



DIAGNOSIS AND MANAGEMENT OF

Clostridium difficile (*C. diff*) Infection

This care process model (CPM) was developed jointly by Intermountain Healthcare's Antibiotic Stewardship Committee, Division of Infectious Diseases, Multiple-Drug Resistant Organism (MDRO) subcommittee, Central Laboratory, and experts in gastroenterology. Based on expert opinion, Society for Healthcare of America/Infectious Disease Society of America^{IDSA} Clinical Practice Guidelines, and American College of Gastroenterology^{AJG} Guidelines, this CPM provides best-practice recommendations for diagnosis and management of *Clostridium difficile* (*C. diff*) infections in adults, including guidance for when and which antibiotics should be used.

► KEY POINTS

- **C. diff is common and preventable.** *C. diff* accounts for 20% to 30% of cases of antibiotic-associated diarrhea and is the most commonly recognized cause of infectious diarrhea in healthcare settings.^{IDSA} Cases often appear in clusters and outbreaks within institutions. Healthcare workers' hands are the main means of spread during non-outbreak periods, indicating that handwashing is critical. Other appropriate infection-control measures (gowns, gloves, room cleaning with bleach, etc.) are essential to the control of spread within hospitals (see back page for prevention tips).
- **Several studies have demonstrated that C. diff is usually induced by antibiotics.** Olson et al reported that 96% of patients with symptomatic *C. diff* took antibiotics within 14 days of diarrhea onset, and all patients received antibiotics within the previous 3 months.^{OLS} Both length of antibiotic exposure and exposure to multiple antibiotics increase the risk for infection.^{IDSA}
- **Antibiotics are overprescribed.** Up to 50% of antibiotic prescriptions are either inappropriate (wrong drug) or unnecessary (not needed).^{CDC} Reducing this number could decrease the incidence of *C. diff*.
- **C. diff is a serious illness that requires coordinated treatment.** *C. diff* can range from a mild, irritating illness to a prolonged, life-threatening infection. Appropriate treatment of *C. diff*, and the management of complications, is complex and may require a coordinated effort from Infectious Diseases, Gastroenterology, and Internal Medicine.

► Why Focus on C. diff?

- **C. diff is a serious public health threat.** In the United States, *C. diff* causes 250,000 infections and 14,000 deaths per year, and it costs at least \$1 billion in excess medical costs per year.^{CDC}
- **The Centers for Disease Control and Prevention (CDC) has raised C. diff to a threat level of urgent.** Because *C. diff* spreads rapidly and is naturally resistant to many drugs used to treat other infections, the CDC called *C. diff* an "immediate public health threat that requires urgent and aggressive action" in its 2013 Threats Report.^{CDC}
- **A more virulent strain resistant to fluoroquinolones has emerged.** Deaths related to *C. diff* increased 400% between 2000 and 2007, in part due to this more virulent strain.^{CDC} A 2005 study of 8 healthcare facilities showed that this resistant strain accounted for 50% or more of the isolates from 5 of the 8 facilities included in the study.^{NEJM}

The inside pages of this tool provide an algorithm and associated notes, and can be folded open and posted in your office or clinic. The back page provides prevention tips, references, and resources.

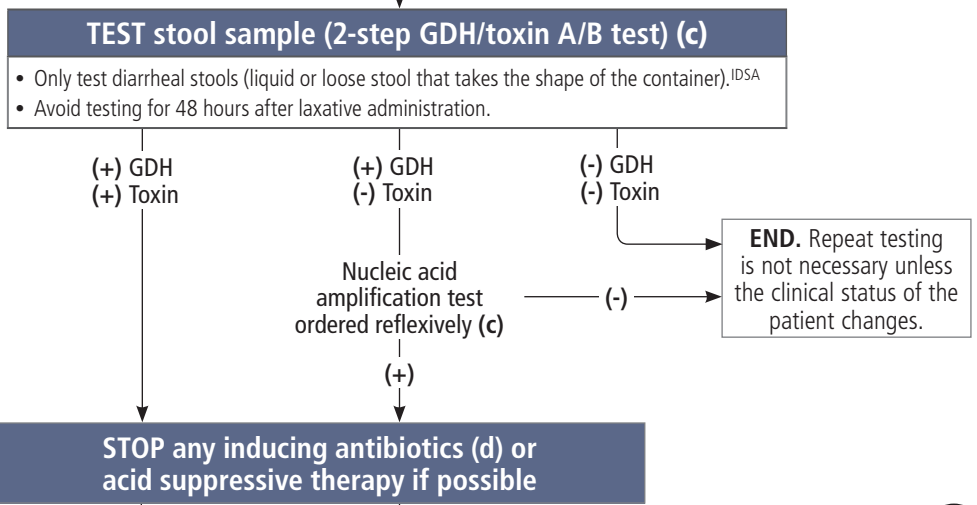
► GOALS

- Prevent *C. diff* by ensuring appropriate antibiotic use with the help of Intermountain's Antibiotic Stewardship Programs.
- Prevent the spread of *C. diff* by optimizing infection-control measures.
- Treat *C. diff* appropriately by determining severity of infection and prescribing appropriate antibiotics based on severity.
- Manage recurrent *C. diff* in a coordinated, cost-effective way.



▶ **ALGORITHM: DIAGNOSIS**

Signs and Symptoms of C. diff Infection (a)(b)



DIAGNOSE C. diff infection; ASSESS severity^{IDSA, AJG}

MILD	MODERATE	SEVERE	SEVERE-COMPLICATED
Presents with diarrhea as the only symptom	Presents with diarrhea and additional symptoms (but not signs and symptoms that meet the definition of severe or severe-complicated)	Presents with diarrhea and has or develops ≥2 of the following during the course of disease: <ul style="list-style-type: none"> Hypoalbuminemia <2.5 mg/mL WBC ≥15,000 cells/μL or bandemia >20% of neutrophils Fever ≥38.0°C Systolic blood pressure <100 mm Hg due to C. diff Clinical diagnosis of ileus Abnormal abdominal CT imaging findings due to C. diff infection Serum creatinine level ≥1.5 times the preinfection level Age ≥65 years 	Meets criteria for severe disease AND presents with or develops any of the following as a result of the C. diff infection: <p>Clinical:</p> <ul style="list-style-type: none"> Admission to the ICU Sustained hypotension requiring volume repletion and/or vasoactive medications Significant abdominal distention Mental status change <p>Radiographic:</p> <ul style="list-style-type: none"> Ascites Ileus Pancolitis Colonic dilation or megacolon <p>Laboratory:</p> <ul style="list-style-type: none"> WBC >35,000 or <2,000 cells/μL Serum lactate >2.2 mmol/L Any evidence of end organ failure

EDUCATE patient (e)

ALGORITHM NOTES: DIAGNOSIS

(a) Risk factors. Longer exposure to antimicrobials and exposure to multiple antimicrobials increase the risk of C. diff infection. Antimicrobial use usually precedes C. diff, but there are occasional reports of C. diff without antimicrobial use.^{IDSA}

Other risk factors include advanced age, duration of hospitalization, cancer chemotherapy, HIV, GI surgery, and manipulation of the GI tract (including tube feeding).^{IDSA}

(b) Signs and symptoms of C. diff infection include:

- New onset, unexplained diarrhea (≥3 in ≤24 consecutive hours) not attributed to another cause (e.g., laxative use).
- Fever, cramping, abdominal discomfort, and a peripheral leukocytosis (found in fewer than half the patients).^{IDSA}

(c) Testing. Laboratory testing should be used to confirm clinical suspicion of infection and should always be interpreted with the clinical context in mind. Intermountain microbiology laboratories use 2 different testing strategies:

Combined GDH/toxin A/B antigen test (at all sites except Primary Children’s Hospital and Utah Valley Regional Medical Center)

- This is a 2-step algorithm. A combined glutamate dehydrogenase (GDH)/Toxin A/B test is done first. A second test (PCR-based) is done reflexively if the first test yields an indeterminate result.

- Results possible:
 - Positive GDH and Positive Toxin = POSITIVE
 - Negative GDH and Negative Toxin = NEGATIVE
 - Positive GDH and Negative Toxin = INDETERMINATE
 - Refer to PCR-based test (done reflexively) for final result. If second test is positive, C. diff diagnosis is confirmed. If second test is negative, C. diff test is negative, and the patient does not require treatment.

Direct nucleic acid amplification test

- Results possible:
 - Positive for toxigenic C. diff
 - Negative for toxigenic C. diff
- Used as first-line test at Primary Children’s Hospital and Utah Valley Regional Medical Center AND as a reflex second-line test at all other sites for INDETERMINATE tests.

(d) Inducing antibiotics may influence the risk of C. diff recurrence and the duration of symptoms.

(e) Patient education. Use the Krames Clostridium difficile Infection HealthSheet to support patient education. (See back for directions for accessing this sheet.)



▶ ALGORITHM: TREATMENT

C. diff Infection Diagnosis (first infection)

PRESCRIBE antibiotics for first infection (f)

MILD-MODERATE	SEVERE	SEVERE-COMPLICATED
Metronidazole , 500 mg orally 3 times daily for 10 days <div style="border: 1px solid black; padding: 5px; text-align: center;">If no improvement in 5–7 days</div>	Vancomycin , 125 mg orally 4 times daily for 10 days (g) <div style="border: 1px solid black; padding: 5px; text-align: center;">If no improvement in 7 days</div>	<ul style="list-style-type: none"> If no abdominal distention: Vancomycin, 125 mg orally 4 times daily AND metronidazole, IV 500 mg 3 times daily (duration depends on clinical response) If ileus, toxic megacolon, and/or significant abdominal distention: Vancomycin, 500 mg orally 4 times daily AND metronidazole, IV 500 mg 3 times daily AND vancomycin, rectally 4 times daily (500 mg vancomycin in 500 mL normal saline) (duration depends on clinical response) <div style="border: 1px solid black; padding: 5px; text-align: center;">If no improvement in 48–72 hours</div>
Switch to vancomycin , 125 mg orally 4 times daily for 10 days	Consult Infectious Diseases and/or Gastroenterology for evaluation of emerging therapies (e.g., fecal microbiota therapy [FMT] (h), fidaxomicin, etc.)	<ul style="list-style-type: none"> Consult Colorectal Surgery for consideration of colectomy for severely ill patients with refractory shock and serum lactate of >5 mmol/L and a peripheral WBC of >50,000 cells per μL Consult Infectious Diseases and/or Gastroenterology for further management and evaluation of emerging therapies (e.g., FMT (h), fidaxomicin, etc.)

NOTE: Test of cure is unnecessary if symptoms resolve unless the clinical status of the patient changes.

Suspicion of Recurrent C. diff Infection (i)

TEST stool sample (c)

(-) → END. Evaluate for other diagnoses.

(+) ↓

MANAGE recurrent C. diff

	MILD-MODERATE	SEVERE	SEVERE-COMPLICATED
First recurrence	Same antibiotic used for first infection (metronidazole or vancomycin) (j)	Same treatment as severe primary infection	Same treatment as severe-complicated primary infection
Second recurrence	Vancomycin , 125 mg orally 4 times daily for 14 days, THEN 125 mg twice daily for 7 days, THEN 125 mg once daily for 7 days, THEN 125 mg every 2 or 3 days for 2 weeks		
Third recurrence	<ul style="list-style-type: none"> Stabilize with vancomycin, 125 mg orally 4 times daily (plus IV metronidazole and vancomycin retention enema if meets criteria under first infection, SEVERE-COMPLICATED above) Consult Infectious Diseases and/or Gastroenterology for evaluation of emerging therapies (e.g., FMT, fidaxomicin, etc.) 		

NOTE: Test of cure is unnecessary if symptoms resolve unless the clinical status of the patient changes.

ALGORITHM NOTES: TREATMENT

(f) Antiperistaltics. Avoid antiperistaltic agents for patients with *C. diff*. Antiperistaltics may obscure symptoms and precipitate toxic megacolon.^{IDSA}

(g) Intravenous vancomycin taken orally is equally efficacious and more cost effective than vancomycin tablets.

(h) Fecal microbiota therapy (FMT).

• **Indications** for FMT:

- Recurrent or relapsing *C. diff* (defined as **a**. At least 3 episodes of mild to moderate infection and failure of a 6–8 week taper of vancomycin with or without an alternative antibiotic OR **b**. At least 2 episodes of severe infection resulting in hospitalization and associated with significant morbidity)
- Moderate *C. diff* infection not responding to standard therapy for at least a week
- Severe or fulminant *C. diff* infection with no response to standard therapy after 48 hours

• **Contraindications to FMT:** Toxic megacolon, sepsis, significant immunosuppression, spontaneous bleeding, and conditions that increases risk of perforation.

• **FMT protocol.** Intermountain's *Fecal Microbiota Therapy Protocol* provides indications, screening requirements, etc.

• **FMT education.** Use Intermountain's fact sheets to educate the patient:

- [Fecal Microbiota Therapy: Information for Recipients](#)
- [Fecal Microbiota Therapy: Information for Donors](#)



(i) C. diff recurrence. Recurrences generally occur within 4 weeks of completing therapy.

Not all patients with recurrent diarrhea after a *C. diff* infection have recurrent *C. diff*. A repeat positive test in a patient with minimal or no symptoms should not prompt retreatment.

(j) Metronidazole. Do not prescribe metronidazole for long-term therapy because of potential for cumulative neurotoxicity.^{IDSA}



Intermountain measures:

- Incidence of infection (hospital-acquired and healthcare-associated community onset)
- Initial antibiotic therapy
- Total antimicrobial use
- Rate of recurrence
- Mortality

► PREVENTION: GENERAL

To reduce *C. diff* infections, follow these prevention tips:

- Minimize unnecessary antimicrobial use by:
 - Treating infection, not colonization or contamination. Not every bacterial culture requires antibiotic therapy. Ensure that a true infection is present before prescribing an antibiotic.
 - Reviewing all antimicrobial medications and microbiology results **after 48 hours of use** to determine if modifications can be made.
 - Using the **narrowest spectrum antimicrobial** to treat suspected or proven infections.
 - Providing **indications** with every antimicrobial order.
- Recommending routine use of probiotics for the prevention of *C. diff* is not recommended. There are limited data to support the use of probiotics, and there is a potential risk of bloodstream infection.^{IDSA}
- Only use acid-suppressing medications (H2B/PPI) when clinically indicated.

► PREVENTION: IN THE HOSPITAL

- Initiate contact isolation for patients with:
 - **Any diarrhea** suspected to be infectious
 - Suspected or known ***C. diff* infection**
 - **Recurrent diarrhea** and a **history of recent *C. diff* infection**
 - **Confirmed case of *C. diff* infection** (contact isolation required for the duration of hospitalization)
- Adhere to good hand hygiene practices with use of SOAP AND WATER following glove removal if *C. diff* infection is suspected or confirmed.
- Disinfect personal equipment used for patients with *C. diff* infection with sodium hypochlorite containing disinfectant (bleach). When using disinfectants, follow recommendations regarding appropriate kill time and always wear appropriate personal protective equipment (gown and gloves).

This CPM presents a model of best care based on the best available scientific evidence at the time of publication. It is not a prescription for every physician or every patient, nor does it replace clinical judgment. All statements, protocols, and recommendations herein are viewed as transitory and iterative. Although physicians are encouraged to follow the CPM to help focus on and measure quality, deviations are a means for discovering improvements in patient care and expanding the knowledge base. Send feedback to Eddie Stenehjsem, MD, MSc, Intermountain Healthcare, Infectious Diseases, Eddie.Stenehjsem@imail.org.

References

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- CDC Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States, 2013. <http://www.cdc.gov/drugresistance/threat-report-2013>. Accessed November 18, 2013.
- IDSA Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the Society for Healthcare Epidemiology of America (SHEA) and the Infectious Diseases Society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.
- NEJM McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med*. 2005;353:2433-2441.
- OLS Olson MM, Shanholtzer CJ, Lee JT Jr, Gerding DN. Ten years of prospective *Clostridium difficile*-associated disease surveillance and treatment at the Minneapolis VA Medical Center, 1982–1991. *Infect Control Hosp Epidemiol*. 1994;15:371–381.

Intermountain patient tools

To order copies, go to i-printstore.com.

- [Fecal Microbiota Therapy: Information for Recipients](#)
- [Fecal Microbiota Therapy: Information for Donors](#)

Krames patient tools

To find and print the *Clostridium difficile Infection* Krames HealthSheet at your desktop:

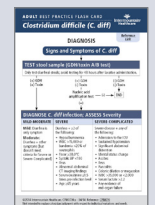
1. Open the [Patient Education Library](#) page by typing PEN in your address bar (within the firewall).
2. Click the KRAMES On-Demand button.
3. Type "*Clostridium difficile*" in the search bar. The *Clostridium difficile Infection* HealthSheet appears at the top of the list.

This HealthSheet will also appear in the Cerner EMR as a suggested patient education item.

Intermountain provider tools

Available from intermountain.net and intermountainphysician.org:

- [Antibiotic Best Practices web page](#)
- [Fecal Microbiota Therapy Protocol](#)
- [Clostridium difficile \(C. diff\) Flash Card](#)



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