Clostridium Difficile Infection in Adults
Treatment and Prevention

Definition:
Clostridium Difficile colonizes the human intestinal tract after the normal gut flora has been altered by antibiotic therapy and causes antibiotic-associated colitis.

Risk factors:
- Antibiotic use is the most widely recognized and modifiable risk factor for Clostridium difficile.
- Age > 65 year.
- Recent hospitalization.

Clinical manifestations:
1. Nonsevere CDI include watery diarrhea (≥3 loose stools in 24 hours) with lower abdominal pain and cramping, low-grade fever, and leukocytosis.
   * Criteria proposed for nonsevere CDI (based on expert opinion) include white blood cell count ≤15,000 cells/mL and serum creatinine <1.5 mg/dL; prospectively validated severity scores for CDI are needed.
2. Severe CDI include diarrhea, severe lower quadrant or diffuse abdominal pain, abdominal distention, fever, hypovolemia, lactic acidosis, hypoalbuminemia, and marked leukocytosis.
   * Criteria proposed for severe CDI (based on expert opinion) include white blood cell count >15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL.
3. Fulminant colitis (severe, complicated CDI) may be characterized by hypotension or shock, ileus, or megacolon.
4. **Recurrent C. difficile** infection is defined by resolution of CDI symptoms while on appropriate therapy, followed by reappearance of symptoms within two to eight weeks after treatment has been stopped.

**Diagnosis:**

- The diagnosis of *C. difficile* infection is established via a positive stool test for *C. difficile* toxin(s) or *C. difficile* toxin gene

- **Laboratory testing** should be pursued only in patients with clinically significant diarrhea, since testing cannot distinguish between CDI and asymptomatic carriage (which does not warrant treatment). For patients with ileus, laboratory diagnosis via perirectal swab for toxin assay or anaerobic culture may be performed.

- **Radiographic imaging** of the abdomen and pelvis is warranted for patients with clinical manifestations of severe illness or fulminant colitis to evaluate for presence of toxic megacolon, bowel perforation, or other findings warranting surgical intervention.

- **Lower gastrointestinal endoscopy** is not warranted in patients with typical clinical manifestations of *C. difficile* infection, a positive laboratory test, and/or clinical response to empiric treatment. In general, endoscopy may be pursued for circumstances in which an alternative diagnosis is suspected that requires direct visualization and/or biopsy of the bowel mucosa. It may also be helpful for patients with ileus or fulminant colitis in the absence of diarrhea since it may allow visualization of pseudomembranes (severe inflammation of the inner lining of the bowel), a finding that is highly suggestive of *C. difficile* infection.

**GENERAL PRINCIPLES**

**Antibiotic management** — An important initial step in the treatment of CDI is discontinuation of the inciting antibiotic agent(s) as soon as possible. Treatment with concomitant antibiotics (i.e., antibiotics other than those given to treat *C. difficile* infection) is associated with prolongation of diarrhea, increased likelihood of treatment failure, and increased risk of recurrent CDI. If ongoing antibiotics are essential for treatment of the primary infection, if possible, it may be prudent to select antibiotic agents that are less frequently implicated in antibiotic-associated CDI.
Infection control — Patients with suspected or proven *C. difficile* infection should be placed on contact precautions, and health care workers should wash hands before and after patient contact. Hand hygiene with soap and water may be more effective than alcohol-based hand sanitizers in removing *C. difficile* spores, since *C. difficile* spores are resistant to killing by alcohol.

Diarrhea management — In addition, antimitoty agents such as loperamide and opiates have traditionally been avoided in CDI, but the evidence that they cause harm is equivocal. Supportive care with attention to correction of fluid losses and electrolyte imbalances is also important. Patients may have regular diet as tolerated.

**PREVENTION**

**Initial episode** — Strategies for preventing an initial episode of *C. difficile* infection include:

- Minimizing antibiotic use.
- Avoiding gastric acid suppression.
- Use of probiotics in some circumstances.

**Recurrent episode** — Strategies for preventing a recurrent episode of *C. difficile* infection include those summarized above for preventing an initial episode of CDI.

Additional strategies include:

- **secondary prophylaxis** during concomitant antibiotic use – In patients with a recent history of CDI who require systemic antibiotic therapy, secondary prophylaxis with oral vancomycin may reduce the likelihood of CDI recurrence. The optimal dose of oral vancomycin for secondary prophylaxis is uncertain; reasonable regimens may consist of standard dosing (125 mg orally four times daily) or reduced dosing (125 to 250 mg twice
Metronidazole should not be used for secondary prophylaxis because of its dose-dependent association with peripheral neuropathy.

- **Monoclonal antibodies** – Adjunctive use of monoclonal antibodies against *C. difficile* toxin may reduce the recurrence rate of *C. difficile* infection. Bezlotoxumab (a monoclonal antibody that binds to *C. difficile* toxin B) received US Food and Drug Administration approval in 2016 for secondary prevention of *C. difficile* infection in patients at high risk for recurrence (including patients >65 years of age and those with a prior history of CDI).

- **Gastrointestinal colonization by nontoxigenic *C. difficile* strains** – Gastrointestinal colonization by nontoxigenic *C. difficile* strains has been shown to prevent CDI with exposure to a toxigenic.
### Antibiotic regimens for the treatment of *Clostridium difficile* infection in adults

<table>
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<th>Clinical definition</th>
<th>Treatment*</th>
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<tr>
<td><strong>Nonsevere disease</strong>&lt;br&gt;Supportive clinical data: White blood cell count ≤15,000 cells/mL and serum creatinine &lt;1.5 mg/dL</td>
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<td><strong>Initial episode</strong></td>
<td>• Vancomycin 125 mg orally four times daily for 10 days, OR&lt;br&gt;• Fidaxomicin 200 mg orally twice daily for 10 days&lt;br&gt;• If above agents are unavailable: Metronidazole 500 mg orally three times daily for 10 days†&lt;br&gt;</td>
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<td><strong>First recurrence</strong></td>
<td>• If vancomycin was used for the initial episode:&lt;br&gt;• Vancomycin pulsed-tapered regimen:&lt;br&gt;  • 125 mg orally four times daily for 10 to 14 days, then&lt;br&gt;  • 125 mg orally twice daily for 7 days, then&lt;br&gt;  • 125 mg orally once daily for 7 days, then&lt;br&gt;  • 125 mg orally every 2 or 3 days for 2 to 8 weeks, OR&lt;br&gt;• Fidaxomicin 200 mg orally twice daily for 10 days&lt;br&gt;• If fidaxomicin or metronidazole was used for the initial episode: Vancomycin 125 mg orally four times daily for 10 days&lt;br&gt;</td>
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<td><strong>Second or subsequent recurrence</strong></td>
<td>• Vancomycin pulsed-tapered regimen (outlined above), OR&lt;br&gt;• Fidaxomicin 200 mg orally twice daily for 10 days, OR&lt;br&gt;• Vancomycin followed by rifaximin:&lt;br&gt;• Vancomycin 125 mg orally four times per day for 10 days, then&lt;br&gt;• Rifaximin 400 mg three times daily for 20 days, OR&lt;br&gt;• Fecal microbiota transplantation§&lt;br&gt;</td>
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<td><strong>Severe disease</strong>&lt;br&gt;Supportive clinical data: White blood cell count &gt;15,000 cells/mL and/or serum creatinine ≥1.5 mg/dL</td>
<td>• Vancomycin 125 mg orally four times daily for 10 days, OR&lt;br&gt;• Fidaxomicin 200 mg orally twice daily for 10 days&lt;br&gt;</td>
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<td><strong>Fulminant disease</strong>&lt;br&gt;(previously referred to as severe, complicated <em>C. difficile</em> infection)†&lt;br&gt;Supportive clinical data:&lt;br&gt;Hypotension or shock; ileus, megacolon</td>
<td>• Enteric vancomycin plus parenteral metronidazole:&lt;br&gt;• Vancomycin 500 mg orally or via nasogastric tube four times daily, AND&lt;br&gt;• Metronidazole 500 mg intravenously every 8 hours&lt;br&gt;• If ileus is present, rectal vancomycin may be administered as a retention enema (500 mg in 100 mL normal saline per rectum; retained for as long as possible and readministered every 6 hours)§&lt;br&gt;</td>
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CDI: *Clostridium difficile* infection.<br>＊All randomized trials have compared 10-day treatment courses, but some patients (particularly those treated with metronidazole) may have delayed response to treatment; in such circumstances, extending treatment duration to 14 days is reasonable.<br>†Metronidazole should be avoided in patients who are very elderly or infirm or who develop CDI in association with inflammatory bowel disease.<br>§Fecal microbiota transplantation (FMT) is the preferred management approach for patients with third or subsequent recurrence. Appropriate antibiotic treatment for at least two recurrences (ie, three CDI episodes) should be attempted prior to offering FMT.<br>○The criteria proposed for defining severe or fulminant CDI are based on expert opinion and may need to be reviewed upon publication of prospectively validated severity scores for patients with CDI. Systemic absorption of enteral vancomycin can occur in patients with mucosal disruption due to severe or fulminant colitis; this consideration is particularly important for patients with renal insufficiency (creatinine clearance < 10 mL/minute). Therefore, monitoring serum vancomycin levels is warranted for patients with renal failure who have severe colitis and require a prolonged course (>10 days) of enteral vancomycin therapy.<br>5 Rectal vancomycin may be administered as a retention enema, either in addition to oral vancomycin (if the ileus is partial) or in place of oral vancomycin (if the ileus is complete). Administration of intracolonic vancomycin is associated with risk of colonic perforation. Therefore, use of intracolonic vancomycin should be restricted to patients who are not responsive to oral therapy, and the procedure should be performed by personnel with expertise in administering enemas.<br><br>Adapted from: McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis 2018, by permission of Oxford University Press on behalf of IDSA and SHEA. Copyright © 2018. http://www.idsociety.org/PracticeGuidelines/.
References:


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