Health PEI

ANTIMICROBIAL STEWARDSHIP SUBCOMMITTEE

Antimicrobial Therapy for *Clostridioides difficile* Infection in Adults

Definitions

- *Clostridioides difficile* infection (CDI) is defined by new onset of three or more unexplained unformed or watery stools* in 24 hours **AND** either:
  - Positive *C. difficile* testing results OR
  - Colonoscopic or histopathologic findings of pseudomembranous colitis

  *Note: patients with severe disease complicated by toxic megacolon or ileus may not have loose stools; use clinical judgment
- Recurrent CDI: Recurrence of CDI within 8 weeks following the onset of a successfully treated previous episode.

Investigations & Work-up

- Assess patient and consider other causes of diarrhea or loose stools (i.e. medications, underlying conditions, or interventions such as enteral feeds)
- If clinical suspicion of CDI, send stool for *C. difficile* testing. May consider retesting if high clinical suspicion of CDI in symptomatic patients with an initial negative test **if** in the setting of worsening illness or a CDI outbreak.
- Do NOT test asymptomatic patients, approximately 3 to 14% of adults admitted to hospital carry *C. difficile*.
- Do NOT complete a test of cure; at least 60% of successfully treated patients will continue to test CDI positive, but do not require therapy if they are asymptomatic.
- Empiric treatment of suspected recurrent CDI without first sending confirmatory testing is discouraged – while up to 30% of patients will have a recurrent episode after first diagnosis of CDI, altered bowel habits with recurrent diarrhea is common and up to 35% test negative for CDI.

Treatment Considerations

- Initiate empiric therapy while waiting for diagnostic testing if a substantial delay in testing is expected OR patient symptoms are consistent with severe CDI.
- Discontinue therapy with the inciting antimicrobial agent if possible
- If discontinuation of concomitant antimicrobials is not possible:
  - De-escalate to the narrowest effective spectrum of activity (see table: Antimicrobials and Risk of CDI) and use the shortest effective duration of therapy
  - Once CDI symptoms have resolved and CDI treatment course has been completed, may consider initiating oral vancomycin prophylaxis for the remaining duration of concomitant antibiotic therapy to decrease the risk of recurrence (see Prevention of Recurrent CDI for details regarding dosing and duration).
- Stop all anti-peristaltic and pro-motility agents unless clearly indicated (e.g., loperamide, diphenoxylate, opioids, metoclopramide, domperidone, etc.)
- Early surgical consultation recommended for patients with CDI who meet one or more of the following clinical indicators associated with poor prognosis:
  - hypotension with or without vasopressors
  - ileus or significant abdominal distention
  - Peritonitis or significant abdominal tenderness
  - altered mental status
  - white blood cell count ≥20,000 cells/mL
  - serum lactate levels >2.2 mmol/L
  - admission to intensive care unit
  - end organ failure (e.g., requiring mechanical ventilation, renal failure)
  - failure to improve after three to five days of maximal medical therapy
- Vancomycin administered intravenously is ineffective for the treatment of CDI

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Treatment – Initial Episode

Severity	Treatment Recommendations
Mild-to-Moderate • WBC lower than 15 x10^9/L **AND** • Serum creatinine less than 1.5 x baseline level[1]	**Initial Episode** Vancomycin 125 mg PO q6h x 10 days[2] **OR** **If contraindication to, treatment failure[4] of or intolerance to oral vancomycin:** Fidaxomicin 200 mg PO q12h x 10 days* **OR** **If the patient cannot access oral vancomycin or fidaxomicin due to prohibitive cost, may consider:** metroNIDAZOLE 500 mg PO q8h x 10 days[2,3]
Severe • WBC greater than or equal to 15 x10^9/L **OR** • Serum creatinine greater than 1.5 x baseline level[1]	**Initial Episode** Vancomycin 125 mg PO q6h x 10 days[2] **OR** **If contraindication to, treatment failure[4] of or intolerance to oral vancomycin:** Fidaxomicin 200 mg PO q12h x 10 days*
Fulminant • Hypotension/shock • Ileus OR megacolon ****Urgent surgical consult required****	**Any Episode** Vancomycin 500 mg PO/NG q6h x 10 days[2] **PLUS** metroNIDAZOLE 500 mg IV q8h[3,5] **OR** **If contraindication to, treatment failure[4] of or intolerance to oral vancomycin:** Fidaxomicin 200 mg PO q12h x 10 days* PLUS metroNIDAZOLE 500 mg IV q8h[3,5] **If ileus or vomiting, ADD to above regimens:** vancomycin 500 mg in 100 mL NS retention enema q6h[6]

[1] In patients where the baseline creatinine level is unavailable, use an absolute serum creatinine level of 135 mmol/L as a breakpoint.
[2] Consider extending treatment duration to 14 days if clinically improving but without symptom resolution by 10 days of therapy.
[3] Avoid the use of metroNIDAZOLE in pregnant or breastfeeding women
[4] Vancomycin treatment failure: defined as 14 days of vancomycin therapy without acceptable clinical improvement and without other identified cause of persistent diarrhea
[5] Continue add-on IV metroNIDAZOLE until the patient is no longer critically ill (usually 5-7 days)
[6] In normal circumstances, vancomycin is not absorbed via the GI tract; however, in fulminant CDI, intestinal epithelial integrity may be disrupted, and could lead to systemic drug absorption. Consider monitoring serum vancomycin levels in patients with fulminant CDI who are receiving high dose vancomycin (500 mg q6h) via the oral and rectal routes concomitantly to rule out drug accumulation.

Treatment – Recurrent Episodes

Category	Treatment Recommendations
First recurrence	Vancomycin 125 mg PO q6h x 14 days **OR** **May consider Vancomycin Taper-Pulse Regimen:** Vancomycin 125 mg PO q6h x 14 days, then 125 mg PO q12h x 7 days, then 125 mg PO q24h x 7 days, then 125 mg PO q48h x 21 days, then 125 mg PO q72h x 21 days, then STOP **OR** **If contraindication to, treatment failure[1] of or intolerance to oral vancomycin**: Fidaxomicin 200 mg PO q12h x 10 days*
Second recurrence	**Vancomycin Taper-Pulse Regimen:** Vancomycin 125 mg PO q6h x 14 days, then 125 mg PO q12h x 7 days, then 125 mg PO q24h x 7 days, then 125 mg PO q48h x 21 days, then 125 mg PO q72h x 21 days, then STOP **OR** Fidaxomicin 200 mg PO q12h x 10 days* Consider consulting infectious disease specialist or medical microbiologist.
Third or more recurrence	Initiate vancomycin 125 mg PO q6h and consult an infectious disease specialist or medical microbiologist.

[1] Vancomycin treatment failure: defined as 14 days of vancomycin therapy without acceptable clinical improvement and without other identified cause of persistent diarrhea

*** Fidaxomicin is restricted in hospital and requires Special Authorization for PEI Pharmacare (10 day course ~$2000)**

Criteria for coverage:

- A second or subsequent recurrence following treatment with oral vancomycin; **or**
- Treatment failure with oral vancomycin for the current CDI episode; **or**
- An intolerance or contraindication to oral vancomycin

- Re-treatment criteria
  - Re-treatment with fidaxomicin will only be considered for an early relapse occurring within 8 weeks of the start of the most recent fidaxomicin course

Clinical Notes:

1. Treatment failure is defined as 14 days of vancomycin therapy without acceptable clinical improvement
2. Intolerant is defined as demonstrating serious adverse effects to treatments. The nature of intolerance(s) must be clearly documented

Claim Notes:

- Should be prescribed by, or in consultation with, an infectious disease specialist/medical microbiologist (preferred) or an internist (if infectious disease or medical microbiology consult is not available)
- Requests will be approved for 200mg twice a day for 10 days

Additional Information

Prevention of Recurrent CDI

- The best method to prevent CDI is to minimize the frequency and duration of exposure to antibiotics frequently associated with CDI.
- The use of proton pump inhibitors (PPIs) has been associated with CDI and may increase the risk of recurrent CDI. Evaluate appropriateness of PPI therapy, and discontinue PPI if use is inappropriate.
- May consider oral vancomycin prophylaxis (OVP) to prevent further recurrence during subsequent non-CDI systemic antibiotic use in patients at high risk of recurrence:
    - Hospitalized for severe CDI in past 3 months AND either:
        - Greater or equal to 65 years old, OR
        - Immunocompromised
    - Recommended dose: vancomycin 125 mg PO once to twice daily for duration of systemic antibiotic use plus 5 days

Probiotics

- Infectious Diseases Society of America (IDSA) states there is insufficient data to recommend the use of probiotics for primary prevention of *C. difficile*.[1] However, probiotics may be considered for those taking antibiotics, particularly those at higher risk of *C. difficile*.[11]
- No consensus in the literature on strain, strength, or dose.[1]
    - Commonly used species: Lactobacillus rhamnosus GG, Lactobacillus casei, Lactobacillus acidophilus, Kefir (*Expert opinion, 1 cup BID-TID, avoid in diabetics), Saccharomyces boulardii, mixed strain formulations (often proprietary blends)
- No consensus on duration of therapy. Can consider fixed 14 day course, duration of antibiotic use, OR duration of antibiotic use and up to 7 days following completion.
- The use of **probiotics may be inappropriate** in the following patient groups: immunocompromised patients, neutropenic patients, patients under the age of 18 (for the purposes of these guidelines) and patients admitted to the ICU.

Antimicrobials and Risk of CDI

Frequently Associated	Occasionally Associated	Rarely Associated
– Fluoroquinolones – Clindamycin – 3rd/4th/5th Generation Cephalosporins – Carbapenems – Beta-lactam/beta-lactamase inhibitors	– Macrolides – Penicillins (narrow spectrum) – 1st Generation Cephalosporins – Sulfamethoxazole/trimethoprim – Sulfonamides	– Aminoglycosides – Tetracyclines – Metronidazole – Vancomycin – Nitrofurantoin – Fosfomycin

Infection Control Precautions

- To prevent transmission, implement contact precautions when CDI suspected or confirmed (3 or more loose watery stools within a 24 hour period):
  - Accommodate patient in a private room (if possible) - if not possible, please consult Infection Prevention and Control
  - Contact precautions (gown and gloves)
  - Soap and water are used instead of alcohol-based hand rub (ABHR) for the physical and mechanical removal of spores.
  - Hand hygiene with soap and water should be performed at the point-of-care and at a designated hand hygiene sink. If a designated hand hygiene sink is not available at the point-of-care, ABHR is used and hand hygiene with soap and water is performed immediately after leaving patient care area.
- In consultation with Infection Control, contact precautions are maintained until:
  - CDI is ruled out, and/or diarrhea is determined as not infectious; or
  - If CDI is confirmed, until symptoms have stopped for at least 48 hours and at least one of the following: a baseline normal bowel movement, a formed bowel movement or no bowel movements.

These guidelines are an adaptation of New Brunswick Anti-infective Stewardship Committee **Antimicrobial Therapy for Clostridioides difficile Infection May 2023**

References:

1. McDonald LC, *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), Clinical Infectious Diseases. 2018. cix1085, https://doi.org/10.1093/cid/cix1085
2. Sirbu BD, et al. Vancomycin Taper and Pulse Regimen with Careful Follow-up for Patients With Recurrent Clostridium difficile Infection. Clinical Infectious Diseases. 2017;65(8):1396–9
3. Loo VG, Davis I, Embil J, *et al*. Association of Medical Microbiology and Infectious Disease Canada treatment practice guidelines for Clostridium difficile infection. Official Journal of the Association of Medical Microbiology and Infectious Disease Canada 3.2, 2018. doi:10.3138/jammi.2018.02.13
4. Vancouver Coastal Health Antimicrobial Stewardship Treatment Guidelines for Common Infections (2011)
5. *Clostridioides (Clostridium) difficile* infection in Adults. Nova Scotia Health Antimicrobial Handbook. May 2019. https://library.nshealth.ca/AMS/Home Accessed: March 31, 2023
6. Guery B, *et al.* MJGT; EXTEND Clinical Study Group. Extended-pulsed fidaxomicin versus vancomycin for Clostridium difficile infection in patients 60 years and older (EXTEND): a randomised, controlled, open-label, phase 3b/4 trial. Lancet Infect Dis. 2018 Mar;18(3):296-307. doi: 10.1016/S1473-3099(17)30751-X. Epub 2017 Dec 19. PMID: 29273269.
7. Skinner AM, *et al.*. A Tapered-pulsed Fidaxomicin Regimen Following Treatment in Patients With Multiple Clostridioides difficile Infection Recurrences. Clin Infect Dis. 2021 Sep 15;73(6):1107-1109. doi: 10.1093/cid/ciab233. PMID: 33714998.
8. Kelly CR *et al.* ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol. 2021 Jun 1;116(6):1124-1147. doi: 10.14309/ajg.0000000000001278. Erratum in: Am J Gastroenterol. 2022 Feb 1;117(2):358. PMID: 34003176.
9. Johnson S, *et al.* Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021 Sep 7;73(5):e1029-e1044. doi: 10.1093/cid/ciab549. PMID: 34164674.
10. Rux C & Sarna K. Is oral vancomycin prophylaxis (OVP) beneficial for secondary prevention of Clostridioides difficile infection (CDI)? Drug Information Group. College of Pharmacy – Chicago. https://dig.pharmacy.uic.edu/faqs/2020-2/november-2020-faqs/is_oral_vancomycin_prophylaxis_ovp_beneficial_for_secondary_prevention_of_clostridioides_difficile_infection_cdi/ Accessed: April 21, 2023
11. Goldenberg, J., Yap, C., Lytvyn, L., Lo, C., Beardsley, J., Mertz, D. and Johnston, B. (2017). Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database of Systematic Reviews.