

TITLE: CLOSTRIDIUM DIFFICILE INFECTION (CDI): GUIDELINES FOR THE MANAGEMENT OF ADULT PATIENTS

POLICY/GUIDELINES:

Diagnosis of *Clostridium difficile* disease is based on clinical symptoms in combination with testing by PCR. The choice of which agent should be utilized to treat the infection should be based on the clinical severity of the disease, as per criteria presented below.

PURPOSE:

Clostridium difficile is a bacterial enteric pathogen that causes a broad range of clinical disease from asymptomatic colonization or mild diarrhea to life-threatening pseudomembranous colitis. *C. difficile* produces disease by toxin production in the colon via two toxins, toxin A and toxin B. The usual presentation is watery diarrhea and cramps associated with antibiotic use. The major risk factors for CDI are antecedent antibiotic exposure, hospitalization, and advanced age. During the past few years, an increase in frequency and severity of CDI has been observed with recognition of a new strain designated the NAP-1 strain. This strain has been associated with epidemics in Canada, the United States, and Europe. These guidelines are aimed at standardizing the diagnosis and treatment of CDI to minimize the morbidity and mortality associated with the disease.

APPLICABILITY:

Prescribers, nurses, and pharmacists

PROCEDURE:

Diagnosis

A. Clinical diagnosis

- a. Diarrhea, defined as watery or unformed stools, occurring ≥ 3 times a day for at least 2 days, usually associated with abdominal cramping, fever, dehydration, and peripheral leukocytosis OR pseudomembranes seen on lower GI endoscopy AND no other recognized etiology for diarrhea
- b. Infrequently, CDI may result in toxic megacolon or ileus, and the patient may paradoxically have no diarrhea, but instead have atypical symptoms suggestive of an acute surgical abdomen.
- c. Other causes of diarrhea should be considered and ruled out. Some common causes include tube feeds, drugs [e.g. proton-pump inhibitors, metoclopramide (Reglan[®]), sodium polystyrene sulfonate (Kayexalate[®]), metformin (Glucophage[®]), lactulose, laxatives, magnesium], exacerbations of underlying medical conditions (e.g., IBD, ischemic colitis).

B. Laboratory diagnosis:

- a. Send a stool specimen for *C. difficile* toxins to the microbiology laboratory.
 - i. The laboratory now performs a real-time PCR assay with primers specific for the toxin B gene. The sensitivity and specificity of this PCR assay has been reported as 93-97% and 93-96%, respectively, compared to toxigenic anaerobic culture or cytotoxicity (EIA) assay.
 - ii. It is unnecessary to send multiple specimens for *C. difficile* testing given the high sensitivity of the PCR assay.
 - iii. It is prudent to consider other causes of diarrhea and to discontinue *C. difficile* treatment and presumptive isolation precautions if initial PCR testing is negative. Follow-up PCR testing to guide decisions regarding duration of treatment in asymptomatic or clinically improving patients is not recommended.
- b. *C. difficile* can be ruled out with a negative PCR result.

Infection Control

- A. "SPECIAL Plus Contact Isolation" is a category of contact isolation that requires gowns and gloves for room entry, the use of Purell® before contact, and hand washing with antiseptic soap (e.g., 2% chlorhexidine or equivalent) after contact.
 - a. Alcohol-based hand products (Purell®) have not been proven adequate for killing *C. difficile* spores.
- B. "SPECIAL Plus Contact Isolation" is required for all patients who test positive for *C. difficile* toxin.
 - a. For confirmed *C. difficile* cases, removal of isolation is permitted following resolution of diarrhea symptoms (patient is without symptoms for ≥ 72 hours). Please consult with the Department of Infection Prevention and Control.
- C. When *C. difficile* is suspected, the patient *should be* placed on presumptive "SPECIAL Plus Contact Isolation" immediately.
 - a. In the majority of cases, *presumptive* isolation may be discontinued after a negative *C. difficile* PCR result.

Treatment

- A. Stop all non-essential antimicrobial agents.
- B. Consider anti- *C. difficile* therapy as recommended below (see table).
- C. Discontinue all antiperistaltic, stool softeners, laxative medications [e.g. loperamide, diphenoxylate with atropine (Lomotil®), bismuth subsalicylate, narcotics, docusate (Colace®), senna]
- D. Prophylaxis
 - a. Use of metronidazole or oral vancomycin as prophylaxis for CDI is not recommended. Administration of metronidazole and oral vancomycin to asymptomatic carriers may disrupt normal gut flora and does not

predictably eradicate *C. difficile*.

- b. Administration of probiotics to prevent primary CDI is not recommended and poses a potential risk of bloodstream infection.
- E. Duration of therapy should be 10–14 days and at least 10 days after symptoms have significantly improved. A longer duration of therapy may be necessary for recurrent CDI or when patients remain on other antibiotic therapy.
- F. Recurrence
 - a. Recurrence can occur in 6-25% of patients. This often occurs with return of symptoms within 1 – 8 weeks after discontinuing CDI therapy.
 - b. Many patients respond to retreatment with the original agent used to treat the initial episode and should receive the original therapy at standard doses. First recurrences that present with a more severe clinical picture (see table) compared to the initial episode may warrant the use of oral vancomycin.
 - c. Second and subsequent recurrences should be treated with vancomycin to avoid long term neurotoxicity associated with metronidazole. Longer courses, higher dosing, and a taper/pulse regimen of vancomycin should all be considered. ID consultation is strongly recommended.
 - i. Administering vancomycin over an extended time period at decreasing doses (tapered) followed by intermittent delivery every 3 days (pulsed) gradually clears *C. difficile* as spores germinate. This dosing strategy may aid in restoration of the normal flora. The impact of this regimen, which utilizes lower doses of vancomycin, on the development of vancomycin-resistant strains is unknown.

Treatment Regimens for CDI ¹		
Severity Category	Severity criteria (once clinical and/or laboratory diagnosis made as above)	Treatment Regimen
Mild-Moderate Disease	<ul style="list-style-type: none"> Diarrhea (defined as watery or unformed stools, occurring ≥ 3 times a day for at least 2 days) which may be accompanied by mild to moderate abdominal discomfort, elevated WBC count, fever 	<ul style="list-style-type: none"> Stop all non-essential antibiotics Metronidazole 500 mg PO every 8 hrs <u>OR</u> 250 mg PO every 6 hrs² May take 4-6 days for diarrhea to completely resolve If no significant improvement in at least 4 days, reassess and consider changing treatment to vancomycin 125 mg PO every 6 hours.³ If significant clinical deterioration to severe disease, consider treatment recommendations below for severe disease.
Severe Disease	<p>The above criteria <u>plus</u> at least one of the following:</p> <ul style="list-style-type: none"> In the ICU <u>OR</u> If non-ICU, at least 2 of the following criteria: <ul style="list-style-type: none"> WBC count $\geq 15,000$ cells/mm³ albumin < 2.5 mg/dL age ≥ 65 years <u>OR</u> Endoscopically or histologically confirmed pseudomembranous colitis 	<ul style="list-style-type: none"> Stop all non-essential antibiotics Consider Infectious Diseases consultation Consider General Surgery consultation Consider Gastroenterology consultation Vancomycin 125 mg PO or via NGT every 6 hours³
Severe-Complicated Disease	<p>Severe disease as above <u>plus</u> the following:</p> <ul style="list-style-type: none"> Toxic megacolon, perforation, colectomy, or septic shock secondary to CDI requiring vasopressive therapy 	<ul style="list-style-type: none"> Stop all non-essential antibiotics Consider Infectious Diseases consultation Consider General Surgery consultation Consider Gastroenterology consultation Vancomycin 125 mg PO or via NGT every 6 hours³ + metronidazole 500 mg IV every 8 hours⁴ <p>For patients with ileus:</p> <ul style="list-style-type: none"> Metronidazole 500 mg IV q8h + vancomycin 125 mg PO or via NGT every 6 hours (if possible)⁵ Consider rectal vancomycin 500 mg in 250 mL NS every 6 hours as a retention enema (clamp rectal tube x 1 hr with each dose)⁶

1 These are general guidelines and may not apply to all patients. Clinical judgment must be utilized in all cases. Consult Infectious Diseases for any patient-specific management questions.

2 If metronidazole is contraindicated [concomitant ethanol intake, concomitant medications containing ethanol (e.g., tipranavir), disulfiram treatment, pregnancy, hypersensitivity], use oral vancomycin.

3 If oral vancomycin is chosen, extreme caution should be used with concomitant use of cholestyramine (or other bile acid sequestrants). Cholestyramine binds vancomycin in the gut and may reduce its efficacy. Separate administration times of cholestyramine and oral vancomycin by at least 2-3 hours.

4 Data regarding IV metronidazole are anecdotal but it may be added to vancomycin PO in severe CDAD cases with ileus or significant residuals.

5 Intravenous vancomycin is NOT effective for the treatment of CDAD and is NOT a substitute for oral vancomycin. Cases of CDAD have been reported in patients receiving intravenous vancomycin.

6 While rectal administration of vancomycin may be very helpful in severe cases with ileus, caution should be utilized in its administration to avoid perforation. Avoid vigorous or forceful administration of rectal vancomycin.

RESPONSIBILITY:

Joint Subcommittee on Anti-Infective Use

REFERENCES:

1. Bartlett JG. *Clostridium difficile*: old and new observations. *J Clin Gastroenterol* 2007; 41: S24-S29.
2. Bartlett JG. Antibiotic-associated diarrhea. *N Engl J Med* 2002 Jan 31;346(5):334-9.
3. Owens RC. *Clostridium difficile*-associated disease: an emerging threat to patient safety: insights from the Society of Infectious Diseases Pharmacists. *Pharmacotherapy* 2006; 26(3):299-311.
4. Aslam S, Hamill RJ, Musher DM. Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. *Lancet Infect Dis* 2005; 5: 549-57.
5. Johnson S, Homann SR, Bettin KM, et al. Treatment of asymptomatic *Clostridium difficile* carriers with vancomycin or metronidazole. *Ann Intern Med* 1992; 117: 297-302.
6. Zar FA, Bakkanagari SR, Moorthi KMLST, et al. 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.
7. Huang H, Weintraub A, Fang H, et al. Comparison of a commercial multiplex real-time PCR to the cell cytotoxicity neutralization assay for diagnosis of *Clostridium difficile* infections. *J Clin Microbiol* 2009; 47: 3729-31.
8. Kvach EJ, Ferguson D, Riska P, et al. Comparison of BD GeneOhm Cdiff real-time PCR assay with a two-step algorithm and a toxin A/B ELISA for diagnosis of toxigenic *Clostridium difficile* infection. *J Clin Microbiol* 2009; 47: 373-8.
9. Barbut F, Braun M, Burghoffer B, et al. Rapid detection of toxigenic strains of *Clostridium difficile* in diarrheal stools by real-time PCR. *J Clin Microbiol* 2009; 47: 1276-77.
10. BD GeneOhm Cdiff Assay Package insert (dated 2009-04). http://www.bd.com/geneohm/english/products/pdfs/cdiff_pkginsert.pdf Accessed November 9, 2009.
11. Cohen SH et al. Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults: 2010 Update by the Society for Healthcare Epidemiology of American (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol* 2010;31(5):431-455.
12. Kelly CP, LaMont JT. *Clostridium difficile* – More difficult than ever. *N Engl J Med* 2008;359:1932-40.
13. Tedesco FJ, Gordon D, Fortson WC. Approach to patients with multiple relapses of antibiotic-associated pseudomembranous colitis. *Am J Gastroenterol* 1985;80:867-868.

POLICY/GUIDELINE DATES:

Issued: June 2007
Reviewed: May 2008
Revised: March 2011
Medical Board Approval: May 2011