Beth Israel Deaconess Medical Center

Interdisciplinary Practice Guidelines for the Diagnosis and Treatment of *Clostridium difficile* Infection (CDI)

The purpose of these treatment guidelines is to offer guidance to providers when treating a patient with CDI. These guidelines will not cover all potential clinical scenarios and clinical judgment is required for optimal application.

1. **Suspected CDI** – Most patients with CDI have exposure to antibiotics within the prior 3 months. Symptoms may include watery diarrhea (≥ 3 unformed stools/24 hours), fever, anorexia, nausea and abdominal pain/tenderness. Ileus may be present in some cases and be associated with abdominal distension and little or no diarrhea. A neutrophilic leukocytosis is common.

   Note: Other causes of diarrhea should be considered. In addition to other infectious agents, common causes of diarrhea in hospitalized patients include recent administration of hyperosmolar tube feeds, drugs (e.g., proton pump inhibitors, lactulose, and laxatives), and/or exacerbations of underlying medical conditions (e.g. inflammatory bowel disease, ischemic colitis).

2. **Initial measures:**
   a. Send stool for nucleic acid amplification assay
      i. The ***illumi****gene*® *C. difficile* assay (Lab Manual - *Clostridium difficile* Amplified DNA assay) is a sensitive and specific test for toxigenic *C. difficile*. This test replaced both the EIA and PCR (send out) assays.
      ii. If positive (or strong clinical suspicion pending positive assay) then proceed with treatment algorithm.
      iii. Due to the sensitivity of this test, submit no more than one stool sample per week and only submit unformed stool samples.
   b. Discontinue treatment with the implicated antibiotic(s) if possible
   c. Initiate steps to correct fluid losses and electrolyte imbalances
   d. Avoid/discontinue antiperistaltic agents (loperamide, diphenoxylate/atropine and opiates) as well as prokinetic agents (e.g., metoclopramide) and laxatives
   e. If positive nucleic acid amplification assay, place patient on contact isolation. Observe infection control policies (Infection Control Manual Infection Control of *C. difficile*)

3. **Other diagnostic tools**
   a. If colonoscopy is performed and reveals characteristic pseudomembranes, progress to treatment algorithm.
   b. If CT scan or xray reveals evidence of pan-colitis or complication such as megacolon, progress to treatment algorithm for Severe or Severe-Complicated CDI

4. **Stratify patients with CDI** based on severity of illness
    a. Mild- Moderate
        i. Diarrhea (≥ 3 but ≤ 6 unformed stools/24 hours) and
        ii. Fever < 101°F (38.3°C) and
        iii. WBC < 15,000/uL and
        iv. Not significantly immunocompromised and
        v. Not a patient with known inflammatory bowel disease and
        vi. Normal albumin (> 2.5 mg/dl) or unchanged from baseline and
        vii. Normal serum creatinine (≤ 1.2 mg/dl) or not significantly changed (< 1.5 X baseline)
    b. Severe
        i. Diarrhea (> 6 unformed stools/24 hours) or
        ii. Fever ≥ 101°F (38.3°C) or
        iii. WBC ≥ 15,000/uL or
        iv. Immunocompromised or
        v. Patient with known inflammatory bowel disease or
        vi. Hypoalbuminemia (≤ 2.5 mg/dl) or
        vii. Serum Cr increase of 1.5 X baseline or
        viii. Transfer from outside hospital for treatment of CDI or
        ix. CT scan or xray reveals evidence of pan-colitis

        NOTE 1: age >65 years is associated with more severe presentations when combined with other risk factors

        NOTE 2: acute reduction in stool output in a patient with severe CDI may suggest ileus/megacolon and these possibilities should be assessed
    c. Severe-Complicated
        i. ICU level care for CDI or
        ii. Evidence of sepsis or
        iii. Presence of ileus or
        iv. Elevated serum lactate (> 2.5 mmol/L) or
        v. WBC ≥ 50,000/uL or
        vi. Hemodynamic instability or pressor requirement or
        vii. Severe abdominal pain or distention or abdominal rigidity or
        viii. CT scan or xray reveals evidence of complication such as megacolon or
        ix. Confluent pseudomembranous colitis seen on colonoscopy

        NOTE 1: age >65 years is associated with more severe presentations when combined with other risk factors

        NOTE 2: acute reduction in stool output in a patient with severe CDI may suggest ileus/megacolon and these possibilities should be assessed

5. **Treatment**
    a. Mild- Moderate
        i. Oral metronidazole 500 mg every 8 hours[1-3]
        ii. If no clinical response (i.e. decrease in diarrhea, resolution of fever, decrease in WBC) in 3-5 days then change to:
        Oral vancomycin 125 mg every 6 hours[2-4]
    b. Severe

i. Oral vancomycin 125 mg every 6 hours[2-4] (use nasogastric tube if necessary)
ii. If no clinical response after 48 hours, add:
IV metronidazole 500 mg every 8 hours
iii. If vomiting or other risk of poor delivery of enteral vancomycin, consider IV metronidazole for initial treatment in this group
iv. Consider Colorectal Surgery or Acute Care Surgery consultation[5]
v. Consider Infectious Diseases consultation

c. Severe-Complicated
i. Initiate empiric treatment of suspected severe-complicated cases while awaiting nucleic acid amplification assay results.
ii. **It is strongly recommended that providers URGENTLY consult Colorectal Surgery or Acute Care Surgery** for consideration of colectomy[5]. If surgery is indicated, perform emergent colectomy prior to lactate reaching 5 mmol/L and prior to WBC exceeding 50,000 for best outcome. If possible, perform subtotal colectomy with rectal sparing.
iii. Oral vancomycin 500 mg every 6 hours (use nasogastric tube if necessary) plus IV metronidazole 500 mg every 8 hours.[1,2,4] Vancomycin dose should be reduced to 125 mg every 6 hours with clinical improvement and certainly before hospital discharge
iv. Particularly in the setting of ileus or more proximal diverting ostomy, add ***rectal vancomycin*** (Pharmacy - Vancomycin Enema for *Clostridium difficile* Infection) ***if determined to be safe by Surgery and/or GI***. Vancomycin enema dosing should be 500 mg in 100 ml of normal saline instilled via rectal catheter as a retention enema every 6 hours (retention for 30 minutes).
v. Consider Infectious Diseases consultation

6. **Patient education –** (Infection Control - Patient information sheet for *C. difficile*)

==========

Footnotes:

[1]**Metronidazole** – Orally administered metronidazole is nearly completely absorbed in the small bowel. The presence of hypotension, vomiting, ileus or other cause of poor absorption from the GI tract warrants IV administration of metronidazole. Otherwise, there is no benefit to the IV route (vs. oral administration) for metronidazole.

[2] **Treatment Duration** - Generally 10-14 days. Some experts recommend continuing therapy for 7-10 days after symptoms have resolved. In cases when the offending antibiotic can not be discontinued, some experts recommend continuing CDI therapy through completion of the offending antibiotic.

[3]There is **no proven benefit to combination therapy** for uncomplicated CDI.

[4]**Vancomycin** – The correct dose for oral vancomycin is 125 mg PO every 6 hours for all but the most severe cases. Enteral administration of vancomycin achieves extremely high luminal concentrations and there are no data to suggest that higher doses produce superior efficacy. However, because there are very limited comparative data in severe-

complicated disease the higher dose (500 mg PO every 6 hours) is favored in this specific patient group by expert opinion (CIII level recommendation). Enteral vancomycin is not absorbed to a significant degree under most circumstances, although it may accumulate in patients with severe colitis and renal failure. BIDMC uses IV vancomycin solution to compound oral doses. Vancomycin capsules are very expensive and many outpatient pharmacies do not compound the IV solution for oral use, so patients should typically be discharged on the lower dose (125 mg PO every 6 hours). Parenteral (IV) vancomycin does not reach the bowel lumen and is never appropriate treatment for CDI.

[5]**Emergency colectomy** reduces mortality in some patients with fulminant CDI. In one series of ICU patients observed during an outbreak of hypervirulent CDI, colectomy reduced mortality by 78%. Mortality after colectomy was much higher for patients with preoperative lactate ≥ 5 mmol/L and/or WBC >50,000, so for greatest mortality benefit colectomy should be considered and if indicated performed in patients with severe/complicated disease prior to lactate reaching 5 mmol/L.

==========

Other notes regarding the treatment of CDI:

1. **Fidaxomicin** was recently approved by FDA to treat *C. difficile* infection. It was not studied in severe-complicated infection or in patients with multiple recurrences. In moderate-severe disease, it was non-inferior to oral vancomycin, but there were fewer recurrences in some subsets. It is ~ 100x more expensive than orally administered vancomycin. It is currently non-formulary pending further review.
2. **Cholestyramine has limited utility** as a toxin binder and also binds vancomycin, so it cannot be coadministered with enteral vancomycin unless the doses are separated by several hours. This drug **should generally be avoided** most patients with CDI.
3. **Other currently available drugs** with potentially useful activity against CDI include tigecycline, nitazoxanide and rifaximin; however these should not be considered first line agents. In consultation with Infectious Diseases, tigecycline may warrant consideration in severe/complicated cases as it is a parenteral drug that may reduce toxin production and has shown benefit in a small case series (Herpers, et al. Clin Infect Dis. 2009).
4. **IVIG**: While there are some anecdotal data to suggest a benefit, the best data available to date do not support the efficacy of IVIG in the treatment of patients with severe CDI (Juang, et al. Am J Infect Control 2007). Use of IVIG was not included as recommended treatment in the SHEA/IDSA Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults (Cohen, et al. Clin Infect Dis. 2010) due to lack of evidence from controlled trials.
5. **Monoclonal antibodies to *C. difficile* toxins** are not currently FDA-approved and did not affect treatment outcomes in a Phase 2 clinical trial (although they did reduce the rate of relapse) (Lowy, et al. NEJM 2010)
6. The role of **probiotics** as treatment or prevention of CDI is not well substantiated and can not be recommended at this time.
7. Due to prolonged persistence of *C. difficile* nucleic acid in the stool, even after successful treatment, the *C. difficile* nucleic acid amplification assay should not

be repeated during or shortly after treatment. The **nucleic acid amplification assay should not be used as a "test of cure"**.

8. **Relapse of CDI** after treatment is common regardless of the initial treatment. If possible, minimize antibiotic use, particularly agents that will tend to alter bowel flora, in patients with prior CDI to reduce the risk of relapse. The initial treatment regimen may be repeated for the first relapse. The literature on treatment of subsequent recurrences is based mostly on small cases series. The following algorithm suggests a reasonable treatment strategy for patient with recurrences (modified from Kelly and Lamont, NEJM 2008)

First recurrence

Mild-Moderate infection

Metronidazole at a dose of 500 mg orally 3 times daily for 10 to 14 days

Severe infection or unresponsiveness to or intolerance of metronidazole

Vancomycin at a dose of 125 mg orally 4 times daily for 10 to 14 days

Severe/Complicated infection – see 5.c. above

Second recurrence

Vancomycin in tapered and pulsed doses

125 mg orally 4 times daily for 14 days

125 mg orally 2 times daily for 7 days

125 mg orally once daily for 7 days

125 mg orally once every 2 days for 8 days (4 doses)

125 mg orally once every 3 days for 15 days (5 doses)

Third recurrence

Vancomycin at a dose of 125 mg orally 4 times daily for 14 days, followed by

Rifaximin at a dose of 400 mg orally twice daily for 14 days

Further recurrences, despite treatment as above

Suggest Gastroenterology or Infectious Diseases Consultation

Selected References:

Bartlett JG. The case for vancomycin as the preferred drug for treatment of *Clostridium difficile* infection. Clin Infect Dis 2008;46:1489-92.

Boyanton BL Jr, Sural P, Loomis CR, Pesta C, Gonzalez-Krellwitz L, Robinson-Dunn B, Riska P. Loop-mediated isothermal amplification compared to real-time PCR and enzyme immunoassay for toxigenic *Clostridium difficile* detection.
J Clin Microbiol. 2012 Mar;50(3):640-5.

Byrn JC, Maun DC, Gingold DS, Baril DT, Ozao JJ, Divino CM. Predictors of mortality after colectomy for fulminant *Clostridium difficile* colitis. Arch Surg 2008;143:150-4; discussion 5.

Cohen SH, Gerding DN, Johnson S, Kelly CP, Loo VG, McDonald LC, Pepin J, Wilcox MH. 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.

Cornely OA, Crook DW, Esposito R, Poirier A, Somero MS, Weiss K, Sears P, Gorbach S; for the 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 Feb 7 . [Epub ahead of print]

Fekety R, Silva J, Kauffman C, Buggy B, Deery HG. Treatment of antibiotic-associated *Clostridium difficile* colitis with oral vancomycin: comparison of two dosage regimens. Am J Med 1989;86:15-9.

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.

Gerding DN, Muto CA, Owens RC, Jr. Treatment of *Clostridium difficile* infection. Clin Infect Dis 2008;46 Suppl 1:S32-42.

Herpers BL, Vlaminckx B, Burkhardt O, Blom H, Biemond-Moeniralam HS, Hornef M, Welte T, Kuijper EJ. Intravenous tigecycline as adjunctive or alternative therapy for severe refractory *Clostridium difficile* infection. Clin Infect Dis. 2009 Jun 15;48(12):1732-5.

Hu MY, Maroo S, Kyne L, et al. A prospective study of risk factors and historical trends in metronidazole failure for *Clostridium difficile* infection. Clin Gastroenterol Hepatol 2008;6:1354-60.

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;44:846-8.

Juang P, Skledar SJ, Zgheib NK, et al. Clinical outcomes of intravenous immune globulin in severe *Clostridium difficile*-associated diarrhea. Am J Infect Control 2007;35:131-7.

Kelly CP. A 76-year-old man with recurrent *Clostridium difficile*-associated diarrhea: review of C. difficile infection. JAMA 2009;301:954-62.

Kelly CP, LaMont JT. *Clostridium difficile*--more difficult than ever. N Engl J Med 2008;359:1932-40.

Kyne L, Kelly CP. Recurrent *Clostridium difficile* diarrhoea. Gut 2001;49:152-3.
Lamontagne F, Labbe AC, Haeck O, et al. Impact of emergency colectomy on survival of patients with fulminant *Clostridium difficile* colitis during an epidemic caused by a hypervirulent strain. Ann Surg 2007;245:267-72.
Leffler DA, Lamont JT. Treatment of *Clostridium difficile*-associated disease. Gastroenterology 2009;136:1899-912.
Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of *Clostridium difficile*-associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353:2442-9.
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.
Lowy I, Molrine DC, Leav BA, Blair BM, et al. Treatment with monoclonal antibodies against *Clostridium difficile* toxins. N Engl J Med. 2010 Jan 21;362(3):197-205.
Luo RF, Banaei N. Is repeat PCR needed for diagnosis of *Clostridium difficile* infection? J Clin Microbiol. 2010 Oct;48(10):3738-41.
McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. N Engl J Med 2005;353:2433-41.
Musher DM, Logan N, Bressler AM, Johnson DP, Rossignol JF. Nitazoxanide versus Vancomycin in *Clostridium difficile* Infection: A Randomized, Double-Blind Study. Clin Infect Dis 2009.
Owens RC, Jr., Donskey CJ, Gaynes RP, Loo VG, Muto CA. Antimicrobial-associated risk factors for *Clostridium difficile* infection. Clin Infect Dis 2008;46 Suppl 1:S19-31.
Pepin J. Vancomycin for the treatment of *Clostridium difficile* Infection: for whom is this expensive bullet really magic? Clin Infect Dis 2008;46:1493-8.
Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for *Clostridium difficile*-associated diarrhea: a cohort study during an epidemic in Quebec. Clin Infect Dis 2005;41:1254-60.
Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. CMAJ 2005;173:1037-42.
Pepin J, Valiquette L, Gagnon S, Routhier S, Brazeau I. Outcomes of *Clostridium difficile*-associated disease treated with metronidazole or vancomycin before and after the emergence of NAP1/027. Am J Gastroenterol 2007;102:2781-8.
Salcedo J, Keates S, Pothoulakis C, et al. Intravenous immunoglobulin therapy for severe *Clostridium difficile* colitis. Gut 1997;41:366-70.
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;45:302-7.

Author: Howard S. Gold, MD, Medical Director of Antimicrobial Management, Silverman Institute for Health Care Quality and Safety, and Division of Infectious Diseases

Sponsor: Kenneth Sands, MD, MPH, Senior Vice President, Silverman Institute for Health Care Quality and Safety

Advisors: Monica Golik, PharmD, Ciaran Kelly, MD, James Kirby, MD, J. Thomas Lamont, MD, Daniel Leffler, MD, Christopher McCoy, PharmD, Deborah Nagle, MD, Mark Callery, MD, Jonathan Critchlow, MD, Todd Pollack, MD

Approval Body: Pharmacy and Therapeutic Committee March 9, 2011
Medical Executive Committee March 16, 2011

Original Date Approved: March 16, 2011

Revisions: 4/12

Next Review Date: March 2014

Key Words for Search Engine: Clostridium difficile, difficile, CDI, Cdiff, CDAD, diarrhea, antibiotic