Guidelines for the Management of *Clostridium difficile*-Associated Disease (CDAD) in Adult Patients
(last updated 8/27/08)

Background information:
*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 CDAD are antecedent antibiotic exposure, hospitalization, and advanced age. During the past few years, an increase in frequency and severity of CDAD 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 CDAD to minimize the morbidity and mortality associated with the disease.

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, CDAD 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 EIA test performed by the laboratory for *C. difficile* toxins A and B has limited sensitivity.
      ii. If an initial stool specimen is negative and clinical suspicion of *C. difficile* remains high, a second specimen may be sent. Sending 3 stool specimens only increases the sensitivity by ~10% and may not be beneficial.
      iii. Any delays between obtaining the stool specimen and its processing in the microbiology laboratory can decrease the sensitivity of the test further.
      iv. Formed stools are less likely to be *C. difficile* toxin positive than are diarrheic stools.
   b. *C. difficile* cannot definitively be ruled out even if multiple stool samples test negative for toxins A and B.

Infection Control

A. Contact isolation for all patients who test positive for *C. difficile* toxin.
   a. Removal of contact isolation is permitted following resolution of diarrhea symptoms ie: without diarrhea for > 72 hours. Please consult with the Department of Epidemiology.

B. When *C. difficile* is suspected, the patient should be placed on presumptive contact isolation immediately. If suspicion for *C. difficile* remains high, patient should remain on isolation even if stool specimens are negative for toxins A/B.

C. When caring for patients with suspected or confirmed *C. difficile*, hand washing with germicidal soap (e.g., 2% chlorhexidine or equivalent) is required.
   a. Alcohol-based hand products (Purell®) have not proven to be adequate for killing *C. difficile* spores.
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. While rectal administration of vancomycin may be very helpful in severe cases with ileus, caution should be utilized in its administration to avoid perforation.

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

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.

Recurrence can occur in 20-25% of patients. This often occurs with return of symptoms within 1 – 8 weeks after discontinuing CDAD therapy. Many patients respond to retreatment with the original agent and should receive the original therapy at standard doses initially.

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 CDAD or when patients remain on other antibiotic therapy.

### Treatment regimens for CDAD

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<thead>
<tr>
<th>Severity category</th>
<th>Severity criteria (once clinical and/or laboratory diagnosis made as above)</th>
<th>Treatment regimen</th>
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<tr>
<td><strong>Mild - moderate disease</strong></td>
<td>• 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</td>
<td>• Stop all non-essential antibiotics&lt;br&gt;• Metronidazole 500 mg PO every 8 hrs OR 250 mg PO every 6 hrs&lt;br&gt;• May take 4-6 days for diarrhea to completely resolve&lt;br&gt;• If no significant improvement in at least 4 days, reassess and consider changing treatment to vancomycin 125 mg PO every 6 hours. If significant clinical deterioration to severe disease, consider treatment recommendations below for severe disease.</td>
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<td><strong>Severe disease</strong></td>
<td>The above criteria plus at least one of the following: • At least 3 of the following criteria: o fever &gt; 38.3 °C attributed to CDAD o elevated WBC count &gt;20,000 cells/mm³ o albumin &lt;2.5 mg/dL o age ≥ 65 years o admission to ICU OR • Endoscopically or histologically confirmed pseudomembranous colitis OR • Toxic megacolon, perforation, colectomy, or septic shock requiring admission to the intensive care unit (ICU) requiring vasopressive therapy</td>
<td>• Stop all non-essential antibiotics&lt;br&gt;• Consider Infectious Diseases consultation&lt;br&gt;• Consider General Surgery consultation&lt;br&gt;• Consider Gastroenterology consultation&lt;br&gt;• Vancomycin 125 mg PO or via NGT every 6 hours. For patients with ileus: • Metronidazole 500 mg IV q8h + vancomycin 125 mg PO or via NGT every 6 hours (if possible)&lt;br&gt;• 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)</td>
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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, 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.

References: