

Carolina Antimicrobial Stewardship Program **GUIDELINE**

Diagnosis and Management of *Clostridioides difficile* Infection in Adult and Pediatric Patients

The purpose of this guideline is to aid clinicians in the diagnosis and management of patients with *Clostridioides difficile* infection. The diagnostic approach and medications recommended in this guideline are specific to what is available at UNC McLendon Laboratories and on formulary.

DIAGNOSIS OF CDI

Clinicians should suspect CDI in patients with acute diarrhea (≥ 3 loose stools in 24h) without an alternative explanation such as laxative use or tube feeds. CDI should particularly be suspected in the setting of relevant risk factors: recent systemic antibiotic use, hospitalization, advanced age, or use of proton pump inhibitors. When ordering a *C. difficile* assay, the ordering provider will be asked to answer several questions to ensure appropriateness of the test. UNC McLendon Laboratories uses a combination glutamate dehydrogenase (GDH) plus toxin assay arbitrated by a nucleic acid amplification test (NAAT) which assists in determining colonization versus infection (Figure 1). Test of cure is not recommended as *C. difficile* may still be detectable after a course of appropriate therapy and does not indicate persistent disease.

FIGURE 1. CDI DIAGNOSTIC ALGORITHM

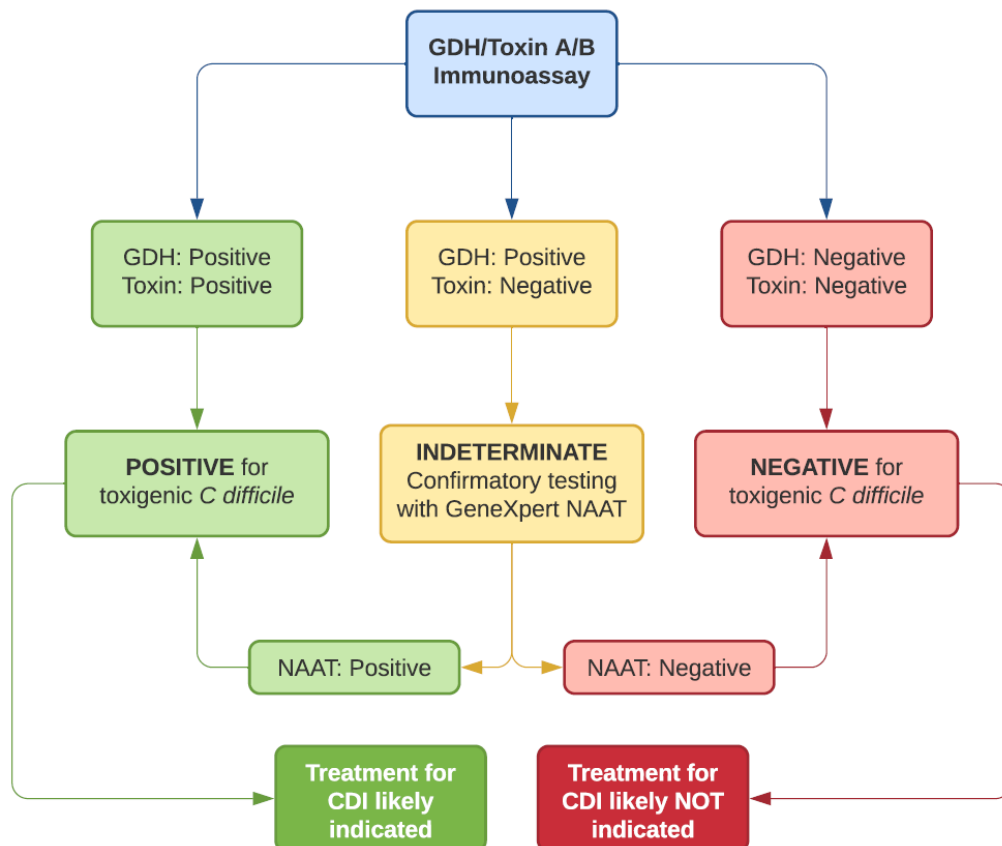
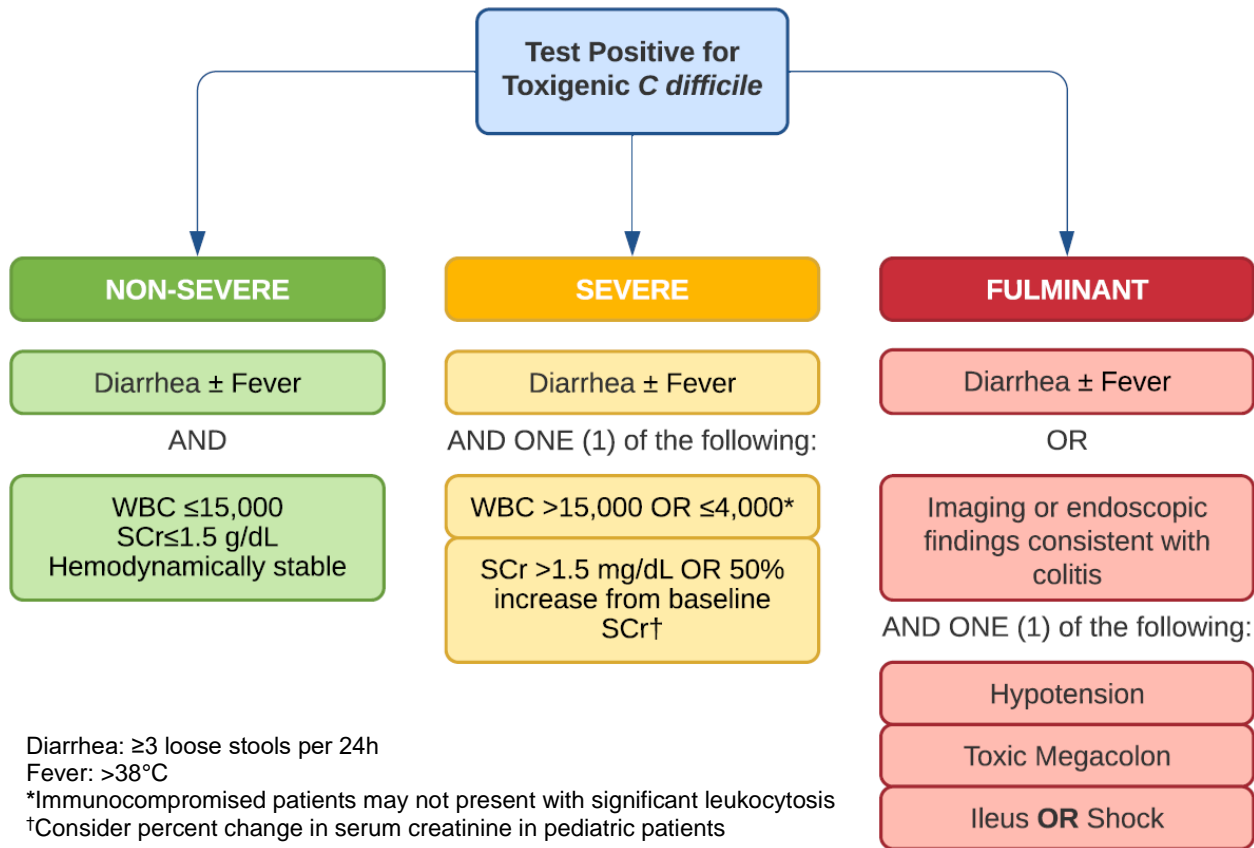


FIGURE 2. DETERMINING CDI SEVERITY


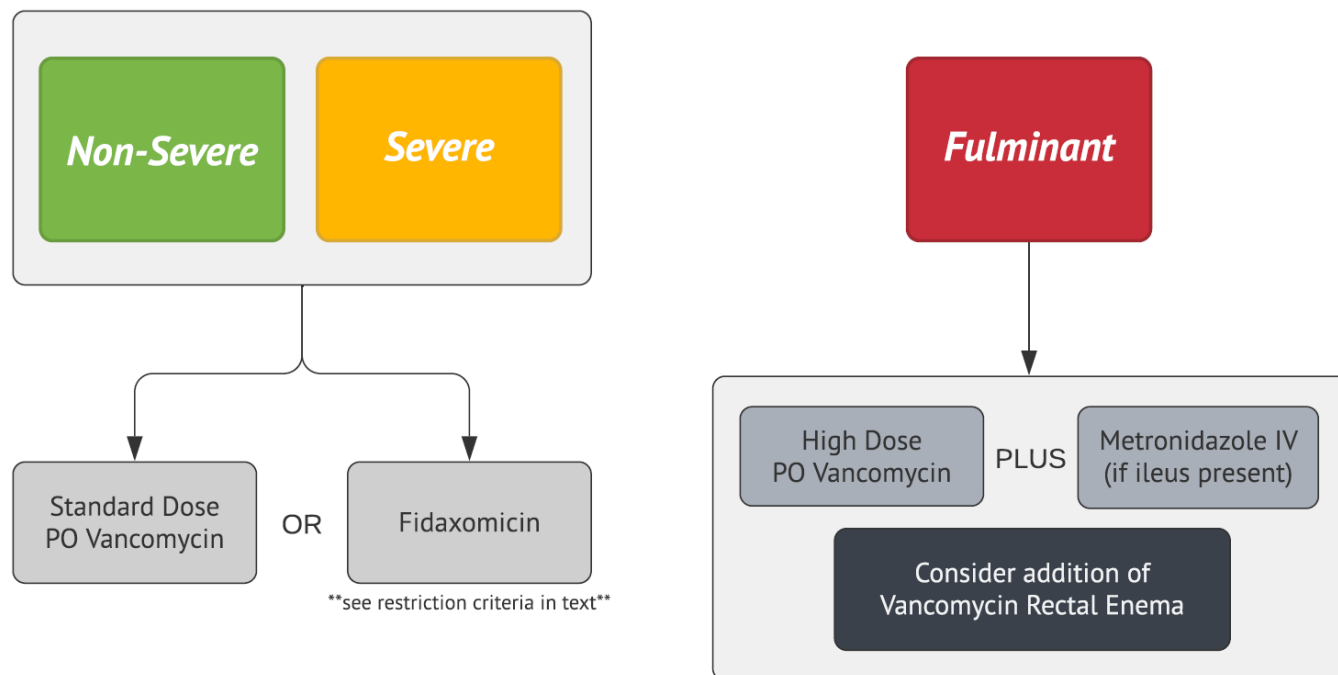
MANAGEMENT OF CDI: GENERAL CONSIDERATIONS

Therapy of CDI depends on disease severity as well as the patient's history of CDI episodes. Options for therapy typically include antibiotics that target *C difficile* but may also include fecal microbiota transplant (FMT). Fidaxomicin and enteral vancomycin remain primary therapies for patients with an initial episode of CDI. Fidaxomicin has demonstrated non-inferiority to vancomycin in successful treatment of initial episodes of CDI. Additionally, pooled analyses have demonstrated a higher chance of sustained clinical response of CDI four weeks after end of therapy with fidaxomicin compared to vancomycin. This finding suggests patients at high risk of recurrent CDI would benefit most from use of fidaxomicin compared to vancomycin for initial CDI episode. For that reason, the Carolina Antimicrobial Stewardship Program recommends the use of fidaxomicin over vancomycin in this subgroup as opposed to all patients diagnosed with initial CDI (see specific criteria below).

In settings when a patient meets criteria for fidaxomicin but they are unable to obtain the medication (e.g., financial barriers), then enteral vancomycin is an appropriate alternative therapy. See additional section below regarding patient assistance programs for Dificid® (fidaxomicin). See Table 1 for dosing recommendations.

For admitted patients with severe or fulminant CDI and/or who are not improving on recommended therapies as described in Figure 3, it is recommended to consult ID, GI, and general surgery services; additional or changes in therapies may be warranted.

FIGURE 3. MANAGEMENT OF INITIAL EPISODE OF CDI BASED ON SEVERITY



The patient must meet the following criteria in order to receive fidaxomicin (must meet one):

1. Recurrent disease (defined as new CDI within 8 weeks of completing previous CDI therapy)
 2. **OR** – any TWO of the following risk factors:
 - a. Age \geq 65 years old
 - b. Severe *C difficile* infection (defined as WBC >15,000 cells/mL or SCr >1.5mg/dL)
 - c. Immunocompromised state (active malignancy, receiving immunosuppressive medications, or history of SOT/HSCT)
 - d. Concomitantly receiving systemic antibiotics for indication other than CDI
 - i. The following low risk antibiotics when used as monotherapy do not qualify:
 1. Amoxicillin, ampicillin, 1st gen cephalosporins, fosfomycin, macrolides, nitrofurantoin, penicillin, tetracyclines, and trimethoprim/sulfamethoxazole
 3. Continued use from home
 4. Approved use by ID or GI consult service or ASP
- Approved courses of fidaxomicin are limited to 10 days duration
 - Use of fidaxomicin for long-term suppression or prophylaxis is NOT permitted (may consider using PO vancomycin 125mg once daily)

Additional Guidance on Fidaxomicin for Clinicians:

- Fidaxomicin is NOT recommended for treatment of fulminant CDI.

In patients with CDI, all antibiotics not targeting *C difficile* should be reviewed and stopped as soon as feasible. Additionally, ongoing use of proton pump inhibitors should be reassessed, and discontinued if no longer necessary. Please refer to the Proton Pump Inhibitor Guidelines found on the [Pharmacy Clinical Guideline](#) Intranet page for more information.

In addition to Standard Precautions, patients with CDI should be placed on Enteric Precautions. These additional precautions may be discontinued 30 days after the completion of antibiotics targeting CDI. For more information, please refer to the [Isolation Precautions](#) policy.

MANAGEMENT OF CDI: PEDIATRIC CONSIDERATIONS

Compared to adults, pediatric patients are generally at lower risk of CDI, complications of CDI, and CDI recurrences, though all do occur. In addition, there is less evidence supporting one antibiotic over another. In general, **standard-dose enteral vancomycin is the preferred therapy for pediatric patients with an initial CDI episode.**

Severe CDI in children must be managed inpatient for IV hydration and close monitoring. Consultation with Pediatric GI and/or ID is recommended. The recommended treatment is standard-dose enteral vancomycin, though fidaxomicin may be used in patients who meet the previously described criteria. Adjunctive intravenous metronidazole is not generally required in pediatric severe CDI. See Table 1 for dosing recommendations.

Pediatric patients with fulminant colitis should be managed in the ICU. Consultation with Pediatric GI, Pediatric Surgery, and Pediatric ID is warranted. Medical therapy includes high-dose enteral vancomycin. Intravenous metronidazole should be added for patients with ileus, as enteral vancomycin may not reach the colon. In such cases, rectal instillation of vancomycin may be considered. In patients who fail to respond to medical therapy, surgery (usually subtotal or total colectomy) may be required.

MANAGEMENT OF CDI: PERIPARTUM & BREASTFEEDING CONSIDERATIONS

Clostridioides difficile infection in peripartum patients has increased over the last couple decades and is associated with significant morbidity and mortality. These patients are at higher risk of severe disease and poor outcomes. For this reason in addition to the lack of safety and efficacy data for fidaxomicin and observed failures of metronidazole in these settings, enteral vancomycin remains the standard of therapy for peripartum patients as endorsed by the ACG CDI guidelines.

Patients may continue to breastfeed while being treated for CDI, and the recommended therapy is enteral vancomycin. Similar to enteral vancomycin, fidaxomicin is not expected to be excreted into breast milk in clinically significant quantities; however, studies are needed to establish the safety of fidaxomicin in this setting, further supporting the recommendation of vancomycin in breastfeeding patients.

MANAGEMENT OF CDI: ADJUNCTIVE THERAPY

Bezlotoxumab is a monoclonal antibody directed against toxin B produced by *C difficile* that may also be considered as an adjunct therapy in a select group of patients at high risk of CDI recurrence. Bezlotoxumab is restricted to clinic use only and consultation with an infectious diseases physician is recommended. Risks versus benefits must be weighed for patients with congestive heart failure (CHF), as use of bezlotoxumab has been associated with CHF exacerbations in clinical trials. Use of bezlotoxumab in patients <18 years of age has not been formally evaluated. Consultation with Pediatric ID is recommended if considering bezlotoxumab in patients <18 years of age.

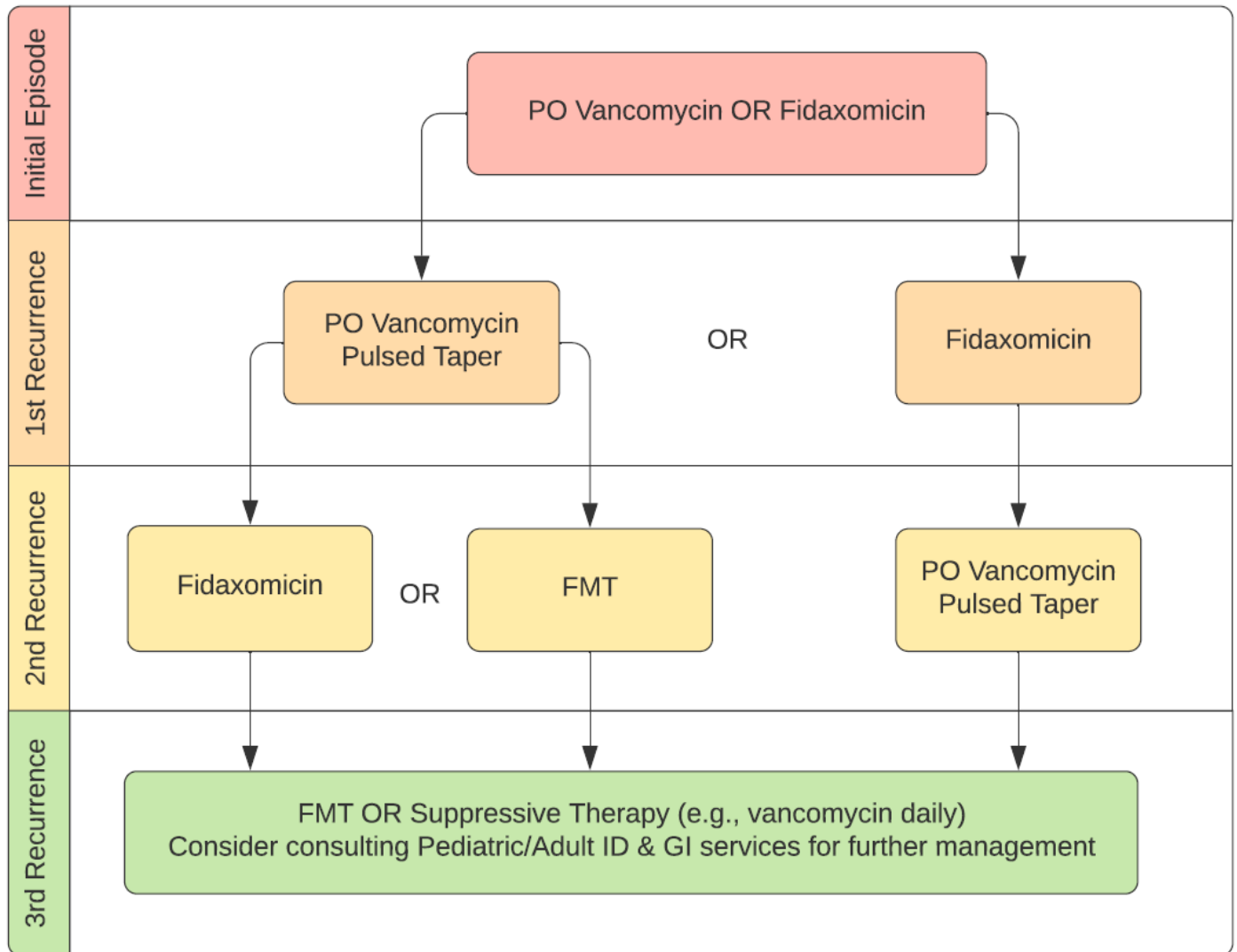
The patient must meet the following criteria in order to receive bezlotoxumab:

- Patient must meet ALL of the following:
 - Outpatient status
 - Currently receiving antibiotic therapy for CDI (e.g., treatment OR suppressive therapy)
- PLUS one of the following risk factors for recurrence:
 - Age ≥65 years
 - Recurrent episode of CDI within 6 months of prior episode
 - Severe CDI upon presentation (see Figure 2)
 - Immunocompromised state (defined as active malignancy, receiving immunosuppressive medications, or history of solid organ or stem cell transplant)

MANAGEMENT OF RECURRENT CDI: GENERAL CONSIDERATIONS

A subsequent case of CDI, defined as clinical symptoms and diagnostic studies consistent with CDI, occurring within 8 weeks of a prior case should be considered a recurrence. Patients with one recurrence are more likely to have subsequent recurrences. Patient-specific factors (e.g., FMT candidacy, financial & compliance barriers, etc.) should be taken into consideration when approaching management of recurrent CDI episodes. In clinically stable patients where FMT is pursued, consider use of suppressive antibiotics (e.g., vancomycin 125 mg PO daily) following their initial treatment course, and refer the individual to outpatient gastroenterology. If FMT is ultimately not pursued, continuation of suppressive antibiotics must be revisited. Consider the algorithm below (Figure 4) when approaching management of patients with recurrent CDI. For pediatric patients experiencing first episode of recurrent CDI, consultation with Pediatric ID and/or Pediatric GI is recommended.

FIGURE 4. POSSIBLE ALGORITHM FOR MANAGEMENT OF RECURRENT CDI



FINANCIAL CONSIDERATIONS FOR PATIENTS

Fidaxomicin tablets and suspension are available on the UNC Medical Center inpatient formulary; however, the suspension dosage form of fidaxomicin may be difficult to obtain outpatient. Additionally, both fidaxomicin dosage forms are associated with a significant cost that may not be covered by insurance and may warrant additional steps to obtain coverage outpatient (e.g., prior authorization or manufacturer assistance). Consider visiting the following patient assistance program websites to explore alternative means of providing outpatient coverage of fidaxomicin:

- [Dificid® \(fidaxomicin\) tablets Patient Assistance Program](#)
- [Dificid® \(fidaxomicin\) suspension Patient Assistance Program](#)

Some patients may qualify for medication assistance through the UNC Pharmacy Assistance Program (PAP). Applications in English & Spanish can be found on the intranet links below. Of note, Dificid (fidaxomicin) and Zinplava (bezlotoxumab) are not covered by UNC PAP.

- [UNC Pharmacy Assistance Program Application](#) (ENGLISH)
- [UNC Pharmacy Assistance Program Application](#) (SPANISH)

REFERENCES

1. Johnson S, Lavergne V, Skinner AM, Gonzales-Luna AJ, Garey KW, Kelly CP, & Wilcox MH. (2021). 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. *Clinical Infectious Diseases*, 73(5), e1029-1044. doi: 10.1093/cid/ciab549.
2. Kelly C, Fischer M, Allegretti J, LaPlante K, Stewart D, Limketkai B, & Stollman N. (2021). American College of Gastroenterology Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections. *American Journal of Gastroenterology*, 116(6). 1124-47. doi: 10.14309/ajg.0000000000001278
3. McDonald, L., Gerding, D., Johnson, S., Bakken, J., Carroll, K., & Coffin, S. et al. (2018). 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*, 66(7), e1-e48. doi: 10.1093/cid/cix1085.
4. Zinplava™ (bezlotoxumab) [prescribing information]. Whitehouse Station, NJ: Merck & Co., Inc.; June 2016.
5. Zinplava™. In: Lexi-Drugs®, Hudson, Ohio: Lexi-Comp, Inc.; November 2020.

TABLE 1. CDI-TARGETED THERAPIES: DOSING & OTHER CONSIDERATIONS

Medication	Dose & Duration		Financial & Other Considerations
	Pediatric (max = adult dose)	Adult	
Vancocin (vancomycin)	Standard Dose		<p>Many commercial insurers will cover, though some may require prior authorization</p> <p>Available through UNC Pharmacy Assistance Program (PAP) for qualified patients</p>
	10mg/kg/DOSE PO q6h x10d	125mg PO q6h x10d	
	High Dose		
	10mg/kg/DOSE PO q6h x10d	500mg PO q6h x10d	
	Taper Regimen*		
	10mg/kg/DOSE PO q6h x10-14d, then q12h x7d, then q24h x7d, then q48h x7d	125mg PO q6h x10-14d, then q12h x7d, then q24h x7d, then q48h x7d	
	Rectal Retention Enema (500mg/100mL)		
Age 1-3yo: 50mL PR q6h x10d 4-9yo: 75mL PR q6h x10d >9yo: 100mL PR q6h x10d	500mg (100mL) PR q6h x10d		
Dificid (fidaxomicin) **See restriction criteria in text**	16mg/kg/DOSE PO q12h x10d	200mg PO q12h x10d	<p>Often requires prior authorization</p> <p>Patient assistance program through Merck available for qualified patients; see text for details</p> <p>NOT available through UNC PAP</p>
Flagyl (metronidazole)	Fulminant CDI:		<p>Not recommended for non-fulminant CDI, though may be used as an alternative if patient access to vancomycin or fidaxomicin is limited</p> <p>Available through UNC PAP for qualified patients</p>
	10mg/kg/dose IV q8h x10d	500mg IV q8h x10d	
Zinplava (bezlotoxumab) **See restriction criteria in text**	N/A	10mg/kg IV x1 dose during course of CDI therapy	<p>May only be administered in clinic / outpatient setting</p> <p>Requires benefits investigation / prior authorization</p> <p>NOT available through UNC PAP</p> <p>Has not been evaluated for patients <18 yo</p>

*Taper regimens may be tailored to patient response and/or plans for FMT.