Role of Live Biotherapeutic Products (LBPs) in the Treatment of *Clostridioides difficile*

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UIC College of Pharmacy

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Disclosures

The presenter does not have any conflicts or financial disclosures in relation to the content of this presentation.

The faculty mentor is a current consultant to Ferring Pharmaceuticals. Any relevant conflicts have been resolved.

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Objectives

1. Explain the mechanism of Live Biotherapeutic Products (LBPs) and their role in the management of *Clostridioides difficile* (C. diff.) infections
2. Review the safety and efficacy data of historical and present Fecal Microbiota Transplants (FMTs)
3. Describe the literature supporting new FDA-approved LBPs

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Clostridioides difficile Infection (CDI) and the Role of Live Biotherapeutic Products

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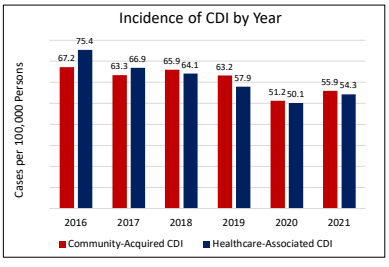
Epidemiology

- CDC Emerging Infections Program
  - Data from 10 counties
  - Population of 12.2 million people
  - ~12% recurrence rate
- CDC threat report (2017):
  - 223,900 hospitalized cases
  - 12,800 deaths



CDC. Antibiotic Resistance Threats in the United States, 2019.
CDC. *Clostridioides difficile* Infection (CDI) Tracking, 2022

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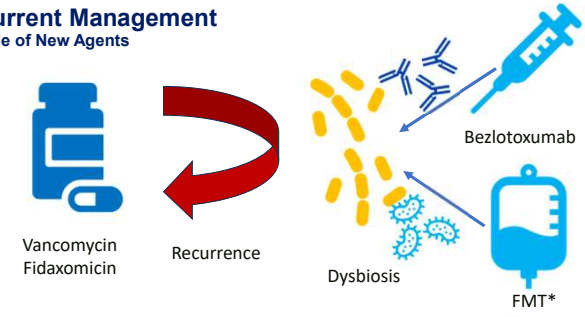
Current Management
Role of New Agents



*FMT: Fecal Microbiome Transplantation

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What are Live Biotherapeutic Products?

- Transfer of fecal material
  - Transplants he… thy m… es to infe… d patie…
  - Clini…
- E…
- Early in …
  - Ful… echanism under investigation
  - Ideal methods to be determined

LBP = FMT

LBP = FMT

2023 ICHP ANNUAL MEETING

Tennant M. *The Yale Global Health Review.* December 1, 2016.

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Mechanisms of Fecal Microbiome Transplantation
Why it Works

- Successful restoration of microbiome
  - Recipient diversity index matching donors
  - Recipient species colonization matches donors

Microbiome regulates local growth factors
- Deconjugating 1º bile acids into 2º bile acids
- Bacteriotoxins with G+ activity

Microbiome regulates cytokine expression
- Responsible for local immune regulation
- Reduces proinflammatory cytokines

= human data

= mouse data

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Hernández Del Pino RE, et al. *Journal of Leukocyte Biology*. 2021;109(1):195-210
Leffler DA, Lamont JT. *N Engl J Med.* 2015;372(16):1539-1548
Littmann ER, et al. *Nat Commun.* 2021;12(1):755
Lozupone et al. *ISME J* **5**, 169–172 (2011).

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You are counseling a patient in clinic with recurrent CDI about potentially using an LBP. The patient asks you to describe how the therapy works. The best response is:

A. LBPs introduce Bacteroides spp. depleted by CDI which will outcompete *C. diff.* for resources.

B. LBPs are used instead of antibiotic therapy and cause the innate immune system to attack *C. diff.*

C. LBPs replace a variety of commensal bacteria, creating an environment to prevent *C. diff.* overgrowth.

D. LBPs are used for initial infection as they prevent *C. diff.* spores from attaching to the gut lumen.

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Safety and Efficacy Data of FMT Products

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Fecal Microbiome Transplantation
Clinical Success

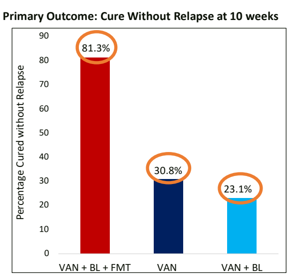
- ≥18 years old
- Relapse after ≥1 treatments
- *C. difficile* toxin (+)

Randomization Double-blinded

- Vancomycin + BL + FMT
- Vancomycin
- Vancomycin + BL

Key Takeaways
First RCT Evaluating FMT
High Efficacy vs. Antibiotic Therapy

Primary Outcome: Cure Without Relapse at 10 weeks



VAN: Vancomycin 500 mg po QID x 4 days
BL: Bowel lavage
FMT: Fecal microbiome transplantation

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van Nood E. et al. *N Engl J Med.* 2013;368(5):407-415.

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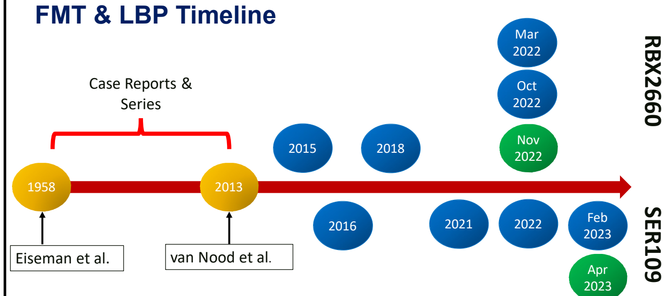
FMT & LBP Timeline



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Eiseman B, et al. Surgery. 1958;44(5):854-859
van Nood E. et al. *N Engl J Med.* 2013;368(5):407-415

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FMT Modern Efficacy
Systematic Review and Meta-analysis

Baunwall et al. 2020
- 45 studies: RCT and cohort
- 8w cure: 84% single dose (80-88%)
- 8w cure: 91% repeat dose (89-94%)

Pomares Bascuñana et al. 2021
- 15 studies: RCT, cohort, and cases within 5 years
- Effectiveness: 82% (75%-89%)

Baunwall SMD, et al. *EClinicalMedicine*. 2020;29-30:100642
Pomares Bascuñana RA, et al. *Lett Appl Microbiol*. 2021;73(2):149-158.

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Safety Data
Reports from 50 Publications

Gastrointestinal
Abdominal pain, bloating, diarrhea, nausea, flatulence

Systemic
Fever

Procedural
Nasal irritation, sore throat, bowel perforation, GI bleed, aspiration

Autoimmune
IBD disease flare, rheumatoid arthritis, peripheral neuropathy

Infectious
Peritonitis, pneumonia, diverticulitis, appendicitis, bacteremia, UTI

Pathogen Transmission
Norovirus, Cytomegalovirus, multi-drug resistant organisms

DeFilipp Z, et al. *N Engl J Med*. 2019;381(21):2043-2050.
Li YT, et al. *Aliment Pharmacol Ther*. 2016;43(4):445-457.
Wang S, et al. *PLoS ONE*. 2016;11(8):e0161174.

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Donor Screening

- Human immunodeficiency virus
- Hepatitis A
- Hepatitis B
- Hepatitis C
- Syphilis
- Norovirus
- Rotavirus
- Adenovirus
- Ova and parasites

- *Clostridioides difficile*
- Vancomycin-resistant enterococci
- Methicillin-resistant *Staphylococcus aureus*
- ESBL and CRE genes
- Shiga-toxin *E. coli*
- *Vibrios*
- *Salmonella*
- *Listeria*
- SARS-CoV-2 (after 12/01/2019)

ESBL = Extended-Spectrum Beta Lactamase Inhibitor
CRE = Carbapenem Resistant *Enterobacterales*
SARS-CoV-2 = Severe acute respiratory syndrome coronavirus 2

Gilson PE. *Cell Host & Microbe*. 2020;27(2):173-175.

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A physician colleague asks you about what historical data exists for FMTs. The best response is:

A. FMT data from clinical trials have shown high efficacy and safety.

B. FMT data are restricted to case reports making it difficult to assess efficacy and safety.

C. FMT data from clinical trials have shown high efficacy but frequent serious adverse events.

D. FMT data are restricted to case reports but have shown variable efficacy and high safety.

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Newly Approved Therapy: RBX2660

Fecal microbiota, live-jslm

Rebyota™

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Product Description – RBX2660

- 50g stool/150 mL PEG/NS enema
- $1x10^8 – 5x10^{10}$ CFU/mL mixed culture
  - $1x10^5$ Bacteroides CFU
- Standardized donors
- Frozen sample: stored from -60 °C to -90 °C
- Administer within 72 hours of last antibiotic dose

Drugs.com. *Rebyota Images*. Accessed online March 2023.
Rebyota. Package insert. Ferring Pharmaceuticals, Inc. 2022.

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Clinical Trials - Overview

Excluded
- Immunocompromised, gastrointestinal comorbidity, alternative pathogen or diagnosis
- *Not applicable to PUNCH CD3 OLS*

Demographics
- ~65 years old
- ~2/3 female
- >90% white
- ~90% vancomycin lead-in

Adverse Events
- 69.7% RBX2660 vs 60.2% placebo
- None life-threatening
- No pathogen-traced infections
- Study discontinuation <1%

Aggregate Clinical Trial Data

Participants (%) N=620	Doses of RBX2660
324 (52.3%)	1
270 (43.5%)	2
14 (2.3%)	3
12 (1.9%)	4

Blaun T, et al. *Open Forum Infect Dis.* 2021;8(Suppl 1):S611.

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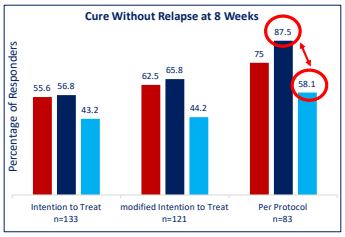
Clinical Trials – PUNCH CD2
Efficacy of RBX2660 vs Placebo

- ≥18 years old
- Relapse after ≥2 treatments
- *C. difficile* (+)
- Antibiotic treatment course

→ 2 doses RBX2660
→ 1 dose RBX2660 + 1 dose Placebo
→ 2 doses Placebo

Randomization
Double-blinded



Key Takeaways
Not All Patients Need 2 Enemas
Long Term Safety Data

Dubberke ER, et al. *Infect Dis Ther.* 2023;12(2):703-709.

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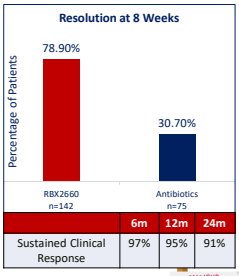
Clinical Trials - PUNCH Open Label
RBX2660 vs Historical Control

- ≥18 years old
- Relapse after ≥2 treatments
- *C. difficile* (+)
- Antibiotic treatment course

→ 2 doses RBX2660
→ Antibiotics (historical)

Not Randomized



	6m	12m	24m
Sustained Clinical Response	97%	95%	91%

Key Takeaways
Long Term Sustained Response
Long Term Safety Data
High Efficacy vs. Antibiotics

Orenstein R, et al. *BMC Infect Dis.* 2022;22(1):245.

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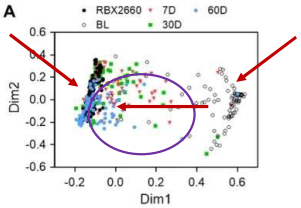
Clinical Trials – PUNCH Open Label
Similarity of Stool Cultures



Treatment Responders
n = 105

Orenstein R, et al. *BMC Infect Dis.* 2022;22(1):245.

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Clinical Trials – PUNCH CD3
Efficacy of RBX2660 vs Placebo

- ≥18 years old
- Relapse after ≥1 treatments
- *C. difficile* (+)
- Antibiotic treatment course

→ 1 dose RBX2660
→ Placebo
→ Optional dose 2

Treatment Failure

Randomization
Double-blinded

1° Outcome: Posterior probability of success
Bayesian modeling including PUNCH CD-2
Cutoff per FDA requirement 0.97503 (α = 0.025)

2° Outcomes

Overall RBX2660 response	83.6%
Placebo arm response	62.5%
Sustained response in both arms	90%

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

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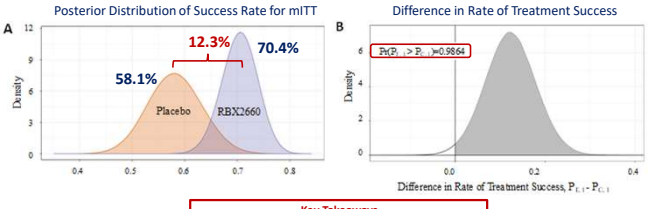
Clinical Trials – PUNCH CD3
Primary Outcome



Key Takeaways
Efficacy Significantly Better Than Placebo
Resulted in Drug Approval

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

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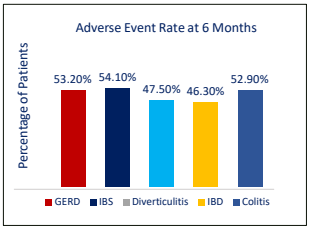
Interim Results – PUNCH CD3 OLS
Single Dose in Previously Excluded Comorbidities

- ≥18 years old
- Relapse after ≥1 treatments
- *C. difficile* (+)
- Antibiotic treatment course

→ One dose of RBX2660



Key Takeaways
Expected Safety in GI Comorbidities
Expected Efficacy in GI Comorbidities

Khanna S, et al. *Am J Gastroenterol.* 2022;117(10S):e94-e96.

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Newly Approved Therapy: SER109

Fecal microbiota spores, live-brpk

Vowst™

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Product Description – SER109

- 4 oral capsules daily x 3 days
- $1x10^6$ – $3x10^7$ spore CFU / capsule
  - Phyla *Firmicutes* Spores
  - Non-spore removal: ethanol and filtration
- Shelf life: 36 months at 2-25°C
- Administration
  - 10 oz Magnesium citrate night before
  - 2-4 days after last antibiotic dose

Drugs.com. *Vowst Images*. Accessed online July 2023.
US FDA. Summary Basis for Regulatory Approval. April, 2023.
Vowst. Package insert. Seres Therapeutics, Inc. 2023.

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Clinical Trials - Overview

Excluded
- Immunocompromised, gastrointestinal comorbidity, alternative pathogen or diagnosis
- Concomitant loperamide, cholestyramine, diphenoxylate/atropine

Demographics
- ~65 years old
- ~2/3 female
- >90% white
- ~80% vancomycin lead-in

Adverse Events
- One hypersensitivity reaction
- No serious adverse events drug-related
- No pathogen-traced infections

Trial Name and Population	Treatment Related Adverse Event Rate
Khanna et al (N = 30)	50%
ECOSPOR (n = 59)	55%
ECOSPOR III (n = 89)	51%
ECOSPOR IV (N = 263)	53.6%

Khanna, et al. *The Journal of Infectious Diseases.* 2016;214(2):173-181.
McGovern BH, et al. *Clinical Infectious Diseases.* 2021;72(12):2132-2140.
Feuerstadt P, et al. *N Engl J Med.* 2022;386(3):220-229.
Sims, [illegible] *Netw Open.* 2023;6(2):e225758.

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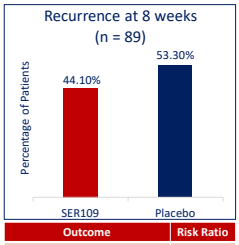
Clinical Trials - ECOSPOR
SER109 vs Placebo

- ≥18 years old
- Relapse after ≥1 treatment
- *C. difficile* (+)
- Antibiotic treatment course
- 10 oz Magnesium citrate bowel prep

→ 4 capsules SER109
→ Placebo

Randomization
Double-blinded

Key Takeaways
Dose-Response Relationship
Long Term Safety Data



Outcome	Risk Ratio
1 dose SER109 vs Placebo	1.2 (0.8-1.9)

McGovern BH, et al. *Clinical Infectious Diseases.* 2021;72(12):2132-2140.

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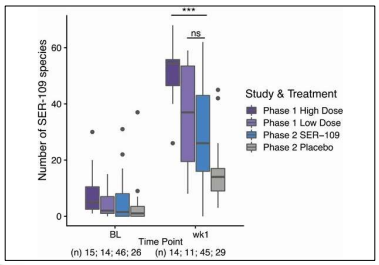
Clinical Trials - ECOSPOR
Dose vs Engraftment Post-hoc



McGovern BH, et al. *Clinical Infectious Diseases.* 2021;72(12):2132-2140.

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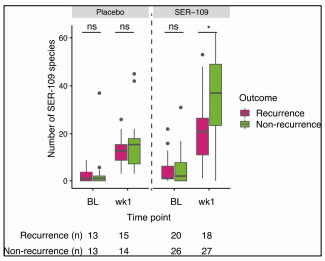
Clinical Trials - ECOSPOR
Engraftment vs Recurrence



McGovern BH, et al. *Clinical Infectious Diseases*. 2021;72(12):2132-2140.

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Clinical Trials – ECOSPOR III
SER109 vs Placebo

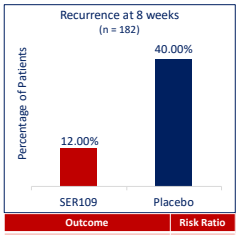
- ≥18 years old
- Relapse after ≥1 treatment in 12m
- *C. difficile* **toxin** (+)
- Antibiotic treatment course
- 10 oz Magnesium citrate bowel prep

4 capsules SER109 x3 days

Placebo

Randomization
Double-blinded

Key Takeaways
High-Dose Efficacy Superior to Placebo
High Sustained Clinical Response



Outcome	Risk Ratio
8-week Recurrence Risk SER109 vs Placebo	0.32 (0.18-0.58)
Sustained Clinical Response SER109	88%

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

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Clinical Trials – ECOSPOR IV
Single arm

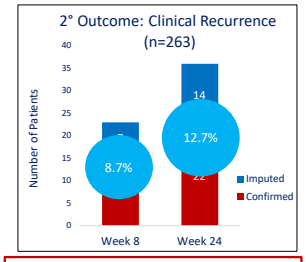
- ≥18 years old
- Relapse after ≥1 treatment
- *C. difficile* (+)
- 10-42d antibiotic treatment

- ECOSPOR III recurrence
- *C. difficile* EIA (+)

10oz MgCt bowel prep

4 capsules daily x3 days

1° Outcome: Adverse Events up to 24 weeks
- Overall 53.6% (141/263)
- 1 hypersensitivity reaction



Key Takeaways
Short Term Safety of High Dose
Sustained Clinical Response

Sims, M. *JAMA Netw Open*. 2023;6(2):e2255758.

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A pharmacist colleague asks you to describe the differences between RBX2660 and SER109 clinical trial data. The best response is:

A. The patient population enrolled in the PUNCH studies were older and more diverse.

B. The ECOSPOR studies showed a much higher sustained clinical response.

C. Engraftment was only studied in the ECOSPOR trials.

D. The PUNCH studies have published data for patients with IBD.

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Summary: *C. difficile* and LBPs

What We Do Know

- Successful LBP engraftment resembles donor microflora and alters local colonic environment
- Clinical success is correlated with engraftment and has 90% sustained response
- LBPs remain consistently more effective than antibiotic monotherapy for the treatment of CDI
- LBPs remain consistently safe both short-term and long-term

What We Don't Know

- The full relationship between colonic microbiota, the adaptive immune response, and *C. difficile* infection
- Desirable product contents and formulation
- Why some patients are unresponsive to LBPs
- The safety of LBPs in specialty populations

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Supplemental Resources

Mechanistic Review:

Littmann, E.R., Lee, JJ., Denny, J.E. et al. Host immunity modulates the efficacy of microbiota transplantation for treatment of Clostridioides difficile infection. Nat Commun 12, 755 (2021).

Product Review:

Wang JW, Kuo CH, Kuo FC, et al. Fecal microbiota transplantation: Review and update. *Journal of the Formosan Medical Association*. 2019;118:S23-S31

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20. Orenstein R, Dubberke ER, Khanna S, et al. Durable reduction of Clostridioides difficile infection recurrence and microbiome restoration after treatment with RBX2660: results from an open-label phase 2 clinical trial. *BMC Infect Dis.* 2022;22(1):245.

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Citations

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