Smells like C. diff: Updates in *Clostridioides difficile* management

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Case

- 72 year-old woman, hospitalized 2 weeks ago for pyelonephritis and received IV cefepime → PO levofloxacin
- 8 watery stools/day
- WBC 18,000; Creatinine 1.8 mg/dL

- Do you test?
- Which test?
- How severe is this infection?
- What treatment would you start?

Learning objectives

By the end of this session you should be able to:

- Recognize CDI risk factors
- Interpret diagnostic tests for CDI
- Classify disease severity, and select evidence-based treatment
- Manage recurrent CDI
- Understand new microbiome-based therapies

Why CDI Still Matters

One of the most common healthcare-associated infections

*Community > healthcare-associated (62.1 vs 54.0 per 100,000)

Significant morbidity, readmissions, and cost; infection prevention metric linked to CMS reimbursement

Recurrence remains a major challenge

"What is the most frustrating part of managing CDI?"

CDC; Retrieved July 2026

What is Clostridioides Difficile

- Gram-positive, anaerobic, spore-forming organism
- Produces toxins A and B
- Spores survive for months in the environment
- Colonizes the intestines (toxigenic *C. difficile* asymptomatic colonization range 0.5 to 51.5%)
- Overgrowth takes over the normal GI microbiome, resulting in clinical symptoms

Bednárik DS et al. *Lancet Reg Health Eur*.

The Antibiotic Connection

Which antibiotic worries you the most?

- Clindamycin
- Fluoroquinolones
- penicillin–β-lactamase inhibitor combinations
- Cephalosporins
- Carbapenems

Brown KA et al. *J Infect Dis*. 2026

Visual Abstract

Drugs Associated with *C. difficile* Infection (CDI): A Pharmacopeia Wide Case-Cohort Study

Methods

Exposure: non antibiotic and antibiotic use in past 1-90 days

Outcome: first incidence of *C. difficile* (testing, hospitalization and treatment data)

16,196 cases **549,831 controls**

Analysis: Adjusted regression for age, sex, year-quarter, region, comorbidities, drug exposure

Results

Selected Drugs		Population-Attributable Risk (95% CI)
antibiotic	amoxicillin-clavulanate	**12.4** (12.2 to 12.5)
antibiotic	ciprofloxacin	**9.6** (9.3 to 9.8)
antibiotic	cephalexin	**8.8** (8.5 to 9.0)
antibiotic	clindamycin	**8.4** (8.3 to 8.4)
non-antibiotic	pantoprazole	**7.9** (6.8 to 8.9)
non-antibiotic	ferrous fumarate	**5.5** (5.0 to 6.0)
non-antibiotic	metformin	**-5.0** (-6.1 to -4.0)

Conclusion

This study provides insights into CDI etiology, and avenues for stewardship and drug repurposing to combat CDI

Brown KA, Coburn B, Hernandez A, Langford BJ, Leung V, MacFadden D, Rooney AM, Schwartz KL, Daneman N.
The Journal of Infectious Diseases, 2025

Risk Factors for Initial CDI

- Recent antibiotics (last 3 months)
- Age >65 years
- Exposure to Healthcare settings
- Immunosuppression, including Chemotherapy & Transplantation
- Non antibiotic medications (pantoprazole, ferrous fumarate) – *why?*

Brown KA, et al. *J Infect Dis*. 2026
Clarke LM, Allegretti JR. *Aliment Pharmacol Ther*. 2024

Why Recurrence Is Such a Problem

Approximately 70% of recurrences occur within 4 weeks of treatment

After first recurrence, risk of subsequent recurrent → 40-50%

van Prehn J, et al. *JAMA*. 2025

Who is most likely to return?

- Prior CDI recurrence (strongest predictor of future recurrence)
- Age (≥65 years)
- Severe index episode
- Repeated antibiotic exposure
- Chemotherapy, history of organ transplant
- Chronic immunosuppressive therapy

van Prehn J, et al. JAMA. 2025

Case #1

Which of the following patients are the highest risk of recurrence? All had an episode of CDI in the last 4 weeks

A. 24 year-old male with a history of celiac disease admitted for mononucleosis and received IV ceftriaxone for 3 days
B. 67 year-old female with renal transplant, recent intra-abdominal abscess planned for an additional 3 weeks of IV antibiotics
C. 52 year-old female treated for a cat bite

Who should be tested?

- ≥3 unformed stools within 24 hours
- Evaluate if other therapies may be causative
  - Laxatives
  - Tube feeds
- High clinical suspicion given underlying risk factors

What not to do

Don't:

- Test formed stool (formed stools should be rejected by the laboratory, **except for patients with ileus or potential toxic megacolon)**
- Test asymptomatic patients
- Treat positive NAAT alone, without symptoms

Understanding the Tests

- Nucleic acid amplification test (NAAT-PCR)
- Glutamate dehydrogenase assay (GDH)
- Enzyme immunoassay (EIA-Toxin test)

How good is the test

Test	Sensitivity (95% CI)	Specificity (95% CI)	Detection Target
NAAT	96% (93–98%)	94% (93–95%)	Toxin-encoding genes
GDH antigen	94% (89–97%)	90% (88–92%)	GDH protein (all strains)
Toxin A/B EIA	83% (76–88%)	99% (98–99%)	Free toxins A and B
NAAT + Toxin A/B	82.9% (80–86%)	99.6% (99.4–99.7%)	Combined
GDH + Toxin A/B	81.8% (79–85%)	99.5% (99.4–99.6%)	Combined

J Michael Miller, et al. *Clinical Infectious Diseases*, 2024

In practice

- NAAT = highly sensitive
- Toxin assay = highly specific

Combined, multistep testing for the most diagnostic accuracy

(NAAT + EIA) or (GDH + EIA)

- **Can you smell C. diff? In short, no**

infectious diarrhea → volatile organic compounds (VOC), overlap

VOC patterns when analyzed by an E-Nose,* could indicate CDI may be present but still was less sensitive and specific than combined testing.

Garner, C.E, et al. FASEB J. 2007

Test interpretation recall

A 60 y/o male with a past medical history of COPD and HTN is admitted and is being treated for community acquired pneumonia. On day five of hospitalization he develops profuse diarrhea and has 7 watery bowel movements. Multistep testing for C. Difficile testing is sent and the results are as follows:

- NAAT+
- GDH+
- Toxin –

Q)What does the patient have?

A) C. Difficile colonization

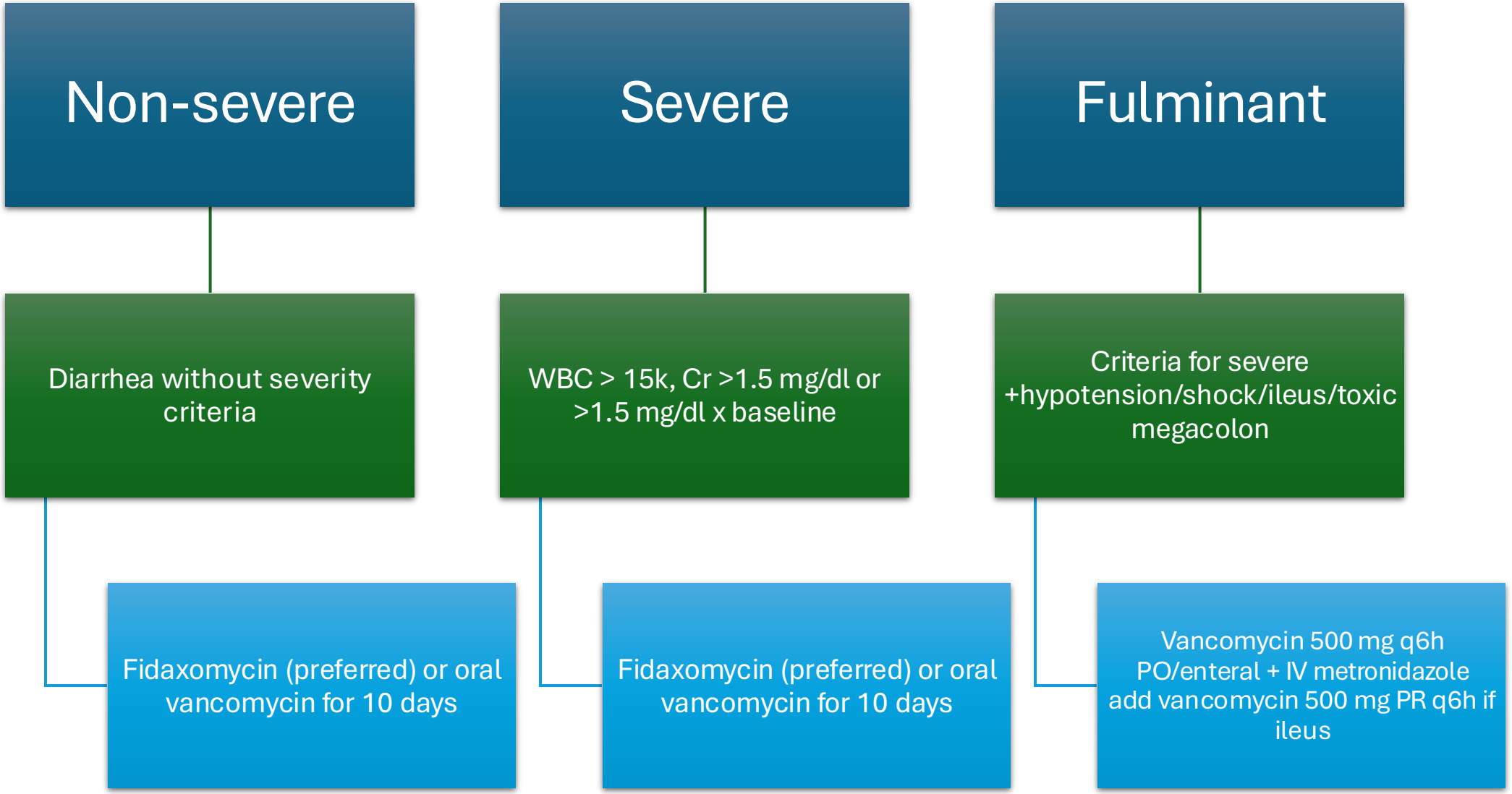
B) C. Difficile infection

C) Testing is incomplete

Why is stratifying severity important?

- Management depends on severity
- Prognosis is linked to severity
- Assists in clarifying where surgical consult may be needed

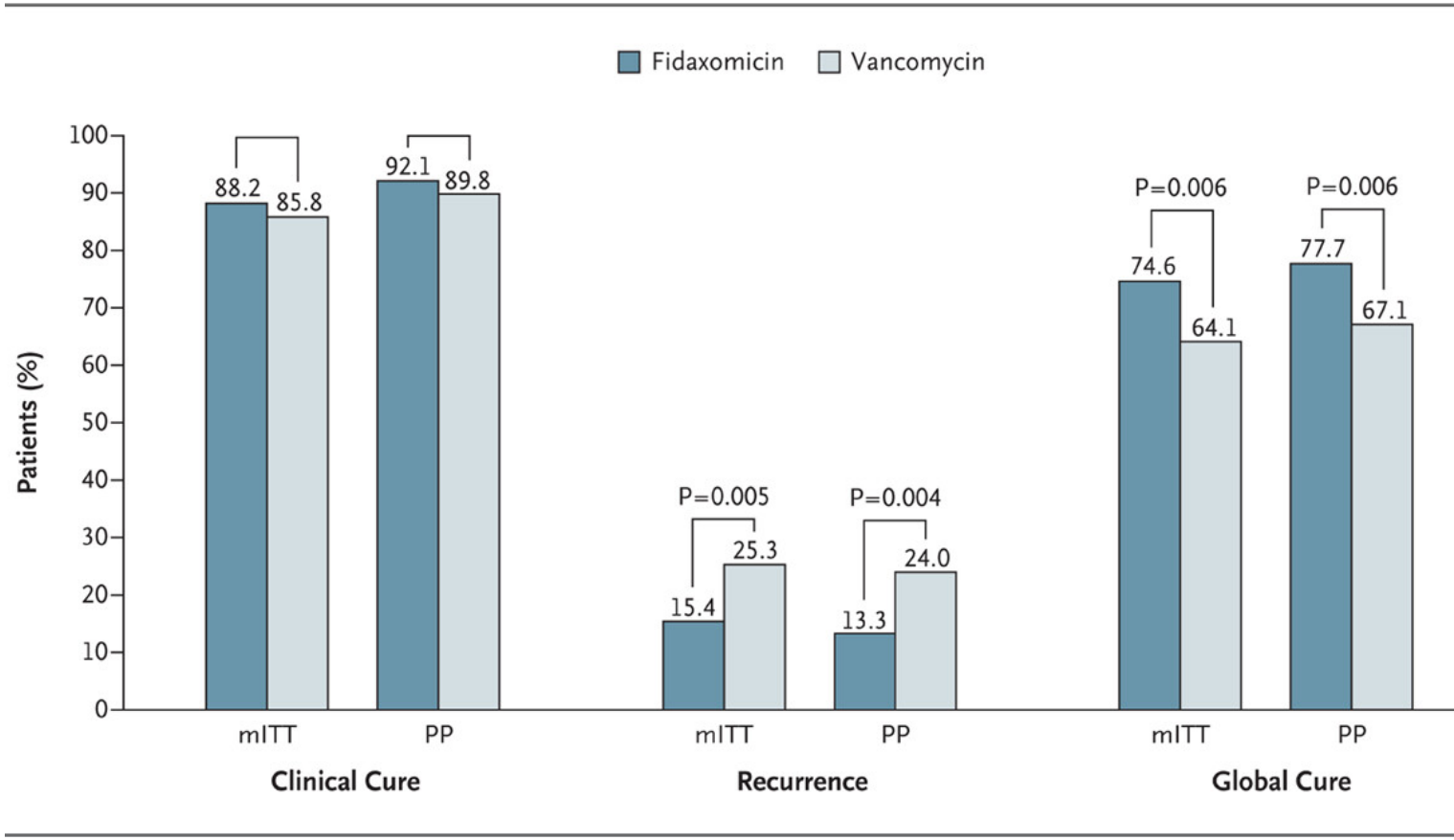
Fischer M. Clin Gastroenterol Hepatol. 2026



Fischer M. Clin Gastroenterol Hepatol. 2026

First episode of CDI

- ‘In patients with initial episode, we suggest standard course of fidaxomicin’ for 10 days over vancomycin
- Discontinue the inciting antibiotic/medication as soon as clinically feasible
- Why fidaxomycin? - microflora-sparing properties



Johnson S, et al. Clinical Infectious Diseases. 2021
Beinortas T, et al. Lancet Infect Dis. 2018

Recurrence

Within 8 weeks of completing therapy and resolving symptoms

- Three options:
  1. Fidaxomicin as standard, or
  2. Fidaxomycin as a taper (EXTEND trial) or
  3. Vancomycin taper
- Fecal microbiota-based therapies should be offered after treatment of a second recurrence (third C difficile infection episode)

Fischer M. Clin Gastroenterol Hepatol. 2026
Johnson S, et al. Clinical Infectious Diseases. 2021
Guery B, et al. *Lancet Infect Dis*. 2018

Fecal microbiota transplant

- Fecal microbiota spores, live-brpk, fecal microbiota, live-jslm, or conventional fecal microbiota transplant
- Well tolerated, adverse effects rare (1.4% had serious adverse events in a systematic review)
- Guidelines recommend against FMT in severely immunocompromised individuals e.g cytotoxic chemo, advanced HIV (CD4 <200) due to risk of transmitting infections

Marcella C, et al. *Aliment Pharmacol Ther*. 2021;

Role for suppression?

- Answer: Rarely
- Prolonged, low dose, suppressive vancomycin regimen for secondary prophylaxis
- 125 mg daily
- Whom to suppress?
  - Patients with multiple recurrent episodes who are not candidates for FMT, or failed FMT
  - Prolonged anticipated ongoing antibiotics exposure with prior recurrences
  - Limited life expectancy

Fischer M. Clin Gastroenterol Hepatol. 2026

Fulminant CDI

Multidisciplinary management

- **High-dose vancomycin 500 mg q6h** (oral/enteral)
- + **IV metronidazole 500 mg q8h**
- + **rectal vancomycin 500 mg q6h** if ileus is present.
- Multi-dose FMT via lower endoscopy should be considered;
- FDA-approved commercial products have **not** been studied for fulminant disease.

Fischer M. Clin Gastroenterol Hepatol. 2026
Johnson S, et al. Clinical Infectious Diseases. 2021

Probiotics?

Probiotics are not advised for prevention of initial or recurrent CDI.

Prophylactic vancomycin during systemic antibiotics is not recommended.

What’s new on the block!

VA CSP 596 Trial (NEJM, July 28, 2026) — Landmark New Data

- **Compared vancomycin taper** and **fidaxomicin** to **standard 10-day vancomycin** in patients with **first or second recurrence**
- **Neither taper nor fidaxomicin demonstrated superiority** over standard vancomycin for sustained clinical response
- Trial limited by power of the study. The authors note that **tapered/pulsed fidaxomicin regimens** (not tested in this trial) might improve outcomes and warrant further study

VOWST(Live-brpk/ SER109)

- Approved by FDA in 2023
- Live biotherapeutic; approved for CDI recurrence prevention in adults ≥18 years after standard-of-care treatment.
- **Oral capsule** - purified spores from **donor-derived Firmicutes species** - abundant in healthy gut and deficient in rCDI.
- Manufacturing: Ethanol-based purification of donor stool → isolate spores → eliminate everything else
- **4 capsules daily for 3 consecutive days**, initiated 2–4 days after completing anti-CDI therapy.

Feuerstadt P, et al. American Journal of Gastroenterology. 2024

VOWST(Live-brpk SER109)

- Administration: Bowel preparation with **296 mL magnesium citrate** is required the day before, with fasting ≥8 hours before the first dose
- Achieved **88% sustained clinical response at 8 weeks vs 60% placebo** (RR 0.32, $p<0.001$
- Issues: Cost, insurance approval, timing and outpatient follow-up
- Cannot do inpatient typically!

Rebyota (Fecal Microbiota, Live-jslm)

- **Broad-spectrum, whole-consortium** donor-derived product
- Administered as a **single 150 mL rectal dose** in a clinical setting, within 24–72 hours of completing anti-CDI antibiotics.
- Cannot do inpatient
- Unlike Vowst's narrow Firmicutes spore composition, Rebyota contains a diverse array of fecal anaerobes, including **Bacteroidetes and Clostridia**

Khanna S, et al. American Journal of Gastroenterology. 2024

Feature	Vowst	Rebyota
Composition	Purified Firmicutes spores	Broad whole-consortium fecal anaerobes
Route	Oral (4 caps/day × 3 days, at home)	Single rectal dose (in-office)
Bowel prep	Magnesium citrate required	None
Mechanism	Firmicutes engraftment → secondary bile acids, SCFAs	Broad microbiome restoration → Bacteroidia engraftment, bile acid conversion
Phase III efficacy (8 wk)	88% vs 60% placebo	70.6% vs 57.5% placebo
FDA approved	April 2023	November 2022

VE303

- Novel oral microbiome-directed therapy
- 8 strains of nonpathogenic, nontoxigenic, commensal strains of Clostridia
- **Phase 2 trial -** Compared with placebo, high-dose VE303 prevented CDI among high-risk participants (low dose showed no benefit vs placebo)
- CDI recurrence rate: 13.8% for the high-dose VE303 group, 37.0% for the low-dose VE303 group, and 45.5% for the placebo group.
- Manufactured from **clonal cell banks** rather than donor stool - theoretically offers advantages in standardization, scalability, and elimination of pathogen transfer risk.

Louie T, et al. JAMA. 2023

In real-life

- Price check fidaxomicin – can switch to PO vancomycin during course if not covered on discharge
- Manufacturer assistance program exists for fidaxomicin
- Expert consultation for multiple recurrences: Infectious Disease vs Gastroenterology
  - Get outpatient follow-up for microbiome therapies
  - Get insurance approval (Vowst newer, harder to get approved)
- Review antibiotic plan – is it necessary? Can spectrum be narrowed?

Key Takeaways

- Treat the clinical infection, not colonization
- Stratify CDI severity
- First episode → choose fidaxomicin (generic available since 2025) due to lower risk of recurrence
- For first recurrence, chose a taper
- Manage the underlying risk factors for CDI!
- For second recurrence consider microbiota therapy - Vowst (oral), Rebyota (rectal), FMT

Patient counseling

- Reassure that CDI transmission to family members is uncommon.
- Handwashing with soap, and consider disinfecting areas of the home potentially contaminated with C difficile spores
- Probiotics: No good data to support use. Contraindicated in severely immunocompromised patients
- Stool re-testing should only be performed for persistent worsening of diarrheal symptoms

Questions?