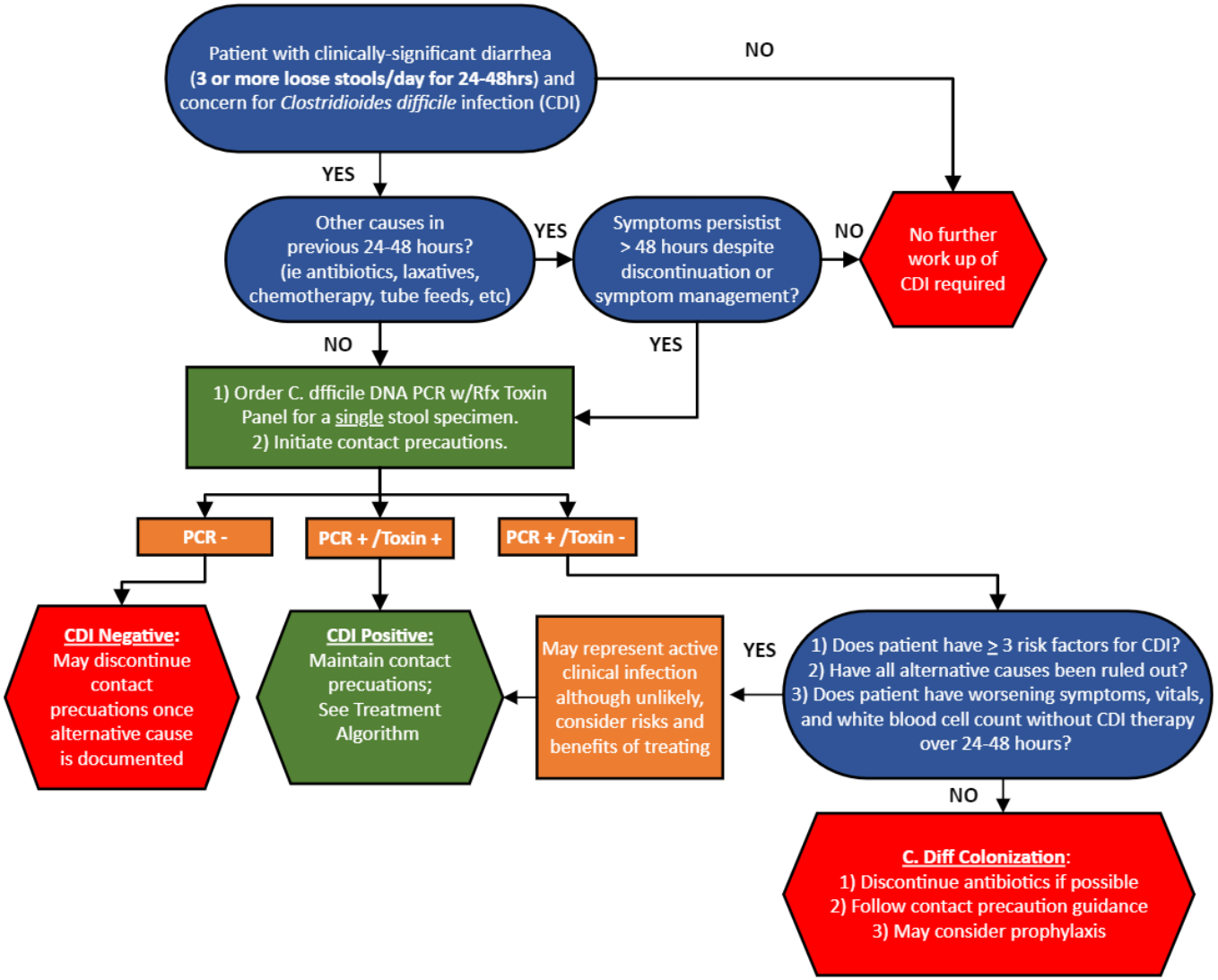
VASP *Clostridioides difficile Infection* – Adult Inpatient Management

This guidance document is meant to provide general recommendations and does not supersede clinical decision making



Diagnostic Considerations:

- VUMC relies on a two-step algorithm for the diagnosis of *Clostridioides difficile* (C. *difficile*) infections (CDI).
    1. Molecular screen (Simplexa C. diff Direct) to test for presence of toxigenic C. *difficile* via the toxin B gene (tcdB).
        - While C. diff can produce both enterotoxin A and cytotoxin B, all toxigenic strains will produce toxin B indicating a better marker for detection.
        - Negative Predictive Value (NPV): 97.1% when compared against culture + toxin assay
    2. If molecular screen is positive, a rapid toxin antigen test is completed (C. DIFF QUIK CHEK COMPLETE ®) simultaneously looking for toxin A and B.
        - FDA package labeling for this test indicates: Sensitivity: 88%; NPV: 98.1% (n=1,126)
        - Other studies have found lower sensitivities for toxin enzyme immunoassays (EIA) at ~78.3%. [8]
            - Given the lower sensitivity for EIA tests, PCR +/Toxin – results should not be interpreted in isolation as the clinical context and risk factors of the patient could indicate a true infection[9,10]
- Patients should be experiencing clinically significant diarrhea (≥3 liquid stools per day) without any alternative causes identified.
    1. Testing is only performed on loose or watery stool specimens.
    2. Ileus due to CDI occurs in less than 1% of cases. If suspected, the provider must specifically request testing on a formed stool specimen via verbal communication with lab personnel prior to submission.
- Repeat testing to assess for C. *difficile* eradication (also known as a "test of cure") is not necessary. Many successfully treated patients will continue to test positive for weeks or months after resolution of symptoms.[4]
- Gastrointestinal (GI) pathogen panel testing is not needed to assess for CDI. This panel tests for a wide variety of pathogens that cause infectious diarrhea and is much more expansive than the standard C. *difficile* two-step testing. When the C. *difficile* PCR with RFx toxin is ordered, place the patient on contact precautions and follow VUMC infection prevention guidance regarding discontinuation of isolation.
- The laboratory will not perform repeat testing for C. *difficile* sent within 7 days of a prior positive result. For negative results, the laboratory will perform a maximum of 2 C. *difficile* tests within 7 days.
- A negative test is NOT required for removal from isolation. Follow VUMC Infection Prevention guidance on isolation and C. difficile

Risk factors for C. *difficile* infections/recurrence when assessing cause of diarrhea and interpretation of C. *difficile* testing results:

3. **<u>High Risk Antibiotics</u> in previous 90 days** (Fluoroquinolones, Clindamycin, Carbapenems, and 3rd/4th generation cephalosporins)
4. Healthcare exposure in the previous 12 weeks
5. Age > 65 years
6. Chronic Acid Suppression
7. Solid Organ Transplant
8. Hematopoietic Stem Cell transplant
9. Cancer chemotherapy
10. Chronic Kidney Disease / End Stage Renal Disease
11. Prolonged hospital length of stay
12. Gastrointestinal procedure
13. History of CDI

Table 1. Interpreting C. *difficile* Panel Results

C. *difficile* DNA PCR: Not detected	Toxigenic C. *difficile* is not present in this patient (97% NPV). Continue work up for alternative causes.
C. *difficile* DNA PCR: Detected C. *difficile* Toxin Ag: Not detected	Likely represents colonization of toxigenic C. *difficile;* however toxin is not currently present. Interpret in clinical context of the patient: 1. Is the patient at high risk for CDI (<u>≥</u> 3 risk factors)? 2. Have all alternative causes for diarrhea been ruled out? 3. Arethe patient's symptoms, white blood cell count/labs, and vitals worsening off CDI therapy? If yes to above, weigh the risks and benefits of treating CDI.
C. *difficile* DNA PCR: Detected C. *difficile* Toxin Ag: Detected	Patient is currently experiencing CDI, follow treatment algorithm based off risk factors accordingly.

Treatment Considerations:

Non-fulminant CDI	Immunocompetent Patients	Immunosuppressed Patients*
Initial Episode	**Preferred** • Vancomycin 125mg QID x 10 days ‡ **High risk patients (≥3 risk factors)** • Fidaxomicin 200 mg† BID PO x 10 days	**Preferred:** • Fidaxomicin 200 mg† BID PO x 10 days **Second line options:** • Vancomycin 125mg QID x 10 days
First Recurrence	**Preferred** • Fidaxomicin 200 mg† BID PO x 10 days **Second line options if standard dose Fidaxomicin was previously given:** • Fidaxomicin 200 mg† BID PO x 5 days then 200mg daily every other days 7-25 • Vancomycin 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 days for 2 weeks	**Consult Infectious Disease** **Preferred:** • Fidaxomicin 200 mg† BID PO x 10 days **Second line options if standard dose Fidaxomicin was previously given:** • Fidaxomicin 200 mg† BID PO x 5 days then 200mg daily every other for days 7-25 • Vancomycin 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 days for 2 weeks
Second or Subsequent Recurrence	**Consult Infectious Disease** **Preferred** • Fidaxomicin 200 mg† BID PO x 10 days **Second line options if standard dose Fidaxomicin was previously given:** • Fidaxomicin 200 mg† BID PO x 5 days then 200mg daily every other day for days 7-25 • Vancomycin 125 mg 4 times daily for 10–14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 days for 2 weeks	

Fulminant CDI	All Patients Regardless of Immunocompetence
Fulminant CDI: Hypotension, shock, megacolon, or ileus due to CDI	**Consult Infectious Disease and Surgical Services** • Vancomycin 500mg QID by mouth or NG tube + Metronidazole 500mg Q8h IV **Adjunctive therapy:** • Can consider adding rectal retention enema of vancomycin 500 mg Q6h if ileus or fecal diversion occurs. ○ Not indicated in toxic megacolon for risk of bowel perforation.

*Solid organ transplant, Stem Cell transplant, Absolute neutrophil count (ANC) ≤ 500 cells/mm^3, B-cell depleting agents (Rituximab, ocrelizumab, ofatumumab)
†Fidaxomicin should not be used for patients who are PCR+/Toxin-.Restricted to infectious diseases, page 317-4376 for approval. Confirm that patient can afford this medication once discharged prior to ordering inpatient. See Coverage Resources.
‡ 14 days can be considered in those without complete resolution on day 10 of therapy
§ Restricted to outpatient use and should be given with fidaxomicin or vancomycin. Consider whether a patient can afford this medication once discharged prior to ordering. See Coverage Resources. This medication should be avoided in those with congestive heart failure.

Coverage resources for fidaxomicin:

- Affordability at discharge should be confirmed before ordering fidaxomicin while inpatient to ensure the course can be completed without a prolonged hospital stay.
- In cases that the patient's insurance does not reduce price to an affordable level, consider the following options:
  - Commercial insurance: Enroll patient in savings card at https://www.dificid.com/savings-coupon/
  - TennCare: Completely covered if the patient has a positive CDI test
  - Medicare: Assist patient in applying for the Assistance Fund
  - Uninsured or any of the above options fail: Merkhelps.com

Prophylaxis Considerations:

- Oral vancomycin 125 mg 1-2 times daily may be considered for secondary prevention in the following patients receiving systemic antimicrobials who have a history of CDI in the previous 90 days or ≥ 2 recurrences:
  - Solid organ transplant
  - Stem Cell Transplant
  - ANC ≤ 500 cells/mm^3
  - B-cell depleting agents (rituximab, ocrelizumab, ofatumumab)
  - Patients with ≥ 3 risk factors
- Oral vancomycin for secondary prevention should be discontinued within 7 days of systemic antimicrobial discontinuation.
- There is insufficient evidence to recommend probiotics for secondary prevention of CDI.
  - Probiotics should be avoided in transplant patients or patients with intestinal discontinuity for concern of translocation and systemic infection.

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