Understanding and Managing *C. difficile* Infection: Pathogenesis, Treatment, and Recurrence Prevention

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Conflict/Disclosure

Emily Drwiega declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings and honoraria.

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Objectives

- Review the pathogenesis of *Clostridioides difficile* infection and recurrence.
- Select an appropriate treatment option for patients with a *Clostridioides difficile* infection.
- Discuss options for the prevention of recurrent *Clostridioides difficile* infection.

3

Pharmacy Technician Objectives

- Recall the symptoms associated with *Clostridioides difficile* infection and recurrence.
- Recognize treatment options for patients with *Clostridioides difficile* infection.
- Identify available methods for treatment and prevention of recurrent *Clostridioides difficile* infection.

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Pretest Question #1

Which of the following statements best describes *Clostridioides difficile* and its pathogenesis?

A. **Disruption of normal gut flora can result in overgrowth of C. difficile in the GI tract.**
B. **C. difficile directly penetrates the intestinal mucosa, leading to ulcer formation.**
C. **C. difficile spores rely on fat intake from your diet to become active.**
D. **C. difficile infection occurs following ingestion of contaminated water.**

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Pretest Question #2

Which of the following statements is TRUE regarding treatment of initial CDI?

A. **Based on the 2021 IDSA/SHEA guidelines, fidaxomicin and vancomycin are recommended equally.**
B. **Fidaxomicin is a twice daily oral option for the treatment of the first *C. difficile* infection episode.**
C. **Tapered regimen of vancomycin for an initial *C. difficile* infection episode should be continued for at least 6 weeks.**
D. **Metronidazole is the preferred first-line treatment for initial *C. difficile* infection, regardless of severity.**

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Pretest Question #3

Which of the following is the most appropriate treatment approach for a patient presenting with their first recurrence of *C. difficile* infection, approximately 2 months after their first episode which was successfully treated with 10 days of oral vancomycin?

A. **Repeat a 10-day course of oral vancomycin**
B. **Initiate oral metronidazole to be continued for 14 days**
C. **Oral vancomycin for 10 days, followed by bezlotoxumab**
D. **Fidaxomicin twice daily for a total of 10 days**

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Pretest Question #4

Which of the following statements is TRUE and evidence-based regarding the prevention of recurrent *C. difficile* infection?

A. **There are two, FDA-approved, live biotherapeutic products that have demonstrated efficacy in preventing subsequent *C. difficile* recurrences.**
B. **Daily oral vancomycin should be taken indefinitely after treatment completion of an initial *C. difficile* infection episode.**
C. **Avoiding dietary sources of fiber has demonstrated efficacy in preventing recurrent *C. difficile* infection**
D. **When compared head-to-head, fecal microbiota transplantation (FMT) was inferior to fecal microbiota, live-jslm (Rebyota).**

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Clostridioides difficile (*C. diff*) and its Pathogenesis

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Clostridioides difficile

- Gram-positive, anaerobic, spore-forming bacteria
- Sheds in feces
- Spores can contaminate surfaces, devices, etc.
- Transferred to patient via contaminated surface or people
- Laboratory tests may be positive in colonized individuals
- Symptomatic patients should be isolated and under contact precautions
- Can asymptomatically colonize patients

Feuerstadt P, et al. *BMC Infect Dis*. 2023;23(1):132.
McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.
C. diff. Centers for Disease Control and Prevention. https://www.cdc.gov/c-diff/hcp/clinical-overview/index.html Accessed: Nov 16, 2024.

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Symptoms & Complications

Symptoms of infection	Complications
• Watery diarrhea • Fever • Abdominal pain • Loss of appetite • Nausea	• Dehydration • Colitis • Toxic megacolon • Sepsis • Colectomy

McDonald LC, et al. *Clin Infect Dis*. 2018;66(7):e1-e48.
Feuerstadt P, et al. *BMC Infect Dis*. 2023;23(1):132.
C. diff. Centers for Disease Control and Prevention. https://www.cdc.gov/c-diff/hcp/clinical-overview/index.html Accessed: Nov 16, 2024.

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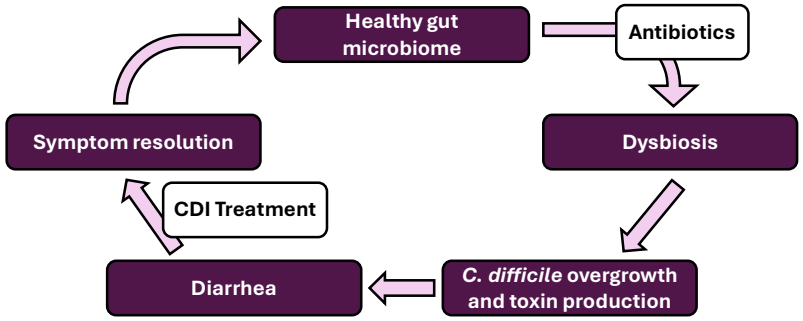
Pathogenesis



CDI: *C. difficile* infection

Adapted with permission from Danny Schreiber, PharmD

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C. difficile Background

500,000 patients affected by CDI in the US, each year

The most important risk factor for infection is antibiotic use

1 in 11 people >65 years die within one month of hospital-associated CDI

$5 billion in estimated inpatient costs of CDI in the US annually

CDI: *C. difficile* infection

Feuerstadt P, et al. *BMC Infect Dis.* 2023;23(1):132.
C. diff. Centers for Disease Control and Prevention. https://www.cdc.gov/c-diff/hcp/clinical-overview/index.html Accessed: Nov 16, 2024.

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Treatment of *C. difficile* Infection

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IDSA/SHEA: Initial CDI Episode Treatment

Preferred	• Fidaxomicin x 10 days
Alternative	• Vancomycin x 10 days
Non-severe & above are unavailable	• Metronidazole x 10-14 days

CDI: *C. difficile* infection
IDSA: Infectious Diseases Society of America.
SHEA: The Society for Health Epidemiology and America

Johnson S, et al. *Clin Infect Dis.* 2021;73(5):e1029-e1044.

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Vancomycin

- Dose: Vancomycin 125 mg given 4 times daily by mouth for 10 days
- Available as oral capsule and oral solution
- Minor absorption of oral dosage forms
- Adverse effects:
  - Abdominal pain
  - Nausea/vomiting
  - Hypokalemia
  - Fever

CDI: *C. difficile* infection

Johnson S, et al. *Clin Infect Dis.* 2021;73(5):e1029-e1044.
Vancocin [package insert]. ANI Pharmaceuticals. Dec. 2021.

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Fidaxomicin

- Dose: Fidaxomicin 200 mg by mouth twice daily for 10 days
- Available as oral capsule and oral suspension

Minimal systemic absorption

- Adverse effects:
  - Nausea/vomiting
  - Abdominal pain
  - Gastrointestinal hemorrhage

Johnson S, et al. *Clin Infect Dis*. 2021;73(5):e1029-e1044.
Difficid [package insert]. Merck & Co., Inc. Jan. 2020.

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Vancomycin vs. Fidaxomicin

Vancomycin

- Taken four times daily
- Generic medication available

Fidaxomicin

- Only taken twice daily
- Narrower spectrum than vancomycin
- Patient assistance programs and copay cards available

Clinical Trial Comparison

- Clinical cure non-inferior between the two groups
- Significantly reduced recurrences in the fidaxomicin group
- No difference in quantity of adverse effects or serious adverse events

Johnson S, et al. *Clin Infect Dis*. 2021;73(5):e1029-e1044.
Louie TJ, et al. *N Engl J Med*. 2011;364(5):422-31.

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Recurrent *C. difficile* Infection

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CDI Recurrence

- Development of another episode of CDI within 8 weeks of a prior treated episode
- Each recurrence increases risk for future recurrence

- Risk factors for recurrent infection
  - Advanced age
  - Antibiotics (not for CDI)
  - Gastric acid suppression
  - Hypervirulent strain
  - Severe underlying disease
  - History and severity of prior CDI
  - Prolonged hospital stay

Song JH, Kim YS. *Gut Liver*. 2019;13(1):16-24.
Johnson S, et al. *Clin Infect Dis*. 2021;73(5):e1029-e1044.

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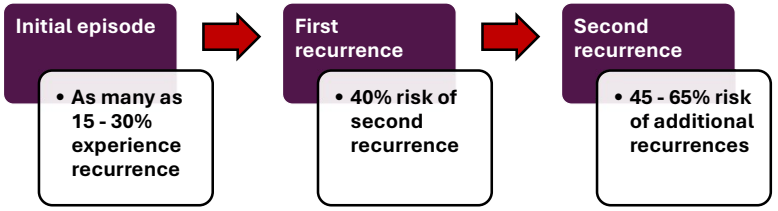
Risk of Recurrence



Song JH, Kim YS. *Gut Liver*. 2019;13(1):16-24.

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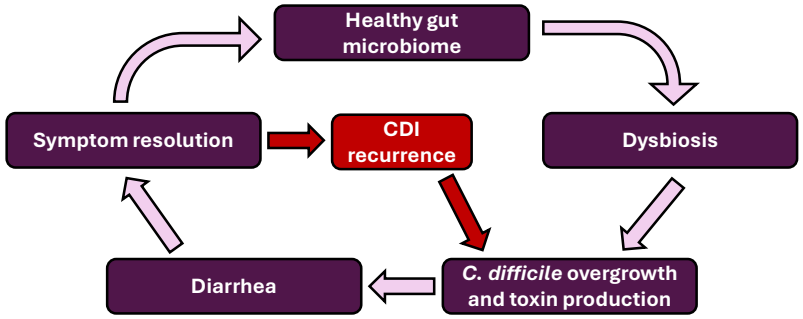
Pathogenesis



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IDSA/SHEA: First CDI Recurrence

Preferred	• Fidaxomicin x 10 days OR pulsed over 20 days
Alternative	• Vancomycin tapered/pulsed over 8 weeks
Adjunctive Treatment	• Bezlotoxumab x 1 dose

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SHEA: The Society for Health Epidemiology and America

Johnson S, et al. *Clin Infect Dis*. 2021;73(5):e1029-e1044.

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IDSA/SHEA: Second or Subsequent CDI Recurrence

Preferred	• Fidaxomicin x 10 days OR pulsed over 20 days • Vancomycin tapered and pulsed • Vancomycin x 10 days followed by rifaximin x 20 days
Preferred if ≥ 2 recurrences	• Fecal microbiota transplant (FMT)
Adjunctive Treatment	• Bezlotoxumab x 1 dose

CDI: *C. difficile* infection
IDSA: Infectious Diseases Society of America.
SHEA: The Society for Health Epidemiology and America

Johnson S, et al. *Clin Infect Dis*. 2021;73(5):e1029-e1044.

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Bezlotoxumab

- Monoclonal antibody which binds *C. difficile* toxin B
- Dose: Bezlotoxumab 10 mg/kg IV infusion for 1 dose
- Use: for the prevention of future CDI recurrences
- Adverse effects:
  - Nausea
  - Headache
  - Fever
- Caution use in individuals with heart failure
- Does NOT treat CDI and must be used in combination with antibiotics for treatment

CDI: *C. difficile* infection

Johnson S, et al. *Clin Infect Dis*. 2021;73(5):e1029-e1044.
Song JH, Kim YS. *Gut Liver*. 2019;13(1):16-24.

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Bezlotoxumab Logistics

- Brand name only
- Expensive medication cost
  - Medication copay cards and patient assistance programs available
- Infusion considerations:
  - Administration cost
  - Location for infusions
  - Lengthy visits for administration

Johnson S, et al. *Clin Infect Dis*. 2021;73(5):e1029-e1044.

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FMT

- Transfer of fecal matter from a donor to a recipient in attempt to correct dysbiosis and restore gut microbiota to diverse normal flora
- Administration dosage forms/routes
  - Capsules
  - Enema
  - Colonoscopy
  - Gastrostomy tube
  - Jejunostomy tube
  - Nasoduodenal/nasogastric tube

FMT: fecal microbiota transplant

Minkoff NZ, et al. *Cochrane Database Syst Rev*. 2023;4(4):CD013871.

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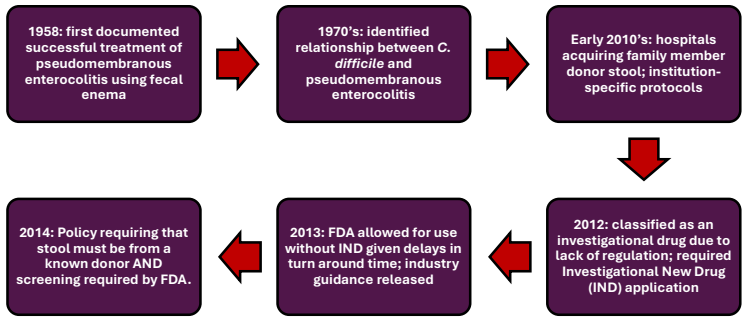
FMT Timeline



Wang Y et al. *Antibiotics*. 2024;13(5):436.

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FMT Risk & Screening

2019 FDA Safety Alert

2 patients developed invasive, drug-resistant *E. coli* following FMT; both immunocompromised	Same donor was found to have specific *E. coli* strain	Additional donor screening and stool testing prior to FMT

FMT: fecal microbiota transplant

McSeveney M. Food and Drug Administration. June 13, 2019. https://www.fda.gov/news-events/fda-brief/fda-brief-fda-warns-about-potential-risk-serious-infections-caused-multi-drug-resistant-organisms. Accessed Nov. 11, 2024.

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Live Biotherapeutic Products

Newly Approved

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Live Biotherapeutic Products (LBPs)

A biological product that:

- "contains live organisms, such as bacteria"
- "is applicable to the prevention, treatment, or cure of a disease or condition of human beings"
- "is not a vaccine"

Guidance for Industry. Food and Drug Administration. Accessed: 11 Nov. 2024.

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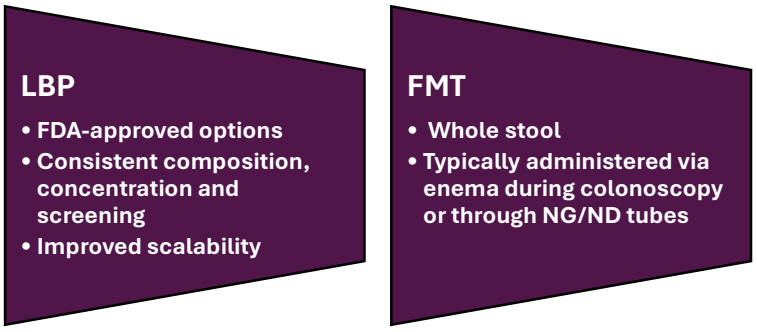
LBP vs FMT



FMT: fecal microbiota transplant
LBP: live biotherapeutic products

Wang Y et al. *Antibiotics*. 2024;13(5):436.

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Fecal microbiota, live-jslm (Rebyota™)

- Dose: between $1x10^8$ and $5x10^{10}$ CFU per mL of fecal microbes, prepared with PEG 3350 and 0.9% sodium chloride
  - No bowel prep required
- Contents: 150 mL suspension for rectal administration x 1 dose
- Approved for the prevention of future CDI recurrence in individuals ≥ 18 years old, following antibiotic treatment for recurrent CDI
  - FDA approved November 2022

CDI: *C. difficile* infection

Wang Y et al. *Antibiotics*. 2024;13(5):436.
Hunt A, at al. *Am J Health Syst Pharm*. 2024;81(15):e402-e411.

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PUNCH CD 3 – Phase III Trial

Study Design & Methods

- Randomized, double-blind, placebo-controlled trial
- Enrolled with ≥ 1 recurrence and completion of antibiotics or ≥ 2 episodes of severe CDI warranting hospitalization
- Used data borrowing and Bayesian analysis
- Non-responders were offered open-label Rebyota

Primary endpoint

- Treatment success: no CDI-related diarrhea at 8 weeks

CDI: *C. difficile* infection

Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

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PUNCH CD 3 – Results

	Placebo (n=87)	Rebyota (n=180)
Median (range) age in years	60.0 (26-86)	64.0 (19-93)
Male sex, n (%)	27 (31.0)	57 (31.7)
Race, n (%) Black White	 6 (6.9) 78 (89.7)	 8 (4.4) 168 (93.3)
Treatment antibiotic, n (%) Vancomycin Fidaxomicin	 78 (89.7) 5 (5.7)	 157 (87.2) 12 (6.7)
More than 3 prior CDI episodes, n (%)	28 (32.2)	69 (38.3)

Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

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PUNCH CD 3 - Efficacy

Rebyota demonstrated superiority to placebo for treatment success in the mITT population (70.4% vs 58.1%, respectively)

mITT: modified intent to treat

Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

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PUNCH CD 3 - Efficacy

Rebyota demonstrated superiority to placebo for treatment success in the mITT population (70.4% vs 58.1%, respectively)

92.1% in the Rebyota group and 90.6% in the placebo group had treatment success at 8 weeks and it was maintained through 6 months

mITT: modified intent to treat

Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

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PUNCH CD 3 - Efficacy

Rebyota demonstrated superiority to placebo for treatment success in the mITT population (70.4% vs 58.1%, respectively)

92.1% in the Rebyota group and 90.6% in the placebo group had treatment success at 8 weeks and it was maintained through 6 months

65 participants received open-label Rebyota following lack of treatment response in either group; 80% and 83.6% success in the placebo and Rebyota groups, respectively

mITT: modified intent to treat

Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

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PUNCH CD 3 – Safety

- **Adverse events were more frequent in the Rebyota group (55.6%) as compared to placebo (44.8%)**
- **Gastrointestinal symptoms were the most common**
- **Most adverse events occurred within the first 2 weeks**

Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

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Rebyota - Screening

- **Donors screened via physical exam, questionnaires, and both blood and stool lab tests**
- **Health-workers, persons recently hospitalized, participants in medical tourism are excluded as donors, given high risk of colonization**
- **Ferring excludes donors with high risk of MDROs**

MDRO: multi-drug resistant organisms

Wang Y et al. *Antibiotics*. 2024;13(5):436.
Rebyota [package insert]. Ferring Pharmaceuticals. Accessed. 20 Nov. 2024.

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Rebyota: Administration and Storage

Kit for administration provided by the manufacturer, delivered via gravity flow

Must be stored in an ultracold freezer. If in refrigerator, give within 5 days. Room temp prior to administration

Remain laying down to reduce cramping and expulsion

Hunt A, at al. *Am J Health Syst Pharm*. 2024;81(15):e402-e411.
Rebyota [package insert]. Ferring Pharmaceuticals Inc. Nov. 2022.

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Fecal microbiota spores, live brpk (Vowst)

- Dose: 4 capsules taken once daily by mouth for 3 days
- Approved for the prevention of future CDI recurrence in individuals ≥ 18 years old, following antibiotic treatment for recurrent CDI
  - FDA approved April 2023 (formerly SER-109)
- Each capsule contains $1x10^6$ to $3x10^7$ CFU of *Firmicute* spores

Wang Y et al. *Antibiotics*. 2024;13(5):436.
Press Announcement. Food and Drug Administration. Apr 26 2023. https://www.fda.gov/news-events/press-announcements/fda-approves-first-orally-administered-fecal-microbiota-product-prevention-recurrence-Clostridioides. Accessed Nov. 17, 2024.

CDI: *C. difficile* infection

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ECOSPOR IV – Phase III Trial

Study Design & Methods

- Open-label, single-arm clinical trial
- Cohort 1: patients with recurrence from ECOSPOR III
- Cohort 2: new patients with ≥ 1 CDI recurrence

Primary endpoint

- Safety and tolerability through 24 weeks

CDI: *C. difficile* infection

Sims MD. *JAMA Network Open*. 2-23;6(2):e2255758.

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ECOSPOR IV – Results

	Cohort 1: Vowst (n=4)	Cohort 1: Placebo (n=25)	Cohort 2 (n=234)
Mean age (SD) in years	85.0 (11.8)	69.5 (11.4)	63.1 (15.8)
Male sex, n (%)	2 (50.0)	9 (36.0)	72 (30.8)
Race, n (%)			
Black	0 (0)	0 (0)	14 (6.0)
White	4 (100)	25 (100)	214 (91.5)
Treatment antibiotic, n (%)			
Vancomycin	4 (100)	18 (72.0)	169 (72.2)
Fidaxomicin	0 (0)	7 (28.0)	65 (27.8)
More than 3 prior CDI episodes, n (%)	4 (100)	25 (100)	157 (67.1)

SD: Standard deviation

Sims MD. *JAMA Network Open*. 2-23;6(2):e2255758.

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ECOSPOR IV – Safety

- 141 patients (53.6%) experienced treatment-emergent adverse events (TEAEs)
  - Only 32 (12.2%) were deemed related or possibly related
  - Most commonly: diarrhea, flatulence, nausea
- No TEAEs leading to study withdrawal

Sims MD. *JAMA Network Open*. 2-23;6(2):e2255758.

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ECOSPOR IV - Efficacy

8.7% (23/263) had CDI recurrence within 8 weeks; 4/29 (13.8%) in cohort 1 and 19/234 (8.1%) in cohort 2. 13 more patients developed recurrence by week 24.

Sustained clinical response was 91.3% and 86.3% at weeks 8 and 24, respectively.

In patients with a first recurrence 6.5% (5/77) recurred again within 8 weeks. Similarly, in patients with two or more prior recurrences, 9.7% (18/186) recurred again.

CDI: *C. difficile* infection

Sims MD. *JAMA Network Open*. 2-23;6(2):e2255758.

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Vowst - Screening

- Donors screened via physical exam, questionnaires, and both blood and stool lab tests
- Routinely tested for many transmissible pathogens
- Donors do not have dietary restrictions

Wang Y et al. *Antibiotics*. 2024;13(5):436.
Vowst [Package insert]. Seres Therapeutics. Accessed 20 Nov. 2024.
Seres Therapeutics Inc. Summary Basis for Regulatory Action. 26 Apr 2023.

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Vowst: Administration and Storage

Prep with 300 mL oral magnesium citrate the night prior to first dose

Store between 2 °C and 25 °C; Do not store in the freezer

Administer 2 to 4 days after the end of CDI treatment

CDI: *C. difficile* infection

Hunt A, at al. *Am J Health Syst Pharm*. 2024;81(15):e402-e411.

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Comparing Rebyota and Vowst

	Rebyota	Vowst
Dosage form	Rectal suspension	Oral capsule
Bowel prep?	No	Yes
Duration of therapy	1 dose	Twice daily for 3 days
Storage	Ultracold freezer, ≤5 days refrigeration	Refrigerate

Wang Y et al. *Antibiotics*. 2024;13(5):436.

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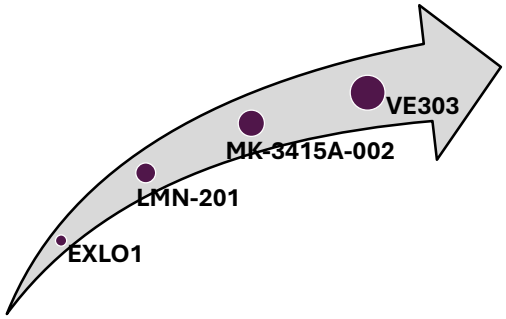
Therapies in the Pipeline



Clinicaltrials.gov. Accessed 20 Nov. 2024.

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LBPs Place in Therapy?

- In comparison to FMT?
- Tapers? Timing?
- After how many episodes?
- In comparison to bezlotoxumab?
- What should be given at treatment prior?

FMT: fecal microbiota transplant

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Take Home Points

- Metronidazole is no longer recommended for CDI unless both fidaxomicin and vancomycin are unavailable.
- Each episode of CDI recurrence increases risk for future recurrence.
- There are two FDA-approved live biotherapeutic products approved for the prevention of CDI recurrence.
- There are no head-to-head trials comparing FMT and LBPs.

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Resources

- **IDSA/SHEA 2017 *C. difficile* Infection Guidelines**
  - **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 the Society for Healthcare Epidemiology of America (SHEA). *Clin Infect Dis.* 2018;66(7):e1-e48.**
- **IDSA/SHEA 2021 *C. difficile* Infection Guideline Update**
  - **Johnson S, Lavergne V, Skinner AM, et al. Clinical Practice Guidelines for the Management of *Clostridioides difficile* Infection in Adults: 2021 Update by SHEA/IDSA. *Clin Infect Dis.* 2021.**
- **2021 ACG Clinical Guidelines**
  - **Kelly CR, Fischer M, Allegretti JR, et al. ACG Clinical Guidelines: Prevention, Diagnosis, and Treatment of *Clostridioides difficile* Infections. *Am J Gastrenterol.* 2021;116(6):1124-1147.**

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