

CLOSTRIDIoidES DIFFICILE (C. DIFF)

PRACTICAL PROVIDER QUICK-REFERENCE ALGORITHM

1. WHEN TO SUSPECT / TEST

NEW, UNEXPLAINED DIARRHEA: ≥ 3 unformed stools in 24 hours
Review/hold laxatives when appropriate; assess alternative causes; send UNFORMED stool only.

2. DIAGNOSTIC TESTING

GDH antigen + C. difficile toxin A/B EIA (TOXIN ASSAY)

Toxin A/B EIA: detects free C. difficile toxin A and/or B in stool. A positive toxin assay in a patient with compatible diarrhea strongly supports active CDI.

NAAT/PCR FOR DISCORDANT RESULTS: use reflex NAAT/PCR when GDH and toxin results are discordant. Toxin A/B EIA detects free toxin and is more supportive of active toxin-mediated disease. NAAT/PCR detects a toxin gene; it does not prove current toxin production and may be positive in colonization.

GDH	Toxin A/B EIA	Interpretation / Action
+	+	CDI likely if compatible diarrhea - treat.
-	-	CDI unlikely - seek another cause.
+	-	DISCORDANT - reflex NAAT/PCR. PCR+ may be active CDI or colonization; correlate clinically.
-	+	Unusual discordance - verify per laboratory algorithm and correlate clinically.

3. REPEAT TESTING / TEST OF CURE

NO TEST OF CURE. Do not routinely repeat testing after clinical recovery. Tests may remain positive for weeks. Do not treat PCR positivity, stool odor, or stool color alone.

4. SEVERITY & INITIAL TREATMENT

NON-SEVERE WBC $\leq 15,000$ AND Cr < 1.5 mg/dL	SEVERE WBC $> 15,000$ OR Cr ≥ 1.5 mg/dL	FULMINANT Hypotension/shock, ileus or megacolon
Vancomycin 125 mg PO QID x10 d OR fidaxomicin 200 mg BID x10 d	Vancomycin 125 mg PO QID x10 d OR fidaxomicin 200 mg BID x10 d	Vancomycin 500 mg PO/NG QID + metronidazole 500 mg IV q8h If ileus: consider vancomycin 500 mg PR q6h. Urgent ID/GI/Surgery/ICU.

5. FIRST RECURRENCE

Preferred: fidaxomicin 200 mg BID x10 d OR extended-pulsed: 200 mg BID x5 d, then 200 mg every other day x20 d.
Alternative: vancomycin taper/pulse; standard vancomycin may be reasonable in selected first recurrence.

6. VANCOMYCIN TAPER / PULSE

125 mg PO QID x10-14 d $\rightarrow$ 125 mg BID x7 d $\rightarrow$ 125 mg daily x7 d $\rightarrow$ 125 mg every 2-3 days x2-8 weeks

7. SECOND / SUBSEQUENT RECURRENCE

Fidaxomicin (standard or extended-pulsed), vancomycin taper/pulse, or vancomycin 125 mg QID x10 d then rifaximin 400 mg TID x20 d. Consider microbiota restoration/FMT pathway.

8. SECONDARY PROPHYLAXIS DURING SYSTEMIC ANTIBIOTICS

NOT ROUTINE. ID/ASP-directed for selected very-high-risk patients. If chosen: commonly used ACG-based regimen is vancomycin 125 mg PO once daily during systemic antibiotics and for 5 days afterward.

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C. DIFFICILE - PRACTICAL PROVIDER DIAGNOSIS & TREATMENT FLOW SHEET

1. WHEN TO SUSPECT / TEST

- **Test patients with new, unexplained clinically significant diarrhea:** generally ≥ 3 unformed stools in 24 hours.
- Send **unformed stool only** (stool that takes the shape of the container).
- Review laxatives/stool softeners and other explanations: enteral feeds, medications, overflow diarrhea, viral illness, inflammatory disease, etc.
- Use Contact/Enteric Precautions while a symptomatic patient is being evaluated.

DO NOT TEST: formed stool; asymptomatic patients; chronic baseline loose stool without a meaningful change; or simply to document cure.

2. DIAGNOSTIC TESTING

Preferred: MULTISTEP TESTING ALGORITHM

STEP 1 - GDH antigen + C. difficile toxin A/B EIA (TOXIN ASSAY)

GDH antigen: detects a C. difficile-associated antigen. It is a sensitive screening test but does not determine whether toxin is being produced.

Toxin A/B EIA (toxin assay): detects free C. difficile toxin A and/or B in stool. A positive toxin assay in a patient with compatible diarrhea strongly supports active CDI. Toxin EIA is less sensitive than GDH or NAAT/PCR, so a negative toxin assay alone does not completely exclude CDI.

GDH	Toxin A/B EIA	Interpretation / Action
+	+	CDI likely if compatible diarrhea - treat.
-	-	CDI unlikely - seek another cause.
+	-	DISCORDANT - reflex NAAT/PCR. PCR+ may be active CDI or colonization; correlate clinically.
-	+	Unusual discordance - verify per laboratory algorithm and correlate clinically.

STEP 2 - NAAT/PCR FOR DISCORDANT RESULTS

GDH(+)/toxin(-)/PCR(+): toxigenic C. difficile is present, but this does not automatically establish active CDI. It may represent active disease with toxin below EIA detection or colonization. Treat only when the clinical syndrome is compatible.

GDH(+)/toxin(-)/PCR(-): CDI is unlikely; seek another cause of diarrhea.

TOXIN ASSAY vs PCR
Toxin A/B EIA detects free toxin in stool and is more supportive of active toxin-mediated disease.
NAAT/PCR detects a toxin gene; it does not prove current toxin production and may be positive in colonization.
TREAT THE PATIENT - NOT THE PCR.

Specimen caveat: C. difficile toxin is unstable; delayed processing or failure to refrigerate appropriately can contribute to false-negative toxin results.

3. REPEAT TESTING / TEST OF CURE

- **Do not routinely repeat C. difficile testing during the same diarrheal episode.**
- **Do not perform a test of cure.** Patients may remain test-positive for 6 weeks or longer after clinical recovery.
- If symptoms resolved and later recur with new clinically significant diarrhea, reassess as a possible recurrence and test an appropriate unformed specimen.
- Soft stool, foul odor, altered color, or PCR positivity alone does not establish recurrent CDI.

4. SEVERITY & INITIAL TREATMENT

NON-SEVERE CDI: WBC $\leq 15,000$ cells/ μ L AND serum creatinine < 1.5 mg/dL.

SEVERE CDI: WBC $> 15,000$ cells/ μ L OR serum creatinine ≥ 1.5 mg/dL.

FULMINANT CDI: hypotension/shock, ileus, or megacolon.

Clinical category	Recommended practical regimen	Key notes
Non-severe	Vancomycin 125 mg PO QID x10 days OR fidaxomicin 200 mg PO BID x10 days	IDSA/SHEA conditionally prefers fidaxomicin when feasible because of improved sustained response/lower recurrence; vancomycin remains an accepted alternative.
Severe	Vancomycin 125 mg PO QID x10 days OR fidaxomicin 200 mg PO BID x10 days	Monitor stool burden, WBC, renal function, hydration, abdominal findings and hemodynamics.
Fulminant	Vancomycin 500 mg PO/NG QID + metronidazole 500 mg IV q8h If ileus: consider vancomycin 500 mg PR q6h	Medical emergency. Early ID, GI, Surgery and critical-care involvement.

5. FIRST RECURRENCE

- **Preferred:** fidaxomicin 200 mg PO BID x10 days.
- **Extended-pulsed fidaxomicin:** 200 mg PO BID x5 days, then 200 mg PO every other day for 20 days.
- **Alternative:** oral vancomycin taper/pulse. A standard 10-day vancomycin course remains an option in selected first recurrences.

6. VANCOMYCIN TAPER / PULSE - EXAMPLE

Vancomycin 125 mg PO QID x10-14 days
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 125 mg PO BID x7 days
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 125 mg PO daily x7 days
 ↓
 125 mg PO every 2-3 days x2-8 weeks

7. SECOND OR SUBSEQUENT RECURRENCE

- **Fidaxomicin** 200 mg PO BID x10 days OR extended-pulsed regimen above.
- **Vancomycin taper/pulse.**
- **Vancomycin** 125 mg PO QID x10 days, followed by rifaximin 400 mg PO TID x20 days.
- Consider a **microbiota-restoration/FMT pathway** after appropriate recurrent-CDI antibacterial treatment; coordinate with ID/GI and current product/FDA guidance.

8. SECONDARY PROPHYLAXIS DURING SYSTEMIC ANTIBIOTICS

NOT ROUTINE PROPHYLAXIS. Consider only for carefully selected patients at very high risk for recurrent CDI, ideally after ID/Antimicrobial Stewardship review. Guideline positions and evidence are not uniform.

Patients in whom prophylaxis may be considered:

- Age ≥65 years with recent CDI and substantial recurrence risk.
- Multiple prior CDI episodes or previous recurrence triggered by systemic antibiotics.
- Recent severe CDI, significant immunocompromise, or unavoidable broad-spectrum/prolonged systemic antibiotic exposure.

If prophylaxis is selected: a commonly used ACG-based regimen is **vancomycin 125 mg PO once daily** during systemic antibiotic therapy and for **5 days after** completion.

Caveats: this is secondary prophylaxis, not treatment of active CDI. Potential disadvantages include microbiome disruption and selection pressure for resistant organisms (including VRE).

9. SUPPORTIVE / ANTIMICROBIAL STEWARDSHIP MEASURES

- Discontinue the **inciting antibiotic** whenever clinically possible; otherwise narrow spectrum and shorten duration.
- Review unnecessary acid suppression and **diarrhea-provoking medications**.
- Maintain **hydration and electrolyte** replacement as needed.
- **Do not treat asymptomatic colonization.**

10. INFECTION PREVENTION

- Initiate **Contact/Enteric Precautions** for suspected CDI while evaluation is underway.
- Use **gown and gloves**; dedicate equipment when feasible.
- Emphasize **soap-and-water** handwashing after CDI patient/resident care, especially during outbreaks or when hands are visibly soiled.
- Use an **EPA List K sporicidal agent** for daily and terminal environmental cleaning.
- CDC recommends maintaining Contact Precautions for **at least 48 hours after diarrhea resolves**; facilities may extend precautions according to **local policy**.

11. PROVIDER PEARLS

1. CDI is a clinical syndrome plus appropriate laboratory evidence.
2. A positive PCR does not equal active CDI.
3. Do not order a test of cure.
4. Post-CDI dysbiosis can cause persistent altered bowel habits without recurrent infection.
5. Fulminant CDI requires urgent escalation.

12. REFERENCES / GUIDELINE BASIS

1. CDC. Clinical Guidance for C. diff Infection Prevention in Acute Care Facilities. Updated 2026.
2. CDC. Clinical Testing and Diagnosis for C. diff Infection.
3. Johnson S, et al. SHEA/IDSA 2021 Clinical Practice Guideline Update for Management of Clostridioides difficile Infection in Adults. Clin Infect Dis. 2021.
4. Kelly CR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol. 2021.
5. Current local formulary, laboratory algorithm, FDA microbiota-product guidance, and institutional Infection Prevention/ASP policy should supersede this quick-reference sheet when more restrictive.

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For adult hospital, skilled nursing facility, and long-term-care provider education. This quick reference does not replace bedside clinical judgment or institution-specific policy.