

<b>Guideline/Protocol Title:</b>	<b>Management of <i>Clostridioides difficile</i> Infection (CDI) in Adults</b>
<b>Approval Date:</b>	10/20/2021
<b>Last revision Date:</b>	NEW

<b>PURPOSE:</b>	To provide guidance for the treatment of adult patients with <i>Clostridioides difficile</i> infection
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<b>EXECUTIVE SUMMARY</b>
Summarized below are recommendations intended to improve the diagnosis and management of <i>Clostridioides difficile</i> infection (CDI) in adults here at UC Davis Medical Center. CDI is defined by the presence of symptoms (usually diarrhea) and either a stool test positive for <i>C. difficile</i> toxins or detection of toxigenic <i>C. difficile</i> , or colonoscopic or histopathologic findings revealing pseudomembranous colitis. This guideline is adapted to the recommendations of the 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 <i>Clostridioides difficile</i> Infection in Adult. This guideline reflects summaries of evidence-based recommendations and is in line with the consensus of the UC Davis Medical Center Infectious Diseases group.

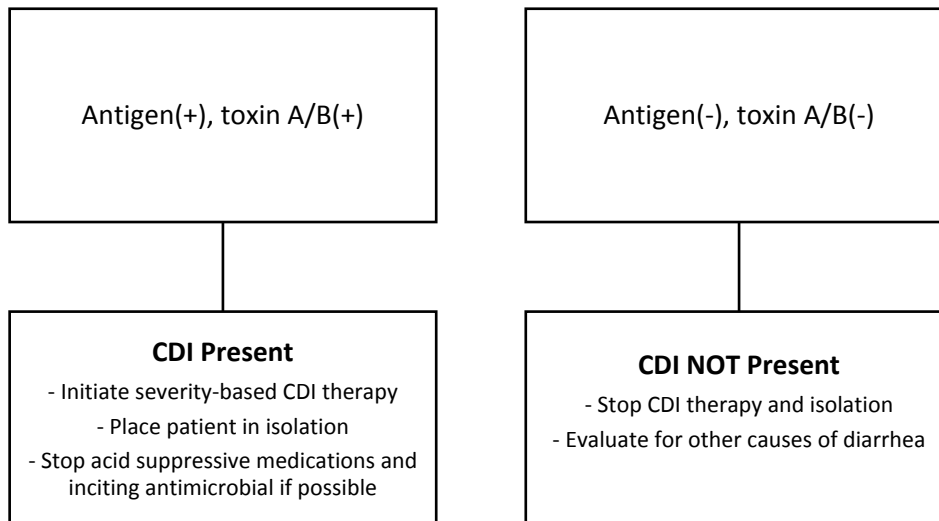
<b>BACKGROUND / INTRODUCTION</b>
There are no established guidelines for the treatment of <i>Clostridioides difficile</i> infection (CDI) at University of California, Davis Health System (UCDHS). Since the establishment of the first <i>Clostridioides difficile</i> infection (CDI) guidelines by the Infectious Diseases Society of America (IDSA) there have been several updated iterations reflect further advancements in evaluation, diagnosis, and treatment of patients with CDI. Most recently, in June of 2021, the next iteration of IDSA/SHEA CDI guidelines was published, thus prompting the development of an institutional guidelines to ensure that local recommendations are in line with the current published evidence and are uniform.

**When to test for CDI?**

- Patients experiencing new onset diarrhea with  $\geq 3$  watery stools in 24 hours along with unexplained leukocytosis.
- If there is an alternative cause of diarrhea, only send test if high clinical suspicion for CDI, otherwise high rate of false positives. Do not send if diarrhea caused by: Laxative/enema use, tube feeds, ischemic bowel, medication side effect, short bowel, IBS/IBD

**CDI Test Interpretation**

\*If *C. diff* surveillance positive, the patient is colonized and does not require treatment for CDI



#### Stage of Disease:

- **Non-Severe:** White blood cell (WBC) count < 15,000 cells/uL **AND** serum creatinine is < 1.5 mg/dL (unless attributable to pre-existing co-morbidities).
- **Severe:** WBC ≥ 15,000 cells/μL **OR** serum creatinine elevation > 1.5 mg/dL (not attributable to pre-existing co-morbidities).
- **Fulminant:**
  - Hypotension or shock due to CDI **OR**
  - Radiographic and clinical evidence of ileus (lack of stooling/flatus, abdominal distension with air fluid levels on radiography) not attributable to another process **OR**
  - Toxic megacolon (severe disease with colonic distension on radiography > 6 cm in any segment) **OR**
  - Peritonitis on exam, free air in abdomen by radiography **AND/OR**
  - Colonic perforation
- **Recurrent:** Renewed disease meeting the above diagnostic criteria after initial resolution of symptoms has occurred **AND** occurring within 8 weeks of previous episode or after new systemic antibiotic use.
  - Note: after clinical response, it may take weeks for stool consistency and frequency to become entirely normal.
- **Multiple Recurrences:** ≥ 2 recurrences of disease following the initial episode with each distinct episode meeting the diagnostic criteria above.

### Treatment Recommendations for CDI

Clinical Severity/Stage	First Line Regimen	Alternative Regimen	Adjunct Therapy
Initial Episode, Non-severe	Vancomycin 125 mg PO q6h x 10 days	Fidaxomicin 200 mg PO BID x 10 days	
Initial Episode, Severe	Vancomycin 125 mg PO q6h x 10 days	Fidaxomicin 200 mg PO BID x 10 days	
Fulminant	Vancomycin 500 mg PO/NG q6h + Metronidazole 500 mg IV q8h		Rectal Vancomycin <sup>a</sup>
First Recurrence	Fidaxomicin 200 mg BID x 10 days	Vancomycin 125 mg PO q6h x 10 days  <b>OR</b> Vancomycin 125 mg q6h x 10 – 14 days, then BID x 7 days, then once daily x 7 days, then every 2-3 days x 2-8 weeks	Bezlotoxumab 10 mg/kg IV once during treatment
Second or Subsequent Recurrence	Vancomycin 125 mg q6h x 10 – 14 days, then BID x 7 days, then once daily x 7 days, then every 2-3 days x 2-8 weeks	Vancomycin 125 mg q6h PO x 10 days <b>OR</b> <u>If Fidaxomicin not previously used:</u> Fidaxomicin 200 mg BID x 10 days <b>OR</b> Fidaxomicin BID x 5 days followed by once every other day x 20 day	Bezlotoxumab 10 mg/kg IV once during treatment

a: Consider rectal Vancomycin (500 mg in 100 mL NS enema q6h) if ileus present. Avoid if toxic megacolon.

### Criteria for Bezlotoxumab use:

- Recurrent CDI episode within the past six months

**OR**

- $\geq 1$  of the following are present:
  - Age  $\geq 65$  years
  - Immunocompromised (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
  - Severe CDI on presentation

### SUPPORTING EVIDENCE

#### CDI Initial Episode

Newly updated guidelines recommend fidaxomicin as the preferred therapy for an initial episode as well as first, second, and subsequent recurrence. Vancomycin is recommended as an alternative treatment option. Studies have shown that fidaxomicin has a better-sustained response after 4 weeks of ending therapy compared to vancomycin (RR 1.16, 95% CI 1.09 - 1.24). However, the difference in clinical cure (RR 1, 95% CI 0.96 - 1.04) and adverse effects (RR 1.02, 95% CI 0.76 - 1.36) are comparable between the groups. Fidaxomicin failed to show a reduction in all-cause mortality (RR 0.90, 95% CI 0.66 - 1.23). [4-7] Therefore, the UCDHS CDI guideline recommends vancomycin as first-line therapy for initial CDI as the clinical cure rate and adverse effects were similar to fidaxomicin, and it is relatively inexpensive. Fidaxomicin would be used as an alternative regimen or first line for the high-risk patient population (age  $>65$  years, immunocompromised).

#### CDI Recurrence

The UCDHS CDI guideline recommends fidaxomicin for 1st recurrence as studies have shown higher sustained response following 30 days end of therapy compared to vancomycin (RR 1.23, 95% CI 1.01 - 1.49). Studies have shown a relative risk of 2 (95% CI 0.88 - 4.54) for sustained response to fidaxomicin after 30 days end of therapy for  $>2$  recurrences compared to vancomycin. Vancomycin (extended, tapered, or pulse regimen) has been used successfully in treating multiple recurrences of CDI. [4-6] Therefore, the UCDHS CDI guideline recommends vancomycin tapered and pulse regimen as a first-line treatment option and fidaxomicin as an alternative option for second or subsequent recurrence.

#### Fulminant CDI

The UCDHS CDI guidelines recommend vancomycin +metronidazole +/- vancomycin enema to treat fulminant CDI. There is no data supporting the use of fidaxomicin for fulminant CDI.

#### Adjunct Therapy

The UCDHS CDI guidelines recommend bezlotoxumab as an adjunct therapy in case of recurrent CDI episode within the past 6 months as 2 RCTs have shown reduced CDI recurrence (RR: .62; 95% CI 0.51 - 0.75) and hospital readmission (RR: .46; 95% CI 0.29 - 0.71) with bezlotoxumab along with the standard of care antibiotics. Bezlotoxumab can also be considered for patients with an initial episode of CDI with  $\geq 1$  risk factor of recurrence ( $\geq 65$  years, immunocompromised, or severe CDI on presentation) as it is associated with risk difference of  $-15.1\%$  (95% CI  $-22.0\%$  to  $-8.1\%$ ) compared to  $-1.5\%$  (95% CI  $-10.7\%$  to  $7.7\%$ ) without any risk factors. [8-9]. The timing of administration of bezlotoxumab had no effect on cure or recurrence in at study including over 1500 participates, they authors recommend administration during the treatment course 10 to 14 days. Rates were lower in the bezlotoxumab group compared to placebo. [10]

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<b>Approving committee(s):</b>	Antibiotic Subcommittee; P&T Committee

Revision History	
Revision Date	Update(s)
10\2021 (NEW)	NA