Diagnosis and Presentation

- **Common signs and symptoms:** Fever, abdominal cramping and pain, elevated WBC count, and severe diarrhea. Diarrhea is the key clinical feature of disease and can range from mild to moderate, fulminant, and sometimes fatal pseudomembranous colitis. Rarely (<1%), a symptom-free patient with ileus and colonic distention will present with minimal or no diarrhea.

- **Who should be tested?**
  - Patients with unexplained and new onset ≥3 loose stools in 24 hours along with other signs or symptoms of CDI. To adequately assess a patient’s risk of having CDI, consideration should be given to iatrogenic causes of diarrhea, including laxatives, medications, and enteral feeds. The pre-test probability of a patient having CDI is much lower for these patients.
  - The pre-test probability of CDI is also diminished if the patient has no recent history of antibiotic exposure, including surgical prophylaxis.
  - Formed stool specimens will be rejected by the lab as CDI tests are not approved for testing formed stools.
  - Do not repeat testing within 7 days during the same episode of diarrhea. Other causes of diarrhea should be investigated if diarrhea is persistent after a negative C. difficile test.
  - *C. difficile* testing should not be performed as a test of cure. Tests may remain positive even after effective treatment.

- **Diagnosis** is best supported by presence of signs or symptoms of CDI + a positive stool test for the organism/toxin OR colonoscopic or histopathologic findings of pseudomembranous colitis.

- A multi-step approach is recommended for *C. difficile* testing. At WFBH, a *C. difficile* EIA test is used which simultaneously detects the antigen and the toxin. Results of both the antigen and the toxin EIA tests are reported together.

- Polymerase chain reaction (PCR) testing for *C. difficile* is overly sensitive, and it is no longer recommended alone due to risk of false-positives. The PCR may be useful to adjudicate discrepant EIA results among patients with clinical features strongly suggestive of CDI. However, the decision to adjudicate should not delay initiation of therapy for such patients. PCR testing for *C. difficile* requires prior authorization from CAUSE or via formal ID consultation.

- Enteric Contact Precautions should be in place for patients with suspected CDI. *C. difficile* colonization is frequently acquired through health system exposure, emphasizing the importance of infection control measures. Handwashing with antimicrobial soap and water is preferred over alcohol-based products. Contact precautions should continue for at least 48 hours after cessation of diarrhea.

**Risk factors**

- Recent antimicrobial or antineoplastic agent use (previous 12 weeks)
- Advanced age
- Duration of hospitalization
- Severity of illness
- Recent health care exposure (previous 12 weeks)
- Alteration in gastrointestinal tract (ulcerative colitis, GVHD, GI surgery)
- Transplant recipients or patients with chronic kidney disease

*Almost every antibiotic has been associated with *C. difficile* infection (High risk: 3rd/4th generation cephalosporins, fluoroquinolones, carbapenems, and clindamycin)*
### Treatment Principles

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<tr>
<th>Key Points</th>
<th>Rationale</th>
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<td>Discontinue offending antibiotics or de-escalate as soon as possible</td>
<td>Concurrent antibiotics may interfere with resolution of CDI and may increase the risk of recurrence. If continuation of systemic antibiotics is required, ID consultation or discussion with CAUSE delegate is recommended to determine optimal selection and duration of concurrent antibiotic.</td>
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<td>Avoid gastric acid suppression if possible</td>
<td>Gastric acid suppression, especially with proton pump inhibitors, is a risk factor for CDI, in both hospitalized and ambulatory patients. Re-evaluation of the need for such therapies should take place at regular intervals.</td>
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<td>Avoid anti-peristaltic agents (e.g. loperamide)</td>
<td>Use of anti-peristaltic agents may obscure symptoms and precipitate toxic megacolon.</td>
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<td>Surgical intervention (colectomy)</td>
<td>Colorectal or General Surgery consultation should be considered in patients with rapidly progressive severe CDI, megacolon, colonic perforation, acute abdomen, or patients with septic shock and associated organ failure.</td>
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<td>Probiotics</td>
<td>There is insufficient data to recommend probiotics as adjunctive treatment of CDI.</td>
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<tr>
<td>Cholestyramine</td>
<td>There is insufficient data to recommend cholestyramine as adjunctive treatment of CDI. Cholestyramine has the potential to bind oral vancomycin and reduce its effectiveness.</td>
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### Antibiotic therapy for *Clostridium difficile* Infection

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<tr>
<th>Clinical Definition</th>
<th>Supportive Data</th>
<th>Recommended Treatment</th>
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| Initial episode, non-severe | Leukocytosis with WBC count <15,000 cells/mL AND serum creatinine <1.5 mg/dL | • Preferred: Vancomycin 125 mg orally 4 times daily for 10 days  
• Alternative treatment if vancomycin is unavailable: Metronidazole 500 mg orally 3 times daily for 10-14 days |
| Initial episode, severe | Leukocytosis with WBC count ≥ 15,000 cells/mL OR serum creatinine ≥ 1.5 mg/dL | • Preferred: Vancomycin 125 mg 4 times daily for 10 days  
• Alternative treatment if vancomycin is unavailable: Fidaxomicin\(^b\) 200mg orally 2 times daily for 10 days |
| Initial episode, fulminant | Hypotension or shock, ileus, megacolon | • Preferred: Vancomycin 500 mg orally 4 times daily. Metronidazole 500 mg IV every 8 hours should be administered together with vancomycin. If ileus, consider adding rectal instillation of vancomycin (500mg in 100mL 0.9% sodium chloride PR every 6 hours). |
| First recurrence (second episode) | | • Preferred: Vancomycin 125 mg orally 4 times daily for 10-14 days followed by a prolonged tapered and pulsed vancomycin regimen (e.g. 125 mg orally 2 times daily for 1 week, then once daily for 1 week, and then every 2 or 3 days for 2-8 weeks) |
| Second or subsequent recurrence | | • Preferred: Vancomycin 125 mg orally 4 times daily for 10-14 days followed by fecal microbiota transplantation (GI consultation recommended) |

\(^{a}\) For patients without pre-existing renal dysfunction; \(^{b}\) Fidaxomicin requires prior authorization by CAUSE or formal ID consultation for inpatient use.

### Preventing Recurrence of CDI

In a prospective, controlled clinical trial, the addition of bezlotoxumab to anti-*Clostridium difficile* therapy resulted in fewer cases of CDI recurrence. It had the greatest benefit among patients with the highest risk for CDI recurrence, including patients age ≥ 65 years, immunocompromised, severe CDI or Zar score ≥ 2, and a history of one or more recurrences. However, the effect was relatively small (11% reduction in absolute percent of patients with recurrence versus placebo).

Bezlotoxumab may be considered for patients with risk factors for CDI recurrence AND only after the patient has failed previous therapies, including fecal microbiota transplantation. Of note, bezlotoxumab is restricted to the Gastrointestinal (GI) and Infectious Diseases (ID) clinic setting.