SHC Clinical Pathway

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

Table 1. CDI Treatment Guidelines for SHC Indexed by Severity

Clinical Severity/Stage	First Line Regimen	Alternative Regimen
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)	<u>If Metronidazole used first</u>: - Vancomycin 125mg PO q6h x 10-14 days - Fidaxomicin 200mg PO x 10 days <u>If Vancomycin or Fidaxomicin used first</u>: - 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.

<u>Fidaxomicin + Bezlotoxumab Restriction Criteria</u>

†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.[2,5] 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),[18] 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.[19-22] 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.[10] 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.[1,2,23] 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).[1,2]

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/uL AND serum creatinine is <1.5mg/dL (unless attributable to pre-existing co-morbidities).[2]
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.[2]
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.[1,2,11,14-17]
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.[1,2,4,17] 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.[1,2,4]

D. Treatment

In addition to the below recommendations, unnecessary antimicrobial agents and proton pump inhibitors should be discontinued.[2,4]

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.[2,24-29]
    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).[30,31] 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.[2]

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.[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]

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.[2,24-27]

b. Alternative therapy:
   - Fidaxomicin 200mg PO BID for 10d may be considered.[2,28,29,36-43] 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.[2,54]
- Fidaxomicin 200mg PO BID for 10 days,[2,4,36-43] especially if not used previously, though one small series suggested higher rates of recurrence in those with ≥2 prior recurrences.[55]
- Vancomycin 125mg PO q6h for 14 days followed by Rifaximin 400mg PO BID for 14 days.[56,57]
- Fecal Microbiota Transplant.[58-61] 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.[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]

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.[4,62,63] 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.[64-72] 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.[64,65,72-74] Metronidazole and tetracyclines, particularly doxycycline, are the antibiotic classes associated with the least risk of CDI and may even be protective.[65,72-74] 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.[64,69,74]

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,[1,2,4,75-77] though a recent meta-analysis showed

benefit if probiotics were started within 2 days of initiation of broad-spectrum antibiotics.[78] IF USED: Preparations should include greater than 1 x 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 that other types of probiotics,[78] 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.[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.[79,80]

F. Infection Control

The current recommendation is for inpatients with positive *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.[1,2,81]

IV. References

1. Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH; Society for Healthcare Epidemiology of America; Infectious Diseases Society of America. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010 May; 31(5): 431-55.
2. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, Dubberke ER, Garey KW, Gould CV, Kelly C, Loo V, Sammons JS, Sandora TJ, Wilcox MH. 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). Clin Infect Dis. 2018; 66(7): e1-e48.
3. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of Clostridium difficile infection. N Engl J Med. 1989 Jan 26; 320(4): 204-10.
4. Debast SB, Bauer MP, Kuijper EJ; Committee. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. Clin Microbiol Infect. 2014 Mar; 20 Suppl 2: 1-26.
5. Luo RF, Banaei N. Is repeat PCR needed for diagnosis of Clostridium difficile infection? J Clin Microbiol. 2010 Oct; 48(10): 3738-41.
6. Musher DM, Stager C. Diagnosis of Clostridium difficile infection. Clin Infect Dis. 2012 Jun; 54(11): 1675-6.
7. Kufelnicka AM, Kirn TJ. Effective utilization of evolving methods for the laboratory diagnosis of Clostridium difficile infection. Clin Infect Dis. 2011 Jun 15; 52(12): 1451-7.
8. Chhatrala R, Patel S, Chow W. Pseudomembranes Do Not Always Indicate Clostridium difficile Infection. Clin Gastroenterol Hepatol. 2014 Dec; 12(12): A21-2.
9. Tang DM, Urrunaga NH, De Groot H, von Rosenvinge EC, Xie G, Ghazi LJ. Pseudomembranous Colitis: Not Always Caused by Clostridium difficile. Case Rep Med. 2014; 2014: 812704.
10. Senchyna F, Gaur RJ, Gombar S, Truong CY, Schroeder LF, Banaei N. Clostridium difficile PCR cycle threshold predicts free toxin. J Clin Microbiol. 2017 Sep; 55(9): 2651-60.
11. Kyne L, Merry C, O'Connell B, Kelly A, Keane C, O'Neill D. Factors associated with prolonged symptoms and severe disease due to Clostridium difficile. Age Ageing. 1999 Mar; 28(2): 107-13.
12. Loo VG, Poirier L, Miller MA, Oughton M, Libman MD, Michaud S, Bourgault AM, Nguyen T, Frenette C, Kelly M, Vibien A, Brassard P, Fenn S, Dewar K, Hudson TJ, Horn R, René P, Monczak Y, Dascal A. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med. 2005 Dec 8; 353(23): 2442-9.
13. Pépin J, Valiquette L, Alary ME, Villemure P, Pelletier A, Forget K, Pépin K, Chouinard D. Clostridium difficile-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004 Aug 31; 171(5): 466-72.
14. Levine CD. Toxic megacolon: diagnosis and treatment challenges. AACN Clin Issues. 1999 Nov; 10(4): 492-9.
15. Gan SI, Beck PL. A new look at toxic megacolon: an update and review of incidence, etiology, pathogenesis, and management. Am J Gastroenterol. 2003 Nov; 98(11): 2363-71.
16. Lamontagne F, Labbé AC, Haeck O, Lesur O, Lalancette M, Patino C, Leblanc M, Laverdière M, Pépin J. Impact of emergency colectomy on survival of patients with fulminant Clostridium difficile colitis during an epidemic caused by a hypervirulent strain. Ann Surg. 2007 Feb; 245(2): 267-72.
17. Olson MM, Shanholtzer CJ, Lee JT Jr, Gerding DN. Ten years of prospective Clostridium difficile-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982-1991. Infect Control Hosp Epidemiol. 1994 Jun; 15(6): 371-81.
18. Guerrero DM, Becker JC, Eckstein EC, Kundrapu S, Deshpande A, Sethi AK, Donskey CJ. Asymptomatic carriage of toxigenic Clostridium difficile by hospitalized patients. J Hosp Infect. 2013 Oct; 85(2): 155-8.

19. Polage CR, Gyorke CE, Kennedy MA, Leslie JL, Chin DL, Wang S, Nguyen HH, Huang B, Tang YW, Lee LW, Kim K, Taylor S, Romano PS, Panacek EA, Goodell PB, Solnick JV, Cohen SH. Overdiagnosis of Clostridium difficile infection in the molecular test era. JAMA Intern Med. 2015 Nov; 175(11): 1792-801.
20. Baker I, Leeming JP, Reynolds R, Ibrahim I, Darley E. Clinical relevance of a positive molecular test in the diagnosis of Clostridium difficile infection. J Hosp Infect. 2013 Aug; 84(4): 311-5.
21. Planche TD, Davies KA, Cohen PG, Finney JM, Monahan IM, Morris KA, O'Connor L, Oakley SJ, Pope CF, Wren MW, Shetty NP, Crook DW, Wilcox MH. Differences in outcome according to Clostridium difficile testing method: a prospective, multicenter diagnostic validation study of C. difficile infection. Lancet Infect Dis. 2013 Nov; 13(11): 936-45.
22. Polage CR, Chin DL, Leslie JL, Tang J, Cohen SH, Solnick JV. Outcomes in patients tested for Clostridium difficile toxins. Diagn Microbiol Infect Dis. 2012 Dec; 74(4): 369-73.
23. Kyne L, Warny M, Qamar A, Kelly CP. Asymptomatic carriage of Clostridium difficile and serum levels of IgG antibody against toxin A. N Engl J Med. 2000 Feb 10; 342(6): 390-7.
24. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. Clin Infect Dis. 2007 Aug 1; 45(3): 302-7.
25. Johnson S, Louie TJ, Gerding DN, Cornely OA, Chasan-Taber S, Fitts D, Gelone SP, Broom C, Davidson DM, Polymer Alternative for CDI Treatment (PACT) investigators. Vancomycin, metronidazole, or tovelamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. Clin Infect Dis. 2014 Aug 1; 59(3): 345-54.
26. Stevens VW, Nelson RE, Schwab-Daugherty EM, Khader K, Jones MM, Brown KA, Greene T, Croft LD, Neuhauser M, Glassman P, Goetz MB, Samore MH, Rubin MA. Comparative effectiveness of vancomycin and metronidazole for the prevention of recurrence and death in patients with Clostridium difficile infection. JAMA Intern Med. 2017 Apr; 177(4): 546-53.
27. Nelson RL, Suda KJ, Evans CT. Antibiotic treatment for Clostridium difficile-associated diarrhoea in adults. Cochrane Database Syst Rev. 2017; 3: CD004610.
28. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, Gorbach S, Sears P, Shue YK; OPT-80-003 Clinical Study Group. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Engl J Med. 2011 Feb 3; 364(5): 422-31.
29. Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, Sears P, Gorbach S; OPT-80-004 Clinical Study Group. Fidaxomicin versus vancomycin for infection with Clostridium difficile in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis. 2012 Apr; 12(4): 281-9.
30. Belmares J, Gerding DN, Parada JP, Miskevics S, Weaver F, Johnson S. Outcome of metronidazole therapy for Clostridium difficile disease and correlation with a scoring system. J Infect. 2007 Dec; 55(6): 495-501.
31. Kapoor K, Chandra M, Nag D, Paliwal JK, Gupta RC, Saxena RC. Evaluation of metronidazole toxicity: a prospective study. Int J Clin Pharmacol Res. 1999;19(3):83-8. PubMed PMID: 10761537
32. Wilcox MH, Gerding DN, Poxton IR, Kelly C, Nathan R, Birch T, Cornely OA, Rahav G, Bouza E, Lee C, Jenkin G, Jensen W, Kim YS, Yoshida J, Gabryelski L, Pedley A, Eves K, Tipping R, Guris D, Kartsonis N, Dorr MB, MODIFY I and MODIFY II Investigators. Bezlotoxumab for prevention of recurrent Clostridium difficile infection. New Engl J Med. 2017 Jan; 376(4): 305-17.
33. Lowy I, Molrine DC, Leav BA, Blair BM, Baxter R, Gerding DN, Nichol G, Thomas WD, Leney M, Sloan S, Hay CA, Ambrosino DM. Treatment with monoclonal antibodies against Clostridium difficile toxins. New Engl J Med. 2010 Jan; 362(3): 197-205.
34. Birch T, Golan Y, Rizzardini G, Jensen E, Gabryelski L, Guris D, Dorr MB. Efficacy of bezlotoxumab based on timing of administration relative to start of antibacterial therapy for *Clostridium difficile* infection [published online ahead of print May 16 2018]. J Antimicrob Chemother. Accessed May 29 2018.
35. Ritter TE, Hengel RL, Fitzsimmons CJ, Garey K, Van Anglen LJ, Schroeder CP, Marcella SW, Hawkshead JJ. Real world experience of bezlotoxumab for prevention of recurrent *C. difficile* infection: a single-arm multicenter pilot study in office infusion centers. Paper presented at: Digestive Disease Week; June, 2018; Washington, DC. https://ddw.scientificposters.com/epsAbstractDDW.cfm?id=1. Accessed August 17 2018.
36. Mullane KM, Miller MA, Weiss K, Lentnek A, Golan Y, Sears PS, Shue YK, Louie TJ, Gorbach SL. Efficacy of fidaxomicin versus vancomycin as therapy for Clostridium difficile infection in individuals taking concomitant antibiotics for other concurrent infections. Clin Infect Dis. 2011 Sep; 53(5): 440-7.
37. Crook DW, Walker AS, Kean Y, Weiss K, Cornely OA, Miller MA, Esposito R, Louie TJ, Stoesser NE, Young BC, Angus BJ, Gorbach SL, Peto TE; Study 003/004 Teams. Fidaxomicin versus vancomycin for Clostridium difficile infection: meta-analysis of pivotal randomized controlled trials. Clin Infect Dis. 2012 Aug; 55 Suppl 2: S93-103.
38. Babakhani F, Bouillaut L, Sears P, Sims C, Gomez A, Sonenshein AL. Fidaxomicin inhibits toxin production in Clostridium difficile. J Antimicrob Chemother. 2013 Mar; 68(3): 515-22.
39. Louie TJ, Cannon K, Byrne B, Emery J, Ward L, Eyben M, Krulicki W. Fidaxomicin preserves the intestinal microbiome during and after treatment of Clostridium difficile infection (CDI) and reduces both toxin reexpression and recurrence of CDI. Clin Infect Dis. 2012 Aug; 55 Suppl 2: S132-42.
40. Babakhani F, Bouillaut L, Gomez A, Sears P, Nguyen L, Sonenshein AL. Fidaxomicin inhibits spore production in Clostridium difficile. Clin Infect Dis. 2012 Aug; 55 Suppl 2: S162-9.
41. Eiland EH, Sawyer AJ, Massie NL. Fidaxomicin use and clinical outcomes for Clostridium difficile-associated diarrhea. Infect Dis Clin Pract. 2015 Jan; 23(1): 32-5.
42. Fehér C, Múñez Rubio E, Merino Amador P, Delgado-Iribarren Garcia-Campero A, Salavert M, Merino E, Masedo Garrido E, Díaz-Brito V, Álvarez MJ, Mensa J. The efficacy of fidaxomicin in the treatment of Clostridium difficile infection in a real-world clinical setting: a Spanish multi-centre retrospective cohort. Eur J Clin Microbiol Infect Dis. 2017 Feb; 36(2): 295-303.
43. Vargo CA, Bauer KA, Mangino JE, Johnston JEW, Goff DA. An antimicrobial stewardship program's real-world experience with fidaxomicin for treatment of Clostridium difficile infection: a case series. Pharmacotherapy. 2014 Sep; 34(9): 901-9.
44. Napolitano LM and Edmiston, Jr CE. *Clostridium difficile* disease: diagnosis, pathogenesis, and treatment update. Surgery. 2017; 162(2): 325-48.
45. Apisarnthanarak A, Razavi B, Mundy LM. Adjunctive intracolonic vancomycin for severe Clostridium difficile colitis: case series and review of the literature. Clin Infect Dis. 2002 Sep 15; 35(6): 690-6.
46. Larson KC, Belliveau PP, Spooner LM. Tigecycline for the treatment of severe Clostridium difficile infection. Ann Pharmacother. 2011 Jul; 45(7-8): 1005-10.
47. Garneau JR, Valiquette L, Fortier LC. Prevention of Clostridium difficile spore formation by sub-inhibitory concentrations of tigecycline and piperacillin/tazobactam. BMC Infect Dis. 2014 Jan; 14: 29.

48. Manea E, Sojo-Dorado J, Jipa RE, Benea SN, Rodríguez-Baño J, Hristea A. The role of tigecycline in the management of Clostridium difficile infection: a retrospective cohort study. Clin Microbiol Infect. 2018; 24(2): 180-4.
49. Brinda BJ, Pasikhova Y, Quilitz RE, Thai CM, Greene JN. Use of tigecycline for the management of Clostridium difficile colitis in oncology patients and case series of breakthrough infections. J Hosp Infect. 2017 Apr; 95(4): 426-32.
50. LaSalvia MT, Branch-Elliman W, Snyder GM, Mahoney MV, Alonso CD, Gold HS, Wright SB. Does adjunctive tigecycline improve outcomes in severe-complicated, non-operative Clostridium difficile infection? Open Forum Infect Dis. 2017 Feb; 4(1): ofw264.
51. Sailhamer EA, Carson K, Chang Y, Zacharias N, Spaniolas K, Tabarra M, Alam HB, DeMoya MA, Velmahos GC. Fulminant *Clostridium difficile* colitis: patterns of care and predictors of mortality. Arch Surg. 2009; 144(5): 433-9.
52. Osman KA, Ahmed MH, Hamad MA, Mathur D. Emergency colectomy for fulminant *Clostridium difficile* colitis: striking the right balance. Scand J Gastroenterol. 2011; 46(10): 1222-7.
53. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. Ann Surg. 2011 Sep; 254(3): 423-7; discussion 427-9.
54. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent Clostridium difficile disease. Am J Gastroenterol. 2002 Jul; 97(7): 1769-75.
55. Spiceland CM, Khanna S, Pardi DS. Outcomes with fidaxomicin therapy in *Clostridium difficile* infection. J Clin Gastroenterol. 2018; 52(2): 151-4.
56. Garey KW, Ghantoji SS, Shah DN, Habib M, Arora V, Jiang ZD, DuPont HL. A randomized, double-blind, placebo-controlled pilot study to assess the ability of rifaximin to prevent recurrent diarrhoea in patients with Clostridium difficile infection. J Antimicrob Chemother. 2011 Dec; 66(12): 2850-5.
57. Johnson S, Schriever C, Galang M, Kelly CP, Gerding DN. Interruption of recurrent Clostridium difficile-associated diarrhea episodes by serial therapy with vancomycin and rifaximin. Clin Infect Dis. 2007 Mar 15; 44(6): 846-8.
58. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis. 2011 Nov; 53(10): 994-1002.
59. Sofi AA, Silverman AL, Khuder S, Garborg K, Westerink JM, Nawras A. Relationship of symptom duration and fecal bacteriotherapy in Clostridium difficile infection-pooled data analysis and a systematic review. Scand J Gastroenterol. 2013 Mar; 48(3): 266-73.
60. Mattila E, Uusitalo-Seppälä R, Wuorela M, Lehtola L, Nurmi H, Ristikankare M, Moilanen V, Salminen K, Seppälä M, Mattila PS, Anttila VJ, Arkkila P. Fecal transplantation, through colonoscopy, is effective therapy for recurrent Clostridium difficile infection. Gastroenterology. 2012 Mar; 142(3): 490-6.
61. Quraishi MN, Widlak M, Bhala N, Moore D, Price M, Sharma N, Iqbal TH. Systematic review with meta-analysis: the efficacy of faecal microbiota transplantation for the treatment of recurrent and refractory *Clostridium difficile* infection. Aliment Pharmacol Ther. 2017; 46: 479-93.
62. Nair S, Yadav D, Corpuz M, Pitchumoni CS. Clostridium difficile colitis: factors influencing treatment failure and relapse--a prospective evaluation. Am J Gastroenterol. 1998 Oct; 93(10): 1873-6
63. Hebert C, Du H, Peterson LR, Robicsek A. Electronic health record-based detection of risk factors for Clostridium difficile infection relapse. Infect Control Hosp Epidemiol. 2013 Apr; 34(4): 407-14.
64. Pakyz AL, Jawahar R, Wang Q, Harpe SE. Medication risk factors associated with healthcare-associated Clostridium difficile infection: a multilevel model case-control study among 64 US academic medical centres. J Antimicrob Chemother. 2014 Apr; 69(4): 1127-31.
65. Baxter R, Ray GT, Fireman BH. Case-control study of antibiotic use and subsequent Clostridium difficile-associated diarrhea in hospitalized patients. Infect Control Hosp Epidemiol. 2008 Jan; 29(1): 44-50.
66. Lin HJ, Hung YP, Liu HC, Lee JC, Lee CI, Wu YH, Tsai PJ, Ko WC. Risk factors for Clostridium difficile-associated diarrhea among hospitalized adults with fecal toxigenic C. difficile colonization. J Microbiol Immunol Infect. 2015 Apr; 48(2): 183-9.
67. Roohullah A, Moniwa A, Wood C, Humble M, Balm M, Carter J, Weinkove R. Imipenem versus piperacillin/tazobactam for empiric treatment of neutropenic fever in adults. Intern Med J. 2013 Oct; 43(10): 1151-4.
68. Khan FY, Abu-Khattab M, Anand D, Baager K, Alaini A, Siddique MA, Mohamed SF, Ali MI, Al Bedawi MM, Naser MS. Epidemiological features of Clostridium difficile infection among inpatients at Hamad General Hospital in the state of Qatar, 2006-2009. Travel Med Infect Dis. 2012 Jul; 10(4): 179-85.
69. Shah K, Pass LA, Cox M, Lanham M, Arnold FW. Evaluating contemporary antibiotics as a risk factor for Clostridium difficile infection in surgical trauma patients. J Trauma Acute Care Surg. 2012 Mar; 72(3): 691-5.
70. Cadena J, Thompson GR 3rd, Patterson JE, Nakashima B, Owens A, Echevarria K, Mortensen EM. Clinical predictors and risk factors for relapsing Clostridium difficile infection. Am J Med Sci. 2010 Apr; 339(4): 350-5.
71. Vernaz N, Hill K, Leggeat S, Nathwani D, Philips G, Bonnabry P, Davey P. Temporal effects of antibiotic use and Clostridium difficile infections. J Antimicrob Chemother. 2009 Jun; 63(6): 1272-5.
72. Brown KA, Khanafer N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob Agents Chemother. 2013 May; 57(5): 2326-32.
73. Doernberg SB, Winston LG, Deck DH, Chambers HF. Does doxycycline protect against development of Clostridium difficile infection? Clin Infect Dis. 2012 Sep; 55(5): 615-20.
74. Stevens V, Dumyati G, Fine LS, Fisher SG, van Wijngaarden E. Cumulative antibiotic exposures over time and the risk of Clostridium difficile infection. Clin Infect Dis. 2011 Jul 1; 53(1): 42-8.
75. Johnston BC, Ma SS, Goldenberg JZ, Thorlund K, Vandvik PO, Loeb M, Guyatt GH. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. Ann Intern Med. 2012 Dec 18; 157(12): 878-88.
76. Goldenberg JZ, Ma SS, Saxton JD, Martzen MR, Vandvik PO, Thorlund K, Guyatt GH, Johnston BC. Probiotics for the prevention of Clostridium difficile-associated diarrhea in adults and children. Cochrane Database Syst Rev. 2013 May 31; 5: CD006095.
77. Allen SJ, Wareham K, Wang D, Bradley C, Hutchings H, Harris W, Dhar A, Brown H, Foden A, Gravenor MB, Mack D. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet. 2013 Oct 12; 382(9900): 1249-57.
78. Shen NT, Maw A, Tmanova LL, Pino A, Ancy K, Crawford CV, Simon MS, Evans AT. Timely use of probiotics in hospitalized adults prevents Clostridium difficile infection: a systematic review with meta-regression analysis. Gastroenterology. 2017; 152(8): 1889-1900.

79. Enache-Angoulvart A, Hennquin C. Invasive *Saccharomyces* infection: a comprehensive review. Clin Infect Dis. 2005; 41(11): 1559-68.
80. Gouriet F, Million M, Henri M, Fournier PE, Raoult D. *Lactobacillus rhamnosus* bacteremia: an emerging clinical entity. Eur J Clin Microbiol Infect Dis. 2012; 31: 2469-80.
81. Dubberke ER, Gerding DN, Classen D, Arias KM, Podgorny K, Anderson DJ, Burstin H, Calfee DP, Coffin SE, Fraser V, Griffin FA, Gross P, Kaye KS, Klompas M, Lo E, Marschall J, Mermel LA, Nicolle L, Pegues DA, Perl TM, Saint S, Salgado CD, Weinstein RA, Wise R, Yokoe DS. Strategies to prevent clostridium difficile infections in acute care hospitals. Infect Control Hosp Epidemiol. 2008 Oct; 29 Suppl 1: S81-92.

V. Document Information

A. Original Author/Date: Matthew Hitchcock, MD, MPH, 8/15/2017

B. Gatekeeper: Antimicrobial Stewardship Program

C. Review and Renewal Requirement

This document will be reviewed every three years and as required by change of law or practice

D. Revision/Review History:

Stan Deresinski, MD: 08/2018
Marisa Holubar, MD: 08/2018
Emily Mui, PharmD: 08/2018
Lina Meng, PharmD: 08/2018
Amy Chang, MD: 08/2018

E. Approvals

1. Antimicrobial Subcommittee: 8/17/2017, 9/6/2018
2. P&T: 9/15/2017

Stanford Health Care
Stanford, CA 94305