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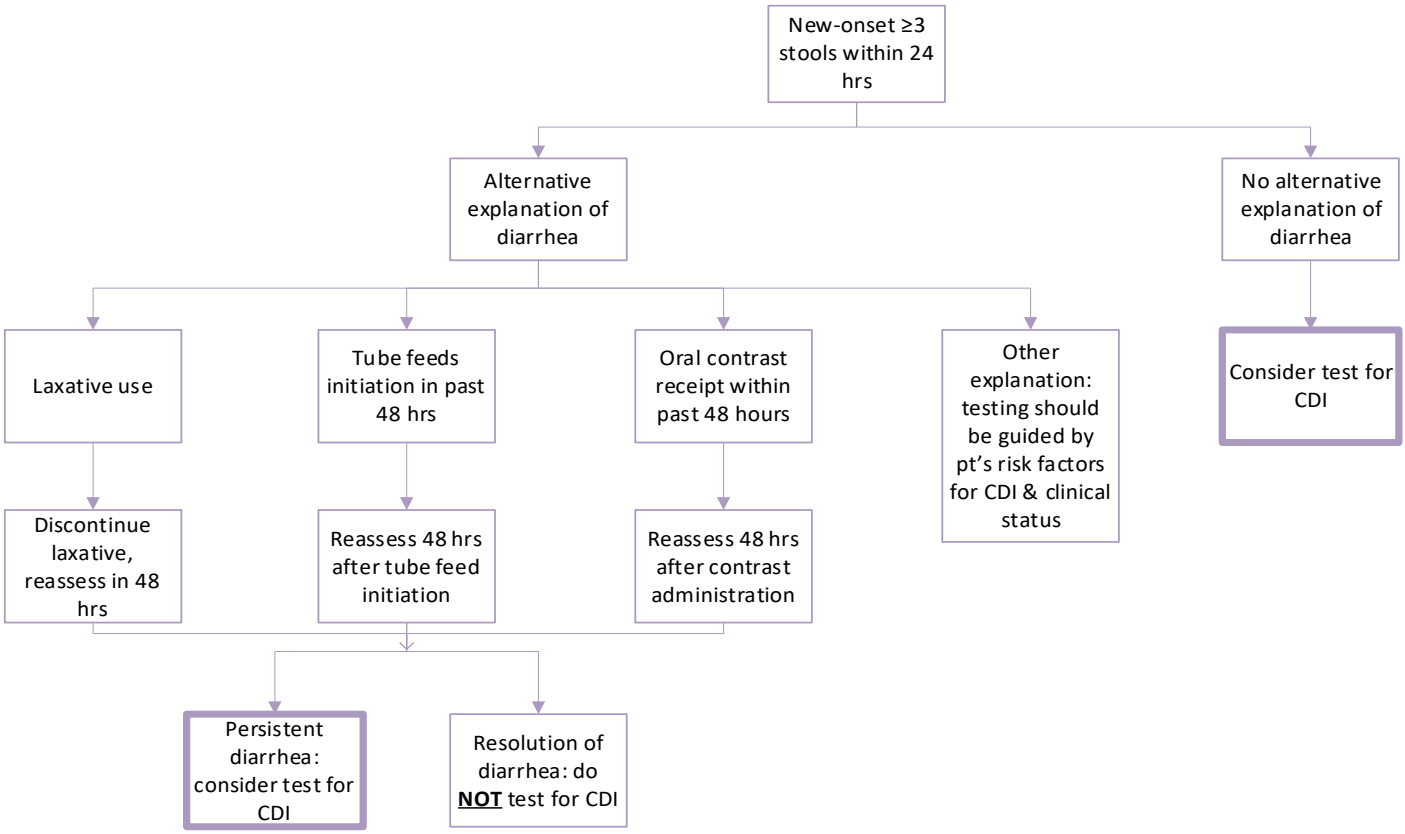
GUIDELINES FOR TREATMENT OF CLOSTRIDIOIDES DIFFICILE COLITIS IN ADULTS

Prior studies show that 3-26% of hospitalized patients are asymptomatically colonized with *C. difficile*. Available assays are not able to distinguish between *C. difficile* infection and colonization, and treatment of asymptomatic colonization is not recommended.

Patients with new-onset diarrhea without an alternative explanation should be considered for CDI testing. Diarrhea is defined as ≥3 unformed stools in 24 hours. A large percentage of hospitalized patients have other reasons for diarrhea, such as laxatives, chemotherapy, and enteral tube feeds. When possible, one should consider first stopping therapies to which diarrhea may otherwise be attributed (e.g., laxatives), and then reassess prior to testing for CDI.



1. The "*Clostridioides difficile* by PCR" assay is the preferred test for CDI. The "Gastrointestinal Pathogen Panel" is a multiplex PCR assay that, in addition to CDI, tests for 21 other primarily community-acquired gastrointestinal pathogens and costs ~3x more than the dedicated C. difficile by PCR" assay. The GI Panel is intended for use in patients with diarrhea that began prior to or within three days of hospitalization and there is concern for other etiologies aside from *C. difficile*. Both tests provide the same diagnostic information regarding C. difficile: a PCR and a toxin result. There is no role for performing both tests simultaneously or performing a *C. diff* PCR after a positive GI Panel result. These practices do not change management, lead to overutilization of testing resources, and should be avoided. Either assay may remain positive for up to 30 days after successful treatment; tests of cure should not be performed. As such, orders for repeat testing within 14 days of positive will be rejected by Microbiology Lab. In addition, repeat testing within 7 days of a negative test will also be rejected by Microbiology Lab due to low likelihood of acute infection within this time frame. The ordering provider will be notified by pager, and in situations with a significant change in clinical status accompanied with high clinical suspicion, may contact the lab to request that testing proceed.
2. In the presence of an ileus, rectal swabs or solid stool in a cup are acceptable specimen types. Rectal swabs must be submitted dry (without transport fluid), as the dilutionary effect of the liquid Amies transport may impact the sensitivity of the *C. difficile* PCR and toxin EIA.

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PCR Result	EIA Toxin Result	Interpretation
Negative	--	No *C. difficile* present. The negative predictive value of this test for ruling-out C. difficile-associated diarrhea approaches 99%
Positive	Positive	Toxigenic *C. difficile* present.
Positive	Negative	The gene that produces *C. difficile* toxin is detected, but toxin is not detected. This may represent either colonization or active clinical infection. Clinically correlate to determine if treatment is warranted.

Treatment of *Clostridioides difficile* colitis

For all patients:
- Discontinue/change antibiotics if possible.
- Avoid PPI/H2 blockers without an appropriate indication.
- Implement infection control measures

Clinical Setting	Initial Episode[1,2]	First Recurrence[1,2,4] ≤ 90 days from prior episode	Second Recurrence[1,4,6] ≤ 90 days from prior episode
Non-Fulminant Disease Consider Infectious Diseases and Surgery consultation in patients with severe disease (defined as WBC ≥15,000, absolute neutrophil count ≤500, or SCr ≥1.5 times premorbid level)	Preferred treatment: **Vancomycin** 125 mg PO QID x 10 days Solid organ transplant patients:[5] **Fidaxomicin** 200 mg PO BID x10 days[7,8] OR **Vancomycin** 125 mg PO QID x10 days True vancomycin allergy (not vancomycin infusion reaction): **Fidaxomicin** 200 mg PO BID x10 days **Metronidazole** 500 mg PO TID x10-14 days can be considered in non-severe CDI if above agents are unavailable to patient due to cost	Infectious Diseases consultation is recommended If vancomycin was used for the initial episode: **Fidaxomicin** 200 mg PO BID x10 days[7,8] OR **Fidaxomicin** 200 mg PO BID x5 days then 200 mg PO every other day x20 days[7,8] OR **Vancomycin** 125 mg PO QID x14 days then taper[6] over 5-11 weeks If fidaxomicin was used for the initial episode: **Fidaxomicin** 200 mg PO BID x10 days[7,8] OR **Fidaxomicin** 200 mg PO BID x5 days then 200 mg PO every other day x20 days[7,8]	Infectious Diseases consultation is strongly recommended The following options may be considered in consultation with Infectious Diseases[6]: - Repeat **Vancomycin** taper - **Fidaxomicin** 200 mg PO BID x10 days - **Fidaxomicin** 200 mg PO BID x5 days then 200 mg PO every other day x20 days - Fecal microbiota transplant: OpenBiome (preferred; administered inpatient or outpatient) or Rebyota (outpatient only) - Kefir staggered protocol - Bezlotoxumab 10 mg/kg IV once in addition to standard of care antibiotics for prevention of future recurrence (administered as outpatient)
Fulminant Disease (Hypotension or septic shock, ileus, bowel obstruction, toxic megacolon, bowel perforation or peritonitis)	Surgery and Infectious Diseases Consultation are strongly recommended **Vancomycin** 500 mg PO QID + **Metronidazole** 500 mg IV q8h[3] If ileus, bowel obstruction, or fecal diversion, add **Vancomycin** by enema q6h Duration: Minimum of 14 days of therapy, depending on clinical response.	Surgery and Infectious Diseases Consultation are strongly recommended Repeat primary therapy then taper **vancomycin** over 5-11 weeks[6] Alternative if vancomycin taper cannot be performed: **Fidaxomicin** 200 mg PO BID x10 days	Surgery and Infectious Diseases Consultation are strongly recommended If vancomycin taper was NOT used for the first recurrence: Repeat primary therapy then taper[6] **vancomycin** over 5-11 weeks. If vancomycin taper was used for the first recurrence, the following options may be considered in consultation with Infectious Diseases[6]: - Repeat Vancomycin taper - **Fidaxomicin** 200 mg PO BID x10 days - Fecal microbiota transplant: OpenBiome (administered inpatient or outpatient) - Kefir staggered protocol
	See footnote 6c for fecal microbiota transplant in treatment refractory CDI. See footnote 10 for diverting loop ileostomy protocol.		

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Initial/Recurrent CDI Considerations

1. Failure is defined as no improvement or worsening symptoms after 48-96 hours of primary therapy. In failing patients, look for alternative explanations/diagnoses, continue C. *difficile* treatment doses until resolution, and consider infectious diseases and surgery consultation.
2. Randomized trials have all utilized 10-day durations of therapy. Extension of course to 14 days may be considered in patients who have not had symptom resolution by day 10.
3. Parenteral administration of metronidazole has poor intraluminal penetration and should not be used alone for treatment. Parenteral vancomycin has no significant luminal accumulation and should not be used for C. difficile treatment.
4. Consider the use of vancomycin prophylaxis in patients that had a first or greater recurrence of CDI or fulminant disease in the past 90 days and require antimicrobials for a different infection. Other patients (including first occurrence of CDI) may be considered candidates for prophylaxis on a case-by-case basis in consultation with Infectious Diseases. The dose of prophylactic vancomycin is 125 mg daily to BID and the duration should be at least 50% of the expected duration of antibiotic therapy for the other infection. **Using fidaxomicin as prophylaxis is not recommended.**
5. The choice of fidaxomicin or vancomycin for initial episode in solid organ transplant patients should consider the degree of immunosuppression, severity of disease, and concomitant administration of antibiotics.
6. Alternative and/or adjunctive agents:
    a. Vancomycin tapers should begin after the treatment course is completed. Example of PO **vancomycin** taper: 125 mg PO BID x7 days, then 125 mg PO daily x7 days, then 125 mg PO every other day x7 days, then 125 mg PO every 3 days x2-8 weeks. Patients on tapered doses of PO vancomycin should continue to be monitored for signs and symptoms of C. difficile disease.
    b. Kefir staggered protocol: **Vancomycin** 125 mg QID x2 weeks, 375 mg q72h x2 weeks, 250 mg q72h x2 weeks, and 125 mg q72h x2 weeks PLUS kefir (5-oz glass with each meal (at least 3 glasses per day)) for 15 weeks.
    c. Fecal microbiota transplantation (FMT) is a highly effective option for patients with recurrent CDI. Proximal colon administration of FMT has been demonstrated to be more effective than distal colon administration. Michigan Medicine uses stool preparations obtained from OpenBiome to perform FMTs in both the inpatient and outpatient settings or fecal microbiota, live-jslm (Rebyota™) to perform FMTs in the outpatient setting. OpenBiome is the preferred FMT product. Rebyota is only administered in the distal colon. Patients with recurrent CDI (defined as having two or more episodes) or CDI not responsive to standard pharmacologic therapies by day 5 may be considered for FMT. Patients with hypotension or shock, ileus, megacolon, severe sepsis, peritonitis, or bowel perforation attributed to CDI are generally not candidates for FMT. For inpatient use, infectious diseases and gastroenterology consultation are required. For outpatient use, patients should be referred to the infectious diseases clinic. For OpenBiome monograph CLICK HERE. For Rebyota monograph CLICK HERE. For additional FMT resources CLICK HERE.
    d. The role of probiotics in prevention and treatment of *C. difficile* colitis is unclear, and their use is not currently recommended for inpatients. Avoid the use of probiotics in immunocompromised patients (transplant recipients, unintact gut mucosa, neutropenic patients, HIV/AIDS patients, etc) and patients with severe C. *difficile* colitis.
    e. Cholestyramine binds PO vancomycin and may decrease its efficacy. Avoid concomitant use.

Outpatient Treatment Considerations

7. A patient assistance program is available for fidaxomicin (https://www.merckconnect.com/dificid/patient-assistance.html?hcpUser=yes)
8. For fidaxomicin use, outpatient coverage should be verified at time of treatment initiation by emailing pharm-transitions-of-care@med.umich.edu

Fulminant Disease/Surgical Considerations

9. Intracolonic vancomycin 500 mg in 500 mL of normal saline every 6 hours given as retention enema using the following procedure: 18-inch Foley catheter with a 30-ml balloon inserted into rectum, balloon inflated, vancomycin instilled, catheter clamped for 60 minutes, deflate and remove. In patients who do not have the entire colon in place (i.e., a colorectal stump due to Hartman's procedure), a smaller volume of enema (100 mL) is acceptable
10. Postoperative diverting loop ileostomy regimen consists of antegrade vancomycin flushes (500 mg in 500 mL of Lactated Ringers; q8 hours for a duration of 10 days) via a 24 French Malecot catheter in the efferent limb of the ileostomy and intravenous (IV) metronidazole (500 mg q8 hours) for 10 days. See Reference Neal MD, et al. Ann Surg 2011;254:423-7.

Reference:

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. Available at: https://www.idsociety.org/practice-guideline/clostridioides-difficile-2021-focused-update/

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Antimicrobial Subcommittee Approval: 03/2023	Originated: 07/2014
P&T Approval: 04/2023	Last Revised: 03/2023

Revision History:

1/20: Added diverting loop ileostomy footnote
7/21: Updated testing criteria and proccess
9/21: Updated vancomycin infusion reaction terminology
7/22: Updated initial treatment options
3/23: Revised FMT recommendations