Pharmacologic Strategies for CDI: From First-Line Therapy to Recurrent Infections

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Disclosures

None

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Objectives

1. Describe the pathophysiology of *Clostridioides difficile* infection (CDI)
2. Review the evolution of CDI management guidelines
3. Review current guidelines and recommendations for CDI management
4. Assess management strategies for severe and recurrent CDI, including new therapies

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CDI is An Urgent Public Health Threat That Can Lead to Life-Threatening Complications

- CDC classifies CDI as an “Urgent Threat”
- CDI is the most frequently identified health care-associated infection in the United States
- Clinical illness range in severity from mild diarrhea to fulminant colitis and death
- Appropriate management requires understanding various diagnostic assays and therapeutic options as well as relevant measures of infection prevention

Guh A., Kutty P., Clostridioides difficilie Infection. Center for Disease Control. Ann Intern Med. 2018 October 02; 169 (8).

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Incidence of CDI and Trends

In 2022, the CDC's Emerging Infections Program (EIP) identified an incidence rate of **116.1 cases per 100,000 persons**. Notably, **65% of cases had used antibiotics in the prior 12 weeks**[1]

Historically, the national burden of CDI has been substantial. In 2011 there were 476,400 cases with 65.8% classified as health-care associated. By 2017, the number of cases remained similar at 462,100 but the proportion of health-care associated infections decreased to 51% indicating **a shift towards more community-associated cases**[2]

1. EIP Accessed March 30, 2025 via https://www.cdc.gov/healthcare-associated-infections/php/haic-eip/cdiff.html?utm 2. Guh A., Winston L, Olson J. et al. Trends in U.S. Burden of *Clostridioides difficile* Infection and Outcomes. N. Engl J Med. 2020. April 02; 382 (14): 1320-1330.

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CDI Overview

Clostridioides difficile is a highly contagious, spore-forming, toxin producing, gram-positive anaerobic bacterium that can cause

- **Watery diarrhea**
  - **≥3 unformed stools/24 hours for at least 2 days**
- Abdominal pain, cramping, and/or nausea
- Fever
- Colitis and toxic megacolon

1. Cymbal M, et al. Am J Med. 2024;137(7):571-576. 2. Zhu D, et al. Front Cell Infect Microbiol. 2018;8:29. 3. Burke KE, et al. Gut Liver. 2014;8(1):1-6. 4. Ofosu A. Ann Gastroenterol. 2016;29(2):147-154.

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Colitis vs. Toxic Megacolon

Feature	Colitis	Toxic Megacolon
Definition	Inflammation of the colon	Severe, life-threatening complication of colitis
Severity	Mild to Severe	Fulminant, systemic illness
Colon Dilation	Not typically present	Market dilation (> 6 cm) of colon on imaging
Bowel Motility	Still active (diarrhea common)	Loss of peristalsis – risk of paralytic ileus
Risk of perforation	Low	High – medical emergency
Imaging Findings	Thickened colon wall (on CT)	Gross dilation, possible free air or air-fluid levels
Treatment	Medical management	Urgent Supportive care, surgical consult often needed

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Risk Factors for *Clostridioides difficile* Infection

- Antibiotic use: Clindamycin, cephalosporins, carbapenems, and fluoroquinolones have been implicated most frequently, but all antibiotics have been associated. Risk increases with duration of use and number of antibiotics
- Antineoplastic agents
- Hospital or nursing home care, although community-associated disease without previous hospital or nursing home exposure is becoming more common
- Advanced age
- Underlying disease: Cancer, renal failure, generalized debility
- Gastrointestinal manipulation: Surgery, tube-feeding, and enemas; use of proton-pump inhibitors or H_2-receptor blockers may also be associated

Guh A., Kutty Preeta. Center for Disease Control and Prevention. HHS Public Access. Ann Intern Med. 2018. October 02; 169 (7).

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Key Strategies Clinician Can Use to Reduce the Likelihood of CDI

Antibiotic Stewardship

- Antibiotic use is the #1 modifiable risk factor for CDI
- Limit broad-spectrum/high-risk antibiotics (e.g., fluoroquinolones, clindamycin, Zosyn)
- Review and de-escalate therapy routinely
- Target overuse in UTIs, respiratory infections, and outpatient settings

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Key Strategies Clinician Can Use to Reduce the Likelihood of CDI

Infection Presentation Measures

- Gloves and gowns for patient contact
- Handwashing with soap and water (especially after contact with stool or soiled environments) – C.difficile spores are highly resistant to alcohol – hand sanitizer alone will not kill
- Private rooms until 48 hrs after diarrhea resolution
- Use of disposable or dedicated equipment
- Environmental cleaning: daily and terminal disinfection with sporicidal agents in high-risk settings

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Disinfectants Must Be Sporicidal and EPA-registered to be effective against *C.difficile* spores

- The EPA maintains **List K**, which includes all registered antimicrobial products effective against *C.difficile* spores.
- Commonly Used Agents: Sodium hypochlorite (bleach-based products), Hydrogen peroxide-based agents (often containing also peracetic acid).
- Product selection, proper dilution, **contact time ("wet time"),** and surface coverage are essential
  - Contact/Wet Time - the amount of time a surface must remain visibly wet with a disinfectant for it to effectively kill or inactivate pathogens, including *C.difficile* spores. Refer to individual product manufacturer labeling

List K: EPA's Registered Antimicrobial Products Effect against Clostridium difficile spores. Accessed March 30, 2025 via: https://19january2017snapshot.epa.gov/pesticide-registration/list-k-epas-registered-antimicrobial-products-effective-against-clostridium_.html?utm

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How CDI Happens: Disruptions, Colonization, and Toxin Production

- Normal gut flora disrupted
- Ingested *C.difficile* spores survive stomach acid and reach the colon
- In the absence of protective microbiota, spores germinate and colonize
- Toxigenic strains produce Toxin A and Toxin B

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The Role of Toxins A & B – Tissue Damage and Inflammation

Toxin A (enterotixin): causes inflammation, fluid secretion, mucosal injury

Toxin B (cytotoxin): more potent – cases direct damage to the epithelial cells

Disruption of tight junctions – increased intestinal permeability

Results in pseudomembranous colitis, dirreah, and sometimes toxic megacolon

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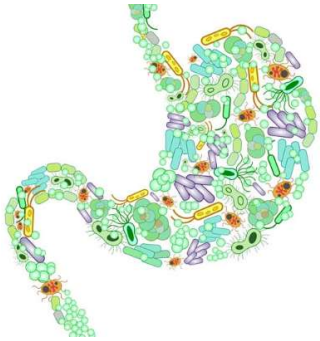
Why Colonization ≠ INFECTION

- Many people (especially elderly or hospitalized) may be colonized with *C.difficile*
- Only toxigenic strains that produce A/B toxin cause clinical disease
- This distinction is why toxin testing and symptoms assessment are critical



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CDI Diagnosis: Two-Step Testing Algorithm[1,2]

Step 1: Initial Screening – High Sensitivity

- Glutamate Dehydrogenase **(GDH) Antigen Test**
- Detects *C.difficile* organism (not toxin)

Step 2: Toxin Detection – High Specificity

- **Toxin A/B Enzyme Immunoassay (EIA)**
- Detects toxins directly
- Lower sensitivity (53-60%) but higher specificity (97-100%)

1. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol. 2021;116(6):1124-1147; 2. 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):e1-e48. 3. Lee HS, et al. Infect Dis Ther. 2021;10(2):687-697.

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Interpretation

GDH	Toxin	Interpretation	Next Steps
+	+	CDI likely	Treat, consistent with CDI
+	-	Inconclusive	Reflex to NAAT (PCR)
-	-	CDI unlikely	No treatment
-	+	Unusual pattern,	Possible false-positive, toxin falls below threshold of detection

Lee HS, et al. Infect Dis Ther. 2021;10(2):687-697

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NAAT as Reflex Test vs. One-Step Strategy[1,2]

NAAT Reflex Test

Pros

- Highly sensitive
- Rapid results

Cons

- May detect colonization, leading to over treatment if clinical criteria are not used
- More expensive

NAAT One-Step

- Often preferred in hospitals concerned about overtreatment
- Reduces risk of treating asymptomatic carriers
- Reflex NAAT only used when GDH+/toxin- discordance occurs

1. Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of Clostridioides difficile Infections. Am J Gastroenterol. 2021;116(6):1124-1147; 2. 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):e1-e48.

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Patient Case: Mrs. Thomas

- Mrs. Thomas is a 72-year-old woman residing in a skilled nursing facility. She was transferred to the hospital 3 days ago due to abnormal urinalysis during routine labs. She had no urinary symptoms on arrival (no dysuria, urgency, or fever), but was empirically started on piperacillin-tazobactam (Zosyn) for "possible UTI" based gram-negative positive leukocyte esterase and gram-negative rods. Urine culture is pending.
- **Medical History**: Type 2 Diabetes, Stage 3 Chronic Kidney Disease, Recurrent UTIs, Osteoarthritis
- **Hospital Course**: Now on Day 3 of Zosyn, today she develops 4 episode of water, non-blood diarrhea in 24 hours. Stool sample is sent for CDI testing.
- **CDI Lab Results (Multistep Testing):**
  - GDH antigen: Positive
  - Toxin A/B EIA: Negative
  - Reflex NAAT (PCR): Positive

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Patient Case: Mrs. S

What is the appropriate action for the pharmacist to recommend to address the CDI results?

A. Do not treat — this is likely colonization.

B. Treat for CDI — results and symptoms are consistent with active infection.

C. Repeat the GDH and toxin tests tomorrow to confirm

D. Add empiric vancomycin now and discontinue once results are confirmed.

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Patient Case: Mrs. S

Urine culture result (now finalized) shows > 100,000 CFU/mL of E.Coli. No leukocytosis, fever, dysuria, or other urinary symptoms. What is the appropriate next step?

A. Continue Zosyn until the urine culture sensitive returns

B. Recommend de-escalating Zosyn or oral cephalexin.

C. Recommend discontinuing Zosyn – this is asymptomatic bacteria

D. Switch to narrower IV agent (e.g. ceftriaxone) until the diarrhea resolves

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Treatment – First Episode

ACG 2021[1]	**VAN 125mg 4 times daily x 10 days** **FDX 200mg BID x 10 days (conditional recommendation in first episode severe)** Metronidazole 500mg TID x 10 days may be considered in low-risk patients*
IDSA/SHEA 2021[2]	**FDX 200mg BID x 10 days** VAN 125mg 4 times daily x 10 days Metronidazole 500mg TID x 10 days may be considered if other options unavailable

* first episode non-severe cases only

Bold = Preferred. Non-bold = Alternative. VAN = vancomycin; FDX = fidaxomicin

1. Kelly CR, et al. Am J Gastroenterol. 2021;116(6):1124-1147. 2. Johnson S, et al. Clin Infect Dis. 2021;73(5):e1029-e1044.

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Oral Vancomycin

- Inhibits bacterial cell wall synthesis, bactericidal against *C.difficile*
- Oral formulation stays in the GI tract – do not need to monitor levels
- Dosing
  - Initial CDI: 125 mg orally 4 times daily x 10 days
  - Recurrent CDI: standard or tapered/pulse regimens.
  - Fulminant: higher doses (e.g., 500mg QID)
- Oral solutions available (compounded from IV powder or commercial (Firvanq®) - swallowing difficulties (dysphagia), feeding tube administration (NG/PEG), pediatric patients

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Fidaxomicin (Dificid®)

- Inhibits RNA polymerase → blocks transcription→ bactericidal against *C.difficile*
- Minimal systemic absorption – acts locally in GI tract
- Dosing
  - Initial CDI: 200mg BID x 10 days
  - Recurrent CDI: 200mg BID x 10 days (standard regimen) or 200mg BID x 5 days, followed by 200mg once every other day for 20 days (extended pulsed regimen)
  - Fulminant CDI: not recommended, limited data
- More narrow spectrum vs. oral vancomycin – less collateral damage to microbiome
- Preferred first line agent for initial and recurrent CDI per 2021 IDSA/SHEA
- Lower recurrence rates vs. vancomycin
- More expensive than oral vancomycin

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Fidaxomicin vs. Vancomycin – Pivotal Clinical Trials

Trial 003[1] & Trial 004[2] (Phase 3 Double-Blind RCTs)

- **Clinical cure**: Non-inferior (Trial 003: 82.1% vs. 88.6%; Trial 004: 76.2% vs. 70.5%)
- **Recurrence within 30 days**: **lower** with fidaxomicin
  - Trial 003: 13.0% vs. 26.6% (p = 0.02)
  - Trial 004: 8.3% vs. 32.6% (p = 0.05)

VA Database Study[3] (Retrospective, Propensity-Matched)

- No significant difference in composite of **clinical failure or recurrence**
  - Fidaxomicin: 31.9% (n=213) | Vancomycin: 25.5% (n=639)
- **Mortality rates** at 30, 90, 180 days were **similar between treatment groups**

1. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med 2011;364:422–31.; 2. Gentry CA, Nguyen PK, Thind S, et al. Fidaxomicin versus oral vancomycin for severe *Clostridium difficile* infection: A retrospective cohort study. Clin Microbiol Infect 2019;25:987–93. 3. Gentry CA, Nguyen PK, Thind S, et al. Fidaxomicin versus oral vancomycin for severe *Clostridium difficile* infection: A retrospective cohort study. Clin Microbiol Infect 2019;25:987–93.

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Which of the following is preferred as first-line treatment for an initial episode of *Clostridioides difficile* infection (CDI) according to the 2021 IDSA/SHEA guidelines?

A) Metronidazole 500 mg PO TID for 10 days
B) Vancomycin 125 mg PO QID for 10 days
C) Fidaxomicin 200 mg PO BID for 10 days
D) Vancomycin 500 mg PO QID for 10 days

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Which of the following statements best describes a key difference between fidaxomicin and oral vancomycin?

A) Fidaxomicin has greater systemic absorption, making it unsuitable for GI infections
B) Fidaxomicin is associated with lower recurrence rates but has efficacy in fulminant CDI is uncertain due to limited data
C) Oral vancomycin is more narrow-spectrum, preserving gut flora better than fidaxomicin
D) Fidaxomicin is bacteriostatic, while oral vancomycin is bactericidal

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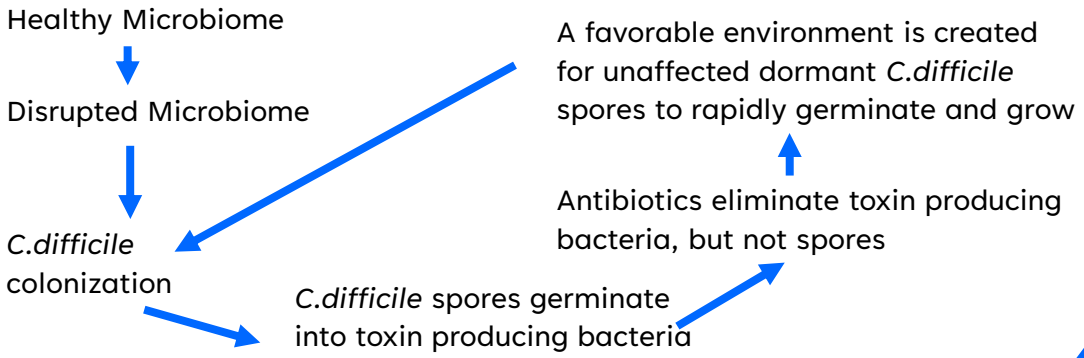
Recurrent CDI



1. McGovern BH, Ford CB, Henn MR, et al. SER-109, an investigational microbiome drug to reduce recurrence after Clostridioides difficile infection: lessons learned from a phase 2 trial. Clin Infect Dis. 2021;72(12):2132-2140. doi: 10.1093/cid/ciaa387; 2. Vincent C, Miller MA, Edens TJ, Mehrotra S, Dewar K, Manges AR. Bloom and bust: intestinal microbiota dynamics in response to hospital exposures and Clostridium difficile colonization or infection. Microbiome. 2016;4:12.; 3. Kelly CP. Can we identify patients at high risk of recurrent Clostridium difficile infection? Clin Microbiol Infect. 2012;18 Suppl 6:21-27. doi: 10.1111/1469-0691.12046

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CDI Can Recur and Continue to Recur

~170,000 cases of recurrent *Clostridioides difficile* infection (rCDI) in the US[1]

~25% risk of rCDI after initial episode[2,3]

Up to 65% risk of subsequent recurrence after initial recurrence[2,3]

- Recurrence usually occurs within 1 to 2 weeks after completion of antibiotic therapy. However, it can also occur months after the initial episode[2,3]
- Patients with rCDI report decrease in quality of life, across measures relating to physical, emotional, professional, and financial consequences[4].

1. Desai K, et al. BMC Infect Dis. 2016;16:303; 2. McFarland LV, et al. Am J Gastroenterol. 2002;97(7):1769-1775; 3. D'Agostino RB Sr, et al. Clin Infect Dis. 2014;58(10):1386-1393; 4. Armstrong EP, et al. Infect Dis Ther. 2023;12(7):1775-1795;

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Risk Factors for rCDI

History of recurrence

Antibiotic Use

Increased age (≥ 65 years)

CDI severity and/or virulence

Prolong inpatient status

History of hospitalization

Comorbidities (e.g., IBD, renal impairment, immunocompromised)

Gastric acid suppression

1. McDonald LC, et al. Clin Infect Dis. 2018;66(1):e1-e48. 2. Kelly CR, et al. Ann Intern Med. 2016;165:609-616.

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Recurrent CDI is Associated with Morbidity and Costs

- rCDI between Jan to Dec 2013 at a single center (n=98)
- During the following year, each patient underwent a mean of 4.4 stool *C.difficile* toxin tests and received a mean of 2.5 prescriptions of oral vancomycin. 84% of patients with rCDI had a CDI related hospitalization in 12 months
- The total mean CDI associated cost per patient with rCDI was $34,103 and hospitalization accounted for the major proportion
- Other factors included: surgery, drug treatment, stool testing/abdominal testing, office visits/ED visits, and fecal transplant

Rodrigues R, et al. Infect Control Hosp Epidemiol. 2017;38(2):196-202. https://pubmed.ncbi.nlm.nih.gov/27817758/

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2021 rCDI Guidelines – First Recurrence

ACG 2021[1]	**FDX recommended after initial course of vancomycin or metronidazole** VAN tapering/pulsed-dose suggested for 1st recurrence after initial course of fidaxomicin, vancomycin, or metronidazole BEZ suggested for consideration to prevent rCDI in patients at high risk
IDSA/SHEA 2021[2]	**FDX preferred for first recurrences – 200mg BID x 10 days (standard), or BID x 5 days then once every other day for 20 days (extended pulse regimen)** VAN tapered, and pulsed regimen (125mg 4 times daily for 10-14 days, 2 times daily for 7 days, once daily for 7 days, and then every 2 to 3 days for 2 to 8 weeks) or VAN standard (125mg 4x daily for 10 days)* BEZ 10mg/kg adjunctive IV during administration of SOC antibiotics

*IDSA/SHEA 2021: vancomycin standard if metronidazole was used for treatment of first episode, otherwise tapered/pulse

Bold = Preferred. Non-bold = Alternative. VAN = vancomcyin; FDX = fidaxomicin; BEZ = bezlotuxumab; SOC = standard of care; 1. Kelly CR, et al. Am J Gastroenterol. 2021;116(6):1124-1147. 2. Johnson S, et al. Clin Infect Dis. 2021;73(5):e1029-e1044.

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2021 rCDI Guidelines – Second Recurrence

ACG 2021[1]	**Oral VAN may be used during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence and for those who are not candidates for FMT, relapsed after FMT, or require ongoing course of antibiotics, suppressive oral VAN may be used** FMT recommended for 2nd or further recurrence after SOC antibiotic treatment BEZ suggested for consideration for patients who are at high risk of recurrence
IDSA/SHEA 2021[2]	**FDX 200mg BID x 10 days (standard) or 200mg BID x 5 days then once every other day for 20 days (extended pulse)** **VAN tapered and pulsed regimen or 125mg 4x daily for 10 days (see first recurrence for doses) followed by rifaximin 400mg 3x daily for 20 days** FMT on 2nd recurrence BEZ adjunctive, IV during administration of SOC antibiotics

Bold = Preferred. Non-bold = Alternative. FMT = investigational fecal microbiota transplantation; VAN = vancomycin; FDX = fidaxomicin; BEZ = bezlotoxumab; SOC = standard of care; 1. Kelly CR, et al. Am J Gastroenterol. 2021;116(6):1124-1147. 2. Johnson S, et al. Clin Infect Dis. 2021;73(5):e1029-e1044.

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Bezlotoxumab (ZinplavaTM) – Removed from Market

- Bezlotoxumab (Zinplava™) injection discontinued as of Jan 31, 2025
- Bezlotoxumab, a human monoclonal antibody, received FDA approval in 2016 to reduce the recurrence of CDI in adults and pediatric patients who are receiving antibiotics for CDI and are at high risk for CDI recurrence.
- It works by binding to *C.difficile* toxin B and neutralizing its effects

https://www.empr.com/news/c-difficile-prevention-therapy-zinplava-discontinued/

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Investigational FMT and OpenBiome

OpenBiome was established as a stool bank providing FMT for treating rCDI

Sept 2024, OpenBiome voluntarily suspended the distribution of investigational FMT for patients with rCDI.

Oct 2024, OpenBiome announced plans to submit an IND to investigate FMTs safety and efficacy in patients lacking approved treatments

Per FDA draft guidance, regulatory compliance issues addressed, and normal operations continued

IND = investigational new drug application
https://openbiome.org/regulatory-and-operations-updates/

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Rifaximin

- Oral rifamycin derivative that inhibits bacterial RNA synthesis by binding to DNA-dependent RNA polymerase
- Minimally absorbed, acts local in the GI tract (minimal DDI)
- Not used for initial or first recurrence
- May be used as a “chaser” after vancomycin in patients with multiple recurrences
- Helps prevent recurrence by suppressing residual C.difficile
- Dose: 200mg oral TID x 20 days
- Some studies show reduced recurrence rates but limited high-quality data.
- Risk of resistance with prolonged use

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Which of the following best explains why *C. difficile* infection frequently recurs after antibiotic treatment?

A) Antibiotics fail to kill *C.difficile* toxin B
B) Dormant *C.difficile* spores survive antibiotic therapy and germinate in a disrupted microbiome
C) *C. difficile* develops antibiotic resistance during initial treatment
D) Antibiotics stimulate overproduction of *C.difficile* toxins

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Which of the following is a recommended treatment approach for a first recurrence of *C.difficile* infection, according to the 2021 IDSA/SHEA guidelines?

A) Fecal microbiota transplant (FMT)
B) Oral metronidazole 500 mg TID x 10 days
C) Vancomycin in a tapered and pulsed regimen
D) Rifaximin 200 mg TID x 20 days

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2024 AGA Guideline Recommendations

Include fecal microbioitc-based therapies: investigational FMT (fecal microbiota transplant) and (new) FDA-approved therapy, fecal microbiota live-jslm and (new) FDA-approved therapy, fecal microbiota spores live-brpk

AGA 2024[1]	Immunocompetent adults with rCDI	Mildly or moderately immunocompromised adults with rCDI	Severely immunocompromised adults with rCDI	Adults hospitalized with severe or fulminant C.difficile infection not responding to antimicrobial therapy
	Upon completion of SOC antibiotics, recommend use of • Investigational FMT • FDA approved fecal microbiota live-jslm • FDA approved fecal microbiota spores live-brpk	Recommends use of • Investigational FMT upon completion of SOC antibiotics	Upon completion of SOC antibiotics, recommends against use of • Investigational FMT • FDA approved fecal microbiota live-jslm • FDA approved fecal microbiota spores live-brpk	Recommends use of • Investigational FMT in patients not responding to SOC antibiotics

SOC = standard of care; AGA, American Gastroenterological Association; Peery AF, et al. Gastroenterology. 2024;166(3):409-434

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Recurrence Prevention Patient Case: Samantha

Samantha's CDI History

- Finished standard of care antibiotics for an initial episode of CDI 2 weeks ago
- After a recent trip, she called her HCP because she was having ~ 4 unformed stools per day and a high fever
- Samantha's gastroenterologist recommended a PCR test for CDI which came back positive
- This is Samantha's FIRST recurrence
- Samantha is fearful that she may have another recurrence

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FDA Approved Fecal Microbiota Therapy

After antibiotics eliminate harmful bacteria, these therapies are thought to facilitate restoration of the microbiome and inhibit the spore germination that can perpetuate the cycle of CDI recurrence

Warnings and Precautions

- Transmissible Infectious Agents: manufacturer from human fecal matter, may carry risk.
- Potential Presence of Food Allergens

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Reboyta® (fecal microbiota, live-jslm)

FDA-approved fecal microbiota-based therapy (Approved Nov 2022)

Indicated to **prevent recurrence of *C. difficile* infection (CDI)** in individuals ≥18 years old following antibiotic treatment for rCDI

Single-dose **rectal suspension** given as an **enema**

Contains **live microbes derived from human stool**, standardized for safety and consistency

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Reboyta® (fecal microbiota, live-jslm)

- Pre-packaged 150mL suspension that is rectally administered at any site of care by a health professional
- No bowel prep/laxatives, hasting, anesthesia, or colonoscopy required
- After administration, patient must be kept in position (left lateral decubitus - lying on left side with knees slightly bent) for 15 minutes to minimize possible cramping
  - Clinical consideration: early evacuation, increased risk if stan up to soon

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Reboyta® Pivotal Trials

PUNCH CD3 Trial patients with documented rCDI [(≥ 1 recurrence after primary episode of CDI or ≥ 2 episodes of severe CDI resulting in hospitalization in the last year)] (n=180) vs. placebo (n=87).

Washout period of 24-72 hours after last dose of antibiotics

Recurrence of CDI within 8 weeks = option for 2nd dose (open label)

Follow up period 24 weeks

Khanna S., Assi M., Lee C. et al. Efficacy and Safety of RBX2600 in PUCH CD3, a Phase III, Randomized, Double-blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection.

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Reboyta® Pivotal Trials

Efficacy

- **70.6% treatment (126/177) vs. 57.5% placebo success rate at 8 weeks (53/85)**
- Of those who saw success, 92.1% (116/126) vs. 90.6% placebo success rate through 24 weeks
- **Post Hoc**
  - Of 32.8% treated at first CDI recurrence, 79.2% (42/53) had no recurrence with treatment vs. 60.6% (20/33) placebo at 8 weeks

Khanna S., Assi M., Lee C. et al. Efficacy and Safety of RBX2600 in PUCH CD3, a Phase III, Randomized, Double-blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection.

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Reboyta® Pivotal Trials

Safety

- Most adverse reactions occurred during the first 2 weeks after administration and were mild to moderate in severity
- Adverse reactions reported by **≥ 3% of recipients**

ADVERSE REACTIONS, n (%)[1]	**REBYOTA** n=180	**Placebo** n=87
Abdominal pain	16 (8.9%)	6 (6.9%)
Diarrhea	13 (7.2%)	3 (3.4%)
Abdominal distension	7 (3.9%)	2 (2.3%)
Flatulence	6 (3.3%)	0
Nausea	6 (3.3%)	1 (1.1%)

Khanna S., Assi M., Lee C. et al. Efficacy and Safety of RBX2600 in PUCH CD3, a Phase III, Randomized, Double-blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection.

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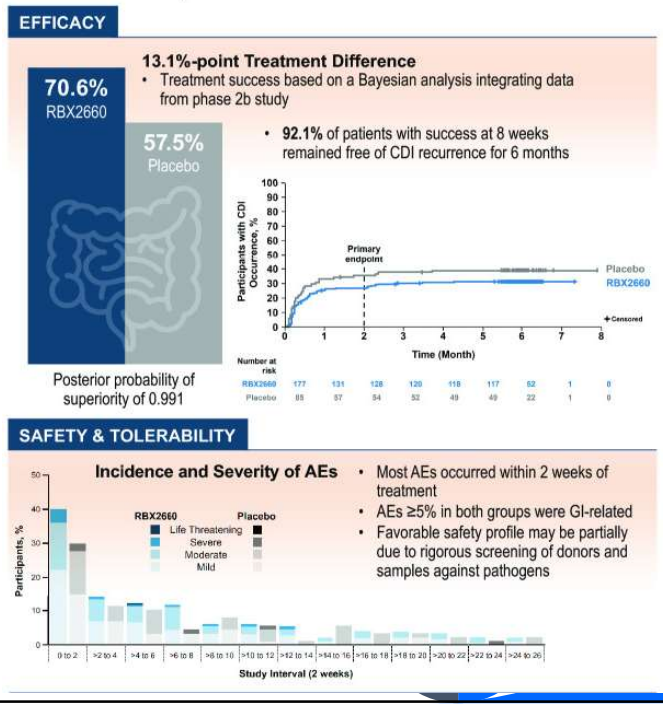

Khanna S., Assi M., Lee C. et al. Efficacy and Safety of RBX2600 in PUCH CD3, a Phase III, Randomized, Double-blind, Placebo-Controlled Trial with a Bayesian Primary Analysis for the Prevention of Recurrent *Clostridioides difficile* Infection.

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Which of the following statements about Rebyota (fecal microbiota, live-jslm) is TRUE?

A. Rebyota requires bowel preparation and sedation prior to administration.
B. Rebyota is indicated for primary prevention of *Clostridioides difficile* infection in adults ≥18 years.
C. In the PUNCH CD3 trial, Rebyota demonstrated improvement in reducing rCDI compared to placebo.
D. Rebyota is administered orally as a capsule containing live microbial spores.

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VOWST (fecal microbiota spores, live-brpk)

FDA-approved fecal microbiota-based therapy (Approved April 2023)

Indicated to **prevent recurrence of *C. difficile* infection (CDI)** in individuals ≥18 years old following antibiotic treatment for rCDI

Oral capsule regimen (duration: 3 days)

Contains **bacterial spores, derived from human stool**, standardized for safety and consistency

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VOWST – How is it Made?

VOWST is a bacterial spore suspension sources from qualified doners and is composed of **firmicutes spores**

- Doner Selection
- Donor Testing
- Refinement
- Filtration
- Final Product

Each lot of VOWST is sources from a single doner. Approximately 1% of the total mass of donor material remains in the final product.

1. Feuerstadt P, et al. N Engl J Med. 2022;386(3):220-229;. 2. McChalicher C, et al. Open Forum Infect Dis. 2022;9(9):ofac448;. 3. McGovern BH, et al. Clin Infect Dis. 2021;72(12):2132-2140.; 4. VOWST [Prescribing Information]. Cambridge, MA: Seres Therapeutics, Inc. and Nestlé Health Science. 06/2024.

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VOWST – Why Firmicutes Spores?

Firmicutes spores are a major phylum of gram-positive bacteria in the gut. Spores are dormant, highly resilient forms of bacteria that survive harsh conditions, possess several inherent attributes:

- Resistance to gastric acid and oxygen, enabling oral delivery
- Produce metabolites (secondary bile acids) that inhibit *C.difficile* germination and growth
- Germination of spores into replicating vegetative bacteria to outcompete *C.difficile* for nutrients and space

McChalicher CWJ, et al. J Infect Dis. 2023;228(10):1452-1455

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VOWST – Dosing and Administration

Before the first dose of VOWST:

- Step 1: Finish the full course of antibiotics.
- Step 2: Laxative within 1-3 days of finishing antibiotics. Drink 10 oz of a laxative (magnesium citrate)
- Step 3: Do not eat or drink (except for a small amount of water) for at least 8 hours before starting the first dose of VOWST – for example, fast overnight.

Treatment with VOWST

- Step 4: The next day, treatment with VOWST begins.
  - Take VOWST before the first meal on an empty stomach.
  - Dose is 4 capsules taken orally once a day for 3 days in a row.

VOWST should not be taken at the same time as antibiotics or laxative.

VOWST does not require refrigeration and can be stored at room temperature

VOWST [Prescribing Information]. Cambridge, MA: Seres Therapeutics, Inc. and Nestlé Health Science. 06/2024.

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VOWST – Pivotal Trials

ECOSPOR III was a randomized, double-blind, placebo controlled trial in **patients with ≥ 2 recurrences of CDI**. Patients received VOWST (n=89) or placebo (n=93).

Primary Endpoint: recurrence at 8 weeks

Secondary Endpoints: AEs through 24 weeks; Recurrence at 4, 12, and 24 weeks

Baseline characteristics: 43% or patients younger than 65 years of age, 73% received vancomycin, 66% had ≥ 1 **comorbid condition**

Feuerstadt P, et al. N Engl J Med. 2022;386(3):220-229

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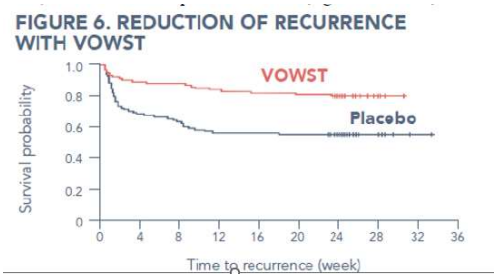
VOWST – Pivotal Trials

Efficacy

- % without CDI recurrence
  - At 8 weeks (88% VOWST vs. 60% placebo; 28% difference, p< 0.001)
  - **At 24 weeks (79% WOST vs. 53% placebo; 26% difference, p< 0.001)**
- **NNT of 4** to avoid 1 recurrence of C.difficile infection



NNT = number needed to treat. Feuerstadt P, et al. N Engl J Med. 2022;386(3):220-229

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VOWST – Pivotal Trials

Safety

- The most common adverse reactions (reported in ≥ 5% of VOWST treated participants at a rate greater than placebo): abdominal distension (31.1%), fatigue (22.2%), constipation (14.4%), chills (11.1%), and diarrhea (10.0%).
- Most adverse reactions occurred within 10 days of starting treatment. Median duration was less than or equal to 5 days. The majority of reactions were reported a mild or moderate in severity. No serious adverse events considered related to VOWST.

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VOWST- Pivotal Trials

ESCOPOR IV: a phase 3, open label, single-arm study in participants with ≥ 1 CDI recurrence (no comparator arm)

Primary Endpoint: Safety and tolerability up to 24 weeks

Secondary Endpoint: Recurrence up to weeks 4, 8, 12, and 24 weeks

Cohort 1: previously enrolled in ECOSPOR III and experienced a CDI recurrence within 8 weeks after receipt of VOWST (n=29, non responders)

Cohort 2: adult, at least one CDI recurrence, symptom resolution following standard of care antibiotic [n=234 new adults, 77 (29.3%) first CDI recurrence]

Efficacy Results: **91% participants (8 weeks) and 85% participants (24 weeks)**, were **recurrence free**. **First recurrence rate vs. second or more recurrence was similar** [5 of 77 (6.5%) vs. 18 of 186 (9.7%)] at 8 weeks.

Safety Results: Majority of ADR were mild to moderate most common GI [flatulence, diarrhea, and nausea (3-4%)]

Sims MD, et al. JAMA Netw Open. 2023;6(2):e2255758.

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Which if the following statements about VOWST (fecal microbiota spores, live) is TRUE?

A. VOWST is indicated for initial episodes of *Clostridioides difficile* infection in combination with standard antibiotics.
B. VOWST should be taken concurrently with antibiotics to maximize its efficacy.
C. VOWST is an oral microbiota-based product used to reduce recurrence of C. difficile infection following antibacterial treatment.
D. VOWST is administered as a single-dose infusion in a healthcare setting.

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Treatment – Fulminant CDI

Definition of fulminant CDI is supported by hypotension or shock, ileus, megacolon

ACG 2021[1]	VAN 500mg oral every 6 hours daily 48-72 hours, lower dose to 125mg every 6 hours once clinical improvement +/- IV metronidazole 500mg every 8 hours Ileus: add VAN enema 500mg every 6 hours
IDSA/SHEA 2021[2]	VAN 500mg 4 times daily by mouth or NG tube. If ileus consider rectal installation addition. IV metronidazole should be administered together with oral or rectal VAN, particularly if ileus is present

VAN = vancomycin

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Adjunctive Therapies and What to Avoid in CDI

- Avoid antimotility agents (e.g., loperamide) due to risk of toxic megacolon
- Bile acid binders (e.g., cholestyramine): limited evidence; avoid co-admin with vancomycin due to interactions
- Psyllium husk: may aid in recover phase; potential benefit in restoring gut microflora
- Avoid probiotics – quality control is suboptimal with inconsistencies, case reports of bloodstream infections in critically ill patients

Kelly CR, et al. Am J Gastroenterol. 2021;116(6):1124-1147

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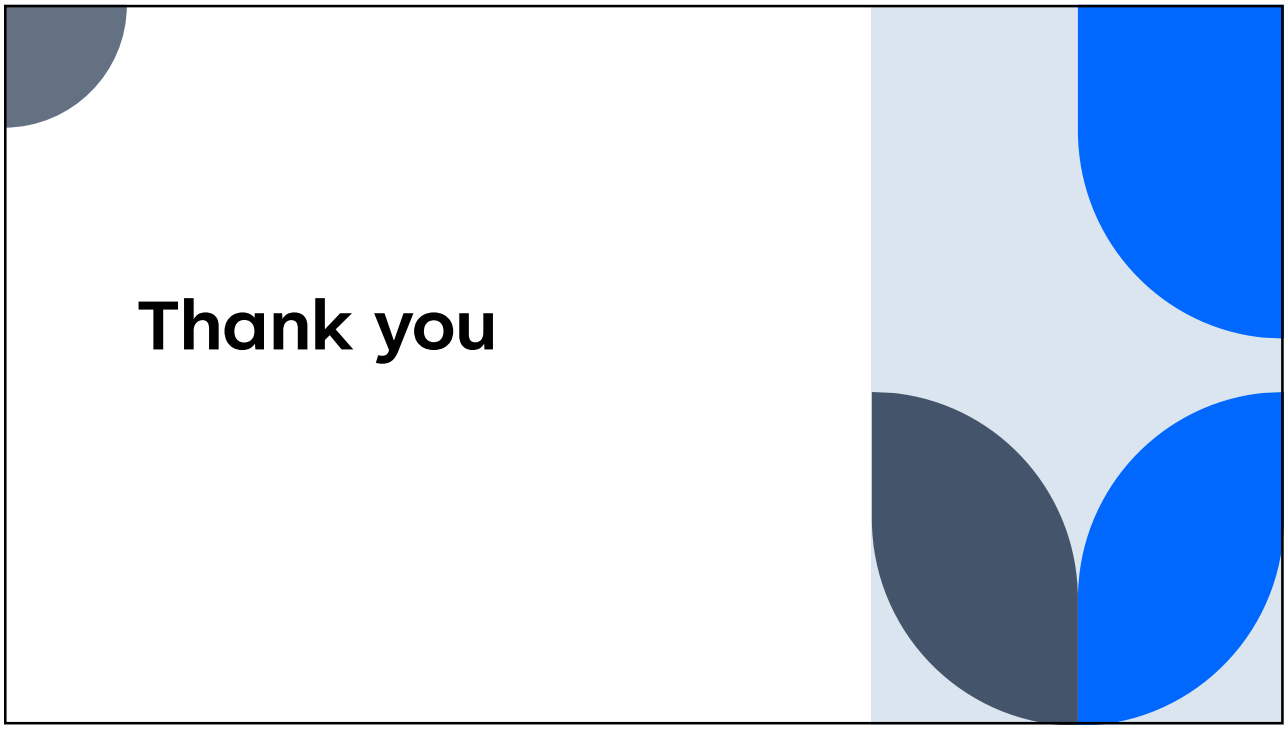

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