C. difficile (C. diff) Infection

Inpatient
Outpatient

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Indications for C. diff Testing:

1. Patient with sign/symptoms of Severe or Fulminant/Complicated C. diff infection

2. Patient with new onset diarrhea (≥ 3 unformed stools, Bristol score ≥ 5, in 24 hours)

plus

- Host Risk Factors for C. diff:
  - Antibiotic exposure in the last 12 weeks
  - On PPI
  - Hospitalized in the last 12 weeks
  - Predisposing condition

and

- No laxatives for ≥ 48 hours (they can cause *false positive* C. diff NAAT result)

and

- Suspected non-infectious causes of diarrhea excluded

Age ≥ 3 years with new-onset diarrhea?
(In patients with ileus or toxic megacolon, diarrhea may be absent)

No → **Age < 1 year:** Testing for C. diff with diarrhea **is strongly discouraged** due to the high prevalence of asymptomatic carriage
Age 1 - < 3 years: Testing for C. diff is **not routinely recommended** unless alternative etiologies of diarrhea have been excluded

Yes

Patient meets **indications** for C. diff testing?

No → Alternative etiology of diarrhea to be considered

Yes*

*Any concern for Fulminant/Complicated C. diff
If OP, admit the patient and Consult ID, GI, and Surgery ACT as clinically indicated

Onset of diarrhea ≥ 72 hours after admission?

Yes → Prefer
C. diff toxin gene by NAAT (CDIFTN) $$

Consider GIIA if there is concern for fulminant or complicated C. diff infection, suspected viral gastroenteritis vs other bacterial enterocolitis in the setting of a possible outbreak, or persistent diarrhea > 5–7 days without a clear alternative etiology.

No
(OP or IP < 72 hours of admission)

Prefer
GI infection array (GIIA) $$$$

C. diff result will not be reported in EPIC if < 3 years old

C. diff PCR result?

Negative → **C. diff excluded**

- Likely C. diff colonization and not true infection
- Alternative etiology of diarrhea to be considered
- Consider ID consult if any concern for false negative EIA

Positive

Result of reflex Toxin EIA ?

Negative → (same as above)

Positive

C. diff confirmed

Do NOT REPEAT C. diff testing:
- Within 7 days of a negative test
- Within 14 days of a positive test
- For test of cure

If receiving systemic antibiotics:
Reassess the indication for ongoing need.
Discontinue as early as possible when clinically feasible.

Initial episode/ 1st recurrence?

No (2nd/subsequent recurrence)

Assess Severity

Fulminant/Complicated*

Severe or Non-Severe

*Fulminant/Complicated C. diff
Consult ID, GI, and Surgery
ACT as clinically indicated

Assess Severity

Fulminant/Complicated*

Severe or Non-Severe

Go to Management
Initial/1st recurrence

In the absence of clinical improvement **after 5 days of appropriate anti-C. diff therapy,** ID consult is recommended, along with re-evaluation for other potential etiologies of diarrhea.

Go to Management
2nd or Subsequent Recurrence

NAAT: nucleic acid amplification test
EIA: enzyme immunoassay

Microbiology, Epidemiology & Colonization

Microbiology

- Clostridioides difficile is a gram-positive, anaerobic, spore-forming bacterium that can produce toxins A and B resulting in clinical disease.
- Symptoms of acute C difficile infection (diarrhea or colitis) is caused by activity of **toxin in the colon**, as toxins A and B can inactivate GTP- binding proteins, leading to apoptosis and inflammation.

Epidemiology

- **Community-associated C. difficile infection** has been rising in children accounting for **70% of cases of C. difficile infection cases**. This increase rate appears to coincide with the adoption of highly sensitive nucleic acid amplification test (NAAT) platforms for the diagnosis of C. difficile.
- C. difficile is **the leading infectious cause of healthcare-associated diarrhea** in all age groups, which accounts for 4-25% of cases.

Colonization

- *The American Academy of Pediatrics* recommends evaluating alternative causes of diarrhea in children <3 years with a positive C. difficile test, as they are often colonized.
  - In children < 1 year of age, C. difficile can be detected in **up to 50%** of asymptomatic infants and detection of C. difficile may represent **an incidental finding in this age group**.
  - C. difficile colonization rates decrease to 1-3 % by 3 years of age, similar to rates in that of non-hospitalized adults.
  - Therefore, testing for C. difficile should **not** be routinely performed **in children aged < 3 years old.**
- **Patients with underlying diseases have increased colonization rates, for example:**
  - Malignancy (15-30%)
  - Cystic fibrosis (33-50%)
  - Inflammatory bowel disease (11-20%)
  - Hematopoietic cell transplant recipients (up to 40%)
- Colonized patients **with underlying conditions** also have a higher risk of developing C. difficile infection. Efforts should be made **to differentiate true C. difficile infection from colonization** in these children.

Prevalence of C. difficile Colonization Rates in Children

Age	Toxigenic C. difficile colonization rate
< 1 year	14% (41% with both toxigenic and non-toxigenic strains colonization)
1-2 years	Up to 13%
2 -< 3 years	1-3%; After this age group, rate of colonization similar to rates in that of non-hospitalized adults

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Age < 3 years

- In NCH, given high rates of asymptomatic carriage of toxigenic C. difficile in young children, test results will not be available in GIIA in those < 3 years of age (result not reported).
- In children < 3 years old with **host risk factors** and compatible clinical symptoms, where **no alternative etiology** is identified, C. difficile testing may be considered. If clinically indicated or highly suspected, **physicians may request the NCH laboratory to release the hidden C. difficile result** in GIIA.

Age	Testing recommendation
< 1 year	Testing for C. difficile in children < 12 months with diarrhea **is strongly discouraged** due to the high prevalence of asymptomatic carriage of toxigenic C. difficile. Additionally infants rarely develop true C. diff infection despite colonization with toxigenic C. difficile.
1 - < 3 years	C. difficile testing **should not routinely be performed** in children 1 - < 3 years of age with diarrhea, unless other infectious or noninfectious causes have been excluded. C. difficile testing is **only** recommended for patients with prolonged or worsening diarrhea, with **HOST RISK FACTORS** and with no alternative etiology identified.

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Non Infectious Disease Cause of Diarrhea

- Diarrhea due to dietary (lactose, sugars, tube feeding, etc)
- Diarrhea as a known medication side effect
- Diarrhea due to underlying GI conditions including but not limited to:
  - Irritable bowel syndrome
  - Inflammatory bowl disease
  - Malabsorption syndrome

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Host Risk Factors

- **Previous antibiotic exposure preceding 12 weeks is the single <u>most important</u> risk factor for C. diff infection**
  - Nearly all antibiotics, but particularly exposure to fluoroquinolones, clindamycin, combination penicillins (broad spectrum), 2nd/3rd/4th generation cephalosporins, and carbapenems in preceding 12 weeks have been associated with pediatric community associated C. diff infection
  - Carbapenems and 3rd and 4th generation cephalosporin antibiotics remain the most strongly associated with healthcare facility-onset C. diff infection
- **Use of Proton Pump Inhibitor**
- **Hospitalization in the previous 12 weeks**
- **Predisposing/Co-morbid conditions**
  - Hematopoietic stem cell or solid organ transplant recipients
  - Immunocompromised state (e.g. malignancy)
  - Underlying gastrointestinal illness (e.g. Inflammatory bowel disease)
  - Underlying bowel disease (e.g. Hirschsprung disease)
  - Recent gastrointestinal tract surgery or procedure
  - Presence of nasogastric, gastrostomy or jejunostomy tubes
  - Chronic kidney disease or end-stage renal disease

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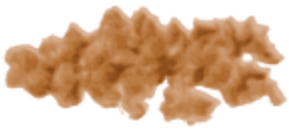
Bristol Stool Chart

Do **NOT** order C. diff testing if Bristol stool Type ≤ 4

Type 1		Separate hard lumps, like nuts (hard to pass)
Type 2		Sausage-shaped but lumpy
Type 3		Like a sausage but with cracks on the surface
Type 4		Like a sausage or snake, smooth and soft
Type 5		Soft blobs with clear-cut edges
Type 6		Fluffy pieces with ragged edges, a mushy stool
Type 7		Watery, no solid pieces. **Entirely Liquid**

Lewis SJ, Heaton KW (1997) Stool form scale as a useful guide to intestinal transit time. Scandinavian Journal of Gastroenterology 32: 920–4

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Severity Assessment

- Classification of severity of C. difficile infection is based on expert opinion and extrapolated from adult data, and there are no pediatric-specific C. diff infection severity data.
- In severe or fulminant/complicated disease, laboratory criteria includes, but is not limited to CBC with diff. and chemistry. Abdominal imaging should also be considered.

	Non-severe Disease	Severe Disease	Fulminant/Complicated Disease
Clinical Criteria	• Mild to moderate non-bloody diarrhea • Mild to moderate abdominal discomfort or tenderness	• Fever • Severe or bloody diarrhea • Severe abdominal pain or tenderness • Dehydration requiring IV fluid	• Ileus • Toxic megacolon • Hemodynamic instability with or without use of vasopressors
Supportive Laboratory Criteria	No notable laboratory abnormalities	• WBC ≥ 15,000 cells/ mm3 • Acute kidney injury	Same as severe

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Diagnostic Testing Methods

By selecting symptomatic patients at increased risk for clinically significant C. diff infection, inappropriate testing or treatment can be reduced.

C. difficile infection (CDI) Diagnostic Testing Framework

	Testing warranted if:	Do NOT test if:
When	• Diarrheal stool (≥ 3 unformed stools/day with Bristol score ≥ 5) • In patients with unformed stool at baseline, a clinically significant increase in stool frequency and volume over baseline*	• Bristol score ≤ 4 • Receiving laxatives or stool softeners in preceding 48h • Within 7 days of a negative C. difficile PCR^ result • Within 14 days of a positive C. difficile test • As a test of cure
Who	At risk children ≥ 3 years of age	< 3 years of age **with** risk factors for C. difficile in whom other causes of diarrhea have been excluded
What	See **diagnostic algorithm** • Diarrhea onset as outpatient or < 72h from admission, prefer **GIIA** • New-onset diarrhea ≥ 72 hours after admission prefer pathogen-specific C. difficile testing (CDIFTN) as the first-line test in patients ≥ 3 years of age & • GIIA may be considered in those < 3 years of age, especially with any concern for nosocomial viral gastroenteritis, persistent diarrhea > 5-7 days without a clear alternative etiology.	• Molecular tests should not be used as a stand-alone diagnostic test for CDI as it can't not distinguish colonization vs true infection. • The sensitivity of the GIIA and CDIFTN are comparable, neither tests for free C. difficile toxin.

^ PCR has very high negative predictive value for CDI, in >99%
* In patients with unformed stool at baseline, diarrhea is defined as a significant increase in both stool frequency and volume ≥50% above baseline. Greater than 30 g/kg/day in children, or >200 g/day in teens and adults with colostomies generally constitutes diarrhea. This is distinct from ileostomies and jejunostomies, where normal output is expected to be higher.
& : If CDIFTN is negative and there is ongoing concern for healthcare-associated infectious diarrhea due to other pathogens (e.g. viral gastroenteritis), consider obtaining GIIA thereafter)

Testing strategy and available testing methods

- 2-step testing strategy (PCR/NAAT reflex to Toxin EIA) is strongly recommended when C. difficile infection is a differential diagnosis.
- Detection of toxin in stool is a better predictor of symptomatic C. difficile infection than a positive PCR/NAAT alone.

Summary of Available Testing Methods for C. difficile infection at NCH

	Tests to detect presence of C. difficile toxin gene		Tests to detect presence of C. difficile free toxin	
Test Name	**GIIA**	**C. difficile Toxin Gene by NAAT**	**Toxin A & B by EIA**	**C. difficile Cytotoxin Cell Assay**
Test Code	**GIIA**	**CDIFTN**	**No test code,** automatic reflex if molecular test positive	**XCDFTX (send out)**
Test Method	Multiplex	Singleplex (NAAT)	Enzyme immunoassay	Cell Culture/ Neutralization
Container	**Cary Blair Sterile container**	**Sterile container**	**Sterile container (Cary Blair acceptable)**	**Sterile container**
Detects	Genes that may produce Toxin A & B		Toxin A & B	Toxin B
Advantages	Highly sensitive		Highly specific; Useful to determine true infection vs colonization	
	• Target broad range of infectious etiologies • Rapid TAT	• Only target toxigenic strains of C. difficile, so useful if highly suspected • Cost effective	• Rapid TAT • Cost effective	Cost effective
Disadvantages	Do not differentiate between patients with true infection vs colonization		In < 3 years old, the presence of toxin still may not result in true C. diff infection	
	Expensive		Lower sensitivity compared to cytotoxin cell assay	Long TAT (~3-5 days)
Estimated Cost to Patient^	$709	$201		$43
Operation Time	2-4h	24h (only run once daily)	2-4h after molecular test result	3-5 days

Abbreviation: GI, gastrointestinal; PCR, polymerase chain reaction; NAAT, nucleic acid amplification technique; TAT, turnaround time.
^as of 2/2022

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Recurrent C. difficile infection

- Recurrent C. difficile infection is defined as a **symptomatic patient** with a positive C. difficile stool specimen following a C. difficile infection episode that occurred in the previous **2 to 8 weeks**.
  - Risk of recurrent C. difficile infection include the presence of underlying conditions (e.g. cancer, IBD, recent surgery, medical device dependent, and antibiotics exposure)
  - Approximately **25%** of patients experience a first recurrent C. difficile infection after completing initial anti-C. difficile antibiotic therapy.
  - After a recurrence, the chance of further recurrences goes up to **40-60%.**
  - Multiple recurrences (≥ 2 recurrences) are observed in ~9%

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Management: Initial/1st Recurrence

- **PO vancomycin** is recommended for treatment of initial, non-severe infection in children and PO metronidazole should be considered when PO vancomycin is not available
- ID consultation is required for utilization of **PO fidaxomicin** in treatment of infection.
  - Fidaxomicin was approved by FDA in Jan 27, 2020 for infection in children ≥ 6 months of age.
  - Phase 3 multi-center prospective trial in children demonstrated no difference in clinical response at the end of therapy between fidaxomicin and vancomycin. However, at 30 days post-treatment, fidaxomicin was associated with a higher rate of sustained response (68% vs. 50%), with an adjusted treatment difference of 18.8% (95% CI, 1.5%–35.3%).
  - Due to the substantially higher cost of fidaxomicin relative to vancomycin and the lack of robust pediatric data, fidaxomicin is recommended as a second-line option for recurrent or refractory C. difficile infection.
- If refractory or recurrent C. difficile infection (≥ 3 episodes) is a concern in the outpatient setting, consider referral to Infectious Diseases Clinic for further evaluation and management guidance
- Reassess the indication for ongoing systemic antibiotics daily and discontinues as early as possible if clinically feasible
- In the absence of clinical improvement after 5 days of appropriate anti-C diff therapy, an ID consult is recommended, along with re-evaluation for other potential etiologies of diarrhea.

Initial C. diff Infection or 1st Recurrence

Severity	Treatment	Dosing	Maximum/Dose
Non-Severe	PO Vancomycin x 10 days (preferred)	10mg/kg/dose QID	125mg
	OR	*OR*	
	For initial episode, PO Metronidazole x 10 days only when PO vanco is unavailable	< 12 months: 7.5mg/kg/dose QID Children and adolescents: 7.5mg/kg/dose TID to QID	500mg
Severe	PO Vancomycin x 10 days	10mg/kg/dose QID	500mg
Fulminant/ Complicated	*EITHER*	*EITHER*	
	PO Fidaxomicin^	0 - < 6yrs: 16mg/kg/dose BID ≥ 6yrs: 200mg/dose BID	200mg
	OR	*OR*	
	PO Vancomycin	10mg/kg/dose QID	500mg
	IN ADDITION TO	*IN ADDITION TO*	
	PR* Vancomycin	1–3 yrs: 50 mL/dose QID 4–9 yrs: 75 mL/dose QID ≥ 10 yrs: 100 mL/dose QID	1–3 yrs: 250 mg 4–9 yrs: 375 mg ≥ 10 yrs: 500 mg
	AND	*AND*	
	IV Metronidazole	10mg/kg/dose TID	500mg

*PR (per rectum); If ileus, consider adding rectal instillation of vancomycin enema solution via rectal foley, retain for 1 hour q 6h. IV metronidazole alone is NOT appropriate therapy for CDAD.

^ Use of fidaxomicin recommended in consultation with ID.

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Management: 2nd or Subsequent Recurrence of C. diff Infection

- Reassess the indication for ongoing systemic antibiotics daily and discontinues as early as possible if clinically feasible
- In the absence of clinical improvement **after 5 days of appropriate anti-C diff therapy**, an ID consult is recommended, along with re-evaluation for other potential etiologies of diarrhea.
- **If ≥ 3 recurrences**, strongly recommend **GI and ID consult** for further assistance

2nd or Subsequent C. diff Recurrence			
Severity	**Treatment**	**Dosing**	**Maximum/Dose**
Non-Severe	PO Vancomycin x 10-14 days with a tapered and pulsed regimen	10mg/kg/dose QID • then 10mg/kg/dose BID x 7 days • then 10mg/kg/dose QDay x 7 days • then 10mg/kg/dose QOD x 2-8 weeks	125mg
	OR	*OR*	
	PO Fidaxomicin^ x 10 days (per ID recommendation only)	0 - < 6yr: 16mg/kg/dose BID ≥ 6yr: 200mg/dose BID	200mg
	OR	*OR*	
	PO Vancomycin x 10 days	10mg/kg/dose QID	125mg
	FOLLOWED BY	*FOLLOWED BY*	
	PO Rifaximin# x 20 days	10mg/kg/dose TID	400mg
Severe	PO Vancomycin x 10-14 days with a tapered and pulsed regimen	10mg/kg/dose QID • then 10mg/kg/dose BID x 7 days • then 10mg/kg/dose QDay x 7 days • then 10mg/kg/dose QOD x 2-8 weeks	125mg
	OR	*OR*	
	PO Fidaxomicin^ x 10 days (per ID recommendation only)	0 - < 6yr: 16mg/kg/dose BID ≥ 6yr: 200mg/dose BID	200mg
	OR	*OR*	
	PO Vancomycin x 10 days	10mg/kg/dose QID	125mg
	FOLLOWED BY	*FOLLOWED BY*	
	PO Rifaximin# x 20 days	10mg/kg/dose TID	400mg
Fulminant/ Complicated	*EITHER*	*EITHER*	
	PO Fidaxomicin^ (per ID recommendation only)	0 - <6yr: 16mg/kg/dose BID ≥ 6yr: 200mg/dose BID	200mg
	OR	*OR*	
	PO Vancomycin	10mg/kg/dose QID	500mg
	IN ADDITION TO	*IN ADDITION TO*	
	PR* Vancomycin	1–3 yrs: 50 mL/dose QID 4–9 yrs: 75 mL/dose QID ≥ 10 yrs: 100 mL/dose QID	1–3 yrs: 250 mg 4–9 yrs: 375 mg ≥ 10 yrs: 500 mg
	AND	*AND*	
	IV Metronidazole	10mg/kg/dose TID	500mg

*PR (per rectum); If ileus, consider adding rectal instillation of vancomycin enema solution via rectal foley, retain for 1 hour q 6h. IV metronidazole alone is NOT appropriate therapy for CDAD.

Rifaximin is not approved by the US Food and Drug Administration (FDA) for use in children <12 years of age, thus, there is no pediatric approved dosing for CDAD.

^ Use of fidaxomicin recommended in consultation with ID.

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Metrics

Pathway Goal

- Clostridioides (formerly Clostridium) difficile infection (CDI) can be associated with increased mortality, prolonged hospitalization, increased hospital costs. This guideline will provide evidence-based recommendations for the diagnosis and management of CDI in children, including diagnostic and antibiotic stewardship, focusing on appropriate CDI testing and targeted therapy.

Quality Measures

Outcome Metrics

- Rate of anti-C. difficile antibiotic use per 1,000 patient-days: % treated outside of guideline-recommended indications
- Number of GIIA or CDIFTN tests ordered per 1,000 inpatient-days, % tested outside of guideline-recommended indications.

Process Metrics

- Pathway Utilization

Balancing Metrics

- Monitor for potential missed or delayed diagnoses: 7-day revisit rate to ED/UC or readmission after discharge due to confirmed C. diff (PCR+/EIA+) after initial discordant C. diff testing (i.e., PCR+/EIA-)
- Percentage of patients with GIIA ordered and confirmed other infectious etiology after negative CDIFTN

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Clinical Pathway Development

This clinical pathway was developed using the process described in the NCH Clinical Pathway Development Manual Version 6, 2022. Clinical Pathways at Nationwide Children's Hospital (NCH) are standards which provide general guidance to clinicians. Patient choice, clinician judgment, and other relevant factors in diagnosing and treating patients remain central to the selection of diagnostic tests and therapy. The ordering provider assumes all risks associates with care decisions. NCH assumes no responsibility for any adverse consequences, errors, or omissions that may arise from the use or reliance on these guidelines. NCH's clinical pathways are reviewed periodically for consistency with new evidence; however, new developments may not be represented, and NCH makes no guarantees, representations, or warranties with respect to the information provided in this clinical pathway.

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