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Executive Summary
Guideline Overview
This guideline contains recommendations for the prevention, diagnosis, management, and treatment of *Clostridium difficile* infection (CDI) in pediatric and adult patients, and is heavily influenced by documents released by the Society of Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA) and the American Academy of Pediatric (AAP).

Key Revisions (2017 Periodic Review)
1. The following tables were added to the guideline: Low/High risk antibiotics potential for C. Diff infection, Enhanced contact precautions measures for patients with CDI, Risk factors for first infection with *Clostridium difficile* in adults with diarrhea, When to test for C diff Infection, and Criteria to consider for Moderate to Severe CDI in adults.
2. New recommendations for hospital area restrictions for symptomatic patients, infection control in the ambulatory clinic and infection control at home.
3. New adult and pediatric C. Diff treatment algorithms.
5. New recommendation for inpatient use of bezlotoxumab for CDI preventive therapy.

Key Practice Recommendations

**Prevention**
1. Compliance with UW Health enhanced contact precautions for patients with onset of diarrhea or with suspected CDI should be immediately implemented. *Clostridium difficile* isolation precautions should remain in place for the duration of hospitalization or 90 days from the last positive test (whichever is longer).
2. Hand washing with soap and water upon exit and barrier precautions, including gloves and gowns, should be used upon entry by all health-care workers, patients, and visitors within the room of any patient with known or suspected CDI.
3. Single patient-use disposable equipment should be used for prevention of *Clostridium difficile* transmission. Non-disposable medical equipment should be dedicated to the patient’s room and other equipment should be thoroughly cleaned with an approved sporicidal agent, as appropriate, after use in patients with CDI.
4. Education should be provided to the patient and family related to *Clostridium difficile* risk during antibiotic therapy.
5. The use of proton pump inhibitors should be minimized, if possible, as the duration of PPI therapy has been associated with CDI in adult patients. Switching to H2 blockers may be considered, if stopping therapy all together cannot be achieved.
6. Probiotics may be considered for primary prevention of CDI in immunocompetent adults prescribed an antibiotic course with a high risk antibiotic, and should be considered for patients who are otherwise at risk of CDI. The preferred probiotic at UW Health is *Lactobacillus GG*.
7. Prophylaxis with metronidazole or vancomycin may be considered in patients with a recent diagnosis of CDI that require subsequent broad spectrum antibiotic therapy.
8. For patients remaining on therapeutic antibiotics, consideration should be given to continuing ‘dose reduced’ (i.e., vancomycin 125 mg PO BID or metronidazole 500 mg PO once daily or BID) through the course of therapy and for 5 days following completion.
Diagnosis
1. Patients > 3 years of age experiencing diarrhea (≥ 3 unformed stools in the previous 24 hours) without an alternative etiology and at-risk for CDI should be evaluated for the presence of *Clostridium difficile*.
2. Testing of patients younger than one year of age is discouraged due to high colonization rates in asymptomatic patients. Testing of children age 12-36 months should only be considered in the setting of appropriate risk factors and with evaluation of other potential etiologies.
3. Evaluation of patients without diarrhea or risk factors should be avoided. Routine screening for *Clostridium difficile* in patients without diarrhea is not recommended and asymptomatic carriers should not be treated.
4. Testing for *Clostridium difficile* should be performed on diarrheal (unformed) stool specimens, unless ileus due to *Clostridium difficile* is suspected.
5. Polymerase chain reaction (PCR) testing of stool samples for toxigenic *Clostridium difficile* is preferred for standard diagnostic testing. Repeat testing for *Clostridium difficile* by PCR is not recommended and testing for cure should not routinely be performed.

Treatment
1. The most important treatment for *Clostridium difficile* is prevention.
2. Discontinue therapy or deescalate spectrum with inciting antimicrobial agent(s) as soon as possible, when feasible.
3. Initiate treatment with first choice therapeutic options metronidazole and/or vancomycin. Duration of therapy should generally not exceed 14 days, except when concomitant antibiotics need to be administered in which case treatment may be extended for 5 days after finishing the concomitant antibiotic.
4. Anti-peristaltic agents should be avoided in patients with suspected or confirmed CDI as they may obscure symptoms of infection.
5. Low-dose metronidazole (500 mg PO once or twice daily) or low-dose vancomycin (125 mg orally twice daily) may be considered in patients who have a history of CDI and are being treated with antibiotics for a non-CDI infection.
6. Fidaxomicin is usually reserved for adult patients that relapse or have recurrence after treatment with metronidazole and vancomycin, and in adult patients with low levels of neutralizing antibodies to *Clostridium difficile*.
7. Fecal microbiota therapy (FMT) is an acute treatment for relapsing disease and may be considered under unique circumstances. For adults and pediatric patients, it should be done in consultation with Infectious Disease and Gastroenterology services and with the Pediatric Infectious Diseases and Pediatric Gastroenterology services respectively.

Scope
**Disease/Condition(s):** *Clostridium difficile* infection (CDI)

**Clinical Specialty:** Infectious Disease/Control, Gastroenterology, Preventive Medicine, Primary Care, Emergency Medicine, All Inpatient Services, Pediatric Infectious Disease, Pediatric Gastroenterology

**Intended Users:** Physicians, Nurses, Advanced Practice Providers, Pharmacists, Environmental Services staff

**Objective(s):** To provide recommendations for the diagnosis and management of patients with CDI. The guideline also contains guidance for prevention of CDI and infection control within the inpatient and ambulatory settings.
Target Population: Pediatric and adult patients at risk for or diagnosed with *Clostridium difficile* infection.

Interventions and Practices Considered:

Diagnosis
- Testing of stool for *Clostridium difficile* via polymerase change reaction (PCR) (preferred) or by cytotoxin assay
- Computer tomography (CT) scanning of the abdomen and pelvis in severe cases

Management/Treatment
- Antimicrobial use restriction
- Avoidance of antiperistaltic agents
- Initiate treatment including metronidazole, vancomycin, and/or fidaxomicin
- Surgical consultation
- Fecal microbiota therapy

Prevention
- Hospital-based infection control programs
- Antibiotic use restrictions
- Enhanced Contact Precautions
- Use of private rooms, when applicable
- Hand hygiene and barrier precautions
- Disinfection of environmental surfaces with sporicidal agents

Major Outcomes Considered:
- Sensitivity and specificity of diagnostic testing
- Rates of CDI
- Morbidity/Mortality
- Number of cases of severe disease nosocomially acquired and requiring surgical intervention
- Length of hospital stay
- Rates of relapse in hospital or requiring hospital readmission within 60 days of hospital associated CDI episode
- Xenex UV light disinfection use on high risk units and where use is available

Methodology

Methods Used to Collect/Select the Evidence:
Electronic database searches (e.g., PUBMED) were conducted by the guideline author(s) and workgroup members to collect evidence for review. Expert opinion and clinical experience were also considered during discussions of the evidence.

Methods Used to Formulate the Recommendations:
The workgroup members agreed to adopt recommendations developed by external organizations and/or arrived at a consensus through discussion of the literature and expert experience. All recommendations endorsed or developed by the guideline workgroup were reviewed and approved by other stakeholders or committees (as appropriate).
Methods Used to Assess the Quality of the Evidence/Strength of the Recommendations:
Recommendations developed by external organizations maintained the evidence grade assigned within the original source document and were adopted for use at UW Health.

Internally developed recommendations, or those adopted from external sources without an assigned evidence grade, were evaluated by the guideline workgroup using an algorithm adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (see Figure 1 in Appendix A).

Rating Scheme for the Strength of the Evidence/Recommendations:
See Appendix A for the rating scheme(s) used within this document.

Recognition of Potential Health Care Disparities: Clostridium difficile is the most common cause of infectious diarrhea in hospitalized patients in high-income countries like the United States.1

Introduction
Clostridium difficile infection (CDI) is the most frequent cause of health care-associated diarrhea and is now the most common hospital-acquired infection.2-5 Because of the increasing incidence, severity, and costs associated with CDI, there is a substantial need to prevent exposure and transmission of CDI, as well as to improve the treatment of patients with CDI.6

Clostridium difficile is a spore forming, anaerobic, gram positive, bacilli responsible for 15-25% of cases of nosocomial diarrhea and 20-30% of antibiotic associated diarrhea in adult patients. Toxigenic species are capable of producing toxin A, toxin B, a binary toxin, or a combination. Clostridium difficile infection can manifest from symptomless carriage and minor diarrhea to fatal pseudomembranous colitis and toxic megacolon, sepsis, bowel perforation and death.4,7 Mortality rates from CDI increased from 5.7 per million population in 1999 to 23.7 per million in 2004.8 It is projected to nationally cause $3.2 billion in health care costs.

In recent years a particularly virulent strain of Clostridium difficile, BI/NAP1, has become a major pathogen in the development of CDI. BI/NAP1 has increased virulence characteristics including: increased toxin production, binary toxin, hyper-sporulation, and resistance to fluoroquinolone antibiotics.4,7 Recurrence of CDI is highest in the 7-14 days after completion of initial therapy, but persists for up to 90 days. The risk of recurrence increases as the number of infections or reinfections increase.4,7

Studies in pediatrics have also shown an increase in the prevalence of hospital acquired and community acquired C. difficile in recent years.9-11 However, unlike in the adult population, the prevalence remains low, and the clinical symptomatology is less severe. Community acquired infections account for ~70% of cases.10,11 The diagnosis of CDI in young children and infants remains challenging in the setting of low prevalence rates of infection and high rates of asymptomatic carriage in this population.12 Numerous studies have demonstrated high colonization rates (30-70%) of both toxigenic and non-toxigenic C. difficile in asymptomatic infants younger than 12 months.12-14 This asymptomatic colonization rate has been shown to decrease as children over the next two years. By age 3, the rate is is < 3%, similar to that in adults.13,14
Recommendations

Disease Prevention

Probiotics for disease prevention

Due to the lack of controlled clinical trials, probiotics are not currently recommended by the American Academy of Pediatrics for primary prevention of CDI in pediatric patients. (UW Health Very low quality of evidence, strong recommendation) However, it is reasonable to consider prescribing probiotics for the primary prevention of CDI in most immunocompetent adult patients receiving therapeutic, antibiotic therapies. (UW Health Class Low quality of evidence, strong recommendation) Adult patients prescribed high-risk antibiotics or who exhibit additional risk factors, including the use of two or more antibiotic therapies (see Risk Factors), should be considered for probiotic therapy. (UW Health Moderate quality of evidence, strong recommendation) The most common adverse events experienced by patients on probiotics included abdominal cramping, nausea, fever, soft stools, flatulence, and taste disturbances. No specific probiotic formation has shown superior results; therefore the preferred probiotic at UW Health is *Lactobacillus GG*. (UW Health Class Moderate quality of evidence, strong recommendation)

<table>
<thead>
<tr>
<th>Low risk antibiotics</th>
<th>High risk antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Fluoroquinolones</td>
</tr>
<tr>
<td>Macrolides (e.g., azithromycin)</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-4&lt;sup&gt;th&lt;/sup&gt; generation cephalosporins</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole* prophylaxis or treatment duration less than 5 days</td>
<td>Beta-lactamase inhibitor combinations</td>
</tr>
<tr>
<td>Tetracyclines</td>
<td>Sulfmonamides or</td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Trimethoprim/sulfamethoxazole*</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>Clindamycin</td>
</tr>
<tr>
<td></td>
<td>Carbapenems</td>
</tr>
<tr>
<td></td>
<td>Vancomycin</td>
</tr>
<tr>
<td></td>
<td>≥ 2 antibiotics of any risk</td>
</tr>
</tbody>
</table>

* “Low risk” trimethoprim/sulfamethoxazole use is considered prophylaxis or treatment duration less than 5 days. “High risk” sulfonamide or trimethoprim/sulfamethoxazole use is considered dosing ≥ 10mg/kg/day AND duration ≥ 7 days.

| Table 1. Low/High-risk antibiotics potential for C. Diff infection

Infection Control for hospital admission with C Diff Diagnosis

A hospital-based infection control program in conjunction with a hospital antimicrobial stewardship program can help to decrease the incidence of CDI. (SHEA-IDSA Evidence Grade A, Category II)

Appropriate antibiotic utilization

It is recommended that prescribers be educated to minimize the use of antibiotics, especially high risk (see Table 1.) (SHEA-IDSA Evidence Grade A, Category II) such as broad spectrum cephalosporins, clindamycin, and fluoroquinolones. (SHEA-IDSA Evidence Grade C, Category III)

Ulcer protection therapy/Proton pump inhibitors

Use of proton pump inhibitors (PPI) should be minimized as duration of PPI therapy has been associated with CDI in adults. (UW Health Low quality of evidence, strong recommendation) Switching to H<sub>2</sub> blockers may be considered, if stopping therapy all together cannot be achieved.
Patient room placement and contact precautions

Inpatients with known or suspected CDI should be placed in a private room (preferred) or in a room with another patient with documented CDI.4,14,21,23 (SHEA-IDSA Evidence Grade B, Category III) Isolation of patients should not wait until a positive *Clostridium difficile* test is returned. (UW Health Moderate quality of evidence, strong recommendation) Enhanced contact precautions should be initiated and maintained for the duration of hospitalization or 90 days from the last positive test (whichever is longer). Patients readmitted to the hospital within 90 days should also be placed in contact isolation and re-evaluated by Infection Control.

Barrier precautions, including gloves (SHEA-IDSA Evidence Grade A, Category I) and gowns (SHEA-IDSA Evidence Grade B, Category III), should be used by all health-care workers and visitors upon entry to the room of any patient with known or suspected CDI. Hand washing with soap and water upon leaving the room should be used by all health-care workers, patients, and visitors upon exiting the room of any patient with known or suspected CDI.4,14,21,23-25 Alcohol hand rub or sanitizer alone is not sufficient in disinfecting or removing *Clostridium difficile* spores.24

Single-use disposable equipment, including stethoscopes, should be used for prevention of CDI transmission. Equipment that is not disposable should be thoroughly cleaned with a sporicidal agent after use in a patient with CDI.4,14,23,25,26 (UW Health High quality of evidence, strong recommendation) UW Health Environmental Services should utilize sporicidal agents for daily cleaning and cleaning at discharge of the isolation room(s), in order to effectively kill *Clostridium difficile* spores on surfaces.4,23 (SHEA-IDSA Evidence Grade B, Category II) Ultraviolet (UV) light disinfection at discharge may also be undertaken to reduce environmental burden of *Clostridium difficile*. (UW Health Low quality of evidence, weak/conditional recommendation) Table 2 summarizes key contact precaution measures clinicians and staff should adhere to with patients who have CDI.

Table 2. Enhanced contact precautions measures for patients with CDI

<table>
<thead>
<tr>
<th>Hospital Precautions</th>
<th>Staff specific precautions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rooming</strong> – patient placed in private room or with another patient with documented CDI infection</td>
<td><strong>Hand hygiene before gloves</strong> – Use alcohol gel or soap and water prior to wearing gloves</td>
</tr>
<tr>
<td><strong>Signage</strong> – contact precautions posted on door, alcohol dispenser in/or assigned room covering dispense</td>
<td><strong>Wash with soap and water before exiting</strong> – wash hands with soap and water after patient encounter</td>
</tr>
<tr>
<td><strong>Duration</strong> - Contact precautions should be initiated/maintained for entirety of admission or 90 days from the last positive test (whichever is longer). Patients readmitted to the hospital within 90 days should also be placed in contact isolation, and patients awaiting fecal microbiota transplant (FMT)</td>
<td><strong>Disposable equipment</strong> – When possible, disposable equipment (including stethoscopes) should be used; otherwise all equipment must be cleaned with sporicidal agent</td>
</tr>
<tr>
<td><strong>Accessibility</strong> – Personal protective equipment (PPE) should stocked and available in necessary sizes; room sink should be easily accessible for washing hands</td>
<td><strong>PPE wearing</strong> – Put on gowns and gloves prior to entering room and gown should be tied; PPE may be disposed in room once patient interaction complete and proper hand washing should occur thereafter</td>
</tr>
</tbody>
</table>
Hospital area restrictions
Symptomatic patients should be restricted to their room and not be allowed to common areas of the hospital (e.g., lobby, gift shop, cafeteria, children’s hospital playrooms and school rooms, etc.) Ambulation in the hallways is allowed when part of medical care routine. *(UW Health Low quality of evidence, strong recommendation)*

During ambulation, must patient must wear *clean* clothing or a clean hospital gown, thoroughly perform hand hygiene before leaving the room or wear gloves, and refrain from contact with other patients. Staff accompanying the patient is expected to wear clean PPE. Any gloves worn by staff and/or the patient should not be used to push elevator buttons or come into contact with other common surfaces. These precautions are in accordance with *UW Health policy 4.1.8 Standard Precautions and Isolation* and for more information, refer to *UW Health policy 4.1.8 Standard Precautions and Isolation plan*.

**Infection control in the ambulatory clinic**
If a patient presents with diarrhea and there is concern for CDI in the ambulatory setting, all clinicians and clinic staff should follow staff specific precautions as noted in Table 2, prior to entering the patient’s room. *(UW Health Low quality of evidence, strong recommendation)* Example scenarios where enhanced contact precautions should be followed in the ambulatory clinic setting include:

- Patient with active CDI flag in medical record who presents to clinic with diarrhea
- Patient that presents to clinic with chief complaint of diarrhea and states having 5 bowel movements per day when normally has only 2 bowel movements a day
- Patient who completed treatment for CDI infection and had resolution of symptoms but presents to clinic with diarrhea and suspicion for CDI relapse

In addition, following the patient’s visit, cleaning should be done with sporicidal agent (e.g., bleach, oxycide) and *not* CaviWipes.

**Infection control at home**
It is strongly recommended that clinicians counsel patients and family members appropriately on infection control precautions to conduct at home. *(UW Health Low quality of evidence, strong recommendation)* Some key infection control precautions to emphasize include:

- Cleaning the home with bleach versus other household cleaners/detergents
- Washing hands with soap and water often, especially after going to the bathroom and before handling food. Use cloth towels once only or use disposable towels.
- Consider using disposable gloves when changing diapers/disposable undergarments of infected individual. Diapers should be disposed of properly and hands washed with soap and water after disposing gloves.
- If possible, designate a bathroom for the affected household member/patient’s use only.
- Launder linens and clothing with bleach, wash with warm/hot water, and dry on non-low heat setting. Clean and disinfect laundry “basket” with bleach between handling clean and dirty laundry.

Additional infection precautions can be found in the Health Facts for You - What you Need to know about Clostridium difficile Infection.
Diagnosis

Clinical Characteristics and Risk Factors

Adult Patients:
Testing of adult patients without diarrhea or risk factors should be avoided.21 (UW Health Moderate quality of evidence, strong recommendation) In rare cases, patients may present with ileus and/or colonic distention in the absence of diarrhea.4

In addition to the following, risk of CDI is also known to be proportional to the total amount of antibiotic exposure on a hospital unit.20 Individual risk factors for first infection with Clostridium difficile in adult patients with diarrhea are listed in Table 3.2,4,5,27,28

Table 3. Risk factors for first infection with Clostridium difficile in adults with diarrhea

<table>
<thead>
<tr>
<th>Risk factors for C. diff infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Exposure to antimicrobial agents and exposure to multiple antimicrobials especially:</td>
</tr>
<tr>
<td>o High-risk antibiotics (Table 1)</td>
</tr>
<tr>
<td>o Two or more antibiotics</td>
</tr>
<tr>
<td>• Increasing age (in particular ≥ 64 years of age)</td>
</tr>
<tr>
<td>• Prior hospitalization for any reason within last 90 days</td>
</tr>
<tr>
<td>• Current hospitalization (LOS ≥ 7 days)</td>
</tr>
<tr>
<td>• Immunosuppression (e.g. HIV, solid organ or hematopoietic stem cell transplant)</td>
</tr>
<tr>
<td>• Comorbidities (e.g., cystic fibrosis, inflammatory bowel disease, diabetes mellitus, chronic kidney disease)</td>
</tr>
<tr>
<td>• Cancer chemotherapy</td>
</tr>
<tr>
<td>• Gastrointestinal surgery</td>
</tr>
<tr>
<td>• Manipulation of GI tract for any reason:</td>
</tr>
<tr>
<td>o Gastrosotomy or jejunostomy tube feedings</td>
</tr>
<tr>
<td>o H2 blockers</td>
</tr>
<tr>
<td>o Proton Pump Inhibitors</td>
</tr>
<tr>
<td>• Manipulation of GI tract for any reason (e.g., gastrosotomy or jejunostomy tube feedings)</td>
</tr>
</tbody>
</table>

Pediatric Patients:
Although the epidemiology of Clostridium difficile infection in children has shown an increase in incidence over the past decade, Clostridium difficile infection remains much less common and when present, less severe in children than adults.

The studies on risk factors for CDI in children are limited; however, observational studies suggest risks similar to adults (i.e., recent antibiotic exposure, immunosuppression including receipt of immunosuppressive therapy, inflammatory bowel disease, renal insufficiency, manipulation of the GI tract with gastrostomy and jejunostomy tubes or impairment of humoral immunity.14,25 Children with malignancy are at highest risk of CDI among hospitalized children.29

Diagnostic Testing
Testing for Clostridium difficile or its toxins should be done only on diarrhea (unformed stool), unless ileus due to Clostridium difficile is suspected.4,27 (SHEA-IDSA Evidence Grade B, Category II) Polymerase chain reaction (PCR) testing is sensitive and specific and is recommended for standard diagnostic testing.4 (UW Health Moderate quality of evidence, strong recommendation)
Repeat testing for *Clostridium difficile* by PCR for diagnostic purposes is strongly discouraged and **testing for cure (i.e., at end of treatment) is not recommended**.\(^4\,14\,25\) (SHEA-IDSA Grade B, Category III) It is estimated that 50-65% of patients remain PCR positive at 14 days following initial diagnosis (i.e., after completing a course of treatment and without clinical signs and symptoms of infection). These patients should not be retested without a change in clinical status suggesting a CDI relapse.\(^30\,31\) Testing directly for cytotoxin by cell culture methodology can be considered at the advice and consultation with Infectious Disease and Gastroenterology.

Direct visualization via colonoscopy or histologic findings of pseudomembranous colitis can also infer *Clostridium difficile* infection.\(^4\,14\)

**Adult Patients:**
Adult patients experiencing diarrhea (≥ 3 unformed stools in the previous 24 hours) with CDI risk factors and no alternate etiology for diarrhea should be tested for *Clostridium difficile* toxin. (UW Health Moderate quality of evidence, strong recommendation) Patients without diarrhea or risk factors should not be tested. Adult patients with inflammatory bowel disease patients experiencing flare symptoms should also be tested and isolated given the prevalence of *Clostridium difficile* infection in patients with IBD (1.7% compared to 0.4% in general population).\(^2\)

**Pediatric Patients:**
In the pediatric population, asymptomatic carriage of *Clostridium difficile* can be as high as 70% in infants in the first month of life, averaging 30-40% in the first two years of life and < 3% by age 3.\(^14\,32\) Clinical illness in children less than 12 to 24 months is rare. Additionally, infants and toddlers frequently have soft and loose stools, the cause of which can be multifactorial. Therefore, laboratory testing for *Clostridium difficile* in infants < 1 year of age is discouraged unless in the presence of Hirschsprung’s disease or other severe motility disorders, or in an outbreak situation.\(^14\) (UW Health High quality of evidence, weak/conditional recommendation)

Testing can be considered in children age 12 to 36 months with the appropriate clinical findings (i.e., ≥ 3 diarrheal stools in 24 hours and additional risk factors). However, alternative diagnoses (i.e., antibiotic associated diarrhea, other microbial etiologies) should first be considered in this age group as the false-positive rate for *Clostridium difficile* as a causative agent of disease is high in the younger population.\(^14\,25\,33\) (UW Health Class Low quality of evidence, weak/conditional recommendation) It is reasonable to test pediatric patients age 3-17 years with the appropriate clinical findings (i.e., ≥ 3 unformed stools in the previous 24 hours) and associated risk factors for *Clostridium difficile* toxin.\(^14\) (UW Health Moderate quality of evidence, weak/conditional recommendation)

**Table 4** summarizes who to test and when to not test. For specific testing guidance in the inpatient setting, refer to the [Adult Inpatient Clostridium difficile Infection Testing algorithm](#) and [Pediatric Inpatient Clostridium difficile Infection Testing algorithm](#).
### Table 4. When to test for C Diff Infection

<table>
<thead>
<tr>
<th>Population</th>
<th>When to test…</th>
<th>DO NOT test…</th>
</tr>
</thead>
</table>
| Adults     | • Patient with diarrhea (≥ 3 unformed stools* in the previous 24 hours), particularly those with risk factors, and no alternative etiology for diarrhea  
• Patients with IBD with flare symptoms  
• Hospital admitted patients within first 48 hours of admission with complaints of or any unexplained loose stools prior to admission (see testing algorithm)  
• Patient treated for CDI with prior resolution of symptoms who may have new infection (i.e., symptomatic, diarrhea) | • Patients < 12 months without appropriate clinical findings  
• Patients on laxatives  
• Any admitted patient age ≥ 3 years with < 3 unexpected liquid/loose stools after 48 hours of admission  
• A patient still taking oral vancomycin for CDI  
• Patients treated for CDI without complete resolution of symptoms with possible relapse  
• If pt had a C diff test result within last 7 days  
• Asymptomatic patients for nursing home placement  
• Patient near end of CDI treatment (i.e., testing for cure) |
| Pediatric  | • Patients ≥ 12 months with appropriate clinical findings (≥ 3 unformed stools* in the previous 24 hours), particularly those with risk factors and no alternative etiology for diarrhea  
• Hospital admitted patients > 3 years within first 48 hours of admission with complaints of or any unexplained loose stools prior to admission (see testing algorithm)  
• Patient treated for CDI infection with resolution of symptoms who may have new infection | |

*Stool episodes should be measured as ≥ 3 unformed stools from patient’s baseline bowel movements per day

### Antimicrobial Treatment of Initial Infection

Daily assessment for signs and symptoms is necessary to assess efficacy of all treatments. **When feasible, discontinuation of therapy with inciting antimicrobial agent(s) as soon as possible is recommended as the first step in treatment.**7,14,25 *(UW Health High quality of evidence, strong recommendation)*

In general, antiperistaltic agents should be avoided in patients with suspected or confirmed CDI since they may obscure symptoms and precipitate toxic megacolon.4,14 *(SHEA-IDSA Evidence Grade C, Category III)*

Multiple oral agents provide redundant coverage and should not be given simultaneously. Examples include oral vancomycin and oral metronidazole OR oral vancomycin and oral fidaxomicin. *(UW Health Low quality of evidence, weak/conditional recommendation)* Oral metronidazole is 90% absorbed and it is not recommended to give concomitantly with full-dose intravenous metronidazole. *(UW Health Moderate quality of evidence, weak/conditional recommendation)* Oral vancomycin and fidaxomicin are NOT absorbed from the GI tract. If treatment of non-CDIs outside of the GI tract requires vancomycin, the intravenous form can be given simultaneously with the oral form without risk of toxicity. Conversely, patients being treated with intravenous vancomycin will NOT achieve adequate levels in the GI tract and are
NOT being effectively treated for CDI. *(UW Health Very low quality of evidence, weak/conditional recommendation)*

The duration of therapy generally should not exceed 14 days for most patients. Exceptions may include treatment of severe *Clostridium difficile* infection or treatment of a relapse of disease AND extended therapy while on broad-spectrum or other antibiotics with the potential to increase rates of *Clostridium difficile* relapse. *(UW Health Class Low quality of evidence, weak/conditional recommendation)*

**Adult Patients:**

Therapy without diagnostic suspicion is not appropriate. *(UW Health Low quality of evidence, weak/conditional)* The decision to treat CDI (Table 6) should be based upon the severity of infection as determined by thoughtful clinical decision making. 

Adults with mild disease typically present with diarrhea with minimal additional findings. For treatment of mild disease, begin metronidazole 500 mg PO three times daily for 10 to 14 days. *(UW Health Class High quality of evidence, strong recommendation)* Patients with mild CDI who are intolerant/allergic to metronidazole, or in women who are pregnant/breastfeeding, should begin vancomycin at standard dosing, 125 mg PO four times daily for 10-14 days. *(UW Health High quality evidence, strong recommendation)* Patients with a history of neuropathy or current alcohol use which cannot be stopped during therapy should receive vancomycin over metronidazole.

Table 5 outlines criteria typically associated with adult patients who have moderate to severe or severe CDI.

<table>
<thead>
<tr>
<th>Moderate to severe CDI in adults if:</th>
<th>Severe, complicated CDI in adults if:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• immunocompromised (e.g., HIV, chronic steroid use, chemotherapy)</td>
<td>• ICU/IMC admission</td>
</tr>
<tr>
<td>• on hemodialysis</td>
<td>• Ileus</td>
</tr>
<tr>
<td>or meet some of the following criteria:</td>
<td>• Toxic megacolon</td>
</tr>
<tr>
<td>o age &gt; 60 years</td>
<td>• Diverting ileostomy, or</td>
</tr>
<tr>
<td>o albumin &lt; 2.5 mg/dL</td>
<td>• Significant abdominal distension</td>
</tr>
<tr>
<td>o WBC &gt; 15,000 cells/mm³</td>
<td>• SIRS</td>
</tr>
<tr>
<td>o abdominal tenderness, or</td>
<td>• Hypotension with or without required use of vasopressors felt to be related to CDI</td>
</tr>
<tr>
<td>o elevated serum creatinine &gt; 1.5x the premorbid level.</td>
<td>• WBC &gt; 30,000 cells/mm³ or &lt; 1,000 cells/mm³</td>
</tr>
<tr>
<td></td>
<td>• Serum lactate &gt; 2.2. mmol/L, or</td>
</tr>
<tr>
<td></td>
<td>• End organ failure felt to be related to CDI</td>
</tr>
</tbody>
</table>

Ultimately, the distinction between mild and moderate to severe disease is a clinical decision based on age, comorbidities, and the constellation of other findings. For treatment of moderate to severe disease in adults, begin vancomycin 125 mg PO four times daily for 10 to 14 days. *(UW Health High quality of evidence, strong recommendation)* Dose escalation of vancomycin is rarely necessary as intraluminal concentrations of vancomycin far exceed the concentrations of *Clostridium difficile*. 

As above, the ultimate decision regarding severity should be made considering the entirety of the individual case. For treatment of severe disease with additional complications (such as toxic megacolon, systemic inflammatory response syndrome, etc.), in addition to surgical
consultation, begin vancomycin 500 mg PO/NG four times daily PLUS metronidazole 500 mg IV three times daily.\textsuperscript{3,4} Tigecycline 100 mg IV once then 50mg IV every 12 hours may be considered as an alternative for metronidazole IV in patients with severe refractory CDI when there is a need for continuation of concomitant anti-infectives which may worsen the condition.\textsuperscript{35,36} (UW Health Low quality of evidence, weak/conditional recommendation)

For treatment of severe CDI in adult patients with ileus or patients with diverting ileostomy consider adding vancomycin rectal instillation.\textsuperscript{4,35} (UW Health Low quality of evidence, weak/conditional recommendation) The recommended dose is 500 mg in approximately 100 mL normal saline per rectum four times daily.\textsuperscript{4} Vancomycin rectal administration is NOT routinely recommended in neutropenic patients due to the risk of infection with manipulation of the rectum. (UW Health Very low quality of evidence, weak/conditional recommendation)

### Table 6. Adult Treatment Recommendations for First \textit{Clostridium difficile} Infection

<table>
<thead>
<tr>
<th>Infection Severity</th>
<th>Adult Treatment Recommendations for First Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Metronidazole 500 mg PO three times daily for 10-14 days.*&lt;br&gt;*Exceptions: Patients with an intolerance/allergy, who are pregnant, have a history or neuropathy, or cannot stop alcohol use during therapy should receive vancomycin.</td>
</tr>
<tr>
<td>Moderate to Severe</td>
<td>Vancomycin 125 mg PO four times daily for 10-14 days</td>
</tr>
<tr>
<td>Severe, complicated</td>
<td>Vancomycin 500 mg PO/NG four times daily PLUS Metronidazole 500 mg IV three times daily**&lt;br&gt;**Exceptions: Patients with severe refractory CDI and need to continue concomitant anti-infectives may be considered for Tigecycline 100 mg IV once then 50 mg IV every 12 hours as alternative.</td>
</tr>
<tr>
<td>Severe, ileus or diverting ileostomy</td>
<td>Consider adding vancomycin 500 mg rectally in approximately 100 mL normal saline four times daily</td>
</tr>
</tbody>
</table>

**Pediatric Patients:**<br>When possible, the first step in therapy is discontinuation of inciting antimicrobial agent(s) and may suffice in many instances.\textsuperscript{14,37} Therapy without diagnostic suspicion is usually not appropriate.\textsuperscript{4} (UW Health Low quality of evidence, weak/conditional recommendation) Treatment decisions should be based upon the severity of \textit{Clostridium difficile} symptoms (Table 7).\textsuperscript{14,25}

Metronidazole is recommended as first line therapy for initial infection in pediatric patients with mild to moderate disease (i.e., diarrhea, low grade fever, mild abdominal pain). The suggested dose for metronidazole is 30 mg/kg/day enterally in 4 divided doses, with a maximum daily dose of 2,000 mg/day.\textsuperscript{14,25} (UW Health High quality of evidence, weak/conditional recommendation)

Severe disease should be treated with enteral vancomycin or vancomycin by enema with suggested dosing of 40 mg/kg/day in 4 divided doses (max 2,000 mg/day). Vancomycin may also be given with or without intravenous metronidazole 30-40 mg/kg/day in 3 divided doses (max 1500 mg/day).\textsuperscript{14,25} (UW Health High quality of evidence, weak/conditional recommendation)
Table 7. Pediatric Treatment Recommendations for First *Clostridium difficile* Infection

<table>
<thead>
<tr>
<th>Infection Severity</th>
<th>Pediatric Symptoms and Criteria</th>
<th>Pediatric Treatment Recommendations for 1st Infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild to Moderate</td>
<td>Any of the following:</td>
<td>Metronidazole 30 mg/kg/day enteral in 4 divided doses (max 2,000 mg/day)</td>
</tr>
<tr>
<td></td>
<td>• Watery diarrhea</td>
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<tr>
<td></td>
<td>• Low grade fever</td>
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<tr>
<td></td>
<td>• Mild abdominal pain</td>
<td></td>
</tr>
<tr>
<td>Severe*</td>
<td>Any of the following:</td>
<td>Severe disease: Vancomycin 40 mg/kg/day enteral or rectal enema in 4 divided doses (max 2,000 mg/day) OR Severe, complicated disease: Vancomycin 40 mg/kg/day enteral or rectal enema in 4 divided doses (max 2,000 mg/day) PLUS Metronidazole 30-40 mg/kg/day in 3 divided doses (max 2,000 mg/day)</td>
</tr>
<tr>
<td></td>
<td>• Systemic toxicity</td>
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<tr>
<td></td>
<td>(e.g., high-grade fever,</td>
<td></td>
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<tr>
<td></td>
<td>rigors)</td>
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</tr>
<tr>
<td></td>
<td>• Hospitalization in the PICU</td>
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</tr>
<tr>
<td></td>
<td>• Pseudomembranous colitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Toxic megacolon</td>
<td></td>
</tr>
</tbody>
</table>

*Note: Neutropenic patients, or those having underlying gastrointestinal disease such as inflammatory bowel disease or Hirschsprung’s disease, are more likely to have severe disease.

Relapse Prevention in Adult Patients

Recurrence of CDI is highest in the 7-14 days after completion of initial therapy. The risk of recurrence also increases as the number of recurrences increase.4,7 Risk factors for recurrent CDI include:8,38

- All of the factors as outlined for initial infection (see above)
- Continued exposure to organisms (i.e., using a contaminated toothbrush, incorrectly cleaning home environment or clothing, failing to perform appropriate hand hygiene)
- Relapsing CDI from endogenous source (i.e. spores in GI tract)
- Poor host IgG antibody response to toxin A

Probiotics have not been shown to be effective as adjunctive therapy for treatment or in the prevention of relapse or recurrent CDI. In addition, there is a risk of developing a bloodstream infection in patients who are heavily immunosuppressed.17,39,40 (UW Health Class Very low quality of evidence, weak/conditional recommendation) For adult patients who are not immunocompromised, it is reasonable to consider probiotics for the prevention of the index of primary infection given the use of probiotics in these patients is relatively harmless. Use of probiotics in secondary and subsequent relapses is not recommended at this time.

For adult patients with a history of CDI in the last 90 days and who are receiving antibiotics for a non-C. Difficile infection, prophylactic low dose vancomycin (vancomycin 125 mg orally twice daily) or low dose metronidazole (500 mg orally once or twice daily) may be reasonable for CDI relapse prevention. Continuation of low dose vancomycin or low dose metronidazole may also be considered in a patient who has a history of CDI, is being treated for a non-C. Diff infection and who subsequently develops a new CDI while receiving the inciting antibiotic.

The following case examples depict scenarios in which low dose prophylaxis vancomycin may be considered.

**Case Example #1:** A 65 year old male who is undergoing chemotherapy for colon cancer was treated for C. Diff infection in January 2016. Patient is admitted to hospital in February 2017 for...
Pneumonia. Patient receives antibiotics for pneumonia and is also given prophylactic low-dose vancomycin. Patient is instructed to take low-dose vancomycin for duration of pneumonia antibiotic course and to continue 5 days thereafter.

**Case Example #2:** A 60 year old female with diabetes is being treated for endocarditis. While on antibiotic therapy for endocarditis infection, patient gets a CDI. Patient then continues her antibiotics for endocarditis, receives therapeutic dosing for vancomycin to treat CDI for 14 days and then is instructed to take low-dose vancomycin to prevent CDI relapse for the duration of endocarditis antibiotic regimen and continue the low-dose vancomycin for 5 days thereafter.

**Case Example #3:** A 40 year old male patient is receiving antibiotics for a complicated intra-abdominal infection (cIAI). Antibiotics are planned for 14 days duration. On day 3 of therapy, patient develops a *Clostridium difficile* infection. The patient receives 11 days of concomitant cIAI and *C diff* therapy. Patient should receive treatment dosing (vancomycin orally 4 times a day) for 7 days following completion of cIAI antibiotic therapy.

It is recommended that for patients who develop a CDI while on a concomitant broad-spectrum antibiotic, the patient should complete at least 10-14 days of *Clostridium difficile* treatment and receive at least 7 days of CDI treatment therapy without concomitant broad-spectrum antibiotic therapy. *(UW Health Class Low quality of evidence, weak/conditional recommendation)*

For patients who are treated with low-dose vancomycin prophylaxis, it is recommended that the patient continue low-dose CDI prophylaxis for 5-7 days following discontinuation of primary antibiotic (as described in case example #1.)

In stable adult patients receiving vancomycin, conversion to metronidazole may be considered to reduce the risk of emergence of vancomycin-resistant enterococci and prevent development of metronidazole-associated neuropathy. *(UW Health Moderate quality of evidence, weak/conditional recommendation)* Due to consideration for medication cost, metronidazole may be considered when the discussion of neuropathy risk is completed.

If long-term therapy (usually greater than 14 days) low-dose therapy is being considered in adults, the preferred agent is oral vancomycin, in light of the risk of neurotoxicity. This is because the use of metronidazole and that fidaxomicin has no data to support prophylactic use. *(UW Health Very low quality of evidence, weak/conditional recommendation)*

### Antimicrobial Treatment of Relapse/Recurrent Infection

**Adult Patients:**

Adult patients relapsing after primary treatment with metronidazole should be given a trial of vancomycin before considering fidaxomicin. *(UW Health Moderate quality of evidence, weak/conditional recommendation)*

Sequential therapy with vancomycin followed by rifaximin may be effective for the treatment of recurrent CDI in adults. *(UW Health Low quality of evidence, weak/conditional recommendation)* Vancomycin pulse after taper is: vancomycin 125 to 500 mg PO every 3 days for up to 3 weeks. *(UW Health Low quality of evidence, weak/conditional recommendation)* If vancomycin is to be used for subsequent recurrences, consider use of vancomycin followed by rifaximin 200 mg/day PO 2 times daily for 14 days. *(UW Health Low quality of evidence, weak/conditional recommendation)*
There is limited evidence to support use of G.I. lavage (e.g., GOLYTELY solution) as an adjunct to agents routinely used to treat chronic, relapsing \textit{Clostridium difficile} infection. However, G.I. lavage may be useful for clearing \textit{Clostridium difficile} organisms, spores, and associated toxins from the intestine of patients with relapsing infections.\(^\text{45}\) (\textit{UW Health Low quality of evidence, weak/conditional recommendation}) Use of this product associated with surgical temporizing ileostomy may be considered.

For adult patients with BI/NAP1/027, there was no clinical difference in benefit between vancomycin and fidaxomicin.\(^\text{46}\) Therefore, vancomycin is the preferred agent and fidaxomicin should be used for non-NAP1 strains only. (\textit{UW Health Moderate quality of evidence, strong recommendation}).

\textbf{Table 8. Adult Treatment Recommendations for Relapse \textit{Clostridium difficile} Infection}

<table>
<thead>
<tr>
<th>Relapse</th>
<th>Adult Treatment Recommendations for Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Recurrence</td>
<td>Vancomycin 125 mg PO four times daily for 10-14 days*</td>
</tr>
<tr>
<td></td>
<td>*\textit{Exception:} For adult patients with BI/NAP1/027, there was no clinical difference in benefit between vancomycin and fidaxomicin. Therefore, vancomycin is the preferred agent and fidaxomicin should be used for non-NAP1 strains only.</td>
</tr>
<tr>
<td>Second Recurrence or Further Recurrence</td>
<td>Vancomycin Taper: Vancomycin 125 mg PO twice daily for 7 days, then 125 mg PO daily for 7 days, then 125 mg PO every 2 days for 7 days, then 125 mg PO every 3 days for 7 days then cease treatment(^4,4,4) (\textit{UW Health Class IIb, Level of Evidence C})</td>
</tr>
<tr>
<td></td>
<td>Vancomycin pulse after taper: Vancomycin 125-500 mg PO every 3 days for up to 3 weeks</td>
</tr>
<tr>
<td></td>
<td>Consider consultation by Gastroenterology or Infectious Disease and Fidaxomicin 200 mg PO twice daily for a maximum of 10 days</td>
</tr>
<tr>
<td></td>
<td>Consider Vancomycin 125 mg PO four times daily for 10-15 days followed by Rifaximin 200 mg/day PO twice daily for 14 days</td>
</tr>
</tbody>
</table>

\textbf{Fidaxomicin}\(^\text{46}\)

Adult patients with relapse or recurrence may be considered candidates for fidaxomicin under the guidance of Gastroenterology or Infectious Disease. The ability for a patient to pay for fidaxomicin as an outpatient should be assessed prior to initiating inpatient fidaxomicin treatment due to cost. The recommended dose of fidaxomicin is:

- Fidaxomicin 200 mg orally twice daily for a maximum of 10 days. (\textit{UW Health High quality of evidence, strong recommendation})
- Treatment should NOT be extended beyond 10 days.

Fidaxomicin is not FDA-approved in children, and is typically reserved for adult patients with the following conditions:

- Documented (PCR positive or colonoscopy proven) recurrent CDI requiring hospitalization. (\textit{UW Health Moderate quality of evidence, weak/conditional recommendation})
- Relapse during current hospitalization. (\textit{UW Health Moderate quality of evidence, weak/conditional recommendation})
- Outpatient with relapse(s) of disease not requiring hospitalization (\textit{UW Health Class Low quality of evidence, weak/conditional recommendation})
• Patients with documented low levels of neutralizing antibodies to Clostridium difficile (since this test is not available with rapid turnaround time, use under this indication would likely take 10-14 days). The role of both IVIG infusion and fidaxomicin is uncertain at this time. (Low quality of evidence, weak/conditional recommendation)

• Patients who have relapsed within 4 weeks of treatment of fidaxomicin are not candidates for repeated courses. (UW Health Low quality of evidence, weak/conditional recommendation)

• Patients who have relapsed within more than 4 weeks of treatment of fidaxomicin, received antibiotics with these 4 weeks, and have recurrent CDI may be considered for repeated courses of fidaxomicin. (UW Health Low quality of evidence, weak/conditional recommendation)

• Fidaxomicin has been shown to be equally efficacious as vancomycin for primary treatment, and may result in less frequent relapse. However, since patients were only followed for 30 days, the prevention was not fully determined. Fidaxomicin may be prescribed for first episode CDI under unusual circumstances with the approval of Infectious Disease or Gastroenterology.

Appendix D outlines the treatment pathway for adult patients with CDI.

Pediatric Patients:
• In pediatric patients with first recurrence, metronidazole is recommended. (UW Health High quality of evidence, weak/conditional recommendation) Metronidazole should be administered 30 mg/kg/day enterally in 4 divided doses with a maximum dose of 2,000 mg/day.14

• For subsequent recurrences of CDI in pediatric patients a vancomycin taper may be considered, especially under consultation by Pediatric Infectious Disease or Pediatric Gastroenterology. The pediatric vancomycin taper can be: vancomycin 10 mg/kg 4 times daily for 10-14 days, then vancomycin 10 mg/kg 2 times daily for 7 days, then 10 mg/kg once daily for 7 days, then 10 mg/kg every 2-3 days for 2-8 weeks (max = 125 mg/dose).47 (UW Low quality of evidence, weak/conditional recommendation)

• Studies are limited in children for the use of rifaximin after a vancomycin taper for subsequent recurrences and is not recommended.14

Appendix E outlines the treatment pathway for pediatric patients with CDI.

Non-Antimicrobial Interventions for Recurrent Infection

Intravenous Immune Globulin (IVIG)
Randomized control trials have demonstrated conflicting results and conflicting evidence of benefit for the use of intravenous immune globulin (IVIG) treatment for CDI. IVIG failed to decrease the risk of colectomy or mortality in a study of pair matched adults with severe CDI, however no testing of IgG levels was performed.48 Clinical studies did NOT measure Clostridium difficile neutralizing antibody titers in the IVIG preparations. Therefore, not all patients with low titers may benefit from IVIG.

Use of this therapy should be indicated by Infectious Disease and Gastroenterology, Pediatric Infectious Disease and Pediatric Gastroenterology attending physicians, as outlined within the
Bezlotoxumab
Bezlotoxumab is a monoclonal antibody that binds and neutralizes C diff toxins A and B respectively. In clinical studies, bezlotoxumab has demonstrated efficacy in adults receiving antibiotic therapy and bezlotoxumab for CDI versus antibiotic therapy alone for the prevention of CDI recurrence. Thus, bezlotoxumab is not indicated for treatment of CDI and only for prevention of CDI recurrence.

It is recommended to adhere to the following when utilizing bezlotoxumab in patients at UW Health for CDI recurrence prevention: (UW Health Low quality of evidence, weak/conditional recommendation)

- Bezlotoxumab should be used in conjunction with a C. difficile treatment (i.e., vancomycin or metronidazole).
- Bezlotoxumab should be used with Infectious Diseases approval (through ID consult).
- It is reserved for patients with a new C. difficile PCR-confirmed diagnosis AND failure of fecal microbiota transplant (FMT) on two occurrences with confirmation that fecal microbiota therapy (FMT) was performed according to administration protocol and not by colonoscopy, or
- FMT failure by colonoscopy on one occurrence, or
- The patient has one of the following contraindications to receiving FMT:
  - is profoundly immunosuppressed
  - is CMV-negative transplant patient
  - is admitted to ICU level of care with C. difficile-related sepsis.

Additionally, it is recommended that bezlotoxumab administration occur no sooner than 72 hours after initiation of C. difficile treatment regimen (i.e., vancomycin or metronidazole) to maximize effect of bezlotoxumab in preventing recurrence. For additional information on bezlotoxumab use at UW Health, refer to Lexicomp internally.

Fecal microbiota therapy (FMT)
Due to the growing epidemic of CDI, alternative therapies for recurrent CDI are emerging including fecal microbiota therapy. FMT is the delivery of stool from a healthy donor into the colon of a patient with recurrent CDI, via the upper gastrointestinal route (nasoduodenal infusion), via the colon by enema, or oral administration with frozen fecal microbiota capsule. Fecal bacteriotherapy has emerged as an effective and safe option for patients with relapsing CDI, refractory to other therapies.

Fecal microbiota therapy may be considered in pediatric (UW Health Class Moderate quality of evidence, weak/conditional recommendation) or adult patients (UW Health Low quality of evidence, weak/conditional recommendation) who meet the following eligibility criteria. All FMT candidates should be assessed by an Infectious Disease or Pediatric Infectious Disease provider. All cases should also be coordinated and managed by a specialist (i.e., Infectious Disease and Gastroenterology, Pediatric Infectious Disease or Pediatric Gastroenterology attending physicians).
Eligibility Criteria for FMT:

- Patients must have documented *Clostridium difficile* infection with stool testing for *Clostridium difficile* and documented relapse of this infection despite appropriate treatment (i.e. 3rd episode of CDI). Relapsing CDI is defined by patients who have received an initial 10-14 day course of oral metronidazole or oral vancomycin (first episode); followed by one recurrence unresponsive to an extended tapering regimen (usually 4 to 8 weeks) of vancomycin and/or 10-day course of fidaxomicin.
- Patients should not be considered eligible for FMT if currently completing a course of anti-infectives (other than targeted CDI therapy with oral vancomycin or oral metronidazole or oral fidaxomicin) for other infectious conditions.
- Patients should generally be clinically stable in the outpatient setting to qualify for the procedure.

**UW Health Implementation**

**Potential Benefits:**
- Appropriate diagnosis, treatment and prevention of CDI in pediatric and adult patients
- Decrease in overall hospital acquired infections rate

**Potential Harms:**
- Side effects and adverse events associated with use of medical and pharmacotherapy treatments

**Pertinent UW Health Policies & Procedures**

1. UWHC Policy 11.14- Collection of Stool Specimens for Laboratory Examination
2. UWHC Policy 13.07- Standard Precautions and Transmission-based Precautions (Isolation) for Inpatient Settings
3. UWHC Policy 13.08- Hand Hygiene
4. UWHC Policy 13.28- Precautions & Transmission Based Precautions
5. UWHC Policy 13.29- Isolation Practice for Multi-Drug Resistant Organisms
6. UWHC Policy 6.1.9- Restricted Primarily Ambulatory Administered Medications in Hospitalized Patients
7. UWHC Policy 6.1.5- Formulary Restricted Clinic Administered Medication Pharmacy Department Review and Use of Non-UW Health Supplied Medications Administered in Clinics
8. Patient Header Infectious Flags- Inpatient and Ambulatory Settings within CSC
9. Infection Prevention and Control Program
10. Cleaning and Disinfection Instructions

**Patient Resources**

1. HFFY #7219- What You Need to Know About Clostridium difficile Infection
2. HFFY #7575- Fecal Bacteriotherapy
3. HFFY #7585- Getting Ready for a Fecal Bacteriotherapy Procedure
4. HFFY #7602- What You Need To Know as a Stool Provider
5. Healthwise: C Diff Colitis
6. Healthwise: C dif colitis: Pediatric
7. Health Information- Clostridium difficile Colitis
8. Kids Health- Stool Test: C. Difficile Toxin
Guideline Metrics
1. UW Hospital Clinical definition- Hospital Acquired *Clostridium difficile* Infection
   (Measured per rate of hospital onset *Clostridium difficile* infection rate per 10,000 patient days.)
2. National Health Safety Network (NHSN)- LabID definition (Measured per amount of observed to expected ratio of infections, and reported as Standardized Infection Ratio (SIR).)

Implementation Plan/Clinical Tools
1. Guideline will be posted on uConnect in a dedicated location for Clinical Practice Guidelines.
2. Release of the guideline will be advertised in the Physician/APP Briefing newsletter.
3. Content and hyperlinks within clinical tools, documents, or Health Link related to the guideline recommendations (such as the following) will be reviewed for consistency and modified as appropriate.

Companion Documents
1. UW Health Intravenous Immunoglobulin (IVIG) - Pediatric/Adult - Inpatient/Ambulatory Clinical Practice Guideline
2. Recommended Empiric Regimens to Reduce Fluoroquinolone Exposure – Adult - Inpatient

Best Practice Alerts (BPA)
C Diff Positive Result- Last 48 Hours Not On Tx [3000900]

Delegation Protocols
Clostridium difficile – Adult – Inpatient [96]
Clostridium difficile Testing – Adult – Infectious Disease Clinic [107]

Order Sets & Smart Sets
IP – Clostridium difficile Treatment – Adult – Supplemental [5316]

Disclaimer
Clinical practice guidelines assist clinicians by providing a framework for the evaluation and treatment of patients. This guideline outlines the preferred approach for most patients. It is not intended to replace a clinician’s judgment or to establish a protocol for all patients. It is understood that some patients will not fit the clinical condition contemplated by a guideline and that a guideline will rarely establish the only appropriate approach to a problem.
Appendix A. Evidence Grading Scheme(s)

Figure 1. GRADE Methodology adapted by UW Health

<table>
<thead>
<tr>
<th>Step 1: Identify Type of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Randomized controlled trial (HIGH)</td>
</tr>
<tr>
<td>• Observational study (LOW)</td>
</tr>
<tr>
<td>• Expert consensus (VERY LOW)</td>
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<table>
<thead>
<tr>
<th>Step 2: Consider Downgrade or Upgrade</th>
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<tbody>
<tr>
<td>• Risk of bias</td>
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<tr>
<td>• Inconsistency</td>
</tr>
<tr>
<td>• Indirectness</td>
</tr>
<tr>
<td>• Imprecision</td>
</tr>
<tr>
<td>• Publication bias</td>
</tr>
<tr>
<td>• Large consistent effect</td>
</tr>
<tr>
<td>• Dose response</td>
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<tr>
<td>• Confounders only reducing size of effect</td>
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<table>
<thead>
<tr>
<th>Step 3: Assign Quality of Evidence</th>
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<tbody>
<tr>
<td>• High</td>
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<tr>
<td>• Moderate</td>
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<tr>
<td>• Low</td>
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<tr>
<td>• Very Low</td>
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<table>
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<tr>
<th>Step 4: Consider External Factors</th>
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<tbody>
<tr>
<td>• Balance of benefits/harms</td>
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<tr>
<td>• Patient preferences</td>
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<td>• Cost-effectiveness</td>
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<tr>
<th>Step 5: Assign Strength of Recommendation</th>
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</thead>
<tbody>
<tr>
<td>• Strong</td>
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<tr>
<td>• Weak/Conditional</td>
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GRADE Ranking of Evidence

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
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<tbody>
<tr>
<td>High</td>
<td>We are confident that the effect in the study reflects the actual effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>We are quite confident that the effect in the study is close to the true effect, but it is also possible it is substantially different.</td>
</tr>
<tr>
<td>Low</td>
<td>The true effect may differ significantly from the estimate.</td>
</tr>
<tr>
<td>Very Low</td>
<td>The true effect is likely to be substantially different from the estimated effect.</td>
</tr>
</tbody>
</table>

GRADE Ratings for Recommendations For or Against Practice

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>The net benefit of the treatment is clear, patient values and circumstances are unlikely to affect the decision.</td>
</tr>
<tr>
<td>Weak/conditional</td>
<td>Recommendation may be conditional upon patient values and preferences, the resources available, or the setting in which the intervention will be implemented.</td>
</tr>
</tbody>
</table>
**Does the patient have LESS than 3 unexpected liquid/loose stools beyond their known or established baseline within the past 24 hours?**

- **Yes**: ORDER the Test
  - Place on enhanced contact isolation.

- **No**: Do NOT Test

**NOTE**: It is important to consider whether the diarrhea could be a result of recent or overuse of medications or therapies associated with diarrhea including: stool softeners, laxatives, enemas, bowel preps, etc. Further, more than 55% of positive CDI tests are in clinic or on admission to UW Health suggesting CDI is more common in the community than traditionally believed. Do not test asymptomatic patients but thoroughly evaluate GI symptoms on admission and consider CDI early on as a potential causative pathogen in symptomatic patients.

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### In the FIRST 48 hours of admission

**Does the patient complain of or have any unexplained loose stools prior to admission?**

- **Yes**: ORDER the Test
  - Place on enhanced contact isolation.

- **No**: Do NOT Test

---

### AFTER 48 hours following admission

**Does the patient have LESS than 3 unexpected liquid/loose stools beyond their known or established baseline within the past 24 hours?**

- **Yes**: Do NOT Test

- **No**: Can the diarrhea be the result of the patient currently or recently (past 48 hours) being introduced to a new medication or therapy associated with diarrhea such as any of the following: stool softeners, laxatives, enemas, bowel preps, lactulose, tube feeds, or IV contrast?

- **Yes**: Do NOT Test
  - Consider altering therapy. Re-evaluate 24-48 hours after suspending affecting agent. If agent cannot be suspended, exercise clinical judgment and if appropriate proceed to the next ("No") step below.

- **No**: Place patient on enhanced contact isolation. Maintain isolation until diarrhea resolves or an alternative, non-infectious cause of diarrhea has been determined.

**Is the patient low-risk (i.e. afebrile, no elevated WBC, no abdominal pain, no recent antibiotic use, not an IBD patient nor any recent/frequent healthcare encounters)?**

- **Yes**: Do NOT Test
  - Pre-test probability is low. Consider alternative causes of diarrhea.

- **No**: ORDER the Test
  - Continue enhanced contact isolation. Do NOT test for cure.

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**DISCLAIMER**: Laboratory limit: 1 Test every 7 days.

Complex patients, including obstruction cases, may not readily conform to this algorithm. As always, sound clinical judgement should be applied in conjunction with the information provided here. In some instances, expert opinion should be solicited.
Pediatric Inpatient PCR Testing Algorithm for Clostridium difficile infection (CDI)

Testing should NOT be completed in patients younger than 3 years of age.*

In the FIRST 48 hours of admission (patient age > 3 years)*

Does the patient complain of or have any unexplained loose stools prior to admission? This includes pediatric patients with known inflammatory bowel disease experiencing diarrhea.

Yes → Place on enhanced contact isolation. Strongly consider testing.

No → Do NOT Test

NOTE: During 18 recent months at UW 79% of the 47 pediatric patients with CDI were identified in clinic, the emergency department or within the first 48 hours of admission. In a recent study, 23% of community onset pediatric cases had no risk factors for CDI (5). Do not test asymptomatic patients but thoroughly evaluate GI symptoms on admission and consider CDI early on as a potential causative pathogen in symptomatic patients.

AFTER 48 hours following admission (patient age > 3 years)*

Does the patient have LESS than 3 unexpected liquid/loose stools beyond their known or established baseline within the past 24 hours?*1, 2, 4

Yes → Do NOT Test

No → Can the diarrhea be the result of the patient currently or recently (past 48 hours) being introduced to a new medication or therapy associated with diarrhea such as any of the following: stool softeners, laxatives, enemas, bowel preps, lactulose, tube feeds, narcotic withdrawal or oral contrast?*5

Yes → Place on enhanced contact isolation. Maintain isolation until diarrhea resolves or an alternative, non-infectious cause of diarrhea has been determined.

No → Did the diarrhea resolve/improve on its own prior to testing? Has the order been placed and the specimen unable to be collected/obtained for more than 8 hours?

Yes → Consider altering therapy. Re-evaluate 24+ hours after suspending affecting agent—especially purgatives. If agent cannot be suspended, exercise clinical judgment and if appropriate proceed to the next (“No”) step below.

No → ORDER the Test

Continue enhanced contact isolation. Do not test for cure.

Ordering should be applied in conjunction with the information provided here. In some instances, expert opinion should be solicited.

* Because of the high prevalence of asymptomatic carriage of toxigenic CDI in infants and young children up to 3 years of age, routine testing for CDI is not recommended. If completed it should be conducted with testing for alternative causes of diarrhea, such as norovirus and rotavirus. CDI should not be assumed to be causative of diarrhea unless there is no other plausible explanation.

References (7-11 peds specific)
5. Brazier JS. J Antimicrob Chemother1998; 41

Guideline: Clostridium difficile – Pediatric/Adult – Inpatient/Ambulatory/Emergency Department

DISCLAIMER:
Laboratory limit: 1 Test every 7 days.

Complex patients, including obstruction cases and patients with inflammatory bowel disease may not readily conform to this algorithm. As always, sound clinical judgement should be applied in conjunction with the information provided here. In some instances, expert opinion should be solicited.
**Consider alternative to metronidazole if:**
- Intolerant/allergy to metronidazole
- Pregnant/breastfeeding
- History of neuropathy
- Current alcohol use that can’t be stopped for therapy

**Moderate to Severe CDI if patient:**
*Immunocompromised (e.g., HIV, chronic steroid use, chemotherapy), on hemodialysis, or meet some of following criteria:
- Age > 60 years
- Albumin < 2.5mg/dL
- WBC ≥ 15 000 cells/mm³
- Abdominal tenderness
- Elevated serum creatinine 1.5x premorbid level

**Second or Further Recurrence CDI Treatment**
Vancomycin Taper: Vancomycin 125 mg PO twice daily for 7 days, then 125 mg PO daily for 7 days, then 125 mg PO every 2 days for 7 days, then 125 mg PO every 3 days for 7 days
Vancomycin pulse after taper: Vancomycin 125-500 mg PO every 3 days for up to 3 weeks
Consider consultation by Gastroenterology or Infectious Disease and Fidaxomicin 200 mg PO twice daily for a maximum of 10 days
Consider Vancomycin 125 mg PO four times daily for 10-15 days followed by Rifaximin 200 mg/day PO twice daily for 14 days

**Relapse prevention/Management of Recurrence**
Low dose metronidazole or low dose vancomycin may be considered in patients who:
- have a history of CDI and develop a new CDI while taking an antibiotic for a non-CDI infection.
- are being treated with antibiotic for a non-CDI infection within 90 days of a CDI
*Suggested dosing:* metronidazole 500 mg PO once or twice daily OR vancomycin 125 mg BID. Recommended: Low dose therapy for duration of non-CDI antibiotic therapy and for 5-7 days thereafter

**Infection Control at Home counseling points:**
- Clean home with bleach
- Wash hands with soap and water often
- Designate bathroom for infected household member
- Launder linens/clothes with bleach in warm/hot water

*Remember! Enhanced contact precautions if patient is symptomatic and there’s CDI flag in chart! or high suspicion of relapse within 90 days of last positive test*

Reference: *Clostridium difficile – Pediatric/Adult – Inpatient/Ambulatory/Emergency Department*
**Clostridium difficile Infection (CDI) Pediatric Treatment Algorithm**

**Consider alternative to metronidazole if:**
- Intolerant/allergic to metronidazole
- Pregnant/breastfeeding
- History of neuropathy
- Cannot stop alcohol use during treatment

**Pediatric CDI disease categories**

- **Mild to Moderate disease**: watery diarrhea without systemic toxicity (mild abdominal pain and low-grade fever may be present)

- **Severe disease**: Evidence of systemic toxicity (e.g., high grade fever, rigors); may be severe, complicated by hypotension, shock, ileus; pseudomembranous colitis, toxic megacolon

  Note: Patients with underlying gastrointestinal disease such as inflammatory bowel disease or Hirschsprung’s disease more likely to have severe disease

**Second or Further Recurrence Treatment**

Vancomycin taper may be considered, especially under consultation with Pediatric Infectious Disease and/or Pediatric Gastroenterology.

Vancomycin Taper:
vancomycin 10 mg/kg 4 times daily for 10-14 days, then vancomycin 10 mg/kg 2 times daily for 7 days, then vancomycin 10 mg/kg once daily for 7 days, then vancomycin 10 mg/kg every 2-3 days for 2-8 weeks (max = 125 mg/dose).

**Fecal microbiota therapy criteria:**
- Documented C Diff infection with stool test and documented relapse despite appropriate treatment (i.e., 3rd episode of CDI)
- NOT currently completing a course of anti-infectives (other than targeted CDI therapy with oral vancomycin or oral metronidazole) for other infectious conditions
- Clinically stable in ambulatory setting

**Infection Control at Home counseling points:**
- Clean home with bleach
- Wash hands with soap and water often
- Designate bathroom for infected household member
- Launder linens/clothes with bleach in warm/hot water

**WHEN TO TEST PEDIATRIC PATIENTS**

**Patients ≥ 3 years:**
Test if patient with diarrhea (≥ 3 unformed stools from baseline bm/day in the previous 24 hours), with risk factors and no alternative etiology for diarrhea

**Patients < 36 months:**
- Consider alternative etiologies for diarrhea (e.g., antibiotic associated diarrhea) before testing given high false-positive rate in younger population.
- **TEST only** if patient has appropriate clinical findings (e.g., 3 unformed stools from baseline bm/day in the previous 24 hours) with additional risk factors or, Patient has appropriate clinical findings AND concern of outbreak situation
- **TEST if patient < 1 year,** has appropriate clinical findings and in the presence Hirschsprung's disease or other severe motility disorders

**DO NOT TEST...**
- If patient actively taking laxatives
- Patient still taking oral vancomycin
- Patient treated with CDI without complete resolution of symptoms for possible relapse
- If patient has test result in past 7 days
- Patient near end of treatment (i.e., testing for cure)

**C. Diff Infection**

≥ 3 loose/liquid stools in previous 24 hours with risk factors may also present low grade fever, mild abdominal pain

**First occurrence?**

YES  →  **Does pt have severe disease?**

YES →  **Discontinue inciting antibiotic, if possible**

NO →  **First recurrence?**

YES →  **Consider Peds Infectious Disease or Peds Gastroenterology consult**

NO →  **Refer to treatment for second or further recurrence**

**Treat with vancomycin 30 mg/kg/day enterally in 4 divided doses (max 2000 mg/day)**

**FMT?**

YES →  **Care and management coordinated by Peds Infectious Disease or Peds Gastroenterology**

**Is patient candidate for FMT?**

YES →  **Treat as clinically indicated**

NO →  **Treat with metronidazole 30 mg/kg/day enterally in 4 divided doses (max 2000 mg/day)**

**If treating, is pt intolerant/allergy metronidazole or needs alternative?**

YES →  **Treat with vancomycin 10 mg/kg/dose 4 times a day for 10-14 days (max 125 mg/dose)**

NO →  **Vancomycin taper**

Treat with vancomycin 40 mg/kg/day enteral or rectal enema in 4 divided doses (max 2000 mg/day)

**OR**

Severe, complicated disease:
Vancomycin 40 mg/kg/day enteral or rectal enema in 4 divided doses (max dose 2000 mg/day) PLUS Metronidazole 30-40 mg/kg/day in 3 divided doses (max 2000 mg/day)
References


