Johns Hopkins All Children’s Hospital

Clostridioides difficile Clinical Pathway

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This pathway is intended as a guide for physicians, physician assistants, nurse practitioners and other healthcare providers. It should be adapted to the care of specific patient based on the patient’s individualized circumstances and the practitioner’s professional judgment.
Rationale

This clinical pathway was developed by a consensus group of JHACH Infectious Diseases physicians and pharmacists, hospitalists, intensivists, emergency physicians and advanced practice providers, gastroenterologists, and oncologists to standardize the diagnostic testing and management of children who present with suspected *Clostridioides difficile* infection (CDI). This clinical pathway does not address infection prevention activities related to the isolation of CDI patients and necessary environmental procedures. This clinical pathway does not address the evaluation or management of other causes of diarrhea due to infectious agents or otherwise.

This clinical pathway addresses the following clinical questions and problems:

- In which patients should CDI be considered?
- In which patients is *C. difficile* testing appropriate?
- When may additional testing be appropriate for patients with CDI?
- What treatment options are available for patients with CDI?
- When is inpatient consultation or outpatient referral to Infectious Diseases appropriate for CDI?
- What clinical scenarios warrant inpatient management, either floor or ICU status, for CDI?
- When is surgical consultation appropriate for CDI?

Background

*Clostridioides difficile* (formerly *Clostridium difficile*) is a spore-forming, toxin-producing, Gram-positive bacillus, which has become the main causative agent of antibiotic-associated and hospital-associated infective diarrhea in children and in adults. *C. difficile* infection (CDI) can present with symptoms ranging from mild diarrhea to pseudomembranous colitis and toxic megacolon. Though classically considered a hospital-associated infection, recent data suggest that community-acquired infection may be more frequent.

The most common modifiable risk factor for CDI remains antibiotic exposure. Most antibiotics have had reported associations with the development of CDI, but this association is seen most frequently with penicillins, macrolides, clindamycin, cephalosporins, and fluoroquinolones. Other risk factors include hospitalization, underlying chronic medical conditions, such as malignancy, solid organ or hematopoietic stem cell transplant, renal insufficiency, Hirschsprung disease, inflammatory bowel disease, gastrostomy or jejunostomy tubes, and possibly acid-suppressive therapy.
**Clostridioides difficile** colonization, *i.e.*, detectable presence of organism without clinical symptoms, complicates the appropriate diagnosis of CDI. Colonization is a particularly common diagnostic dilemma in the pediatric patient population, as colonization rates vary widely from approximately 40% colonization among infants to less than 3% colonization among school-aged children. Colonization may occur with either toxigenic or non-toxigenic strains, and the colonizing strain may change throughout a person’s lifetime. A patient may have asymptomatic colonization even with toxigenic strains. As many diagnostic tests aim to detect toxins or toxigenic strains, colonized patients are at risk of unnecessary treatment for CDI. Specific clinical criteria are necessary to determine which pediatric patients require diagnostic testing and eventual treatment.

The Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA) recently (2017) published new guideline updates particularly for the diagnosis and care of adult patients with CDI. Guidance for the diagnosis and management of pediatric patients was also included in the IDSA/SHEA guideline; however, limited pediatric data are available to support guideline changes similar to those supported by the adult literature. This JHACH clinical pathway aims to address those differences and to provide local guidance. Additionally, The Children’s Oncology Group (COG), recently (February 2019) endorsed the “Guideline for the Management of Clostridium Difficile Infection in Children and Adolescents with Cancer and Pediatric Hematopoietic Stem-Cell Transplantation Recipients” developed by the Pediatric Oncology Group of Ontario (POGO). This JHACH clinical pathway also incorporates recommendations outlined in these clinical pathway.

**Diagnosis**

**Diagnostic Testing by Clinical Presentation and Risk Factors**

Patients with *C. difficile* infection (CDI) may present with a spectrum of severity, ranging from mild to severe diarrhea. Some patients may present with mucus or blood within their stool. Patients are at increased risk for CDI if they have a history of the following: recent antibiotic therapy, antineoplastic therapy, inflammatory bowel disease (such as Crohn disease, ulcerative colitis, or Hirschsprung disease), repeated enema use, gastrointestinal stimulants use, renal insufficiency, or recent gastrointestinal surgery or endoscopy. Infection with *C. difficile* should also be considered in patients with acute diarrhea that remains otherwise unexplained. Infection may also be considered in patients with a history of solid organ or hematopoietic stem cell transplantation. There is an increased association in patient with gastrostomy or jejunostomy tubes. Some data suggest an association with proton pump inhibitor therapy. These symptoms and risks are summarized in **Table 1**. These factors should be considered before proceeding with evaluation as per **Figure 1**.

**Diagnostic Testing by Age Group**

As the pediatric population has higher *C. difficile* colonization rates as compared with the adult population, the diagnosis of CDI is challenging. Diagnosis among patients under 2 years of age
is particularly challenging, as *C. difficile* colonization rates range from more than 40% among infants less than 1 year old to approximately 10-20% among those in the second year of life. Due to the high rate of *C. difficile* colonization and the high rate of other infectious or dietary etiologies of diarrhea, other etiologies for diarrhea should be excluded prior to consideration of CDI in children less than 2 years of age. If CDI remains a concern in this age group, consultation with Infectious Diseases is required, either by authorization of testing via conversation or by formal consultation. Authorization by an Infectious Diseases attending will be required to order *C. difficile* testing; tests without such authorization will be canceled by Microbiology. Diagnostic tests alone are not sufficient to differentiate between colonization and infection; therefore, a patient must meet select clinical criteria before the diagnosis of CDI should be considered and before testing should be performed. Patients greater than 2 years of age have colonization rates similar to that of adults and, therefore, may be tested much like adults with regard to their symptomatology.

**Diagnostic Testing by Stool Characteristics**

The primary consideration for patients with suspected CDI should be stool frequency and character. Patients should have a history of diarrhea, defined as 3 or more unformed stools within a 24-hour period. Unformed stools can be defined as stools that take the shape of their container; this can be further categorized by the Bristol Stool Chart, stool types 5 through 7 ([Figure 2](#)). Some patients may have decreased or no stool output at the time of presentation due to ileus or toxic megacolon; however, these patients will typically have a history of diarrhea prior to the development of ileus. Diagnostic testing should not be performed on formed stool (Bristol Stool Chart, stool types 1 through 4; [Figure 2](#)). The Microbiology Lab will reject formed stool specimens received for *C. difficile* testing.

**Other Conditions That May Influence Diagnosis**

Chronic medical conditions, medications, and certain diets can lead to persistent diarrhea. Those with chronic medical conditions may be at particular risk for CDI given their exposure to medical care facilities or risk-associated therapies. However, these underlying medical conditions and therapies should be considered prior to consideration of CDI. Those with inflammatory bowel diseases should be assessed for adherence to or for optimization of their medications. Those with enteral tube feedings should be assessed for any adjustment that may improve stool output. Patients receiving intensive chemotherapy regimens known to induce diarrhea should be monitored, but CDI should only be considered if symptoms are prolonged or more severe than anticipated. Patients receiving laxatives should have these medications discontinued and their stool monitored for improvement prior to consideration of possible CDI.

**Ancillary Testing and Clinical Findings for Disease Classification**

Patients with suspected CDI should be stratified by disease severity, as this affects patient disposition and therapeutic options. Asymptomatic patients should not be tested. Patients with mild symptoms would be considered as having non-severe disease and could potentially be
treated as an outpatient if clinical status warrants. Patients with fever, ill appearance, intolerance of oral intake or medication, emesis, moderate/severe dehydration, abdominal pain, symptoms of ileus or toxic megacolon, or signs/symptoms of sepsis should be considered for possible severe or fulminant disease. Such patients should be evaluated with CBC and serum creatinine. If ileus or toxic megacolon is a consideration, a CT of the abdomen/pelvis with IV contrast and PO/enteral contrast (if tolerated) should also be considered. Rectal contrast administration is generally not necessary. Guidance for the administration of IV contrast in patients with acute or chronic renal injury is available in the JHACH “Guideline for Prevention of IV Contrast-Induced Nephropathy and Gadolinium-Induced Nephrogenic Systemic Fibrosis.” Patients with leukocytosis more than 15000 cells/mm$^3$ or more than 50% increase in serum creatinine from baseline are categorized with severe disease. Those with hypotension, pancolitis, toxic megacolon, intestinal perforation, or other needs for ICU management are categorized with fulminant disease.

The above definitions for severe and fulminant disease are extrapolated from the adult literature to the pediatric population. These definitions are not sufficiently robust among pediatric patients with cancer or who have undergone hematopoietic stem cell transplantation (HSCT). Specifically, the usefulness of above definition for “severe disease” is limited among patients who may be neutropenic. As such, guidelines supported by the Children’s Oncology Group (COG) caution the use of these definitions in pediatric patient with cancer or HSCT. The COG-supported definition for “severe disease”—those who have toxic megacolon, pseudomembranous colitis, or hemodynamic instability—correlates most closely to the IDSA/SHEA definition for “fulminant disease”. To resolve the differences between the COG and IDSA/SHEA definitions, this JHACH clinical pathway suggests that the term “severe disease” will include those patients with cancer or HSCT who have evidence of acute renal injury or if the clinician feels the patient’s clinical symptoms and risk of prolonged neutropenia raise concern of severe disease. For purposes of this JHACH clinical pathway, the term “fulminant disease” will apply to patients with cancer or HSCT who have evidence of toxic megacolon, pseudomembranous colitis, or hemodynamic instability. Patients with cancer or HSCT should be managed and treated based on these latter definitions throughout this clinical pathway.

**Microbiology Laboratory Testing**

There are several laboratory testing regimens recommended for the detection of *C. difficile*. Currently, JHACH utilizes a two-step method for testing. Testing is performed directly from unformed stool specimens. First, the Cepheid Xpert *C. difficile* RT-PCR Assay is used as a screen. The RT-PCR assay provides qualitative results based on detection of three targets: Toxin B gene (*tcdB*), Binary Toxin gene (*cdt*), and the *tcdC* gene sequence. Relative to reference (enriched) culture, the Xpert *C. difficile* RT-PCR Assay had a sensitivity and specificity of 93.49% and 94.02%, respectively. If the RT-PCR assay is positive, then the lab will reflexively perform a confirmatory Alere *C. diff* Quik Chek Complete™ toxin A/B assay, which uses antibodies specific for toxins A and B of *C. difficile*. Relative to reference bacterial tissue culture, the Alere *C. diff* Quik Chek Complete™ toxin A/B assay has a sensitivity and specificity of 87.8% and 99.4%, respectively.
Interpretation of two-step PCR and toxin assay testing is summarized in Table 2. If both tests (PCR and toxin A/B assay) are positive, then the sample demonstrates toxigenic C. difficile. If the PCR test is positive but the toxin A/B assay is negative, the patient is potentially colonized with C. difficile. If the toxin A/B assay is indeterminate, then a new, fresh unformed (Bristol Scale 5 -7; Figure 2) stool specimen must be submitted.

As of the publication of this clinical pathway, C. difficile testing will be performed 7 days per week from approximately 5:00am through 8:00pm. For patients seen in the Emergency Center with suspected non-severe disease who are considered for outpatient management and who are seen outside of these hours, a specimen collection supplies (specimen container, tongue blades, and specimen collection toilet hat) may be provided for the patient to provide the laboratory specimen at a later time.

This test will only be performed on unformed stool (Bristol Scale 5-7; Figure 2). The Microbiology Lab will reject specimens containing formed stool.

Patients with fulminant disease, ileus, or toxic megacolon may not be able to produce a stool specimen. The Xpert C. difficile assay is not FDA-approved for use with rectal swab specimens. Please consult with the Infectious Diseases service regarding testing in this clinical scenario.

Authorization by an Infectious Diseases attending will be required to order C. difficile testing for patients less than 2 years of age; tests for patients within this age group without such authorization will be canceled by Microbiology.

Repeat testing within 4 weeks after an initial positive test is not appropriate, as the test may remain persistently positive after successful treatment. Likewise, repeat testing as a test-of-cure is not appropriate.
The following substances may potentially lead to assay interference and should be removed from skin prior to specimen collection (test with documentation in parentheses):
  o Vagisil Cream (PCR)
  o Zinc oxide paste (PCR)

The following substances have not demonstrated assay interference (test with documentation in parentheses):
  o Anusol® Plus (PCR)
  o Barium sulfate (toxin assay)
  o Dulcolax® (PCR)
  o E-Z-HDTM High Density Barium Sulfate for suspension (PCR)
  o Fecal fats (PCR; toxin assay)
  o Fleet® (PCR)
  o Hydrocortisone Cream (PCR)
  o Imodium® (PCR; toxin assay)
  o K-Y Jelly/Gelée® (PCR)
  o Kaopectate® (PCR; toxin assay)
  o Metronidazole (PCR; toxin assay)
  o Monistat® (PCR)
  o Mucin, porcine (PCR; toxin assay)
  o Pepto-Bismol® (PCR; toxin assay)
  o Preparation H® (PCR)
  o Preparation H Portable Wipes (PCR)
  o Unilever (PCR)
  o Vaginal Contraceptive Film (VCF), (PCR)
  o Vancomycin (PCR; toxin assay)
  o Vaseline (PCR)
  o Whole blood (PCR; toxin assay)

There is no data on the effects of colonic washes, barium enemas, laxatives, or bowel preparations on the performance of the *C. diff* Quik Chek Complete™ toxin A/B assay.
Table 1. Clinical Symptoms and Risk Factors That May Increase Suspicion of *Clostridioides difficile* Infection (CDI).

These symptoms and risk factors may be considered prior to pursuing evaluation as per Figure 1.

- Presence of mucus or blood in stool
- History of recent antibiotic exposure
- History of antineoplastic therapy
- History of underlying gastrointestinal disease, *e.g.*, Crohn Disease, Ulcerative Colitis, or Hirschsprung Disease
- Patients with or at risk of neutropenia
- History of gastrointestinal surgery or endoscopy
- Repeated use of enemas
- Use of gastrointestinal stimulants
- History of proton pump inhibitor therapy
- Renal insufficiency
- History of solid organ or hematopoietic stem cell transplantation
- History of gastrostomy or jejunostomy tube
- Recent history of inpatient hospitalization
- Recent residence in a skilled care facility
- History of close contact with another patient known to have *C. difficile* infection
- Persistent acute diarrhea that remains otherwise unexplained
Figure 1. Diagnostic Work-Up of Patient with Suspected *Clostridioides difficile* Infection (CDI)

Has the patient had 3 or more unformed stools within the past 24 hours? Refer to Bristol Stool Chart, Stool Types 5 – 7 (Figure 2)

Yes → Is patient more than 2 years of age?

Yes → Did the patient have a positive *C. difficile* (CD) test in the past 4 weeks?

Yes → Do not repeat CD testing. May treat as primary occurrence (if previously untreated) or as recurrent disease (if previously treated) if no other etiology for symptoms.

No → Order CD testing. Interpretation per Table 2.

No → Does the patient have any of the following?

- Fever
- Ill appearance
- Inability to tolerate oral intake or medication
- Emesis
- Moderate or severe dehydration
- Abdominal pain/distension or decreased stool output, concerning for ileus or toxic megacolon
- Signs or symptoms of sepsis

Yes → Consider the following lab evaluation, in addition to any other evaluation appropriate for your differential diagnosis:

- CBC
- Basic Metabolic Panel (BMP)
- CT Abdomen/Pelvis with IV contrast and with PO/enteral contrast if tolerated (if concern for ileus, toxic megacolon, or perforation)

No → DISEASE CLASSIFICATION

**NON-SEVERE DISEASE**  
Suspected CDI without evidence of severe disease

**SEVERE DISEASE**  
Suspected CDI with at least one of the following:

- WBC ≥15000 cells/mm³
- Increase in serum creatinine >50% from baseline
- Concerning clinical status among patients with cancer, neutropenia, or history of hematopoietic stem cell transplantation

**FULMINANT DISEASE**  
Suspected CDI meeting severe criteria *plus at least one* of the following:

- Hypotension
- Toxic megacolon
- Pseudomembranous colitis on abdominal CT scan
- Intestinal perforation
- ICU care needed for CDI management

CONTINUE TO EMERGENCY CENTER PATHWAY (Figure 3) OR INPATIENT PATHWAY (Figure 4).
For diagnosis of suspected *C. difficile* infection, a patient should have 3 or more unformed stools in a 24-hour period. Unformed stool may be defined as stool which takes the shape of its container. Such stool also may correspond to stool types 5 through 7 on the Bristol Stool Chart.

Table 2. Interpretation of Two-Step *C. difficile* Testing (PCR with reflex to Toxin A/B)

<table>
<thead>
<tr>
<th>PCR Test Result</th>
<th>Toxin A/B Test Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>Will not be performed</td>
<td>Patient is not colonized or infected with <em>C. difficile</em>. Treatment is not indicated.</td>
</tr>
<tr>
<td>Positive</td>
<td>Negative</td>
<td>Patient may be colonized with <em>C. difficile</em>. Treatment may or may not be indicated depending on clinical presentation.</td>
</tr>
<tr>
<td>Positive</td>
<td>Positive</td>
<td>Patient has toxigenic <em>C. difficile</em> present. Treatment likely indicated.</td>
</tr>
<tr>
<td>Positive</td>
<td>Indeterminate</td>
<td>Unable to interpret. New stool specimen will be required.</td>
</tr>
</tbody>
</table>
Emergency Center Management

Patients presenting to the Emergency Center with suspected *C. difficile* infection (CDI) should be screened for need of testing and disease classification as demonstrated in Figure 1. In patients under 2 years of age, other etiologies of diarrhea should be considered prior to consideration of CDI, and any testing or treatment of CDI in this age group must be coordinated with the Infectious Diseases service. Testing within this age group requires authorization by an Infectious Diseases attending; tests received without such authorization will be canceled by the Microbiology lab. Additionally, consideration should be given to any underlying chronic medical condition or medication that may cause diarrhea prior to consideration of testing for CDI. If CDI remains the working diagnosis and testing is deemed appropriate, the patient should be stratified into a disease severity classification: non-severe, severe, or fulminant disease.

As of the publication of this clinical pathway, *C. difficile* testing will be performed 7 days per week from approximately 5:00am through 8:00pm. For patients seen in the Emergency Center with suspected non-severe disease who are considered for outpatient management and who are seen outside of these hours, a specimen collection supplies (specimen container, tongue blades, and specimen collection toilet hat) may be provided for the patient to provide the laboratory specimen at a later time. Disposition of the patient should be based on overall clinical status; therefore, disposition should not be delayed while awaiting results of *C. difficile* testing.

In all patients with suspected CDI, any previous inciting antimicrobial therapy should be discontinued if possible.

Patients with non-severe disease (those who do not meet criteria for severe or fulminant disease) may be managed either as an outpatient or as an inpatient, depending upon their clinical presentation. Those who are febrile, ill-appearing, dehydrated, and intolerant of oral intake may benefit from inpatient care and rehydration. Those who are afebrile, relatively well appearing, well hydrated or mildly dehydrated, and tolerant of oral intake could be considered for outpatient management. In either case, empiric therapy for CDI may be delayed while awaiting results of *C. difficile* testing. Disposition of the patient should be based on clinical status and not delayed while awaiting test results. If managed as an outpatient, the family may be contacted after a positive result and prescribed therapy at that time. For those patients considered eligible for outpatient management but who are unable to produce a stool specimen during the Emergency Center visit, the patient’s family should receive stool collection supplies (specimen container, tongue blades, and specimen collection toilet hat) and an order for a *C. difficile* test prior to discharge to home. Outpatients with a primary occurrence or first recurrent episode may follow-up with their primary care provider. Management of patients with second or greater recurrent episodes of CDI, or of those with complicating underlying conditions, must be done in coordination with the Infectious Diseases service, regardless of intended outpatient or inpatient status.
Patients with severe disease are those who have a leukocytosis of greater than 15000 cells/mm³, or those with a 50% or greater increase in serum creatinine from baseline. As baseline serum creatinine may not always be known, suspicion of acute renal injury would be sufficient to meet this criterion. Such patients should be admitted for inpatient care and rehydration. Patients should be admitted to either the inpatient floor or the ICU depending on their clinical status. Empiric CDI therapy should be started for those patients with severe disease while awaiting the results of *C. difficile* testing. Continuation, de-escalation, or discontinuation of therapy can be managed by the inpatient service once test results are available. Infectious Diseases consultation should be considered.

Patients with fulminant disease are those who present with vital sign instability (particularly hypotension), evidence of pancolitis, symptoms of ileus or toxic megacolon, evidence of intestinal perforation, or who otherwise require intensive care. Infectious Diseases must be consulted on all such patients. Surgery should be consulted early for all patients with evidence of ileus, toxic megacolon, or intestinal perforation. Initiation of empiric CDI therapy should be started while awaiting confirmatory testing.

The above definitions for severe and fulminant disease are extrapolated from the adult literature to the pediatric population. These definitions are not sufficiently robust among pediatric patients with cancer or who have undergone hematopoietic stem cell transplantation (HSCT). Specifically, the usefulness of the above definition for “severe disease” is limited among patients who may be neutropenic. As such, guidelines supported by the Children’s Oncology Group (COG) caution the use of these definitions in pediatric patients with cancer or HSCT. The COG-supported definition for “severe disease”—those who have toxic megacolon, pseudomembranous colitis, or hemodynamic instability—correlates most closely to the IDSA/SHEA definition for “fulminant disease”. To resolve the differences between the COG and IDSA/SHEA definitions, this JHACH clinical pathway suggests that the term “severe disease” will apply to patients with cancer or HSCT who have evidence of acute renal injury or if the clinician feels the patient’s clinical symptoms and risk of prolonged neutropenia raise concern of severe disease. For purposes of this JHACH clinical pathway, the term “fulminant disease” will include those patients with cancer or HSCT who present with toxic megacolon, pseudomembranous colitis, or hemodynamic instability. Patients with cancer or HSCT should be managed and treated based on these latter definitions throughout this clinical pathway.

For patients who present with sepsis in addition to suspected CDI, please also see the separate JHACH sepsis clinical pathway for additional details regarding the evaluation, management, and treatment. May also contact Infectious Diseases for guidance.

Repeat testing within 4 weeks after an initial positive test is not appropriate, as the test may remain persistently positive after successful treatment. Likewise, repeat testing as a test-of-cure is not appropriate.
Figure 3. Emergency Center Management Pathway of Patients with Suspected *Clostridioides difficile* Infection (CDI)

**Patient with suspected CDI screened per Figure 1. C. difficile test ordered (when appropriate).**

Does the patient have any of the following?
- Fever
- Ill appearance
- Inability to tolerate oral intake or medication
- Emesis
- Moderate or severe dehydration
- Abdominal pain/distension or decreased stool output, concerning for ileus or toxic megacolon
- Signs or symptoms of sepsis

**NON-SEVERE DISEASE**

Suspected CDI without evidence of severe disease

- Consider discharge to home and outpatient management if clinically well. (See box above at top right for more detail.)
- Consider admission to inpatient floor if clinically ill.
- Discontinue any inciting antibiotic therapy if possible.
- May delay empiric therapy while awaiting *C. difficile* test results. See Table 3.
- If second or greater recurrence, consult Infectious Diseases.
- Consider outpatient management.
- May consider discharge to home while awaiting test results before starting therapy.
- If testing is positive (see Table 2), treatment as per Table 3.
- If second recurrence or greater, contact Infectious Diseases to select treatment and to arrange outpatient follow-up.
- Should follow with primary care physician within 3 days.
- Test-of-cure is not warranted.

**SEVERE DISEASE**

Suspected CDI with at least one of the following:
- WBC ≥15000 cells/mm³
- Increase in serum creatinine >50% from baseline
- Concerning clinical status among patients with cancer, neutropenia, or history of hematopoietic stem cell transplantation
- Start empiric therapy while awaiting *C. difficile* test results. See Table 3.
- Consider admission to either inpatient floor or PICU, depending on clinical status.
- Consider consultation with Infectious Diseases.
- Discontinue any inciting antibiotic therapy if possible.
- See separate Sepsis Clinical Pathway where appropriate.

**FULMINANT DISEASE**

Suspected CDI meeting severe criteria plus at least one of the following:
- Hypotension
- Toxic megacolon
- Pancolitis on abdominal CT scan
- Intestinal perforation
- ICU care needed for CDI management
- Start empiric therapy while awaiting *C. difficile* test results. See Table 3.
- Admit to PICU.
- Consult Infectious Diseases.
- Discontinue any inciting antibiotic therapy if possible.
- If concern for ileus, toxic megacolon, or perforation, consult Surgery.
- See separate Sepsis Clinical Pathway where appropriate.
Admission

Admission to an inpatient service depends upon the patient’s clinical status and disease severity.

Patients who are afebrile, relatively well-appearing, tolerant of oral intake or medication, and suspected to have non-severe disease potentially can be managed as an outpatient.

Patients with non-severe disease (those who do not meet criteria for severe or fulminant disease) who are febrile, ill-appearing, dehydrated, and intolerant of oral intake may benefit from inpatient care and rehydration. Such patients may be admitted to the inpatient floor, unless other medical conditions dictate that higher-level care is necessary.

Patients with severe disease (those who have a leukocytosis of greater than 15000 cells/mm$^3$, or those with a 50% or greater increase in serum creatinine from baseline) should be admitted for inpatient care and rehydration. As baseline serum creatinine may not always be known, suspicion of acute renal injury would be sufficient to meet this criterion. Patients should be admitted to either the inpatient floor or the ICU depending on their clinical status. Those with severe dehydration, severe electrolyte abnormalities, or significant abnormalities in vital signs may benefit from intensive care.

Patients with fulminant disease (those who present with hypotension, evidence of pancolitis, symptoms of ileus or toxic megacolon, evidence of intestinal perforation, or who otherwise require intensive care) should be admitted to the intensive care unit.

The above definitions for severe and fulminant disease are extrapolated from the adult literature to the pediatric population. These definitions are not sufficiently robust among pediatric patients with cancer or who have undergone hematopoietic stem cell transplantation (HSCT). Specifically, the usefulness of the above definition for “severe disease” is limited among patients who may be neutropenic. As such, guidelines supported by the Children’s Oncology Group (COG) caution the use of these definitions in pediatric patients with cancer or HSCT. The COG-supported definition for “severe disease”—those who have toxic megacolon, pseudomembranous colitis, or hemodynamic instability—correlates most closely to the IDSA/SHEA definition for “fulminant disease”. To resolve the differences between the COG and IDSA/SHEA definitions, this JHACH clinical pathway suggests that the term “severe disease” will apply to patients with cancer or HSCT who have evidence of acute renal injury or if the clinician feels the patient’s clinical symptoms and risk of prolonged neutropenia raise concern of severe disease. For purposes of this JHACH clinical pathway, the term “fulminant disease” will include those patients with cancer or HSCT who present with toxic megacolon, pseudomembranous colitis, or hemodynamic instability. Patients with cancer or HSCT should be managed and treated based on these latter definitions throughout this clinical pathway.

For patients who present with sepsis in addition to suspected CDI, please also see the separate JHACH sepsis clinical pathway for additional details regarding the evaluation, management, and treatment. May also contact Infectious Diseases for guidance.
Inpatient Management

Patients currently admitted to an inpatient service who develop symptoms suspicious for *C. difficile* infection should be screened for diagnosis and testing as per Figure 1. In patients under 2 years of age, other etiologies of diarrhea should be considered prior to consideration of CDI, and any testing or treatment of CDI in this age group must be coordinated with the Infectious Diseases service. Testing within this age group requires authorization by an Infectious Diseases attending; tests received without such authorization will be canceled by the Microbiology lab. Additionally, consideration should be given to any underlying chronic medical condition or medication that may cause diarrhea prior to consideration of testing for CDI. If CDI remains the working diagnosis and testing is deemed appropriate, the patient should be stratified into a disease severity classification: non-severe, severe, or fulminant disease.

Those admitted to an inpatient service from the Emergency Center should have been screened for diagnosis and testing as per Figure 1 and managed as per Figure 3 prior to admission.

Patients with suspected CDI should be managed based upon their disease severity.

In all patients with suspected CDI, any previous inciting antimicrobial therapy should be discontinued if possible.

Patients with non-severe disease are those who do not meet criteria for severe or fulminant disease. Those who are febrile, ill-appearing, dehydrated, and intolerant of oral intake may benefit from inpatient care and rehydration. Empiric therapy for CDI may be delayed while awaiting results of *C. difficile* testing. If testing is negative (see Table 2), then other etiologies for symptoms should be considered, and any CDI-directed therapy may be discontinued. If *C. difficile* testing is positive (see Table 2), therapy may be initiated as per Table 3. Management of patients with second or greater recurrent episodes of CDI, or of those with complicating underlying conditions, must be done in coordination with the Infectious Diseases service.

Patients with severe disease are those who have a leukocytosis of greater than 15000 cells/mm$^3$, or those with a 50% or greater increase in serum creatinine from baseline. As baseline serum creatinine may not always be known, suspicion of acute renal injury would be sufficient to meet this criterion. Such patients should be admitted for inpatient care and rehydration. Patients should be admitted to either the inpatient floor or the ICU depending on their clinical status. Empiric CDI therapy should be started for those patients with severe disease while awaiting the results of *C. difficile* testing. Infectious Diseases consultation should be considered. If testing is negative (see Table 2), then other etiologies for symptoms should be considered, and any CDI-directed therapy may be discontinued. If *C. difficile* testing is positive (see Table 2), therapy may be initiated as per Table 3.

Patients with fulminant disease are those who present with vital sign instability (particularly hypotension), evidence of pancolitis, symptoms of ileus or toxic megacolon, evidence of intestinal perforation, or who otherwise require intensive care. Infectious Diseases must be
consulted on all such patients. Surgery should be consulted early for all patients with evidence of ileus, toxic megacolon, or intestinal perforation. Initiation of empiric CDI therapy should be started while awaiting confirmatory testing. If testing is negative (see Table 2), then other etiologies for symptoms should be considered, and any CDI-directed therapy may be discontinued. If *C. difficile* testing is positive (see Table 2), therapy may be initiated as per Table 3.

The above definitions for severe and fulminant disease are extrapolated from the adult literature to the pediatric population. These definitions are not sufficiently robust among pediatric patients with cancer or who have undergone hematopoietic stem cell transplantation (HSCT). Specifically, the usefulness of the above definition for “severe disease” is limited among patients who may be neutropenic. As such, guidelines supported by the Children’s Oncology Group (COG) caution the use of these definitions in pediatric patients with cancer or HSCT. The COG-supported definition for “severe disease”—those who have toxic megacolon, pseudomembranous colitis, or hemodynamic instability—correlates most closely to the IDSA/SHEA definition for “fulminant disease”. To resolve the differences between the COG and IDSA/SHEA definitions, this JHACH clinical pathway suggests that the term “severe disease” will apply to patients with cancer or HSCT who have evidence of acute renal injury or if the clinician feels the patient’s clinical symptoms and risk of prolonged neutropenia raise concern of severe disease. For purposes of this JHACH clinical pathway, the term “fulminant disease” will include those patients with cancer or HSCT who present with toxic megacolon, pseudomembranous colitis, or hemodynamic instability. Patients with cancer or HSCT should be managed and treated based on these latter definitions throughout this clinical pathway.

For patients who present with sepsis in addition to suspected CDI, please also see the separate JHACH sepsis clinical pathway for additional details regarding the evaluation, management, and treatment. May also contact Infectious Diseases for guidance.

Patient discharge may be considered when the patient is no longer febrile, has vital signs that have normalized, is able to tolerate oral intake or medication, and diarrhea has improved and can be contained. Repeat *C. difficile* testing is not to be used as a test of cure. Patient may follow with their primary care provider if his/her course was non-severe, uncomplicated, and either a primary occurrence or first recurrent episode. Patients with severe, fulminant, otherwise complicated, or multiply recurrent episodes should follow as an outpatient with Infectious Diseases, at their discretion, and with their primary care provider. Patient is deemed non-contagious and may return to school when diarrhea resolves.

Repeat testing within 4 weeks after an initial positive test is not appropriate, as the test may remain persistently positive after successful treatment. Likewise, repeat testing as a test-of-cure is not appropriate.
Figure 4. Inpatient Management Pathway of Patients with Suspected *Clostridioides difficile* Infection (CDI)

**Patient Currently Inpatient (Floor or ICU) at time of suspected CDI**

- Screen patient for diagnosis as per Figure 1. 
- *C. difficile* testing ordered (when appropriate).

**Patient Admitted from Emergency Center with suspected CDI**

- Previously screened as per Figure 1 and managed as per Figure 3.

**Non-Severe Disease**

- Suspected CDI without evidence of severe disease
  - May delay empiric therapy while awaiting *C. difficile* test results.
  - Discontinue any inciting antibiotic therapy if possible.
  - If *C. difficile* testing is positive (see Table 2), then treat as per Table 3.
  - If second or greater recurrence, consult Infectious Diseases for management.

**Severe Disease**

- Suspected CDI with at least one of the following:
  - WBC ≥15000 cells/mm³
  - Increase in serum creatinine >50% from baseline
  - Concerning clinical status among patients with cancer, neutropenia, or history of hematopoietic stem cell transplantation
  - Start empiric therapy while awaiting *C. difficile* test results. See Table 3.
  - Consider admission to PICU, if warranted by clinical status.
  - Consider consultation with Infectious Diseases.
  - Discontinue any inciting antibiotic therapy if possible.
  - If *C. difficile* testing is negative (see Table 2), then discontinue therapy and consider other etiology for symptoms.
  - See separate Sepsis Guideline where appropriate.

**Fulminant Disease**

- Suspected CDI meeting severe criteria plus at least one of the following:
  - Hypotension
  - Toxic megacolon
  - Pancolitis on abdominal CT scan
  - Intestinal perforation
  - ICU care needed for CDI management
  - Start empiric therapy while awaiting *C. difficile* test results. See Table 3.
  - Admit to PICU.
  - Consult Infectious Diseases.
  - Discontinue any inciting antibiotic therapy if possible.
  - If *C. difficile* testing is negative (see Table 2), then discontinue therapy and consider other etiology for symptoms.
  - If concern for ileus, toxic megacolon, or perforation, consult Surgery.
  - See separate Sepsis Guideline where appropriate.

**Discharge Considerations**

**Discharge Criteria**

- Able to tolerate oral intake and maintain hydration
- Able to tolerate oral medication
- Diarrhea has improved and can be contained
- Vital signs have normalized

**Outpatient Follow-Up**

- Follow with primary care provider within 1 week of discharge.
- Follow in Infectious Diseases clinic if multiply recurrent CDI, at ID’s discretion.
- Patient is considered non-contagious when diarrhea resolves. May return to school at that time.
- Test-of-cure is not warranted.
Management

Patients with *C. difficile* infection (CDI) will require various levels of supportive care and rehydration based upon their clinical presentation. Likewise, antibiotic management in these patients is based upon their clinical classification (non-severe, severe, and fulminant disease; see Figure 1) or recurrence. Antibiotic choice is not based on presence of primary or secondary immune deficiency. Among patients with cancer or who have undergone hematopoietic stem cell transplantation, categorization into non-severe or severe disease should be exercised with caution. As such patients may be neutropenic or may be unable to elicit leukocytosis, categorization as severe disease should be deferred to the provider’s clinical judgement of symptoms and risk of prolonged neutropenia. Antibiotic choices are summarized in Table 3.

**Antibiotic Agents**

Metronidazole remains the primary drug of choice for most patients with non-severe CDI. The oral/enteral route is preferred for therapy. Intravenous metronidazole is an option for patients unable to tolerate oral/enteral medications; however, the efficacy of IV metronidazole is not established. Metronidazole is available in capsules, tablets, and oral suspension.

Vancomycin remains the second-line choice for pediatric patients with non-severe CDI. In adult patients, data now support the use of vancomycin as primary therapy for non-severe CDI; however, there are insufficient data to support vancomycin primary therapy in pediatric patients with non-severe CDI. Vancomycin is the first-line therapy for patients with severe or fulminant CDI or for patients who present with recurrent disease. Vancomycin should only be given by oral, enteral, or rectal route for the treatment of CDI. Intravenous vancomycin is not appropriate therapy for CDI, as it does not enter the intestinal lumen. Vancomycin is available in capsule form for oral/enteral administration. Oral solution is available commercially, or it may be compounded using the IV powder. For patients with fulminant disease and unable to tolerate oral/enteral intake, vancomycin can be prepared as a rectal retention enema. Therapeutic drug level monitoring is not necessary for patients receiving oral, enteral, or rectal vancomycin therapy alone, as the drug is minimally systemically absorbed via this route. Additionally, there is no contraindication to concomitant therapy with oral/enteral/rectal vancomycin for CDI and intravenous vancomycin for treatment of other infections if necessary. In scenarios when both oral/enteral/rectal and intravenous vancomycin therapy are necessary, therapeutic drug monitoring must be performed. In patients with cancer, history of HSCT, or neutropenia, the Oncology or BMT and ID services must be notified before considering rectal administration of vancomycin.

Other agents have been studied for use in treatment of CDI. Fidaxomicin has been approved for adult patients for routine treatment of severe CDI; however, this drug has not been approved for pediatric use. Nitazoxanide has been supported by small randomized controlled trials; however, it is not recommended for routine treatment of CDI. There is insufficient data to support the efficacy of rifaximin, tigecycline, and bacitracin for treatment of CDI. None of these
medications are recommended for the routine treatment of CDI of any disease classification in pediatric patients.

**Antibiotic Therapy for Primary CDI Episodes and First Recurrence**

Patients who are asymptomatic, *i.e.*, patients without diarrhea or those whose diarrhea of any cause has recently resolved, should not be tested or treated for *C. difficile* infection.

For patients with a primary occurrence of non-severe disease, oral/enteral metronidazole remains the drug of choice among pediatric patients. Recommended duration of therapy is 10 days.

Use either oral/enteral metronidazole or oral/enteral vancomycin for the treatment of non-severe CDI in children and adolescents with cancer and pediatric HSCT patients.

For patients with primary occurrence of severe disease, or for patients with first episode of recurrence, oral/enteral vancomycin is the drug of choice. Recommended duration of therapy is 10 days.

For patients with fulminant disease, treatment choice is based upon the patient’s ability to tolerate oral/enteral intake. For those able to tolerate oral/enteral medications, oral/enteral vancomycin should be given concomitantly with intravenous metronidazole. For those unable to tolerate oral/enteral medications, or for those with ileus or toxic megacolon, intravenous metronidazole should be given in conjunction with vancomycin as a rectal retention enema. Recommended duration is for 10 days of therapy.

**Therapy for Patients with Second or Greater CDI Recurrence**

For patients with second or greater recurrence of disease, Infectious Diseases must be consulted for either inpatient or outpatient management. In such cases, vancomycin taper and pulse therapy is likely to be considered. In patients who have failed vancomycin taper and pulse therapy, fecal microbiota transplant will likely be considered.
Table 3. Treatment Considerations for Patients with Confirmed *Clostridioides difficile* Infection

<table>
<thead>
<tr>
<th>Occurrence</th>
<th>Infection Severity*</th>
<th>Clinical Manifestations</th>
<th>Recommended Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic</td>
<td>None</td>
<td></td>
<td>No therapy. Treatment can promote relapsing infection.</td>
</tr>
<tr>
<td>Non-Severe</td>
<td>CD testing positive (see Table 2) with diarrhea but no manifestations of severe disease</td>
<td>Special considerations vary by subcategory.</td>
<td>Metronidazole PO/enteral for 10 days 10 mg/kg/dose 3 times daily (max 500mg/dose) OR For Patients with Cancer, Neutropenia, or HSCT: May use either Metronidazole PO/enteral x 10 days 10mg/kg/dose PO 3x/day (max 500mg/dose) OR Vancomycin PO/enteral x 10 days 10mg/kg/dose q6h (max 125mg/dose) Consultation with Infectious Diseases strongly recommended.</td>
</tr>
<tr>
<td>Severe</td>
<td>CD testing positive (see Table 2) with diarrhea and at least one of the following: 1) WBC ≥15000 cells/mm³, OR 2) Increase in serum creatinine &gt;50% from baseline OR 3) Concerning clinical status among patients with cancer, neutropenia, or history of HSCT</td>
<td>Special considerations vary by subcategory.</td>
<td>Vancomycin PO/enteral for 10 days 10 mg/kg/dose PO q6h (max 125mg/dose) Consultation with Infectious Diseases strongly recommended.</td>
</tr>
<tr>
<td>Fulminant</td>
<td>Above criteria plus at least one of the following: 1) Hypotension 2) Toxic megacolon 3) Pancolitis on abdominal CT scan 4) Intestinal perforation 5) ICU care needed for CDI management</td>
<td>Special considerations vary by subcategory.</td>
<td>If able to tolerate PO/enteral: Vancomycin PO/enteral for 10 days 10 mg/kg/dose PO q6h (max 500mg/dose) PLUS Metronidazole IV for 10 days† 10 mg/kg/dose IV q8h (max 500mg/dose) IF ileus or inability to tolerate PO/enteral: Vancomycin Rectal‡§ 500mg/100mL in Normal Saline as retention enema q6h PLUS Metronidazole IV (dose as above) Early surgical consultation strongly recommended. Consult Infectious Diseases.</td>
</tr>
<tr>
<td>First Recurrence</td>
<td>Base therapy upon severity of illness, using recommendations for initial episode. If Metronidazole was used for primary occurrence, use Vancomycin PO/enteral for first recurrence.</td>
<td>Special considerations vary by subcategory.</td>
<td>Infectious Diseases consultation required for consideration of vancomycin taper and pulse therapy or fecal microbiota transplantation.</td>
</tr>
<tr>
<td>Second or Greater Recurrence</td>
<td>Special considerations vary by subcategory.</td>
<td>Special considerations vary by subcategory.</td>
<td>Infectious Diseases consultation required for consideration of vancomycin taper and pulse therapy or fecal microbiota transplantation.</td>
</tr>
</tbody>
</table>

*Based on adult criteria; no validated criteria for disease severity in children.
†The efficacy of IV metronidazole is poorly established.
‡Optimal dose and volume for rectal Vancomycin have not been established. Some experts recommend 50mL for ages 1-3 years, 75mL for ages 4-9 years, and 100mL for ages ≥ 10 years.
§In patients with cancer, history of HSCT, or neutropenia, the Oncology or BMT and ID services must be notified before considering rectal administration of vancomycin.
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**Order Sets:**

Order set developed (April 2019), including orders for medications and recommended dosage based upon disease severity and number of disease occurrence.

Will implement EMR alert for *C. difficile* test order for patients less than 2 years of age; will require authorization by Infectious Diseases attending to proceed with testing.

**Outcome Measures**

- Number of *C. difficile* (CD) tests ordered overall
- Number of CD tests in patients less than 2 years of age
- Number of authorizations from Infectious Diseases attendings for CD testing in patients less than 2 years of age.
- Number of specimens for CD tests received by Microbiology rejected due to formed stool.
- Number of specimens for CD tests received by Microbiology rejected due to lack of authorization from ID attending in patients less than 2 years of age.

If resources become available, will consider random chart audits for the following:

- Testing in patients less than 2 years of age – ID authorization and consultation
- 3 or more unformed stools documented
- Inpatient Infectious Diseases consultation performed when necessary (< 2 years of age; multiply recurrent disease, fulminant disease)
- Metronidazole for first occurrence (non-severe disease)
- Vancomycin for first occurrence (severe or fulminant disease; select oncology or neutropenic patients with non-severe disease)
- Vancomycin for first recurrence
- Oral/enteral route given when able
Patient Status:

The following are recommendations for your initial “patient status” order at the time of admission:

- Observation status for severe disease admitted to the general medical floor.
- Inpatient status for severe or fulminant disease requiring admission to the Hematology/Oncology service or ICU.

If your patient develops C. difficile during their hospitalization, please do not change their patient status order, unless directed to do so by the Utilization Management team.

If any concerns or questions regarding patient status, please feel free to contact utilization management via email at achumconcernteam@jhmi.edu.

Documentation Reminders:

The following are the recommended ICD-10 codes to be used for patients with a primary occurrence of C. difficile colitis or for those with recurrent C. difficile disease, respectively:

- A04.72 Clostridium difficile colitis
- A04.71 Recurrent enterocolitis due to Clostridium difficile

It is important to document any conditions complicating your patient’s clinical condition, thus contributing to the need for hospitalization, e.g., metabolic acidosis, dehydration, acute kidney injury/failure, toxic megacolon, bowel perforation, sepsis, etc.

It is important to document any co-morbidities or circumstances that necessitate admission to the hospital, rather outpatient care, e.g., failed outpatient management or immune compromise.


**Disclaimer**

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners and other health care providers in clinical decision-making by describing a range of generally acceptable approaches for the diagnosis, management, or prevention of specific diseases or conditions. The ultimate judgment regarding care of a particular patient must be made by the physician in light of the individual circumstances presented by the patient.

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