.
- Use universal precautions, including wearing and properly disposing of gloves when their use is indicated for patient contact and contact with bodily fluids.
- In an outbreak setting or when caring for patients with known CDAD:
  - Wash hands with soap and water rather than using alcohol-based hand rubs
  - Always use gloves and gowns on entry to a room with a patient with C. difficile infection
  - Accommodate patients with C. difficile infection in a private room with contact precautions if possible
  - Maintain contact precautions for the duration of the diarrhea
  - Disinfect hospital rooms before and after patient stays.
- Conduct CDAD surveillance.
- See table Practice Guidelines for Prevention of C. difficile Diarrhea.

Evidence
- A 2013 guideline from the American College of Gastroenterology on the management of C. difficile infections recommended infection-control measures including contact precautions, a private room for patients with CDAD, antibiotic stewardship programs, hand hygiene, gloves and gowns, single-use disposable equipment, and proper disinfection of contaminated surfaces (1).
- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on C. difficile infection in adults recommended infection-control measures in health care settings, including hand hygiene, gloves and gowns for visitors to patients
with CDAD, single rooms for patients with CDAD, and thorough environmental cleaning and disinfection (2).

- A 2002 CDC guideline for hand hygiene in health care settings made specific recommendations for hand hygiene in different situations (11).

- A 2010 systematic review of measures to prevent CDAD included 38 mostly observational studies. There was little evidence that alcohol-based hand cleansers decreased rates of CDAD; 1 study supported the uses of gloves and none addressed the use of gowns or patient isolation and cohorting. There was evidence that disposable thermometers reduced CDAD and mixed evidence on environmental decontamination. There was strong evidence supporting the restriction of antibiotics, particularly clindamycin, and insufficient evidence to support the treatment of asymptomatic carriers or the use of probiotics (6).

- An observational study evaluated the impact of alcohol-based hand cleanser on rates of resistant staphylococcal infections and CDAD in a hospital. In the multivariate analysis, the use of alcohol-based cleanser had no impact on rates of CDAD (12).

- A prospective trial evaluated the incidence of \textit{C. difficile} infection on two comparable hospital wards before and after instituting a program of vinyl-glove use during all patient contact on one of the two wards. During the 6 months after policy implementation, the rates of CDAD declined on the glove-use wards (from 7.7/1000 discharges to 1.5/1000 discharges, \(P=0.015\)) but stayed constant on the control wards (13).

- A prospective 11-month study determined the epidemiology of \textit{C. difficile} infection on a hospital ward. Among patients with negative \textit{C. difficile} cultures at hospital admission, 21\% developed positive cultures during hospitalization. Among hospital workers caring for patients with positive \textit{C. difficile} cultures, 59\% had positive cultures from their hands (14).

- A prospective observational study assessed the effect of changing to hypochlorite disinfectants on the rates of CDAD among hospitalized patients. The rates of CDAD declined among bone-marrow transplant patients (HR, 0.37 [CI, 0.19 to 0.74]), in whom baseline rates were very high, but were unchanged in general medical patients and patients in the neurosurgical ICU (15).

- A crossover study evaluated the impact of sodium hypochlorite disinfectants on rates of CDAD among elderly hospitalized patients from two different wards. The use of sodium hypochlorite was associated with a lower rate of CDAD on one ward but not on the other (16).

- Several studies found that despite an increased use of alcohol-based hand rubs, \textit{C. difficile} incidence did not decrease (17; 18; 19; 20; 21).

**Rationale**

- The cycle of contamination and subsequent colonization of patients due to \textit{C. difficile} is disrupted by these methods.

**Comments**

- CDAD is mostly a nosocomial infection, but community-onset cases are being reported more frequently. Efficacy of sporicidal agents in reducing CDAD rates is unclear, but they may be beneficial in outbreak settings.

**1.3 Avoid using antibiotic therapy to attempt to eradicate the carrier state for \textit{C. difficile}**

**Recommendations**

- Discourage attempts to eradicate the carrier state using antibiotics.

**Evidence**
• A 2013 guideline from the American College of Gastroenterology on the management of *C. difficile* infections recommended against the routine screening and treatment of asymptomatic patients (1).

• A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults recommended against the identification and treatment of asymptomatic carriers (2).

• A 2010 systematic review of measures to prevent CDAD included 38 mostly observational studies. There was little evidence that alcohol-based hand cleansers decreased rates of CDAD; 1 study supported the uses of gloves and none addressed the use of gowns or patient isolation and cohorting. There was evidence that disposable thermometers reduced CDAD and mixed evidence on environmental decontamination. There was strong evidence supporting the restriction of antibiotics, particularly clindamycin, and insufficient evidence to support the treatment of asymptomatic carriers or the use of probiotics (6).

• A randomized trial compared metronidazole, vancomycin, and placebo in 30 asymptomatic patients colonized with *C. difficile*. Immediately after treatment, 9 of 10 patients receiving vancomycin, 3 of 10 receiving metronidazole, and 2 of 10 receiving placebo had negative stool cultures for *C. difficile*. Among patients receiving vancomycin who initially became *C. difficile* negative, 89% became positive again after 20 days (22).

• A pooled analysis of four studies evaluated the risk for CDAD in hospitalized patients who were asymptomatically colonized with *C. difficile* at the time of admission. The risk for developing CDAD during hospitalization was lower for colonized patients overall (mean difference, 2.3%, *P*=0.021) and for patients who received antibiotics during the hospitalization (mean difference, 3.2%, *P*=0.024) (23).

**Rationale**

Individuals who are colonized and asymptomatic (carrier state) are at low risk for developing CDAD. Attempts to decolonize may increase the risk for CDAD.

**Comments**

The asymptomatic carrier state is also associated with a decreased risk for subsequent development of CDAD.

**1.4 Consider the use of probiotics to prevent antibiotic-associated diarrhea and CDAD in high-risk patients receiving antibiotics.**

**Recommendations**

• Consider the use of probiotics, particularly *Lactobacillus*, to prevent CDAD and other antibiotic-associated diarrhea in high-risk patients receiving antibiotics, including those with a history of CDAD.

**Evidence**

• A 2013 guideline from the American College of Gastroenterology on the management of *C. difficile* infections noted that there is limited evidence for the use of probiotics to prevent recurrent CDAD (1).

• A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults recommended against the use of probiotics to prevent CDAD (2).

• A 2013 Cochrane review of probiotics for the prevention of CDAD included 31 studies, among which 11 were at high risk for bias. Overall, compared with placebo, probiotics reduced the risk for CDAD from 5.5% to 2.0% (RR, 0.36 [CI, 0.26 to 0.51]) while lowering the risk for adverse events (RR, 0.80 [CI, 0.68 to 0.95]) (24).
• A 2012 systematic review of probiotics for the prevention of antibiotic-associated diarrhea included 11,811 participants from 82 randomized trials, most of which involved treatment with *Lactobacillus*. Overall, patients randomly assigned to probiotics were less likely to develop antibiotic-associated diarrhea, with a pooled RR of 0.58 (CI, 0.50 to 0.68). In 14 of the randomized, controlled trials that specifically tested for *C. difficile* infection, the pooled RR for preventing CDAD was 0.29 (CI, 0.17 to 0.49) (25).

• A 2012 systematic review of probiotics for the prevention of CDAD included 20 trials with 3818 participants. Overall, probiotics reduced the risk for CDAD, with a pooled RR of 0.34 (CI, 0.24 to 0.49). There was no increased risk for adverse events in the treatment groups vs. placebo groups (26).

• A 2013 randomized trial compared a preparation of *Lactobacilli* and *Bifidobacteria* with placebo in 2981 hospitalized patients aged over 65 years who were receiving antibiotics. The incidence of antibiotic-associated diarrhea over 8 weeks of observation was 10.8% in the probiotic group and 10.4% in the placebo group ($P=0.71$), and the incidence of CDAD over 8 weeks of observation was 0.8% in the probiotic group and 1.2% in the placebo group ($P=0.35$) (27).

**Rationale**

• The maintenance of a nonpathogenic gut flora with probiotics can prevent antibiotic-associated diarrhea.
2. Diagnosis

Consider CDAD in patients with diarrhea or abdominal pain who have recently received antibiotic therapy or with recent health care facility exposure.

2.1 Ask patients with diarrhea about typical symptoms of CDAD, including watery diarrhea and abdominal pain, and about exposures to antibiotics or to a health care facility.

Recommendations

- Ask patients with suspected CDAD about typical symptoms, including:
  - Diarrhea, which is often watery
  - Abdominal pain
  - Fever
- Ask patients with suspected CDAD about risk factors, including:
  - Age
  - Antibiotic therapy in the last 2 months, though most episodes of CDAD occur from days 4 to 9 of antibiotic treatment
  - Recent hospitalization
  - Other chronic intestinal conditions that might cause diarrhea, specifically IBD
  - Use of gastric-acid suppressive agents, chemotherapy, or immunosuppressants
- Do not order toxin testing in patients without signs and symptoms compatible with CDAD.
- See table Clinical Features of C. difficile Infection by Severity.

Evidence

- A 2014 systematic review of the association between CDAD and antibiotics in hospitalized patients included 13 case-control studies and 1 cohort study with nearly 16,000 total participants. The highest risk was seen with third-generation cephalosporins (OR, 3.20 [CI, 1.80 to 5.71]), followed by clindamycin (OR, 2.86 [CI, 2.04 to 4.02]), second-generation cephalosporins (OR, 2.23 [CI, 1.47 to 3.37]), and fourth-generation cephalosporins (OR, 2.14 [CI, 1.30 to 3.52]) (3).
- A 2013 systematic review of the association between antibiotic use and community-acquired CDAD included eight studies with more than 30,000 participants. Overall, exposure to antibiotics was associated with CDAD (OR, 6.91 [CI, 4.17 to 11.44]). The greatest risk was seen with clindamycin (OR, 20.43 [CI, 8.50 to 49.09]), followed by fluoroquinolones (OR, 5.65 [CI, 4.38 to 7.28]) and cephalosporins (OR, 4.47 [CI, 1.60 to 12.50]). Tetracyclines were not associated with CDAD (OR, 0.91 [CI, 0.57 to 1.45]) and trimethoprim-sulfamethoxazole was associated with a small increase in risk (OR, 1.84 [CI, 1.48 to 2.29]) (4).
- A 2013 systematic review of the association between CDAD and the use of different antibiotics in the community included seven studies. Compared with no antibiotic exposure, clindamycin (OR, 16.80 [CI, 7.48 to 37.76]), fluoroquinolones (OR, 5.50 [CI, 4.26 to 7.11]), and cephalosporins, carbapenems, and monobactams (OR, 5.68 [CI, 2.12 to 15.23]) were most strongly associated with CDAD. Tetracyclines did not increase the risk for CDAD; macrolides, penicillins, and sulfonamides/trimethoprim were associated with lower risk (5).
- A 2012 systematic review of the association between proton-pump inhibitors and CDAD included 23 studies with nearly 300,000 participants. Overall, patients receiving proton-pump inhibitors were at increased risk for CDAD (RR, 1.69 [CI, 1.40 to 1.97]) (28).
• A 2012 systematic review of the relationship between proton-pump inhibitors and CDAD included 30 observational studies. Proton-pump inhibitors significantly increased the risk for CDAD (OR, 2.5 [CI, 1.81 to 2.55]) (29).

• A 2012 systematic review of the risk for CDAD with acid-suppressing drugs and antibiotics included 42 observational studies with a total of 313,000 participants. The use of proton-pump inhibitors increased the risk for developing CDAD (OR, 1.74 [CI, 1.47 to 2.85]; \( P < 0.0010 \)), with lower risk from H₂-receptor antagonists than from proton-pump inhibitors (OR, 0.71 [CI, 0.53 to 0.97]). The use of proton-pump inhibitors plus antibiotics resulted in higher rates of CDAD than the use of proton-pump inhibitors alone (OR, 1.96 [CI, 1.03 to 3.70]) (30).

• A 1998 systematic review of risk factors for CDAD included 49 studies; formal quality assessment of the evidence was not performed. Overall, older age, underlying severe disease, antiulcer medication, nasogastric tube placement, antibiotics, and length of hospital stay were associated with CDAD (31).

• A large case-control study evaluated risk factors for CDAD among U.S. veterans. Patients with CDAD were older, more likely to have multiple comorbid conditions, and more likely to be white (32).

• A case-control study evaluated the association between obesity and CDAD in hospitalized patients. In the multivariate model, a higher BMI (OR, 1.196 per 1-unit increase in BMI [CI, 1.120 to 1.270]) and a history of intra-abdominal surgery (OR, 2.87 [CI, 1.26 to 6.52]) were associated with CDAD (33).

• A 2008 narrative review discussed the diagnosis of CDAD (34).

Rationale

• Current or previous use of antibiotics is the most significant risk factor for *C. difficile* diarrhea.

• The greatest risk for *C. difficile* exposure is in health care settings.

• The number of cases of community-onset CDAD is increasing, and CDAD has been found in other low-risk patients.

Comments

• A 2005 report from the CDC described 23 cases of community-acquired CDAD in patients who were young (48% under age 18); 30% of the patients had no recent history of antibiotics (in the previous 3 months) (35).

• Two hundred children (mean age, 5.4 years) who developed CDAD from 2000 to 2003 had similar risk factors to adults, but 23% required hospitalization (36).

• Ten peripartum women (90% who had taken recent antibiotics) developed CDAD, and 40% required hospitalization (35).

• A multivariate analysis in a case-control study investigating an outbreak of peripartum CDAD revealed that only the use of the combination of ampicillin, gentamicin, and clindamycin was a significant risk factor (OR, 39.0 [CI, 7.5 to 204.0]; \( P < 0.001 \)) (37).

2.2 Recognize the wide spectrum of clinical presentations of CDAD on clinical examination, and look for signs of volume depletion and acute abdomen.

Recommendations

• In patients with suspected CDAD, look for:
  • Fever
  • Abdominal tenderness
  • Rigidity, rebound tenderness, and ileus in severe cases
• Look for signs of volume depletion.
• See table Clinical Features of C. difficile Infection by Severity.

Evidence

• A 1979 case series described 66 patients with CDAD. The mean patient age was 61 years; 97% of patients had diarrhea, 7.6% had colicky abdominal pain, and 4.5% had abdominal distension and megacolon. Diarrhea was generally watery with mucus but no pus or blood. Fever (>37.5°C [99.5°F]) was seen in 66% of patients (38).

• A 1974 prospective study evaluated symptoms and findings in 200 consecutive hospitalized patients who received clindamycin. Overall, 21% developed diarrhea and 10% developed pseudomembranous colitis on proctoscopy. Among patients with PMC, 50% had fever, 80% had abdominal cramps, and 90% had mucousy diarrhea (39).

• Exam findings have correlated with findings at autopsy, surgical exploration, and endoscopy, as shown in a 10-year prospective study (40).

Rationale

• Patients may have a spectrum of exam findings correlating with the spectrum of disease.

Comments

• Emergence of a hypervirulent strain (BI/NAP1/027) that produces more toxin A and B and binary toxin was associated with more severe cases of CDAD in Canadian outbreaks (41; 42; 43; 44). Mortality associated with this strain is high (8%) (45).

2.3 Use appropriate stool testing for C. difficile or its toxins to diagnose CDAD, generally beginning with a PCR test for toxin or a GDH test.

Recommendations

• Be aware of the C. difficile tests performed at your facility and their advantages and disadvantages.

• To test for C. difficile and its toxins:
  • Test unfomed stools only
  • If available, use PCR toxin-gene detection as the initial test of choice
  • Consider an initial GDH test with a confirmatory PCR or enzyme-immunoassay test in patients who initially test positive

• Do not:
  • Send studies to test for cure
  • Repeat testing during the same episode of diarrhea
  • Perform culture whenever possible for epidemiologic investigations.

• See table Laboratory and Other Studies for CDAD.

• See table Stool Tests for Diagnosis of C. difficile Infection.

• See figure Tissue Culture Assay for C. difficile Toxin.

Evidence

• A 2013 guideline from the American College of Gastroenterology on the management of C. difficile infections recommended using a PCR test for C. difficile toxin over an enzyme immunoassay for the diagnosis of CDAD and stated that only stools from patients with diarrhea should be tested (1).

• A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on C. difficile infection in adults recommended testing for C. difficile only on unfomed stools and stated that the cell cytotoxicity assay is more sensitive than the immunoassay. The guideline noted that PCR assays may become the favored test. The guideline
defined CDAD in the presence of diarrhea (three or more unformed stools in 24 hours) plus either a positive stool test for toxigenic *C. difficile* or its toxin or pseudomembranous colitis on either colonoscopy or histopathology (2).

- A 2012 systematic review of molecular techniques for the diagnosis of CDAD included 25 studies of PCR and 6 studies of loop-mediated isothermal amplification. Using toxigenic culture as the reference standard, PCR had a pooled sensitivity of 92% (CI, 91% to 94%) and a pooled specificity of 94% (CI, 94% to 95%). Data regarding loop-mediated isothermal amplification were not pooled (46).

- A 2011 systematic review of the accuracy of GDH assays for the diagnosis of CDAD included 13 studies that compared GDH assays with a gold standard of cell cytotoxin assay or culture. In the pooled analysis, GDH assays had a sensitivity of approximately 92% and a specificity of approximately 92% (47).

- A 2008 systematic review of six commercially available enzyme immunoassays for *C. difficile* toxins included 18 studies. Median sensitivities ranged from 76% to 95% and specificities ranged from 93% to 100% when compared with cell cytotoxicity assays with or without *C. difficile* cultures (48).

- A prospective study compared the accuracy of PCR, enzyme immunoassay, cell culture cytotoxin assay, and anaerobic culture for the diagnosis of CDAD in 350 inpatients with diarrhea, using a clinical reference standard. The sensitivities of culture, PCR, cell culture cytotoxin assay, and toxin A and B ELISA were 100%, 93%, 76%, and 73%, respectively, with specificities of 95.9%, 97.4%, 97.1%, and 97.6%, respectively (49).

- A prospective study evaluated the diagnostic accuracy of perirectal swabs for PCR testing. Compared with stool PCR, perirectal swabs had a sensitivity of 95.7% and a specificity of 100% (50).

- Three studies showed that repeat testing for *C. difficile* toxin has a yield of less than 5% (51; 52; 53).

- A 2011 narrative review described appropriate testing for CDAD. The review noted that nine studies compared the performance of PCR testing with conventional testing for CDAD and found an improved sensitivity of around 90% vs. 40% to 50% for conventional testing; the studies also demonstrated a high specificity for PCR testing (54).

**Rationale**

- Some ELISAs test for only toxin A, whereas others test for toxins A and B. Most clinically significant *C. difficile* strains produce toxin B and will be missed by toxin A-only ELISAs.

- ELISA to detect GDH, a common enzyme present in the organism itself, has high sensitivity and is rapid, but it lacks specificity because it does not distinguish between toxigenic and nontoxigenic strains and GDH may be produced by other *Clostridium* species. A positive result on ELISA for GDH must be tested further for the presence of toxins. This assay is a useful initial screening test.

- Cell cytotoxicity neutralization assay is a functional assay for *C. difficile* toxin B and has some of the best test characteristics for the diagnosis of *C. difficile* infection, including a sensitivity of 67% to 100% and a specificity of 97%; however, the assay requires a tissue-culture facility, which is not widely available in most hospitals, and it takes 24 to 48 hours to perform.

- PCR tests are designed to detect toxin genes and have a high sensitivity of 90% and a high specificity and short turnaround time. They may become the new tests of choice, but the technology is still expensive.

- Culture is the most sensitive test and is the standard against which other clinical tests are compared. Culture will also help identify the toxigenic isolate and is essential for epidemiologic studies. This test is not clinically practical because of its slow turnaround time of 48 hours or more.

**Comments**
Clostridium difficile-associated Diarrhea

- Do not use a GDH test alone to diagnose CDAD because of its poor specificity. It does not detect any of the toxins produced by *C. difficile* but rather detects the bacterial enzyme GDH, which is found in nontoxigenic strains and other Clostridium species (55; 56).
- PCR testing has the best operating characteristics but is expensive and not available at all institutions.
- In patients with severe complicated disease and ileus, a perirectal swab provides a reliable specimen for diagnosis using a PCR assay.

2.4 Use stool cultures to identify molecular types of *C. difficile* during large outbreaks of CDAD.

**Recommendations**
- Send stool for culture and for molecular typing during outbreaks.
- See table Laboratory and Other Studies for CDAD.

**Evidence**
- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults recommended that stool culture be performed during CDAD outbreaks and for epidemiologic studies (2).

**Rationale**
- Stool culture is highly sensitive and allows for molecular typing.

**Comments**
- Stool culture detects both toxigenic and nontoxigenic strains, is highly sensitive, and allows for strain typing during epidemics. A major disadvantage is that stool culture takes 2 or more days to perform and is not specific for toxin-producing strains.
- Molecular typing can aid in tracking outbreaks and emergence of new strains (43); however, lack of consensus regarding a standardized method for typing strains hampers comparison of different studies of outbreaks (57). Very few centers are able to do molecular typing for *C. difficile*.

2.5 Obtain lower GI endoscopy and/or abdominal imaging in selected patients to look for complications or when urgent diagnosis is needed.

**Recommendations**
- Obtain flexible sigmoidoscopy to establish the diagnosis of pseudomembranous colitis and eliminate other possibilities, such as ischemic colitis or IBD, when urgent diagnosis is required.
- Obtain abdominal imaging (x-ray or CT) in severe cases or when the diagnosis of CDAD is unclear or if urgent diagnosis is required and it is not possible to conduct endoscopy.
- Consider abdominal imaging if complications, such as toxic megacolon or perforation, are suspected.
- See table Laboratory and Other Studies for CDAD.
- See figure Pseudomembranous Colitis.
- See figure Acute Toxic Megacolon.
- See figure C. difficile Colitis.

**Evidence**
- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults stated that the presence of
pseudomembranes on lower endoscopy and findings on CT scanning have been considered to be markers of severe disease (2).

- A study described endoscopic findings in 22 patients with PMC (58).
- A retrospective study described findings on CT scan in 152 patients with CDAD. Half (50%) of patients had CT findings of colonic wall thickness greater than 4 mm. Among patients with CT findings, 66% had segmental involvement, most often of the rectum (82%) and sigmoid (82%) colon. Abnormal CT scans were associated with leukocytosis, abdominal pain, and diarrhea (59).
- A prospective study described findings on flexible sigmoidoscopy and colonoscopy in 16 patients with PMC. Overall, pseudomembranes were visible on sigmoidoscopy in 31% and in 85% on colonoscopy (60).

Rationale
- Prompt diagnosis can be achieved with endoscopy.
- Evidence of colitis on abdominal imaging in patients at risk for CDAD is highly suggestive, but not diagnostic, for CDAD.

Comments
- Unprepared flexible sigmoidoscopy rather than full colonoscopy is most helpful. However, flexible sigmoidoscopy may miss up to 10% of cases of CDAD because of more proximal disease.
- Imaging studies, such as plain films or CT of the abdomen, may be useful for diagnosis and may be helpful in diagnosing such complications as toxic megacolon and early perforation.

2.6 Consider the broad differential diagnosis of CDAD, including antibiotic-associated diarrhea and other infectious causes.

Recommendations
- Consider antibiotic-associated diarrhea and other causes in patients presenting with a recent history of antibiotic exposure and diarrhea.
- Consider other causes of diarrhea in patients with negative test results for C. difficile infection or those in whom routine therapy fails, including:
  - Organisms that produce Shiga toxin (verotoxin), such as E. coli
  - Drug therapy with chlorpropamide, gold, and nonsteroidal anti-inflammatory agents
  - Intestinal obstruction
  - Villous adenoma
  - Uremia
  - Ischemic bowel
  - Heavy metal poisoning
  - Crohn's disease
  - Ulcerative colitis
  - Shigella, Salmonella, or Campylobacter infection
  - Hirschsprung's disease
  - Chemotherapy
- See table Clinical Features of C. difficile Infection by Severity.
- See table Differential Diagnosis of Antibiotic-associated Diarrhea.

Evidence
- Mainly consensus.
• A 2002 narrative review discussed the spectrum of CDAD and other antibiotic-associated diarrhea (61).

Rationale
• Most cases of antibiotic-associated diarrhea are not due to *C. difficile*.

Comments
• CDAD has also been reported to occur without any identifiable risk factor.
• Although the differential diagnosis for antibiotic-associated diarrhea is long, if pseudomembranes are found on endoscopy, *C. difficile* is the etiologic cause in over 90% of cases. The presence of pseudomembranes is felt to be nearly pathognomonic for *C. difficile* infection.

2.7 Define disease severity in patients diagnosed with CDAD, identifying severe disease in those with an elevated creatinine level (0.5 times the baseline level or higher) or elevated leukocyte count (≥15,000 cells/microliter).©

Recommendations
• Define disease severity in all patients diagnosed with CDAD.
  - Identify disease as:
    • Mild to moderate in patients with a creatinine level lower than 1.5 times the baseline level, a leukocyte count <15,000 cells/microliter, and no complications (e.g., hypotension, shock, ileus)
    • Severe in patients with an elevated creatinine level (1.5 times the baseline level or higher) or elevated leukocyte count (≥15,000 cells/microliter)
    • “Severe, complicated” in patients with hypotension, shock, ileus, or megacolon

Evidence
• A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults defined disease severity based on creatinine level and leukocyte count, and classified patients with complications as having “severe, complicated” CDAD (2).

Rationale
• Disease severity influences initial therapy.
3. Consultation

Consult a gastroenterologist for patients in whom CDAD is a possibility but testing does not diagnose CDAD and for patients with severe disease. Obtain appropriate specialist consultation for help in managing patients with severe or recurrent CDAD.

3.1 Consider referral to a gastroenterologist when the diagnosis is uncertain.

**Recommendations**
- Consider consulting a gastroenterologist for lower GI endoscopy when:
  - The ELISA test result is negative despite appropriate history and risk factors
  - Rapid diagnosis is warranted due to the patient's critical status, such as with sepsis, acute abdomen, or ileus

**Evidence**
- Consensus.

**Rationale**
- Endoscopy can be performed by the gastroenterology consultant to establish the diagnosis of PMC and eliminate other possibilities, such as ischemic colitis or IBD.

**Comments**
- A December 2004 report described a systematic, national, laboratory surveillance system that had been tracking the incidence of *C. difficile* in the UK since January 2004 and noted that more standardized diagnosis and reporting of CDAD was needed (57).

3.2 Obtain consultation for surgery in patients with signs of severe CDAD.

**Recommendations**
- Consult a surgeon early for consideration of colectomy and ileostomy in patients with signs suggesting severe sepsis due to CDAD.

**Evidence**
- A 2013 guideline from the American College of Gastroenterology on the management of *C. difficile* infections recommended consulting a surgeon for patients with complicated CDAD and recommended considering surgery in patients with hypotension, clinical sepsis with organ dysfunction, mental status changes, leukocyte count ≥50,000 cells/microliter, lactate level ≥5 mmol/L, or failure to improve after 5 days of antibiotic therapy (1).
- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults recommended considering colectomy in patients with severe disease (2).
- A 2008 summary of the literature describing surgery for toxic megacolon from CDAD included 17 case reports. The overall rate of mortality was 50%, and the rate of mortality in patients who underwent surgery was also 50%. Diagnosis was often delayed (62).

**Rationale**
- Timely subtotal colectomy and ileostomy are required for critically ill patients in whom medical therapy has failed.

**Comments**
• A few patients with CDAD may have peritoneal signs, toxic megacolon, or progressive sepsis. The management of these critically ill patients requires an integrated approach among the internist, infectious-disease specialist, gastroenterologist, and surgeon.

3.3 Consult an appropriate medical specialist for patients with a complicated course who do not require surgery.

Recommendations
• Consult a gastroenterologist and/or infectious-disease specialist when patients are refractory to the standard treatment, respond too slowly to treatment, or have multiple relapses.

Evidence
• Consensus.

Rationale
• Colonoscopy may be indicated to exclude other coexisting diseases.

Comments
• Diarrhea is a nonspecific symptom caused by many diseases, and having CDAD once does not confer immunity to other diarrheal disorders.
4. Hospitalization

Hospitalize patients with CDAD when they require treatment that is not available in the outpatient setting.

4.1 Hospitalize patients with CDAD if they are dehydrated, cannot tolerate oral intake, or have signs of acute abdomen.

Recommendations

- Hospitalize patients with:
  - Intravascular fluid depletion
  - Ileus who cannot take oral medication
  - Toxic megacolon or acute surgical abdomen that requires surgical intervention

Evidence

- In a 10-year study of 908 patients with CDAD, 6 of 8 patients with severe ileus were treated successfully with the combination of intravenous metronidazole, vancomycin enema, and nasogastric vancomycin (40).
- A 2008 summary of the literature describing surgery for toxic megacolon from CDAD included 17 case reports. The overall rate of mortality was 50%, and the rate of mortality in patients who underwent surgery was also 50%. Diagnosis was often delayed (62).

Rationale

- Standard supportive measures, such as intravenous fluids, to correct fluid losses and electrolyte imbalance are indicated.
- Vancomycin can be administered via nasogastric tube and rectal tube, and metronidazole can be administered intravenously.
- Timely subtotal colectomy and ileostomy are required in patients who are suspected of impending perforation.

Comments

- Combined medical and surgical care is essential, and prompt consultation with a gastroenterologist, colorectal surgeon, and infectious-disease specialist is prudent in patients with severe CDAD.
5. Therapy

Use antimicrobial agents as first-line drug therapy for CDAD and include nonspecific and supportive measures.

5.1 Stop the offending antibiotic and provide supportive care.

Recommendations

- Discontinue the offending antibiotic, and avoid restarting the offending antibiotic after completion of CDAD treatment.
- Consider switching to another agent that is less likely to cause CDAD when discontinuation of antimicrobial therapy is not possible.
- Correct fluid and electrolyte abnormalities.
- Avoid the use of antiperistaltic agents, especially before starting treatment for CDAD.
- Initiate contact precautions.
- See table Antibiotics Associated with C. difficile Colitis and Diarrhea.

Evidence

- A 2013 guideline from the American College of Gastroenterology on the management of C. difficile infections recommended supportive care for all patients with CDAD, including intravenous fluids, electrolyte repletion, and prophylaxis against venous thromboembolism, and recommended continuing oral or parenteral feeding unless there is ileus or abdominal distension. The guideline also recommended discontinuing any potentially inciting antibiotics (1).
- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on C. difficile infection in adults recommended discontinuing potentially inciting antibiotics if possible (2).
- A 2009 systematic review of the effect of antimotility (antiperistaltic) agents in patients with CDAD included 20 publications reporting on 55 patients. Twenty-three patients received antimitotility agents after starting treatment for CDAD; none of these patients died or developed colonic dilation or megacolon. Twenty-two patients received antimitotility agents before starting treatment for CDAD; all of these patients died or developed colonic dilation or megacolon (63).
- A 3-year, retrospective, cohort study evaluated the risk for recurrent CDAD in patients who received antibiotics after treatment in 246 patients with new-onset CDAD. Overall, 25% of patients received non-CDAD antibiotics during treatment for CDAD and 33% received non-CDAD antibiotics after treatment for CDAD. After controlling for confounders, receipt of antibiotics after CDAD therapy was associated with recurrent CDAD (OR, 3.02 [CI, 1.66 to 5.52]). There was no increased risk for recurrence in patients whose offending antibiotics were stopped before completing CDAD treatment (OR, 0.79 [CI, 0.40 to 1.52]) (64).

Rationale

- Stop the perpetuation of the symptomatic infection.

Comments

- If the underlying indication for use of antibiotics is valid, it is not appropriate to discontinue the implicated agents. Consideration should be given to alternative antibiotics that are less likely to predispose patients to CDAD, including sulfonamides, parenteral aminoglycosides, metronidazole, and tetracycline.
5.2 Use metronidazole as the preferred first-line treatment for mild to moderate CDAD and vancomycin as the preferred first-line treatment for severe CDAD.

**Recommendations**

- Stratify patients into mild to moderate disease, severe disease, or severe, complicated disease.
  - Mild to moderate: patients with a creatinine level lower than 1.5 times the baseline level, a leukocyte count <15,000 cells/microliter, and no complications (e.g., hypotension, shock, ileus)
  - Severe: patients with an elevated creatinine level (1.5 times the baseline level or higher) or elevated leukocyte count (≥15,000 cells/microliter)
  - Severe, complicated: patients with hypotension, shock, ileus, or megacolon
- Treat patients with mild to moderate CDAD with oral metronidazole, 500 mg three times daily, for 10 days.
- Treat patients with severe CDAD or metronidazole intolerance, children under age 10, and nursing or pregnant women with oral vancomycin, 125 mg every 6 hours, for 10 days.
- Treat patients with severe, complicated disease with a combination of oral vancomycin and intravenous metronidazole and consult a surgeon.
- If a patient does not respond to oral metronidazole in 5 to 7 days, switch to oral vancomycin.
- Consider empiric treatment for CDAD, pending diagnostic stool studies, in patients with signs of severe disease.
- In patients who cannot tolerate oral agents, administer metronidazole, 500 mg intravenously, every 8 hours for up to 10 days, and switch to oral metronidazole to complete the 10-day course when oral intake can be resumed.
- Consider the use of a vancomycin enema, 500 mg four times a day, in patients who cannot tolerate oral therapy, have an ileus, or have a colostomy or Hartman's pouch.
- Reserve oral fidaxomicin, 200 mg twice daily for 10 days, for patients with metronidazole and vancomycin intolerance or frequent recurrences.
- See table [Drug Treatment for CDAD](#).

**Evidence**

- A 2013 [guideline](#) from the American College of Gastroenterology on the management of *C. difficile* infections recommended metronidazole for patients with mild CDAD and vancomycin for patients with severe CDAD, both for a 10-day course of therapy. The guideline recommended considering a switch to vancomycin in patients taking metronidazole who fail to respond after 5 to 7 days and recommended oral vancomycin plus intravenous metronidazole for patients with severe, complicated CDAD (1).
- A 2010 [guideline](#) from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults defined disease severity based on creatinine level and leukocyte count, and classified patients with complications as having “severe, complicated” CDAD. The guideline recommended metronidazole as the initial therapy for mild to moderate CDAD and vancomycin as the initial therapy for severe CDAD (2).
- A 2011 [systematic review](#) of various antibiotic treatments for CDAD included 11 studies with 1463 participants. Overall, the rates of clinical cure and recurrence did not differ among patients treated with vancomycin and metronidazole or any other antibiotic. The rates of cure were 79% with vancomycin and 66% with metronidazole (*P*=0.022); recurrence rates ranged from 7% to 17% with vancomycin and from 5% to 21% with metronidazole (6).
• A 2011 Cochrane review of antibiotics for CDAD included 15 studies of nine antibiotics. There was only one placebo-controlled trial showing that vancomycin was superior to placebo. The analysis was limited by the poor quality of the included trials, but no one antibiotic appeared clearly superior to the others (66).

• A randomized trial compared oral vancomycin with oral metronidazole in 172 patients with CDAD, stratified by disease severity. Cure rates were similar in both groups among patients with mild disease, but patients with severe CDAD were more likely to respond to oral vancomycin than metronidazole, with cure rates of 97% and 76%, respectively (P=0.02) (67).

• In a retrospective analysis of data from a prospective cohort study of patients treated for CDAD at the discretion of their physicians, there was no significant difference in resolution of diarrhea by day 6 in mild to moderate disease treated with metronidazole or vancomycin (90% vs. 100%, respectively, P=0.05), but there was a significant difference among patients with severe disease (63% vs. 100%, respectively, P=0.04) (68).

• In a retrospective, chart-review study of 1675 patients with CDAD, the frequency of complications (toxic megacolon, perforation, colectomy, shock, or death) was lower in patients treated with vancomycin (6%) than in patients treated with metronidazole (13%) (41).

• A randomized noninferiority trial compared vancomycin with fidaxomicin in 629 patients with CDAD. Oral fidaxomicin was noninferior to oral vancomycin, with a primary endpoint of clinical cure 2 days after stopping the antibiotic (69).

• A study of 99 patients with CDAD treated with metronidazole found that 38% did not respond to treatment (70).

• In 207 patients with CDAD treated with metronidazole, 22% did not respond to initial treatment, and 28% had recurrences within 90 days (71).

Rationale

• Prospective, randomized trials show no difference in initial response rates to metronidazole and vancomycin.

• Previous exposure to oral or intravenous vancomycin has been associated with vancomycin-resistant enterococcus acquisition.

• Metronidazole is considerably less expensive than vancomycin.

• Fidaxomicin was noninferior to vancomycin in a prospective, randomized trial for clinical cure of CDAD.

Comments

• Oral vancomycin treatment should be reserved for patients with severe disease or metronidazole intolerance. Pregnant or nursing women and children younger than age 10 should also be treated with vancomycin.

• One theoretical advantage of vancomycin is that its colonic levels are extremely high after oral doses (72), whereas the colonic levels of metronidazole are less predictable (73; 74).

• Adding metronidazole to vancomycin does not appear to improve outcomes in patients with severe disease (75).

• Vancomycin-resistant enterococci colonize patients equally as often, regardless of whether metronidazole or vancomycin is used (76).

• Fidaxomicin is considerably more expensive than vancomycin or metronidazole and has no demonstrably higher cure rate than the former. However, it is the only agent that has been shown to decrease recurrent CDAD when compared with vancomycin.
Patients with refractory or multiply recurrent CDAD should be considered for fecal microbiota transplantation. A 2013 meta-analysis showed an 89.7% cure rate in these difficult-to-treat patients (77).

Antimotility drugs may obscure symptoms and worsen the course of CDAD, especially if given before treatment for CDAD.

5.3 Treat a first relapse of CDAD with the same agent used in initial treatment; treat subsequent relapses with tapered or pulsed dosing of vancomycin. 

Recommendations

- Recheck diagnostic studies with each relapse to confirm that CDAD is still the correct diagnosis.
- Treat an initial relapse the same way as the first episode.
- Do not use metronidazole beyond the first relapse or for long-term chronic therapy because of the potential for cumulative neurotoxicity.
- For second and subsequent relapses, use vancomycin.
  - Consider tapered vancomycin dosing, such as 125 mg four times daily for 7 days, three times daily for 7 days, twice daily for 7 days, once daily for 7 days, every other day for 7 days, and every 3 days for 7 days.
  - Consider pulsed vancomycin dosing, in which a standard 10-day course is followed by continued, periodic dosing, for example, a single dose of 125 mg every 3 days for 1 month.
- See table Drug Treatment for CDAD.

Evidence

- A 2013 guideline from the American College of Gastroenterology on the management of C. difficile infections recommended treating the first mild to moderate recurrence with the drug that was initially used, treating the first severe recurrence with vancomycin, and treating subsequent recurrences with pulsed vancomycin. The guideline noted that the evidence in support of pulsed vancomycin is weak (1).
- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on C. difficile infection in adults recommended treating a first CDAD recurrence with the same regimen initially used, and recommended treating subsequent recurrences with tapered or pulsed vancomycin. The guideline noted that cholestyramine and rifampin have not been shown to reduce CDAD recurrence but that rifaximin might be effective (2).
- An observational study evaluated the effectiveness of different antibiotics in 163 patients with recurrent CDAD who were in the placebo arm of a clinical trial. Overall, recurrence rates were similar in patients receiving monotherapy with metronidazole (42.1%) and vancomycin (46.2%). Both tapered dosing (14.3%) and pulsed dosing (31%) of vancomycin resulted in lower rates of recurrence compared with standard medium dosing of vancomycin (71.4%) (78).

Rationale

- A relapse is the recurrence of CDAD after a symptom-free period and after completion of a course of antibiotic therapy.
- Patients who have one relapse have a substantial risk for developing further episodes of CDAD.
- Fifteen to twenty percent of patients treated for first-line therapy will relapse.
- Therapies that assist in restoring normal colonic microflora or boosting the immune response have been effective.

Comments
Patients with at least two previous relapses have about a 65% chance of a subsequent relapse following therapy with vancomycin or metronidazole (79).

Patients with refractory or multiply recurrent CDAD should be considered for fecal microbiota transplantation. A 2013 meta-analysis showed an 89.7% cure rate in these difficult-to-treat patients (77).

Monoclonal-antibody treatment is not FDA approved but appears promising in the prevention of relapse (80).

Randomized trials of rifaximin are lacking; its use should be limited to patients with highly refractory disease for whom multiple therapies have failed.

Support for the use of intravenous immunoglobulin is based on low-quality studies that are subject to biases.

5.4 Consider alternative therapies in patients with highly refractory colitis or multiple relapses.

Recommendations
- In patients with more than two relapses, consider:
  - Treatment with fecal microbiota transplant
  - Treatment with monoclonal antibodies
  - Treatment with probiotics in conjunction with antibiotics
  - Treatment with rifaximin, 400 mg, three times daily
- Consider infectious-disease referral for patients with multiple relapses.
- See table Drug Treatment for CDAD.

Evidence
- A 2013 guideline from the American College of Gastroenterology on the management of C. difficile infections recommended considering fecal microbiota transplant in patients with a third recurrence of CDAD after pulsed vancomycin therapy. The guideline stated that intravenous immune globulin should not be used to treat CDAD except in patients with a known immunodeficiency (1).
- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on C. difficile infection in adults recommended treating a first CDAD recurrence with the same regimen initially used, and recommended treating subsequent recurrences with tapered or pulsed vancomycin. The guideline noted that cholestyramine and rifampin have not been shown to reduce CDAD recurrence but that rifaximin might be effective (2).
- A 2013 systematic review of fecal microbiota transplantation in patients with CDAD included 11 observational studies with 273 participants. In the meta-analysis, 89.7% of patients had clinical resolution of disease, with a trend toward higher rates of resolution in patients who received lower-intestinal delivery of fecal microbiota rather than upper-intestinal delivery (77).
- A 2009 systematic review of pooled immunoglobulin for patients with CDAD included four retrospective studies and five case series of intravenous immunoglobulin and one study of oral immunoglobulin. Overall, there appeared to be benefit to immunoglobulin, but the poor quality of the studies precluded accurate assessment (81).
- A 2008 Cochrane review of probiotics for the treatment of CDAD included four studies, which were small with methodological problems. Only one study found that probiotics were beneficial (82).
- A randomized trial compared 4 days of vancomycin plus fecal restoration (infusion of donor feces into the duodenum) with 14 days of vancomycin with bowel lavage or 14 days of vancomycin alone in 43 adults with relapsed CDAD. Cure rates were significantly higher in the fecal restoration group: 81% (up to 94% after a second infusion from a different donor), compared with 31% in the
vancomycin group and 23% in the vancomycin-plus-lavage group, giving an NNT of 2 for fecal restoration compared with vancomycin (83).

- A randomized trial compared monoclonal antibodies to toxins A and B with placebo in 200 patients with symptomatic *C. difficile* infection who were also receiving antibiotics. The rate of CDAD recurrence was lower in the monoclonal-antibody group than in the placebo group (7% vs. 25%, respectively, *P*<0.001) (80).

- A randomized noninferiority trial compared vancomycin to fidaxomicin in 629 patients with CDAD. Oral fidaxomicin was noninferior to oral vancomycin, with a primary endpoint of clinical cure 2 days after stopping the antibiotic (69).

- A randomized trial compared rifaximin with placebo (both for 20 days) in 68 patients with CDAD immediately after completing initial antibiotic therapy. The recurrence of CDAD was 15% in the rifaximin group and 31% in the placebo group (*P*=0.11), and the rate of recurrent diarrhea was lower in the rifaximin group (21% vs. 49%, *P*=0.018) (84).

**Rationale**
- Alternative therapies may be needed in patients with frequently relapsing CDAD.

### 5.5 Consider surgery in patients with fulminant colitis.

**Recommendations**
- Consider subtotal colectomy (with rectal sparing) and ileostomy in patients with fulminant colitis in whom drug therapy fails or who have complications of colonic perforation and toxic megacolon.

- Monitor serum lactate level and leukocyte count in patients with complicated or severe CDAD and consider surgery in patients with:
  - Leukocyte count ≥50,000 cells/microliter
  - Lactate level ≥5 mmol/L

**Evidence**
- A 2013 guideline from the American College of Gastroenterology on the management of *C. difficile* infections recommended consulting a surgeon for patients with complicated CDAD, and recommended considering surgery in patients with hypotension, clinical sepsis with organ dysfunction, mental status changes, leukocyte count ≥50,000 cells/microliter, lactate level ≥5 mmol/L, or failure to improve after 5 days of antibiotic therapy (1).

- A 2010 guideline from the Society for Healthcare Epidemiology of America and the Infectious Diseases Society of America on *C. difficile* infection in adults recommended considering colectomy in patients with severe disease (2).

- A 2008 summary of the literature describing surgery for toxic megacolon from CDAD included 17 case reports. The overall rate of mortality was 50%, and the rate of mortality in patients who underwent surgery was also 50%. Diagnosis was often delayed (62).

- A retrospective cohort study described outcomes in 165 patients admitted to the ICU with severe CDAD. Fifty-three percent of patients died within 30 days of ICU admission. Independent predictors of death included leukocyte count ≥50,000 cells/microliter (adjusted OR, 18.6 [CI, 3.7 to 94.7]), lactate level ≥5 mmol/L (adjusted OR, 12.4 [CI, 2.4 to 63.7]), being age 75 years or older (adjusted OR, 6.5 [CI, 1.7 to 24.3]), immunosuppression (adjusted OR, 7.9 [CI, 2.3 to 27.2]), and shock requiring vasopressors (adjusted OR, 3.4 [CI, 1.3 to 8.7]). In the multivariate model, undergoing emergency colectomy was associated with lower mortality (adjusted OR, 0.22 [CI, 0.07 to 0.67]) (85).

- A 2002 narrative review discussed the spectrum of pseudomembranous enterocolitis and antibiotic-associated diarrhea and the indications for surgery (61).
Rationale

- Death may ensue if colectomy is not performed in this situation.
6. Patient Counseling

Inform patients about the overall management of CDAD.

6.1 Inform patients about risk factors for CDAD, its treatment, possible relapse, and secondary prevention.

Recommendations

- Advise patients about signs and symptoms of CDAD requiring physician evaluation, including:
  - Recurrent diarrhea, especially if associated with abdominal pain, fever, blood or pus in stools, plus history of antibiotic use in preceding 8 weeks
  - Inability to keep liquids or foods down due to nausea and vomiting in the setting of recent antibiotic use in the past 2 months
  - Recurrent diarrhea in patients who are immunocompromised, elderly, recently in a hospital or nursing home, or who have cancer
- Tell patients that CDAD can be treated with a 10-day course of metronidazole or vancomycin, that there is a substantial relapse rate with the initial therapy (15% to 20%) and a repeated course of treatment may be necessary, and that the risk for recurrence after a relapse is as high as 45% to 65%.
- Instruct patients not to take antidiarrheal medications because they may cause serious complications and worsen their disease.
- To prevent relapse and spread of CDAD, tell patients to:
  - Observe strict hand washing with soap and water
  - Use antibiotic therapy only when deemed absolutely essential by their physician and to notify any other physician who may want to start antibiotic therapy that there is a history of recent CDAD
  - Not use probiotics for the treatment of CDAD

Evidence

- Consensus.

Rationale

- Patient education and adherence to management advice may prevent further nosocomial spread and subsequent recurrences.
7. Follow-up

Schedule regular follow-up to monitor for recurrence or relapse of CDAD.\textsuperscript{7c}

7.1 Provide appropriate follow-up to ensure response to therapy and assess for relapse.\textsuperscript{7c}

Recommendations
- Assess outpatients receiving treatment for CDAD within a few days of initiation of therapy, to ensure appropriate response.
- Consider reassessing patients 2 to 3 weeks after completion of therapy for recurrent symptoms.

Evidence
- A 2011 systematic review of various antibiotic treatments for CDAD included 11 studies with 1463 participants. Overall, rates of clinical cure and recurrence did not differ among patients treated with vancomycin and metronidazole or any other antibiotic. Rates of cure were 79\% with vancomycin and 66\% with metronidazole ($P=0.022$); recurrence rates ranged from 7\% to 17\% with vancomycin and from 5\% to 21\% with metronidazole (\textsuperscript{65}).

Rationale
- A relapse is the recurrence of CDAD after a symptom-free period and after completion of a course of antibiotic therapy.
- Patients who have one relapse have a substantial risk for developing further episodes of CDAD.
- Fifteen to twenty percent of patients treated for first-line therapy will relapse.

Comments
- Patients with at least two previous relapses have about a 65\% chance of a subsequent relapse following therapy with vancomycin or metronidazole (\textsuperscript{79}).

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References


Clostridium difficile-associated Diarrhea


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45. Eggertson L. C. difficile may have killed 2000 in Quebec: study. CMAJ. 2005;173:1020-1. (PMID: 16179430)

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Clostridium difficile-associated Diarrhea


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# Glossary

**BMI**  
body mass index

**CDAD**  
*Clostridium difficile*-associated diarrhea

**CDC**  
Centers for Disease Control and Prevention

**CI**  
confidence interval

**CT**  
computed tomography

**ELISA**  
enzyme-linked immunosorbent assay

**FDA**  
Food and Drug Administration

**GDH**  
glutamate dehydrogenase

**GI**  
gastrointestinal

**HR**  
hazard ratio

**IBD**  
inflammatory bowel disease

**ICU**  
intensive care unit

**NNT**  
number needed to treat

**OR**  
odds ratio

**PCR**  
polymerase chain reaction

**PMC**  
pseudomembranous colitis

**RR**  
risk ratio
## Tables

### Laboratory and Other Studies for CDAD

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%) / Specificity (%)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytotoxin assay</td>
<td>67/97</td>
<td>Requires tissue-culture equipment, not widely available in most hospitals, and takes up to 24-48 hours to perform</td>
</tr>
<tr>
<td>ELISA for toxins A and/or B</td>
<td>76-95/93-100</td>
<td>The method used most widely in the clinical setting and only takes 2-6 hours to perform</td>
</tr>
<tr>
<td>ELISA for GDH</td>
<td>80-100 (pooled value 92)/83-100 (pooled value 92)</td>
<td>Good screening test because it has rapid and high sensitivity, but if results are positive, further testing is required to confirm presence of toxigenic <em>C. difficile</em></td>
</tr>
<tr>
<td>PCR for toxin DNA</td>
<td>92/94</td>
<td></td>
</tr>
<tr>
<td>Culture</td>
<td>100/100 in conjunction with testing the isolate for toxin production</td>
<td>Cultures, especially those using enriched broths, can detect low concentrations of <em>C. difficile</em> in stool and allow typing of isolates as needed</td>
</tr>
<tr>
<td>Plain abdominal x-rays</td>
<td></td>
<td>To assess the presence of colonic dilatation in patients with suspected megacolon or perforation. Not routinely necessary except when complications are suspected</td>
</tr>
<tr>
<td>CT scan</td>
<td></td>
<td>May reveal a thickened colonic wall and toxic megacolon. It suggests colitis but is not specific for CDAD</td>
</tr>
<tr>
<td>Lower GI endoscopy</td>
<td></td>
<td>To establish diagnosis when other study results are negative and clinical suspicion is high, to evaluate severity of disease, or if need for diagnosis is urgent. PMC may not be present early in the disease course</td>
</tr>
</tbody>
</table>

CDAD = *Clostridium difficile*-associated diarrhea; CT = computed tomography; DNA = deoxyribonucleic acid; ELISA = enzyme-linked immunosorbent assay; GDH = glutamate dehydrogenase; GI = gastrointestinal; PCR = polymerase chain reaction; PMC = pseudomembranous colitis.
## Differential Diagnosis of Antibiotic-associated Diarrhea

<table>
<thead>
<tr>
<th>Disease</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
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</tbody>
</table>

*Clostridium difficile*-associated diarrhea  | Diarrhea may range from mild to profuse and may even be absent if the patient has developed ileus. Can occur during or after antibiotic therapy |
| Nonspecific antibiotic-associated diarrhea | Mild diarrhea episodes without a definitive cause and without accompanying symptoms. It usually resolves with simple discontinuation of antibiotic therapy. 80% of antibiotic-associated diarrhea is not CDAD |
| Other pathogens                              | May cause symptoms similar to that of CDAD. Other pathogens include *C. perfringens*, *S. aureus*, *K. oxytoca*, *S. newport*, *C. albicans*, *E. coli*, and *Shigella*. Usually of community onset |
| Chronic intestinal conditions                | Diarrhea and/or inflammatory response, elevated leukocyte count, fever. Inflammatory bowel disease and irritable bowel syndrome can mimic CDAD |

CDAD = *Clostridium difficile*-associated diarrhea.
# Drug Treatment for CDAD

<table>
<thead>
<tr>
<th>Drug or Drug Class</th>
<th>Dosing</th>
<th>Side Effects</th>
<th>Precautions</th>
<th>Clinical Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole (Flagyl, Metro)</td>
<td>500 mg PO tid. If unable to tolerate PO, give 500 mg IV q8hr. Total of 10 days</td>
<td>Nausea, dysgeusia, diarrhea, abdominal pain, neurotoxicity, phlebitis</td>
<td>■ Carcinogenicity. Avoid with pregnancy and nursing. Avoid alcohol. Decrease dose by 50% with severe hepatic disease. Caution with: CKD, warfarin</td>
<td>Mild-moderate CDAD</td>
</tr>
<tr>
<td>Vancomycin (Vancocin)</td>
<td>125 mg PO qid for 10 days. Or, 500 mg in 100 mL NS per rectum q6hr</td>
<td>Nausea, vomiting, abdominal pain</td>
<td></td>
<td>Severe or second recurrence of CDAD. Use rectal form in severe disease with ileus</td>
</tr>
<tr>
<td>Fidaxomicin (Dificid)</td>
<td>200 mg PO bid for 10 days</td>
<td>Nausea, vomiting, abdominal pain</td>
<td></td>
<td>Reserve for metronidazole and vancomycin intolerance or frequent relapses</td>
</tr>
<tr>
<td>Rifaximin (Xifaxan)</td>
<td>400 mg PO tid</td>
<td>Nausea, abdominal pain, pruritus, hypersensitivity reactions, dizziness, peripheral edema</td>
<td>Caution with severe hepatic disease. P-gp substrate</td>
<td>Highly refractory colitis or multiple relapses</td>
</tr>
</tbody>
</table>

= first-line agent; ■ = black box warning; bid = twice daily; CDAD = *Clostridium difficile*-associated diarrhea; CKD = chronic kidney disease; IV = intravenous; NS = normal saline; P-gp = P-glycoprotein; PO = oral; q6hr = every 6 hours; q8hr = every 8 hours; qd = once daily; qid = four times daily; tid = three times daily.

PIER provides key prescribing information for practitioners but is not intended to be a source of comprehensive drug information.
### Practice Guidelines for Prevention of *C. difficile* Diarrhea

<table>
<thead>
<tr>
<th>Guideline</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Limit the use of antimicrobial drugs</td>
<td></td>
</tr>
<tr>
<td>Adhere to hand-hygiene procedures between contact with all patients</td>
<td></td>
</tr>
<tr>
<td>Use contact precautions and single rooms for patients with <em>C. difficile</em> diarrhea</td>
<td></td>
</tr>
<tr>
<td>Wash hands with soap and water after contact with patients with <em>C. difficile</em> diarrhea</td>
<td></td>
</tr>
<tr>
<td>Wear gloves and gowns when contacting patients with <em>C. difficile</em> diarrhea or their environment</td>
<td></td>
</tr>
<tr>
<td>Disinfect objects contaminated with <em>C. difficile</em> with sodium hypochlorite, alkaline glutaraldehyde, or ethylene oxide</td>
<td></td>
</tr>
<tr>
<td>Educate the medical, nursing, and other appropriate staff members about the disease and its epidemiology</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from 1.
## Clinical Features of *C. difficile* Infection by Severity

<table>
<thead>
<tr>
<th>Spectrum of Disease</th>
<th>Diarrhea</th>
<th>Symptoms</th>
<th>Physical Exam</th>
<th>Colonoscopic Exam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic carrier state</td>
<td>Absent</td>
<td>Absent</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Simple antibiotic-associated diarrhea</td>
<td>Mild</td>
<td>None, other than diarrhea</td>
<td>May have mild abdominal tenderness</td>
<td>Normal</td>
</tr>
<tr>
<td>Colitis without pseudomembrane formation</td>
<td>Profuse; fecal leukocytes usually present; may have occult bleeding</td>
<td>Nausea, low-grade fever, anorexia, dehydration, peripheral leukocytosis</td>
<td>Mild to moderate abdominal tenderness</td>
<td>Nonspecific or patchy erythematous colitis without pseudomembranes</td>
</tr>
<tr>
<td>PMC</td>
<td>More profuse diarrhea than in patients with colitis without pseudomembrane formation</td>
<td>High-grade fever, nausea, malaise, peripheral leukocytosis with left shift, dehydration; patients with PMC have a more serious illness than patients with colitis without pseudomembranes</td>
<td>May have marked abdominal tenderness, distension, guarding, and rebound</td>
<td>Pseudomembrane formation (yellowish, raised plaques varying in size from 2 to 10 mm)</td>
</tr>
<tr>
<td>Fulminant colitis</td>
<td>Severe, profuse diarrhea; may be absent if ileus develops</td>
<td>High-grade fever, marked peripheral leukocytosis with left shift; protein-losing enteropathy may lead to hypoalbuminemia and ascites. Complications may include colonic perforation, toxic megacolon, prolonged ileus, and death</td>
<td>Severe abdominal tenderness; may have peritoneal signs and acute abdomen</td>
<td>Sigmoidoscopy and colonoscopy contraindicated due to high risk for perforation</td>
</tr>
</tbody>
</table>

PMC = pseudomembranous colitis.

Data from 61.
### Stool Tests for Diagnosis of *C. difficile* Infection

<table>
<thead>
<tr>
<th>Test</th>
<th>Detects</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polymerase chain reaction</td>
<td>Toxin producing genes</td>
<td>Highly sensitive and specific</td>
<td>Expensive</td>
</tr>
<tr>
<td>Toxin enzyme immunoassay</td>
<td>Toxin A or A and B</td>
<td>Fast (2-6 hours), easy to perform, high specificity</td>
<td>Not as sensitive as the cytotoxin assay</td>
</tr>
<tr>
<td>Glutamate dehydrogenase enzyme immunoassay</td>
<td>Clostridium species enzyme (glutamate dehydrogenase)</td>
<td>Fast, inexpensive, easy to perform</td>
<td>Poor specificity</td>
</tr>
<tr>
<td>Cell culture cytotoxin assay</td>
<td>Toxin B</td>
<td>Used as reference standard, highly sensitive and specific</td>
<td>Requires tissue culture facility, takes 24-48 hours</td>
</tr>
<tr>
<td>Culture</td>
<td>Toxigenic and nontoxigenic <em>C. difficile</em></td>
<td>Sensitive, allows strain typing in epidemics</td>
<td>Requires aerobic culture; not specific for toxin-producing bacteria; takes 2-5 days</td>
</tr>
</tbody>
</table>

# Clostridium difficile-associated Diarrhea

**Stool Tests for Diagnosis of *C. difficile* Infection**

<table>
<thead>
<tr>
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## Antibiotics Associated with *C. difficile* Colitis and Diarrhea

<table>
<thead>
<tr>
<th>Frequently</th>
<th>Infrequently</th>
<th>Rarely</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin and amoxicillin</td>
<td>Trimethoprim</td>
<td>Parenteral aminoglycoside</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td>Sulfonamides</td>
<td>Bacitracin</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Erythromycin</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Chloramphenicol</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

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Figures

Tissue Culture Assay for *C. difficile* Toxin

A. Normal primary human amnion cells. B. Typical actinomorphic changes after application of stool containing *C. difficile* toxins. C. The tissue-cultured cells with the same specimen after neutralization with *Clostridium sordelli* antitoxin. Reprinted from Bartlett with permission from WB Saunders Co. (permission requested and pending).
Pseudomembranous Colitis

Endoscopic view of colon wall demonstrating several pseudomembranes (arrows). Courtesy of Jonathan Leighton, MD, Division of Gastroenterology, Mayo Clinic Scottsdale, Scottsdale, Arizona.
**Acute Toxic Megacolon**

Seen in a patient with fulminant pseudomembranous colitis. Note the thickened and edematous bowel wall (arrow).
**C. difficile Colitis**

*Clostridium difficile* colitis presents endoscopically with shallow mucosal ulcerations and pseudomembranes manifested as raised yellow or off-white plaques on the colorectal mucosa.