Goal:

Guide proper ordering of the CDI PCR and optimize clinical outcomes by recommending medication therapy stratified by risk of CDI recurrence.

Key Points:

- *C. difficile* is a spore-forming, gram-positive, anaerobic bacillus that produces toxins. *C. difficile* accounts for up to 25% of episodes of antibiotic-associated diarrhea and is the most common cause of healthcare-associated diarrhea
- Recognize risk factors for CDI
- Guide appropriate PCR ordering for diagnosis of CDI
- Review techniques for prevention of infection and transmission, including enteric contact precautions
- Identify risk factors for CDI recurrence to determine optimal initial CDI treatment aimed at preventing recurrence

*C. difficile* Infection (CDI)

- Patient exhibits clinical symptoms to include:
  - **Diarrheal stools**: frequent, watery, unformed (conforms to the shape of a container), ≥ 3 per day, and a history of antibiotic exposure
  - **Fever**
  - **Loss of appetite**
  - **Nausea**
  - **Abdominal pain, tenderness, or cramping**
- Stool sample is positive for *C. difficile* by polymerase chain reaction (PCR).

Transmission

- *C. difficile* is shed in feces. Any surface, device, or material (e.g., commodes, bathing tubs, or electronic rectal thermometers) that become contaminated with feces may serve as a reservoir for *C. difficile* spores.
- *C. difficile* spores can be transferred to patients via the hands of healthcare personnel and by a non-disinfected environment.

Risk Factors

- **Prior antibiotics**: clindamycin, cephalosporins, carbapenems, piperacillin-tazobactam and fluoroquinolones are notoriously associated with CDI and should be avoided, especially in patients with other risk factors for or a history of CDI. Alternative agents should be considered.
- Proton pump inhibitors (PPIs) and H2 blockers
- Gastrointestinal surgery and/or manipulation

- Long length of stay in healthcare settings (>14 days)
- Serious underlying illness
- Immunocompromised (e.g., solid tumor malignancy on chemotherapy, hematopoietic stem cell transplant, neutropenia, solid organ transplant, AIDS)
- Advanced age (≥ 65 years)

Testing for Diagnosis

- See Appendix A and B for risk factors, severity of illness, testing / decision support.
- Testing for *C. difficile* toxin B gene by PCR should **only** be ordered in patients with ≥ 3 unformed watery stools in a 24 hour period.
- **Note**: Concurrent receipt of laxatives or opioid antagonists within 24 hours may cause loose stools or an unanticipated surge in output and should be taken into consideration prior to ordering of CDI testing.
- Testing of formed stool will be rejected unless ileus is suspected; if so, the lab must be notified. **Note**: It is quite rare (< 1% cases) for ileus to be caused by *C. difficile*.
- **Note**: To obtain a diagnosis of CDI in the absence of a stool sample, i.e., critically ill patient, one may proceed with flexible sigmoidoscopy to evaluate for the presence of colonic pseudomembranes.
- The utility of the cytotoxin assay for diagnosing active *C. difficile* infection vs. other diarrheal etiologies is limited based on internal data. This test should be used with caution in this setting. Clinical expertise should be used to determine colonization vs. active infection.

- Collect a minimum of 1 mL of stool in a sterile screw-capped container or white-top container of the 3-tube stool collection kit; transport to the lab within 24 hours at room temperature.
- Specimens received after 24 hours without refrigeration will be rejected.
- Place an order for enteric contact isolation.
- Order **only one** stool specimen for *C. difficile* testing of diarrheal episodes.
- Outpatient practitioners will be notified of positive results within 24 hours of receipt in the lab.
- Once a CDI diagnosis is made, it is **NOT** necessary to perform any additional *C. difficile* testing. **PCR is not a test of cure**; it can remain positive for many weeks.
- Due to the high sensitivity of the PCR assay, if diarrhea persists, a repeat assay on a patient with a previously negative *C. difficile* result can be considered at 7 days.
Potential Complications

- Pseudomembranous colitis (PMC)
- Toxic megacolon
- Colon perforation
- Sepsis, Death
- Consider consultation to Infectious Diseases
- Consider consultation to Acute Care Surgery if there is no improvement after 3-5 days of appropriate therapy.
- Recommend immediate/urgent Acute Care Surgery consultation for fulminant or recurrent disease prior to the development of shock or multi-organ system failure due to *C. difficile*.

Prevention

- Minimize the number and duration of antimicrobial agents prescribed.
- Minimize use of PPIs and H₂ blockers.
- Discontinue laxatives, alvimopan (Entereg), methylaltrexone (Relistor) when not absolutely needed to avoid unnecessary CDI testing.
- Consider use of probiotics to prevent recurrence.

Enteric Contact Precautions

- If suspect or proven CDI, patient must be in enteric contact precautions (use orange signage).
- Perform hand hygiene with soap and water prior to leaving the room.
- Alcohol hand rub is NOT effective against *C. difficile* spores.
- Use patient-specific dedicated equipment.
- Continue precautions until diarrhea resolves.
- Clean and disinfect all environmental surfaces and reusable devices with bleach-wipes.
- All enteric contact isolation rooms are to be cleaned with a sporicidal agent daily and upon discharge.
- Ultraviolet disinfection is used daily in bathrooms and as feasible at patient discharge.

Treatment

See Appendix A for recommendations on risk assessment and decision support, and Appendix B for treatment options.

- In some patients, *C. difficile* symptoms will resolve within ~3 days by discontinuing antibiotic(s).
- *C. difficile* infection can be assessed by evaluating clinical signs/symptoms and risk factors for CDI.
  - See Appendix A.
- Do not attempt to treat or decolonize asymptomatic *C. difficile* carriers.
- If a patient fails to respond to current CDI therapy after 72 hours (i.e., elevated WBC, persistent fevers, high stool output), consider switching or escalating therapy (i.e., combination therapy) and/or obtain an Infectious Diseases consult for assistance.
- After successful treatment, retesting of asymptomatic patients is NOT recommended.
- If antibiotics are required for a concurrent infection, prolonged CDI treatment (i.e., secondary prophylaxis) can be decided on a case-by-case basis for patients who are receiving high risk antibiotics for at least 7 days.
  - See footnote #2 on Appendix A for list of high risk antibiotics
  - See Appendix B, Table 3 for dosing
- Avoid use of anti-peristaltic agents, which may obscure symptoms and precipitate toxic megacolon.
- Cholestyramine, colestipol, and other anion-exchange resins bind vancomycin, so should not be used in the management of *C. difficile* infections.

Note: See OSUWMC Fecal Microbiota Transplant (FMT) for the Treatment of Clostridium difficile Infection guideline for additional information on treating *Clostridium difficile*.

Patient Education Materials

- *Clostridium difficile (C. difficile)*
- Preventing the Spread of Infection

References


• Birch T, et al (2018). Efficacy of bezlotoxumab based on timing of administration relative to start of antibacterial therapy for Clostridium difficile infection. JAC. [Epub ahead of print]


### Quality Measures

- Number of patients with *C. difficile*
- Hospital-associated rates and comparisons
- Hand hygiene compliance
- Readmissions due to *C. difficile*

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### Guideline Approved


**Disclaimer:** Clinical practice guidelines and algorithms at The Ohio State University Wexner Medical Center (OSUWMC) are standards that are intended to provide general guidance to clinicians. Patient choice and clinician judgment must remain central to the selection of diagnostic tests and therapy. OSUWMC’s guidelines and algorithms are reviewed periodically for consistency with new evidence; however, new developments may not be represented.
Appendix A. *C. difficile* Risk Assessment and Decision Support

Documented diarrhea?

- De-escalate laxatives and opioid antagonists.\(^1\)
- Reassess in 24 hours.

Have laxatives been ordered and has the patient received them within 24 hours?

- ≥ 3 stools/24 hours?
  - Yes
    - Order enteric precautions.
    - Collect stool for *C. difficile*.
  - No
    - ≥ 3 stools/24 hours?
      - Yes
        - Order enteric precautions.
        - Collect stool for *C. difficile*.
      - No
        - Do not order *C. diff* PCR (cancel if there is an existing order).
        - Consider alternate etiologies.

Does patient meet ANY Major Criteria* -or-

- High risk antibiotic ≥ 7 days\(^2\)
- WBC ≥ 15K
- CDI in past 6 months

Does patient meet ANY Major Criteria* -or-

- High risk antibiotic ≥ 7 days\(^2\)
- WBC ≥ 15K
- CDI in past 6 months

Table 1. Major Criteria

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td></td>
</tr>
<tr>
<td>≥ 2 admissions in previous 60 days</td>
<td></td>
</tr>
<tr>
<td>Prolonged length of stay ≥ 2 weeks</td>
<td></td>
</tr>
<tr>
<td>Multiple( ≥ 3) antibiotics given concomitantly within 72 hours of CDI testing</td>
<td></td>
</tr>
<tr>
<td>Immunocompromised(^3)</td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation ≥ 96 hr when CDI test is ordered</td>
<td></td>
</tr>
<tr>
<td>Recent albumin ≤ 2.5 gm/dl within 7 days of CDI testing</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\) Opioid antagonists include agents such as: Entereg ® (alvimopam), Relistor ® (methylnaltrexone), etc.

\(^2\) High risk antibiotic defined as 3rd/4th generation cephalosporin, carbapenem, piperacillin/tazobactam, fluoroquinolones, and clindamycin

\(^3\) Defined as solid tumor malignancy on chemotherapy, hematopoietic stem cell transplant, neutropenia, solid organ transplant, AIDS
Appendix B. Treatment of C. difficile Infection

<table>
<thead>
<tr>
<th>Clinical Definition</th>
<th>≤2 Risk Factors For Recurrence</th>
<th>≥3 Risk Factors For Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial episode (mild to severe)</td>
<td>Vancomycin</td>
<td>Fidaxomicin*</td>
</tr>
<tr>
<td>Second episode (i.e. first recurrence**)</td>
<td>Vancomycin taper OR Fidaxomicin*</td>
<td>(Vancomycin taper OR Fidaxomicin*) PLUS Bezlotoxumab*^&amp;</td>
</tr>
<tr>
<td>Third episode (i.e. second recurrence**)</td>
<td>(Vancomycin taper OR Fidaxomicin*) PLUS Bezlotoxumab*^&amp;</td>
<td>FMT</td>
</tr>
<tr>
<td>Fourth episode (i.e. third recurrence**)</td>
<td>FMT</td>
<td>Repeat FMT</td>
</tr>
<tr>
<td>Fulminant**(for any episode)</td>
<td>ADD Metronidazole IV^ and rectal vancomycin if complete ileus</td>
<td></td>
</tr>
</tbody>
</table>

*Fidaxomicin and bezlotoxumab require prior approval between 8 am - 5 pm, 7 days a week. Orders received between 8 am - 5 pm must have an authorization code obtained from an Infectious Diseases Consult, the Antimicrobial Stewardship Program (ASP) on-call pager (#9394), or Tiered restriction from specialty practice pharmacists for fidaxomicin for initial CDI episode, and ASP only for bezlotoxumab.

**Recurrence is defined as the patient having ≥3 unformed watery stools in a 24-hour period, >2 weeks and <8 weeks of completing CDI therapy

***Fulminant is defined as hypotension or shock, ileus, or megacolon

^Must have received fidaxomicin treatment course previously before using concurrently with Bezlotoxumab

&Must be given between day 1 and day 10 of C. difficile treatment. Defer to outpatient infusion when able.

#Consider discontinuing when diarrhea improves due to decreased benefit when output decreases

Note: See OSUWMC Fecal Microbiota Transplant (FMT) for the Treatment of Clostridium difficile Infection guideline for additional information on treating C. difficile. A Fecal Microbiota Transplant (FMT) can be considered for patients meeting any of the following criteria:

- Recurrent CDI after ≥2 episodes of mild-to-moderate CDI and failure to respond to appropriate antimicrobial treatment
- ≥2 episodes of severe CDI resulting in hospitalization and significant morbidity within 1 year.
- Severe first episode of active CDI requiring hospitalization and non-responsive to maximal medication therapy.

### Table 1. Risk Factors for Recurrence

<table>
<thead>
<tr>
<th>Age &gt;65 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broad spectrum antibiotics* during or 1 month after C. difficile treatment</td>
</tr>
<tr>
<td>Immunocompromised**</td>
</tr>
<tr>
<td>Severe C. difficile Infection (CDI Score ≥3) (Refer to Table 2)</td>
</tr>
<tr>
<td>Proton Pump Inhibitor</td>
</tr>
<tr>
<td>NAP1 Strain</td>
</tr>
</tbody>
</table>

*Includes 3rd and 4th generation cephalosporins, carbapenems, piperacillin/tazobactam, fluoroquinolones, and clindamycin

**i.e., solid tumor malignancy on chemotherapy, hematopoietic stem cell transplant, neutropenia, solid organ transplant, AIDS

### Table 2. CDI Severity of Illness Score

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Points*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever (100.4°F)</td>
<td>1</td>
</tr>
<tr>
<td>Ileus</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP &lt;100 mmHg</td>
<td>1</td>
</tr>
<tr>
<td>WBC ≥15,000**</td>
<td>1</td>
</tr>
<tr>
<td>WBC ≥30,000**</td>
<td>2</td>
</tr>
</tbody>
</table>

CT Scan Findings***

- thickened colonic wall, colonic dilation, ascites

| 1 finding                      | 1 |
| 2 findings                    | 2 |

*Severe disease is associated with CDI Score ≥3

**Any single reading within 3 days of CDI diagnosis

***Obtaining a CT scan is not mandatory
Table 3. Antibiotic Regimens

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dose and Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin (standard)</td>
<td>125 mg PO QID x10 days</td>
</tr>
<tr>
<td>Vancomycin (fulminant*)</td>
<td>500 mg PO QID x10 days</td>
</tr>
<tr>
<td>Vancomycin (rectal)</td>
<td>500 mg PR QID x10 days</td>
</tr>
<tr>
<td>Vancomycin taper</td>
<td>125 mg PO QID x10-14 days, 125 mg PO BID x7 days, 125 mg PO daily x7 days, 125 mg every 2-3 days x2-8 weeks</td>
</tr>
<tr>
<td>Vancomycin prophylaxis**</td>
<td>125 mg PO BID throughout concomitant antibiotic course plus 7 days after completion</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>200 mg PO BID x10 days</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg IV Q8H x10 days</td>
</tr>
<tr>
<td>Bezlotoxumab</td>
<td>10 mg/kg IV once</td>
</tr>
</tbody>
</table>

*Based on improved outcome in those with recurrences and higher vancomycin dose and less *C. difficile* recovered in stool (McFarland LV, 2002); and consensus national recommendations (McDonald LC, 2017)

**When clinically indicated, vancomycin prophylaxis is recommended regardless of CDI treatment choice