**Patient population**: Adult and pediatric patients with a primary or recurrent episode of *Clostridium difficile* infection (CDI)

**Objectives**:  
1. Provide a brief overview of the epidemiology of, and risk factors for development of CDI  
2. Provide guidance regarding which patients should be tested for CDI, summarize merits and limitations of available diagnostic tests, and describe the optimal approach to laboratory diagnosis  
3. Review the most effective treatment strategies for patients with CDI including patients with recurrences or complications

**Key points for adult patients**:

**Diagnosis**  
- Definitive diagnosis of CDI requires either the presence of toxigenic *C. difficile* in stool with compatible symptoms, or clinical evidence of pseudomembranous colitis (Table 2, Figure 4).  
- Once identified, CDI should be classified according to severity (Table 3).  
- Although risk factors for CDI (Table 1) should guide suspicion for CDI, testing should be ordered only when indicated (Figure 1). [IC]  
- Choice of test should be guided by a multi-step algorithm for the rapid diagnosis of CDI (Figure 2). [IIIC]  
- Single-step PCR testing (not part of the UMHS algorithm) occurs as part of the new Biofire test panel for gastrointestinal pathogens and should not be used if CDI is suspected. [IIIIB] However, if *C. difficile* is detected as part of this panel and the patient’s symptoms are compatible with CDI, then treatment is appropriate and additional testing is unnecessary. [IC]  
- Patients who are asymptomatic, actively being treated or completed treatment for CDI with clinical improvement in symptoms, or have post-infectious irritable bowel syndrome after CDI should not undergo testing for CDI. [IIIC]

**Treatment**: (See Figure 3 and Table 4)  
- **Mild-Moderate CDI**: Patient does not meet criteria for “severe” or “complicated” CDI  
  - metronidazole 500 mg PO TID for 10-14 days [IIB]  
  - In patients with metronidazole allergy, pregnant, nursing, or on warfarin therapy: vancomycin 125 mg PO QID for 10-14 days. [IB]  
- **Severe CDI**: Patients with WBC ≥ 15K, Cr ≥ 1.5x baseline, Age ≥ 65, ANC ≤ 500, Albumin ≤ 2.5, SOT/BMT < 100 days, chronic GVHD (BMT), treatment of rejection in the preceding 2 months (SOT), Small bowel CDI, or inflammatory bowel disease  
  - vancomycin 125 mg PO QID for 10-14 days [IA]  
- **Complicated CDI**: Patients with septic shock, ileus, toxic megacolon, peritonitis, or bowel perforation  
  - Triple therapy=vancomycin 500 mg PO QID, metronidazole 500 mg IV every 8 hours, and vancomycin enema every 6 hours (in patients with ileus, bowel obstruction or toxic megacolon) [IB]  
  - Consult infectious diseases  
  - Consult surgery to assist in management including possible surgical intervention (Table 4, Figure 5).

**Recurrent CDI**: Recurrent symptoms and positive testing for toxigenic *C. difficile* within 8 weeks of prior episode  
- First recurrence:  
  - Classify as “mild-moderate” “severe,” or “complicated,” and treat accordingly [IC]  
- Second or multiple recurrences (third or more episode of CDI):  
  - Consult infectious diseases  
  - Vancomycin PO (dose, need for concurrent IV metronidazole/vancomycin enemas depends on disease classification as noted above) for 10-14 days then taper to 125 mg PO BID for 7 days, 125 mg PO daily for 7 days, and then pulse with 125 mg PO once every 2-3 days for 2-8 weeks. [IIC]  
  - fidaxomicin 200 mg PO BID for 10 days (with approval from the infectious diseases consult service). [IIIE]

**Strength of recommendation**:  
1 = generally should be performed; II = may be reasonable to perform; III = generally should not be performed.

**Level of evidence supporting a diagnostic method or an intervention**:  
A = systematic reviews of randomized controlled trials with or without meta-analysis, B = randomized controlled trials, C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control), D = individual observation studies (case study/year series), E = expert opinion regarding benefits and harm
Key points for pediatric patients ≤ 18 years of age:

**Diagnosis**
- The decision to test children for CDI is complicated given a high rate of asymptomatic carriage, especially in infants < 12 months of age. Although risk factors for CDI should guide suspicion for CDI, testing should be ordered only when indicated (Figure 1). [IIIC] Indications and contraindications for testing pediatric patients are included in Figure 1, but testing is rarely indicated or recommended for infants < 12 months [IIIC] and consultation with pediatric ID is recommended. Children from 12 months to 36 months of age may be diagnosed with CDI if no alternative etiology for diarrhea is identified and with positive diagnostic testing. [IIIC]
- Definitive diagnosis of CDI requires either the presence of toxigenic *C. difficile* in stool with other symptoms, or clinical evidence of pseudomembranous colitis (Table 2). Choice of test should be guided by a multi-step algorithm for the rapid diagnosis of CDI (Figure 2). Single-step PCR testing (not part of the UMHS algorithm) occurs as part of the new Biofire test panel for gastrointestinal pathogens and should not be used if CDI is suspected. [IIIIE] However, if *C. difficile* is detected as part of this panel and the patient’s symptoms are compatible with CDI, then treatment is appropriate and additional testing is unnecessary. [IIIC] Patients who are asymptomatic, actively being treated or completed treatment for CDI with clinical improvement in symptoms, or have post-infectious irritable bowel syndrome after CDI should not undergo testing for CDI. [IIIC]
- Once identified, CDI should be classified according to severity (Table 3). Certain pediatric conditions are associated with severe CDI and should be treated as such (see Table 3). [IIIC]

**Treatment:** (See Figure 3 for general strategy and Table 3 for pediatric-specific dosing recommendations)

**Mild-Moderate CDI:** Patient does not meet criteria for “severe” or “complicated” CDI
- metronidazole 7.5 mg/kg/dose PO QID for 10 days, maximum 500 mg/dose [IIIC]
- OR
- In patients with metronidazole allergy, pregnant, nursing, or on warfarin therapy, or who fail to improve after 3-5 days of PO metronidazole therapy: vancomycin 10 mg/kg/dose PO QID, up to maximum 125 mg/dose x 10 days. [IIIC]

**Severe CDI:** Pediatric patients with ≥ 2 lab criteria (WBC ≥ 15K, Cr ≥ 1.5x baseline, ANC ≤ 500, Albumin ≤ 2.5) OR ANY high-risk condition with Hirschsprung’s Disease or other intestinal dysmotility disorder, neutropenia from leukemia or other malignancy, inflammatory bowel disease, SOT/BMT < 100 days
- vancomycin 10 mg/kg/dose PO QID, up to maximum 125 mg/dose x 10 days [IB]

**Complicated CDI:** Patients with septic shock, ICU admission within 2 days of CDI diagnosis, surgery related to CDI diagnosis, ileus, toxic megacolon, peritonitis, or bowel perforation.
- Triple therapy = vancomycin up to 500 mg PO QID, metronidazole 7.5 mg/kg/dose IV Q6H up to 500 mg/dose, and vancomycin enema 10-20 mL/kg/dose up to 1000 mL/dose every 6 hours of vancomycin 500 mg/L solution [if tolerated, 20 mL/kg/dose every 6 hours is preferred, however in patient with additional administration considerations, a minimum of 10 mL/kg/dose every 8 hours should be used] (in patients with ileus, bowel obstruction or toxic megacolon; bowel perforation is a contraindication to enema therapy) [IIC]
- Consult pediatric infectious diseases
- Consult pediatric surgery to assist in management including possible surgical intervention (Table 4).

**Recurrent CDI:** Recurrent symptoms and positive testing for toxigenic *C. difficile* within 8 weeks of prior episode.

First recurrence:
- Classify as “mild-moderate” “severe,” or “complicated,” and treat accordingly. [IC]

Second or multiple recurrences (third or more episode of CDI):
- Consult pediatric infectious diseases
- Consult pediatric infectious diseases
- vancomycin PO (dose, need for concurrent IV metronidazole/vancomycin enemas depends on disease classification as noted above) for 10-14 days then taper to 125 mg PO BID for 7 days, 125 mg PO daily for 7 days, and then pulse with 125 mg PO once every 2-3 days for 2-8 weeks. [IIIC]
- OR
- fidaxomicin 16 mg/kg/dose BID, max 200 mg per dose, for 10 days [IIIC]; pediatric ID approval is required for use.
Table 1. Risk Factors for CDI

- Past history of CDI
- Current or recent antibiotic use (highest risk within 3 months of exposure)
- Advanced age (65 or older)
- Severe comorbid disease(s)
- Hospitalization within 30 days
- Inflammatory bowel disease (IBD)
- Immunosuppressed state and use of immunosuppressive drugs
- Acid suppressive therapy (especially, proton pump inhibitors)

Additional risk factors specific to pediatrics
- Pediatric patients with history of prematurity, prolonged or frequent hospitalizations, or history of frequent or recent antimicrobial therapy
- Pediatric patients with Hirschsprung’s disease, other intestinal dysmotility disorder, or history of abdominal surgery, including gastrostomy or jejunostomy tubes

Note: Community-associated CDI\(^1\) can be seen in low risk population or in patients without traditional risk factors.

Figure 1. Indications and Contraindications for CDI Testing

\(\text{CDI: Clostridium difficile infection; IBD: inflammatory bowel disease; ID: infectious disease (service); PCR: polymerase chain reaction; WBC: white blood cell count.}\)
Table 2. Definition of *Clostridium difficile* Infection (CDI)

Requires either of the following:
1. A positive laboratory result for presence of toxigenic *C. difficile* in the stool
   PLUS Any of the following symptoms compatible with CDI
   - Diarrhea (≥3 unformed stools in a 24-hour period without an alternate explanation such as laxative use)
   - Radiographic evidence of ileus without alternate explanation (especially if leukocytosis present [WBC >15,000 cells/mm³])
   - Abdominal pain with radiographic evidence of bowel thickening
   - Radiographic evidence of toxic megacolon
   OR
2. Colonoscopic or histopathologic evidence of pseudomembranous colitis.

CDI: *Clostridium difficile* infection; WBC: white blood cell count.

Figure 2. University of Michigan Health System Multistep Algorithm* for the Rapid Diagnosis of *C. difficile* Infection

CDI: *Clostridium difficile* infection; EIA: enzyme immunoassay; GDH: glutamate dehydrogenase; PCR: polymerase chain reaction.

### Table 3. Criteria for Severity Classification of *Clostridium difficile* Infection

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment</th>
<th>Severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild/Moderate</td>
<td>Patient does not meet criteria for “severe” or “complicated” CDI</td>
<td>Mild/Moderate</td>
<td>Patient does not meet criteria for “severe” or “complicated” CDI</td>
</tr>
<tr>
<td></td>
<td>• Diagnosis of CDI (see Table 2) AND</td>
<td></td>
<td>• Diagnosis of CDI (see Table 2) AND</td>
</tr>
<tr>
<td></td>
<td>• None of the criteria in the “severe” or “complicated” columns below</td>
<td></td>
<td>• None of the criteria in the “severe” or “complicated” columns below</td>
</tr>
<tr>
<td>Severe (ANY of the following)</td>
<td>• Age ≥ 65</td>
<td>Severe (at least 2 abnormal lab values OR at least 1 high-risk condition)</td>
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<tr>
<td></td>
<td>• WBC ≥ 15K</td>
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<td>• WBC ≥ 15K</td>
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<td></td>
<td>• Cr ≥ 1.5x baseline</td>
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<td>• Cr ≥ 1.5x baseline</td>
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<td>• ANC ≤ 500</td>
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<td>• ALB ≤ 2.5</td>
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<td>• ALB ≤ 2.5</td>
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<td></td>
<td>• SOT/BMT &lt; 100 days</td>
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<td>• SOT/BMT &lt; 100 days</td>
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<td></td>
<td>• Small bowel CDI</td>
<td></td>
<td>• Small bowel CDI</td>
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<td></td>
<td>• Inflammatory Bowel Disease</td>
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<td>• Inflammatory Bowel Disease</td>
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<tr>
<td></td>
<td>• Treatment of rejection in the preceding 2 months (SOT)</td>
<td></td>
<td>• Hirschsprung’s Disease or other intestinal dysmotility disorder</td>
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<td></td>
<td>• Chronic GVHD (BMT)</td>
<td></td>
<td>• Neutropenia from malignancy</td>
</tr>
<tr>
<td>Complicated (ANY of the following)</td>
<td>• Septic shock – Sepsis with persistent hypotension, requiring vasopressors to maintain MAP ≥ 65 mm Hg and having a serum lactate level ≥ 2 mmol/L despite adequate fluid resuscitation</td>
<td>Complicated (ANY of the following)</td>
<td></td>
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<tr>
<td></td>
<td>• Severe sepsis – Life-threatening organ dysfunction caused by a dysregulated host response to infection. Suspected or documented infection and an acute increase of ≥ 2 SOFA points</td>
<td></td>
<td>• Septic shock</td>
</tr>
<tr>
<td></td>
<td>• Ileus or bowel obstruction</td>
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<td>• Severe sepsis</td>
</tr>
<tr>
<td></td>
<td>• Toxic megacolon</td>
<td></td>
<td>• Ileus or bowel obstruction</td>
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<tr>
<td></td>
<td>• Peritonitis</td>
<td></td>
<td>• Toxic megacolon</td>
</tr>
<tr>
<td></td>
<td>• Bowel perforation</td>
<td></td>
<td>• Peritonitis</td>
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<td></td>
<td>• vancomycin 500 mg PO QID</td>
<td></td>
<td>• Bowel perforation</td>
</tr>
<tr>
<td></td>
<td>• metronidazole 500 mg PO TID for 10-14 days</td>
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<tr>
<td></td>
<td>• Patients with metronidazole allergy, pregnant, nursing, or on warfarin therapy:</td>
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<tr>
<td></td>
<td>• vancomycin 125 mg PO QID for 10-14 days</td>
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<td></td>
<td>• Patients with metronidazole 7.5 mg/kg/dose PO QID for 10 days, maximum 500 mg/dose OR</td>
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<td></td>
<td>• Patients with metronidazole allergy, pregnant, nursing, on warfarin therapy, or who fail to improve after 3-5 days of PO metronidazole therapy: vancomycin 10 mg/kg/dose PO QID, up to maximum 125 mg/dose x 10 days</td>
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</table>

ANC: absolute neutrophil count; ALB: albumin; BMT: bone marrow transplant; CDI: *Clostridium difficile* infection; Cr: serum creatinine; GVHD: graft versus host disease; SOT: solid organ transplant; WBC: white blood cell count. *Please see text regarding treatment of second or greater recurrence of CDI and the role of prophylactic oral vancomycin with concomitant antibiotic use for first or greater CDI episode.

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**Table 4:**

<table>
<thead>
<tr>
<th>Column 1</th>
<th>Column 2</th>
<th>Column 3</th>
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<tr>
<td>Column 4</td>
<td>Column 5</td>
<td>Column 6</td>
</tr>
</tbody>
</table>

**Figure 5:**

**Figure 5:**

**Figure 5:**

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**Appendix:**

**Appendix:**

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**References:**

**References:**

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**Supplementary Material:**

**Supplementary Material:**
Figure 3. *Clostridium difficile* Infection Treatment Algorithm Overview

**Suspected CDI**
- Fluid and electrolyte resuscitation as necessary
- Consider infection control measures
- Stop inciting antibiotics if possible
- Stop acid suppressive medications (especially PPI) if possible

**First episode or first recurrence**
- Disease severity? (See Table 3)
  - **Mild/Moderate**
    - Metronidazole 500 mg PO TID (10-14 days)
  - **Severe**
    - Vancomycin 125 mg PO QID 10-14 days

  - Daily assessment (if distended, include abdominal x-ray)

  - Improve within 3-5 days?
    - Improve
    - Stable, not improved
      - If metronidazole, change to vancomycin 125 QID, then reassess improvement (as above) in 3-5 days.

  - **Complicated**
    - Triple therapy***
    - ID consult****
    - Surgery consult
    - Consider CT scan abdomen pelvis

  - Complicated disease (as above) in 3-5 days.

  - Frequent reassessment (see Table 4 for indication for consideration of surgery).
  - Continue therapy and monitoring for need for surgery until improved.**

  - Complete treatment course

  - ID consult

  - Complete treatment course

**Deterioration: Any of the following:**
- Worsening abdominal distention/pain and/or peritonitis
- Worsening leukocytosis
- Cardiopulmonary or other end organ failure
- Intubation
- Vasopressor requirement
- Mental status changes
- New or worsening Acute Kidney Injury
- Worsening Lactate > 5mmol/L

**Triple therapy:**
- Vancomycin 500mg PO QID
- Metronidazole 500mg IV Q6h
- Vancomycin 500mg in 1000ml retention enema Q6h in setting of ileus, toxic megacolon or bowel obstruction (do not use if risk of colonic perforation). Instill via 18F Foley catheter into rectum with 30ml balloon inflated and Foley clamped as retention enema for 1 hour.

**2nd or greater recurrence**
- Recommend ID consult to discuss treatment options. Treatment options are detailed in the text.

Note: Doses indicated are for adult patients. For pediatric-specific dosing recommendations see Table 3.

BID: twice per day; CDI: *Clostridium difficile* infection; CT: computed tomography; ID: infectious disease (service); IV: intravenous; PO: by mouth; QID: four times per day; TID: three times per day.
Figure 4. Imaging of “accordion sign” and “target sign”

(Left) Accordion sign in 50-year-old woman with *C. difficile* colitis. Marked submucosal edema is present in the right colon (“thumbprint” appearance on longitudinal axis, short arrows). Oral contrast material (arrowhead) is trapped within the lumen. (image from Macari Balthazar Megibow 1999).

(Right) A 65-yo *C. difficile* –positive woman with CT through the mid-abdomen showing diffusely thickened colonic wall appearing as a “target sign” (concentric circles formed by the layers of bowel wall in inflammatory disease) on axial imaging (arrow) (image from AJR:186, May 2006).

Table 4. Indications for Surgical Consult

<table>
<thead>
<tr>
<th>Surgical consultation is appropriate for <em>C. difficile</em> infected patients in these situations:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Any patient with complicated CDI (see Table 3)</td>
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<tr>
<td>- Any patient with CDI and clinical deterioration attributable to CDI, including the following:</td>
</tr>
<tr>
<td>- Worsening abdominal distention/pain and/or peritonitis</td>
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<tr>
<td>- Bowel obstruction</td>
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<tr>
<td>- Intubation</td>
</tr>
<tr>
<td>- Vasopressor requirement</td>
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<td>- Mental status changes</td>
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<tr>
<td>- New or worsening Acute Kidney Injury</td>
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<tr>
<td>- Worsening Lactate &gt; 5mmol/L</td>
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<tr>
<td>- Persistent or worsening leukocytosis (WBC ≥35,000 cells/mm³)</td>
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<td>- Hirschsprung’s disease</td>
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<tr>
<td>- Any patient with failure to improve with standard therapy within 5 days as determined by resolving symptoms and physical exam, resolving WBC/band count</td>
</tr>
</tbody>
</table>

CDI: *Clostridium difficile* infection; WBC: white blood cell count.
Table 5. Guidance on Preemptive Isolation for Patients with Diarrhea.

Preemptive isolation should be considered if patients have diarrhea (3 or more watery stools in 12 to 24 hours) *not caused by laxative use, chemotherapy, enteral feeds or other medical causes AND AT LEAST ONE of the following:
- Current or prior antibiotic use (within 30 days)
- Significant abdominal pain, not caused by incisional pain, dyspepsia, or nausea
- History of C. difficile
- Suspect C. difficile

Place patient in room with curtain or door (NO HALL BEDS)
Place CONTACT PRECAUTIONS-D sign on door/curtain

*1L of colostomy output, >200mL of watery rectal bag output
Clinical Background

Clostridium difficile is a Gram-positive bacillus that can asymptptomatically colonize the gastrointestinal tract or cause symptomatic disease through the production of cytotoxins TcdA and TcdB. Patients usually develop Clostridium difficile infection (CDI) after exposure to antibiotics, and the severity of CDI can range from self-limited diarrheal illness, to a fulminant, life-threatening colitis. Even among those that recover, recurrent disease is common. Despite being first identified in 1978 as the causative agent of pseudomembranous colitis and subsequently garnering significant attention from the medical community, attempts to control C. difficile have not met with much success, especially in hospitals and other acute care settings.

The past decade has seen a significant increase in the incidence of CDI in the United States. In hospitals and nursing homes, there are now at least 450,000 new cases and 29,000 deaths per year. The increased burden of disease is largely attributable to the emergence of several strains, especially polymerase chain reaction (PCR) ribotype 027, which led to a worldwide epidemic. Though CDI occurs in all age groups, infection with ribotype 027, as well as CDI in general, is most common in older adults.

Thus, as the US population ages, the incidence of CDI and adverse outcomes will likely increase. Ninety-two percent of CDI-related deaths occur in adults of age 65 or older, where CDI is the 18th leading cause of mortality. The risk of recurrent CDI is 2-fold higher with each decade of life. The annual rate of CDI-related hospitalizations in those aged >85 years exceeds those of all other age groups combined. All of these epidemiologic trends contribute to an estimated $1.5 billion in excess healthcare costs each year due to CDI.

Rationale for Recommendations

The increased incidence of CDI and its adverse outcomes among hospitalized patients, coupled with the availability of new therapies has complicated the management of CDI. This underscores the need for guidelines that review the evidence and provide recommendations for the prevention, diagnosis, and treatment of CDI in hospitalized patients.

Clinical Problem and Management Issues

Causes and Risk Factors

Risk factors for CDI are listed in Table 1 and elaborated below.

History of CDI. As CDI can be recurrent, a history of CDI is predictive of CDI in patients presenting with diarrhea.

Antibiotic Exposure. Antibiotic use is one of the most significant yet modifiable risk factors for CDI. Number (dose dependent risk), class, and duration of antibiotic use (significantly higher risk if > 7 days) impact the risk for CDI (See Antibiotic Section under Prevention and Treatment).

Advanced Age. Patients age 65 or older are at several fold higher risk for CDI. Older patients are also at higher risk for more severe disease with complications, especially if they have poor preadmission functional status.

Comorbid Conditions, Severity of Disease and Hospitalization. Presence of severe underlying comorbidities has been associated with increased risk of CDI. Severity of comorbid conditions upon admission, and longer hospitalization have all been associated with higher risk for hospital-acquired CDI. Other risk factors for CDI also include gastrointestinal surgery and the use of tube feeds.

Inflammatory Bowel Disease (IBD). Patients with inflammatory bowel disease (IBD) are at higher risk for CDI compared to the general population. Thus, all patients with IBD presenting with diarrhea concerning for possible IBD flare should also undergo C. difficile testing, even in the absence of other risk factors for CDI. In a retrospective study, only 61% of IBD patients with CDI had antibiotic exposure.

Immunosuppression. Immunosuppressed states such as leukemia, lymphoma, HIV, neutropenia, organ transplantation, and use of immunosuppressive drugs significantly increase the risk for CDI. In HIV-infected patients, CDI is the most common cause for bacterial diarrhea and risk of CDI correlates with severity of HIV disease.

Acid Suppressive Therapy. Acid suppressive therapy, including use of proton pump inhibitors (PPIs), elevates the risk of CDI. (For expanded explanation, see “Proton Pump Inhibitors” section on Page 13).

Pediatric Population Risk Factors

Risk factors for acquiring CDI in pediatric populations include a history of prematurity, prolonged or frequent hospitalizations, history of antimicrobial therapy, solid organ transplantation, the presence of gastrostomy or jejunostomy tubes, and the use of proton pump inhibitors (see Table 1). Conditions associated with acquisition of severe CDI are shown in Table 2. Special attention to the importance of Hirschsprung’s disease, neutropenia from leukemia and other malignancies, and inflammatory bowel disease as high-risk factors for severe disease in children should be noted.
Risks in Community-Associated CDI.

Community-associated CDI has a different risk profile, and is less likely to be severe CDI. Community-associated CDI is defined by the Infectious Diseases Society of America as symptom onset occurring in the community or within 48 hours of hospital admission with no prior hospitalization in the past 12 weeks. Community-associated CDI affects populations that were previously thought to be at low risk such as younger adults without the traditional risk factors mentioned above. In a US population-based study involving 385 patients with CDI, 41% of cases met the criteria for community-associated CDI. Patients with community-associated infection were younger (median age of 50 years compared with 72 years), had lower comorbid scores, had less exposure to antibiotics (78% vs 94%), and were less likely to have severe infection.28

Diagnosis

Testing for C. difficile

Patients with diarrhea and risk factors for CDI should undergo testing for C. difficile (Figure 1).

The diagnosis of C. difficile infection (CDI) is based on the combination of both clinical findings (usually diarrhea), as well as laboratory or histopathological findings (see Table 2) for definition of CDI). Clinical severity can range from mild diarrhea to severe, fulminant colitis with paralytic ileus and toxic megacolon. Patients can also have asymptomatic carriage or colonization of Clostridium difficile.

The following signs and symptoms suggest patients who exhibit these features should be tested for the disease. The most common symptom of CDI is diarrhea, defined as 3 or more loose or unformed stool in less than 24 hours, without an alternative cause (e.g., laxative use). The stool may contain occult blood, but melena and hematochezia are atypical. Fever and abdominal pain are present in about 50% of patients, and can be markers for increasing disease severity. Leukocytosis (WBC > 15,000 cells/mm³) occurs frequently and may actually precede diarrhea or other clinical symptoms.

The presence of pseudomembranes on lower endoscopy is essentially pathognomonic for CDI, and occurs in 50% of cases. Endoscopy is not needed for diagnostics, however, as stool studies are readily available and active CDI renders a patient at increased risk for endoscopic complications including perforation.

Less common signs and symptoms of CDI include arthralgias and reactive arthritis, as well as severe protein-wasting diarrhea with resultant hypoalbuminemia, edema and ascites.

Contraindications to testing for C difficile

Because diarrhea occurs in the majority of patients with CDI, individuals without diarrhea should usually not be tested for CDI (Figure 1). The prevalence of asymptomatic colonization with C. difficile is 10–26% among hospitalized patients and may approach 50% among patients residing in long-term care facilities. Test of cure should not be performed in patients who have finished treatment for CDI and have experienced clinical improvement in symptoms because they can have persistent shedding of toxin for up to 6 weeks after completing treatment.29 For the same reason, there is no indication for testing while an individual is being actively treated. However, testing can be performed if symptoms have not resolved following a full treatment course. Finally, it is important to note that some individuals may take several weeks after completing therapy for stool consistency and frequency to become entirely normal. In addition, some individuals may develop a post-infectious irritable bowel syndrome after CDI, which can be difficult to differentiate from true recurrent CDI and clinicians must use their judgment. In this circumstance, clinicians should refrain from repeat testing for C. difficile.

Laboratory Testing Algorithms

Two- or three-stage testing algorithms are preferable to single-step methods.

The optimal rapid laboratory testing algorithm for presence of toxigenic C. difficile in stool has not been established, but there is evidence that two- or three-stage testing algorithms are preferable to single-step methods due to improved specificity.30

For UMHS testing algorithms See Figures 1 and 2.

When possible, testing should be limited to diarrheal stools unless the suspicion for CDI is high and an ileus is present. In select patients (immunocompromised, ileus, or on empiric therapy) the sensitivity of other rapid tests can be low and ID consultation and PCR-based testing should be considered (Appendix A).

The gold standard for organism detection is cytotoxigenic culture and the corresponding gold standard for toxin detection is the cell cytotoxicity assay.31 Both methods require considerable time and expense and are now rarely performed by clinical laboratories.

An overview of symptoms consistent with CDI is provided in Figure 1. To avoid false-positive results (e.g., positive C. difficile testing in the setting of colonization), only diarrheal stools (those that take the shape of the container) should be submitted for testing. An exception to this is the case of patients with suspected CDI and ileus, in which case stool of any consistency can be considered for testing. If a patient with ileus and suspected CDI is unable to produce stool, a rectal swab for tcdB PCR can be sent for after consultation with ID. If a patient has an ileostomy with higher then baseline output (without an alternative explanation) then a
stool specimen can be sent for CDI testing. In patients where there is concern for CDI involving the rectal stump, a rectal swab for direct tcdB PCR may be sent after consultation with ID. (For PCR testing at UMHS, after electronically placing an order for a C. difficile test, phone the lab to request PCR only from the swab. See Appendix A for available diagnostic tests for toxigenic C. difficile).

The recommended UMHS testing algorithm consists of two initial EIA tests (GDH and Toxins A/B), with reflex to a PCR test for tcdB gene for discordant results (Figure 2). Data and recent guidelines support the use of multi-step over single-step testing with EIA for toxigenic C. difficile due to improved test characteristics, though single-step testing via PCR also performed well.30,32 This algorithm has been validated by our clinical laboratory and has a negative predictive value of 99%.35

There are circumstances when false-negative results can occur with EIA testing alone. Immunocompromised patients with symptoms suggestive of CDI (colitis on imaging, ileus with minimal stool production, and/or WBC >15,000 cells/µL with diarrhea) and patients receiving empiric therapy at the time of diagnosis are at risk for a false-negative EIA test.36 In these patients, if PCR testing was not performed, an ID consult and direct PCR for tcdB on stool or via rectal swab should be considered (at UMHS, ordered separately by phone). Finally, single-step PCR testing (not part of the UMHS algorithm) occurs as part of the new Biofire test panel for gastrointestinal pathogens (FilmArray, BioFire Diagnostics Inc., Salt Lake City, UT). This test should not be used if CDI is suspected, and providers should follow the recommendations in Figure 2 and order multi-step testing as indicated. However, if C. difficile is detected as part of the Biofire panel and the patient’s symptoms are compatible with CDI, then a separate order for multi-step testing is unnecessary and providers should refer to our treatment algorithm (Figure 3) and begin therapy as indicated.37

Imaging. In patients with abdominal distention and suspicion for CDI, radiologic evaluation may serve as a useful diagnostic adjunct. This is especially true if there is a concern for CDI-induced ileus or toxic megacolon. Plain film abdominal x-rays may show dilated colon or ileus pattern. If free air is present on x-ray imaging, emergent surgical consult is warranted.6,38

In patients who present with abdominal pain, significant abdominal distention, or other signs of complicated CDI, computed tomography (CT) of the abdomen and pelvis may be considered for further evaluation. Findings on CT may include colonic wall thickening, ascites, megacolon (distension of the colon of >6 cm in transverse width), ileus or perforation.4 Overall CT sensitivity for diagnosis of C. difficile colitis is 52–85%, with specificity of 48–93%.39

The use of enteral, intravenous and rectal contrast is preferred by UMHS Acute Care Surgery group, unless otherwise contraindicated. Some institutions advocate a more rigid adherence to CT scan diagnostic criteria for C. difficile colitis of colon wall thickening of greater than 4 mm combined with any one or more findings of pericolonic stranding, colon wall nodularity, the “accordion” sign (alternating edematous hastrual folds separated by transverse mucosal ridges filled with oral contrast material, simulating the appearance of an accordion39), or otherwise unexplained ascites, with a reported sensitivity of 70% and specificity of 93% (Figure 4).

Patients who have CT findings concerning for severe or complicated CDI, or who are critically ill with documented severe CDI warrant early surgical consultation. Specific findings have not been shown to reliably predict the need for surgical intervention.39,41 However, early involvement of a general surgeon may initiate discussions of treatment options, including consideration for diverting loop ileostomy for antegrade colonic irrigation. (Refer to section on surgical management, Figure 5).

Endoscopy. Colonoscopy may be useful in patients with persistent diarrhea despite negative C. difficile toxin or with toxin-positive CDI refractory to antibiotics. In patients with positive stool testing for CDI, a colonoscopy is not necessary for diagnosis given that pseudomembranes are present only in 50% of patient with toxin-positive CDI.42 Additional indications to perform a colonoscopy in toxin-positive CDI patients include the assessment of CDI severity and the management of severe colonic distension associated with ileus. It is worth noting that a negative flexible sigmoidoscopy does not rule out CDI as sparing of the rectosigmoid colon is common in CDI patients with pseudomembranes on colonoscopy.43

Colonoscopy is contraindicated, especially for diagnostic purposes, in patients with hemodynamic instability or with significant risk for bowel perforation (e.g., fulminant colitis, recent bowel surgeries, bowel obstruction).

Differential Diagnosis of Diarrhea. C. difficile-toxin negative patients with persistent diarrhea should be evaluated further with colonoscopy with random biopsies and esophagogastroduodenoscopy (EGD), with duodenal biopsies for inflammatory and non-inflammatory causes of persistent diarrhea. Inflammatory diarrhea includes inflammatory bowel disease (ulcerative colitis and Crohn’s disease), celiac disease, microscopic colitis (collagenous and lymphocytic colitis), CMV (in immunocompromised hosts), and routine enteric pathogens when patients have exposure history or risk factors. Non-inflammatory causes include, dietary intolerance (lactose, fructose, or rapidly fermentable, short-chain carbohydrates [“FODMAP”]) or small intestinal bacterial overgrowth in patients with significant abdominal bloating. Functional etiologies (irritable bowel syndrome) should be considered when workup is negative for inflammatory and non-inflammatory diarrhea.

Disease Classification

Criteria for disease classification are summarized in Table 3, and discussed below.
Though risk factors for adverse outcomes after CDI have been identified, there is no generally accepted and validated definition for severe CDI. Nonetheless, it is important to classify the episode as mild-moderate, severe, or complicated prior to initiation of CDI therapy. It is imperative to classify CDI by disease severity and whether the CDI episode represents a recurrence, because it influences the choice of therapy. Recurrent CDI often requires a longer duration of therapy, consideration of adjunctive treatments such as antimicrobial “chasers,” or fecal microbiota transplantation (FMT).

CDI can range from self-limited disease to severe infection, sometimes resulting in colectomy or death. Even among those that recover, recurrent disease is common. Although the reasons are incompletely understood, older adults are disproportionately affected by adverse outcomes.

Despite these epidemiologic links, no robust, validated predictive models for the development of adverse outcomes from CDI or recurrence exist for clinical use. Several prediction models for severe disease outcomes based on initial diagnostic criteria have been proposed with variable sensitivity/specificity. Eight different published scores for severe disease have been compared at diagnosis to assess if they predicted complicated CDI in a validation cohort. The scores used a variety of clinical variables including age, medication use, symptoms, vital signs, physical exam findings, laboratory parameters, and abdominal radiographic changes. The agreement between predicted and observed outcomes was variable (Cohen’s κ 0.18–0.69). The “Hines VA” score had the highest κ but was only 73.7% sensitive.

The literature on this topic consists of several studies on predictors of severe disease and observed outcomes was variable (Cohen’s κ 0.18–0.69). The “Hines VA” score had the highest κ but was only 73.7% sensitive. The scores used a variety of clinical variables including age, medication use, symptoms, vital signs, physical exam findings, laboratory parameters, and abdominal radiographic changes. The agreement between predicted and observed outcomes was variable (Cohen’s κ 0.18–0.69). The “Hines VA” score had the highest κ but was only 73.7% sensitive. The classification criteria for CDI used in this guideline are presented in Table 3. These were drafted after considering published guidelines on CDI, and several studies on predictors of adverse outcomes and recurrence, and the expert opinion of this guideline committee’s membership.

This guideline’s definition for recurrence follows the CDC definition. Recurrent disease is defined as the presence of recurrent symptoms and positive testing within 8 weeks of initial onset (the index episode), but after the original symptoms resolved. There are situations, however, when patients will have another episode of CDI soon after this arbitrary 8-week window has elapsed. In such cases, it may not be unreasonable to classify these episodes as recurrent and treat accordingly (Figure 3). This is especially important in patients with risk factors for further recurrences, including the need for concurrent therapy with antimicrobials to treat condition other than CDI, age 65 or older, and use of proton pump inhibitors.

Special Populations

Extra-colonic CDI. Small bowel enteritis secondary to C. difficile is rare, but usually occurs in patients with a partial or total colectomy. The literature on this topic consists primarily of case reports, making it difficult to recommend specific treatment strategies. However, outcomes in small bowel enteritis from CDI can be poor and, these patients warrant aggressive therapy in most cases (see severe and complicated CDI arms in Figure 3).

Inflammatory Bowel Disease. There is a high incidence of CDI in IBD patients. The most likely explanation is the shared risk factor of an altered gut microbiota, known as dysbiosis. Thus, workup of patients presenting with signs and/or symptoms of IBD flare should include testing for CDI. IBD patients at significant risk for CDI include those living in nursing homes, with recent or ongoing hospitalization, with previous broad-spectrum antibiotic use, and with a surgical pouch. Other risk factors include increased severity of colitis and immunosuppression (especially corticosteroids with 3-fold risk increase).

Pediatric population. CDI may be associated with significant morbidity and mortality in children. In general, the diagnosis of CDI in pediatric patients follows the same diagnostic criteria and algorithms for adult patients as discussed above (see Figure 3). However, the accurate diagnosis of CDI in infants and young children represents a special challenge given a high rate of asymptomatic C. difficile colonization in this population. Treatment decisions in this population should be made in conjunction with ID consultation. Please note the following age-specific recommendations for interpretation of testing results:

1. Testing for CDI in infants < 12 months of age is generally not recommended. It is recommended to consult Pediatric ID if CDI is suspected in infants <12 months of age. Testing should be limited to those symptomatic with frequent diarrhea and/or ileus who meet one or more of the following conditions:
   - Have comorbidities associated with severe CDI (see Table 3)
   - Have history of multiple antibiotic exposures
   - C. difficile outbreak situations

   Note: Alternative etiologies for diarrhea should always be considered even in those infants < 12 months of age with a positive test for CDI (e.g., viral gastroenteritis, food allergy, carbohydrate malabsorption, immune-mediated condition, etc.).

2. Children 12 to 36 months of age may have asymptomatic colonization. A positive test result in a symptomatic patient indicates possible CDI. Alternative etiologies for diarrhea should continue to be considered even in those testing positive for CDI.

3. Children >36 months of age who are symptomatic with diarrhea and/or ileus, with positive testing results suggests probable CDI, especially in those with risk factors including history of antibiotic therapy, use of proton pump inhibitors, or comorbidities associated with severe CDI (see Table 1 and Table 3).
Asymptomatic carriage of \textit{C. difficile} varies significantly by age. A review of multiple studies of carriage in healthy infants and young children determined colonization of neonates up to 1 month of age occurs at an average of 37%, between 1 to 6 months of age at an average of 30%, between 6 to 12 months of age at an average of 14%, and by 36 months of age the carriage rate is similar to that of healthy, non-hospitalized adults at < 3%.\textsuperscript{62} Carriage may be transient, and different strains of \textit{C. difficile} may colonize an individual over time as new strains are acquired from the environment. Breastfed infants have lower \textit{C. difficile} carriage rates than do formula-fed infants (14% vs. 30%, respectively), but these differences decrease after 12 months of age.\textsuperscript{62} Given the frequency of asymptomatic colonization, testing for CDI should generally only be performed in children with diarrhea and other risk factors for CDI.\textsuperscript{63} Despite high rates of colonization and significant amounts of detectable toxin, clinical illness with CDI is relatively uncommon in children <36 months of age. Hypotheses regarding the lack of clinical illness in infants and young children include the possibility that neonates and infants lack cellular receptors to bind and process \textit{C. difficile} toxin, preferential colonization by nontoxicogenic or less-pathogenic strains, and protective factors in breast milk and the developing microbiota.\textsuperscript{25,62} Rates of hospitalized infants and young children with positive CDI testing are increasing, but again, many studies do not adequately distinguish CDI disease from asymptomatic colonization.\textsuperscript{25,26,64,65} Therefore, it is critical to consider other etiologies for diarrhea in infants and young children, even in those with positive CDI testing. Consultation with a Pediatric Infectious Diseases specialist may be helpful when considering the need for treatment in young age groups.\textsuperscript{25}

**Pediatric Disease Classification.** In pediatric patients, a diagnosis of CDI may be considered based on a combination of signs and symptoms, generally involving frequent diarrhea, and evidence of \textit{C. difficile} and toxin present in stool (see age-based interpretation of testing results above).

1. In pediatric patients CDI is classified as mild to moderate when lab values are reassuring (e.g., WBC <15,000 cells/mm\(^3\) and serum creatinine <1.5 times baseline level), similar to adult classification schemes (see Table 3).
2. In patients failing to improve after 3 to 5 days of therapy, lab values should be repeated to determine if it is still appropriate to maintain classification as mild to moderate, or if the classification should be escalated to severe.
3. In pediatric patients CDI is determined to be severe when \( \geq 2 \) lab values are abnormal (e.g., WBC \( \geq 15,000 \) cells/mm\(^3\), creatinine \( >1.5 \) times baseline level, ANC \( \leq 500 \), or ALB \( \leq 2.5 \)) OR the presence of high-risk patient factors for severe CDI exists (e.g., Hirschsprung’s disease, neutropenia from leukemia, IBD). Patients with these high-risk factors should generally be classified as, and treated for, at least severe disease (see Table 3).
4. In pediatric patients CDI is determined to be complicated when evidence exists of sepsis, shock, ileus, toxic megacolon, peritonitis, bowel perforation, or other conditions requiring ICU admission within 2 days of CDI diagnosis are present (see Table 3).
5. For pediatric patients meeting severe or complicated clinical criteria (see Table 4), or having risk factors associated with severe CDI disease (see Table 3), testing should be performed as described above (see Figure 2), and empiric therapy should be strongly considered while awaiting results.

The majority of CDI in infants and children is of mild to moderate disease severity criteria.\textsuperscript{26,27,66} Applying the same criteria for adult severe disease to pediatric populations tends to overclassify pediatric disease as severe, hence the need for 2 or more abnormal lab criteria required to make a severe diagnosis (or the presence of a high-risk condition). The frequency of pediatric CDI patients meeting criteria for severe disease is low (~8%), with similar proportions of severe disease noted across all pediatric age groups.\textsuperscript{66}

**Prevention**

**Antibiotics and Prevention**

Nearly all antimicrobial classes have been associated with CDI. However, clindamycin and cephalosporins (especially third-generation cephalosporins) have been consistently associated with the highest risk of CDI. After the emergence of the epidemic \textit{C. difficile} ribotype 027 strain in 2002, fluoroquinolones, have also been associated with a high risk of CDI.\textsuperscript{57,69}

The risk of CDI is highest during antibiotic therapy and in the first month after cessation of antibiotics (7 to 10 fold increased risk compared to patients who did not receive antibiotics). Risk appears to normalize 3 months after cessation of antibiotic therapy.\textsuperscript{70} The use of \( >14 \) Defined Daily Doses (DDDs) of antibiotics in the 3 months prior to CDI had the strongest association with CDI (OR 8.50;95% CI 4.56–15.9). Another study found the risk of CDI increases with cumulative dose and number of antibiotics, as well as days of antibiotic exposure.\textsuperscript{71} Poor clinical outcomes in patients with CDI were independently associated with concomitant use of non-CDI-related antimicrobials,\textsuperscript{72} and are associated with a doubling in risk of failure of CDI therapy.\textsuperscript{73} In addition, use of non-CDI-related antimicrobials within 30 days of an episode of CDI is associated with a 3-fold increase in CDI recurrence.\textsuperscript{74}

Based on the results of these studies, it is imperative that providers stop unnecessary antibiotic therapy to reduce the risk of CDI.

**Use of Prophylactic Vancomycin**

**Recommendations:**
1. Consider use of vancomycin prophylaxis in patients that recently had a first or greater recurrence of CDI and require antimicrobials for a different infection.
2. The dose of prophylactic vancomycin is 125 mg PO BID to QID and the duration of prophylaxis should be at least 50% of the expected duration of antibiotic therapy for the other infection.

There is a paucity of evidence to support the practice of extending or using vancomycin prophylactically in patients that recently were diagnosed with CDI and require non-CDI antibiotics for treatment of a different infection. A recent retrospective study showed that, for patients where the CDI episode was a first or greater recurrence, prophylactic vancomycin reduced the risk of recurrent CDI by nearly 50% when on other antibiotics. Potential downsides of this strategy include selection for resistant organisms such as vancomycin-resistant Enterococcus, onset or worsening of antibiotic-associated diarrhea, and additional expense.

**Probiotics**

Probiotics are not recommended as primary prevention of CDI in hospitalized patients. There are conflicting data on whether probiotics are effective in preventing primary episodes of CDI in patients receiving antibiotics, with the largest RCT to-date including over 2,000 patients failing to replicate possible reductions seen from meta-analyses of smaller, more heterogeneous trials. 75,76 Also, there are concerns regarding safety in patients with certain comorbid conditions (immunocompromised- receiving chemotherapy, recipients of solid organ transplant or bone marrow transplant) which are common among hospitalized patients. The literature has noted invasive infections or poor outcomes with Lactobacillus probiotic use in immunocompromised patients,77 patients with severe acute pancreatitis,78 and patients with central venous catheters.79 As such, we do not recommend the use of probiotics in primary prevention of CDI in hospitalized patients.

**Proton Pump Inhibitors (PPIs)**

PPIs and acid suppression may increase the risk of CDI and recurrence of CDI. Unnecessary use of PPIs should be avoided and acid suppression should be minimized, especially in patients with a history or current diagnosis of CDI. A systematic review of case-control and cohort studies has shown an association between PPIs and increased risk of CDI.8 Although a causal relationship is not clear, this finding is similar to prior systemic reviews.80 A prospective cohort study showed that increasing levels of acid suppression correlated with increased risk of nosocomial CDI, with the highest risk in patients receiving greater than once daily PPI dosing.81

**Infection Control Measures**

**Isolation.** Patients with diarrhea and a positive C. difficile lab test must be placed in Contact Precautions Diarrheal (CP-D). Patients are placed in either a private room or cohorted with another patient with CDI. CP-D rooms are bleach cleaned on a daily basis and upon discharge. Healthcare personnel must wear an isolation gown and gloves upon entry to the room. Healthcare personnel must remove gowns and gloves upon exiting the room and wash hands with soap and water. Any equipment leaving the room is disinfected with bleach.

**Preemptive Isolation** (Initiation of isolation for patients with diarrhea prior to test results). CP-D is not required, but may be utilized at the discretion of Infection Prevention & Epidemiology (IPE) or the provider. (At UMHS, nursing may initiate this by working through the provider or IPE.) See Table 5 for further guidance on preemptive isolation.

**Disinfection and Hygiene.** Both the patient’s immediate environment and the broader environment have been implicated in the spread of C. difficile. Quaternary ammonia-based disinfectants have been shown to be ineffective against C. difficile spores. Bleach is sporicidal and has been shown to decrease the bioburden of C. difficile in the healthcare setting.82-85 An approved hospital sporicidal (such as bleach) must be used on rooms of patients with CDI as well as any equipment leaving those rooms. In locations where bleach is the approved sporicidal, a bleach wipe or 1:10 bleach solution may be used. Additionally, patients undergoing inpatient fecal microbiota transplantation (FMT) should have their rooms cleaned with an approved hospital sporicidal, with the same rigor as used in terminal cleaning, prior to them returning to the room from the endoscopy suite. In addition to using the appropriate disinfectant, the importance of good mechanical cleaning with the product should be emphasized to maximize the mechanical removal of spores.

- Alcohol based hand rub is not effective against C. difficile spores.
- Hands are to be cleaned with soap and water upon exit of a CDI room to ensure mechanical removal of the spores.86

**Duration of Isolation.** Patients are to remain in CP-D for the duration of their hospitalization, as their hospital room will remain contaminated with C. difficile spores as long as they inhabit it. Terminal cleaning and decontamination is not possible with the patient present; spores persist and may continue to be transmitted. Thus, patients must remain in CP-D and the room must be terminally cleaned at discharge. This recommendation for isolation holds even for FMT recipients after their room has been cleaned with bleach following the FMT. In special circumstances, arrangements may be made to move the patient to allow for a terminal clean and the discontinuation of precautions. These are determined on a case-by-case basis with IPE and the clinical team.

**Isolation Practices for Readmission.** When patients with a history of CDI are readmitted, they do not need to be placed in CP-D unless they are readmitted with diarrhea. Patients with a history of CDI that are readmitted with diarrhea should be managed in CP-D until CDI has been ruled out.

**Visitor/Family Recommendations.** For the protection of family members, it is recommended that family and visitors wear an isolation gown and gloves when assisting in the care of a patient with CDI. Family and visitors must wash...
hands with soap and water upon leaving the patient room. Though family and visitors may move about the facility, they should not utilize the unit nourishment room. There is no published evidence that visitors contribute to the spread of CDI in hospitals. Studies have included interventions such as having visitors comply with wearing cover gowns and gloves in CDI rooms, but no studies have evaluated the sole impact of visitors on CDI transmission.

**Isolation of Asymptomatic Carriers.** Except in special circumstances, asymptomatic carriers are not placed in CP-D. At UMHS, the exception to this is the adult bone marrow transplant unit. Adult Bone-Marrow Transplant (BMT) patients are screened for *C. difficile* upon admission and if positive, placed in CP-D for the duration of their hospitalization. Patients are placed in CP-D, even if they don’t currently have symptoms as many of the treatments for which they are admitted can cause them to become symptomatic. Because BMT patients are such a vulnerable population, this protects non-colonized patients from exposure. Please note this policy does not apply to UMHS Pediatric BMT units given the high rate of asymptomatic colonization among young children.

**Medical Treatment of *C. difficile* Infection**

The approach to antibiotic treatment for CDI is shown in Figure 3. Details of the treatment options and considerations are listed below.

Treatment of asymptomatic carriers is not recommended. There is no role for prophylactic CDI therapy in asymptomatic carriers. In a small, randomized placebo controlled trial, only oral vancomycin (not metronidazole) was effective in reducing *C. difficile* carriage. However oral vancomycin treatment was associated with significantly higher rates of *C. difficile* carriage 2 months after treatment. Further study is needed to assess the role of asymptomatic carriers in *C. difficile* transmission and the need for isolation precautions. In a prospective study, 29% of cases of hospital acquired CDI were associated with carriers.

**Antimicrobial Treatment Based on Disease Severity**

Antimicrobial treatment for CDI is based on the severity of the disease:

- **Mild-Moderate CDI:** metronidazole 500 mg PO TID
- **Severe CDI:** vancomycin 125 mg PO QID
- **Complicated CDI:** vancomycin 500 mg PO QID, metronidazole 500 mg IV every 8 hours, and if ileus, small bowel obstruction, or toxic megacolon vancomycin enema every 6 hours.

Two recent, prospective, randomized trials comparing oral metronidazole and oral vancomycin to placebo, found vancomycin was associated with clinical success even after adjusting for disease severity. However, this study was not designed or powered for this secondary analysis that pooled data from 2 RCTs. Another RCT comparing metronidazole and vancomycin, found vancomycin treatment was associated with a higher rate of clinical cure in patients with severe CDI (ZAR 2007). Currently, oral metronidazole is recommended for the treatment of mild/moderate CDI (except with ≥2 recurrences; see Figure 3), and oral vancomycin is recommended in severe CDI. Oral vancomycin is also preferred in pregnant or breastfeeding patients, those with metronidazole allergy, or those receiving concomitant warfarin.

The duration of therapy in the above trials was 10 days. However, some patients may respond slowly to treatment and IDSA guidelines endorse treatment for 10–14 days. Intravenous metronidazole is less efficacious than oral metronidazole or oral vancomycin in the treatment of CDI, and should only be utilized when oral or enteral administration is not feasible.

There is no supportive data for the use of oral vancomycin doses ≥ 125 mg QID in patients with mild, moderate, or severe disease without complications. There is an absence of data regarding the optimal treatment of complicated CDI. Guidelines currently recommend combination therapy with administration of intravenous metronidazole and high-dose oral vancomycin (500mg QID) in patients with complicated CDI. Intracolonic administration of vancomycin may be considered in all patients with complicated CDI, but should be given in patients with ileus, small bowel obstruction, and toxic megacolon. In the absence of data, longer durations of therapy (≥14 days) may be recommended in patients with complicated CDI, and final treatment plan should be formulated in discussion with the infectious diseases consult team.

**C. difficile Enteritis (small bowel involvement).** Patient with CDI of the small bowel should be treated with oral vancomycin 125 mg PO QID. Small bowel involvement with *C. difficile* is rare but has been reported. The majority of patients with *C. difficile* enteritis have either surgically altered intestinal anatomy such as colectomy with ileostomy and/or inflammatory bowel disease. In a review of 56 patients with *C. difficile* enteritis the majority of patients required ICU management and mortality was high (32.1%). In patients with an ileostomy, fever and increased ileostomy output should prompt further evaluation for *C. difficile* infection. The optimal treatment of *C. difficile* enteritis is unknown. However, since these patients are often refractory to metronidazole therapy, often require ICU management, and have a high mortality, vancomycin treatment is recommended.

**Recurrent C. difficile Infection.** The treatment of CDI recurrence depends on how many recurrences the patient has experienced.

- **First recurrence:** Classify as mild-moderate, severe, or complicated and treat accordingly.
- **Second or multiple recurrences** (third or more episode of CDI):
  - vancomycin PO (dose, need for concurrent IV metronidazole/vancomycin enemas depends on...
disease classification as noted in the sections immediately above) for 10–14 days then taper to 125 mg PO BID for 7 days, 125 mg PO daily for 7 days, and then pulse with 125 mg PO every 2-3 days for 2–8 weeks. Duration of taper should be determined in conjunction with the infectious diseases consult services.

OR
- fidaxomycin 200 mg PO BID for 10 days (with infectious diseases consult service approval).

There is a paucity of data regarding the optimal treatment of patients with recurrent CDI. Guidelines currently recommend treatment concordant with severity of disease for the first recurrence (i.e., metronidazole for mild-moderate CDI and vancomycin for severe CDI). Due to the possibility of peripheral neuropathy with prolonged exposure to metronidazole, guidelines recommend vancomycin therapy for second (or further) recurrences. Tapered or pulsed dosing regimens of vancomycin have been shown to reduce the risk of further recurrences compared to placebo in patients with multiple recurrences, and thus are recommended in patients with a second (or further) recurrence.

In a randomized, trial of patients with either a first episode of CDI or first recurrence, fidaxomicin was non-inferior to vancomycin in terms of clinical cure rates. Recurrence rates were lower with fidaxomicin, but only in the subset of patients infected with non-NAP1/027 strains. Due to uncertain cost-effectiveness (~$300/day) compared to vancomycin (especially when vancomycin is compounded from the intravenous formulation), the role of fidaxomicin in CDI therapy remains undefined. At UMHS fidaxomicin requires ID approval and has been reserved for treatment of CDI in patients with documented recurrent disease who have failed a recent vancomycin taper. Fidaxomicin has not been studied in patients with complicated CDI, and should not be utilized in this scenario.

Numerous agents (rifaximin or fidaxomicin “chasers,” which are provided at the end of a vancomycin taper; tigecycline; IVIG; nitazoxanide; etc.) have been studied in patients with refractory or recurrent CDI. The data supporting their use is limited. Rifaximin or fidaxomicin chasers can be considered in patients with multiple recurrences especially in patients who choose not to perform fecal microbiota transplantation (FMT) or who are not candidates for FMT.

To our knowledge, there is a paucity of data evaluating extension of CDI therapy duration for patients receiving non-CDI antibiotics. However, concomitant antimicrobials in the context of CDI are associated with poor clinical outcomes, extended time to resolution of diarrhea, treatment failure, and recurrence of CDI. In one study, the use of non-CDI antimicrobials within 30 days of an episode of CDI was associated with a 3-fold increase in CDI recurrence. Therefore, it may be advisable in patients at high risk for recurrent CDI to overlap and extend anti-

CDI therapy beyond the duration of concomitant antibiotic use. However, there are no data to support providing secondary prophylaxis for all patients with CDI on concomitant antibiotic therapy. Consultation with ID is recommended to determine if the patient would benefit from this practice.

Probiotic Treatment

Probiotics as adjunct treatment of CDI is not recommended in hospitalized patients. There are limited data supporting the use of Lactobacillus-containing probiotic preparations in the treatment of CDI, and use is not recommended.

Two randomized, double-blind, placebo-controlled trials have shown that Saccharomyces boulardii, in conjunction with standard treatment for CDI, significantly reduces the number of further episodes of CDI in patients with a history of recurrent infection. However, a recent meta-analysis only showed a modest but non-significant reduction in recurrent CDI from either S. boulardii or Lactobacillus species. Additionally, the use of Saccharomyces probiotic preparations has been associated with invasive infection in patients with central venous catheters, intestinal disease (abdominal surgery, intestinal obstruction, ulcerative colitis, neoplasm, bowel or gastric ulcerations), and critically ill or immunocompromised patients. In the opinion of this committee, these safety concerns preclude use of S. boulardii for hospitalized patients with CDI.

In patients with multiple recurrences of CDI, who are not candidates for FMT, a regimen of staggered and tapered oral vancomycin in combination with kefir can be considered. A prospective case series of patients with multiple recurrences of CDI found that daily administration of kefir (a probiotic yogurt drink) in combination with a staggered and tapered oral vancomycin or metronidazole regimen achieved a treatment success rate of 84%.

Immunotherapy

Intravenous Gamma globulins (IVIG) can be considered in patients with hypogammaglobulinemia and recurrent CDI, but IVIG in all other patient populations is not recommended. There are no randomized controlled trials on the use of human IVIG. A retrospective analysis of 18 patients with severe CDI treated with IVIG and standard therapy found no difference in clinical outcomes compared with matched controls. In patients with recurrent CDI and hypogammaglobulinemia (<450 mg/dL) in the presence of a cancer or immune deficiency disorder, IVIG can be considered on a case by case basis. In a randomized, double-blind, placebo-controlled Phase II trial, addition of two neutralizing monoclonal antibodies against C. difficile toxins A and B to standard therapy did not impact the initial infection course but did significantly reduce infection recurrence. This therapy is currently being evaluated in Phase III trials.
Recently, two phase-3 studies, MODIFY I and MODIFY II evaluated the efficacy of two monoclonal antibodies, actoxumab (ACT) and bezlotoxumab (BEZ), with activity against TcdA and TcdB, respectively. The study arm with ACT alone was stopped early due to lack of efficacy in an interim analysis. The pooled analysis of the 2327 patients that received either ACT + BEZ or BEZ alone observed recurrent CDI in 15.4% and 16.5%, respectively, versus 26.6% in the placebo arm (P <.001). The safety profiles in the interventional arms were similar to the placebo arm.\(^{113}\)

**Toxin-Binding Polymers and Resins**

Therapy with toxin-binding polymers (tolevamer) and resins (cholestyramine and colestipol) is not recommended.

In two multinational, randomized, controlled trials, clinical success (defined as resolution of diarrhea and absence of abdominal discomfort) of tolevamer (a non-antibiotic, toxin-binding polymer) was inferior to both metronidazole and vancomycin.\(^{89}\) Regarding toxin-binding resins, colestipol was found to be no more effective than placebo at decreasing fecal excretion of C. difficile toxin.\(^{114}\) Cholestyramine, another resin, binds oral vancomycin, which may lead to decreased concentrations of the antibiotic,\(^{115}\) and thus concomitant cholestyramine and oral vancomycin administration should be avoided in patients with CDI.

**Fecal Microbiota transplantation (FMT)**

**Recommendations:**

1. FMT is a good treatment option for multiple recurrences of CDI (after two or more recurrences of CDI within one year) and can be considered in patients with CDI not responsive to standard treatment by day 5, assuming escalation of pharmacologic therapy has already been attempted (Figure 3).

2. At UMHS, outpatient FMT is initiated in the outpatient ID clinic and requires a referral. Inpatient FMT is initiated through consultation of the inpatient ID and GI consult services, though GI consult is unnecessary if the patient is already on the GI inpatient service.

3. Conventional therapy should be pursued for the treatment of primary CDI or first recurrence. There is insufficient experience with FMT to recommend it as a primary approach. More longitudinal data on patients that have undergone FMT are needed; therefore, judicious use of this treatment modality is warranted.

4. Conventional therapy should be pursued first in patients with severe CDI, and FMT is contraindicated in patients with complicated CDI. The safety and efficacy of FMT for these patients has not been established.

5. Caution should be exercised with use of FMT in patients with IBD. Those who undergo FMT for CDI may be at increased risk of IBD flare.

6. Either frozen or fresh stool can be used for FMT in the setting of recurrent CDI.

**Overview.** The human gut microbiome is a diverse community with thousands of bacterial species,\(^{116}\) which likely protects against invasive pathogens.\(^{117,118}\) The pathogenesis of CDI is thought to require disruption of the gut microbiota prior to the onset of symptomatic disease,\(^{119}\) usually through antibiotic exposure.\(^{120}\)

Even after recovery from CDI, some patients retain a susceptible microbiome and can have recurrent CDI.\(^{121}\) This can occur either from recrudescence of the original infection or from reinfection with a new C. difficile strain.\(^{122}\) A small minority of patients (<5%) have difficulty achieving clinical cure with conventional antibiotic therapy and will enter a cycle with multiple recurrences,\(^{123,124}\) often relapsing soon after antibiotics are stopped. Restoration of the gut microbiota through fecal microbiota transplantation (FMT) appears to be the most effective treatment strategy for these patients and has gained widespread acceptance in the medical community.\(^{125}\)

**Indications and Summary of Evidence.** There is insufficient experience with FMT to recommend it for the treatment of primary CDI or first recurrence vs. standard therapy with either vancomycin or metronidazole.\(^{126,127}\) There is also insufficient evidence for treatment of severe CDI or complicated CDI with FMT, though several published case reports suggest that it may be effective.\(^{128,131}\) Based on a wealth of data from case reports, systematic reviews, and clinical trials,\(^{132-144}\) FMT appears quite effective for recurrent CDI with cure rates exceeding 85–90% in most studies.

Thus, the UMHS FMT protocol excludes patients with primary CDI, first recurrence of CDI, or complicated disease but other patients become eligible for FMT with two or more recurrences of CDI (especially within 1 year). Additionally, patients are eligible for FMT with CDI not responsive to standard treatment by day 5, assuming escalation of pharmacologic therapy has already been attempted (Figure 3).

Often, donors are family members or close friends. Some studies suggest that related donors are associated with a higher resolution of CDI than unrelated donors, 93% vs. 84%, respectively. However, the results of a meta-analysis indicated that there was no significant difference between outcomes from related and unrelated donors.\(^{145}\)

Furthermore, a randomized non-inferiority trial conducted in patients with recurrent CDI found that the use of frozen stool for FMT resulted in a rate of clinical resolution of diarrhea that was no worse than that obtained with fresh stool for FMT (per-protocol analysis revealing 83.5% vs. 85.1%; difference, −1.6% [95% CI, −10.5% to ∞]; P=0.01).\(^{146}\)
Protocol. The optimal parameters for FMT, including stool preparation, infusion amount, and infusion route, are not known, but FMT appears highly effective regardless of variability in these specifics. There are three formulations of stool available at UMHS through the non-profit stool bank OpenBiome (Somerville, MA): oral fecal capsules (outpatient only), upper GI (for G- or J-tubes only; nasogastric or Dobhoff tube routes are not available), and lower GI (sigmoidoscopy- or colonoscopy-delivered, in the medical procedures unit). The upper and lower GI infusions can also utilize stool from a directed donor (related or unrelated), selected by the patient and/or their family.

OpenBiome has a rigorous donor selection process that entails thorough screening questionnaires and testing of donors and donor stool in order to ensure safety. The oral capsule formulation has specific exclusion criteria and lower efficacy compared to lower delivery of FMT. The efficacy of capsules is 70% with one administration and 94% with multiple administrations.

Outpatient FMT requires the patient be seen in the infectious diseases (ID) clinic, so the protocol is initiated through a referral to the ID clinic and the ID provider will coordinate the process from that point onward. Inpatient FMT requires consults to be placed to both the ID and gastroenterology (GI) services, if GI is not already the primary service for the patient. The ID/GI inpatient services will coordinate the process from that point onward.

Preparation of the recipient ideally involves cessation of all antibiotics, including those used to treat CDI, 48 hours prior to FMT. In recipients undergoing FMT via colonoscopy a standard colonoscopy bowel preparation usually must also be administered. The ID and GI physicians coordinating the FMT will make any final determinations about exceptions to these criteria or modifications in the FMT preparations.

Safety. FMT is generally safe and effective for most patients with recurrent CDI in the short term (1–2 years). Among most immunocompromised patients, FMT also appears safe. However, patients with IBD may be at increased risk for disease flare, fever, and/or elevation in inflammatory markers following FMT. Though several case reports exist, there is insufficient data on safety or efficacy to support the use of FMT for severe CDI. Of particular concern is a case of toxic megacolon that resulted in death of a patient that received FMT for severe CDI, though it is undetermined whether FMT itself or withdrawal of antibiotics for CDI following FMT contributed to the outcome.

There are few data on long-term safety of FMT, but the intestinal microbiota has been associated with colon cancer, diabetes, obesity, and atopic disorders such as asthma. One study following patients for 3–68 months (mean 17 months) after FMT noted the development of new conditions, including autoimmune disease, ovarian cancer, myocardial infarction, and stroke, though a causal mechanism cannot be inferred from these data. Thus, more longitudinal data on patients that have undergone FMT are needed and at present, judicious use of this treatment modality is warranted.

Avoid Anti-Motility Agents

Anti-motility agents in the initial treatment or treatment adjunct of CDI are not recommended as they can mask symptoms and increase risk of toxic megacolon. In a literature review of 55 patients, 31% of patients who received anti-motility agents without initial treatment of *C. difficile* developed toxic megacolon or colonic dilatation. No significant difference in complications was noted in patients who received anti-motility agents along with treatment of *C. difficile*. Further study is needed to assess role of anti-motility agents to control diarrhea in patients with mild-to-moderate CDI who are already being treated for CDI.

Treatment Response

Treatment response generally occurs after 3–5 days of therapy and is characterized by a decrease in stool frequency, improvement in stool consistency, and improvement in laboratory, radiologic and physiologic parameters.

For patients with mild to moderate CDI with no improvement or worsening of symptoms after 3–5 days of metronidazole therapy, escalation to vancomycin therapy is indicated.

Recurrence of CDI after the initial episode occurs in is approximately 19–25% of patients. Approximately 25-64.7% of patients who have met another recurrence of CDI after first or multiple recurrences.

Surgical Treatment

In patients who have severe, complicated (fulminant) CDI and clinical deterioration despite maximal medical therapy, surgery may confer mortality benefit. However, in advanced fulminant CDI, surgical mortality can be up to 80% (range 19–80%).

The optimal timing for surgical intervention is not well defined, with only expert opinion supporting recommendations. Early surgical involvement may be warranted in patients who are critically ill from CDI. While not every patient requires surgical intervention, patients with complicated CDI (Table 4) warrant early surgical consultation. Indications for surgical consultation and potential considerations for surgery are listed in Table 4.

Delayed surgical intervention may result in increased morbidity and mortality. Prior studies indicate higher mortality rates if surgical intervention occurred after evidence of end-organ failure (e.g. intubation for respiratory failure, vasopressor therapy for hemodynamic instability, or acute renal failure). In one study evaluating timing of surgical intervention for fulminant pseudo-
membranous colitis, patients who survived received surgical consult at a mean of 3.2 days from admission (or onset of symptoms for those already in the hospital), as compared to the nonsurvivors who received surgical consult at a mean of 5.4 days after admission or symptom onset. Likewise, an analysis of the National Inpatient Sample (NIS) database suggested that surgical intervention more than 3 days after admission for CDI may be associated with increased mortality.

Surgical options include total or subtotal colectomy with end ileostomy (total abdominal colectomy, or TAC).

- Partial colectomy is contraindicated: in one retrospective analysis, partial colectomy carried a mortality rate of 100% when compared to TAC.
- In patients with peritonitis, prior abdominal surgeries with adhesions, or frank perforation, exploratory laparotomy with TAC may be warranted.
- Diverting loop ileostomy with antegrade colonic lavage may be associated with reduced mortality when compared to a historical population of patients undergoing total abdominal colectomy, and the majority of patients undergoing the former intervention (93%) achieved colonic preservation. This may also allow for earlier surgical intervention on CDI patients, before the development of end-organ failure and shock progression. However, more research is needed before this can be universally adopted as standard of care.

In patients who are poor surgical candidates, or who are in refractory end-stage septic shock, with continued clinical decline, the risk for morbidity and mortality may be prohibitively high, and a frank discussion with the patient and/or the patient’s family may be warranted regarding goals of care, including the risks and benefits involved with an aggressive attempt at surgery vs. continued nonoperative management with maximal medical therapy.

**Special Populations - Pediatric Treatment**

For pediatric patients, treatment guidelines generally follow those outlined above for adults (see Figure 3). Ideally, discontinuation of antimicrobial agents is the first step in treating CDI and may suffice to resolve symptoms in mild cases. Antiperistaltic medications are not recommended for pediatric patients as these may mask symptoms and precipitate complications, including toxic megacolon.

1. For pediatric patients with mild to moderate disease (see Table 3) who lack significant pediatric risk factors associated with severe disease (see Table 3), metronidazole (7.5 mg/kg/dose QID, orally, maximum 500 mg/dose x 10 days) is the preferred therapy for initial treatment of first episode of CDI.

2. For pediatric patients with criteria meeting severe disease (Table 3), including those with risk factors associated with severe disease (see Table 3), metronidazole allergy, pregnancy/ breastfeeding, or without symptom resolution after 3 to 5 days of oral metronidazole, oral vancomycin is the preferred therapy (10 mg/kg/dose QID, up to maximum 125 mg/dose x 10 days).

3. Combination therapy with vancomycin, both oral and by retention enema, and intravenous metronidazole, or second-line agents, may be considered in complicated high-risk cases with sepsis, shock, ileus, small bowel obstruction, peritonitis, or toxic megacolon (see Triple Therapy in Figure 3). Do not use enema if concern of colonic perforation. Intracolonic vancomycin administered by retention enema (10-20 mL/kg/dose, up to 1000 mL max, of a 500 mg/L solution in normal saline q6h instilled by appropriately-sized Foley catheter inserted into rectum with balloon inflated and Foley clamped for 1 hour; treatment naïve patients should be initiated at 10 mL/kg/dose and escalated as tolerated to a maximum of 20 mL/kg/dose or 1000 mL), and high-dose oral vancomycin (minimum 10mg/kg/dose up to 500 mg/dose QID) in combination with IV metronidazole should be administered. For patients receiving combination therapy including PO, IV, and PR vancomycin or in patient at high risk for systemic absorption, serum vancomycin concentrations should be considered to evaluate for elevated serum concentrations.

4. For pediatric patients with first recurrence of CDI, that is mild to moderate, oral metronidazole is the preferred therapy.

5. For pediatric patients with prolonged or recurrent CDI, metronidazole should not be used for chronic therapy due to possible neurotoxicity. Oral vancomycin is recommended for second or multiple recurrences (10 mg/kg/dose QID, maximum 500 mg/dose, x 10 days), and pulsed or tapered regimens may be beneficial in difficult cases (see adult section above).

6. Criteria for optimal use of second-line agents in recurrent CDI, including nitazoxanide, fidaxomicin, and rifaximin, do not exist in children, and consultation with a Pediatric Infectious Diseases specialist is recommended if considering these options. Pediatric dosing for fidaxomicin is 16 mg/kg/dose BID, max 200 mg per dose; Peds ID approval is required for use of fidaxomicin.

7. Fecal microbiota transplantation (FMT) may be considered in children <18 years old as an outpatient to help prevent recurrence of CDI; consultation with a Pediatric Infectious Disease specialist is recommended. There are currently no mechanisms in place to provide FMT to children <18 years old as an inpatient.

8. Probiotics are not routinely recommended for either prevention or treatment of CDI in infants and children, due to a lack of sufficient evidence in infants and children and a theoretical risk of bacteremia due to gut translocation.

**Summary of Evidence.** It should be recognized that oral vancomycin is the only FDA-approved medication for the treatment of CDI in children; however, metronidazole is currently the accepted first-line medication in otherwise healthy infants and children with mild to moderate disease. Prospective trials evaluating the use of metronidazole or vancomycin for longer than 10 to 14 days in children are lacking. Data does not support a clear benefit for combination therapy vs. oral vancomycin.
monotherapy for treatment of severe CDI. Experience with FMT in pediatrics is limited, but growing evidence suggests that FMT is effective and safe for treatment of chronic CDI in children. An FMT program for inpatients <18 years old is currently unavailable at UMHS; consultation with Pediatric Infectious Diseases is suggested if considering FMT as an option as an outpatient procedure to prevent future recurrences. The American Academy of Pediatrics (AAP) does not currently recommend probiotics for prevention or treatment of CDI in infants and children citing insufficient data. However, a recent Cochrane Database review of 23 randomized controlled trials found moderate quality evidence to suggest that short-term use of probiotics in healthy, immunocompetent adults and children was safe and effective in the prevention of CDI. UMHS guidelines reflect the recommendation of the AAP and do not recommend probiotic use for prevention or treatment of CDI in this patient population.

Special Populations - Inflammatory Bowel Disease

In IBD patients with concomitant CDI and mild IBD flare, antibiotics for CDI should be started without corticosteroids (patient should be maintained on home immunosuppression medications). This recommendation is based on evidence suggesting worse outcomes in IBD patients with CDI on immunosuppression, and a reduction of corticosteroids dose is associated with a lower colectomy rate. However, with a lack of symptom improvement after 48 hours of CDI therapy or in severe IBD flare with concomitant CDI, antibiotics and corticosteroids co-therapy is advised. This strategy is based on clinical data indicating a more severe IBD course (i.e., an increased colectomy rate and mortality) in IBD patients with CDI vs IBD patients without CDI. The recommended practice of IBD experts at UMHS is to use CDI therapy and corticosteroids when IBD patients with concomitant CDI present with a severe IBD flare defined as >6 bloody stools/day and one or more of: Temp>37.5, Pulse >90, Hgb<10.5, ESR>30.

Vancomycin is preferred over metronidazole for the treatment of CDI in IBD patients based on a retrospective study showing fewer readmissions and shorter lengths of stay when IBD patients are treated with vancomycin-containing regimen relative to those treated with metronidazole alone.

Related National/International Guidelines

The UMHS Clinical Guideline on CDI is generally consistent with other guidelines published nationally and internationally, including:


Notable differences in recommendations: Our guideline deviates from the above guidelines in the way that it classifies "mild-to-moderate" vs. "severe" vs. "severe and complicated" disease (see Table 3). The change in classification criteria was undertaken to better reflect additional factors we identified in the literature that can predispose patients to developing complicated C. difficile or more severe manifestations of C. difficile.

Guideline Development Methodology

Funding

The development of this guideline was funded by the University of Michigan Health System.

Guideline Development Team and Disclosures

The multidisciplinary guideline development team consisted of:

- Primary care physicians: Andrea H Kim, MD, Internal Medicine
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- Literature search services were provided by informationists at the Taubman Health Sciences Library, University of Michigan Medical School.

The University of Michigan Health System endorses the Guidelines of the Association of American Medical Colleges and the Standards of the Accreditation Council for Continuing Medical Education that the individuals who present educational activities disclose significant relationships with commercial companies whose products or services are discussed. Disclosure of a relationship is not intended to suggest bias in the information presented, but is made to provide readers with information that might be of potential importance to their evaluation of the information.

No relevant personal financial relationships with commercial entities: Meghan A Arnold, Gregory Eschenauer, PharmD, Tejal N Gandhi MD, John Y Kao,
Strategy for Literature Search

Within the Medline (Ovid) database, the following search strategy was used for most of the search topics, except for the searches on suppurative thrombosis, endocarditis, and vascular infection. The search below is identified as Main in the search strategies document. Because the appropriate indexing terms either do not exist or were applied inconsistently, the main search uses keywords in addition to MeSH terms to arrive at the following main strategy.

1. exp *Clostridium difficile/ or exp *enterocolitis/ or exp *Clostridium Infections/
2. exp *Hirschsprung Disease/
3. limit 2 to “all child (0 to 18 years)”
4. 1 or 3
5. exp animals/ not (exp animals/ and humans/)
6. 4 not 5
7. limit 6 to (english language and yr="2013 -Current”)
8. remove duplicates from 7. The searches on suppurative thrombosis, endocarditis, and vascular infection used the first 3 searches of the main search strategy. The MEDLINE In-Process search was based entirely on keywords.

Results were limited to: English, and 2013 to present. The Main search retrieved 893 references. When the search hedges for Guidelines, Clinical Trials, and Cohort Studies were added, the base results are as follow:
- C-Diff -Guidelines, total results were 8
- C-Diff -Clinical Trials, total results were 27
- C-Diff -Cohort Studies, total results were 59

The search was conducted in components each keyed to a specific causal link in a formal problem structure (available upon request). The search was supplemented with very recent clinical trials known to expert members of the panel. Negative trials were specifically sought. The search was a single cycle.

Level of evidence supporting a diagnostic method or an intervention:
- A = systematic reviews of randomized controlled trials with or without meta-analysis,
- B = randomized controlled trials,
- C = systematic review of non-randomized controlled trials or observational studies, non-randomized controlled trials, group observation studies (cohort, cross-sectional, case-control),
- D = individual observation studies (case study/case series),
- E = expert opinion regarding benefits and harm


Recommendations

Guideline recommendations were based on prospective randomized controlled trials if available, to the exclusion of other data; if RCTs were not available, observational studies were admitted to consideration. If no such data were available for a given link in the problem formulation, expert opinion was used to estimate effect size. The “strength of recommendation” for key aspects of care was determined by expert opinion.

The strength of recommendations regarding care were categorized as:
- I = Generally should be performed
- II = May be reasonable to perform
- III = Generally should not be performed

Review and Endorsement

Drafts of this guideline were reviewed in clinical conferences and by distribution for comment within departments and divisions of the University of Michigan Medical School to which the content is most relevant: Family Medicine, General Medicine, Department of Surgery, Infectious Diseases Division, Gastroenterology Division. Pediatrics and Communicable Diseases and the Division of Pediatric Infectious Diseases. The Executive Committee for Clinical Affairs of the University of Michigan Hospitals and Health Centers endorsed the final version.

References


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### Appendix A. Available diagnostic tests for toxigenic *C. difficile* 

<table>
<thead>
<tr>
<th>Methods</th>
<th>Test Target(s)</th>
<th>Notes on Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reference Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cytotoxigenic Culture</td>
<td>Toxigenic <em>C. difficile</em></td>
<td>Expertise required&lt;br&gt;Takes 24-48 hours&lt;br&gt;Cultures <em>C. difficile</em> and determines if isolate can produce toxin in vitro</td>
</tr>
<tr>
<td>Cell Cytotoxicity Assay</td>
<td>Toxins A or B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Highly sensitive for toxin production&lt;br&gt;Expertise required&lt;br&gt;Takes 24-48 hours</td>
</tr>
<tr>
<td><strong>Rapid Tests</strong></td>
<td></td>
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<tr>
<td>EIA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>GDH</td>
<td>Must be paired with a test for toxin&lt;sup&gt;b&lt;/sup&gt;&lt;br&gt;Sensitivity and specificity vary considerably by manufacturer</td>
</tr>
<tr>
<td>EIA&lt;sup&gt;c&lt;/sup&gt;</td>
<td>Toxins A or B&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Sufficient for diagnosis alone&lt;br&gt;Sensitivity and specificity vary considerably by manufacturer</td>
</tr>
<tr>
<td>NAAT</td>
<td></td>
<td>More expensive than EIA&lt;br&gt;Sensitive and specific for presence of toxigenic <em>C. difficile</em>&lt;br&gt;Possible increase in false positive rate if used alone without specimen screening; increases detection of colonization</td>
</tr>
<tr>
<td>RT-PCR&lt;sup&gt;c&lt;/sup&gt;</td>
<td><em>tcdB</em> or <em>tcdC</em> genes</td>
<td><em>tcdA</em> and <em>tcdB</em> are the genes for toxins A and B, respectively&lt;br&gt;<em>tcdB</em> presence is necessary for disease&lt;br&gt;<em>tcdC</em> is a regulatory gene for toxin production</td>
</tr>
<tr>
<td>LAMP</td>
<td><em>tcdA</em> or <em>tcdB</em> genes</td>
<td>Strains that are <em>tcdA</em>-positive / <em>tcdB</em>-negative do not cause disease; thus false negative results can occur with <em>tcdA</em> testing alone by LAMP</td>
</tr>
</tbody>
</table>

CDI, *Clostridium difficile* infection; EIA, enzyme immunoassay; GDH, glutamate dehydrogenase; LAMP, loop-mediated isothermal amplification; NAAT, nucleic acid amplification testing; RT-PCR, real-time polymerase chain reaction.

<sup>a</sup>*C. difficile* can produce toxin A and/or toxin B. Although both play a role in clinical disease, it is not known if strains producing only toxin A are associated with symptomatic infection in humans.

<sup>b</sup>Non-toxigenic *C. difficile* strains also exist, do not cause disease, and will be GDH positive.

<sup>c</sup>Test available at University of Michigan (EIA for GDH, EIA for toxin A, and RT-PCR)