Management of *C. Difficile* in 2023: The Next Frontier Has Arrived

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Disclosures

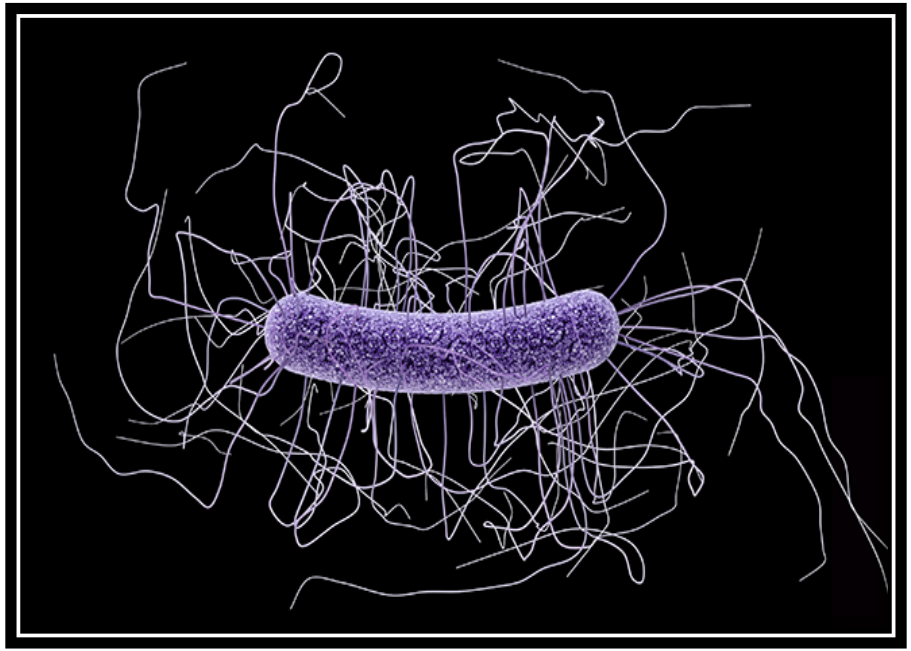
General

- Merck and Co: Speakers Bureau
- Ferring/Rebiotix Pharmaceutical: Consultant, Advisory Board, Speakers Bureau
- SERES Therapeutics: Advisory Board
- Takeda Pharmaceuticals: Advisory Board

Research Support

- Ferring Pharmaceuticals
- SERES Therapeutics
- Finch Therapeutics

What is *Clostridioides difficile*?



- **Gram positive**
- **Spore forming**
- **Anaerobic**
- **Rod**

Microbiology

Vegetative Form

Survives on moist surfaces for up to 6 hours[1]

Susceptible to:[2]

- Gastric acid
- Antibacterial soaps
- Alcohol-based hand sanitizers

Spore Form[2,3]

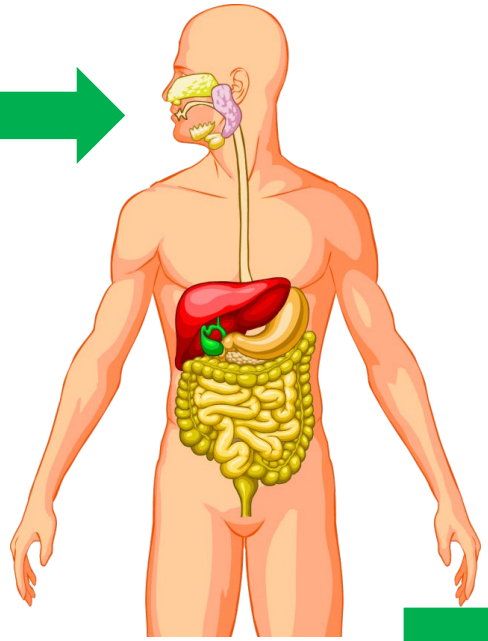
Survives on surfaces for months

Resistant to:

- Gastric acid
- Antibacterial soaps
- Alcohol-based hand sanitizers
- Rapidly changes to vegetative form

Jump RL et al. *Antimicrob Agents Chemother.* 2007;51(8):2883–2887.
Fordtran JS. *Proc (Bayl Univ Med Cent).* 2006;19(1):3–12.
Cohen SH et al. *Infect Control Hosp Epidemiol.* 2010;31(5):431–455.

Pathogenesis and Transmission



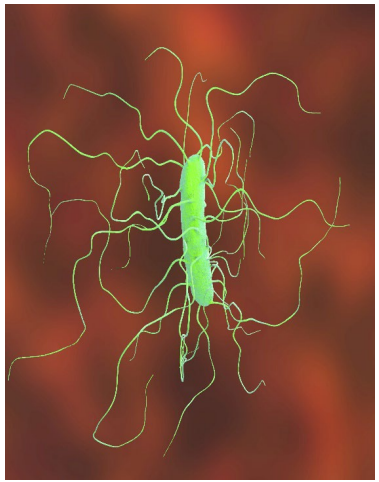
Symptoms

- Diarrhea
- Constipation
- Ileus
- Megacolon

Why Does Treating *C. difficile* illicit this response?

Overall Treatment Tools

Attack the Bacteria



- Metronidazole
- Vancomycin
- Fidaxomicin

Support the Immune System

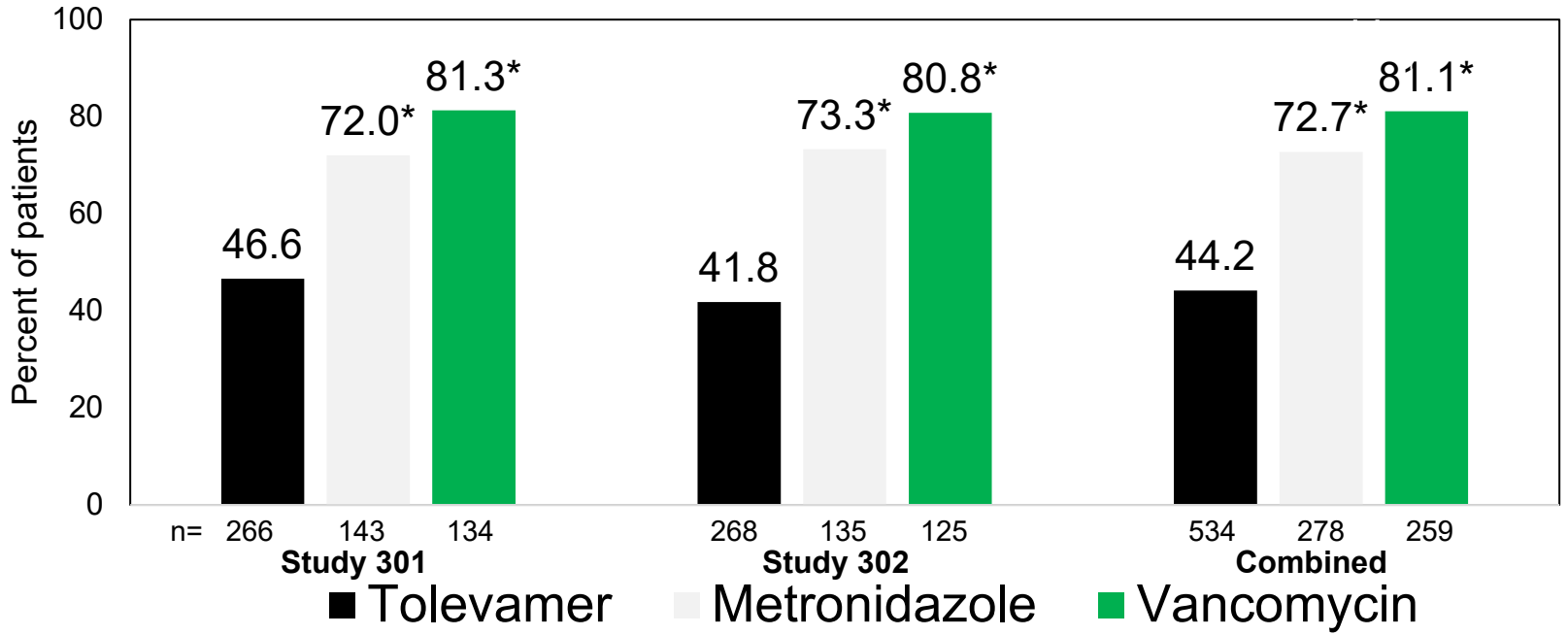
- Fecal Microbiota Transplantation
- Bezlotoxumab

IDSA/SHEA Guideline 2021
Initial Infection

Recommended and Alternative Treatments	Comments
Preferred: Fidaxomicin 200 mg given twice daily for 10 days	Implementation depends upon available resources
Alternative: Vancomycin 125 mg given four times daily by mouth for 10 days	Vancomycin remains an acceptable alternative
Alternative for non-severe CDI, if above agents are unavailable: Metronidazole, 500 mg three times daily by mouth for 10 – 14 days	Definition of non-severe CDI is supported by the following laboratory parameters: White blood cell count of 15,000 cells/mL or lower and a serum creatinine level less than 1.5 mg/dL

Johnson S. et al. Clin Infect Dis 2021:73:e1029-1044

Tolevamer vs. Metronidazole vs. Vancomycin
Clinical Success-Overall Cohort

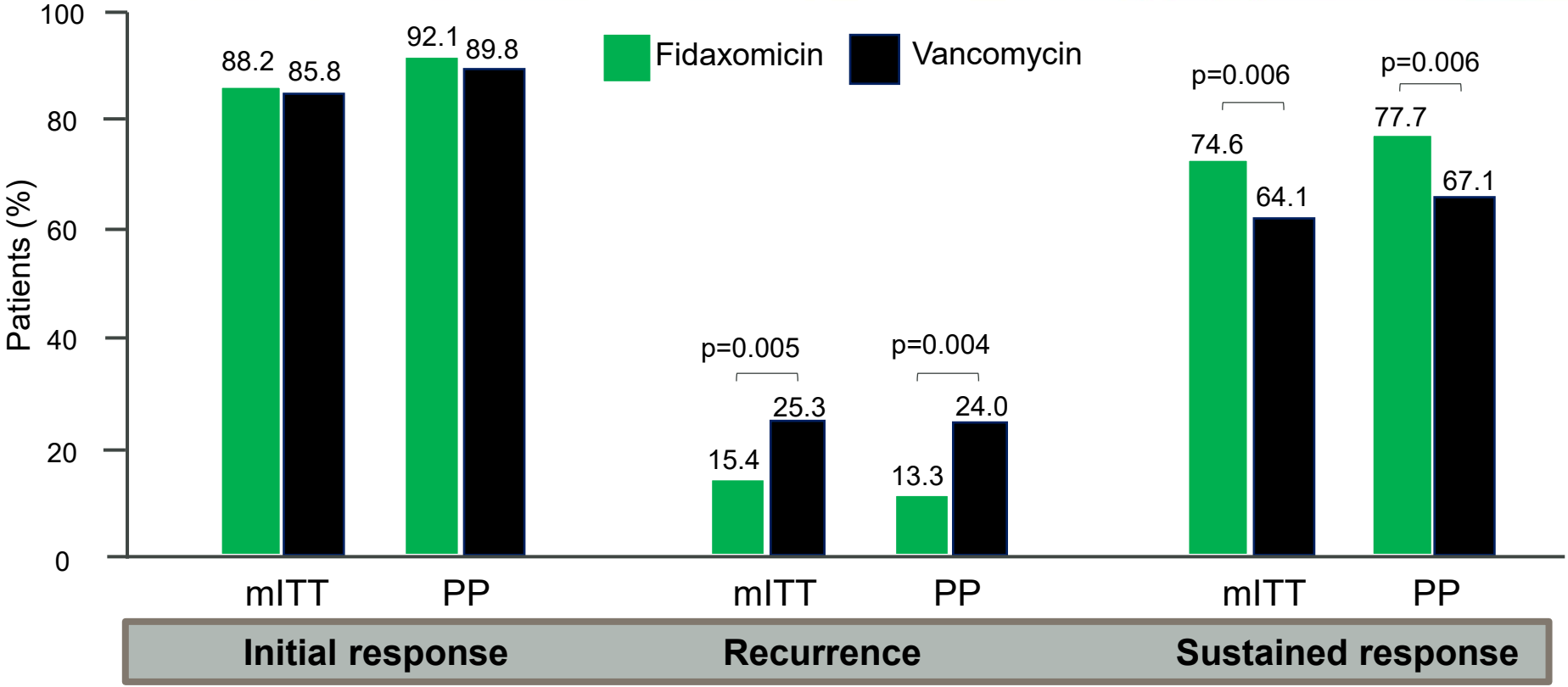


*p<0.001, tolevamer (T) vs metronidazole (M) and T vs vancomycin (V)

**p=0.020, M vs V

Johnson S, et al. *Clin Infect Dis*. 2014;59:345-54.

Fidaxomicin vs. Vancomycin for Initial Episode



Louie et al. *N Engl J Med*. 2011;364(5):422-431.

IDSA/SHEA Guideline 2021
First CDI Recurrence (2nd Episode)

Recommended and Alternative Treatments	Comments
Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for five days followed by once every other day for 20 days	
Alternative: Vancomycin by mouth in a tapered and pulsed regimen	Tapered/pulsed vancomycin regimen example: 125 mg four times daily for 10–14 days, two times daily for seven days, once daily for seven days, and then every two to three days for two to eight weeks
Alternative: Vancomycin 125 mg given four times daily by mouth for 10 days	Consider a standard course of vancomycin if metronidazole was used for treatment of the first episode
Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics**	Data when combined with fidaxomicin are limited. Caution for use in patients with congestive heart failure***

Johnson S. et al. Clin Infect Dis 2021:73:e1029-1044

Vancomycin Taper and Pulse

Taper and pulse

Effectiveness: 83%

(95% CI 69- 94%)

(range 58-100%)

(I^2 = 85%)

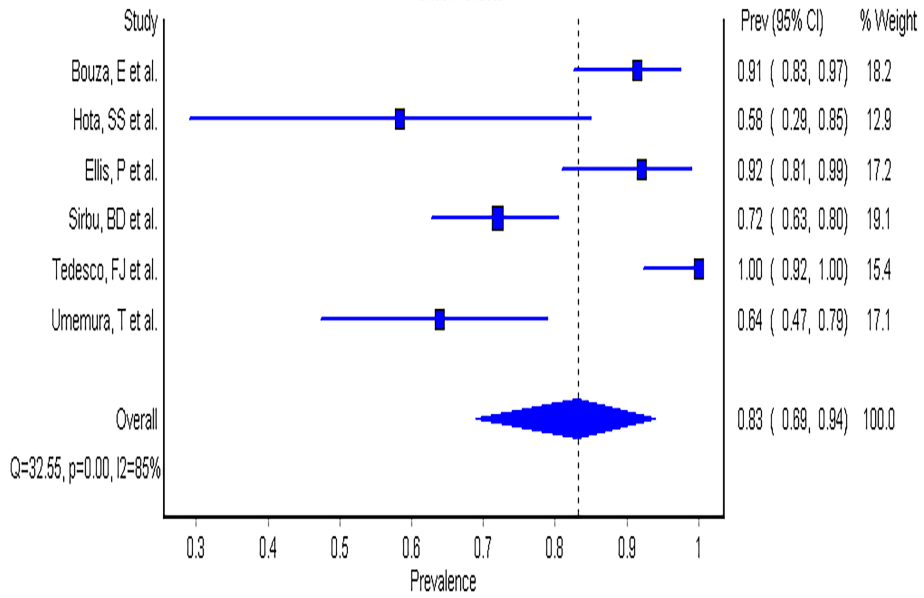
Taper and pulse regimens are superior to:

Taper alone

(WPR 83% vs 68%, p<0.0001)

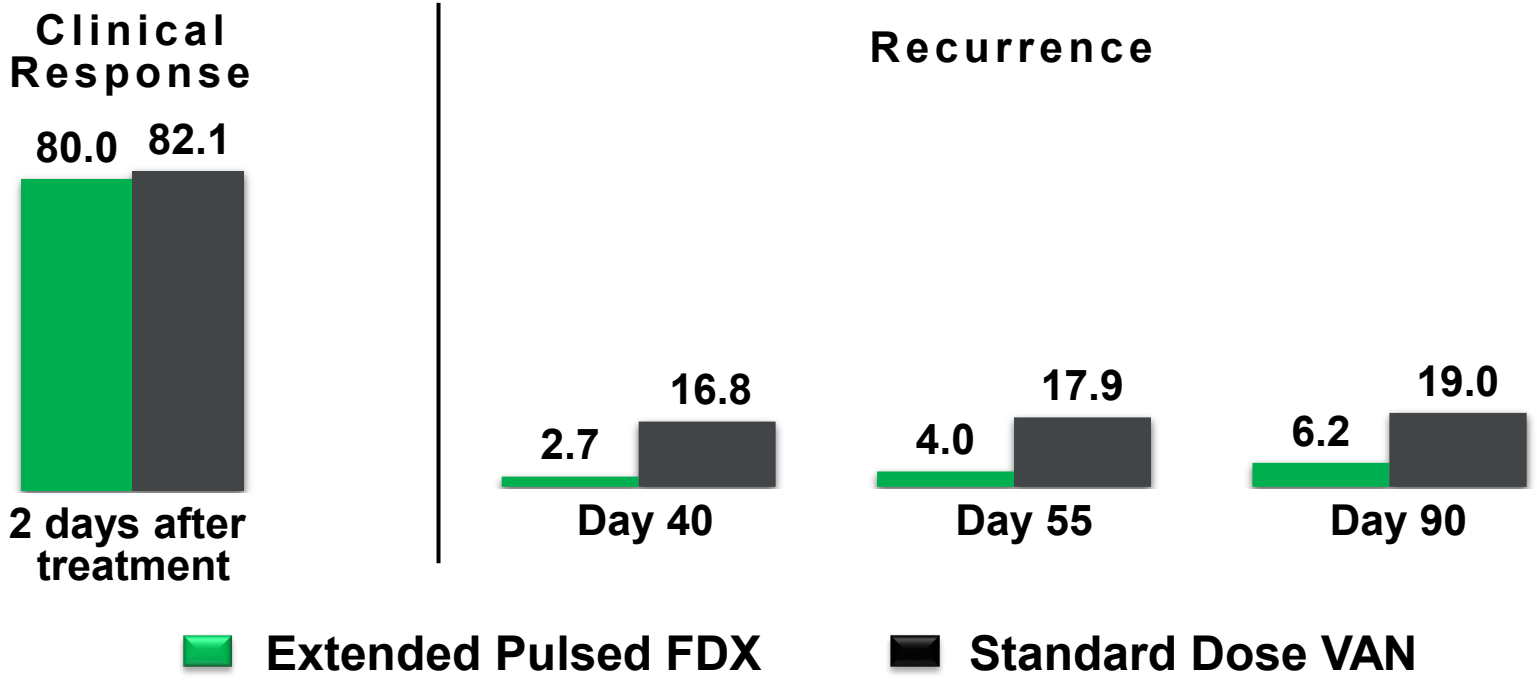
Pulse alone

(WPR 83% vs 54%, p <0.0004)



Sehgal et al. Expert Rev Anti Infect Ther 2022 20 (4):577-583

Extended Pulsed Fidaxomicin versus Vancomycin



Fidaxomicin (FDX): 200-mg oral tablets, twice daily on days 1–5, then once daily on alternate days on days 7–25
Vancomycin (VAN): 125-mg oral capsules, four times daily on days 1–10

Guery et al. *Lancet Infect Dis*. 2017;18(3):296-307

IDSA/SHEA Guideline 2021
Second CDI Recurrence (3rd Episode)

Recommended and Alternative Treatments	Comments
Preferred: Fidaxomicin 200 mg given twice daily for 10 days, OR twice daily for five days followed by once every other day for 20 days	
Vancomycin by mouth in a tapered and pulsed regimen	
Vancomycin 125 mg four times daily by mouth for 10 days followed by rifaximin 400 mg three times daily for 20 days	
Fecal microbiota transplantation	The opinion of the panel is that appropriate antibiotic treatments for at least two recurrences (i.e., three CDI episodes) should be tried prior to offering fecal microbiota transplantation.
Adjunctive treatment: Bezlotoxumab 10 mg/kg given intravenously once during administration of SOC antibiotics**	Data when combined with fidaxomicin

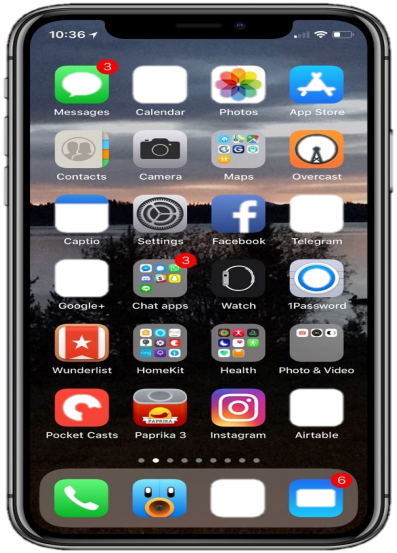
Johnson S. et al. Clin Infect Dis 2021:73:e1029-1044

Treatment of *C. difficile* Infection

Fidaxomicin
Vancomycin

Vegetative phase

Treatment of Recurrent *C. difficile* Infection



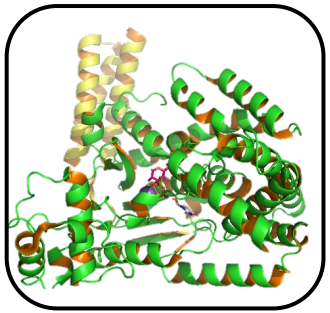
1

Fidaxomicin
Vancomycin

Vegetative phase

2

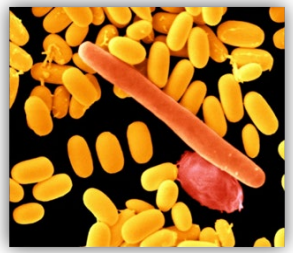
Bezlotoxumab



Toxin B

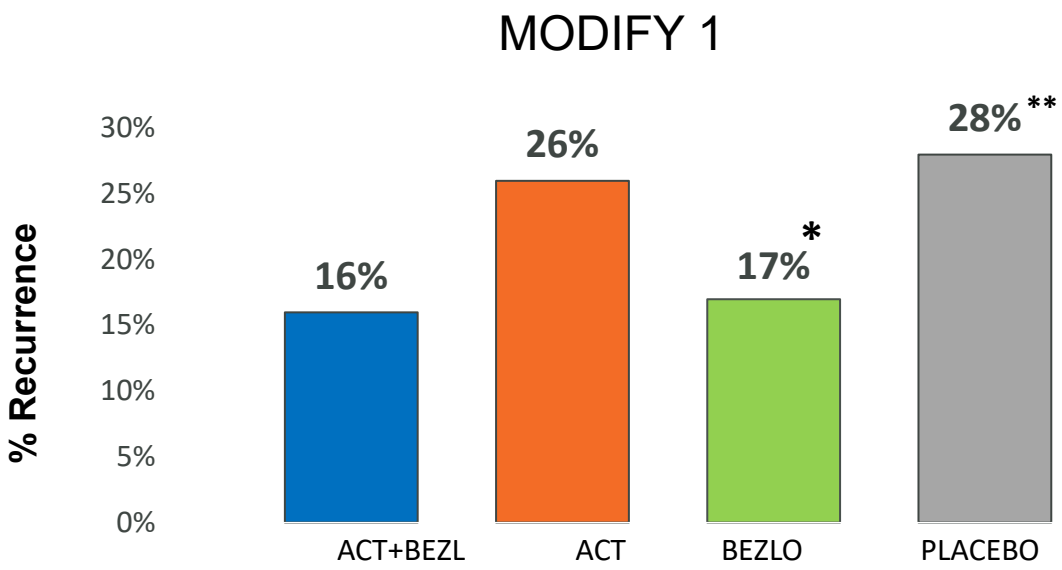
3

Fecal Microbiota
Transplantation

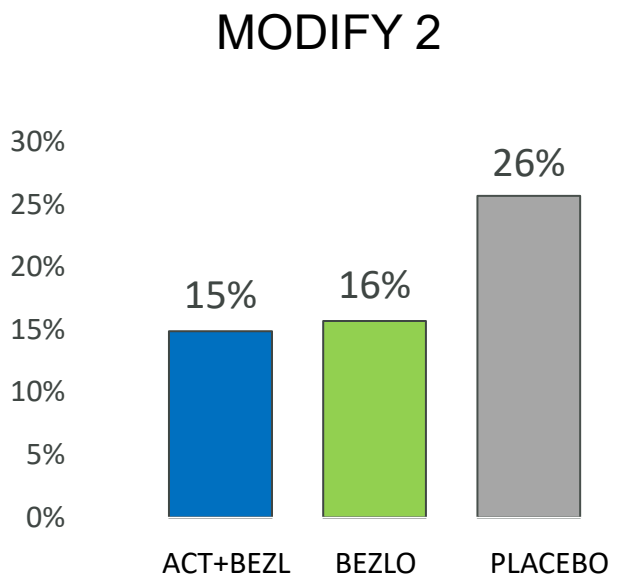


Spore Phase

Bezlotoxumab RCT: MODIFY 1 and MODIFY 2



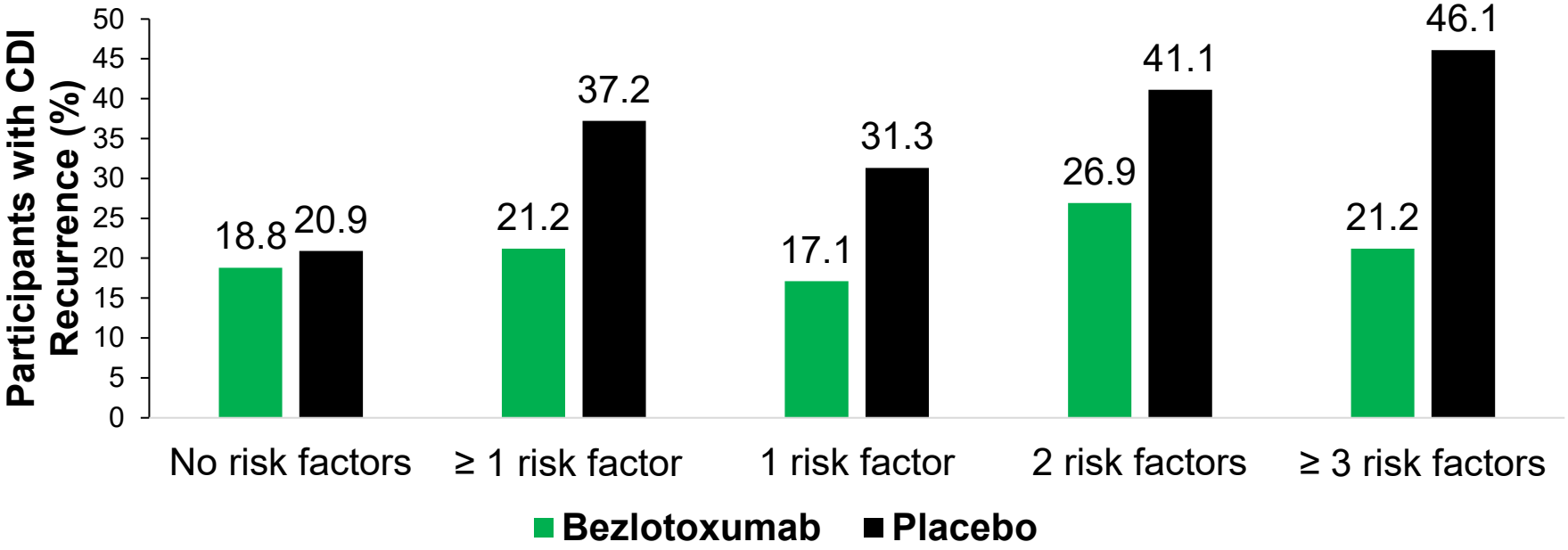
* ACT+BEZLO vs Pbo: p<0.0001
** BEZLO vs Pbo: p=0.0003



* ACT+BEZLO vs Placebo: p<0.0001
** BEZLO vs Placebo: p=0.0003

Wilcox MH et al. *NEJM.* 2017;376;4: 305-317

Bezlotoxumab CDI Recurrence by Number of Risk Factors



Gerding DN, et al. *Clin Infect Dis.* 2018;67(5):649–656

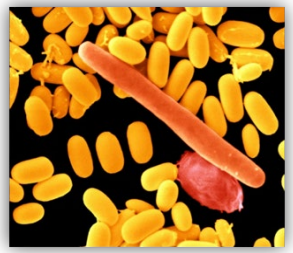
Fecal Microbiota Transplantation

Goals of Treatment for *C. difficile* infection

Fidaxomicin
Vancomycin
Metronidazole

Vegetative phase

Spore Phase



Healthy Diverse Microbiota

FMT in the 2021 Guidelines

&

We recommend patients experiencing their **second or further recurrence of CDI** be treated with FMT to prevent further recurrences (strong recommendation, moderate quality of evidence)

We suggest repeat FMT for patients experiencing a recurrence of CDI **within 8-weeks of an initial FMT** (conditional recommendation, very low quality of evidence)

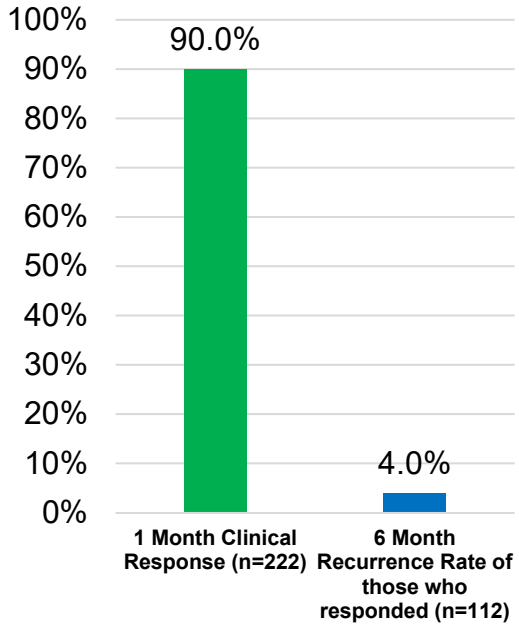
We suggest fecal microbiota transplantation be considered for patients with **severe or fulminant CDI refractory to antimicrobial therapy, particularly, when patients are deemed poor surgical candidates** (strong recommendation, low quality of evidence)

The opinion of the panel is that appropriate antibiotic treatments for **at least two recurrences (i.e., three CDI episodes)** should be tried prior to offering fecal microbiota transplantation.

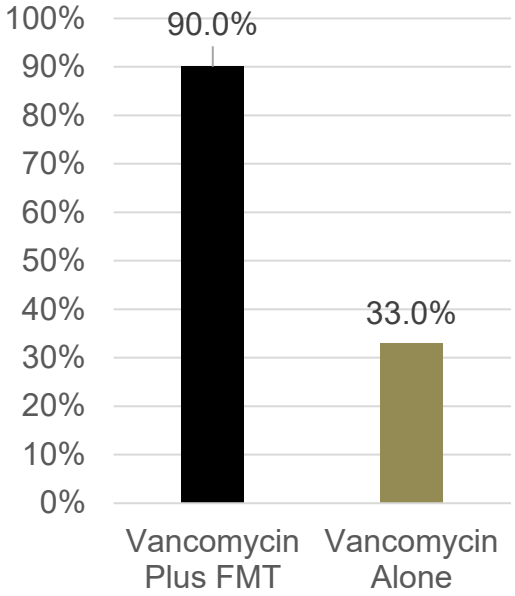
Kelly et al. Am J Gastroenterol. 2021 Jun 1; 116(6):1124-1147
Johnson S. et al. Clin Infect Dis 2021:73:e1029-1044

Foundational Data for FMT in CDI

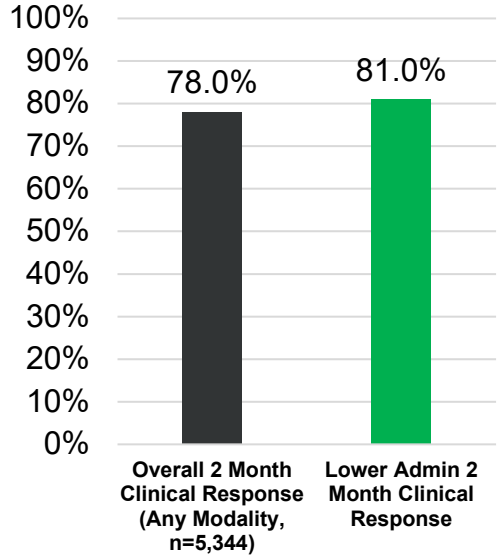
2021
Kelly et al.
AGA FMT Registry



2022
Baunwall et al.
Initial Episode or 1st Recurrence



2022
Osman et al.
Stool Bank



Kelly et al. Gastro 2021 Jan;160(1):183-192

Baunwall et al. Lancet Gastroenterol Hepatol. 2022 Dec;7(12):1083-1091.

Osman et al. Gastroenterology. 2022 Jul;163(1):319-322.

How safe is FMT?

June 2019: A Curve in the Safety Road

FDA

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IN THIS SECTION: Safety & Availability (Biologics)

← Safety & Availability (Biologics)

Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms

Share Tweet LinkedIn Email Print

June 13, 2019

The Food and Drug Administration (FDA) is informing health care providers and patients of the potential risk of serious or life-threatening infections with the use of fecal microbiota for transplantation (FMT). The agency is now aware of bacterial infections caused by multi-drug resistant organisms (MDROs) that have occurred due to transmission of a MDRO from use of investigational FMT.

Summary of the Issue

- Two immunocompromised adults who received investigational FMT developed invasive infections caused by extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli (E.coli)*. One of the individuals died.
- FMT used in these two individuals were prepared from stool obtained from the same donor.
- The donor stool and resulting FMT used in these two individuals were not tested for ESBL-producing gram-negative organisms prior to use. After these adverse events occurred, stored preparations of FMT from this stool donor were tested and found to be positive for ESBL-producing *E. coli* identical to the organisms isolated from the two patients.

Information for Health Care Providers and Patients

In July 2013, FDA issued guidance stating that it intends to exercise enforcement discretion under limited conditions regarding the IND requirements for the use of FMT to treat *Clostridium difficile (C. difficile)* infection in patients who have not responded to standard therapies. The guidance states that FDA intends to exercise enforcement discretion provided that the treating physician obtains adequate consent for the use of FMT from the patient or his or her legally authorized representative. The consent should include, at a minimum, a statement that the use of FMT to treat *C. difficile* is investigational and a discussion of its potential risks. FDA is informing members of the medical and scientific communities and other interested persons of the potential risk of transmission of MDROs by FMT and the resultant serious adverse reactions that may occur.

Patients considering FMT to treat *C. difficile* infection should speak to their health care provider to understand the potential risks associated with the product's use.

Additional Protections for Investigational Use of FMT

DeFillip et al. *NEJM 2019. 381 (21) 2043-2050*

March 2020: Serious Adverse Events

FDA

Search Menu

IN THIS SECTION: Safety & Availability (Biologics)

← Safety & Availability (Biologics)

Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Events Likely Due to Transmission of Pathogenic Organisms

Share Tweet LinkedIn Email Print

March 12, 2020

The Food and Drug Administration (FDA) is informing health care providers and patients of the potential risk of serious or life-threatening infections with the use of fecal microbiota for transplantation (FMT). The agency is now aware of infections caused by enteropathogenic *Escherichia coli* (EPEC) and Shigatoxin-producing *Escherichia coli* (STEC) that have occurred following investigational use of FMT that it suspects are due to transmission of these pathogenic organisms from FMT product supplied by a stool bank company based in the United States. The stool bank provides FMT product manufactured from pre-screened donors to healthcare providers and researchers.

In accordance with FDA's disclosure regulations and general practices, FDA is not disclosing the name of the company at this time.

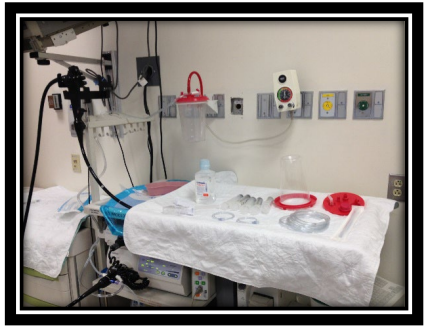
Summary of the Issue

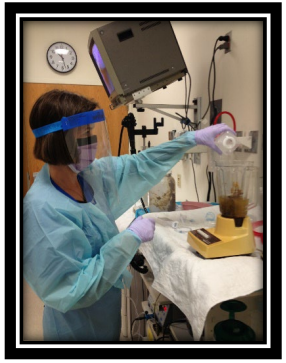
- FDA has been notified of six patients who received the company's FMT product for *Clostridium difficile* (also called *Clostridioides difficile* or *C. difficile*) infection not responsive to standard therapies and who developed infections caused by EPEC (two patients) or STEC (four patients). Four of the six patients required hospitalization.
  - The two patients who developed EPEC infection received FMT product that was prepared from stool from two different donors.

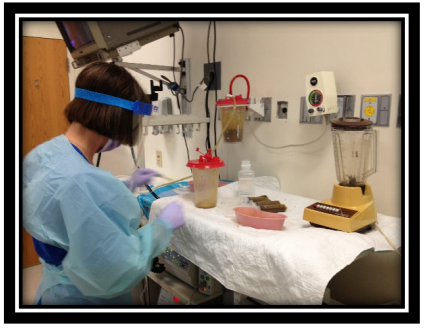
https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse-events

Evolution of FMT

The Past







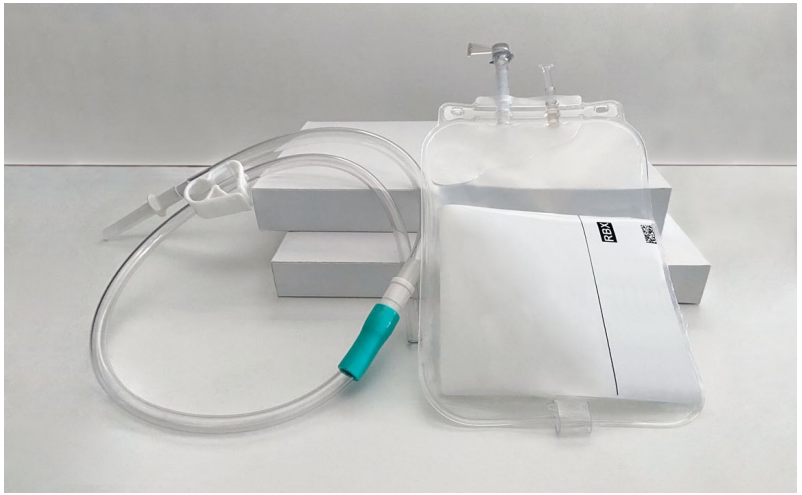
The Present/Future

Current Pharmaceutical Trial Landscape

Company	Study Name	Product Description	Phase	Study Population	Primary outcome
Rebiotix	PUNCH CD 3	RBX2660 Enema	FDA approved	Recurrent CDI	Absence of CDI diarrhea without re-treatment at 8 weeks
Seres Therapeutics	ECOSPOR III	SER-109 Oral Capsule	FDA approved	Recurrent CDI	CDI recurrence at 8 weeks
Vedanta Bioscience	CONSORTIUM	VE303	Phase 2	Recurrent CDI	CDI Recurrence at 8 weeks

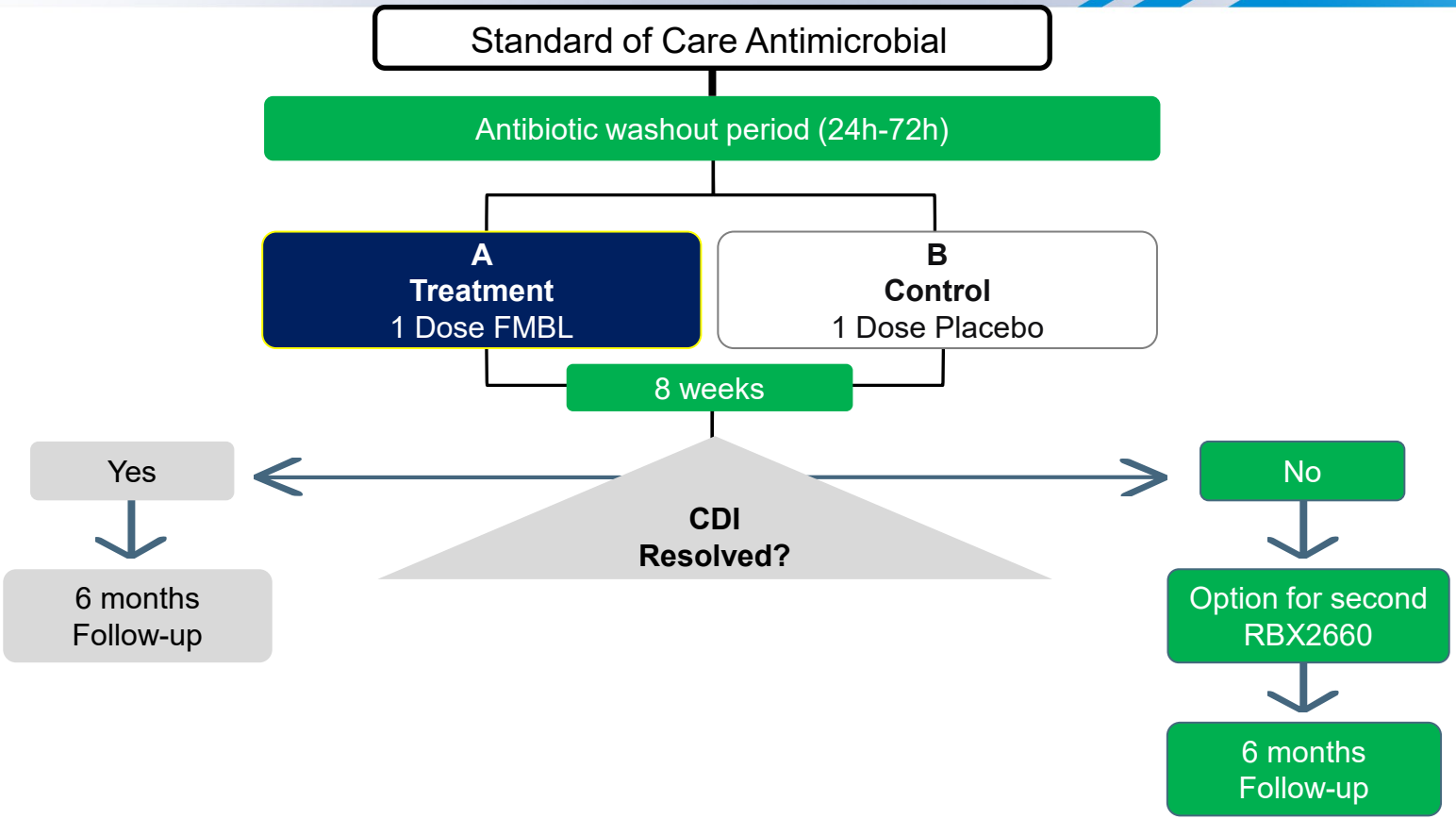
Rebyota (fecal microbiota, live-JSLM)

- Single-dose, microbiota-based live biotherapeutic agent
- Rectally administered
- 150 mL of therapeutic material
- 10^7 microbes per mL or 15 x 10^8 microbes per treatment
- Broad consortium
- A proprietary manufacturing process preserves diverse spore-forming and non–spore-forming bacteria, including *Bacteroides*, in RBX2660

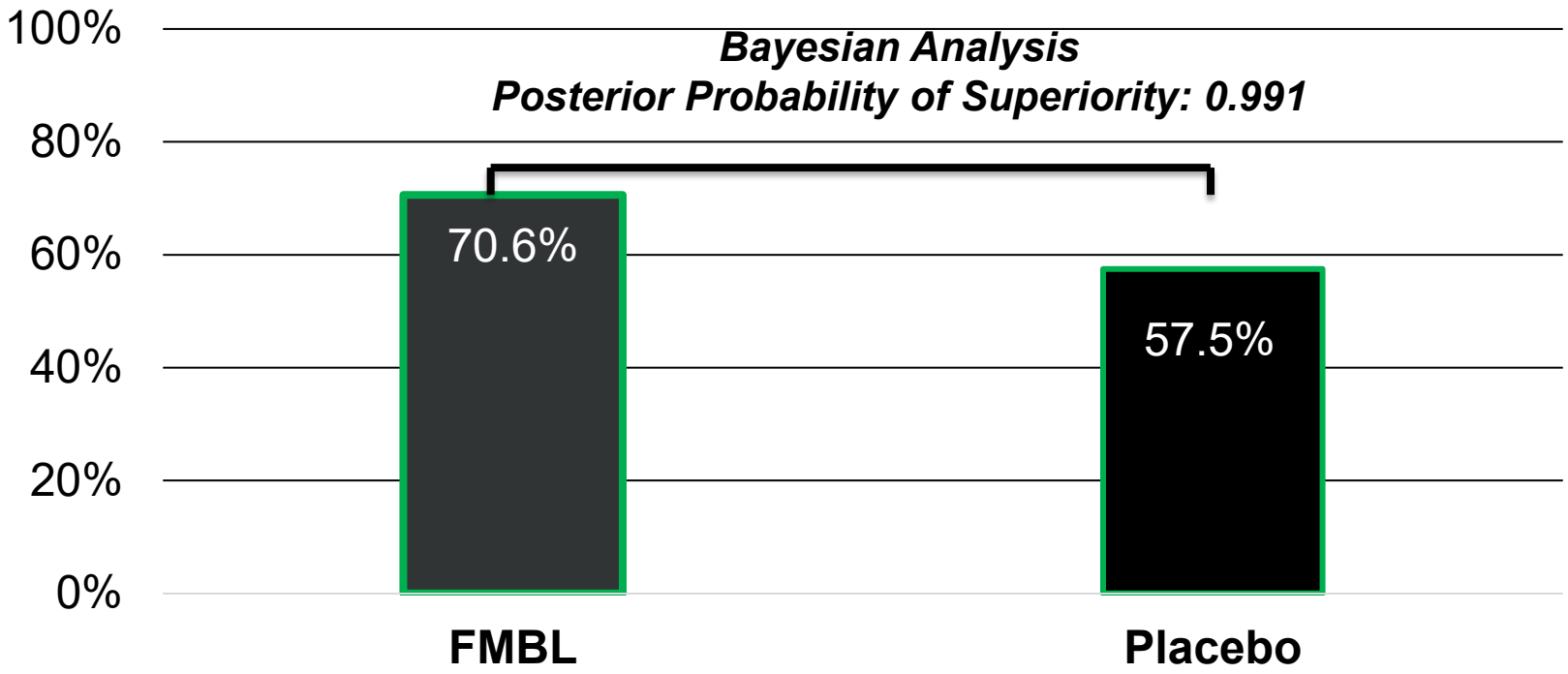


Orenstein R et al. *Clin Infect Dis*. 2016;62:596-602.
Blount KF et al. *Open Forum Infect Dis*. 2019;6:ofz095
Ray A, Jones C. *Future Microbiol*. 2016;11:611-616.

PUNCH-CD3: Phase 3 Trial Design



PUNCH-CD3: Phase 3
FMBL Superior to Placebo



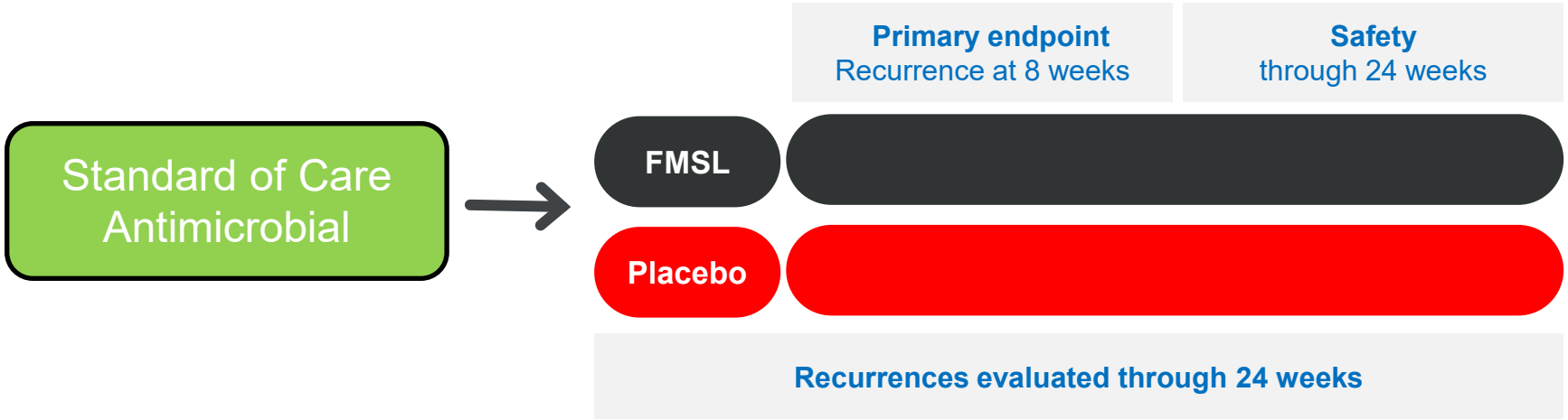
Khanna et al. Drugs. 2022 Oct;82(15):1527-1538

Vowst (fecal microbiota spores, live-BRPK)

- Microbiota-based live biotherapeutic agent administered with 4 capsules daily over 3 days
- Orally administered
- 3 x 10^7 CFU per full treatment
- Narrow consortium
- A proprietary manufacturing process removes most fungi, parasites, viruses and non-spore forming bacteria resulting in predominantly Firmicutes spores

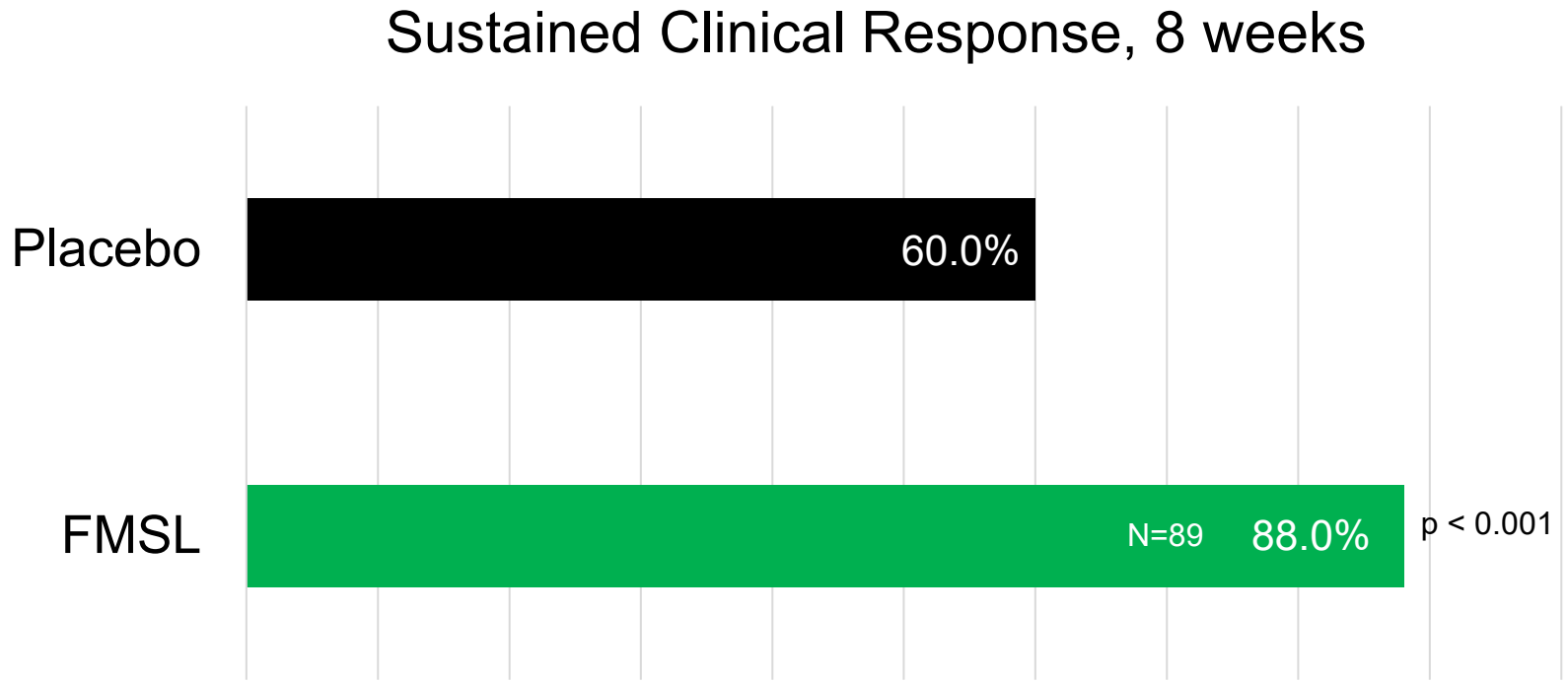
Korman L et al. Gastroenterology 2021;6:S-368.
Feuerstadt et al. N Engl J Med. 2022 Jan 20;386(3):220-229

ECOSPOR-III: Phase 3 Trial Design



Feuerstadt et al. N Engl J Med. 2022 Jan 20;386(3):220-229

ECOSPOR-III: Phase 3
FMSL superior to Placebo



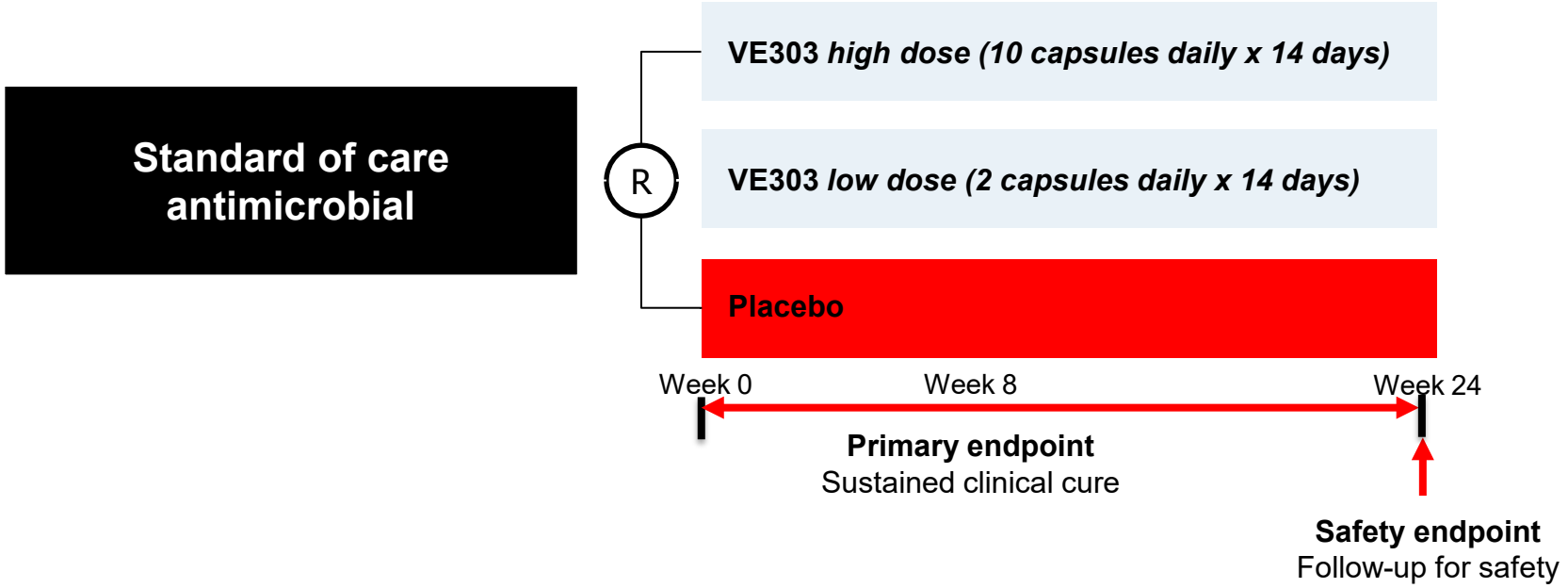
Feuerstadt et al. N Engl J Med. 2022 Jan 20;386(3):220-229

VE303

- Microbiota based live biotherapeutic
- Orally administered
- High Dose: 10 capsule daily for 14 days
- 1.1 x 10^{11} CFU total
- Defined consortium with 8 specific bacterial species which originally derived from healthy human intestinal microbiomes

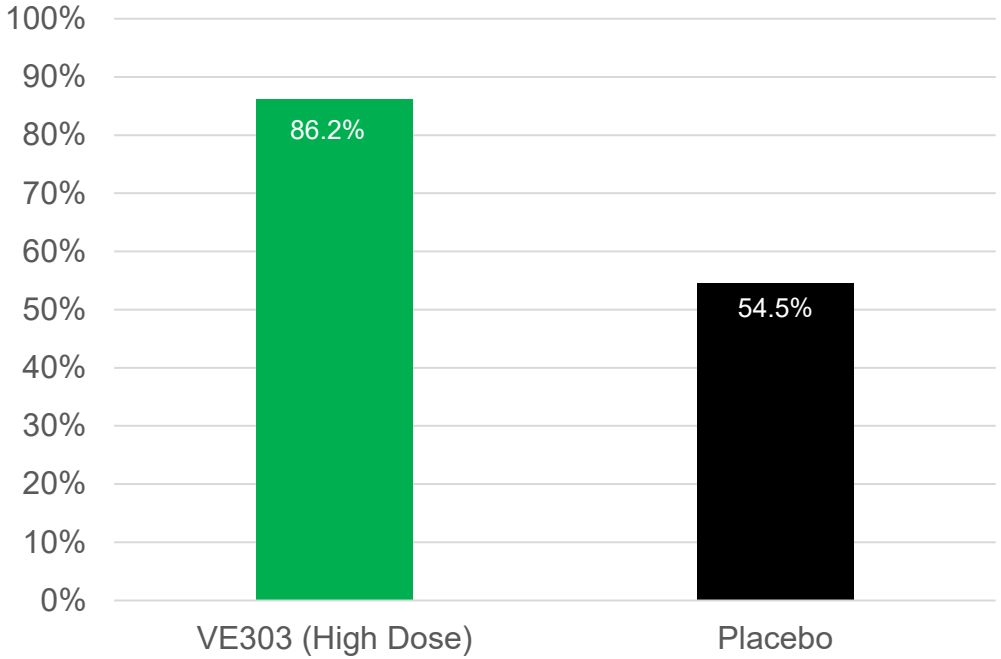
Louie et al. JAMA epub 2023 Apr 15

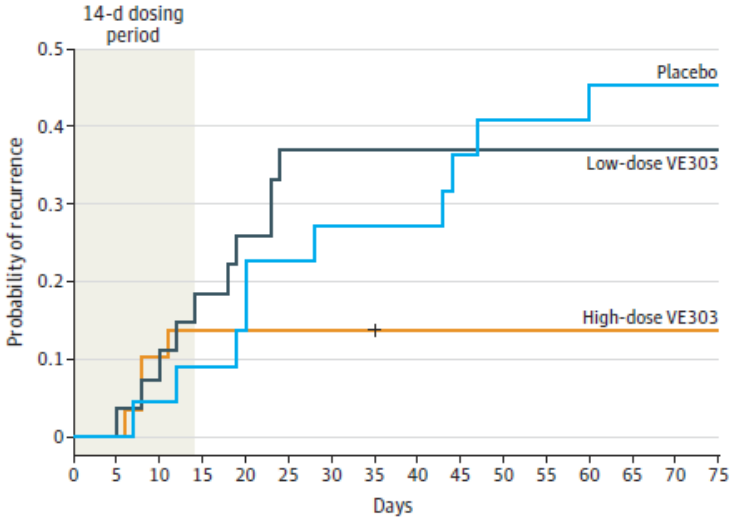
CONSORTIUM TRIAL: Phase 2 Trial Design VE303



Louie et al. JAMA epub 2023 Apr 15

Consortium Trial: VE303 Phase 2 Trial
High Dose VE303 vs. Placebo, 8 weeks





Louie et al. JAMA epub 2023 Apr 15

Be Careful with Comparisons Between Trials…

	RBX2660 PUNCH-CD3	SER-109 ECOSPOR III	VE303 CONSORTIUM
Duration of standard of care antimicrobial	Minimum of 10-consecutive days	10-21 days	Minimum of 10-consecutive days
Episodes of CDI	≥ 1 recurrence	≥ 2 recurrences	≥1 CDI recurrence
Diagnostics	PCR, EIA/GDH	EIA/GDH, CCNA	EIA, PCR, CCNA
Washout Period	24-72 hours	Within 72 hours	0-24 hours
Bowel Purge	None	10 oz Magnesium Citrate prior to dosing	None
Dosing	1, 150 mL enema once *(15 x 10^8 microbes per treatment)*	4 capsules daily for 3 days *(3 x 10^7 spore CFU)*	10 capsules per day for 14 days *(1.1 x 10^{11} CFU total)*

Treatment Algorithm