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. 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. Both length of antibiotic exposure and exposure to multiple antibiotics increase the risk for infection.

- **Antibiotics are overprescribed.** Up to 50% of antibiotic prescriptions are either inappropriate (wrong drug) or unnecessary (not needed). 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.

- **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.

- **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. 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.

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.
ALGORITHM: DIAGNOSIS

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

TEST stool sample (2-step GDH/toxin A/B test) (c)
- Only test diarrheal stools (liquid or loose stool that takes the shape of the container).\textsuperscript{IDSA}
- Avoid testing for 48 hours after laxative administration.

STOP any inducing antibiotics (d) or acid suppressive therapy if possible

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

<table>
<thead>
<tr>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
<th>SEVERE-COMPLICATED</th>
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<tbody>
<tr>
<td>Presents with diarrhea as the only symptom</td>
<td>Presents with diarrhea and additional symptoms (but not signs and symptoms that meet the definition of severe or severe-complicated)</td>
<td>Presents with diarrhea and has or develops ≥2 of the following during the course of disease: • Hypoalbuminemia &lt;2.5 mg/mL • WBC ≥15,000 cells/µL or bandemia &gt;20% of neutrophils • Fever ≥38.0°C • Systolic blood pressure &lt;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</td>
<td>Meets criteria for severe disease AND presents with or develops any of the following as a result of the C. diff infection: Clinical: • Admission to the ICU • Sustained hypotension requiring volume repletion and/or vasoactive medications • Significant abdominal distention • Mental status change Radiographic: • Ascites • Ileus • Pancolitis • Colonic dilation or megacolon Laboratory: • WBC &gt;35,000 or &lt;2,000 cells/µL • Serum lactate &gt;2.2 mmol/L • Any evidence of end organ failure</td>
</tr>
</tbody>
</table>

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

(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.)
Avoid antiperistaltic agents for patients with recurrent or relapsing severe-complicated toxic megacolon, sepsis, if no abdominal distention.

Do not prescribe metronidazole for long-term severe infection diagnosis (first infection).

Consult Colorectal Surgery for consideration of colectomy if ileus, toxic megacolon, and/or significant abdominal distention.

Fecal microbiota therapy (FMT) provides microbiota restoration and is more cost effective than vancomycin tablets.

**ALGORITHM NOTES: TREATMENT**

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

(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](http://www.intermountainmedicine.org) provides indications, screening requirements, etc.

- **FMT education.** Use Intermountain’s fact sheets to educate the patient:
  - [Fecal Microbiota Therapy: Information for Recipients](http://www.intermountainmedicine.org)
  - [Fecal Microbiota Therapy: Information for Donors](http://www.intermountainmedicine.org)

(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.

**ALGORITHM:** TREATMENT

**C. diff Infection Diagnosis (first infection)**

**MILD-MODERATE**

- Metronidazole, 500 mg orally 3 times daily for 10 days
- If no improvement in 5–7 days
- Switch to vancomycin, 125 mg orally 4 times daily for 10 days

**SEVERE**

- Vancomycin, 125 mg orally 4 times daily for 10 days
- If no improvement in 7 days
- Consult Infectious Diseases and/or Gastroenterology for evaluation of emerging therapies (e.g., fecal microbiota therapy [FMT], fidaxomicin, etc.)

**SEVERE-COMPLICATED**

- 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)
- 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, fidaxomicin, etc.)

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

**MANAGE recurrent C. diff**

- **First recurrence**
  - Same antibiotic used for first infection (metronidazole or vancomycin)
  - If no improvement in 5–7 days: Switch to vancomycin
  - If no improvement in 7 days: Consult Infectious Diseases and/or Gastroenterology

- **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**
  - 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.
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.\textsuperscript{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 Stenehjem, MD, MSc, Intermountain Healthcare, Infectious Diseases, Eddie.Stenehjem@imail.org).

References


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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