### SHC Clinical Pathway: Guidelines for the Treatment of *Clostridium difficile* Infection: 2017 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>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/Moderate</td>
<td>Vancomycin 125mg PO q6h x 10-14 days</td>
<td>1. Fidaxomicin 200mg PO BID x 10 days (if criteria met)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2. Metronidazole 500mg PO TID x 10-14 days</td>
</tr>
<tr>
<td>Severe (WBC&gt;15,000, Creatinine &gt;1.5x Baseline)</td>
<td>Vancomycin 125mg PO q6h x 10-14 days</td>
<td>Fidaxomicin† 200mg PO BID x 10 days</td>
</tr>
<tr>
<td>Severe Complicated (septic shock, ileus or toxic megacolon due to CDI)</td>
<td>Vancomycin 500mg PO q6h + Metronidazole IV 500mg TID</td>
<td>Consider PR Vancomycin 500mg in 100ml NS enema q6h Surgical and ID consults indicated</td>
</tr>
<tr>
<td>First Recurrence</td>
<td>Same as above based on severity</td>
<td>Consider use of vancomycin or fidaxomicin† if not used initially</td>
</tr>
<tr>
<td>Multiple Recurrence</td>
<td>For Severe-Complicated, treat as above until stable.</td>
<td>1. Vancomycin PO 125mg q6h x10d, then BID x7d, then daily x7d, then every other day x21d</td>
</tr>
<tr>
<td></td>
<td>For all others, if not previously used: Fidaxomicin† 200mg PO BID x 10d</td>
<td>2. Vancomycin 125mg PO q6h for 14d followed by Rifaximin 400mg PO BID for 14d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Fecal Microbiota Transplant. Consult ID and GI for evaluation</td>
</tr>
</tbody>
</table>

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.

†Restriction criteria for use of fidaxomicin (mild/moderate disease) or bezlotoxumab (ID consultation required) are:

1) Recurrent disease
   OR
2) ≥2 of the following 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)
3) Applies to fidaxomicin only: severe disease
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. Since publication, further advancements and revisions in evaluation, diagnosis, and treatment of patients with CDI require an update to these guidelines to ensure proper management that is in line with current published evidence.

III. **Procedures/Guidelines**

1. **Definitions**

   **Diagnostic Criteria for CDI:**
   
   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.¹⁻³

   **AND**

   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).⁴⁻⁹ Positive stool PCR and negative CT-toxin for toxin B should be considered colonization unless there is no alternative cause of diarrhea present.

   **OR**

   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.¹⁰ 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, swab specimens will be rejected unless prior approval from lab is given).

   **Stage of Disease:**

   After the diagnosis is made, it is important to stage the disease to guide treatment by both severity (ranging from mild to severe-complicated) and symptom recurrence (first recurrence to multiply recurrent).¹¹⁻¹²

   **Mild disease:** Diarrhea only, no systemic inflammatory response as assessed by other symptoms (e.g. fatigue, fever), leukocytosis, or elevated serum creatinine.

   **Moderate disease:** Systemic symptoms present and/or moderate elevations in white blood cell count (WBC) but <15,000 cells/µL AND serum creatinine elevation <1.5 times the premorbid level.

   **Severe disease:** WBC ≥15,000 cells/µL OR serum creatinine elevation ≥1.5 times the premorbid level and attributable to CDI.¹¹⁻¹²
Severe-Complicated: meets criteria for septic shock due to CDI OR radiographic and clinical evidence of ileus (lack of stooling/flatus, abdominal distension with air fluid levels on radiography) 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.\textsuperscript{10,13-16}

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.\textsuperscript{1,16} Note: after clinical response, it may take weeks for stool consistency and frequency to become entirely normal.

Multiply Recurrent: >1 recurrence of disease, with each distinct episode meeting the diagnostic criteria above.\textsuperscript{1}

2. Evaluation/Diagnosis
Testing Criteria for \textit{C. difficile} PCR (Must be met for lab to accept sample):
1. \geq 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 \textit{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.\textsuperscript{4} 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 \textit{C. difficile} is relatively common (12\% of all hospitalized patients in a recent study),\textsuperscript{17} and treatment is not indicated for this. Recent studies, including on-going projects at Stanford, have also shown that patients who are positive for \textit{C. difficile} by PCR but negative by a direct toxin test have low-risk of CDI-related complications and do not require treatment.\textsuperscript{18-21} Stanford recently validated a predicted toxin assay based on the cycle threshold (CT) of the \textit{C. difficile} Xpert PCR and showed 96\% sensitivity at a specific cut-off value.\textsuperscript{9} In light of these clinical findings, Stanford reports both the PCR result and CT-toxin with treatment indicated only for CT-toxin-positive patients. It is important that patients meet testing criteria before sending stool for \textit{C. difficile} toxin PCR to ensure tests are used in patients with the highest pre-test probability of CDI.\textsuperscript{1,22}

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

3. Treatment
In addition to the below recommendations, unnecessary antimicrobial agents and proton pump inhibitors should be discontinued.
Mild/Moderate Disease
Recommended therapy: Vancomycin 125 mg PO q6h for 10-14d.\textsuperscript{23-26}
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 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).\textsuperscript{23-28} Metronidazole may be an appropriate treatment for non-elderly patients with mild disease and without immunosuppression, especially if cost of vancomycin is a barrier to treatment. Fidaxomicin 200mg PO BID for 10 days may be considered if either of the following criteria are met:\textsuperscript{29,30}
1) Recurrent disease (any prior history, though recent infection within the past 8-12 weeks is most significant)
OR ≥2 of the following are present:
   1) Age ≥65
   2) Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
   3) Significant immunocompromise present (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medication)

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 cure of the initial case of CDI.\textsuperscript{31,32} Bezlotoxumab requires an Infectious Diseases consult, may not be given if fidaxomicin is used as primary therapy, and the following criteria must be met:
1) Recurrent disease as defined above
OR ≥2 of the following are present:
   1) Age ≥65 years
   2) Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy)
   3) Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection

Severe Disease
Likely requires hospitalization, should also consider serial abdominal X-rays if abdominal distension or tenderness are present. Consultation with Infectious Diseases is recommended.
Recommended therapy: Vancomycin 125 mg PO q6h for 14d.\textsuperscript{23-26,33-35}
Alternative therapy: Fidaxomicin 200mg PO BID for 10d may be considered.\textsuperscript{29,30,36-43} Fidaxomicin may be used if the following criteria are met:
1) Recurrent disease as defined above
OR ≥2 of the following are present:
   1) Age ≥65 years
   2) Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
   3) Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
   4) Meets criteria for severe CDI

Can also consider use of adjuvant bezlotoxumab 10 mg/kg IV x 1 to reduce the risk of subsequent recurrence, though it has no effect on cure of the initial case of CDI.\textsuperscript{31,32} Bezlotoxumab requires an Infectious Diseases consult, may not be given if fidaxomicin is used as primary therapy, and the following criteria must be met:
1) Recurrent disease as defined above
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1) Age ≥65 years
2) Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
3) Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
4) Meets criteria for severe CDI

Severe-Complicated Disease
Surgical and Infectious Diseases (ID) consultations are strongly indicated.\textsuperscript{13-15} Serial abdominal X-rays are necessary if surgery is deferred. Recommended therapy: Vancomycin 500mg PO q6h and IV metronidazole 500mg TID. Consider PR vancomycin 500mg in a 100ml normal saline retention enema q6h unless toxic megacolon is present as this confers a high perforation risk. The total course should be at least 10d but longer courses can be determined from time of symptom resolution.\textsuperscript{1,35,44}

Alternative therapy: No alternative recommended. Small studies had previously suggested efficacy of tigecycline,\textsuperscript{45,46} though more recent retrospective analyses did not show significant benefit.\textsuperscript{47-49} 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.\textsuperscript{42,43}

Can also consider use of adjuvant bezlotoxumab 10 mg/kg IV x 1 to reduce the risk of subsequent recurrence, though it has no effect on cure of the initial case of CDI.\textsuperscript{31,32}

Bezlotoxumab requires an Infectious Diseases consult, may not be given if fidaxomicin is used as primary therapy and the following criteria must be met:

1) Recurrent disease as defined above
OR ≥2 of the following are present:

1) Age ≥65 years
2) Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection
3) Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications)
4) Meets criteria for severe CDI

Surgical intervention is indicated in case of:\textsuperscript{13-16}

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.

A potential alternative to colectomy may be diverting loop ileostomy and colonic lavage, combined with antibiotic treatment.\textsuperscript{50}
First Recurrence of Disease
The recommendation is for the same therapy as for initial episode, adjusted for severity as above. If metronidazole was used initially, would consider treatment with vancomycin or fidaxomicin if criteria are met.

Multiply Recurrent Disease
Infectious Diseases consultation is indicated. If severe-complicated, treat as above until stabilized, then continue as discussed below.

Treatment choices include the following options:
1. Fidaxomicin 200mg PO BID for 10 days.
2. Vancomycin 125mg PO q6h for 14 days followed by Rifaximin 400mg PO BID for 14 days.
3. Vancomycin PO 125mg q6h for 10 days, then BID for 7 days, then daily for 7 days, then every other day for 21 days or until symptoms tolerate.

Recurrence prevention
Limit repeat antibiotic use and PPI use 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. 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. Macrolides, sulfonamides, penicillin or aminopenicillins and aminoglycosides are likely associated with a relatively lower risk of CDI than the other antibiotic classes listed above. Metronidazole and tetracyclines, particularly doxycycline, are the antibiotic classes associated with the least risk of CDI and may even be protective. 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.

Available evidence for use of probiotic preparations (capsules, powder, yogurts) to prevent CDI occurrence is equivocal due to heterogeneity in studies, and risk is low in immunocompetent patients, though a recent meta-analysis showed benefit if probiotics were started within 2 days of initiation of broad-spectrum antibiotics. IF USED: Preparations should include greater than $1 \times 10^9$ Colony Forming Units (CFU) of either *Saccharomyces cerevisiae* subtype *boulardii*, *Bifidobacterium spp.* or *Lactobacillus spp.* The recent meta-analysis by Shen et al showed no statistical superiority of any specific preparation, but did suggest that preparations containing *Lactobacillus spp.*, either alone or in multi-organismal cocktails with *Bifidobacterium spp.* and/or *Streptococcus spp.* may be more beneficial than other types of probiotics, though the optimal version is yet to be determined. Use should be restricted to prevention in patients currently...
Infection Control

The current recommendation is for inpatients with positive C. difficile toxin PCR, regardless of CT-toxin result, 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{1,75}

IV. References


