SHC Clinical Pathway
Guidelines for the Treatment of *Clostridium difficile* Infection – 2018 Update

Table 1. CDI Treatment Guidelines for SHC Indexed by Severity

<table>
<thead>
<tr>
<th>Clinical Severity/Stage</th>
<th>First Line Regimen</th>
<th>Alternative Regimen</th>
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</table>
| **Non-Severe**          | • Vancomycin 125mg PO q6h x 10-14 days  
                          • Fidaxomicin 200mg PO BID x 10 days (if criteria met)  
                          | Metronidazole 500mg PO TID x 10-14 days  
                          - Only if vancomycin and fidaxomicin are unavailable |
| **Severe** (WBC>15,000, Creatinine >1.5x Baseline) | Vancomycin 125mg PO q6h x 10-14 days  
                          | Fidaxomicin† 200mg PO BID x 10 days |
| **Fulminant** (hypotension or shock, ileus or toxic megacolon due to CDI) | Vancomycin 500mg PO q6h + Metronidazole IV 500mg TID  
                          - Consider PR Vancomycin 500mg in 100ml NS enema q6h if no toxic megacolon  
                          - Surgical and ID consults indicated  
                          | No alternative recommended |
| **First Recurrence** (non-fulminant) | If Metronidazole used first:  
                          - Vancomycin 125mg PO q6h x 10-14 days  
                          - Fidaxomicin 200mg PO x 10 days  
                          | If Vancomycin or Fidaxomicin used first:  
                          - Fidaxomicin 200mg PO x 10 days  
                          - Vancomycin PO 125mg q6h x 10-14d, then BID x 7d, then daily x 7d, then q2-3d x 2-8 weeks  |
| **Multiply Recurrent** (non-fulminant) | • Vancomycin PO 125mg q6h x 10-14d, then BID x 7d, then daily x 7d, then q2-3d x 2-8 weeks  
                          • Fidaxomicin† 200mg PO BID x 10d (if not previously used)  
                          | • Vancomycin 125mg PO q6h for 14d followed by Rifaximin 400mg PO BID for 14d  
                          • Fecal Microbiota Transplant. Consult ID and GI for evaluation |

Bezlotoxumab 10mg/kg IV x 1 may be used as adjuvant therapy for recurrence prevention with any stage of disease with ID consult and if criteria are met and should be strongly considered as part of treatment for recurrent disease. Bezlotoxumab may be given at any time during the 10-14 day course of antimicrobial therapy and it is preferable, for non-medical reasons, that the infusion be administered in the out-patient setting when possible.

**Fidaxomicin + Bezlotoxumab Restriction Criteria**

†Restriction criteria for use of fidaxomicin or bezlotoxumab (ID consultation required for bezlotoxumab):

1) Recurrent disease
   OR
2) ≥2 of the following risk factors for recurrence are present:
   a. Age ≥65
   b. Meets criteria for severe CDI
   c. Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
   d. Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
I. **Purpose:** to provide guidance for the treatment of patients with *Clostridium difficile* infection within Stanford Health Care.

II. **Background**

Guidelines for the treatment of *Clostridium difficile* infection (CDI) were first produced by the Stanford Division of Infectious Diseases and Geographic Medicine in 2015, based, in large part, on the 2010 IDSA/SHEA guidelines.¹ These institutional guidelines were updated in 2017 to reflect further advancements in evaluation, diagnosis, and treatment of patients with CDI. Since this update, the next iteration of IDSA/SHEA guidelines has been published,² thus requiring additional revision to the institutional guidelines to ensure that local recommendations are in line with current published evidence.

III. **Procedures/Guidelines**

A. **Diagnostic Criteria for CDI:**

1. Diarrhea (≥3 unformed stools over 24 or fewer consecutive hours in a hospitalized patient, OR ≥3 unformed stools per day for at least 2 consecutive days or ≥8 loose stools in 48 hours in outpatients) OR significant worsening in patients with chronic diarrhea (e.g. inflammatory bowel disease) OR increased output from any ostomy site in the setting of recent antibiotic use. These criteria are most useful for diagnosis in the absence of obvious alternative explanations such as laxative use or recent initiation of enteral feedings.¹-⁴

AND

2. A positive stool PCR and CT (cycle threshold, see below)-toxin for *C. difficile* toxin B or visualization of pseudomembranous colitis on endoscopy (if other causes of pseudomembranes are felt to be less likely).⁵-¹⁰ Positive stool PCR and negative CT-toxin for toxin B should be considered colonization unless there is truly no alternative cause of diarrhea present.

OR

3. Abdominal distension and severe pain after a period of diarrhea without current stool output may be a rare finding if ileus or toxic megacolon is present.¹¹ In this setting, effort should be made to send a *C. difficile* PCR from a rectal swab with trace amount of stool (notify microbiology lab prior to sending as swab specimens will be rejected unless prior approval from lab is given).¹

B. **Microbiology Lab Testing Criteria for *C. difficile* PCR**

(Must be met for lab to accept sample)

1. ≥3 loose or watery stools per 24 hr.
2. Unformed stool specimen (conforms to the shape of the container). Exceptions include patients with ileus or toxic megacolon. Please contact the lab to request an exception to this policy.
3. No previous PCR test within the last 7 days.
4. No use of laxatives (excluding docusate) within the past 48 hours or recent initiation of enteral feedings.

Stool PCR for *C. difficile* toxin B is thought to be ≥98% sensitive for disease or colonization, and there is no indication for repeat testing within 7 days of a negative result as the result rarely converts during
this period. Repeat testing beyond 7 days from an initial negative test should be done only if initial symptoms resolve and new diarrhea starts. Asymptomatic colonization with toxigenic *C. difficile* is relatively common (12% of all hospitalized patients in a recent study), and treatment is not indicated for this. Recent studies, including on-going projects at Stanford, have also shown that patients who are positive for *C. difficile* by PCR but negative by a direct toxin test have low-risk of CDI-related complications and do not require treatment. Stanford recently validated a predicted toxin assay based on the cycle threshold (CT) of the *C. difficile* Xpert PCR and showed 99% sensitivity at a specific cut-off value. In light of these clinical findings, Stanford now reports only CT-toxin, with treatment indicated in patients who have a positive result. It is important that patients meet testing criteria before sending stool for *C. difficile* toxin PCR to ensure tests are used in patients with the highest pre-test probability of CDI.

There is no indication for test of cure for CDI and patients should be followed clinically for improvement.

### C. Stage of Disease:

After the diagnosis is made, it is important to stage the disease to guide treatment by both severity (ranging from non-severe to fulminant) and symptom recurrence (first recurrence to multiply recurrent).

1. **Non-Severe**: Diarrhea present, systemic inflammatory response as assessed by other symptoms (e.g. fatigue, fever), leukocytosis, or elevated serum creatinine may or may not be present, but white blood cell (WBC) count <15,000 cells/µL AND serum creatinine is <1.5mg/dL (unless attributable to pre-existing co-morbidities).

2. **Severe**: Diarrhea plus systemic inflammatory response as assessed by other symptoms (e.g. fatigue, fever), leukocytosis, or elevated serum creatinine likely present, WBC ≥15,000 cells/µL OR serum creatinine elevation >1.5 mg/dL and not attributable to pre-existing co-morbidities.

3. **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 >6cm in any segment) OR has peritonitis on exam, free air in abdomen by radiography AND/OR colonic perforation.

4. **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.

5. **Multiply Recurrent**: ≥2 recurrences of disease following the initial episode with each distinct episode meeting the diagnostic criteria above.

### D. Treatment

In addition to the below recommendations, unnecessary antimicrobial agents and proton pump inhibitors should be discontinued.

1. **Non-Severe Disease**
   a. Recommended therapy:
      - Vancomycin 125 mg PO q6h for 10-14 days or Fidaxomicin 200mg PO BID for 10 days if specific criteria (see below) are met.
   b. Alternative therapy:
      - Metronidazole 500mg PO TID for 10-14 days.
Note median time to symptom resolution is 5-6 days. If symptoms resolve within 7 days, 10 days of metronidazole therapy is sufficient; if ≥7 days are required for resolution, 14 days may be preferred (do not use for more than 14 days due to potential neurotoxicity). Metronidazole may be a reasonable treatment for non-elderly patients with mild disease and without immunosuppression in the out-patient setting, especially if the cost of vancomycin and fidaxomicin is a barrier to treatment.  

**Fidaxomicin**  
The criteria for use of fidaxomicin in non-severe disease is as follows:  
1) Recurrent disease (any prior history, though recent infection within the past 8-12 weeks is most significant)  
   OR  
2) ≥2 of the following are present:  
   - Age ≥65  
   - Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection  
   - Significant immunocompromise present (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medication)  

**Bezlotoxumab**  
- Can consider use of adjuvant bezlotoxumab 10 mg/kg IV x 1 to reduce the risk of subsequent recurrence, though it has no effect on the resolution of the initial case of CDI.  
- Bezlotoxumab requires an Infectious Diseases consult, may not be given if fidaxomicin is used as primary therapy (due to insufficient data for additive efficacy), and the following criteria must be met:  
  1. Recurrent disease as defined above  
  OR  
  2. ≥2 of the following are present:  
     - Age ≥65 years  
     - Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)  
     - Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection  
- Bezlotoxumab may be given at any time during the 10-14-day course of antimicrobial therapy for CDI and it is preferable, for non-medical reasons, that the infusion be administered in the out-patient setting when possible.  

2. **Severe Disease**  
Likely requires hospitalization for proper management, should also consider serial abdominal X-rays if abdominal distension or significant tenderness are present. Consultation with Infectious Diseases is advised.  
  
a. Recommended therapy:  
   - Vancomycin 125 mg PO q6h for 10-14d.  

b. Alternative therapy:  
   - Fidaxomicin 200mg PO BID for 10d may be considered. Fidaxomicin may be used if the following criteria are met:  
     1) Recurrent disease as defined above  
     OR  
     2) ≥2 of the following are present:  
        - Age ≥65 years
- Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
- Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
- Meets criteria for severe CDI

**Bezlotoxumab**
- Can consider use of adjuvant bezlotoxumab 10 mg/kg IV x 1 to reduce the risk of subsequent recurrence, though it has no effect on the resolution of the initial case of CDI.32,33
- Bezlotoxumab requires an Infectious Diseases consult, may not be given if fidaxomicin is used as primary therapy (due to insufficient data for additive efficacy), and the following criteria must be met:
  1. Recurrent disease as defined above
  OR
  2. ≥2 of the following are present:
     - Age ≥65 years
     - Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
     - Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
- Bezlotoxumab may be given at any time during the 10-14-day course of antimicrobial therapy for CDI and it is preferable, for non-medical reasons, that the infusion be administered in the out-patient setting when possible.34,35

3. **Fulminant Disease**
   Surgical and Infectious Diseases (ID) consultations are strongly indicated.2,4,14-16,44 Serial abdominal X-rays are necessary if surgery is deferred.
   
a. **Recommended antimicrobial therapy:**
   - Vancomycin 500mg PO q6h plus IV metronidazole 500mg TID, especially if ileus is present.2
   - Consider adding PR vancomycin 500mg in a 100ml normal saline retention enema q6h unless toxic megacolon is present as this confers a high perforation risk.2,45
   The total course should be at least 10 days of oral vancomycin, but longer courses can be determined from time of symptom resolution.2,4,45 Once patients are reliably taking medications by mouth and ileus is resolved, IV metronidazole and PR vancomycin can be stopped.
   
b. **Alternative therapy:**
   - No alternative recommended. Small studies had previously suggested efficacy of tigecycline,46,47 though more recent retrospective analyses did not show significant benefit.48-50 Additionally, tigecycline is no longer on formulary at Stanford Hospital and would have to be specially ordered.

Recommend against fidaxomicin use in this setting due to risk of ileus and delayed absorption. Combination therapy with fidaxomicin and other CDI antibiotics is not superior to standard therapy and may reduce rates of clinical and sustained cure compared to use of fidaxomicin alone.42,43
Surgical intervention is indicated in case of:14-16,44,51,52
1) Perforation of the colon
2) Systemic inflammation and deteriorating clinical condition despite maximal antibiotic therapy; this includes the clinical diagnoses of toxic megacolon, acute abdomen and severe ileus. Colectomy should preferably be performed before colitis becomes very severe. Serum lactate may serve as a marker for severity, with operation suggested before lactate exceeds 5.0 mM/dL. Multiple studies suggest improved outcomes with early surgical intervention in fulminant colitis.

Total abdominal colectomy with end ileostomy has most often been performed for management of fulminant CDI, but subtotal colectomy with rectal preservation is also an option.44 A potential alternative to colectomy may be diverting loop ileostomy and colonic lavage, combined with intracolonic antibiotic treatment.53

Bezlotoxumab
- Can consider use of adjuvant bezlotoxumab 10 mg/kg IV x 1 to reduce the risk of subsequent recurrence, though it has no effect on the resolution of the initial case of CDI.32,33
- Bezlotoxumab requires an Infectious Diseases consult, may not be given if fidaxomicin is used as primary therapy (due to insufficient data for additive efficacy), and the following criteria must be met:
  1. Recurrent disease as defined above
     OR
  2. ≥2 of the following are present:
     - Age ≥65 years
     - Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
     - Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
- Bezlotoxumab may be given at any time during the 10-14 day course of antimicrobial therapy for CDI and it is preferable, for non-medical reasons, that the infusion be administered in the out-patient setting when possible.34,35

4. Recurrent Disease
   1) First Recurrence of Disease

   Recommended Therapy: treatment is dependent on severity and prior therapy.
   - Non-Severe or Severe Disease: Vancomycin 125mg PO q6h for 10-14 days if metronidazole was used as primary therapy.2 If vancomycin was used as primary therapy, options include fidaxomicin 200mg PO BID x 10 days or a vancomycin taper with 125mg PO q6h x 10-14 days, then BID x 1 week, then daily x 1 week, then q2-3 days x 2-8 weeks.2,28,29,54 A second course of vancomycin 125mg PO q6h x 10-14 days is also reasonable if fidaxomicin or a vancomycin taper are not feasible. Metronidazole is not recommended as a treatment for recurrent disease.2
   - Fulminant Disease: Management is the same as primary fulminant disease (see above) with oral vancomycin plus IV metronidazole and vancomycin per rectum via retention enema, especially if ileus is present and toxic megacolon is not. The total course of oral vancomycin should be at least 10 days, though completion of a vancomycin taper after initial stabilizing therapy may be more appropriate.

   2) Multiple Recurrent Disease
   - Infectious Diseases consultation is indicated. Fulminant disease should be managed with the same initial therapy as above no matter what number the recurrence.
Treatment choices for non-fulminant, multiply recurrent disease include the following options:

- **Vancomycin PO 125mg q6h for 10-14 days, then BID x 1 week, then daily x 1 week, then q2-3 days x 2-8 weeks**.\(^2\,5^4\)
- **Fidaxomicin 200mg PO BID for 10 days**\(^2,4,3^6-4^3\) especially if not used previously, though one small series suggested higher rates of recurrence in those with ≥2 prior recurrences.\(^5^5\)
- **Vancomycin 125mg PO q6h for 14 days followed by Rifaximin 400mg PO BID for 14 days**.\(^5^6,5^7\)
- **Fecal Microbiota Transplant**.\(^5^8-6^1\) Requires BOTH Infectious Diseases and Gastroenterology consults. Currently only available via colonoscopy at Stanford.

**Bezlotoxumab**

- Can consider use of adjuvant bezlotoxumab 10 mg/kg IV x 1 to reduce the risk of subsequent recurrence, though it has no effect on the resolution of the initial case of CDI.\(^3^2,3^3\)
- Bezlotoxumab requires an Infectious Diseases consult, may not be given if fidaxomicin is used as primary therapy (due to insufficient data for additive efficacy), and the following criteria must be met:
  1. Recurrent disease as defined above
     OR
  2. ≥2 of the following are present:
     - Age ≥65 years
     - Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
     - Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
- Bezlotoxumab may be given at any time during the 10-14 day course of antimicrobial therapy for CDI and it is preferable, for non-medical reasons, that the infusion be administered in the out-patient setting when possible.\(^3^4,3^5\)

**E. Recurrence Prevention**

Limit repeat antibiotic use and PPI use without a clear indication as these are the epidemiologic risk factors most associated with recurrence. An ID consult or urgent ID outpatient referral is suggested, if possible, prior to starting systemic antibiotics in patient with known CDI history as it may be possible to minimize antibiotic use and/or duration. Recommend considering prior CDI, particularly severe or multiply recurrent disease, as a relative contraindication to antibiotics and PPIs and they should be used only if necessary.\(^4,6^2,6^3\) If antibiotic use is necessary in a patient with a history of CDI, recommend avoidance of clindamycin, cephalosporins, monobactams, carbapenems, fluoroquinolones (particularly moxifloxacin), and β-lactamase inhibitor combinations, if possible.\(^6^4-7^2\) Macrolides, sulfonamides, penicillin, aminopenicillins (e.g. ampicillin or amoxicillin), and aminoglycosides are likely associated with a relatively lower risk of CDI than the other antibiotic classes listed above.\(^6^4,6^5,7^2-7^4\) Metronidazole and tetracyclines, particularly doxycycline, are the antibiotic classes associated with the least risk of CDI and may even be protective.\(^5^5,7^2-7^4\) Lower risk antibiotics should be used preferentially where appropriate. Using multiple antibiotics simultaneously should be avoided if possible as each additional agent used increases the risk of CDI; therefore, regimens should be kept as simple as possible.\(^6^4,6^9,7^4\)

Available evidence for use of probiotic preparations (capsules, powder, yogurts) to prevent CDI occurrence is equivocal due to heterogeneity in studies, and these are not recommended for primary CDI prevention in the 2017 IDSA/SHEA guidelines.\(^1,2,4,7^5-7^7\) though a recent meta-analysis showed
benefit if probiotics were started within 2 days of initiation of broad-spectrum antibiotics.\textsuperscript{78} IF USED: Preparations should include greater than 1 x 10\textsuperscript{6} Colony Forming Units (CFU) of either \textit{Saccharomyces cerevisiae} subtype boulardii, \textit{Bifidobacterium spp.} or \textit{Lactobacillus spp.}. The recent meta-analysis by Shen \textit{et al} showed no statistical superiority of any specific preparation, but did suggest that preparations containing \textit{Lactobacillus spp.}, either alone or in multi-organismal cocktails with \textit{Bifidobacterium spp.} and/or \textit{Streptococcus spp.} may be more beneficial that other types of probiotics,\textsuperscript{76} though the optimal version is yet to be determined. Use should be restricted to prevention in patients currently requiring systemic antibiotics, NOT in patients with active CDI.\textsuperscript{75-77} Probiotics are generally considered low-risk interventions in immunocompetent patients, but their use should be carefully considered in immunocompromised patients as risk may outweigh benefit in this population, as some probiotic organisms have caused disease in these patients.\textsuperscript{79,80}

\section*{F. Infection Control}

The current recommendation is for inpatients with positive \textit{C. difficile} CT-toxin PCR to be placed in contact isolation. Hand washing with soap and water (not alcohol-based cleansers) is necessary after contact with CDI patients or in outbreak situations, otherwise standard hand hygiene recommendations apply as per CDC/SHEA guidelines.\textsuperscript{1,2,81}

\section*{IV. References}


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