CARILION CLINIC
Antimicrobial Stewardship

Guideline for the Treatment of *Clostridioides difficile* Infection in Adults and Children

Disclaimer: These guidelines are not intended to replace clinical judgement. Recommendations are intended to optimize the treatment of the majority of patients but cannot account for all clinical situations or presentations. An Infectious Diseases consultation is recommended for complex patients.

Clinical Presentation[1,2]

- Unexplained new onset of diarrhea (≥3 unformed stools over 24 hours) AND evidence of infection (unexplained leukocytosis, fever, abdominal discomfort, etc)
- Complications: dehydration, electrolyte abnormalities, renal failure, sepsis, death

C. difficile Diagnosis[1]

- Ordering *C. difficile* Testing at Carilion Clinic
  - Search for new test by entering "CDIFPR." This should be the initial test for all patients with suspected *C. difficile*
- Two components
  - Step 1: *C. difficile* Toxin B PCR
    - Turnaround time: 1-4 hours
    - If this test is negative, the patient does not have CDI and Step 2 will not be performed
    - If this test is positive, Step 2 testing is conducted
  - Step 2: *C. difficile* Cytotoxicity Assay (CTA)
    - Turnaround time: 48-72 hours
    - If the test is positive, the patient likely has CDI
    - If the test is negative, the patient does NOT have CDI[3]
      - Sensitivity (true positive rate) is estimated to be 99.1% (98.3-100%)
      - Specificity (true negative rate) is estimated to be 99.3% (98.7-100%)
- Testing should only be ordered for patients with ≥3 watery stools within 24 hours AND clinical suspicion of infection
- Testing should NOT be ordered if the patient has formed stools or recent laxative use
- CTA reflex can take up to 72 hours to result
  - The patient should remain in isolation until negative CTA results
  - If suspicion is relatively low and the patient is clinically stable, treatment may be deferred until Step 2 results at the clinical discretion of the provider
- Testing should not be performed as a "test of cure." If negative, this test should not be repeated to rule out *C. difficile* unless several days have passed or the clinical syndrome has changed

Pediatric Testing Recommendations[1]

- Testing for *C. difficile* infection may be performed in children ≥2 years of age with prolonged or worsening diarrhea (≥3 unformed stools within 24 hours)
- Diagnostic testing for *C. difficile* in children <2 years of age is not routinely recommended due to high rates of colonization in this population. Consider performing in patients with diarrhea after other infectious and noninfectious causes have been ruled out

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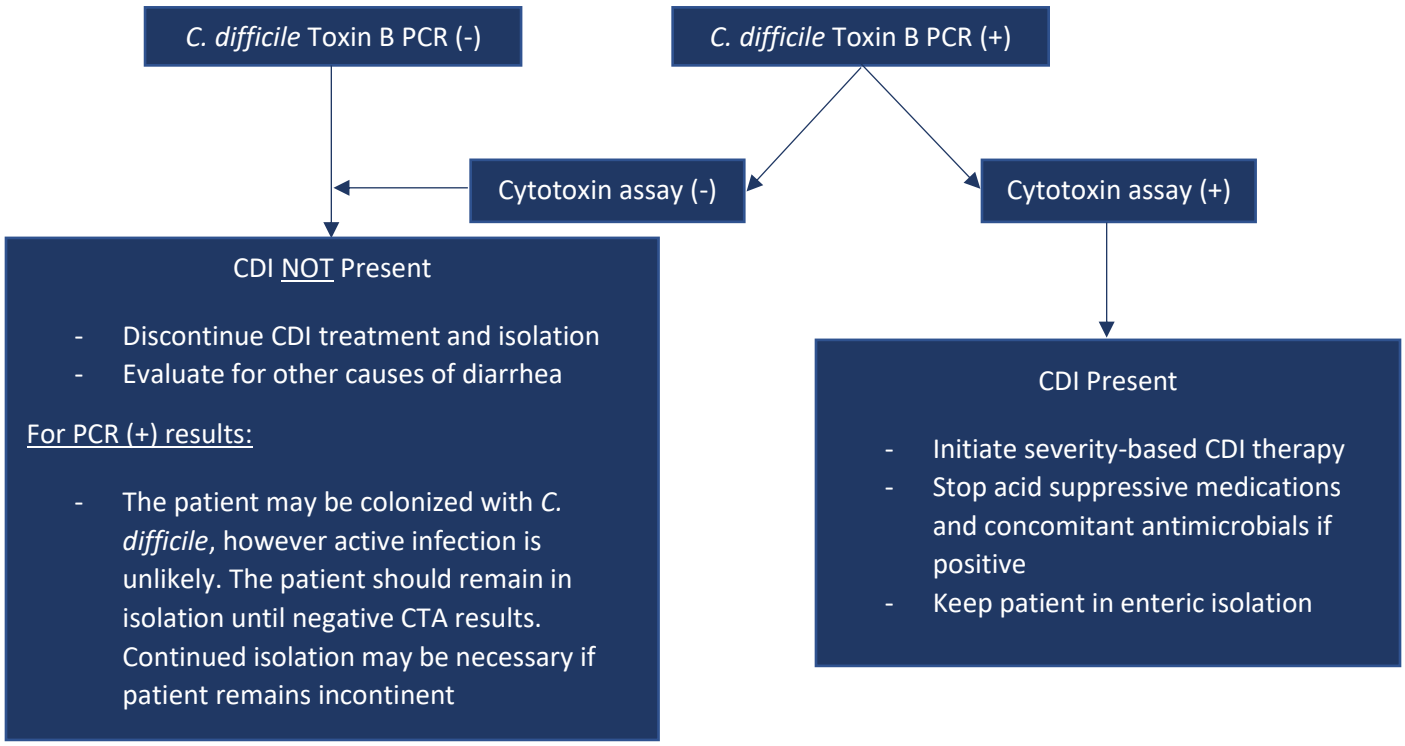
C. difficile Test Interpretation Algorithm at Carilion Clinic



Risk Factors for Initial *C. difficile* Infection[1]

Age ≥65	Recent Antibiotic Use	Proton Pump Inhibitors
GI Manipulation	Chemotherapy	Immune Compromise

Classification of Risk for *C. difficile* Infection by Antibiotic Class[4]

Antibiotic Risk		
High Risk	**Moderate Risk**	**Low Risk***
Clindamycin Fluoroquinolones Cephalosporins (second generation or above)	Vancomycin Penicillins Cephalosporins (first generation) Carbapenems Macrolides Metronidazole	Aminoglycosides Tetracyclines Sulfamethoxazole-Trimethoprim Rifampin Nitrofurantoin
*Low risk does not mean no risk. ALL antibiotics can cause *C. difficile* infections. The use of multiple antibiotics and for duration longer than necessary also increase risk.		

Recurrence[1,5,6]

- Symptom onset meeting above diagnostic criteria AND occurring within 8 weeks from the resolution of symptoms from a previous episode
    - Note: After clinical response, stool consistency and frequency may take weeks to return to normal
- Associated with significant impacts on quality of life, rate of subsequent recurrences, and healthcare costs

Risk Factors for *C. difficile* Recurrence[1,7,8]

Age ≥65

Concomitant Non-CDI Antibiotic Use

Proton Pump Inhibitors

Previous Episode within 6 Months

Immune Compromise

Renal Insufficiency

Severe CDI Presentation

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Assessment of Severity in Adult Patients[1,2]

Non-severe	Serum creatinine <1.5 mg/dL AND white blood cell count ≤15 K/uL
Severe	Serum creatinine ≥1.5 mg/dL OR white blood cell count >15 K/uL
Fulminant	Presence of hypotension or shock requiring vasopressor support, ileus, toxic megacolon

Adult Treatment Recommendations for Non-severe and Severe *C. difficile*[1,2]

<table>
<tr><th colspan="2">Episode</th><th>First-Line Therapy</th><th>Alternative Therapy</th><th>Adjunctive Therapy</th></tr>
<tr><td rowspan="2">1st Episode</td><td>High Risk of Recurrence[a], Severe or Non-severe</td><td>Fidaxomicin[b] 200 mg PO BID x10 days</td><td>Vancomycin 125 mg PO q6h x10 days</td><td rowspan="2"></td></tr>
<tr><td>Low Risk of Recurrence, Non-severe</td><td>Vancomycin 125 mg PO/NG q6h x10 days</td><td>Fidaxomicin[c] 200 mg PO BID x10 days</td></tr>
<tr><td colspan="2">2nd Episode</td><td>Fidaxomicin[b] 200 mg PO BID x10 days</td><td>Vancomycin 125 mg PO/NG q6h x10 days</td><td>Bezlotoxumab[d]
See Appendix A for further details</td></tr>
<tr><td colspan="2" rowspan="2">≥3rd Episode</td><td colspan="3">Strong recommendation: ID consult, early surgical evaluation, evaluation of fecal microbiota transplant</td></tr>
<tr><td colspan="2">Vancomycin 125 mg PO/NG q6h x10 days followed by:
125 mg BID x1 week,
125 mg daily x1 week,
125 mg every 48-72 hours x2-8 weeks</td><td>Bezlotoxumab[d]
See Appendix A for further details</td></tr>
</table>

[a]Risk factors for recurrence: age ≥65, concomitant non-CDI antibiotic use, proton pump inhibitor use, previous episode within 6 months, immunocompromise, renal insufficiency, severe CDI presentation

[b]Fidaxomicin is cost-prohibitive for most skilled nursing facilities. Patients who are stable for discharge may be switched to oral vancomycin upon discharge to finish 10-day course. Stable patients should not be kept inpatient to complete fidaxomicin courses and delay placement

[c]Metronidazole 500 mg PO q8h x10-14 days may be used as an alternative to PO vancomycin in non-severe outpatients in areas where fidaxomicin and vancomycin are not available

[d]Bezlotoxumab should only be used in patients with a previous CDI episode within 6 months AND ≥1 further risk factor for recurrence validated for bezlotoxumab use. See Appendix A for further details regarding bezlotoxumab use

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Adult Treatment Recommendations for Fulminant *C. difficile*[1,2]

Vancomycin 500 mg PO/NG q6h	**AND**	Metronidazole 500 mg IV q8h	**+/-**	Rectal vancomycin
Duration of therapy may be based on clinical course. Therapy may be extended beyond 10-14 days. Metronidazole may not be required for the entire course.				

Pediatric Treatment Recommendations[1,9,10]

Severity		First-Line Therapy	Alternative Therapy
Non-severe	First or Second Episode	Any age: Vancomycin 10 mg/kg PO q6h (max: 125 mg/dose) x10 days **OR** Age ≥6 months: Fidaxomicin 16 mg/kg PO q12h (max: 200 mg/dose) x10 days	Metronidazole 7.5 mg/kg PO q8h (max: 500 mg/dose) x10 days
	Third Episode or Greater	Vancomycin 10 mg/kg PO q6h (max: 125 mg/dose) x10-14 days followed by: Vancomycin 10 mg/kg PO q12h (max: 125 mg/dose) x1 week, 10 mg/kg PO daily (max: 125 mg/dose) x1 week, 10 mg/kg PO q48-72h (max: 125 mg/dose) x2-8 weeks	
Severe/Fulminant[a]	Vancomycin (PO or PR) 10 mg/kg q6h (max: 500 mg/dose) x10 days + Metronidazole IV 10 mg/kg q8h (max: 500 mg/dose) x10 days		
[a]Any of WBC >15 K/uL, acute kidney injury, hypotension/shock, ileus, megacolon			

Prevention of Recurrence:

- Unnecessary proton pump inhibitors should always be discontinued
- Concomitant antibiotics should be discontinued when clinical evidence does not support additional infectious diagnoses
- Probiotics have minimal benefit in active *C. difficile* infection. Probiotic use during active treatment is NOT recommended. However, probiotics following treatment course may be beneficial. Mixed bacterial cultures (i.e. kefir, yogurt) may be more beneficial than single strain capsules. Probiotics should be used with caution in immunocompromised patients[11-13]
- Prophylaxis with oral vancomycin is not routinely recommended due to lack of strong clinical data supporting use. Oral vancomycin has been associated with alterations in the gastrointestinal microbiota, including increased rates of *Candida* spp. and vancomycin-resistant

Enterococcus colonization.[14,15] See Guidelines for *Clostridioides difficile* Prophylaxis in Adults for further details

Appendix A

Bezlotoxumab (Zinplava™) for the Prevention of *C. difficile* Recurrence at Carilion Clinic

Bezlotoxumab is a monoclonal antibody targeting *Clostridioides difficile* toxin B and is currently approved as an adjunct for the management of CDI by the US Food and Drug Administration. Guidelines by the Infectious Society of America and the American College of Gastroenterology recommend bezlotoxumab as an adjunct to standard-of-care for patients with a recurrent CDI within the previous 6 months or patients with first CDI episode and risk factors for recurrence.[1,16] Data from phase III clinical trials suggest bezlotoxumab dosed as 10 mg/kg once given over 60 minutes in combination with oral therapy may reduce the rate of recurrent CDI.[17] A post hoc analysis of these trials found the greatest reduction in rate of recurrence in patients with at least 1 risk factor, with the most common risk factor being history of previous CDI episode.[18] Bezlotoxumab is not dose-adjusted based on weight, renal function, or hepatic function. Adverse effects of bezlotoxumab include nausea, pyrexia, headache, and infusion related reactions. Patients with underlying congestive heart failure may be at increased risk acute heart failure within 12 weeks of receiving bezlotoxumab. This is not thought to be infusion related. Current recommendations from the manufacturer are to use with caution in patients with congestive heart failure, limiting use only to those wherein benefit outweighs risk.[19] No drug interactions are expected to occur. Bezlotoxumab has no antibacterial effect and must be given only as a concomitant therapy at any point during therapy in patients currently on treatment for CDI.[20] There is currently no evidence for the use of bezlotoxumab in patients with fulminant CDI.

Inclusion Criteria for Bezlotoxumab Use

Bezlotoxumab may be prescribed in patients currently receiving therapy for active CDI and have at least one prior episode of CDI within 6 months and have ≥1 risk factors for recurrence. Risk factors for CDI include:

- Age ≥65 years
- Immune compromise
- Severe CDI presentation (SCr ≥1.5 mg/dL OR WBC ≥15 K/uL)

Infectious Diseases Specialty consultation is required in all settings to prescribe bezlotoxumab. Patients who meet the following criteria should NOT receive bezlotoxumab regardless of the number of risk factors:

- Age <18 years
- Pregnancy and/or lactation
- Negative cytotoxin assay
- Not on active CDI therapy

Patients meeting the above criteria may be referred to Carilion Roanoke Memorial Hospital 1S Infusion Center to receive bezlotoxumab 10 mg/kg over 60 minutes once. For non-medical reasons, bezlotoxumab infusion cannot be performed on the date of discharge. However, patients should be instructed to return to the hospital to receive bezlotoxumab before completion of *C. difficile* therapy. Bezlotoxumab is supplied in 40 mL vials with a concentration of 25 mg/mL and must be diluted with 0.9% sodium chloride injection or 5% dextrose injection to a final concentration of 1 mg/L to 10 mg/mL.

Bezlotoxumab Ordering Procedure

☐ Evaluate for appropriateness of bezlotoxumab use in discussion with Infectious Diseases physician

☐ Infectious Diseases physician places referral for bezlotoxumab 10 mg/kg (ABW) IV once for patients meeting the above inclusion criteria

- No premedication is required

☐ Confirm patient appointment at 1S Infusion Center

☐ Place order 24 hours prior to appointment

☐ Document the start date and end date of *C. difficile* antibiotic therapy in order notes

☐ Sign and hold order

☐ Nurse releases signed order during appointment and initiates infusion

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