UWHC Guidelines for the Treatment of Initial and Recurrent Episodes of *Clostridium difficile* Infection
Clinical Practice Guideline

Target Population:
Patients at risk for or diagnosed with initial and recurrent episodes of *Clostridium difficile* Infection

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October 2013
Clinical Practice Guideline Executive Summary

Guideline Title:
UWHC Guidelines for the Treatment of Initial and Recurrent Episodes of Clostridium difficile Infection

Guideline Overview
These clinical practice guidelines are intended to guide clinicians in the assessment, diagnosis, and treatment of initial and recurrent Clostridium difficile infection (CDI). They are compiled from an extensive literature review of current evidence and external clinical practice guidelines related to CDI.

Practice Recommendations

1. Prevention
   1.1. The most important treatment technique for Clostridium difficile is prevention. Compliance with UWHC policies on personal protective equipment, hand-washing, and infection control should be followed.  
      (Class I, Level of Evidence B)
   1.2. Probiotics have rarely been shown to be effective as adjunctive therapy for prevention of primary CDI and there exists a risk of developing a bloodstream infection mainly in patients who are heavily immunosuppressed.  
      (Class IIb, Level of Evidence C)

2. Diagnosis
   2.1. Evaluation of patients without diarrhea or risk factors should be avoided. In rare cases, patients will present with ileus and/or colonic distention in the absence of diarrhea.  
      (Class IIa, Level of Evidence C)
   2.2. Patients experiencing diarrhea (≥3 unformed stools in the previous 24 hours) with risk factors for Clostridium difficile infection (CDI) should be evaluated for presence of C. difficile toxin.  
      (Class IIa, Level of Evidence B)
   2.3. Diagnosis at UWHC may be made through several methods
      2.3.1. Stool sample with toxigenic C. difficile by measurement of toxin A, toxin B, or binary toxin via polymerase chain reaction (PCR).  
      (Class IIa, Level of Evidence B)
      2.3.1.1. The PCR test available at UWHC is highly sensitive (~99%) and specific (~91%) as compared to cell cytotoxicity and immunoassays.
      2.3.1.2. Negative PCR-test results can be reported with high certainty of accuracy and retesting after 7 days is not recommended (Class III, Level B)
      2.3.2. Direct visualization via colonoscopy or histologic findings of pseudomembranous colitis.

3. Treatment
   3.1. Empiric therapy without diagnostic evidence is inappropriate.  
      (Class IIb, Level of Evidence C)
   3.2. Identify patients at risk for CDI and order toxin assay by PCR.  
      (Class IIa, Level of Evidence B)
3.3. Discontinue therapy with inciting antimicrobial agent(s) as soon as possible.² (Class I, Level of Evidence B)

3.4. Classify patients by severity using risk stratification tool.² (Table 1.)

3.4.1. For treatment of mild to moderate disease, begin metronidazole 500 mg PO every 8 hours for 10 to 14 days. (Class I, Level of Evidence B)

3.4.2. For treatment of severe disease, begin vancomycin 125mg PO every 6 hours for 10-14 days. (Class IIa, Level of Evidence B)

3.4.3. For treatment of severe, complicated disease, begin vancomycin 500mg PO/NG every 6 hours PLUS metronidazole 500mg IV every 8 hours.² Tigecycline 100mg IV once then 50mg IV every 12 hours may be considered as an alternative for metronidazole IV in patients with severe refractory CDI when there is a need for continuation of concomitant antiinfectives which may worsen the condition.¹²,¹³ (Class IIb, Level of Evidence C)

3.4.3.1. In patients without enteral access, IV metronidazole is the preferred option. Tigecycline may be an alternative as described above. (Class IIb, Level of Evidence C)

3.4.4. For treatment of severe CDI in patients with ileus or patients with diverting ileostomy consider adding vancomycin rectal instillation.¹² (Class IIb, Level of Evidence C)

3.4.4.1. Order using “vancomycin (VANCOCIN) solution” with route specified as “other”, dose is 500mg 4 times daily with the comments to specify “Please administer RECTALLY as enemas. Use 18 F red rubber catheter inserted up to 4 inches. Dilute to 100mL with sterile 0.9%NS for irrigation. May administer 100mL at a time. DO NOT GIVE ORALLY.”

3.4.4.2. Vancomycin rectal administration is NOT routinely recommended in neutropenic patients due to the risk of infection with manipulation of the rectum. (Class III, Level of Evidence C)

3.4.5. There is limited evidence to support use of G.I. lavage (GOLYTELY) solution as an adjunct to agents routinely used to treat chronic, relapsing CDI. G.I. lavage may be useful for clearing the C. difficile organisms, spores, and associated toxins from the intestine of patients with relapsing infections.¹⁴ (Class IIb, Level of Evidence C)

3.4.6. Daily assessment is necessary to assess efficacy of all treatments.

3.5. Antiperistaltic agents should generally be avoided in patients with suspected or confirmed CDI as they may obscure symptoms and precipitate toxic megacolon.² (Class III, Level of Evidence C)

3.6. Multiple oral agents provide redundant coverage and should not be given simultaneously. Examples include oral vancomycin and oral metronidazole OR oral vancomycin and oral fidaxomicin. (Class IIb, Level of Evidence C)

3.6.1. Oral metronidazole is 90% absorbed and generally should not be given concomitantly with full-dose intravenous metronidazole. (Class III, Level of Evidence C)

3.6.2. Oral vancomycin and fidaxomicin are NOT absorbed from the GI tract. If treatment of infections outside of the GI tract require vancomycin, the intravenous form can be given simultaneously with the oral form without risk of toxicity. Conversely, patients being treated with intravenous vancomycin will NOT achieve adequate levels in the GI tract and are NOT being effectively treated for CDI. (Class III, Level of Evidence C)

3.7. The duration of therapy should generally not exceed 14 days for most patients. Exceptions may include treatment of severe C. difficile infection or treatment of a relapse of disease AND extended therapy while on broad-spectrum or other antibiotics with the potential to increase rates of C. difficile relapse.⁵ (Class IIb, Level of Evidence C)

4. Management of Recurrence

4.1. Prevention of Recurrence

4.1.1. Probiotics have rarely been shown to be effective as adjunctive therapy for the prevention of relapse of CDI and there exists a risk of developing a bloodstream
infection mainly in patients who are heavily immunosuppressed.10,11 (Class IIb, Level of Evidence C)

4.1.2. Continuation of metronidazole or vancomycin for 5-7 days after antibiotics have been discontinued may be considered for assisting in preventing the relapse of disease. In stable patients receiving vancomycin, conversion to metronidazole may be considered to reduce the risk of emergence of vancomycin-resistant enterococci.15-17 (Class IIb, Level of Evidence C)

4.1.3. If long-term (greater than 14 days) therapy is considered, the agent of choice is oral vancomycin in light of the risk of neurotoxicity with the use of metronidazole and that fidaxomicin has no data to support prophylactic use. (Class III, Level of Evidence C)

4.1.4. Tapering or pulsed therapy vancomycin is a potential option for preventing recurrent infection in patients with one or more recurrences of CDI.

4.1.4.1. Vancomycin taper: vancomycin 125mg PO BID x 7 days, then vancomycin 125mg PO daily x 7 days, then vancomycin 125mg PO every 2 days x 7 days, then vancomycin 125mg PO every 3 days x 7 days, then stop.2,18 (Class IIb, Level of Evidence C)

4.1.4.2. Vancomycin pulse after taper: vancomycin 125 to 500 mg PO every 3 days for up to 3 weeks.18 (Class IIb, Level of Evidence C)

4.1.4.3. Sequential therapy with vancomycin followed by rifaximin may be effective for the treatment of recurrent CDI.19 Vancomycin taper as described above should be attempted first. If vancomycin is to be used for subsequent recurrences use vancomycin followed by rifaximin 400-800 mg/day PO divided 2-3 times daily for 14 days. (Class IIb, Level of Evidence C)

5. Fidaxomicin

5.1. The recommended dose is 200 mg orally twice daily for a maximum of 10 days. (Class I, Level of Evidence B) Treatment should NOT be extended beyond 10 days.8

5.2. If further treatment is requested, it should be with oral vancomycin or oral metronidazole

5.3. Pills are film-coated and there is no evidence for crushing or administration of fidaxomicin via nasogastric or other feeding tube, limiting its potential role in intensive care unit patients or those who oral administration is not an option. (Class III, Level of Evidence C)

5.4. For patients with BI/NAP1/027, vancomycin is the preferred agent as fidaxomicin was neither superior for clinical resolution nor superior for the prevention of relapse. (Class IIa, Level of Evidence B) At UWHC, fidaxomicin should be used for non-NAP1 strains only.

5.5. Fidaxomicin is reserved for patients with the following conditions:

5.5.1. Patients with relapse or recurrence after sufficient treatment courses with metronidazole AND subsequently vancomycin (see 3.0). Patients relapsing on metronidazole should be given a trial of vancomycin before considering fidaxomicin. (Class IIa, Level of Evidence C) Similarly, some patients will be considered candidates for a vancomycin tapering regimen trial before considering fidaxomicin.

5.5.1.1. Documented (PCR positive or colonoscopy proven) recurrent CDI requiring hospitalization. (Class IIa, Level of Evidence B)

5.5.1.2. Relapse during current hospitalization. (Class IIa, Level of Evidence B)

5.5.1.3. Outpatients with relapse(s) of disease not requiring hospitalization (B-I)

5.5.2. Patients with documented low levels of neutralizing antibodies to C. difficile (since this test is not available with rapid turnaround time, use under this indication would likely take 10-14 days). The role of both IVIG infusion and fidaxomicin is uncertain at this time. (Class IIb, Level of Evidence B)

5.5.3. Fidaxomicin will NOT be prescribed because a patient falls into a “high risk/severe disease/likely antibody deficient” as defined above without meeting other criteria in this current guideline until evidence supports this indication. (Class III, Level of Evidence C)

5.6. Patients who have relapsed within 4 weeks of treatment of fidaxomicin are not candidates for repeated courses. (Class IIb, Level of Evidence C)
5.7. Patients who have relapsed within 4 weeks of treatment of fidaxomicin, received antibiotics with these 4 weeks and have recurrent CDI may be considered for repeated courses of fidaxomicin. (Class IIb, Level of Evidence C)

6. Intravenous Immune Globulin (IVIG) for Clostridium difficile infection falls under the purview of the UW Health Criteria for the Use of Intravenous Immune Globulin.12

6.1. Randomized control trials with conflicting results and conflicting evidence of benefit. IVIG failed to decrease risk of colectomy or mortality in a study of pair matched adults with severe CDI, no testing of IgG levels was performed.20 IVIG appeared to be effective in preventing recurrence of CDI in 6 children with confirmed deficiency in IgG anti-toxin A levels.21 (Class IIb, Level of Evidence C)

6.2. This indication for ordering of IVIG is limited to the Infectious Disease (pager 3333) and Gastroenterology attending physicians.

6.3. Clinical studies did NOT measure Clostridium difficile neutralizing antibody titres in the IVIG preparations. Therefore, not all patients with low titres may benefit from IVIG.

7. Fecal Enemas or Infusions

7.1. Use may be considered under unique circumstances and should be limited to the Infectious Disease (pager 3333) and Gastroenterology attending physicians.22 (Class IIb, Level of Evidence B)

7.2. Procedure and administration instructions are outlined in Aas, et al.23,24

Companion Documents
Infection control surveillance procedures regarding CDI are available on UConnect: https://uconnect.wisc.edu/servlet/Satellite?cid=1126668293880&pagename=B_EXTRANET_UWH_HOME%2FFlexMemberFile%2FLoad_File&c=FlexMemberFile

Pertinent UWHC Policies & Procedures
UW Health Criteria for the Use of Intravenous Immune Globulin
A. **Scope** (disease/condition, treatment, clinical specialty)
   1. Patients with initial and recurrent *Clostridium difficile* infection (CDI)

B. **Methodology**
   1. A modified Grading of Recommendations Assessment, Development and Evaluation (GRADE) developed by the American Heart Association and American College of Cardiology (Figure 1.) has been used to assess the Quality and Strength of the Evidence in this Clinical Practice Guideline.

   ![Quality of Evidence and Strength of Recommendation Grading Matrix](image)

   **Figure 1. Quality of Evidence and Strength of Recommendation Grading Matrix**

C. **Definitions**
   1. **Risk factors for CDI include**
      1.1. Increasing age (in particular ≥ 64 years of age)
      1.2. Hospitalization for any reason
      1.3. Exposure to antimicrobial agents and exposure to multiple antimicrobials
         1.3.1. Fluoroquinolones
         1.3.2. 1st, 2nd, 3rd and 4th Generation Cephalosporins
1.3.3. Intravenous vancomycin  
1.3.4. Beta-lactimase inhibitor combinations  
1.3.5. Sulfonamides  
1.3.6. Clindamycin  
1.3.7. Two or more antibiotics  
1.4. Cancer chemotherapy  
1.5. Immunosuppression (e.g. HIV, organ transplant)  
1.6. Gastrointestinal surgery  
1.7. Manipulation of GI tract for any reason  
1.7.1. Tube feedings  
1.7.2. H₂ blockers  
1.7.3. Proton pump inhibitors

2. Risk stratification tool (Table 1.)²  
2.1. Mild to moderate CDI is defined as a score of < 2  
2.2. Severe CDI is defined as a score ≥ 2

<table>
<thead>
<tr>
<th>Assign ONE point for each</th>
<th>Assign TWO points for each</th>
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</thead>
<tbody>
<tr>
<td>Age &gt; 60 years</td>
<td>Hospitalization in ICU when onset occurs</td>
</tr>
<tr>
<td>Temperature &gt; 38.3°C (&gt;100.9°F)</td>
<td>Presence of pseudomembranous colitis (as diagnosed via endoscopy or CT)</td>
</tr>
<tr>
<td>Elevated SCr &lt; 1.5X the premorbid level</td>
<td>Elevated SCr &gt; 1.5X the premorbid level</td>
</tr>
<tr>
<td>WBC &gt; 15,000 cells/mm³</td>
<td>WBC &gt; 30,000 cells/mm³ or &lt; 1000 cells/mm³</td>
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<tr>
<td>Albumin &lt; 2.5 mg/dL</td>
<td></td>
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<tr>
<td>Immunocompromised (HIV, chronic steroids, chemotherapy, or other immunosuppressive medications)</td>
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3. GeneXpert® C. difficile assay  
3.1. UWHC uses the GeneXpert® C. difficile diagnostic assay (Cepheid Innovation) to detect CDI.⁴ The GeneXpert® C. difficile assay is a qualitative, in vitro, rapid detection PCR. It specifically amplifies the C. difficile gene responsible for the production of toxin B. Trials indicate a 98.79% sensitivity and a 90.82% specificity, suggesting that negative results can be reported with high certainty of accuracy and retesting after 7 days is not recommended. Prior use of antibiotics does not impact the ability of the assay to accurately detect C. difficile toxin B.  
3.2. The assay has several limitations  
3.2.1. It can detect but does not automatically differentiate NAP1 strains  
3.2.2. Strains that do not produce Toxin B will not be detected  
3.2.3. The ability of the assay to detect toxin B is inhibited if the sample contains zinc oxide paste or Vagisil® cream  
3.3. GeneXpert® has the potential to distinguish the NAP1 strain⁴  
3.3.1. The expanded test for NAP1 strains is currently reserved for patients with at least 1 previously positive C. difficile test or in patients with potentially life threatening CDI but it may be considered for routine testing at UWHC.  
4. Risk factors for recurrent CDI⁵  
4.1. Same as for initial infection (See C.1.)  
4.2. Continued exposure to organisms  
4.3. Continued exposure to antibiotics  
4.4. Relapsing CDI from endogenous source (i.e. spores in GI tract)
4.5. Poor host IgG antibody response to toxin A
4.5.1. Test is available through UWHC reference lab but results require 1-2 weeks for processing

D. Introduction
1. *Clostridium difficile* is a spore forming, anaerobic, gram positive, bacilli responsible for 15-25% of cases of nosocomial diarrhea and 20-30% of antibiotic associated diarrhea. Toxigenic species are capable of producing toxin A, toxin B, a binary toxin, or a combination. *C. difficile* infection can manifest from symptomless carriage and minor diarrhea to fatal pseudomembranous colitis and toxic megacolon, sepsis, bowel perforation and death.\(^5,6\) Mortality rates from CDI increased from 5.7 per million population in 1999 to 23.7 per million in 2004.\(^7\) It is projected to nationally cause $3.2 billion in health care costs. In recent years a particularly virulent strain of *C. difficile*, BI/NAP1, has become a major pathogen in the development of CDI. BI/NAP1 has increased virulence characteristics including: increased toxin production, binary toxin, hypersporulation, and resistance to fluoroquinolone antibiotics.\(^2,6\)

2. Recurrence of CDI is highest in the 7-14 days after completion of initial therapy. The risk of recurrence increases as the number of infections or reinfections increase.\(^2,6\) (See C.4.)

3. Fidaxomicin is a novel macrocyclic antibiotic approved for treatment of *Clostridium difficile* in adult patients.\(^8,9\) The safety and efficacy of fidaxomicin in pediatric patients has not been studied.\(^8\) Two randomized trials designed with non-inferiority end-points demonstrated equivalence to enterally administered vancomycin.\(^9\) Clinical response rates at the end of treatment were similar although sustained clinical response rates without clinical relapse at 25 days appeared superior for fidaxomicin.

E. Recommendations – All recommendations should contain a strength of evidence and strength of recommendation statement. Include companion/collateral documents (e.g., algorithm, tables, forms) and patient resources.
1. Prevention
   1.1. The most important treatment technique for *Clostridium difficile* is prevention. Compliance with UWHC policies on personal protective equipment, hand-washing, and infection control should be followed.\(^2\) (Class I, Level of Evidence B)
   1.2. Probiotics have rarely been shown to be effective as adjunctive therapy for prevention of primary CDI and there exists a risk of developing a bloodstream infection mainly in patients who are heavily immunosuppressed.\(^10,11\) (Class IIb, Level of Evidence C)

2. Diagnosis
2.1. Evaluation of patients without diarrhea or risk factors should be avoided. In rare cases, patients will present with ileus and/or colonic distention in the absence of diarrhea.\(^2\) (Class Ila, Level of Evidence C)

2.2. Patients experiencing diarrhea (≥3 unformed stools in the previous 24 hours) with risk factors for *Clostridium difficile* infection (CDI) should be evaluated for presence of *C. difficile* toxin. (Class Ila, Level of Evidence B).

2.3. Diagnosis at UWHC may be made through several methods
   2.3.1. Stool sample with toxigenic *C. difficile* by measurement of toxin A, toxin B, or binary toxin via polymerase chain reaction (PCR). (Class Ila, Level of Evidence B)
   2.3.1.1. The PCR test available at UWHC is highly sensitive (≈99%) and specific (≈91%) as compared to cell cytotoxicity and immunoassays.\(^4\)
   2.3.1.2. Negative PCR-test results can be reported with high certainty of accuracy and retesting after 7 days is not recommended (Class III, Level B)
   2.3.2. Direct visualization via colonoscopy or histologic findings of pseudomembranous colitis.\(^2\)

3. Treatment
3.1. Empiric therapy without diagnostic evidence is inappropriate.\(^2\) (Class IIb, Level of Evidence C)
3.2. Identify patients at risk for CDI and order toxin assay by PCR.\(^2\) (Class Ila, Level of Evidence B)
3.3. Discontinue therapy with inciting antimicrobial agent(s) as soon as possible.² (Class I, Level of Evidence B)

3.4. Classify patients by severity using risk stratification tool.² (Table 1.)
3.4.1. For treatment of mild to moderate disease, begin metronidazole 500 mg PO every 8 hours for 10 to 14 days. (Class I, Level of Evidence B)
3.4.2. For treatment of severe disease, begin vancomycin 125mg PO every 6 hours for 10-14 days. (Class IIa, Level of Evidence B)
3.4.3. For treatment of severe, complicated disease, begin vancomycin 500mg PO/NG every 6 hours PLUS metronidazole 500mg IV every 8 hours.² Tigecycline 100mg IV once then 50mg IV every 12 hours may be considered as an alternative for metronidazole IV in patients with severe refractory CDI when there is a need for continuation of concomitant antifungals which may worsen the condition.¹²,¹³ (Class IIb, Level of Evidence C)
3.4.3.1. In patients without enteral access, IV metronidazole is the preferred option. Tigecycline may be an alternative as described above. (Class IIb, Level of Evidence C)
3.4.4. For treatment of severe CDI in patients with ileus or patients with diverting ileostomy consider adding vancomycin rectal instillation.¹² (Class IIb, Level of Evidence C)
3.4.4.1. Order using “vancomycin (VANCOCIN) solution” with route specified as “other”, dose is 500mg 4 times daily with the comments to specify “Please administer RECTALLY as enemas. Use 18 F red rubber catheter inserted up to 4 inches. Dilute to 100mL with sterile 0.9%NS for irrigation. May administer 100mL at a time. DO NOT GIVE ORALLY.”
3.4.4.2. Vancomycin rectal administration is NOT routinely recommended in neutropenic patients due to the risk of infection with manipulation of the rectum. (Class III, Level of Evidence C)
3.4.5. There is limited evidence to support use of G.I. lavage (GOLYTELY) solution as an adjunct to agents routinely used to treat chronic, relapsing CDI. G.I. lavage may be useful for clearing the C. difficile organisms, spores, and associated toxins from the intestine of patients with relapsing infections.¹⁴ (Class IIb, Level of Evidence C)
3.4.6. Daily assessment is necessary to assess efficacy of all treatments.
3.5. Antiperistaltic agents should generally be avoided in patients with suspected or confirmed CDI as they may obscure symptoms and precipitate toxic megacolon.² (Class III, Level of Evidence C)
3.6. Multiple oral agents provide redundant coverage and should not be given simultaneously. Examples include oral vancomycin and oral metronidazole OR oral vancomycin and oral fidaxomicin. (Class IIb, Level of Evidence C)
3.6.1. Oral metronidazole is 90% absorbed and generally should not be given concomitantly with full-dose intravenous metronidazole. (Class III, Level of Evidence C)
3.6.2. Oral vancomycin and fidaxomicin are NOT absorbed from the GI tract. If treatment of infections outside of the GI tract require vancomycin, the intravenous form can be given simultaneously with the oral form without risk of toxicity. Conversely, patients being treated with intravenous vancomycin will NOT achieve adequate levels in the GI tract and are NOT being effectively treated for CDI. (Class III, Level of Evidence C)
3.7. The duration of therapy should generally not exceed 14 days for most patients. Exceptions may include treatment of severe C. difficile infection or treatment of a relapse of disease AND extended therapy while on broad-spectrum or other antibiotics with the potential to increase rates of C. difficile relapse.⁶ (Class IIb, Level of Evidence C)

4. Management of Recurrence
4.1. Prevention of Recurrence
4.1.1. Probiotics have rarely been shown to be effective as adjunctive therapy for the prevention of relapse of CDI and there exists a risk of developing a bloodstream infection mainly in patients who are heavily immunosuppressed.¹⁰,¹¹ (Class IIb, Level of Evidence C)
4.1.2. Continuation of metronidazole or vancomycin for 5-7 days after antibiotics have been discontinued may be considered for assisting in preventing the relapse of disease. In
stable patients receiving vancomycin, conversion to metronidazole may be considered to reduce the risk of emergence of vancomycin-resistant enterococci.\(^{15-17}\) (Class IIb, Level of Evidence C)

4.1.3. If long-term (greater than 14 days) therapy is considered, the agent of choice is oral vancomycin in light of the risk of neurotoxicity with the use of metronidazole and that fidaxomicin has no data to support prophylactic use. (Class III, Level of Evidence C)

4.1.4. Tapering or pulsed therapy vancomycin is a potential option for preventing recurrent infection in patients with one or more recurrences of CDI. 4.1.4.1. Vancomycin taper: vancomycin 125mg PO BID x 7 days, then vancomycin 125mg PO daily x 7 days, then vancomycin 125mg PO every 2 days x 7 days, then vancomycin 125mg PO every 3 days x 7 days, then stop.\(^{2,18}\) (Class IIb, Level of Evidence C)

4.1.4.2. Vancomycin pulse after taper: vancomycin 125 to 500 mg PO every 3 days for up to 3 weeks.\(^{18}\) (Class IIb, Level of Evidence C)

4.1.4.3. Sequential therapy with vancomycin followed by rifaximin may be effective for the treatment of recurrent CDI.\(^{19}\) Vancomycin taper as described above should be attempted first. If vancomycin is to be used for subsequent recurrences use vancomycin followed by rifaximin 400-800 mg/day PO divided 2-3 times daily for 14 days. (Class IIb, Level of Evidence C)

5. Fidaxomicin

5.1. The recommended dose is 200 mg orally twice daily for a maximum of 10 days. (Class I, Level of Evidence B) Treatment should NOT be extended beyond 10 days.\(^{8}\)

5.2. If further treatment is requested, it should be with oral vancomycin or oral metronidazole

5.3. Pills are film-coated and there is no evidence for crushing or administration of fidaxomicin via nasogastric or other feeding tube, limiting its potential role in intensive care unit patients or those who oral administration is not an option. (Class III, Level of Evidence C)

5.4. For patients with BI/NAP1/027, vancomycin is the preferred agent as fidaxomicin was neither superior for clinical resolution nor superior for the prevention of relapse. (Class IIa, Level of Evidence B) At UWHC, fidaxomicin should be used for non-NAP1 strains only.

5.5. Fidaxomicin is reserved for patients with the following conditions:

5.5.1. Patients with relapse or recurrence after sufficient treatment courses with metronidazole AND subsequently vancomycin (see 3.0). Patients relapsing on metronidazole should be given a trial of vancomycin before considering fidaxomicin. (Class IIa, Level of Evidence C) Similarly, some patients will be considered candidates for a vancomycin tapering regimen trial before considering fidaxomicin.

5.5.1.1. Documented (PCR positive or colonoscopy proven) recurrent CDI requiring hospitalization. (Class IIa, Level of Evidence B)

5.5.1.2. Relapse during current hospitalization. (Class IIa, Level of Evidence B)

5.5.1.3. Outpatients with relapse(s) of disease not requiring hospitalization (B-I)

5.5.2. Patients with documented low levels of neutralizing antibodies to C. difficile (since this test is not available with rapid turnaround time, use under this indication would likely take 10-14 days). The role of both IVIG infusion and fidaxomicin is uncertain at this time. (Class IIb, Level of Evidence B)

5.5.3. Fidaxomicin will NOT be prescribed because a patient falls into a “high risk/severe disease/likely antibody deficient” as defined above without meeting other criteria in this current guideline until evidence supports this indication. (Class III, Level of Evidence C)

5.6. Patients who have relapsed within 4 weeks of treatment of fidaxomicin are not candidates for repeated courses. (Class IIb, Level of Evidence C)

5.7. Patients who have relapsed within 4 weeks of treatment of fidaxomicin, received antibiotics with these 4 weeks and have recurrent CDI may be considered for repeated courses of fidaxomicin. (Class IIb, Level of Evidence C)

6. Intravenous Immune Globulin (IVIG) for Clostridium difficile infection falls under the purview of the UW Health Criteria for the Use of Intravenous Immune Globulin\(^{12}\)

6.1. Randomized control trials with conflicting results and conflicting evidence of benefit. IVIG failed to decrease risk of colectomy or mortality in a study of pair matched adults with
severe CDI, no testing of IgG levels was performed.\textsuperscript{20} IVIG appeared to be effective in preventing recurrence of CDI in 6 children with confirmed deficiency in IgG anti-toxin A levels.\textsuperscript{21} (Class IIb, Level of Evidence C)

6.2. This indication for ordering of IVIG is limited to the Infectious Disease (pager 3333) and Gastroenterology attending physicians.

6.3. Clinical studies did NOT measure \textit{Clostridium difficile} neutralizing antibody titres in the IVIG preparations. Therefore, not all patients with low titres may benefit from IVIG.

7. Fecal Enemas or Infusions

7.1. Use may be considered under unique circumstances and should be limited to the Infectious Disease (pager 3333) and Gastroenterology attending physicians.\textsuperscript{22} (Class IIb, Level of Evidence B)

7.2. Procedure and administration instructions are outlined in Aas, et al.\textsuperscript{23,24}

F. \textbf{Internal References}

1. UW Health Criteria for the Use of Intravenous Immune Globulin

G. \textbf{External References}


H. Benefits/Harms of Implementation
1. Fidaxomicin
   1.1. Applying efficacy data from clinical trials to 2010 and 2011 CDI rates and relapses at UWHC results in the following Number Needed to Treat (NNT) to prevent 1 patient adverse event (cost is provided based on 10 day course of fidaxomicin equaling $2800).
     1.1.1. Prevention of readmission (3% --> 1.7%): NNT = 73 ($204,000)
     1.1.2. Prevention of index hospitalization (5% --> 2.7%): NNT = 45 ($126,000)
     1.1.3. Prevention of "inpatient complication" (combining #1 & #2)(8% --> 4.4%): NNT = 28 ($78,400)
     1.1.4. Prevention of outpatient relapse (6.7% --> 3.1%): NNT = 39 ($109,200)
     1.1.5. Prevention of any complication (combining 1.1.4 and 1.1.5) (13.6% --> 7.5%): NNT = 16 ($44,800)
     1.1.6. Excess cost for hospitalization for CDI is $28,138 (2011 UWHC estimated cost of hospitalization)

I. Qualifying Statements (optional)

J. Implementation Strategy – Describe specific strategies, aims, performance measures, or plans for implement the CPG recommendations, if presented in the guideline or supplied by the guideline developer.

K. Implementation Tools/Plan –
   1. Use of fidaxomicin requires Infectious Diseases approval (through 3333 pager) or recommendation from Infectious Disease or Gastroenterology attending physicians (as documented in the electronic medical record) AND meeting requirements outlined in section E.5.
   2. Infection control surveillance procedures regarding CDI are available on UConnect.
      2.1. [https://uconnect.wisc.edu/servlet/Satellite?cid=1126668293880&pagename=B_EXTRANET_UWH_HOME%2FFFlexMemberFile%2FLoad_File&c=FlexMemberFile](https://uconnect.wisc.edu/servlet/Satellite?cid=1126668293880&pagename=B_EXTRANET_UWH_HOME%2FFFlexMemberFile%2FLoad_File&c=FlexMemberFile)
   3. Pharmacists will be educated about these guidelines via department inservices.
   4. The pharmacist should be consulted to evaluate insurance coverage and outpatient cost prior to starting fidaxomicin or oral vancomycin. Before beginning treatment with fidaxomicin, patients should either: have anticipated additional hospitalization of 10 or more days, or have sufficient financial resources to pay for the antibiotic (or lack of financial resources via the patient assistance program) to successfully complete the intended 10 day course of therapy. Shorter courses of therapy less than 10 days have not yet been studied in clinical trials.
L. Disclaimer
This Clinical Practice Guideline provides an evidence-based approach for treatment of CDI. It is understood that occasionally patients will not match the conditions considered in the guideline.