JOHNS HOPKINS ALL CHILDREN'S HOSPITAL

Clostridioides difficile Clinical Pathway

JOHNS HOPKINS
All Children's Hospital

Johns Hopkins All Children's Hospital

Clostridioides difficile Clinical Pathway

Table of Contents

Updated: October 2024

Owners: Fernando Bula, MD; Juan Dumois, MD; Allison Messina, MD; Katie Namtu, PharmD

Johns Hopkins All Children's Hospital

Clostridioides difficile Clinical Pathway

Rationale:

This clinical pathway was developed by a consensus group of Johns Hopkins All Children's Hospital (JHACH) Infectious Diseases (ID) 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 (C.) 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 ID appropriate for CDI?
- What clinical scenarios warrant inpatient management for CDI?
- When is surgical consultation appropriate for CDI?

Background:

C. 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 adults. 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 community-acquired infections 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 (HSCT), renal insufficiency, Hirschsprung disease, inflammatory bowel disease (IBD), gastrostomy or jejunostomy tubes, and possibly acid-suppressive therapy.

C. difficile colonization (i.e., detectable presence of organism without clinical symptoms) complicates the appropriate diagnosis of CDI. Colonization is a 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.

Diagnosis:

Diagnostic Testing by Clinical Presentation and Risk Factors:
Patients with 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, IBD (e.g., Crohn's disease, ulcerative colitis Hirschsprung disease), repeated enema use, gastrointestinal stimulants use, renal insufficiency, or recent gastrointestinal surgery or endoscopy. CDI should be considered in patients with acute diarrhea that remains unexplained. Infection may be considered in patients with a history of solid organ or HSCT. There is an increased association in patients with gastrostomy or jejunostomy tubes. Some data suggest an association with proton pump inhibitor (PPI) 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:
The diagnosis of CDI is challenging as the pediatric population has higher *C. difficile* colonization rates as compared with adults. Diagnosis among patients under 2 years of age is 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 before consideration of CDI in children less than 2 years of age. If CDI remains a concern in this age group, consultation with ID is required, either by authorization of testing via conversation or by formal consultation. Authorization by an ID Attending is required to order *C. difficile* testing; tests without 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 adults; therefore, test concerning 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 24 hours. 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 presentation due to ileus or toxic megacolon; however, these patients typically have a history of diarrhea before developing an ileus. Diagnostic testing should not be performed on formed stool (Bristol Stool Chart, stool types 1 through 4; **Figure 2**). Microbiology 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. These underlying medical conditions and therapies should be considered before considering CDI. Those with IBD 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 before 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 are considered as having non-severe disease and potentially be treated as outpatients 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 complete blood count (CBC) and serum creatinine. If ileus or toxic megacolon is a consideration, a computed tomography (CT) of the abdomen/pelvis with intravenous (IV) contrast and oral (PO)/enteral contrast (if tolerated) should also be considered. Rectal contrast administration is generally not necessary. Guidance for 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 of more than 15,000 cells/mm^3 or more than a 50% increase in serum creatinine (SCr) from baseline are categorized with severe disease. Those with hypotension, pancolitis, toxic megacolon, intestinal perforation, or other needs for intensive care unit (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 HSCT. Specifically, the usefulness of the above definition for “severe disease” is limited among patients who may be neutropenic. Guidelines supported by the Children’s Oncology Group (COG) caution using these definitions in pediatric patients with cancer or HSCT. The COG-supported definition of “severe disease”—those who have toxic megacolon, pseudomembranous colitis, or hemodynamic instability—correlates most closely to the Infectious Diseases Society of America (IDSA)/Society for Healthcare Epidemiology of

America (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.

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* real-time polymerase chain reaction (rtPCR) Assay is used as a screen. The rtPCR assay provides qualitative results detecting three targets: Toxin B gene (*tcdB*), Binary Toxin gene (*cdt*), and the *tcdC* gene sequence. Relative to reference (enriched) culture, the Xpert *C. difficile* rtPCR Assay had a sensitivity and specificity of 93.49% and 94.02%, respectively. If the rtPCR assay is positive, 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**.

As of the publication of this clinical pathway, *C. difficile* testing will be performed 7 days per week from approximately 0500 through 2000. For patients seen in the Emergency Center (EC) with suspected non-severe disease who are considered for outpatient management and who are seen outside of these hours, 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 stools (Bristol Scale 5 -7; **Figure 2**). Microbiology 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 ID service regarding testing in this clinical scenario.

Authorization by an ID 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 authorization will be canceled by Microbiology.

Repeat testing within 4 weeks after an initial positive test is inappropriate, 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 the skin before specimen collection (test with documentation in parentheses):

- Vagisil Cream® (polymerase chain reaction (PCR))
- Zinc oxide paste (PCR)

The following substances have not demonstrated assay interference (test with documentation in parentheses):

- Anusol Plus® (PCR)
- Barium sulfate (toxin assay)
- Dulcolax® (PCR)
- E-Z-HDTM High-Density Barium Sulfate for suspension (PCR)
- Fecal fats (PCR; toxin assay)
- Fleet® (PCR)
- Hydrocortisone Cream (PCR)
- Imodium® (PCR; toxin assay)
- K-Y Jelly/Gelée® (PCR)
- Kaopectate® (PCR; toxin assay)
- Metronidazole (PCR; toxin assay)
- Monistat® (PCR)
- Mucin, porcine (PCR; toxin assay)
- Pepto-Bismol® (PCR; toxin assay)
- Preparation H® (PCR)
- Preparation H Portable Wipes® (PCR)
- Unilever (PCR)
- Vaginal Contraceptive Film (VCF), (PCR)
- Vancomycin (PCR; toxin assay)
- Vaseline (PCR)
- 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. difficile* Quik Chek Complete™ toxin A/B assay.

Table 1. Clinical Symptoms and Risk Factors That May Increase Suspicion of CDI
These symptoms and risk factors may be considered before pursuing evaluation 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's 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 PPI therapy
- Renal insufficiency
- History of solid organ or HSCT
- 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 CDI

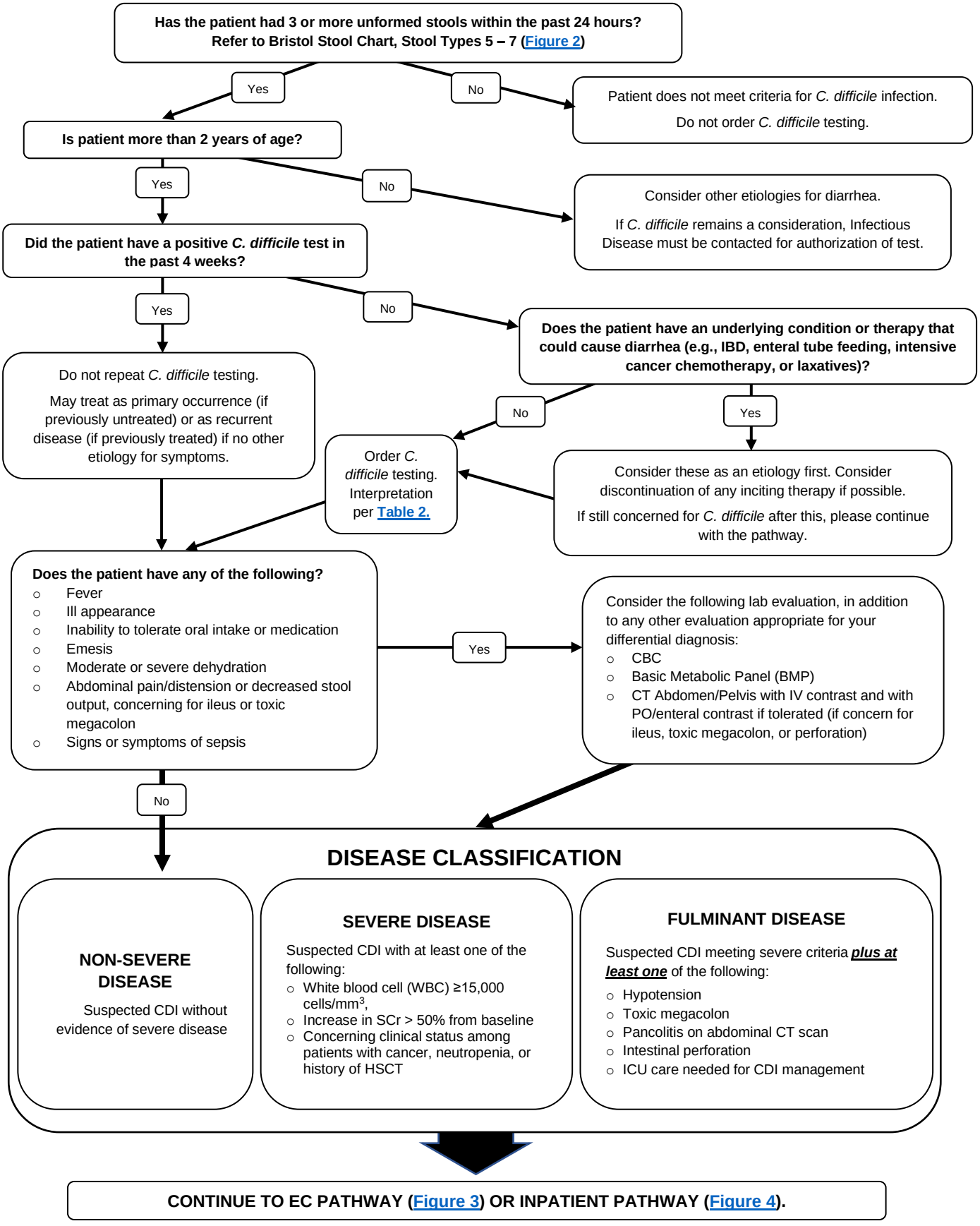


Figure 2. Bristol Stool Chart.

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.

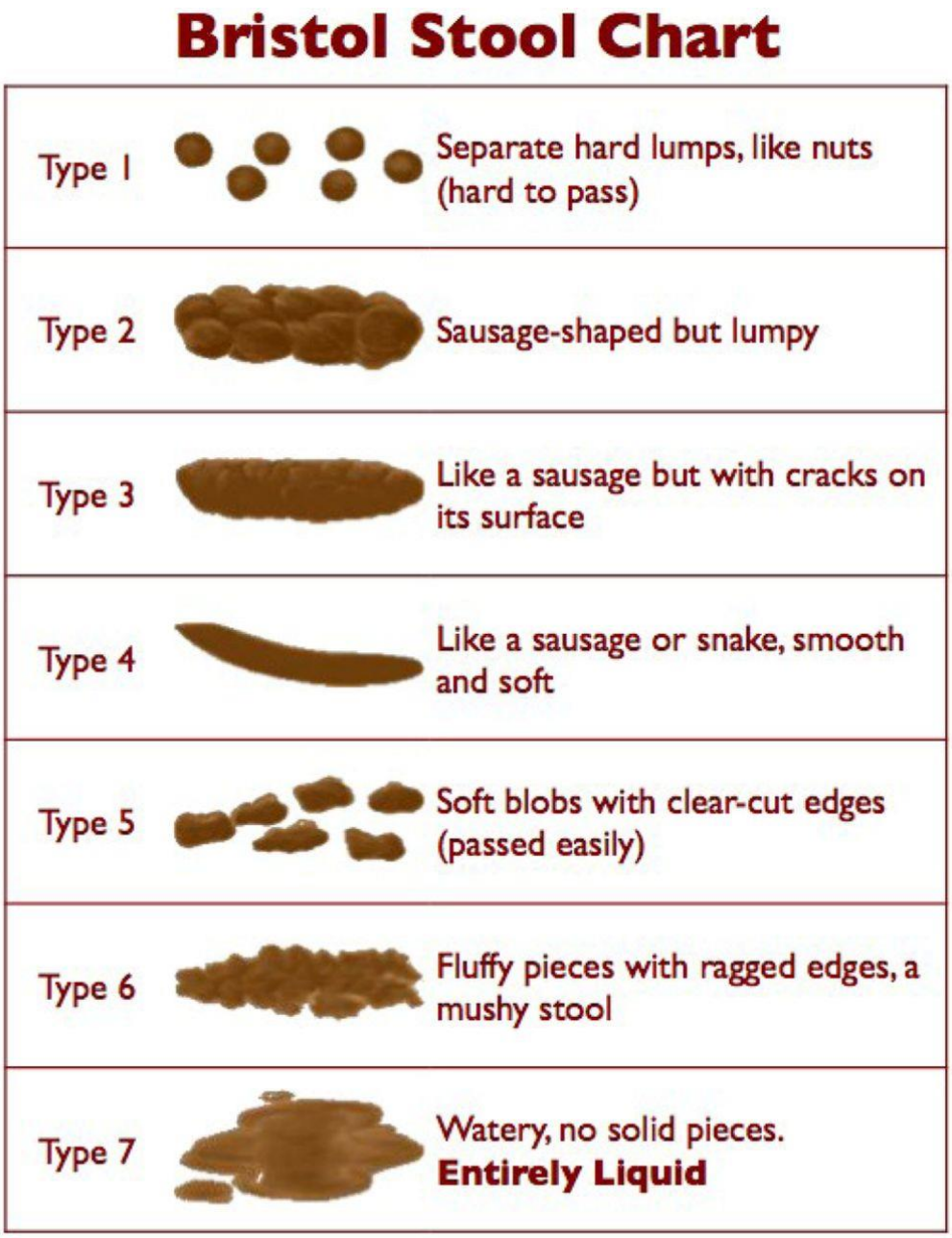


Image credit: Lewis, SJ; Heaton, KW (September 1997). "Stool form scale as a useful guide to intestinal transit time". Scand. J. Gastroenterol. ***32*** *(9): 920–4. doi:10.3109/00365529709011203. PMID 9299672.*

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

C. difficile **PCR (C.difficile Toxin B Gene NAT)**	***C. difficile*** **Toxin (C.difficile Toxin EIA)**	**Result Interpretation**	**Management**
Positive	Positive	*C. difficile* toxin detected If clinical syndrome is consistent with *C. difficile* infection, treat per guidelines	Contact isolation Treat per guidelines
Positive	Negative	*C. difficile* toxin gene present but *C. difficile* toxin not detected PCR-positive samples with no toxin detected by enzyme immunoassay (EIA) more likely represent colonization than infection, but if the clinical syndrome is consistent with severe/fulminant CDI, treat per guidelines Consult ID for questionable cases	Contact isolation CDI treatment is not indicated unless high suspicion for CDI Consult ID for questionable cases
Negative	N/A	No *C. difficile* detected	No isolation or treatment
Positive	Indeterminate	*C. difficile* toxin gene present but *C. difficile* toxin assay uninterpretable If the clinical picture is consistent with CDI, treat per guidelines	Contact isolation Treat per guidelines if clinical suspicion of CDI
Invalid	Positive	*C. difficile* toxin gene uninterpretable result. *C. difficile* toxin detected If the clinical syndrome is consistent with CDI, treat per guidelines	Contact isolation Treat per guidelines if clinical suspicion of CDI
Invalid	Negative	*C. difficile* toxin gene uninterpretable result *C. difficile* toxin NOT detected If suspicion of CDI persists, submit a new stool sample for testing.	No isolation or treatment
Invalid	Indeterminate	Both the *C. difficile* toxin gene and the toxin assay results are uninterpretable If suspicion of CDI persists, submit a new stool sample for testing	No isolation or treatment

EC Management:

Patients presenting to the EC with suspected CDI should be screened for need of testing and disease classification as demonstrated in **Figure 1**.

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

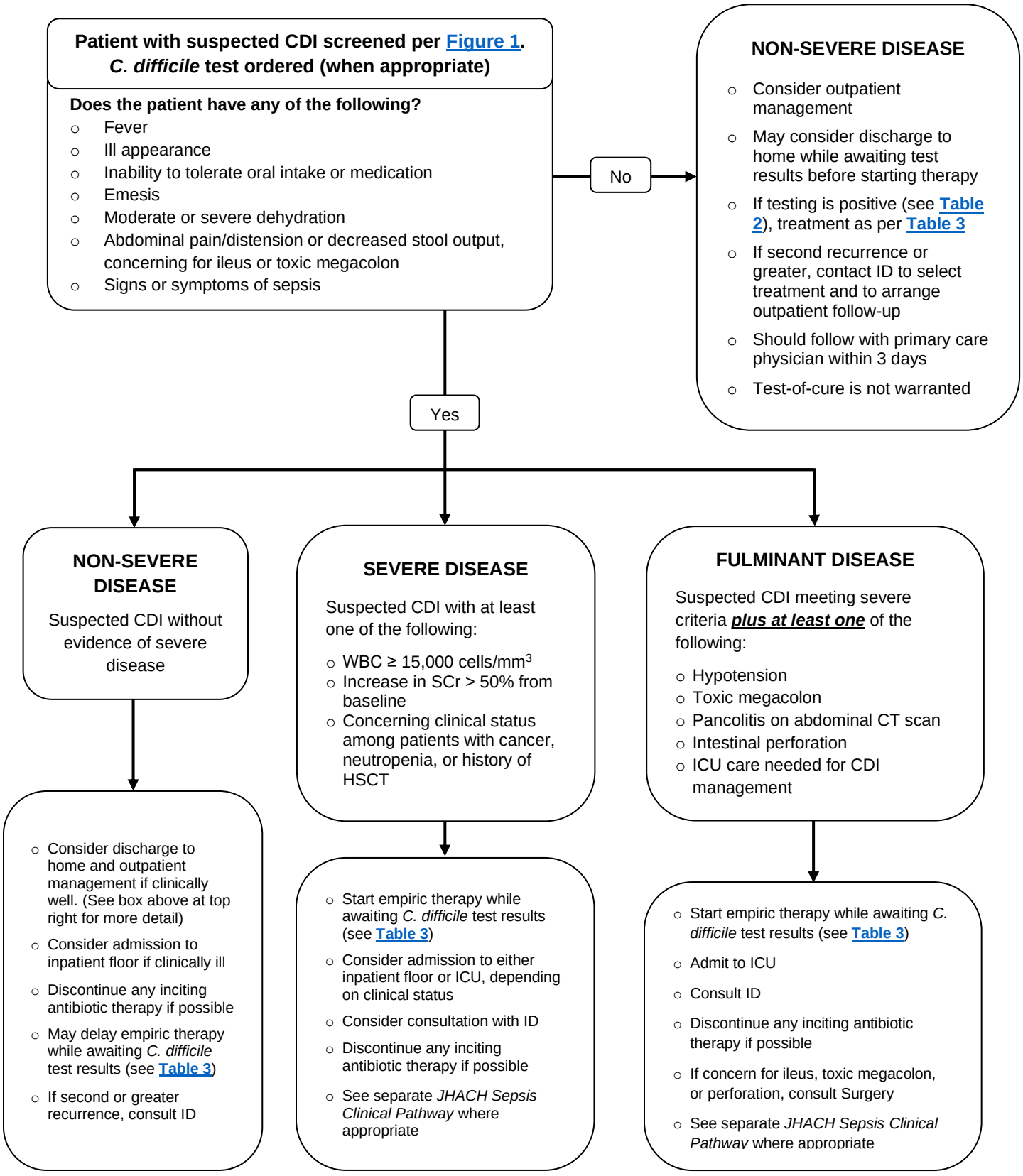
Patients with non-severe disease (those who do not meet the criteria for severe or fulminant disease) may be managed either as an outpatient or inpatient, depending upon their clinical presentation. Those who are febrile, ill-appearing, dehydrated, and intolerant of oral intake may benefit from inpatient 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 the 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 EC 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 before 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 ID service, regardless of intended outpatient or inpatient status.

Patients with severe disease 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. ID consultation should be considered.

ID must be consulted on all patients with fulminant disease. 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.

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 ID for guidance.

Figure 3. EC Management Pathway of Patients with Suspected CDI



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 may be admitted to the inpatient floor unless other medical conditions dictate that higher-level care is necessary.

Patients with severe disease 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 should be admitted to the intensive care unit.

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 ID for guidance.

Inpatient Management:

Patients currently admitted to an inpatient service who develop symptoms suspicious of *C. difficile* infection should be screened for diagnosis and testing as per **Figure 1**.

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

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

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

In patients with non-severe disease empiric therapy for CDI may be delayed while awaiting the results of *C. difficile* testing. If testing is negative (see **Table 2**), other symptom etiologies 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 ID service.

Patients with severe disease 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. ID consultation should be considered. If testing is negative (see **Table 2**), then other etiologies for symptoms should be considered, and any CDI-directed

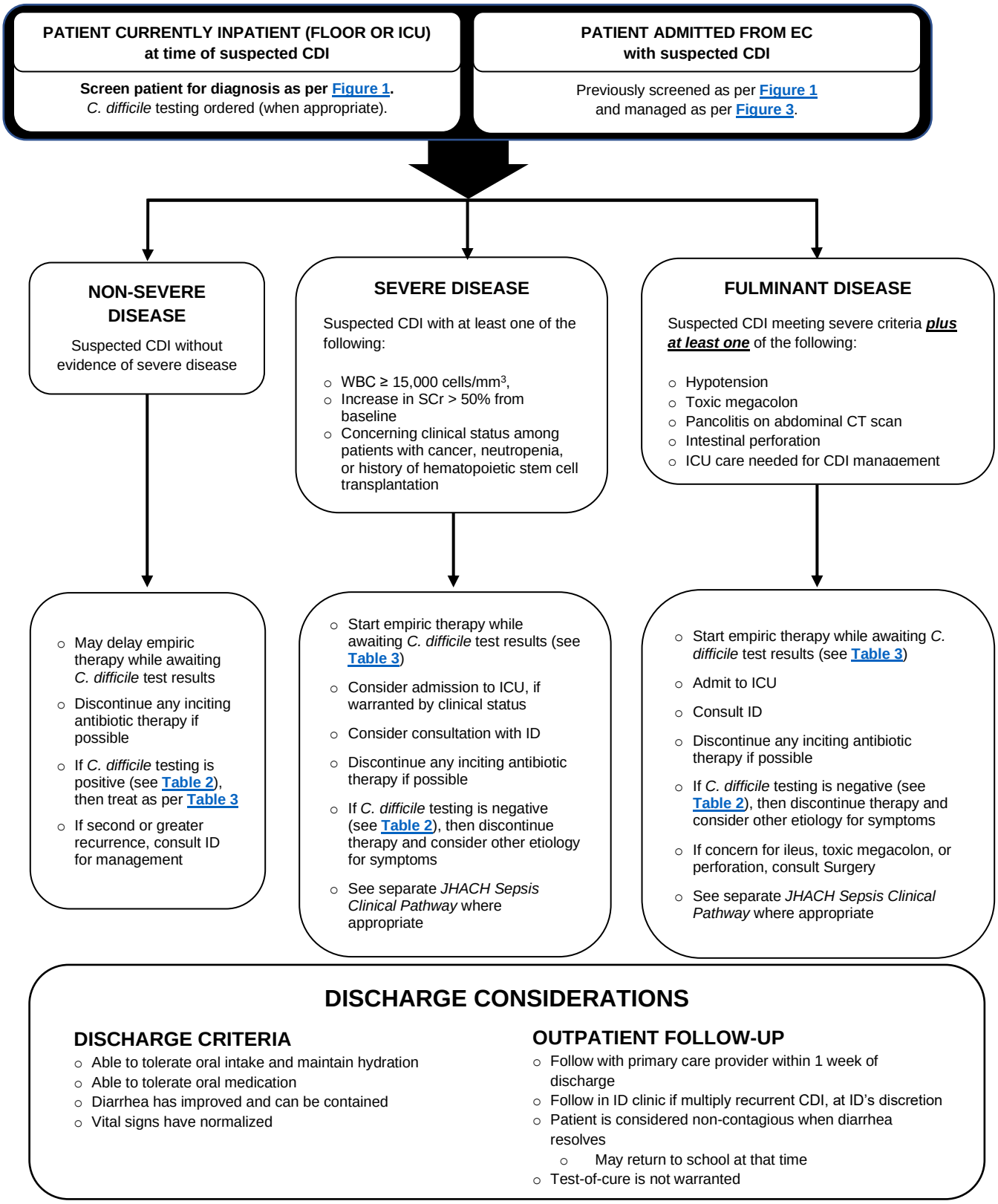
therapy may be discontinued. If *C. difficile* testing is positive (see **Table 2**), therapy may be initiated as per **Table 3**.

Patients with fulminant disease require intensive care. ID 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**.

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 ID 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. The patient may follow up with their primary care provider if his/her course was non-severe, uncomplicated, and either a primary occurrence or the first recurrent episode. Patients with severe, fulminant, otherwise complicated, or multiply recurrent episodes should follow as outpatients with ID, at their discretion, and with their primary care provider. The patient is deemed non-contagious and may return to school when diarrhea resolves.

Figure 4. Inpatient Management Pathway of Patients with Suspected CDI



Management:

Patients with CDI will require various levels of supportive care and rehydration based on their clinical presentation. Likewise, antibiotic management in these patients is based on their clinical classification (non-severe, severe, and fulminant disease; see **Figure 1**) or recurrence. Antibiotic choice is not based on the presence of primary or secondary immune deficiency. Among patients with cancer or who have undergone HSCT, 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 a severe disease should be deferred to the provider's clinical judgment of symptoms and risk of prolonged neutropenia. Antibiotic choices are summarized in **Table 3**.

Antibiotic Agents:
Vancomycin is the preferred therapy choice for pediatric patients with non-severe CDI. An observational cohort study of children with non-severe CDI found earlier symptom resolution with oral vancomycin versus oral metronidazole. 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. IV vancomycin is not an 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 IV vancomycin therapy are necessary, therapeutic drug monitoring must be performed. In patients with cancer, history of HSCT, or neutropenia, the Oncology or Bone Marrow Transplant (BMT) and ID services must be notified before considering rectal administration of vancomycin.

Metronidazole is an alternative agent in the treatment of non-severe CDI. The oral/enteral route is preferred for therapy. IV 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.

Other agents have been studied for use in the treatment of CDI. Fidaxomicin is recommended as a first-line option for an initial episode in adults. Fidaxomicin is only recommended in the setting of multiple recurrences in pediatric patients, as data and experience are limited. 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 the 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 vancomycin is the preferred therapy among pediatric patients. Oral/enteral metronidazole is an alternative agent for non-sever disease. The recommended duration of therapy is 10 days. If the patient improves but has no symptom resolution by day 10, consider extending the duration to 14 days.

For patients with primary occurrence of severe disease, or patients with first episode of recurrence, oral/enteral vancomycin is the drug of choice. The recommended duration of therapy is 10 days. If the patient improves but has no symptom resolution by day 10, consider extending the duration to 14 days.

For patients with fulminant disease, treatment choice is based on 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, IV metronidazole should be given in conjunction with vancomycin as a rectal retention enema. The recommended duration is 10 days of therapy. If the patient improves but has no symptom resolution by day 10, consider extending the duration to 14 days.

Therapy for Patients with Second or Greater CDI Recurrence:

For patients with a second or greater recurrence of disease, ID must be consulted for either inpatient or outpatient management. In such cases, fidaxomicin (preferred therapy) or vancomycin taper and pulse therapy is likely to be considered. In patients who have failed fidaxomicin and/or vancomycin taper and pulse therapy, fecal microbiota transplant will likely be considered.

Monoclonal antibodies for CDI Prevention:

Bezlotuxomab is a monoclonal antibody that binds to C. difficile toxin B to neutralize it and prevent damage to the colonic cells. It is FDA-approved as a one-time dose of 10 mg/kg/dose IV administered **during** active CDI treatment to prevent recurrent CDI after the current episode. It is most beneficial in patients who have multiple risk factors for recurrent CDI such as a history of severe CDI, and immunocompromised hosts. In randomized controlled trials including adults, CDI recurrence was 16 – 17% with bezlotoxumab versus 26 – 28% with placebo. In a randomized controlled trial in children, CDI recurrence was 11% with bezlotoxumab versus 15% with placebo. Bezlotoxumab should NOT be used as part of acute treatment of CDI. Toxin B levels in the stool are significantly reduced after starting appropriate antibiotics for CDI therefore bezlotoxumab is not expected to alter the initial clinical course. Bezlotoxumab is restricted at JHACH and requires approval by ID or Antimicrobial Stewardship.

Vancomycin for secondary prophylaxis for high-risk patients when antimicrobial therapy is initiated:

Prophylactic PO vancomycin to prevent future episodes of CDI when antimicrobials are initiated for the treatment of other infections is generally not recommended. Data on this approach are limited to observational studies. This approach can be considered for severely immunocompromised patients with recent CDI and patients with a history of fulminant CDI within the previous 3 months in consultation with ID.

Table 3. Treatment Considerations for Patients with Confirmed *C. difficile* Infection

Occurrence	Infection Severity*	Clinical Manifestations	Recommended Therapy
Primary Occurrence	**Asymptomatic**	None	No therapy Treatment can promote relapsing infection
	Non-Severe	CD testing positive (see Table 2) with diarrhea but no manifestations of severe disease	**Preferred:** **vancomycin PO/enteral** for **10 days** 10 mg/kg/dose (max dose: 125 mg/dose) q6h Alternative: **metronidazole PO/enteral for 10 days** 10 mg/kg/dose (max dose: 500 mg/dose) 3 times daily
	Severe	CD testing positive (see Table 2) with diarrhea and at least one of the following: 1) WBC ≥ 15,000 cells/mm^3 ***OR*** 2) Increase in SCr > 50% from baseline ***OR*** 3) Concerning clinical status among patients with cancer, neutropenia, or history of HSCT	**vancomycin PO/enteral for 10 days** 10 mg/kg/dose (max dose: 125 mg/dose) PO q6h Consultation with ID is strongly recommended
	Fulminant	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	**If able to tolerate PO/enteral:** **vancomycin PO/enteral for 10 days** 10 mg/kg/dose (max dose: 500 mg/dose) PO q6h ***PLUS*** **metronidazole IV for 10 days**† 10 mg/kg/dose (max dose: 500 mg/dose) IV q8h **If ileus or inability to tolerate PO/enteral:** **vancomycin Rectal**‡§ 500 mg/100 mL in NS as retention enema q6h ***PLUS*** **metronidazole IV** (dose as above) Early surgical consultation is strongly recommended Consult ID
First Recurrence	Base therapy upon the severity of the illness, using recommendations for the initial episode If metronidazole was used for primary occurrence, use vancomycin PO/enteral for the first recurrence		
Second or Greater Recurrence	ID consultation is required for fidaxomicin (restricted formulary agent), vancomycin taper and pulse therapy, or fecal microbiota transplantation **Preferred:** PO fidaxomicin 4 to < 7 kg: 80 mg/dose PO q12h for 10 days 7 to 9 kg: 120 mg/dose PO q12h for 10 days 9 to < 12.5 kg: 160 mg/dose PO q12h for 10 days ≥ 12.5 kg: 200 mg/dose PO q12h for 10 days Alternative: PO vancomycin taper and pulse€ 10 mg/kg/dose (max dose: 125 mg/dose) PO q6h for 10 – 14 days 10 mg/kg/dose (max dose: 125 mg/dose) PO q12h for 5 – 7 days 10 mg/kg/dose (max dose: 125 mg/dose) PO q24h for 5 – 7 days 10 mg/kg/dose (max dose: 125 mg/dose) PO q2 – 3 days for 1 – 2 weeks Fecal microbiota transplant		

* 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 50 mL for ages 1 – 3 years, 75 mL for ages 4 – 9 years, and 100 mL 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

€ Evidence limited to uncontrolled studies in adults. Optimal dosing and interval strategies in children not established

References:

1. Benson L, Song X, Campos J, Singh N. Changing epidemiology of *Clostridium difficile*-associated disease in children. *Infect Control Hosp Epidemiol* 2007; 28:1233–5. (Single-Center, Retrospective Cohort Study)
2. Bolton RP, Tait SK, Dear PR, Losowsky MS. Asymptomatic neonatal colonisation by *Clostridium difficile*. *Arch Dis Child* 1984; 59:466–72. (Single-Center Prospective Cohort Study)
3. Delmée M, Verellen G, Avesani V, Francois G. *Clostridium difficile* in neonates: serogrouping and epidemiology. *Eur J Pediatr* 1988; 147:36–40. (Single-Center Prospective Cohort Study)
4. Donta ST, Myers MG. *Clostridium difficile* toxin in asymptomatic neonates. *J Pediatr* 1982; 100:431–4. (Single-Center Prospective Cohort Study)
5. Diorio C, Robinson PD, Ammann RA, *et al*. Guideline for the Management of *Clostridium difficile* Infection in Children and Adolescents with Cancer and Pediatric Hematopoietic Stem-Cell Transplantation Recipients. *J Clin Oncol* 2018; 36:3162-3171. (International Clinical Practice Guideline)
6. Elstner CL, Lindsay AN, Book LS, Matsen JM. Lack of relationship of *Clostridium difficile* to antibiotic-associated diarrhea in children. *Pediatr Infect Dis* 1983; 2:364–6. (Single-Center Prospective Cohort Study)
7. Gerding DN, Kelly CP, Rahav G, Lee C, Dubberke ER, Kumar PN, Yacyshyn B, Kao D, Eves K, Ellison MC, Hanson ME, Guris D, Dorr MB. Bezlotoxumab for Prevention of Recurrent Clostridium difficile Infection in Patients at Increased Risk for Recurrence. Clin Infect Dis. 2018 Aug 16;67(5):649-656. doi: 10.1093/cid/ciy171. PMID: 29538686; PMCID: PMC6093994.
8. Hongkai Bao, Jennifer Lighter, Yanina Dubrovskaya, Cristian Merchan, Justin Siegfried, John Papadopoulos, Shin-Pung Jen; Oral Vancomycin as Secondary Prophylaxis for *Clostridioides difficile* Infection. *Pediatrics* August 2021; 148 (2): e2020031807. 10.1542/peds.2020-03180.
9. Jangi S, Lamont JT. Asymptomatic colonization by *Clostridium difficile* in infants: implications for disease in later life. *J Pediatr Gastroenterol Nutr* 2010; 51:2–7. (Invited Review)
10. Johnson S, Louie TJ, Gerding DN, et al; Polymer Alternative for CDI Treatment (PACT) Investigators. Vancomycin, metronidazole, or tolevamer for *Clostridium difficile* infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis* 2014; 59:345–54. (Multinational, Randomized Controlled Trial)
11. Kelly, Colleen R. MD, AGAF, FACG1; Fischer, Monika MD, MSc, AGAF, FACG2; Allegretti, Jessica R. MD, MPH, FACG3; LaPlante, Kerry PharmD, FCCP, FIDSA4; Stewart, David B. MD, FACS, FASCRS5; Limketkai, Berkeley N. MD, PhD, FACG (GRADE Methodologist)6; Stollman, Neil H. MD, FACG7. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. The American Journal of Gastroenterology 116(6):p 1124-1147, June 2021. | DOI: 10.14309/ajg.0000000000001278Khanna S, Baddour LM, Huskins WC, *et al*. The epidemiology of *Clostridium difficile* infection in children: a population-based study. *Clin Infect Dis* 2013; 56:1401–6. (Population-based Cohort Study)
12. Kim J, Smathers SA, Prasad P, Leckerman KH, Coffin S, Zaoutis T. Epidemiological features of *Clostridium difficile*-associated disease among inpatients at children's hospitals in the United States, 2001−2006. *Pediatrics* 2008; 122:1266–1270.doi:10.1542/peds.2008-0469. (Multi-Center Retrospective Cohort Study)

13. Lewis SJ and Heaton KW. Stool Form Scale as a Useful Guide to Intestinal Transit Time. *Scandinavian Journal of Gastroenterology*, 1997; 32:9, 920-924, DOI: 10.3109/00365529709011203. (Randomized Controlled Trial)
14. Louie, Thomas J. M.D., Mark A. Miller, M.D., Kathleen, M. Mullane, D.O., Karl Weiss, M.D.
Arnold Lentnek, M.D., Yoav Golan, M.D., Sherwood Gorbach, M.D., Pamela Sears, Ph. D., and Youe-Kong Shue, Ph.D. Fidaxomicin versus Vancomycin for Clostridium difficile Infection. *NEJM* 2011; 364:422-431; DOI: 10.1056/NEJMoa0910812
15. McDonald LC, Gerding DN, Johnson S, *et al.* Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults and Children: 2017 Update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis*, 2018; 66(7): 987-994. (National Clinical Practice Guideline)
16. Nylund CM, Goudie A, Garza JM, Fairbrother G, Cohen MB. *Clostridium difficile* infection in hospitalized children in the United States. *Arch Pediatr Adolesc Med* 2011; 165:451–7. (National Retrospective Cohort Study)
17. Phua TJ, Rogers TR, Pallett AP. Prospective study of *Clostridium difficile* coloniza- tion and paracresol detection in the stools of babies on a special care unit. *J Hyg* (Lond) 1984; 93:17–25. (Single-Center Prospective Cohort Study)
18. Rousseau C, Lemée L, Le Monnier A, Poilane I, Pons JL, Collignon A. Prevalence and diversity of *Clostridium difficile* strains in infants. *J Med Microbiol* 2011; 60:1112–8. (Single-Center Prospective Cohort Study)
19. Sherertz RJ, Sarubbi FA. The prevalence of *Clostridium difficile* and toxin in a nursery population: a comparison between patients with necrotizing enterocolitis and an asymptomatic group. *J Pediatr* 1982; 100:435–9. (Single-Center, Prospective, Comparative Cohort Study)
20. Shirley, Debbie-Ann, William Tornel, Cirle A. Warren, Shannon Moonah; *Clostridioides difficile* Infection in Children: Recent Updates on Epidemiology, Diagnosis, Therapy. *Pediatrics* September 2023; 152 (3): e2023062307. 10.1542/peds.2023-062307
21. Stuart Johnson, Valéry Lavergne, Andrew M Skinner, Anne J Gonzales-Luna, Kevin W Garey, Ciaran P Kelly, Mark H Wilcox, Clinical Practice Guideline by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA): 2021 Focused Update Guidelines on Management of *Clostridioides difficile* Infection in Adults, *Clinical Infectious Diseases*, Volume 73, Issue 5, 1 September 2021, Pages e1029–e1044, https://doi.org/10.1093/cid/ciab549 (National Guideline)
22. Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for *Clostridium-difficile*-associated diarrhoea and colitis. *Lancet* 1983; 2:1043–6. (Prospective Randomized Controlled Trial)
23. Thomas J Sferra, Tomas Merta, Michael Neely, Claudia Murta de Oliveira, Alvaro Lassaletta, Claudia Fortuny Guasch, Mary Beth Dorr, Gregory Winchell, Feng-Hsiu Su, Sarah Perko, Doreen Fernsler, Hetty Waskin, Stephen R Holden, the MODIFY III Study Group, Double-Blind, Placebo-Controlled Study of Bezlotoxumab in Children Receiving Antibacterial Treatment for *Clostridioides difficile* Infection (MODIFY III), *Journal of the Pediatric Infectious Diseases Society*, Volume 12, Issue 6, June 2023, Pages 334–341, https://doi.org/10.1093/jpids/piad031 (Randomized Controlled Trial)
24. Tullus K, Aronsson B, Marcus S, Möllby R. Intestinal colonization with *Clostridium difficile* in infants up to 18 months of age. *Eur J Clin Microbiol Infect Dis* 1989; 8:390–3. (Single-Center Prospective Cohort Study)

25. Tvede M, Schiøtz PO, Krasilnikoff PA. Incidence of *Clostridium difficile* in hospi- talized children. A prospective study. *Acta Paediatr Scand* 1990; 79:292–9. (Single-Center Prospective Cohort Study)
26. van Nood E, Vrieze A, Nieuwdorp M, *et al*. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med* 2013; 368:407–15. (Single-Center, Randomized Controlled Trial)
27. Wenisch C, Parschalk B, Hasenhündl M, *et al*. Comparison of vancomycin, teicoplanin, metronidazole, and fusidic acid for the treatment of Clostridium difficile-associated diarrhea. *Clin Infect Dis* 1996; 22: 813-818. [Erratum: *Clin Infect Dis* 1996; 23:423] (Randomized Controlled Trial)
28. Wolf J, Kalocsai K, Fortuny C, Lazar S, Bosis S, Korczowski B, Petit A, Bradford D, Croos-Dabrera R, Incera E, Melis J, van Maanen R. Safety and Efficacy of Fidaxomicin and Vancomycin in Children and Adolescents with Clostridioides (Clostridium) difficile Infection: A Phase 3, Multicenter, Randomized, Single-blind Clinical Trial (SUNSHINE). Clin Infect Dis. 2020 Dec 17;71(10):2581-2588. doi: 10.1093/cid/ciz1149. PMID: 31773143; PMCID: PMC7744996.
29. Yin J, Kociolek LK, Same RG, Hsu AJ, Amoah J, Tamma PD. Oral Vancomycin May Be Associated With Earlier Symptom Resolution Than Metronidazole for Hospitalized Children With Nonsevere *Clostridiodes difficile* Infections. Open Forum Infect Dis. 2019 Nov 14;6(12):ofz492. doi: 10.1093/ofid/ofz492. Erratum in: Open Forum Infect Dis. 2020 Feb 25;7(2):ofaa041. PMID: 31950069; PMCID: PMC6954469.
30. Zacharioudakis IM, Zervou FN, Dubrovskaya Y, Phillips MS. Oral vancomycin prophylaxis against recurrent Clostridioides difficile infection: Efficacy and side effects in two hospitals. *Infection Control & Hospital Epidemiology*. 2020;41(8):908-913. doi:10.1017/ice.2020.176
31. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of *Clostridium difficile*-associated diarrhea, stratified by disease severity. *Clin Infect Dis* 2007; 45:302–7. (Double-Blind, Randomized Placebo-Controlled Trial)
32. Zilberberg MD, Shorr AF, Kollef MH. Increase in *Clostridium difficile*-related hospitalizations among infants in the United States, 2000–2005. *Pediatr Infect Dis J* 2008; 27:1111–3. (National Retrospective Cross-Sectional Cohort Study)
33. Zilberberg MD, Tillotson GS, McDonald C. *Clostridium difficile* infections among hospitalized children, United States, 1997−2006. *Emerg Infect Dis* 2010; 16: 604-609 doi:10.3201/eid1604.090680. (National Retrospective Cross-Sectional Cohort Study)

Outcome Measures:

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

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

Clostridioides difficile Clinical Pathway
Johns Hopkins All Children's Hospital

Owner(s): Fernando Bula, MD; Juan Dumois, MD; Allison Messina, MD; Katie Namtu, PharmD

Also Reviewed by:

Infectious Diseases: David Berman, DO; Matthew Thomas, MD
Hospitalists: Dipti Amin, MD; Pattie Quigley, MD
Intensive Care: Elliot Melendez, MD; Julia Noether, MD
EC: Joe Perno, MD; Laleh Posey, MD
Gastroenterology: Michael Wilsey, MD
Hematology/Oncology/BMT: Ben Oshrine, MD

Clinical Pathway Management Team: Joseph Perno, MD; Courtney Titus, PA-C

Initially Approved by JHACH Clinical Practice Council: April 16, 2019

First Available on Connect: April 25, 2019

Formatting Updated: 8/8/2019

2024 Update by Antibiotic Stewardship Team

CPC Approval 9/18/24

Date available on website: 10/01/24

Last Revised: 10/1/24

Disclaimer:

Clinical Pathways are intended to assist physicians, physician assistants, nurse practitioners, and other healthcare 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.

The information and guidelines are provided "AS IS" without warranty, express or implied, and Johns Hopkins All Children's Hospital, Inc. hereby excludes all implied warranties of merchantability and fitness for a particular use or purpose concerning the information. Johns Hopkins All Children's Hospital, Inc. shall not be liable for direct, indirect, special, incidental, or consequential damages related to the user's decision to use the information contained herein.