Stanford Division of Infectious Diseases and Geographic Medicine Suggested Guidelines for the Treatment of *Clostridium Difficile* Infection (CDI).

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Record of Changes:
9/1/14: Under “Treatment”- Rifaximin chaser regimen amended to 400mg PO BID for 14 days (changed from 21 days) by consensus.
10/29/14: Under Diagnosis- diarrhea criteria edited to reflect 2010 IDSA and 2013 ESCMID guidelines (3 or greater number of stools over 24 hours, changed from the same over two consecutive days). Pseudomembranous colitis criteria amended to reflect other disease possibilities.

Diagnosis:
Diagnostic Criteria (Distinct from Testing Criteria Below):
1. Diarrhea (≥3 unformed stools over 24 or fewer consecutive hours in a hospitalized patients, 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
2. A positive stool PCR for *C. difficile* toxin B or visualization of pseudomembranes on endoscopy(if other causes of pseudomembranes felt to be less likely)\(^4\)-\(^8\).

OR

Abdominal distension and severe pain after a period of diarrhea without current stooling may be a rare finding if ileus or toxic megacolon present\(^9\). In this setting, effort should be made to send toxin PCR from a rectal swab trace amount of stool (notify microbiology lab prior to sending, swab specimens will be rejected unless prior approval from lab is given).

Testing Criteria (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 if you are requesting an exception to this policy.
3. No repeat testing within the last 7 days.

Important:
Stool PCR for *C. difficile* toxin B is thought to be 98% sensitive for disease or colonization, no indication for repeat testing within 7 days of a negative result. Repeat testing after that only if initial symptoms resolve and new diarrhea starts².

Asymptomatic colonization with toxigenic *C. difficile* is relatively common (12% of all hospitalized patients in a recent study), and treatment is not indicated for this¹⁰. It is therefore important that patients meet testing criteria for CDI, before sending stool for *C. difficile* toxin PCR¹,¹¹. Currently there is no test of cure for CDI. Patients with CDI should be followed clinically for improvement.

**Staging Disease:**
After the diagnosis is made, it is important to stage the disease to guide treatment by both severity (mild -> severe complicated) and symptom recurrence (first occurrence-> multiple recurrence)¹,¹²,¹³:

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

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

• Severe disease¹²,¹³ WBC >=15,000 cells/µL OR serum creatinine elevation >=1.5 times the premorbid level due to CDI.

• Severe Complicated⁹,¹⁴-¹⁷ 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.

• 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.¹,¹⁷. Note: After clinical response, it may take weeks for stool consistency and frequency to become entirely normal.

• Multiply Recurrent disease - >1 recurrence of disease, with each distinct episode meeting the diagnostic criteria above¹.
Treatment:

In addition to recommendations below, discontinue administration of unnecessary antibacterial agents and proton pump inhibitors (PPIs).

Mild/Moderate disease- 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, 14 days may be preferred (do not use for more than 14d due to potential neurotoxicity). ALTERNATIVE THERAPY: Vancomycin 125 mg PO q6h (generic liquid formulation) for 10-14d.

Severe disease- Likely requires hospitalization, also consider serial AXRs if has abdominal distension, tenderness. Consultation with Infectious Diseases is recommended. Antimicrobials: Vancomycin 125 mg PO q6h (generic liquid formulation) for 14d. ALTERNATIVE THERAPY: Fidaxomicin 200mg PO BID for 10d may be considered in failures of prior therapy, particularly if concurrent antibiotics are required, but there are no data available regarding the efficacy of this drug in severe life-threatening disease. Fidaxomicin use is restricted at Stanford, ID consult not required only if patient meets following criteria:

- Proven *C. difficile* disease AND
- Recurrent disease AND
- ≥3 of the following:
  - Age >65 years
  - Significant immunocompromised
  - ≥2 SIRS criteria
  - meets criteria for severe CDI disease
  - Continued broad-spectrum antibacterial therapy.

Severe-Complicated- SURGICAL AND INFECTIOUS DISEASE CONSULTATION STRONGLY INDICATED. Serial AXRs necessary if surgery deferred. Antimicrobials: Vancomycin 500mg PO q6h and IV metronidazole 500mg TID. Consider PR vancomycin 500mg in a 100ml normal saline retention enema q6h unless toxic megacolon (high perforation risk), total course at least 10d but longer courses can be determined from time of symptom resolution. ALTERNATIVE THERAPY: Replace IV metronidazole with IV tigecycline 50mg BID.

Surgical intervention is indicated in case of:

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 (operate 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{35}. 

**First Recurrence**- Same therapy as for initial episode, adjusted for severity as above.

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

Can choose from the following options:
1. Fidaxomicin 200mg PO BID for 10d\textsuperscript{23-29}. See Stanford restriction criteria above.
2. Vancomycin 125mg PO q6h for 14d followed by Rifaximin 400mg PO BID for 14d\textsuperscript{36,37}.
3. Vancomycin PO 125mg q6h for 10d, then BID for 7d, then daily for 7d, then every other day for 21d or until symptoms tolerate\textsuperscript{1,38}.
4. Fecal Microbiota Transplant. Requires BOTH Infectious Diseases and Gastroenterology consults\textsuperscript{39-42}.

**Recurrence prevention:**

Limit repeat antibiotic use and PPI use- these are the epidemiologic risk factors most associated with recurrence. Call ID consult or make urgent ID outpatient referral if possible prior to starting systemic antibiotics in patient with known CDI history, as it may be possible to minimize antibiotic use and duration. Would consider prior CDI, particularly severe or multiply recurrent disease as a relative contraindication to antibiotics and PPIs, e.g use only if absolutely necessary\textsuperscript{24,43,44}. If antibiotic use necessary in a patient with a history of CDI, if possible AVOID clindamycin, cephalosporins, monobactams, carbapenems, fluoroquinolones (particularly moxifloxacin) and β-lactamase inhibitor combinations\textsuperscript{45-53}. Macrolides, sulfonomides, penicillin or aminopenicillins and aminoglycosides are likely associated with a relatively lower risk of CDI than the other antibiotic classes listed above\textsuperscript{45,46,53-55}. Metronidazole and Tetracyclines, particularly doxycycline, are the antibiotic classes associated with the least risk of CDI and may even be protective\textsuperscript{46,53-55}. 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\textsuperscript{45,50,55}.

Probiotics- Available evidence for use of probiotic preparations (capsules, powder, yogurts) to prevent CDI occurrence is equivocal, but risk is low in immunocompetent patients\textsuperscript{1,24,56-58}. IF USED: Preparations should include greater than 1 x 10\textsuperscript{9} Colony Forming Units (CFU) of either *Saccharomyces Cerevisiae* subtype *Boulardii*, *Bifidobacterium spp* or *Lactobacillus spp*. Use should be restricted to prevention in patients currently requiring systemic antibiotics, NOT in patients with active CDI\textsuperscript{56-58}. Use should be carefully considered in immunocompromised patients as risk may outweigh benefit in this population.
Infection Control
Current recommendation is for inpatients with positive *C difficile* toxin PCRs to be placed in contact isolation. Hand washing with soap and water (not alcohol based cleansers) is necessary with soiling of hands or bodily fluids after contact with CDI patients OR in outbreak situations, otherwise standard hand hygiene recommendations apply as per CDC/SHEA guidelines¹,⁵⁹.

Table 1. CDI Treatment Guidelines for SUH Indexed By Severity. NOTE: Only applies if patient meets CDI definition (≥3 unformed stools over 24 or fewer consecutive hours + Positive C. Diff Toxin PCR).

<table>
<thead>
<tr>
<th>Clinical Severity/Stage</th>
<th>First Line Regimen</th>
<th>Alternative Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/Moderate</td>
<td>Metronidazole 500mg PO TIDx10-14d</td>
<td>Vancomycin 125 mg PO q6h x 10-14d.</td>
</tr>
<tr>
<td>Severe (WBC&gt;15K, Cr &gt;1.5x Baseline)</td>
<td>Vancomycin 125 mg PO q6h x 10-14d.</td>
<td>Fidaxomycin 200mg PO BIDx10d.</td>
</tr>
<tr>
<td>Severe Complicated (septic shock, ileus or toxic megacolon due to CDI)</td>
<td>SURGICAL AND INFECTIOUS DISEASES CONSULT Vancomycin 500mg PO q6h + Metronidazole IV 500mg TID. Consider PR Vancomycin 500mg in 100ml NS enema q6h</td>
<td>Replace Metronidazole IV with Tigecycline IV 50mg BID.</td>
</tr>
<tr>
<td>First Recurrence</td>
<td>Same as above based on severity</td>
<td></td>
</tr>
<tr>
<td>Multiple Recurrence</td>
<td>For Severe Complicated – Treat as above until stable. For all others- if not previously used: Fidaxomycin 200mg PO BID x 10d</td>
<td>OR Vancomycin 125mg PO q6h for 14d followed by Rifaximin 400mg PO BID for 14d OR Vancomycin PO 125mg q6h x10d, then BID x7d, then qd x7d, then qod x21d OR Fecal Microbiota Transplant. Consult ID and GI</td>
</tr>
</tbody>
</table>
Table 2. Cost Table of Recommended Antimicrobial CDI Therapies*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Unit</th>
<th>Cost per Unit</th>
<th>Cost per Day</th>
<th>14 day course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole tablet</td>
<td>500mg tablet</td>
<td>$0.38</td>
<td>1.14</td>
<td>15.96</td>
</tr>
<tr>
<td>Metronidazole injection</td>
<td>500mg bag</td>
<td>$1.10</td>
<td>3.30</td>
<td>46.20</td>
</tr>
<tr>
<td>Vanc oral solution</td>
<td>125mg solution</td>
<td>$0.74</td>
<td>2.96</td>
<td>41.44</td>
</tr>
<tr>
<td>Vanc capsule (generic)</td>
<td>125mg capsule</td>
<td>$24.4560</td>
<td>97.82</td>
<td>1,369.48</td>
</tr>
<tr>
<td>Vanc capsule (brand name)</td>
<td>125mg capsule</td>
<td>$27.8610</td>
<td>111.44</td>
<td>1,560.16</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>200mg tab</td>
<td>$100.8105</td>
<td>201.62</td>
<td>2,016.20 (10 days)</td>
</tr>
<tr>
<td>Tigecycline injection</td>
<td>50mg bag</td>
<td>$91.7840</td>
<td>183.56</td>
<td>2,569.84</td>
</tr>
<tr>
<td>Rifaximin</td>
<td>400mg BID</td>
<td>$25.66</td>
<td>51.32</td>
<td>1,077.72 (14-days)</td>
</tr>
</tbody>
</table>

*All dollar amounts noted here reflect the institutional purchase prices paid by Stanford University Hospital and Clinics.
References:


