Managing Recurrent *Clostridioides Difficile* Infection

Advancing the Science of Microbiome-Based Therapies

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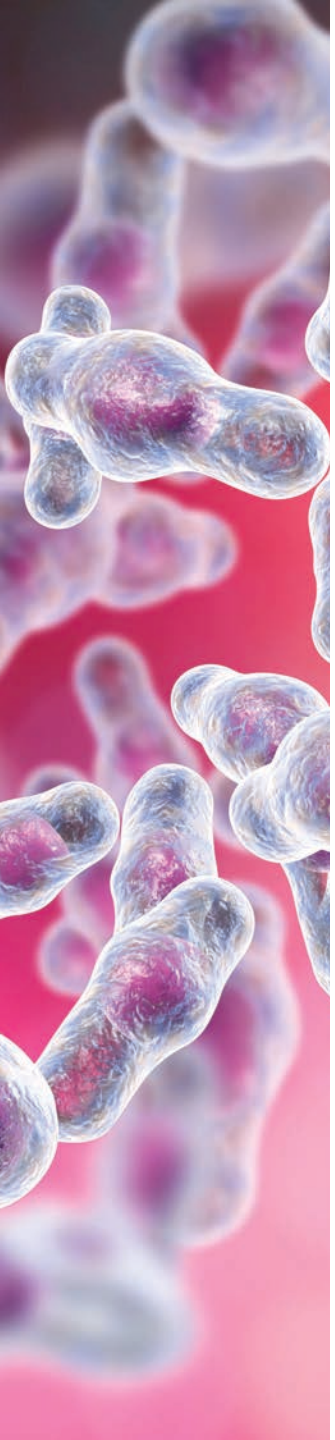

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Presenters

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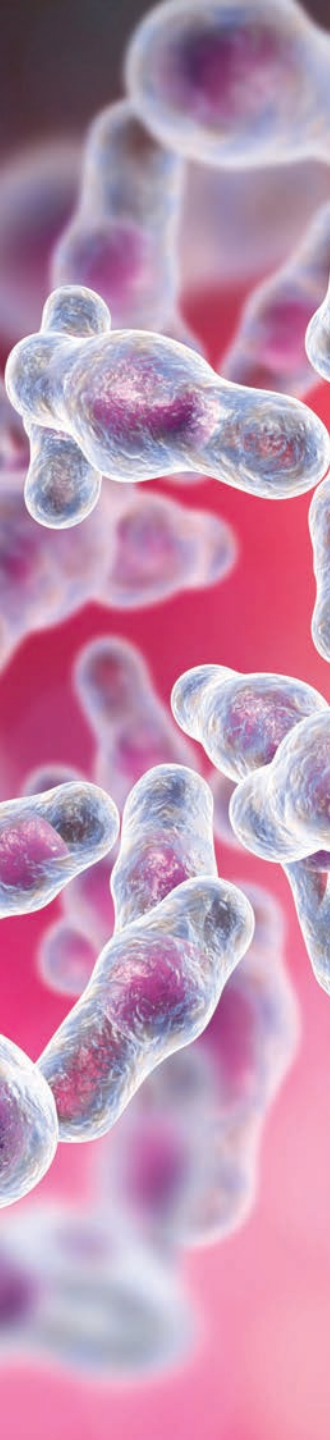
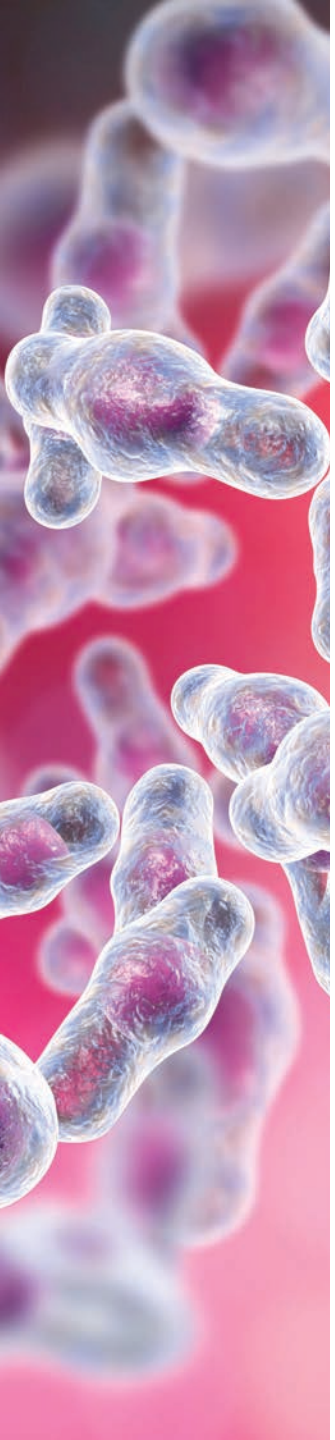


Disclosures

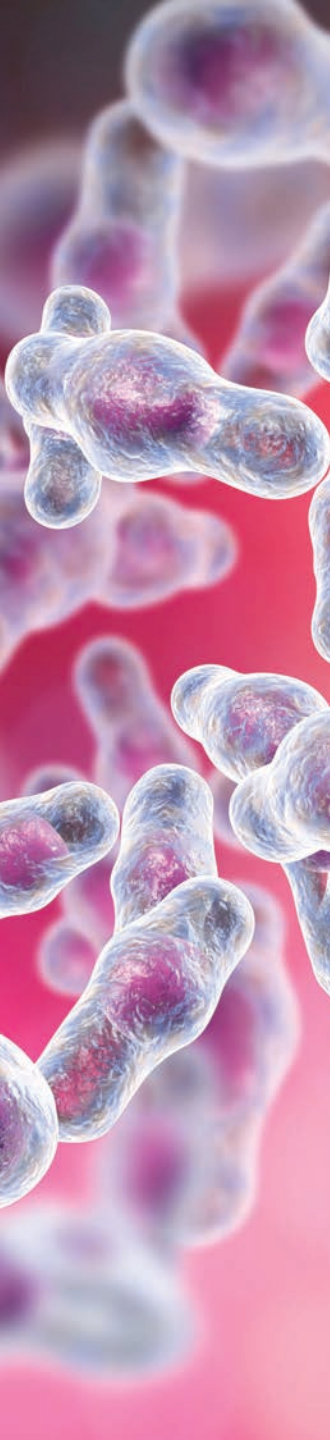
Paul Feuerstadt, MD, FACG, AGAF	• **Consulting fees (eg, advisory boards):** Ferring Pharmaceuticals, Merck and Co., Sanofi, SERES Therapeutics, Takeda Pharmaceuticals • **Contracted research:** Adare Pharmaceuticals, Ferring Pharmaceuticals, SERES Therapeutics, Takeda Pharmaceuticals • **Honoraria:** Ferring Pharmaceuticals, SERES Therapeutics • **Speakers' bureaus:** Ferring Pharmaceuticals, SERES Therapeutics
Anne J. Gonzales-Luna, PharmD, BCIDP	• **Consulting fees (eg, advisory boards):** Ferring Pharmaceuticals, Innoviva Specialty Therapeutics • **Contracted research:** Paratek Pharmaceuticals, Seres Therapeutics
Robert Orenstein, DO	• **Consulting fees (eg, advisory boards):** Ferring Pharmaceuticals • **Contracted research:** Ferring Pharmaceuticals, Finch • **Honoraria:** Rebiotix, a Ferring Company • **Speakers' bureau:** Ferring Pharmaceuticals



Educational Objectives

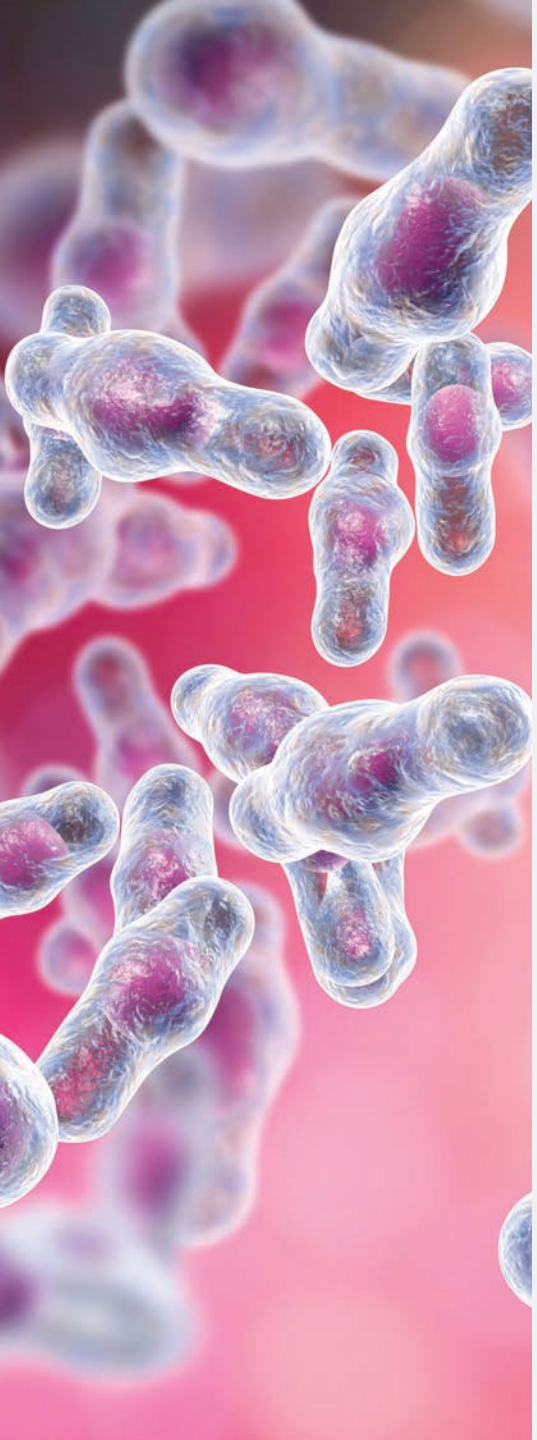
1. Recognize the substantial health burdens associated with CDI and rCDI
2. Describe the pathogenesis of rCDI, including the role of alterations in the intestinal microbiota
3. Discuss antibiotic treatment strategies to optimize the management of rCDI
4. Evaluate the most up-to-date clinical trial data for new and emerging microbiota restoration therapies for prevention of rCDI

CDI, *Clostridioides difficile* infection; **rCDI,** recurrent *Clostridioides difficile* infection.



Agenda

Time	Topic
6:05-6:20 AM	Role of the microbiome in rCDI: Dr. Orenstein
6:20-6:25 AM	Case discussion
6:25-6:40 AM	Selecting antibiotic treatment for rCDI: Dr. Gonzales-Luna
6:40-6:45 AM	Case discussion
6:45-7:05 AM	New/Emerging microbiota-based biotherapies for rCDI: Dr. Feuerstadt
7:05-7:15 AM	Case discussion
7:15-7:20 AM	Post-test
7:20-7:30 AM	Q&A
7:30 AM	Adjourn



Demographic Question

How many patients with CDI do you see per month?

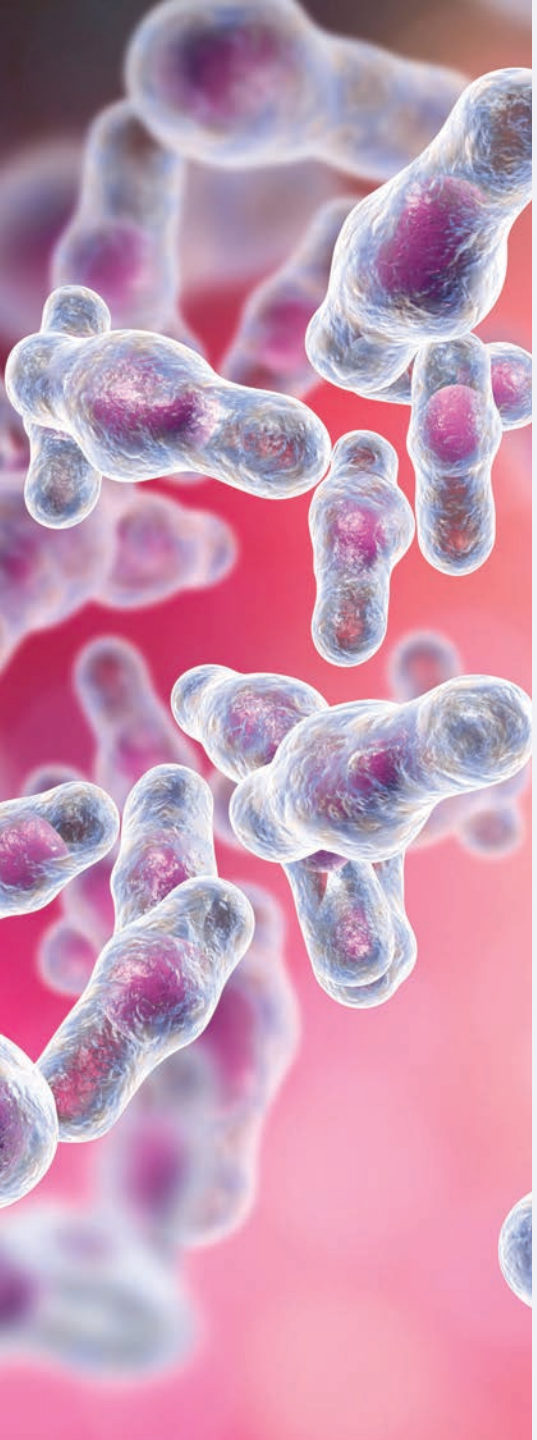
A. 1-2

B. 3-4

C. 5-6

D. >7

CDI, *Clostridioides difficile* infection.

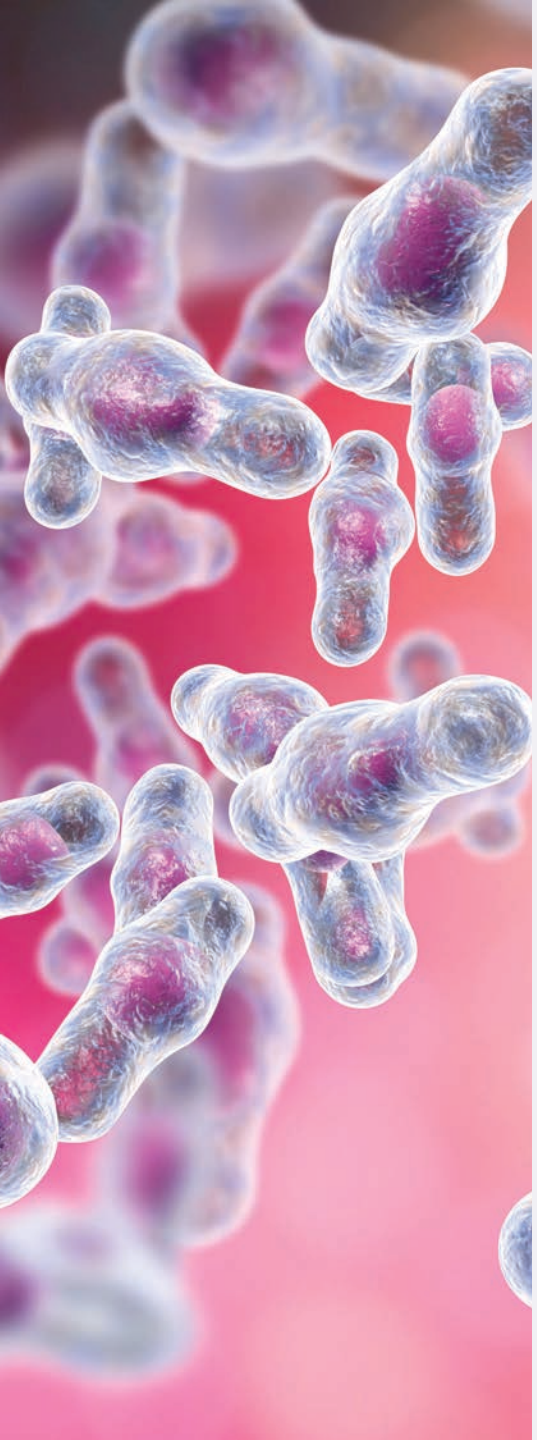


Pre-Test Question 1 (of 4)

Which of the following most affects the microbiota, leaving patients at the greatest risk for CDI and rCDI?

A. Advanced age
B. Recent CDI
C. Antibiotic exposure
D. Gastric acid suppression
E. Contact with an infected person

rCDI, recurrent *Clostridioides difficile* infection.



Pre-Test Question 2 (of 4)

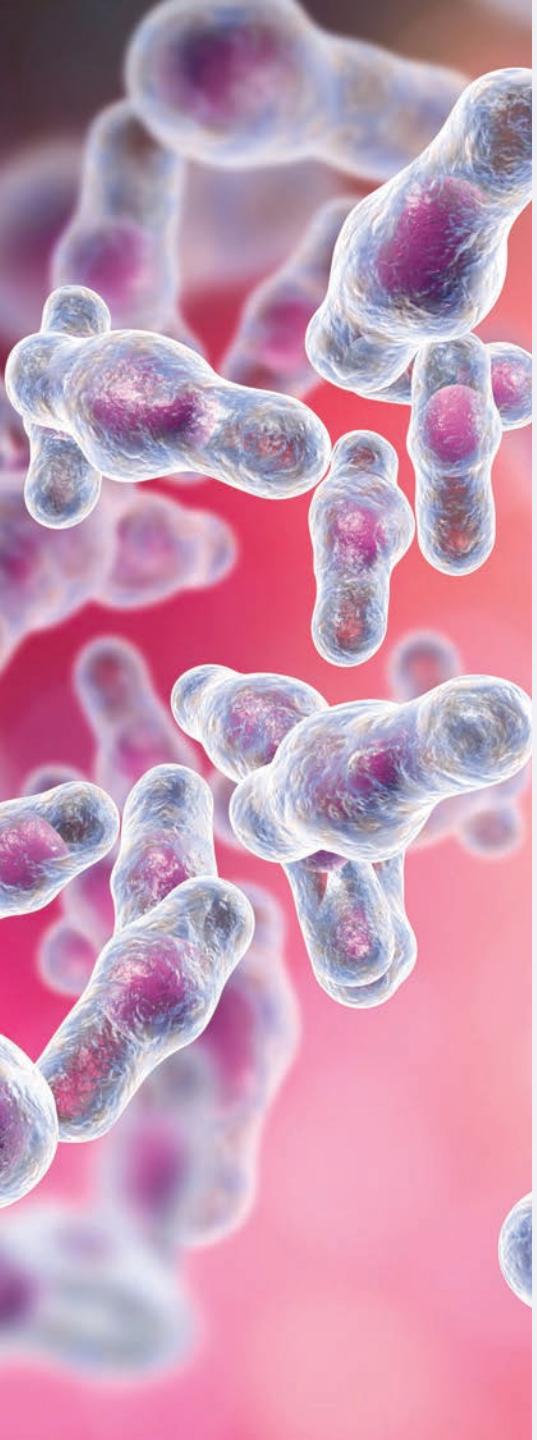
Which of the following are the most important bacterial phyla to prevent CDI?

A. Bacteroidetes and Verrucomicrobia

B. Actinobacteria and Verrucomicrobia

C. Firmicutes and Bacteroidetes

D. Firmicutes and Proteobacteria



Pre-Test Question 3 (of 4)

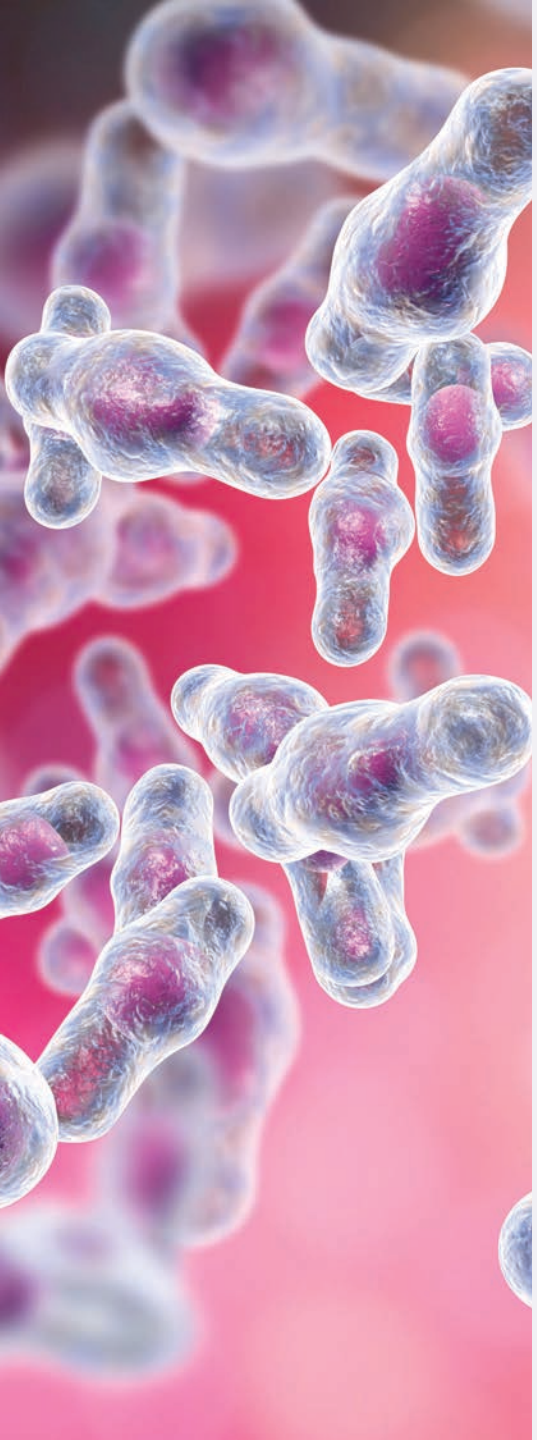
After 2 recurrences (3 episodes) of CDI despite standard antimicrobial treatment, your patient is a candidate for a live biotherapeutic product. She asks why she has to wait to receive the new product. What should you tell her about why the washout period is important?

A. It allows the microbiota time to stabilize before supplementation

B. It purges the microbiota of excess Bacteroidetes

C. It purges the microbiota of residual antimicrobial

D. It allows the microbiota time to restore before supplementation



Pre-Test Question 4 (of 4)

The FDA approved the first LBP in November 2022. Which of the following statements is most accurate regarding FMT vs LBP?

A. FMT has better structured studies than LBP

B. LBPs have a defined consortium of microorganisms, whereas FMT is non-defined consortia

C. Safety assessments are less stringent for LBPs than for FMT

D. Donor screening is more comprehensive for FMT than LBP

LBP, live biotherapeutic product; **FMT,** fecal microbiota transplantation.

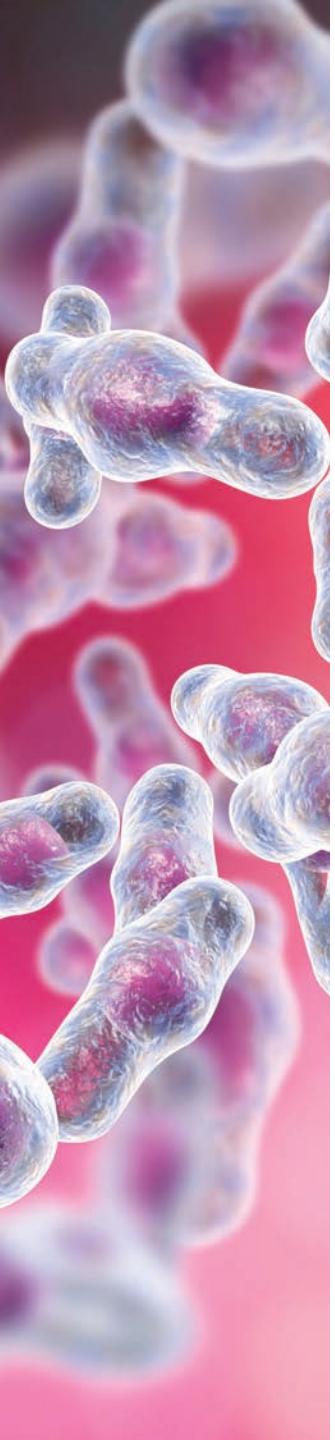
Role of the Microbiome In rCDI

Robert Orenstein, DO

Chair, Infectious Diseases

Mayo Clinic

Phoenix, AZ



Clostridioides difficile: Updated Epidemiology

- In 2017, ~223,900 cases in hospitalized patients and 12,800 deaths
- In 2020, crude overall incidence 101.3 cases per 100,000 persons
  - Slightly higher incidence of community-associated vs health care-associated cases
    - 51.2 vs 50.1 cases per 100,000 persons, respectively
  - Increases with age
  - Higher in women than men
  - Higher in whites than other races
  - Underlying conditions common
    - Charlson Comorbidity Index ≥2 in 40% of cases
  - 61% of cases had antibiotic use in the previous 12 wk
  - 84% of cases were treated
    - Most commonly with vancomycin

Centers for Disease Control and Prevention. www.cdc.gov/hai/eip/Annual-CDI-Report-2020.html

Substantial Clinical, Social, and Economic Burdens of CDI

Clinical

- Mortality
- Sepsis
- Colectomy
- Toxic megacolon
- Severe diarrhea
- Intestinal perforation
- Recurrent infections
- ICU stay
- Renal failure

Social

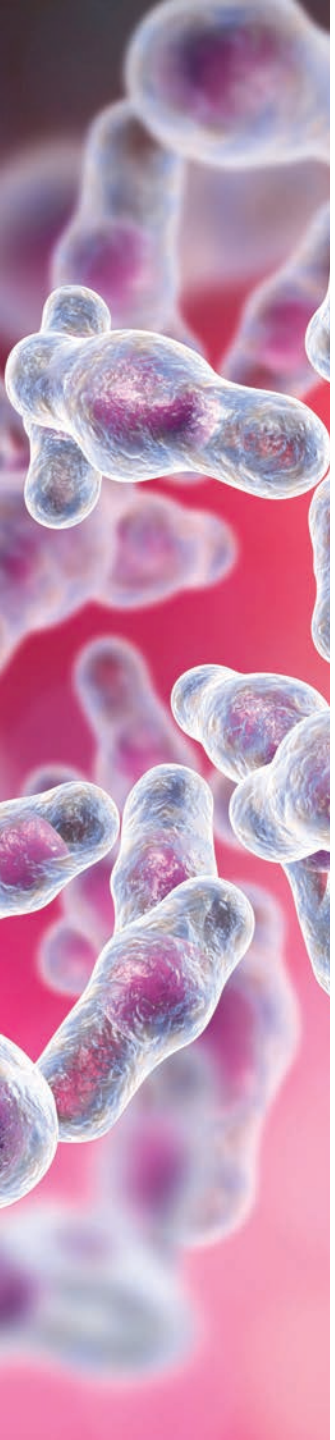
- Depression
- Anxiety
- PTSD
- Social isolation
- Absenteeism
- Lost productivity
- Fear of repeat infections
- Fear of infecting others

Economic

- Hospital readmission
- Inpatient costs
- ED visits
- Length of stay
- Pharmacy costs
- Out-of-pocket costs
- Reimbursement costs
- Reimbursement penalties

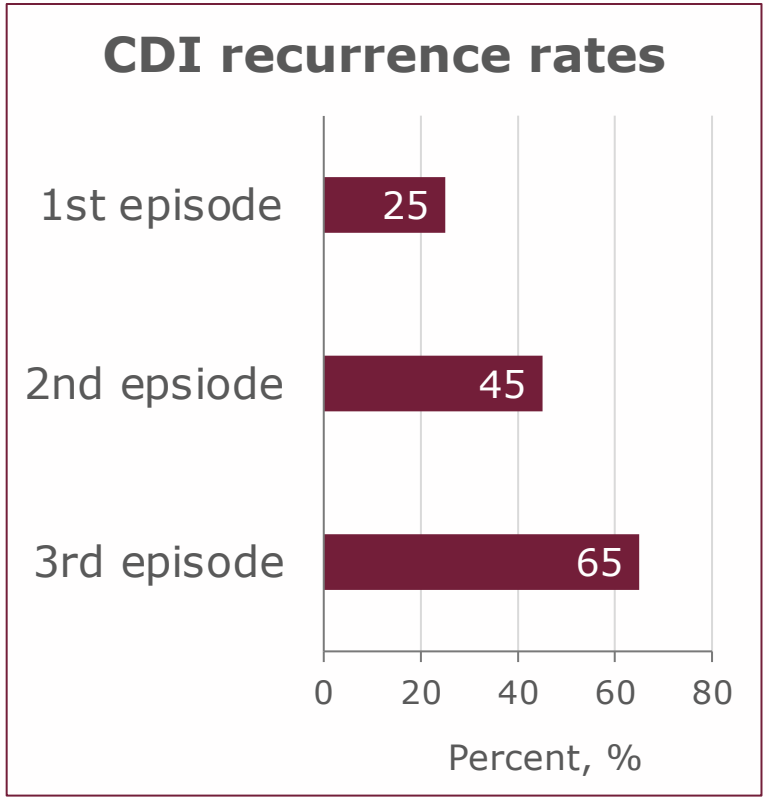
ED, emergency department; **ICU,** intensive care unit; **PTSD,** post-traumatic stress disorder.

Feuerstadt P, et al. *BMC Infect Dis*. 2023;23(1):132.



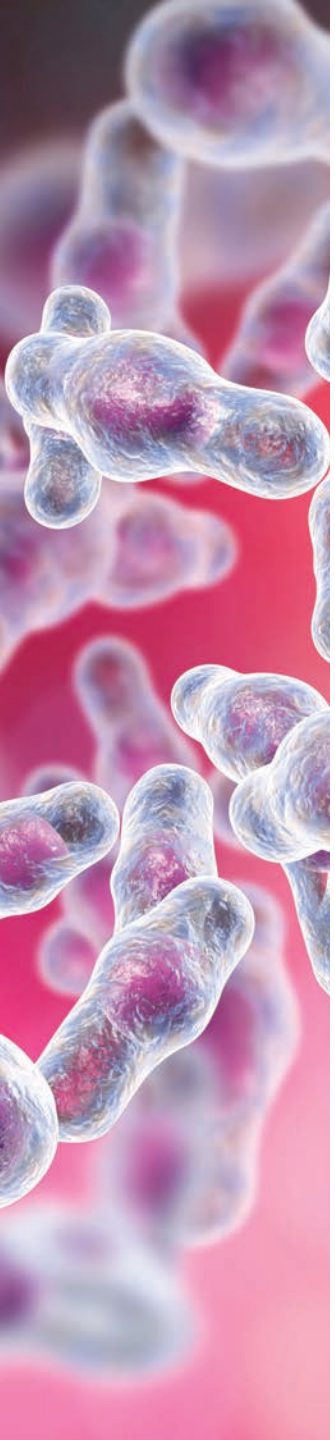
Risk Factors for *C. difficile* Infection

Advanced age (>65 y) • Younger people also have CDI	**1.6-fold increase**
Antibiotic exposure • Key modifiable risk factor for infection	**7- to 10-fold increase**
Comorbidities, immunosuppression • IBD, malignancy, kidney disease, eg	**33% increase**
Hospitalization, residence in skilled nursing facility • Prolonged hospital LOS	
Gastric acid suppression (PPI use)	
Contact with active carriers or those actively infected	
Recent CDI	**>1 recurrence: ≤65% risk**



CDI, *Clostridioides difficile* infection; **IBD,** irritable bowel disease; **LOS,** length of stay; **PPI,** proton pump inhibitor.

Khanna S, Pardi DS. *Mayo Clin Proc*. 2012;87:1106-1117; Khanna S. *J Int Med*. 2021;290:294-309.



Do These Risk Factors Simply Reflect Gut Microbial Diversity? **The 3 Ds of the Human Gut Microbiome**

- The normal human gut microbiome is:

Diverse

- >100 trillion microbes, >2000 species, 12 phyla
- Resilience and redundancy of function
- Responsible for maintaining homeostasis, immune function, epithelial barrier, metabolism, and energy

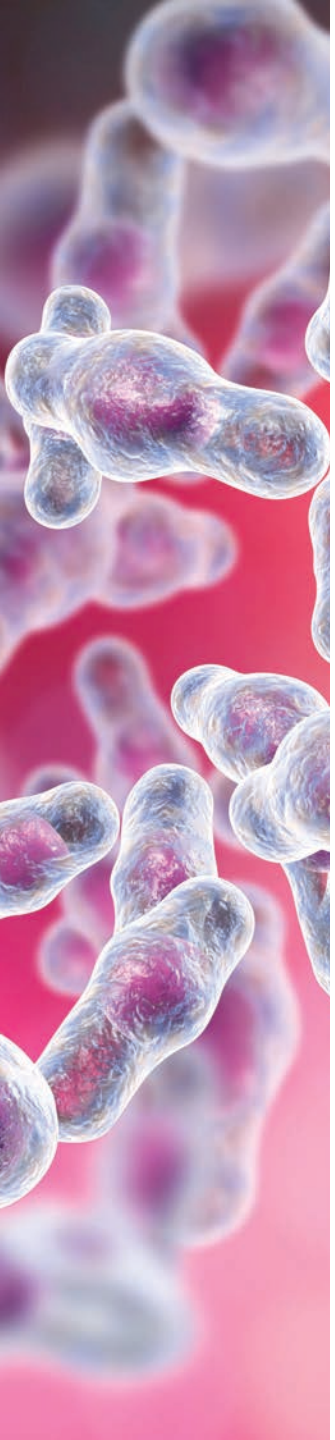
Differentiated

- Composition includes bacteria, fungi, viruses, archaea
- Most of our understanding is focused on the bacterial microbiome
- Major phyla: Bacteroidetes, Firmicutes, Proteobacteria, Actinobacteria, Fusobacteria, Verrucomicrobia

Dynamic

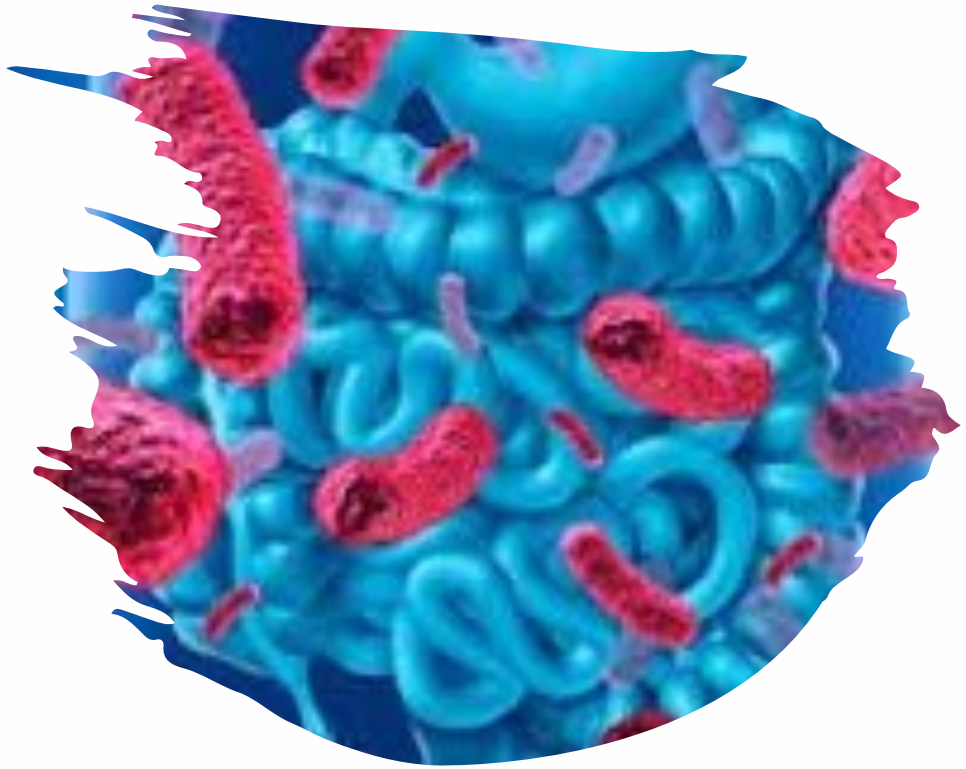
- Shaped by maternal delivery, diet in infancy/adulthood, environment, exposures (ie, antimicrobials)
- Rapid changes between birth and 3 y of age
- Stability and then evolution with loss of diversity with aging

Jandhyala SM, et al. *World J Gastroenterol*. 2015;21:8787-8803.



Roles of Microbiome in Human Health

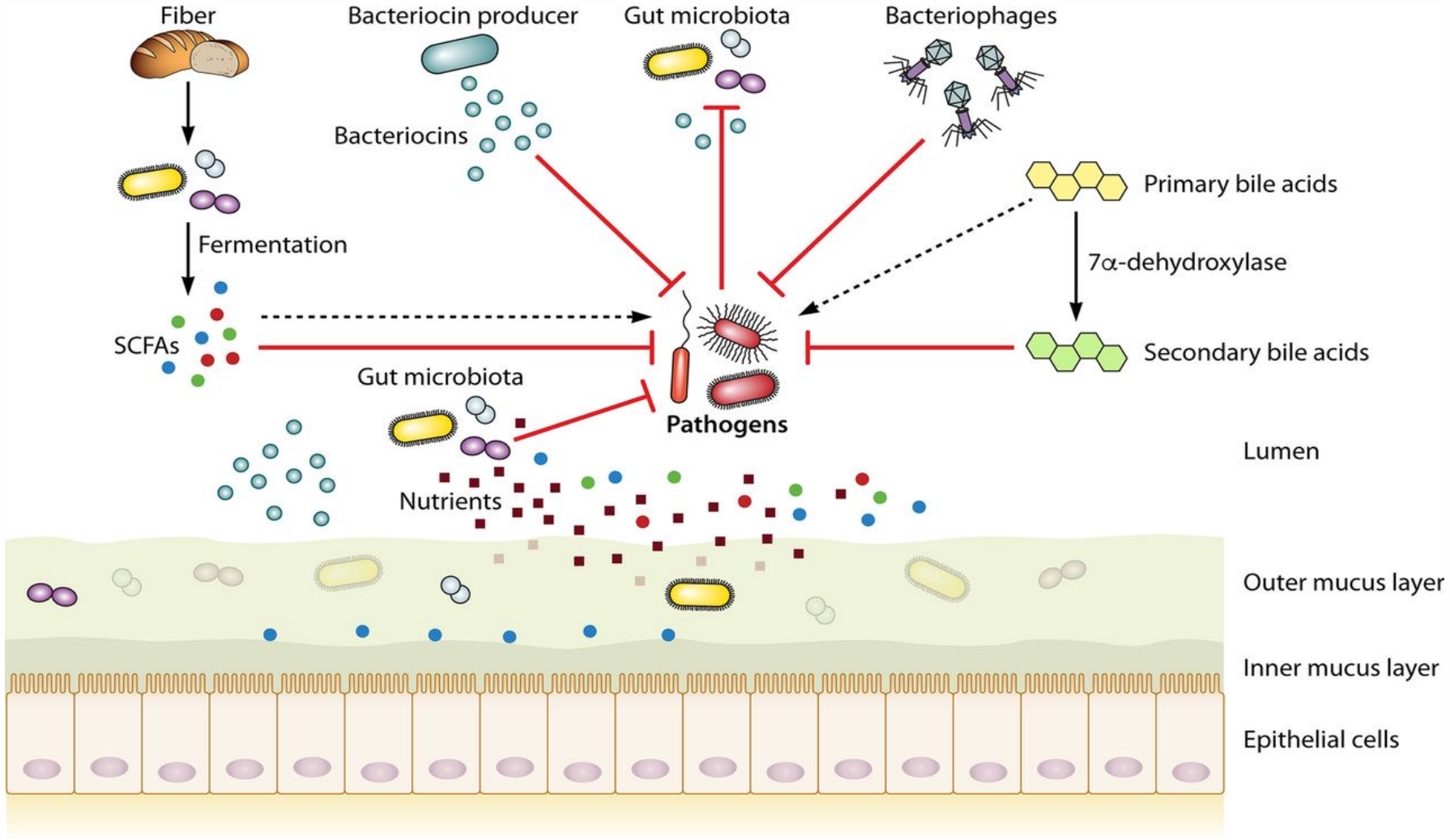
- Digestive function and metabolism
  - Dietary CHOs – synthesis of SCFA (ie, butyrate) – energy for colonocytes
  - Toxins, drug metabolism
- Immune function
  - Innate immune function, Tregs
- Epithelial barrier and colonization resistance
  - Balance/Diversity protects against colonization by exogenous pathogens



CHO, carbohydrate; **SCFA,** short-chain fatty acid; **Treg,** T-regulatory cell.

Bidell MR, et al. *Pharmacotherapy*. 2022;42(11):849-857.

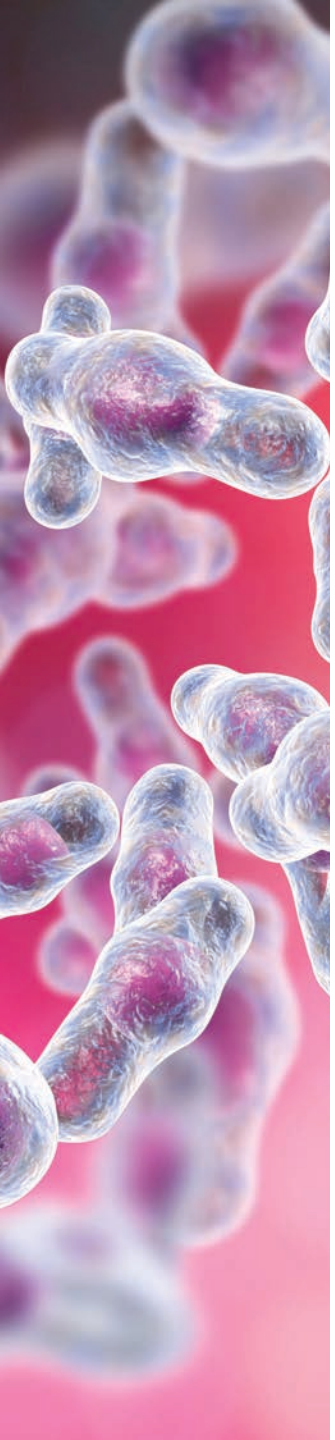
Healthy Gut Microbiota Provide Colonization Resistance

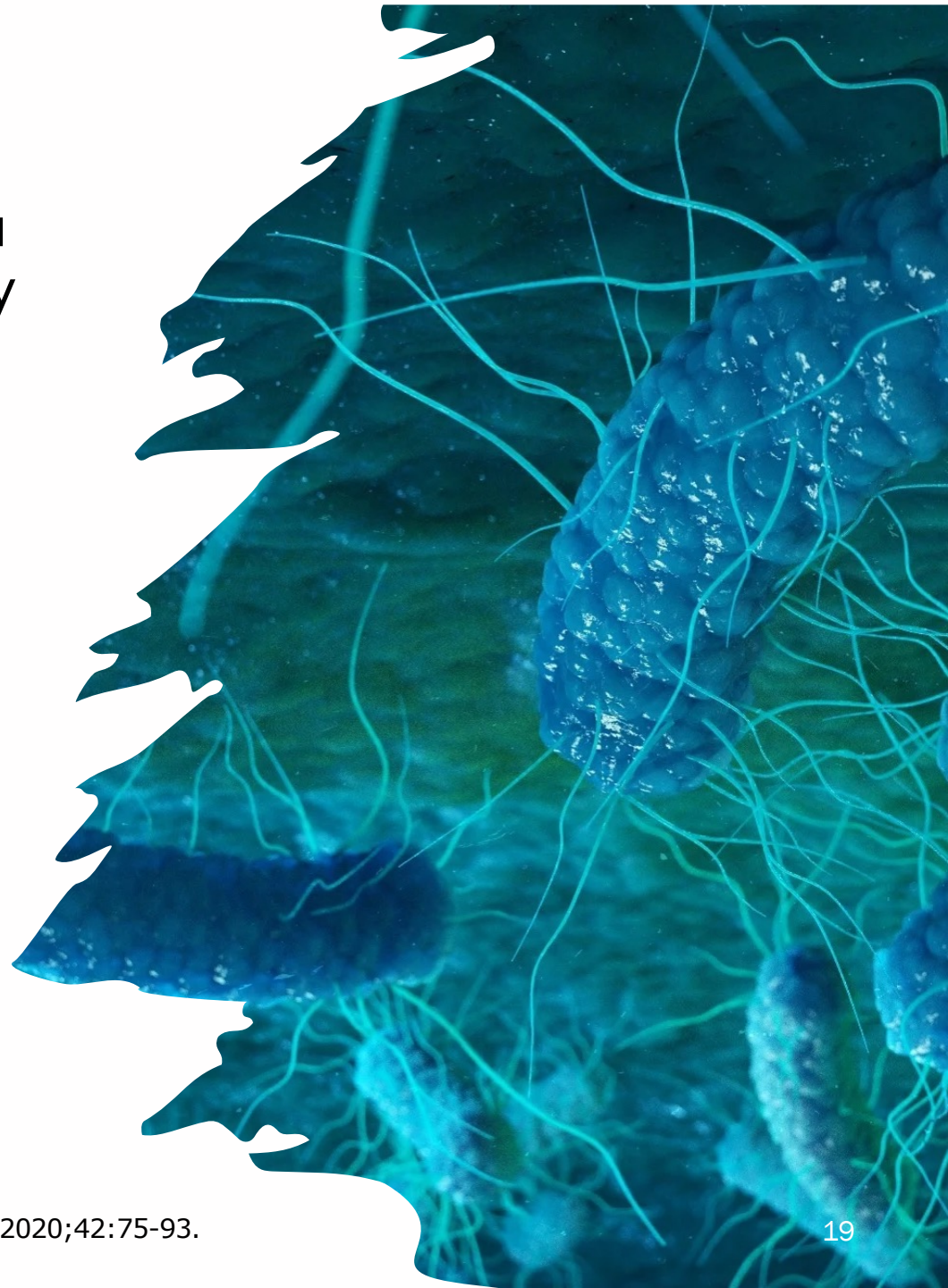


Ducarmon QR, et al. *Microbiol Mole Biol Rev*. 2019;83(3):e00007-e00019.

Dysbiosis

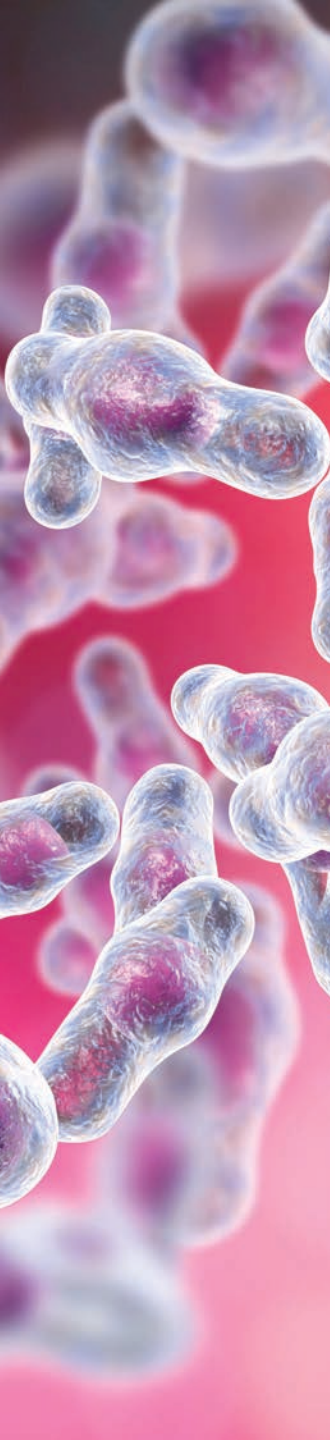
- Disturbance of the microbial milieu in a negative way reduces diversity
- Often leads to reduction in Bacteroidetes and Firmicutes and proliferation of Proteobacteria
- Triggers include antibiotics, stress, diet, medications (eg, PPIs), hygienic factors
- Alters BA metabolism
- Associated with diseases such as cancer, IBD, IBS, obesity, T2DM, RA, and autism





BA, bile acid; **IBS,** irritable bowel syndrome; **RA,** rheumatoid arthritis; **T2DM,** type 2 diabetes mellitus.

Buford TW. *Microbiome*. 2017;5(1):80; Hufnagl K, et al. *Semin Immupathol*. 2020;42:75-93.

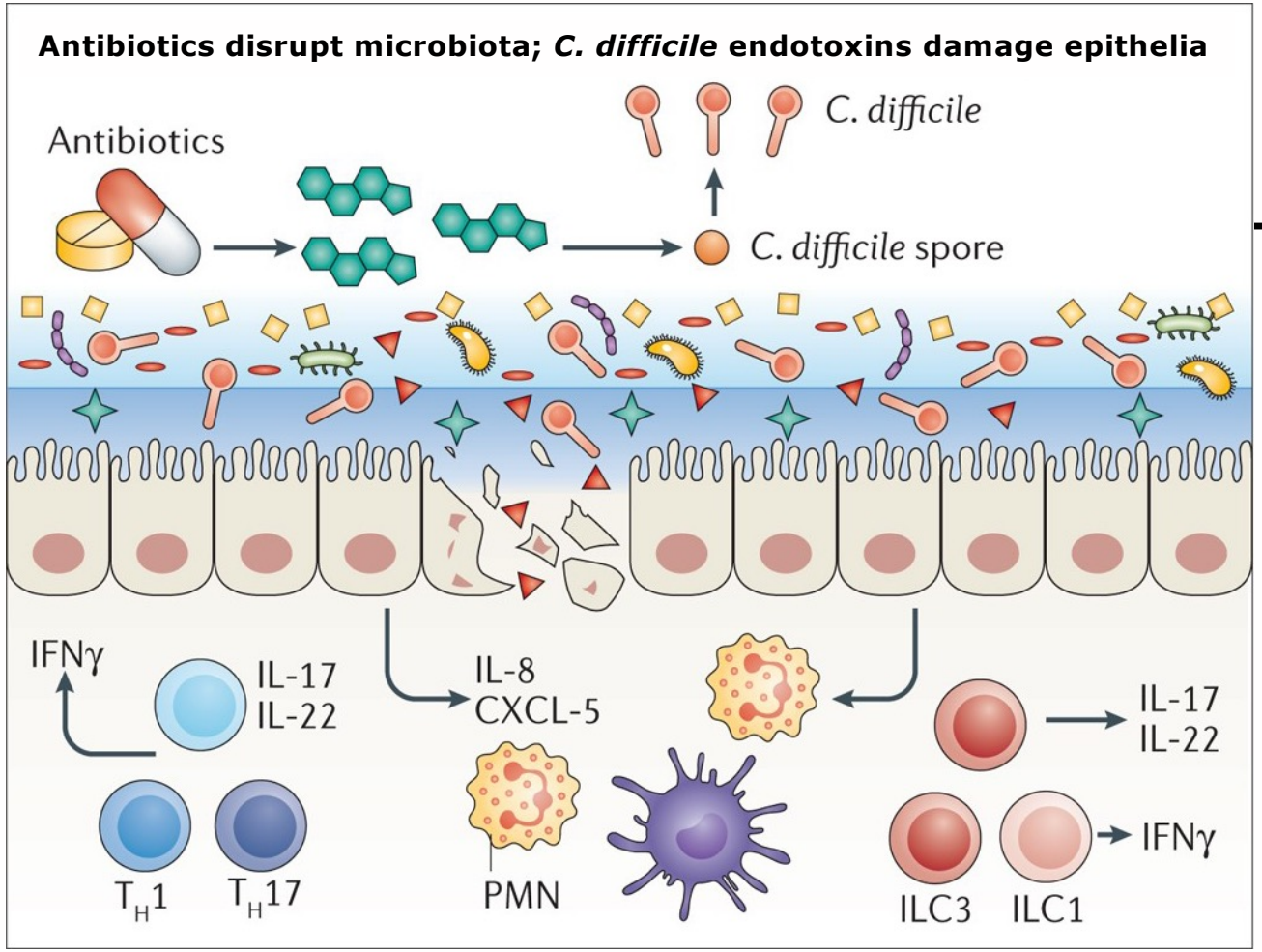


Consequences of Dysbiosis

- Loss of key metabolic actions that enhance gut immunity and protect epithelial integrity
- Primary BAs induce sporulation of *C. difficile*; loss of microbiota prevents conversion of primary BAs to secondary BAs to inhibit sporulation
- Loss of other *Clostridia* spp reduces ability to synthesize secondary BAs (deoxy and lithocholic acid) that inhibit *C. difficile*
- Alteration of the microbial balance in favor of *C. difficile* and elimination of protective barriers

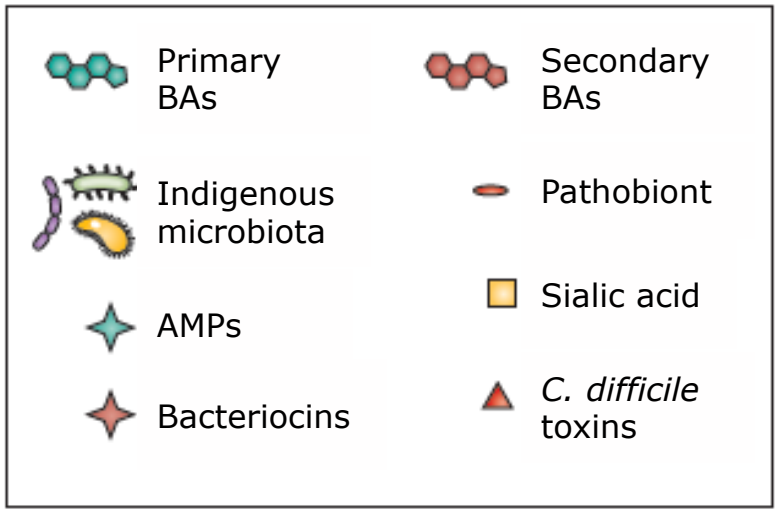
Bidell MR, et al. *Pharmacotherapy*. 2022;42(11):849-857.

Uninhibited Growth of *C. difficile* and Toxins Damages Epithelia



Loss of microbiota

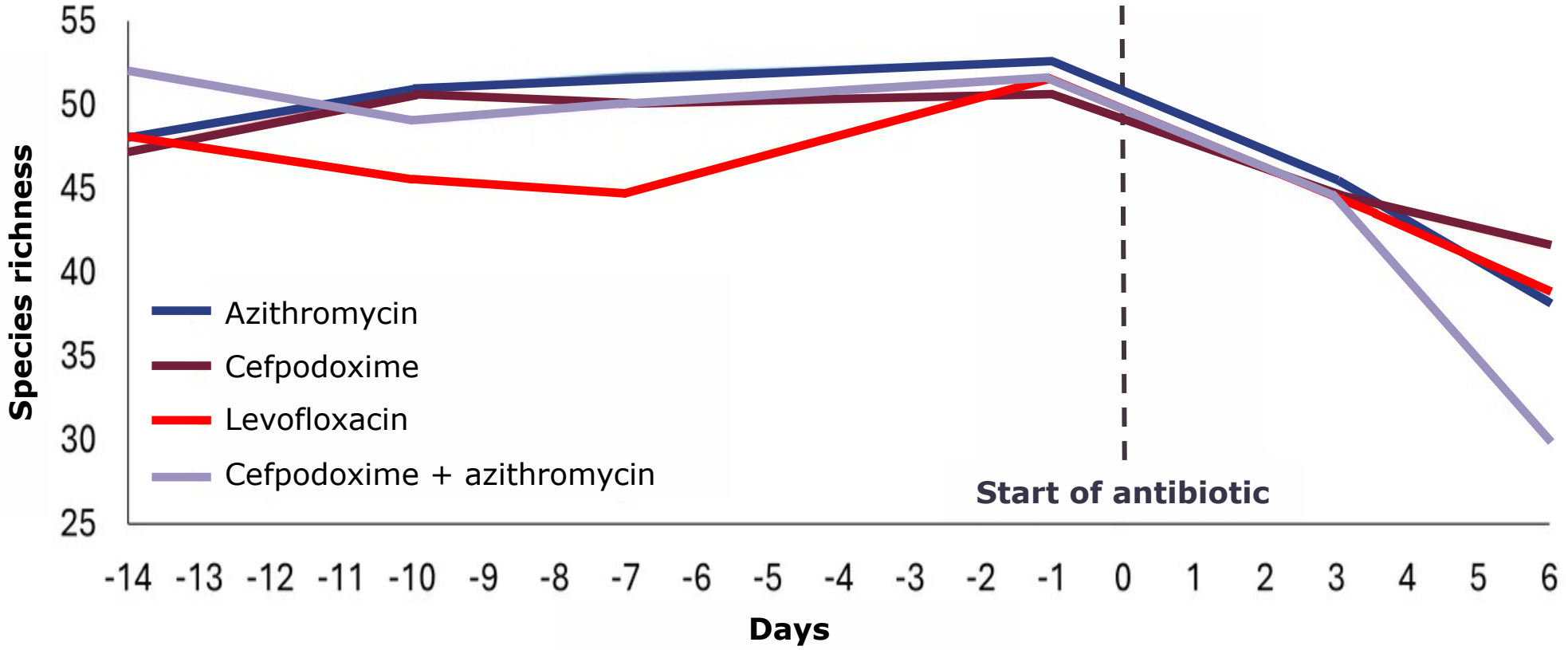
- Decreased mucus
- Loss of AMPs and bacteriocins
- Loss of tight junctions
- IL-8, *CXCL5*, made by epithelial cells
- ↑ *C. difficile*
- ↑ Sialic acid
- No secondary BAs



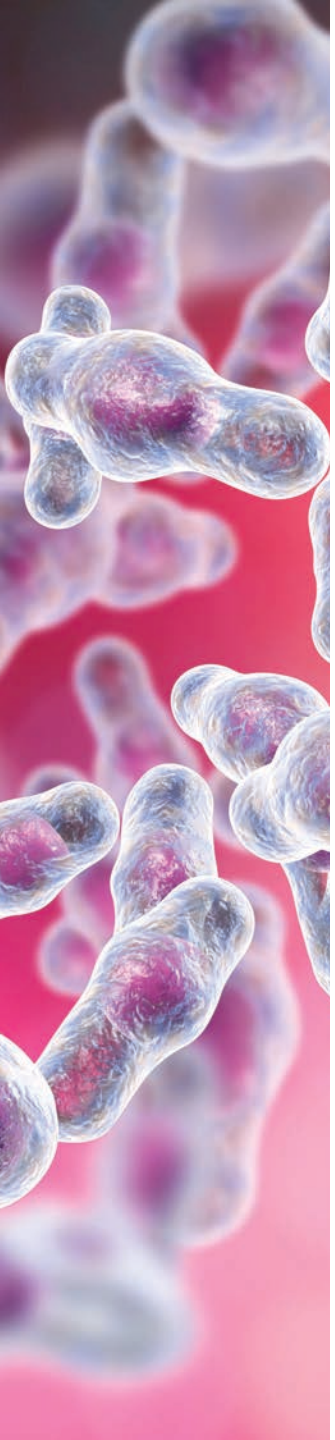
AMP, antimicrobial peptide; **IFN,** interferon; **IL,** interleukin; **ILC,** innate lymphoid cell; **PMN,** polymorphonuclear leukocyte.

Khoruts A, et al. *Nat Rev Gastroenterol Hepatol*. 2016;13(9):508-516.

How Antimicrobials Affect the Gut Microbiome



Anthony WE. *Cell Rep*. 2022;39(2):110649; Patangia DV, et al. *Microbiologyopen*. 2022;11(1):e1260.



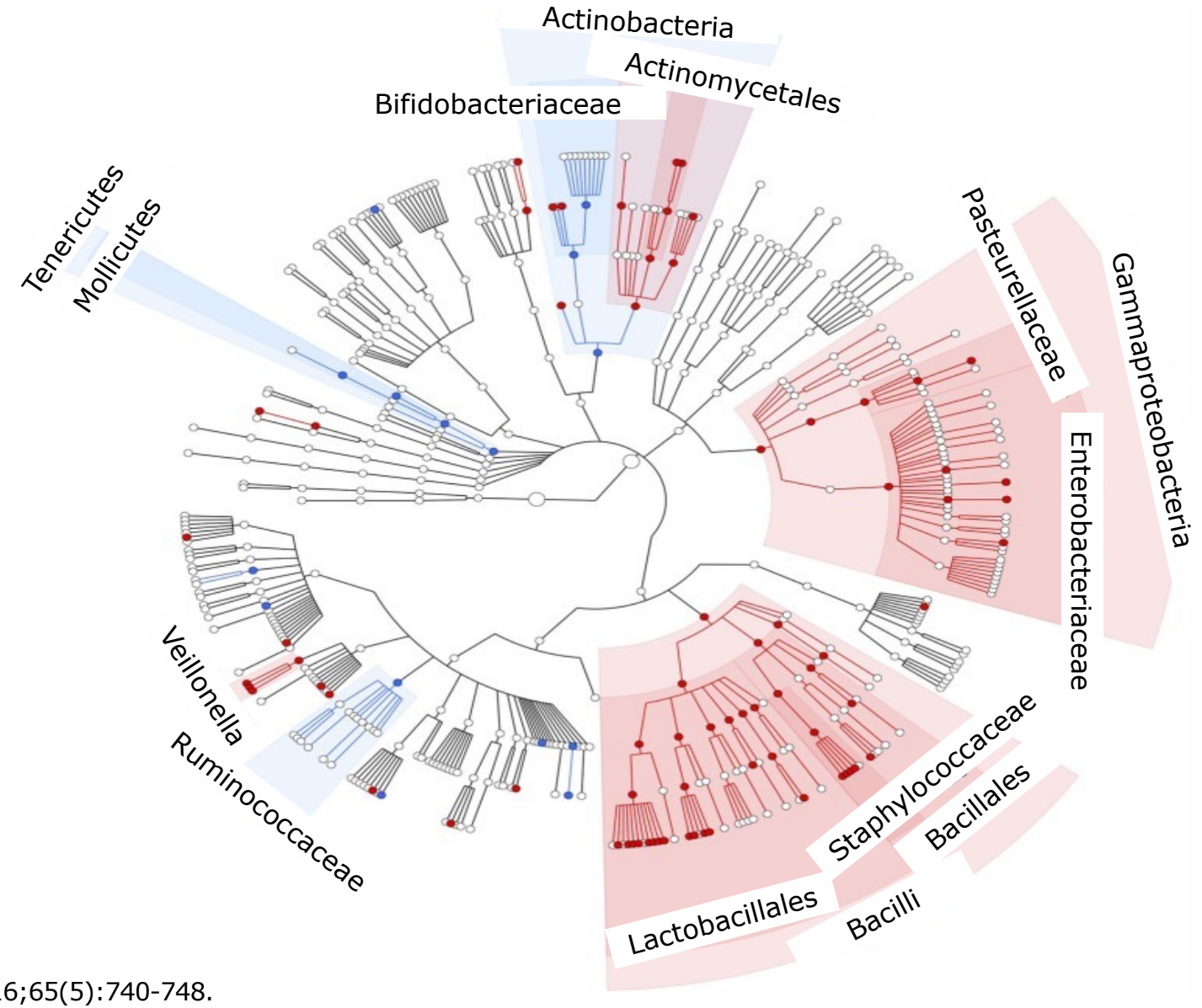
How PPIs Affect the Gut Microbiome

- PPIs reduce gastric acid secretion, leading to profound changes in the colonic microbiota
- Inhibitory effect on commensals, such as *Ruminococcus* and *Dorea* spp, indirect stimulation of oral microbes due to increased pH
- Long-term PPI use affects the survival and induces migration of multiple bacteria along the GI tract, increasing the risk for gut dysbiosis
- Functional biomarkers for PPI-associated gut microbiota are highly enriched in CHO metabolic pathways
  - Glycolysis/Gluconeogenesis, pyruvate metabolism
  - Amino sugar and nucleotide sugar metabolism
  - Fructose and mannose metabolism

GI, gastrointestinal.

Bruno G. *World J Gastroenterol*. 2019;25(22):2706; Imhann F, et al. *Gut*. 2016;65(5):740-748; Seto CT, et al. *Microbiome*. 2014;2:42; Zhang J, et al. *BMC Microbiol*. 2023;23(1):171.

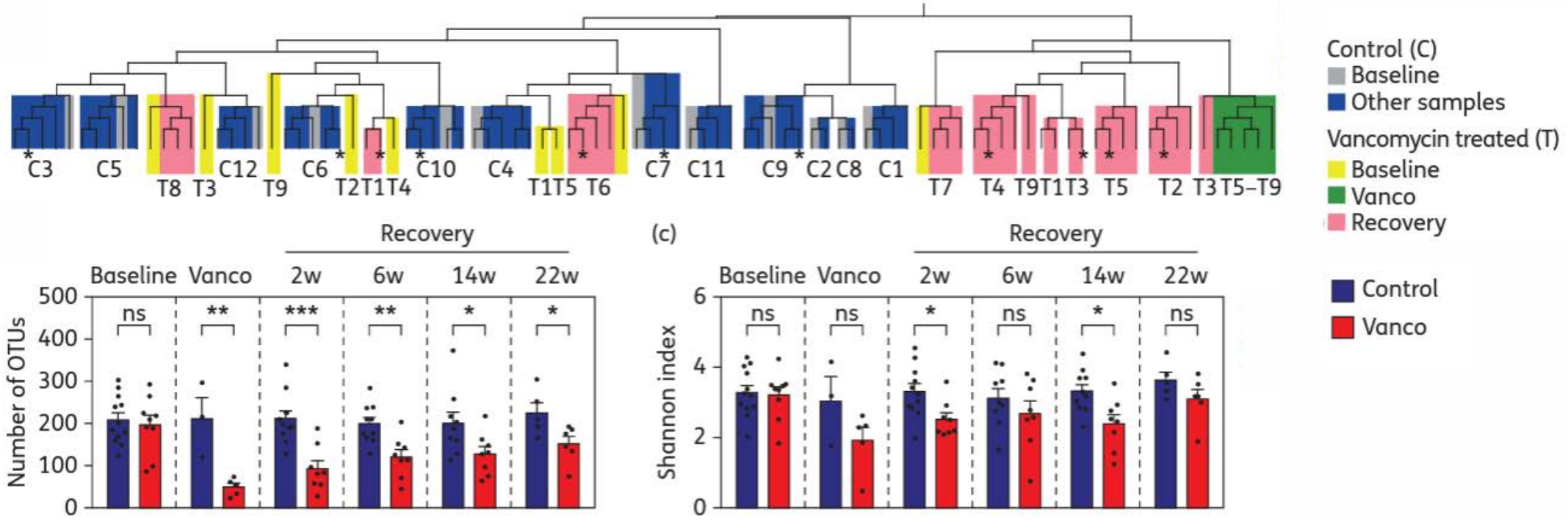
Effects of PPIs on Colonic Microbiota



Imhann F, et al. *Gut*. 2016;65(5):740-748.

PO Vancomycin Treatment of *C. difficile* and the Microbiome

- Induces drastic, consistent changes in human intestinal microbiota
- Upon vancomycin cessation, the microbiota recovery rate varies



*P<0.05. **P<0.01. ***P<0.001.

OTU, operational taxonomic unit; **ns,** not significant; **PO,** oral.

Isaac S, et al. *J Antimicrob Chemother*. 2017;72(1):128-136.

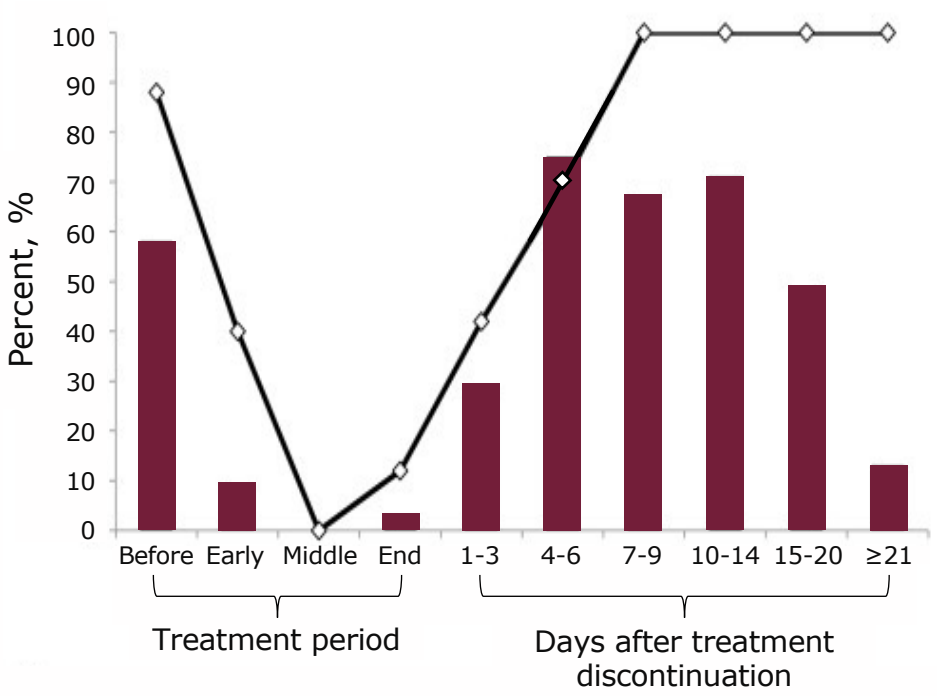
Effect of Bezlotoxumab on the Gut Microbiome

- Mice treated with vancomycin had reduced diversity
- Mice treated with the combination of actoxumab+bezlotoxumab had restored microbiome diversity
- Mice treated with vancomycin and actoxumab+bezlotoxumab also experienced a reduction of bacterial diversity during vancomycin treatment
  - However, they were able to recover initial proportions of *Blautia* and *Lactobacillus*

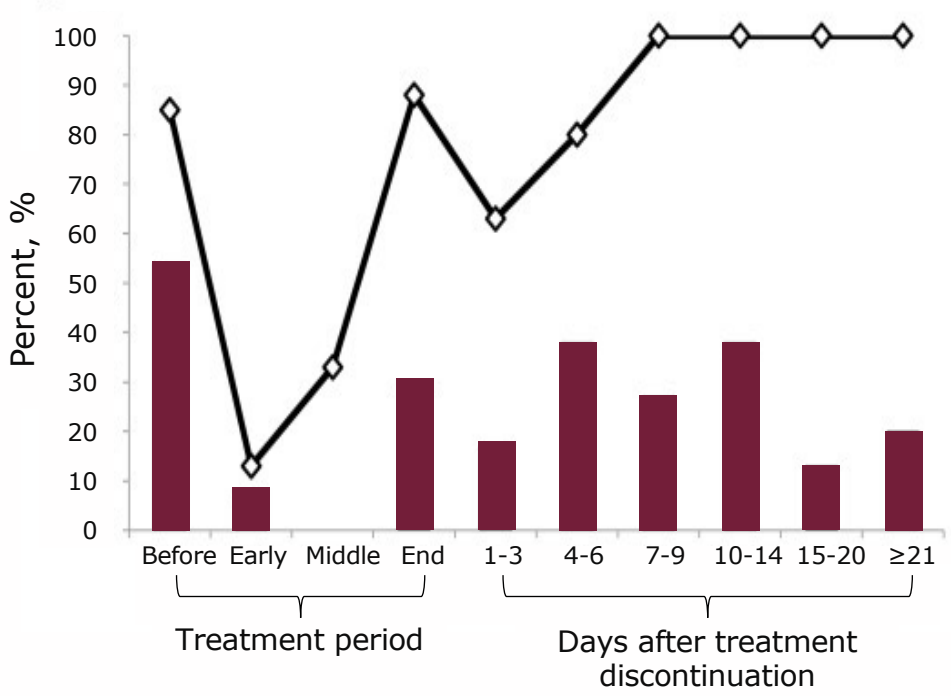
Dzunkova M. et al. *Front Cell Infect Microbiol*. 2016;6:119.

Window of Vulnerability After Treatment of CDI

- Vancomycin 4-5 d, window of 21-28 d



Vancomycin



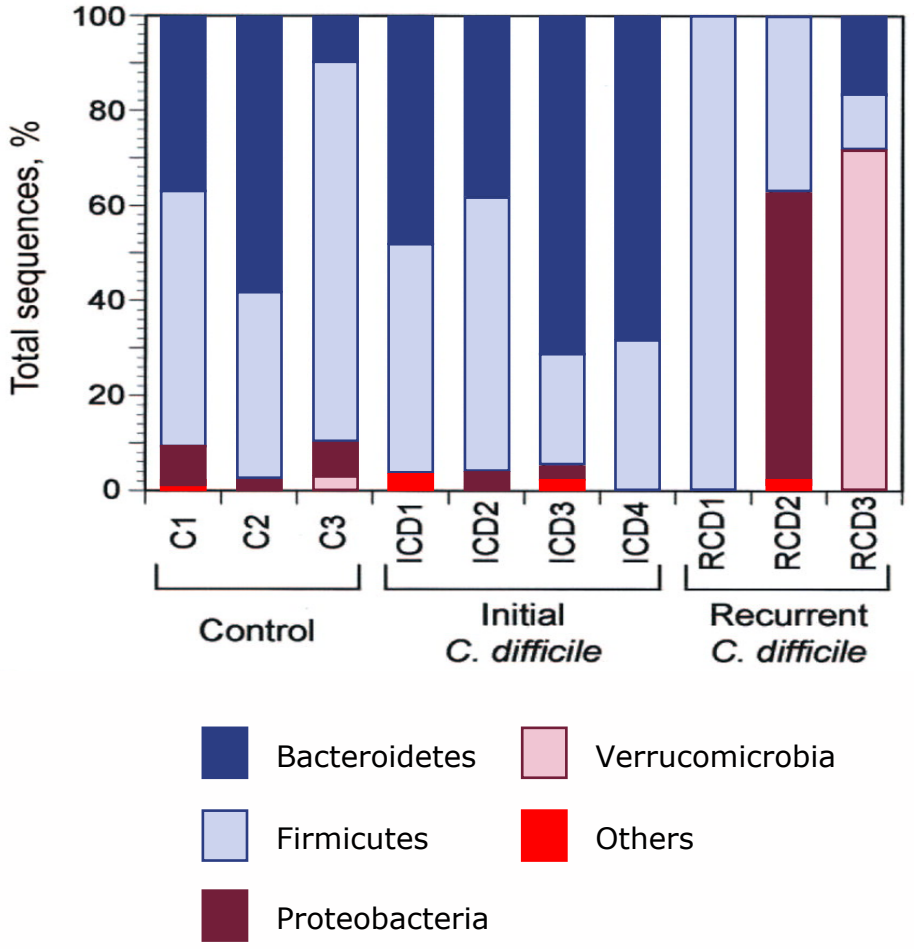
Metronidazole

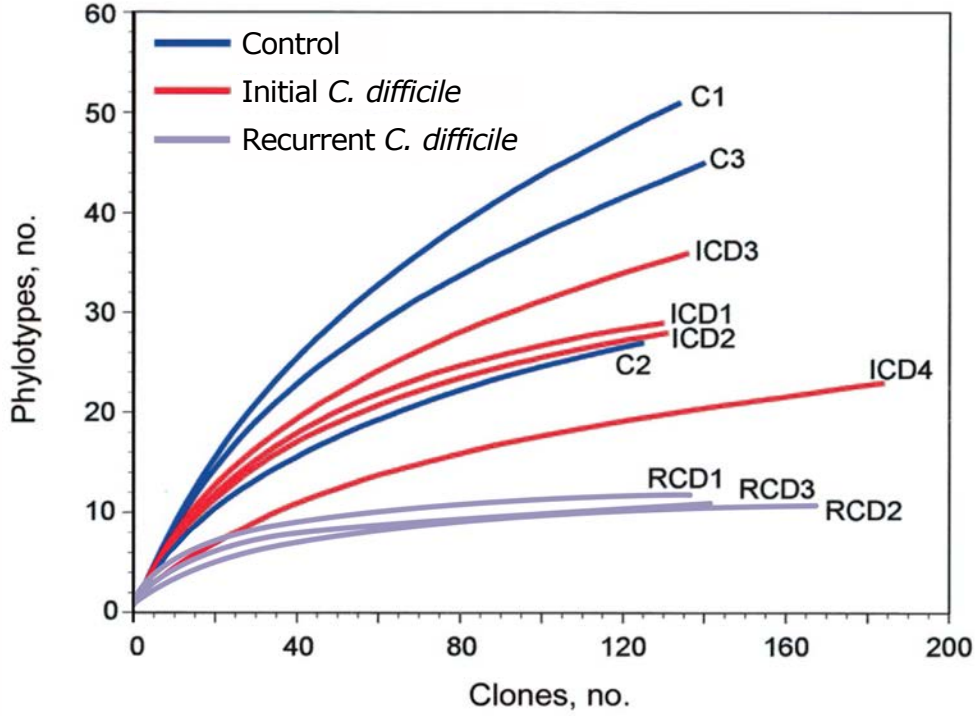
Growth in suspension

Growth in filtrate

Abujamel T, et al. *Plos One*. 2013;8(10)e76269.

Effect of CDI and rCDI in Gut Microbiome Diversity

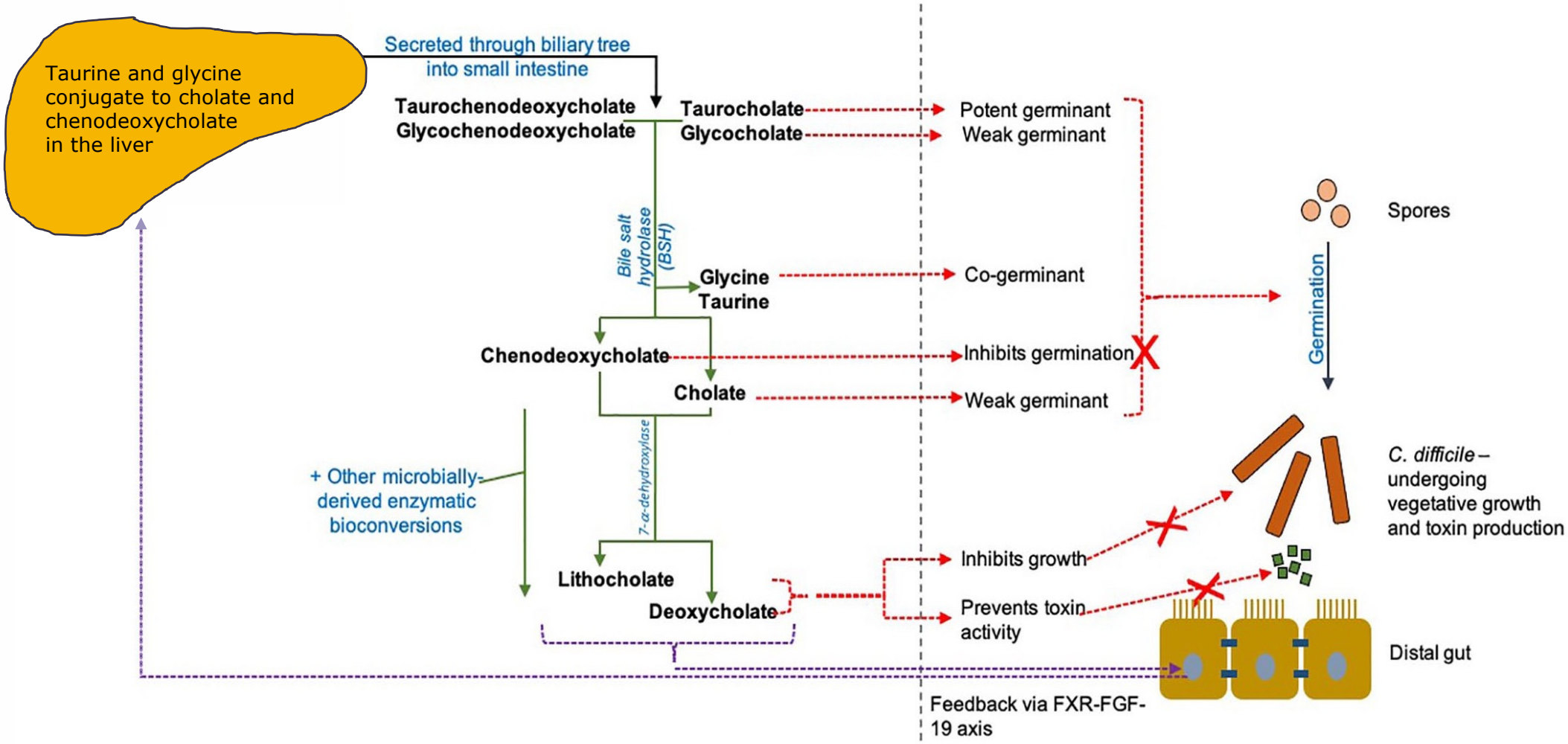




ICD, initial *C. difficile*; **RCD,** recurrent *C. difficile*.

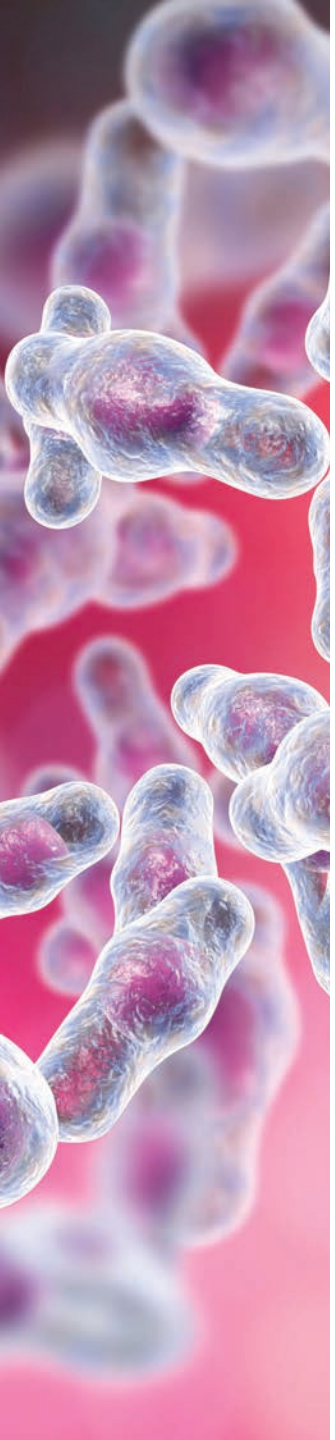
Chang JY. *J Infect Dis*. 2008;197(3):435-438.

C. difficile Vulnerability and BA Concentrations



BSH, bile salt hydrolase; **FGF,** fibroblast growth factor; **FXR,** farnesoid X receptor.

Mullish BH, Allegretti JR. *Therap Adv Gastroenterol*. 2021;14:17562848211017725.



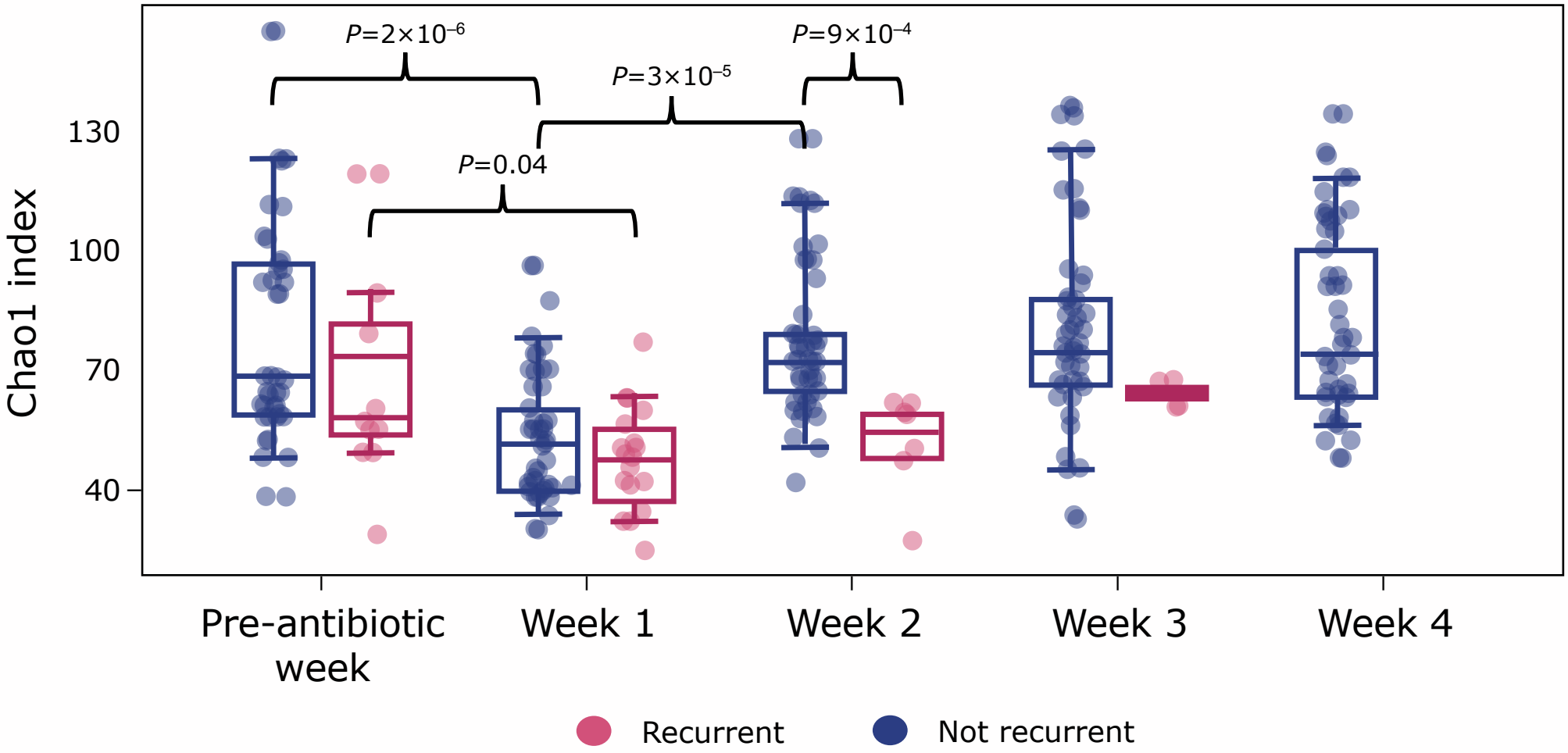
Metabolomics Can Predict Recurrent CDI

- Metabolic changes in rCDI reflect:
  - Host inflammation or intestinal injury
  - Lack of microbial deconjugation activity
  - Host alterations in immune and inflammatory abilities
- Rate of recovery from dysbiosis was slower in those with recurrence and incomplete recovery 2 wk after CDI treatment
- At 1 wk after CDI treatment, a specific metabolic profile predicted recurrence
  - Increased sphingolipids, PhLp, and sphingomyelins

PhLp, phospholipid.

Dawkins JJ, et al. *Microbiome*. 2022;10(1):87.

Ecologic Diversity Recovers More Slowly in rCDI



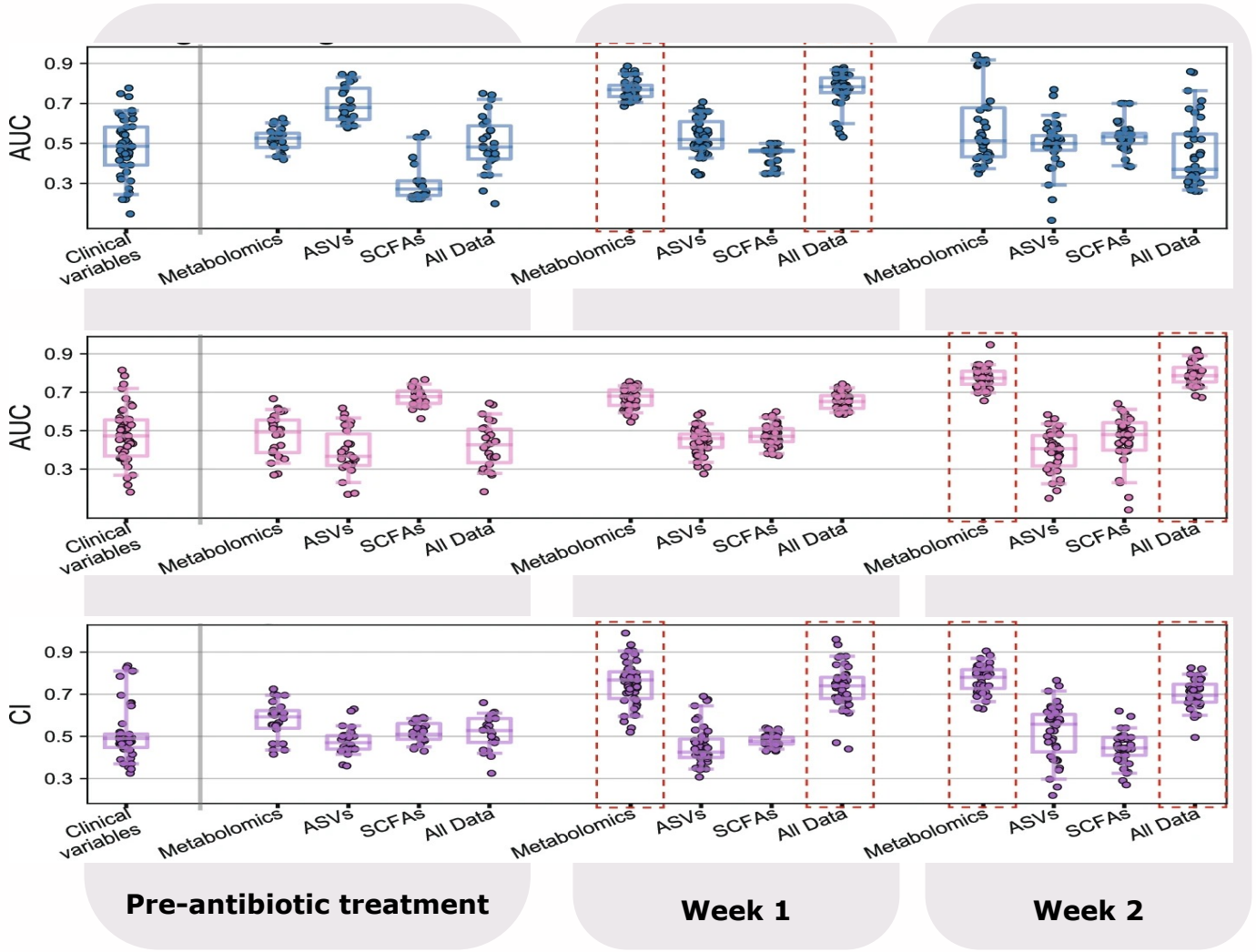
Dawkins JJ, et al. *Microbiome*. 2022;10(1):87.

Metabolomics Is the Best predictor of CDI Recurrence

Logistic regression

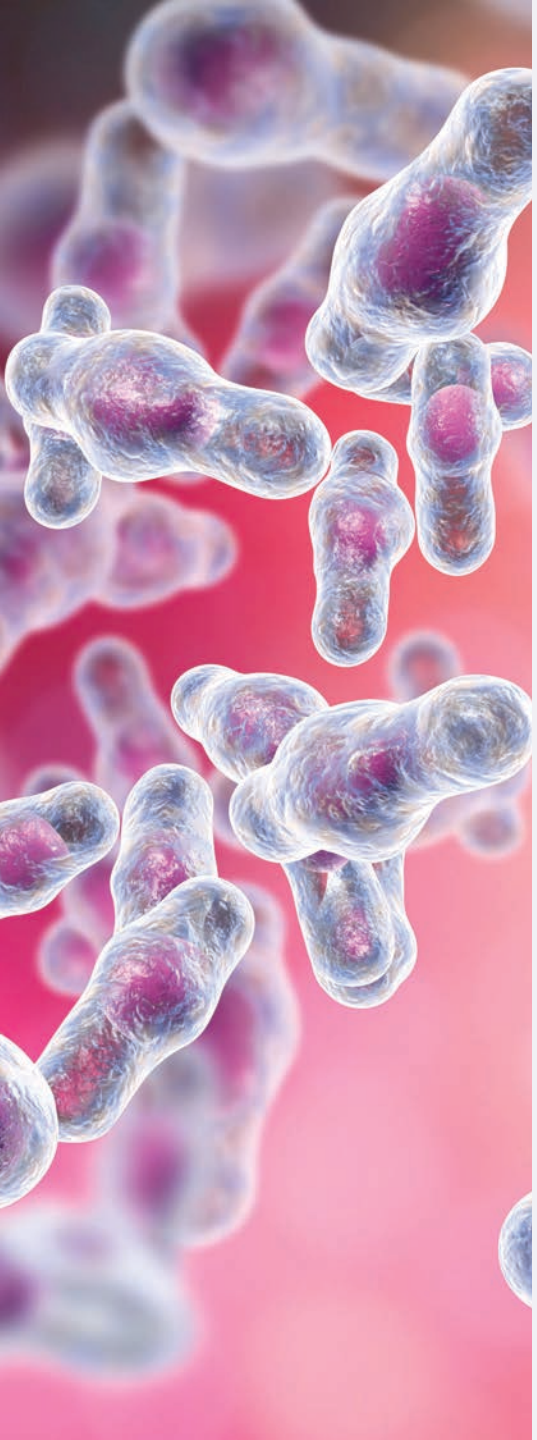
Random forest

Cox regression



ASV, amplicon sequence variant; **AUC,** area under the curve; **CI,** concordance index.

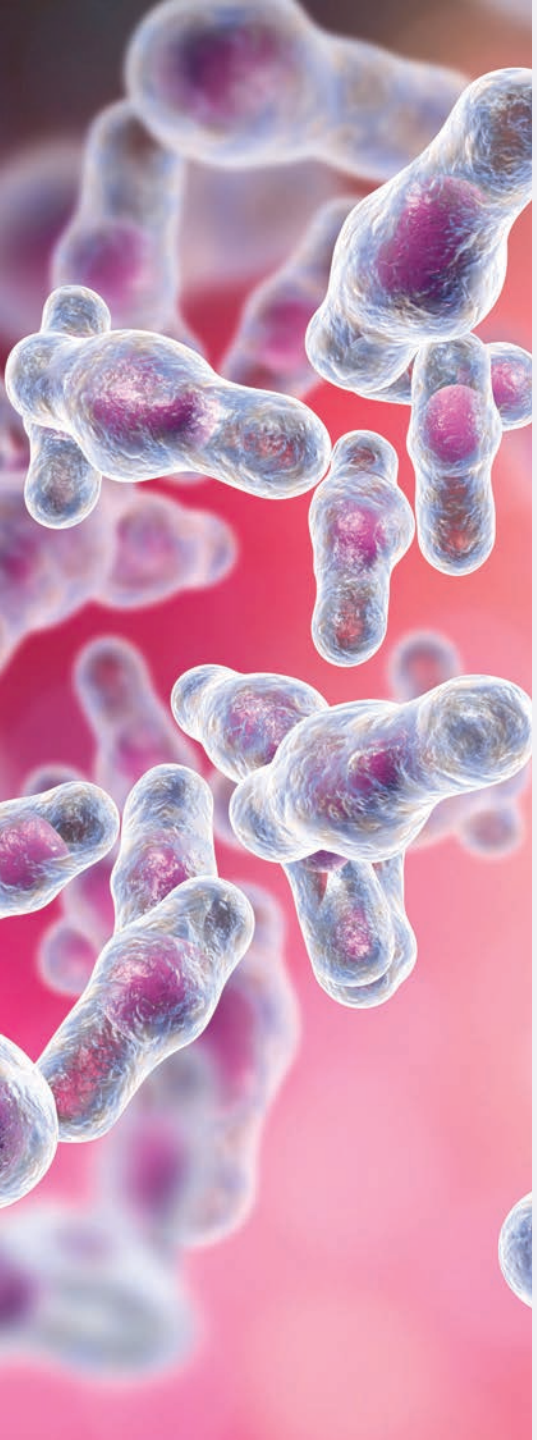
Dawkins JJ, et al. *Microbiome*. 2022;10(1):87.



Case: Introducing Lorraine

- 60-year-old woman
- Presents in May 2023 with sudden onset of 6 to 8 liquid bowel movements per day
- Cramping abdominal pain (3/10)
  - Diffuse
  - Relieved with bowel movement
- Occasional sweats
- No recent travel, sick contacts, or antimicrobial exposure

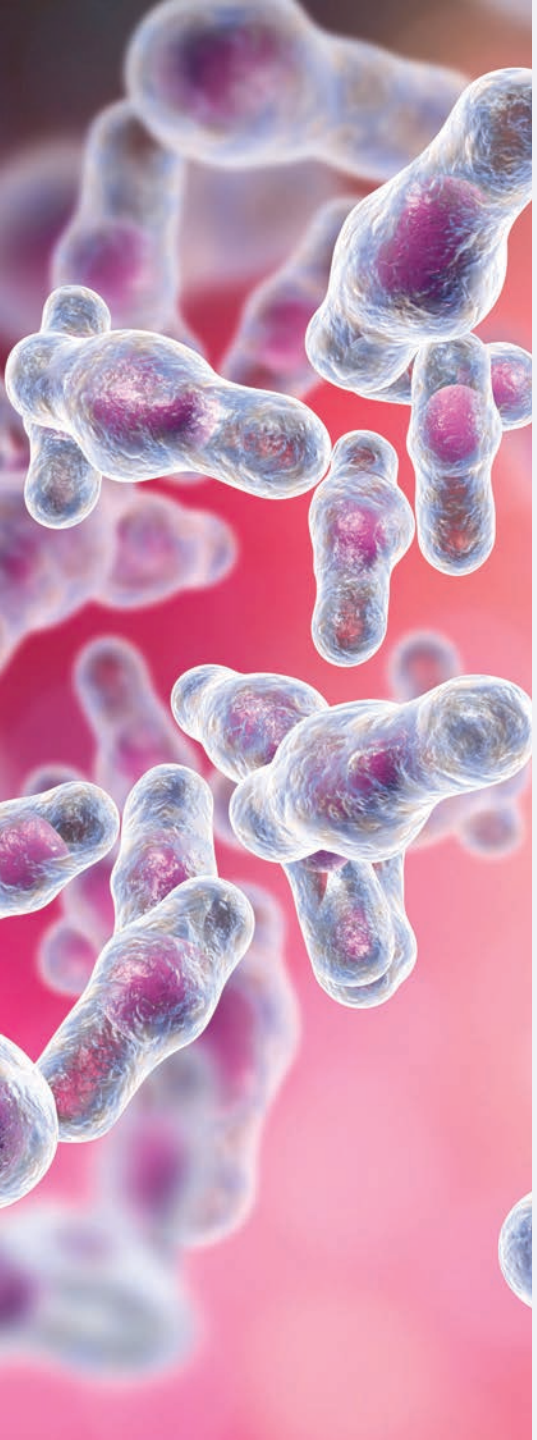
Cr, creatinine; **WBC,** white blood cell.



Case: Introducing Lorraine

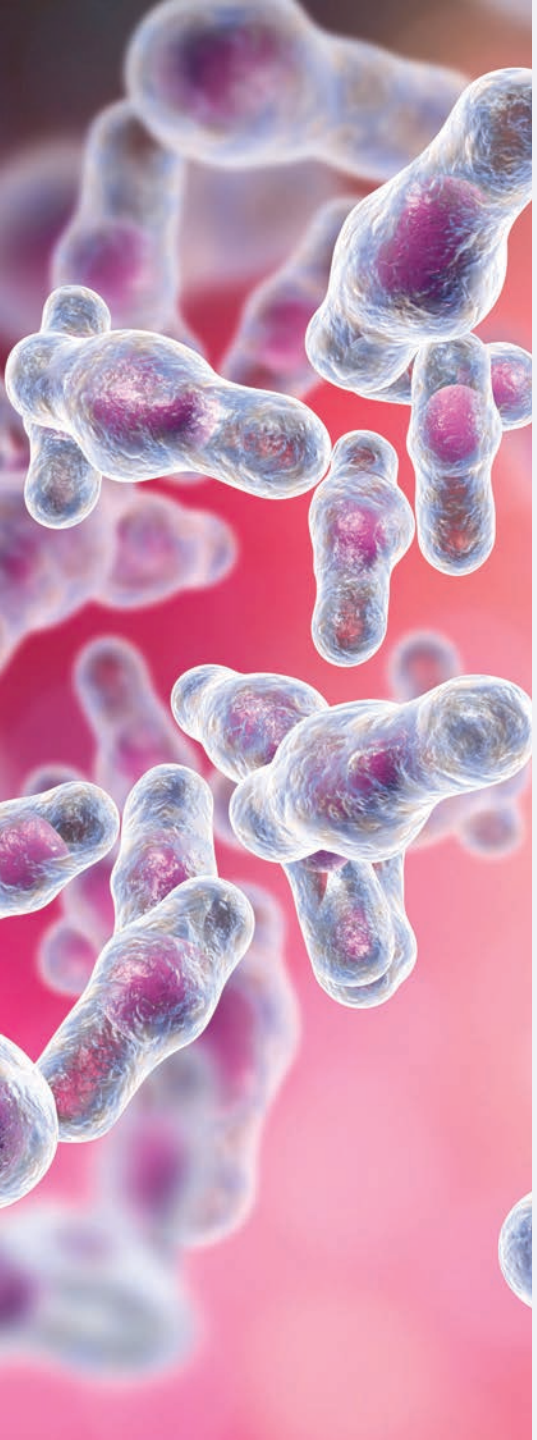
- Medical history
  - Hypertension
  - Diabetes
  - GERD
  - *C. difficile* infection (March 2023)
- Surgical history
  - Appendectomy
- Initial blood work results
  - WBC: 11,000×103/mL
  - Cr: 1.1 mg/dL

GERD, gastroesophageal reflux disease.



Case: Lorraine's Diagnosis

- Which stool assay would be most appropriate to confirm a diagnosis of *C. difficile* infection in Lorraine?
  - A. Glutamate dehydrogenase (GDH)
  - B. Enzyme-linked immunoassay (EIA)
  - C. Polymerase chain reaction (PCR)
  - D. EIA plus GDH adjudicated by PCR



Case: Lorraine's Likely Microbiota Deficiency

- What are the most common deficiencies in the microbiota that might have led to Lorraine's presentation with *C. difficile*?

  A. Deficiency of Proteobacteria and Firmicutes

  B. Deficiency of Firmicutes and Verrucomicrobia

  C. Deficiency of Bacteroidetes and Firmicutes

  D. Deficiency of Proteobacteria and Verrucomicrobia

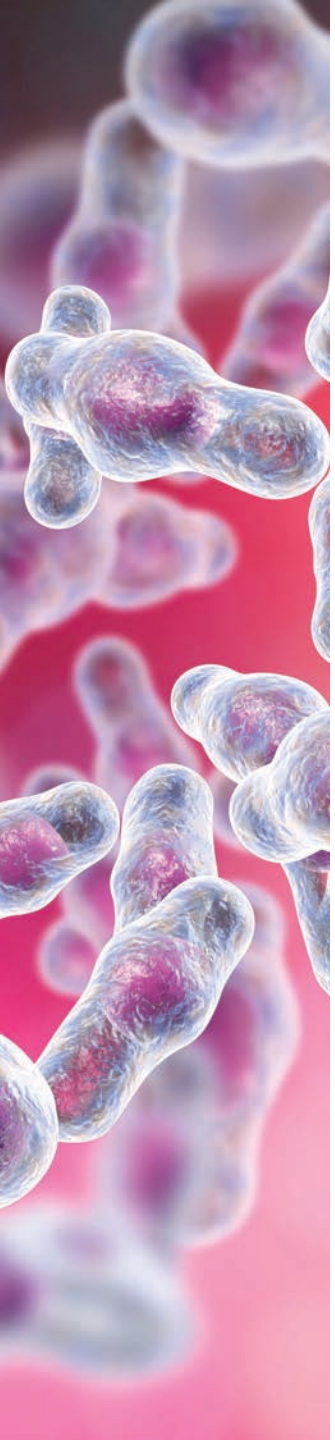
Selecting Antibiotic Treatment for rCDI

Anne J. Gonzales-Luna, PharmD, BCIDP

Assistant Professor

University of Houston College of Pharmacy

Houston, TX



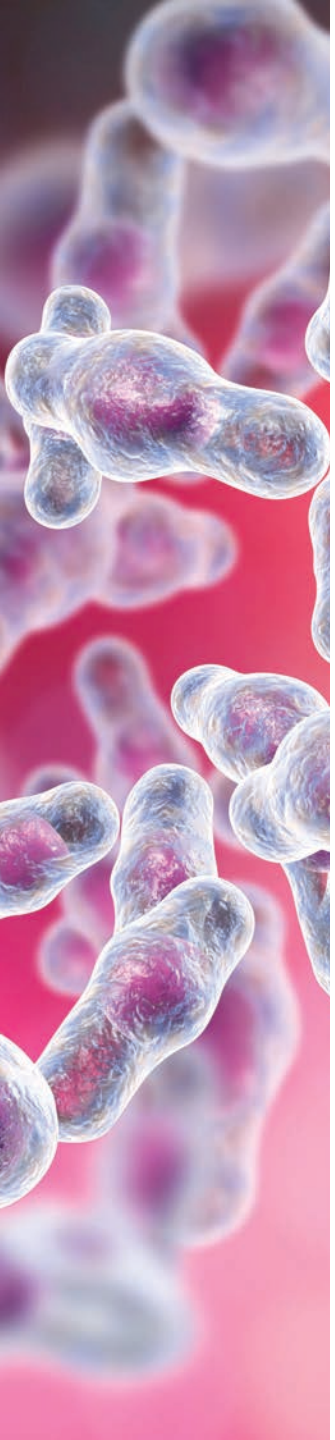
My Goals Today

Part 1:

Challenge our confidence in using antibiotics to treat CDI

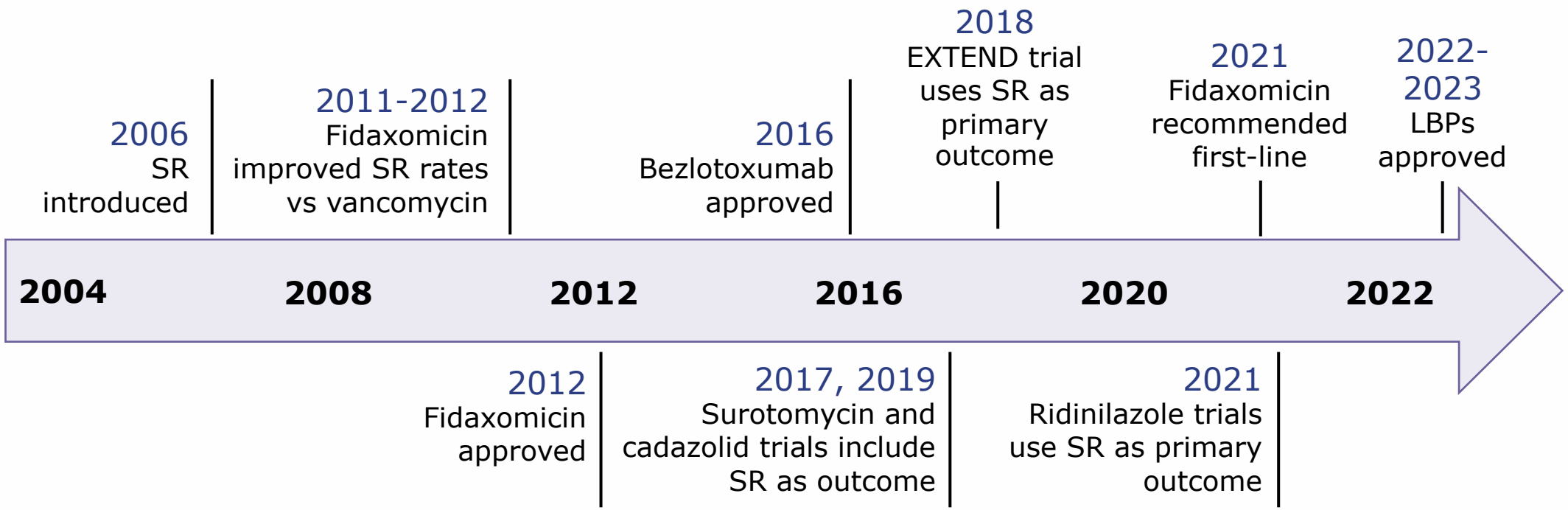
Part 2:

Explore strategies to optimize antibiotic use



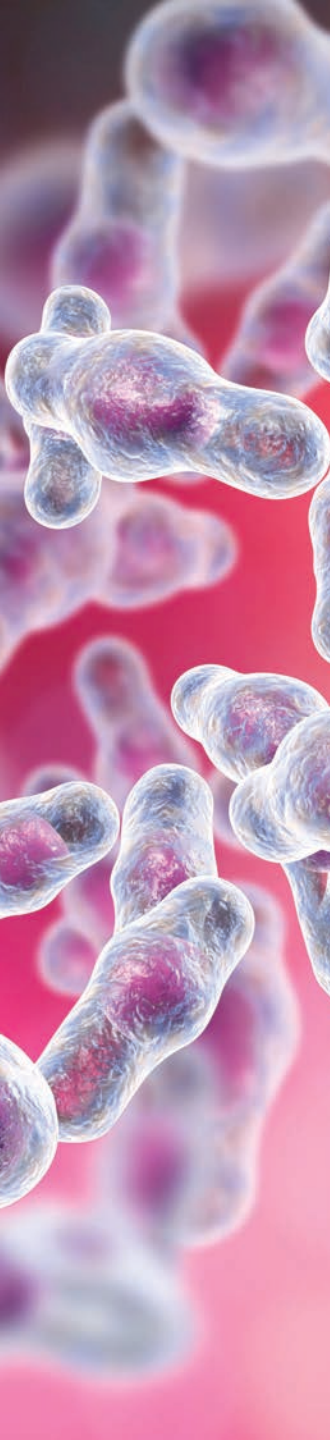
A Changing Treatment Paradigm

- Growing appreciation for antibiotic spectrum, microbiome effects, and associated rates of recurrence
- Reflected in phase 3 clinical trials: end points shifted from initial cure to **sustained response (SR)** in adults

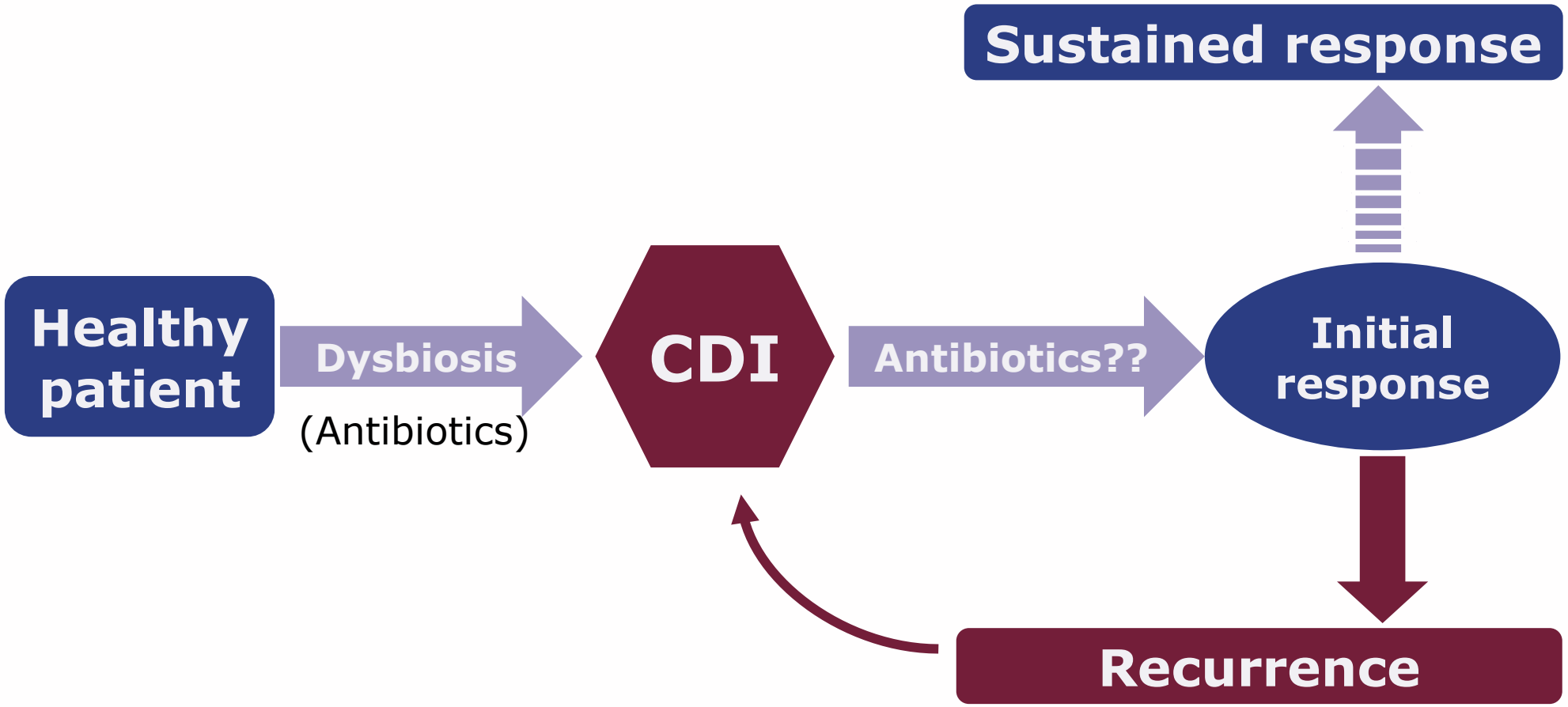


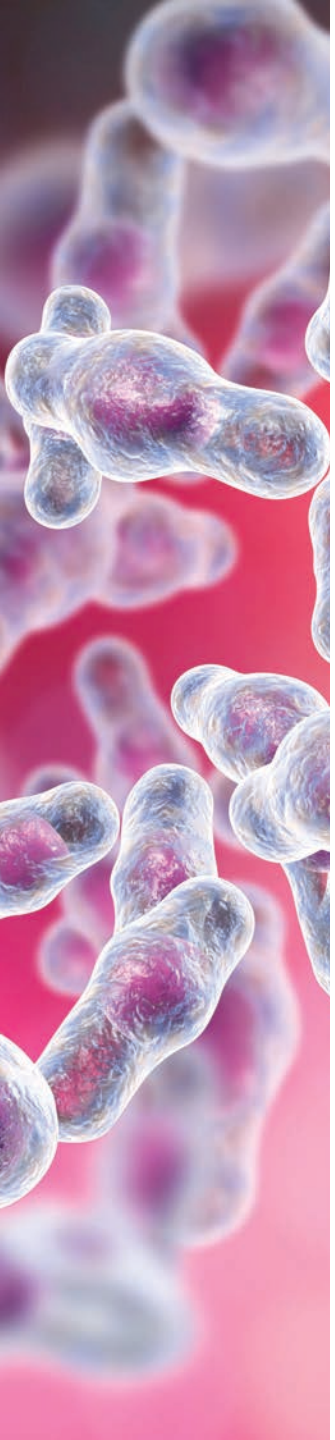
LBP, live biotherapeutic product.

Gonzales-Luna AJ, et al. *Lancet Infect Dis*. 2023;23(7):e259-e265; Johnson S, et al. *Antimicrob Agents Chemother*. 2012;56(8):4043-4045.



An Antibiotic-Centric CDI Framework





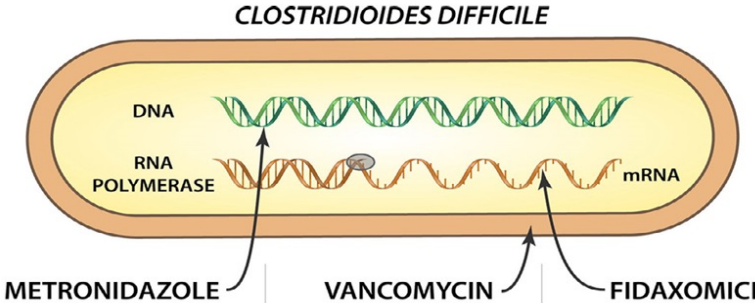
Antibiotic-Associated Dysbiosis

Characteristics increasing microbiota disruption	Microbiota effects

• Biliary excretion
• Spectrum of activity
  ○ Anti-anaerobic
• Cumulative exposures
  ○ Combination therapy
  ○ Duration of therapy
  ○ Dose
	• Reduced species diversity
	• Reduced overall abundance
	• Increased abundance of antibiotic-resistant organisms/genes

Jernberg C, et al. *Microbiology (Reading)*. 2010;156(pt 11):3216-3223; Stevens V, et al. *Clin Infect Dis.*2011;53(1):42-48. Zimmermann P, Curtis N. *J Infect.* 2019;79(6):471-489.

CDI Antibiotic Comparison: PD, PK, and Microbiologic Properties



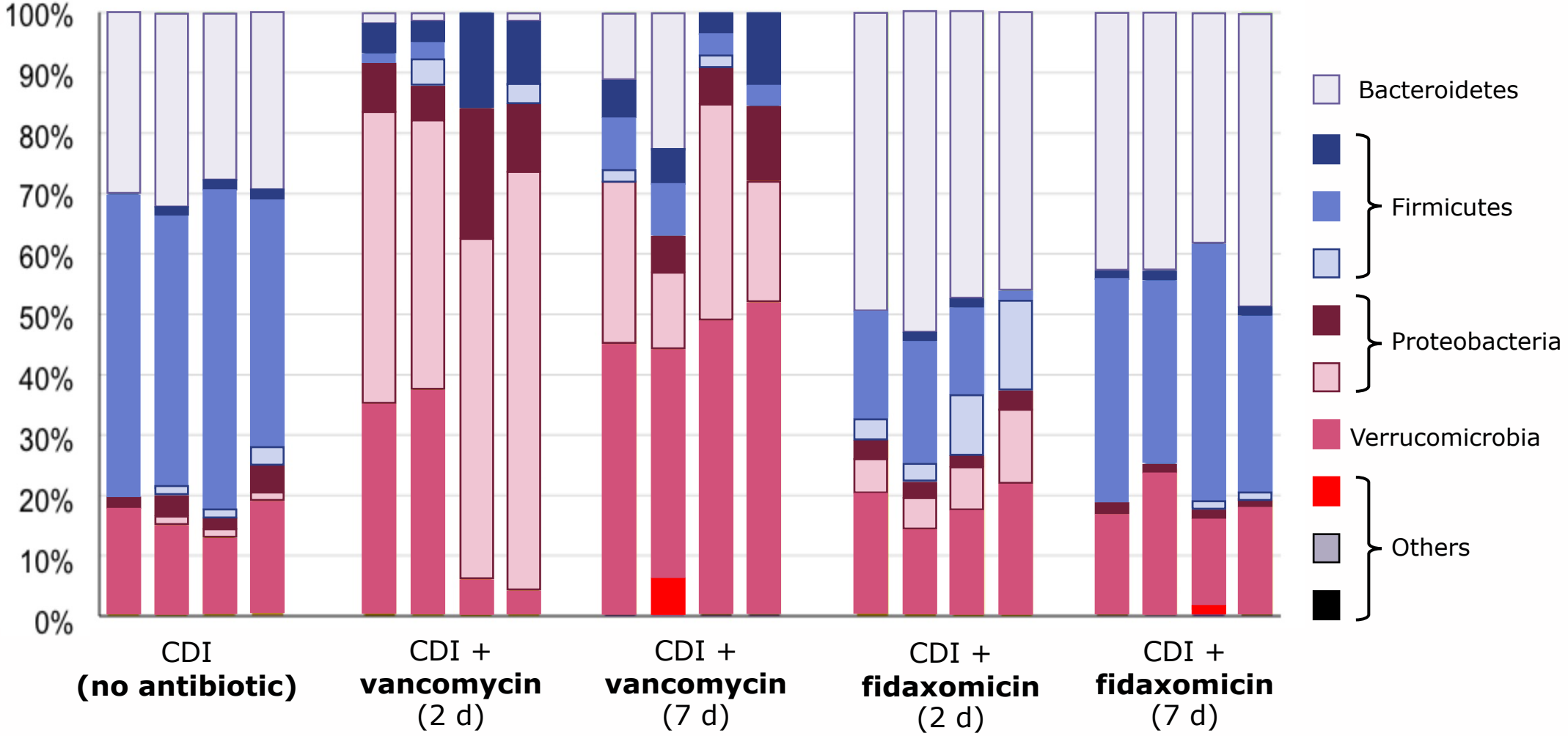
	METRONIDAZOLE	VANCOMYCIN	FIDAXOMICIN
SYSTEMIC ABSORPTION	HIGH	LOW	LOW
STOOL CONCENTRATION	LOW	HIGH	HIGH
REDUCTION OF BIOACTIVITY BY FAECES	HIGHEST	LOWER	LOWER
EFFECT ON DIVERSITY OF MICROBIOTA	REDUCTION	REDUCTION	PRESERVATION
STOOL SHEDDING DECLINE	SLOW	RAPID	RAPID
ENVIRONMENTAL CONTAMINATION	HIGHEST	LOWER	LOWER (STEEPER)
SPOROCIDAL EFFECT	—	NO	YES
INHIBITION OF SPORULATION	NO	NO	YES

- Supportive
- Less supportive
- Non-supportive
- — No data

PD, pharmacodynamic; **PK,** pharmacokinetic.

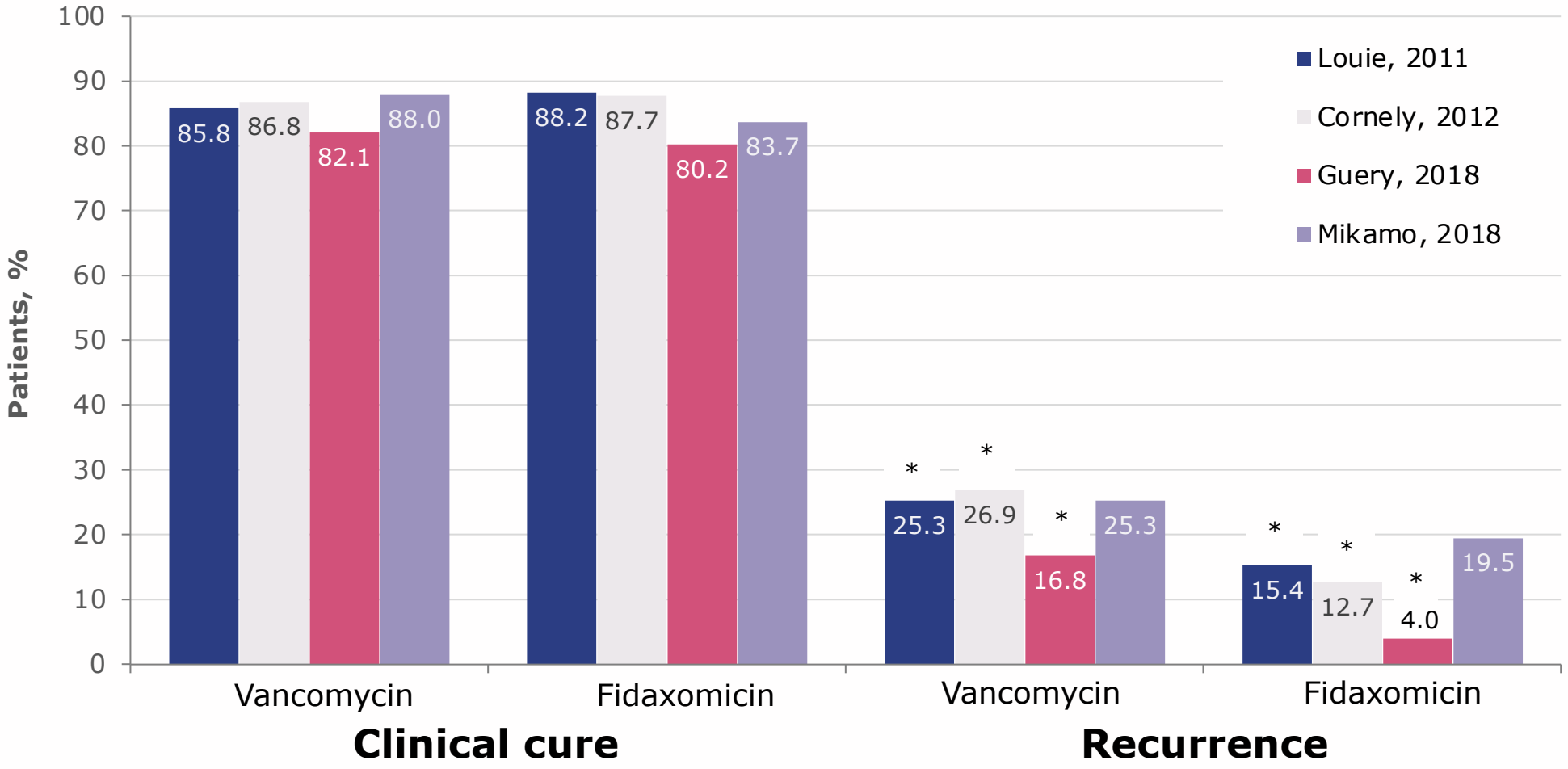
Krutova M, et al. *Int J Infect Dis*. 2022;124:118-123.

CDI Antibiotic Dysbiosis: Relative Abundance (%)



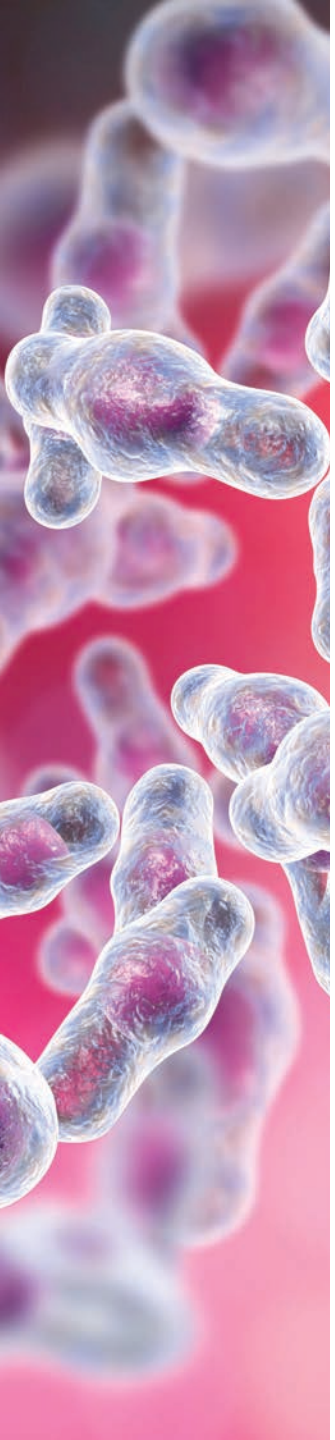
Yamaguchi T, et al. *J Infect Chemother*. 2020;26:483-491.

CDI Antibiotic-Associated Recurrence



*Statistically significant ($P<0.05$).

Cornely OA, et al. *Lancet Infect Dis*. 2012;12(4):281-289; Guery B, et al. *Lancet Infect Dis*. 2018;18(3):296-307; Louie TJ, et al. *N Engl J Med*. 2011;364(5):422-431; Mikamo H, et al. *J Infect Chemother*. 2018;24(9):744-752.



ACG 2021 Guidelines for CDI: Antibiotics

Initial episode

Non-severe	Severe	Fulminant
PO vancomycin 125 mg 4 times daily × 10 d *or* **Fidaxomicin** 200 mg twice daily × 10 d *or* May consider **PO metronidazole** 500 mg 3 times daily × 10 d in low-risk patients	**PO vancomycin** 125 mg 4 times daily × 10 d *or* **Fidaxomicin** 200 mg twice daily × 10 d	**PO vancomycin** 500 mg 4 times daily × 48-72 h → 125 mg 4 times daily ×10 d +/- **IV metronidazole** 500 mg 3 times daily + *(if ileus)* **Rectal vancomycin** 500 mg 4 times daily

FMT if refractory to antibiotics

First recurrence

Tapering/Pulsed-dose vancomycin

Vancomycin or metronidazole for initial episode → **fidaxomicin**

≥2 recurrences

FMT via colonoscopy or capsules (enema if other methods unavailable)

Long-term, suppressive PO vancomycin if relapsed after FMT, not candidate for FMT, or continually/ frequently requires antibiotics

All

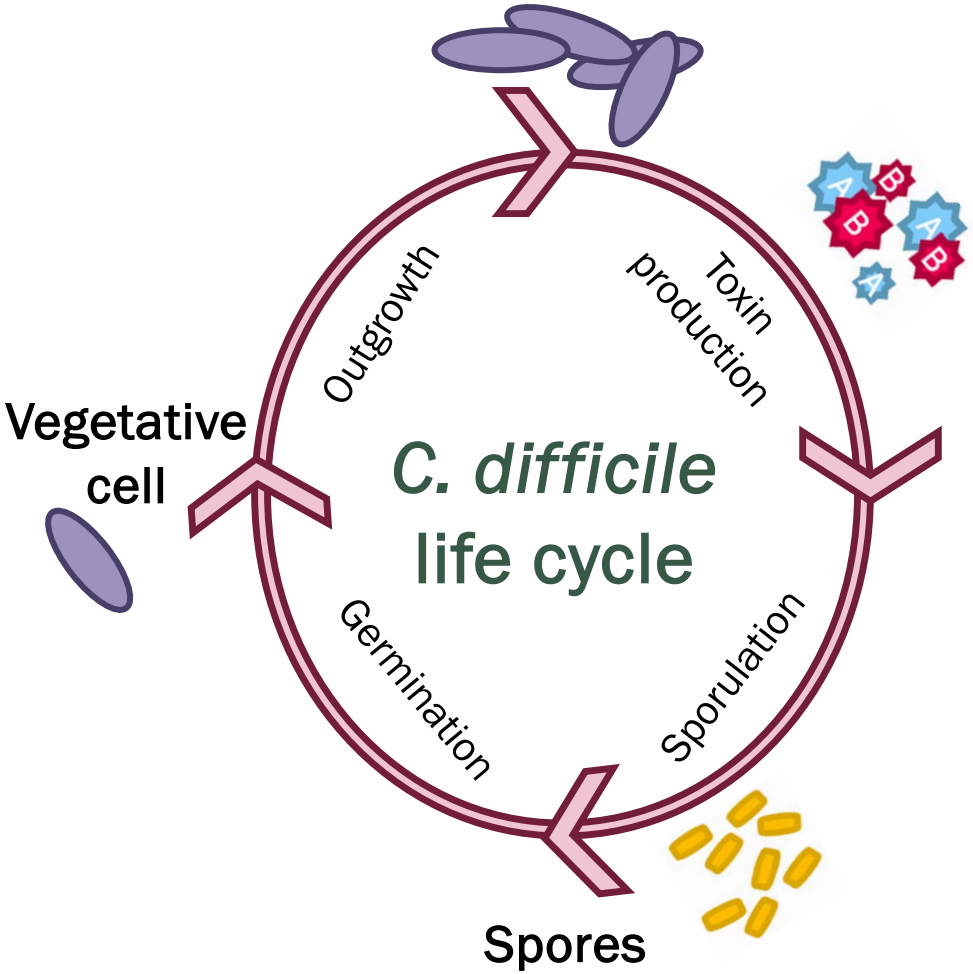
Bezlotoxumab for prevention of recurrence in patients at high risk for recurrence: ≥65 y of age and **1)** experiencing a second CDI episode in past 6 mo; **2)** immunocompromised; or **3)** have severe CDI

FMT, fecal microbiota transplantation; **IV,** intravenous.

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

Rationale for Tapered and Pulsed Regimen

- Repeating cycles of antibiotic-free periods and pulses of antibiotics
  - Antibiotic-free periods → spores allowed to germinate
  - Antibiotic pulse → kills off newly germinated vegetative *C. difficile* cells
- Various vancomycin regimens
  - ACG recommendation: standard course for 10-14 d → then decrease dose by 25% to 50% every 1-2 wk with no skipped days → then pulsed at a 125-mg dose, skipping 1-2 d, for 2-4 wk

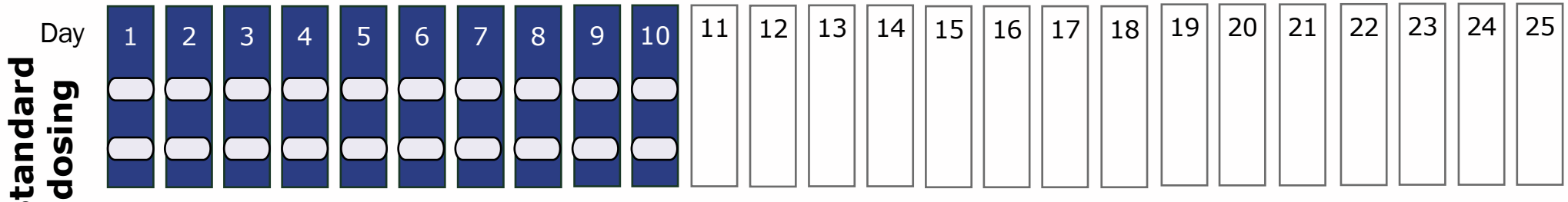


ACG, American College of Gastroenterology.

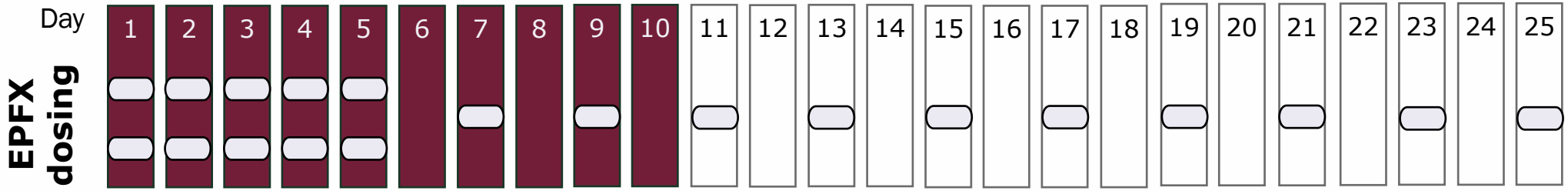
McFarland LV, et al. *Am J Gastroenterol*. 2002;97(7):1769-1775.

Tapered and Pulsed Fidaxomicin

- EXTEND trial of EPFX vs vancomycin



200 mg PO tablets, twice daily on days 1-10



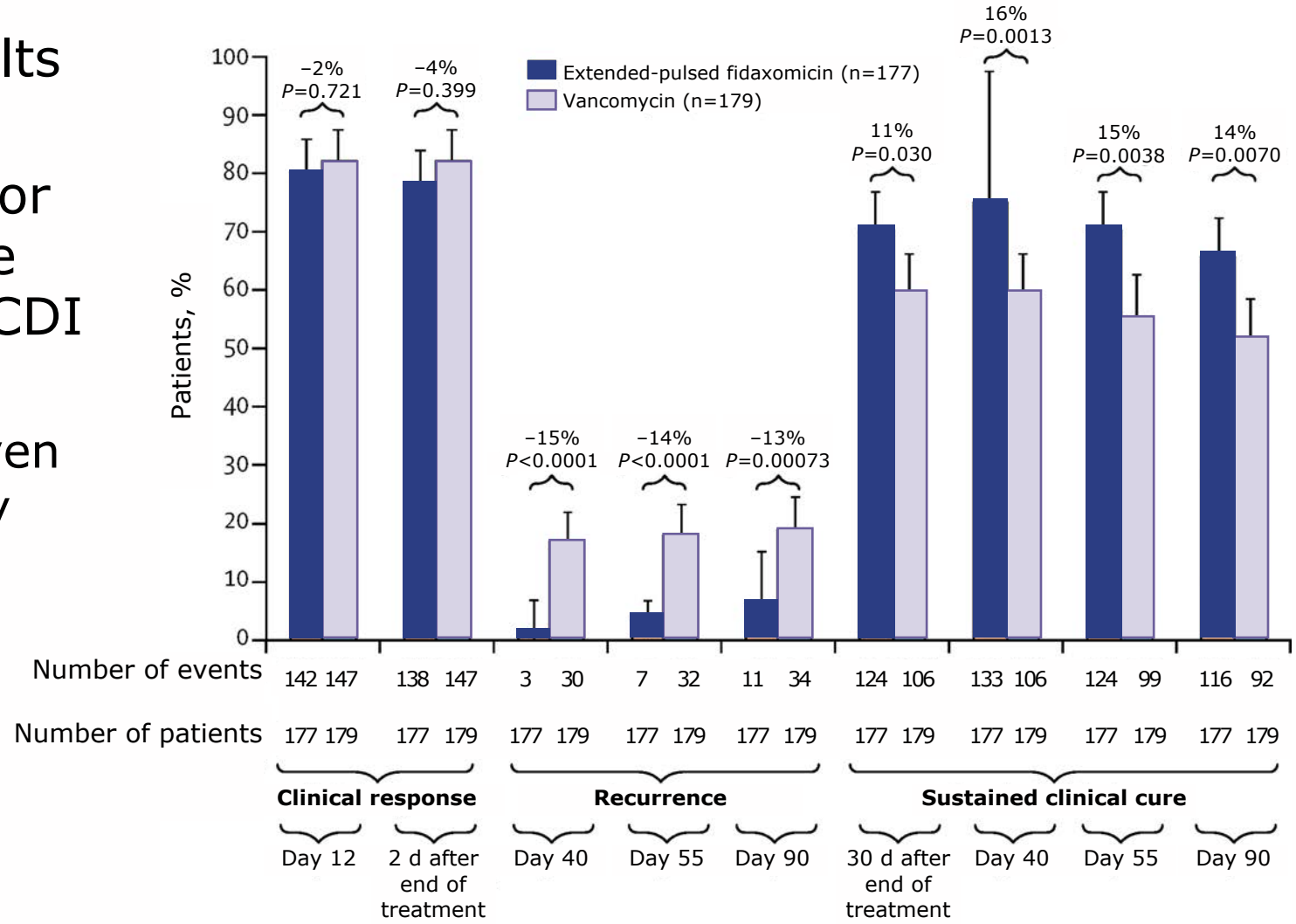
200 mg PO tablets, twice daily on days 1-5, then once daily on alternate days for days 7-25

EPFX, extended-pulsed fidaxomicin.

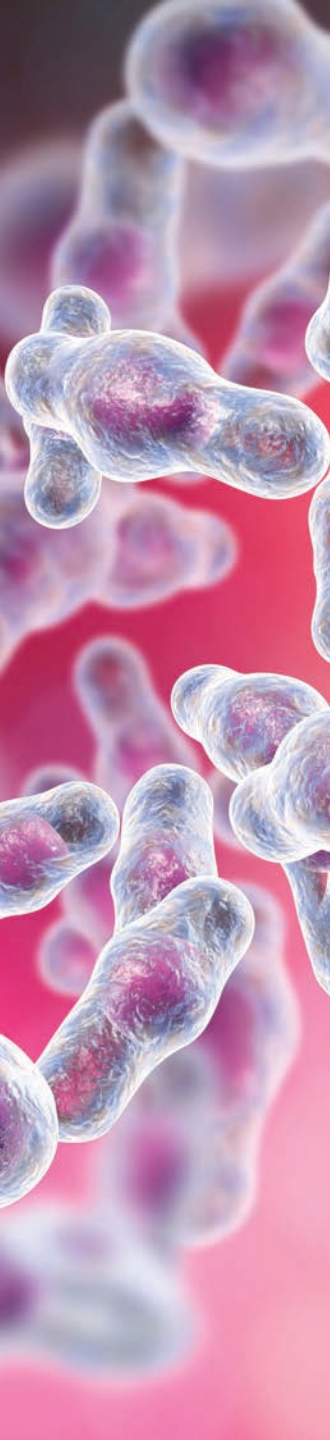
Guery B, et al. *Lancet Infect Dis*. 2018;18(3):296-307

EXTEND Trial Outcomes

- Hospitalized adults >60 y of age
- EPFX was superior to standard-dose vancomycin for CDI sustained cure
  - Difference driven by significantly lower rates of recurrence



Guery B, et al. *Lancet Infect Dis*. 2018;18(3):296-307

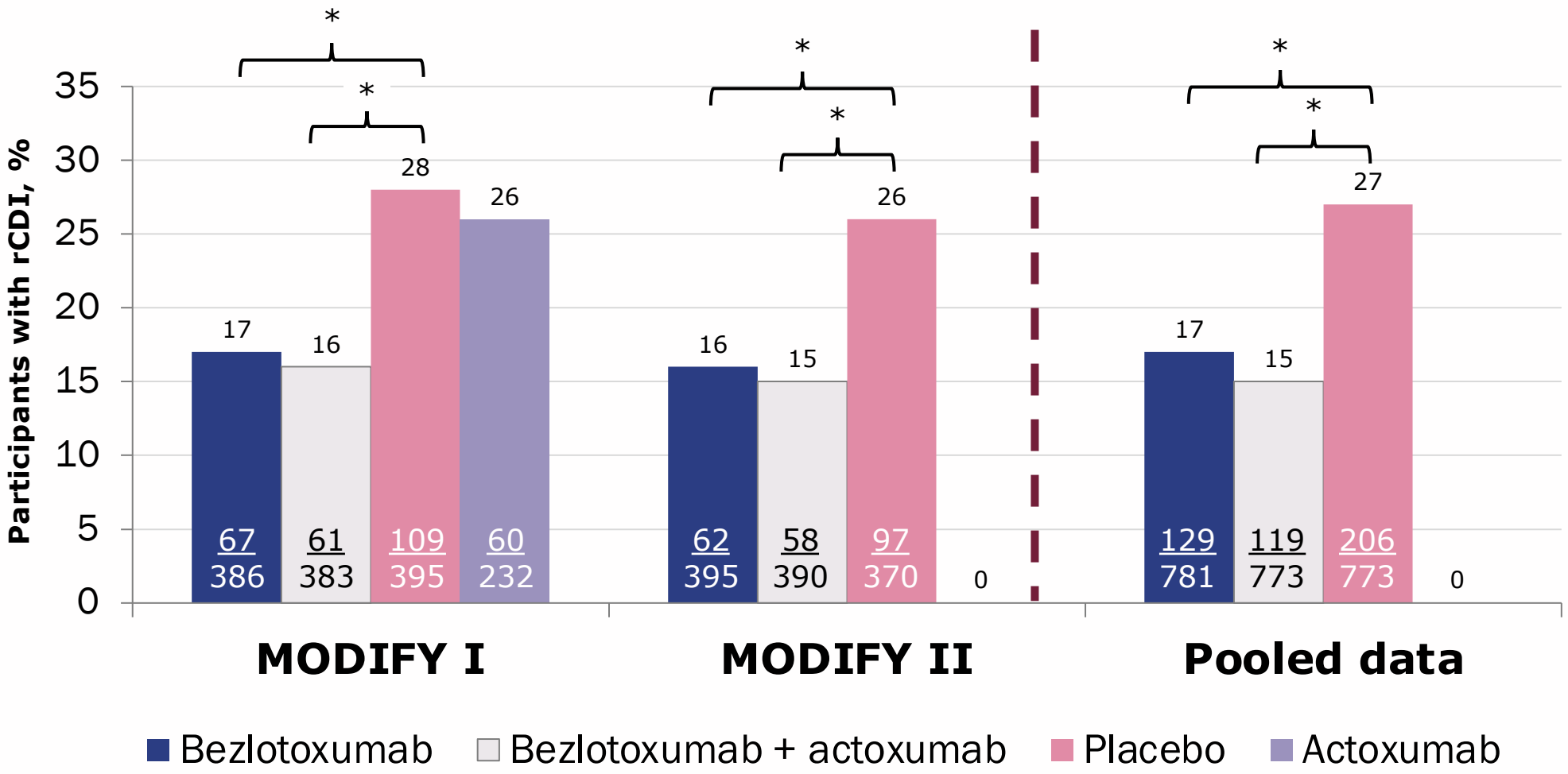


A Non-Antibiotic Option to Prevent rCDI: Bezlotoxumab

- Fully human IgG1 mAb that binds to *C. difficile* toxin B
  - Indication: to reduce rCDI in patients ≥18 y of age who are receiving antibiotic treatment for CDI and are at high risk for recurrence
- Single dose of 10 mg/kg administered as IV infusion over 60 min
  - Half-life=19 d
- Should be given at any time during active CDI antibiotic treatment
- Use with caution in patients with heart failure
  - Reserve use for when benefit outweighs risk

Ig, immunoglobulin; **mAb,** monoclonal antibody.

MODIFY Trials: 12-wk Recurrence

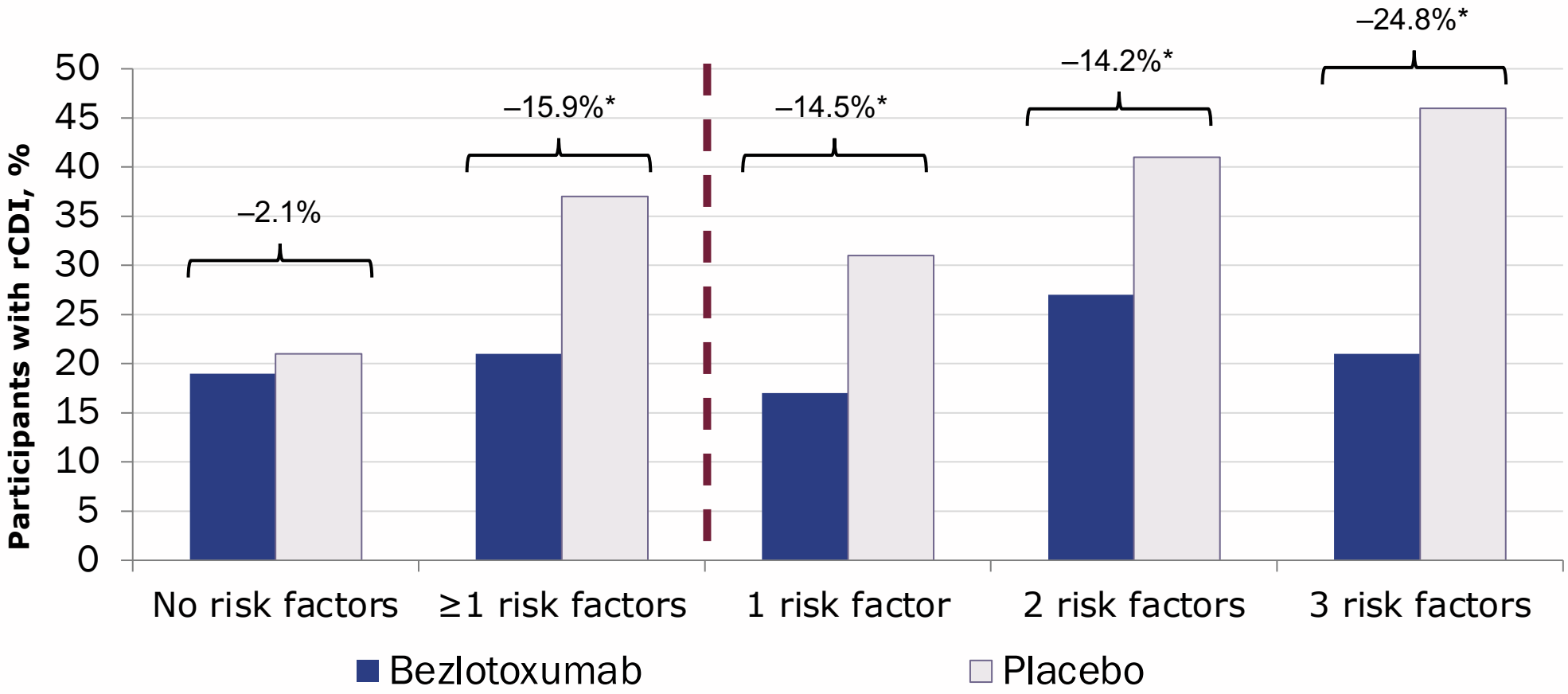


- SOC PO antimicrobials were metronidazole (47%), vancomycin (48%), and fidaxomicin (4%)

*P<0.001.

Wilcox MH, et al. *N Engl J Med*. 2017;376(4):305-317.

Bezlotoxumab in High-Risk Patients

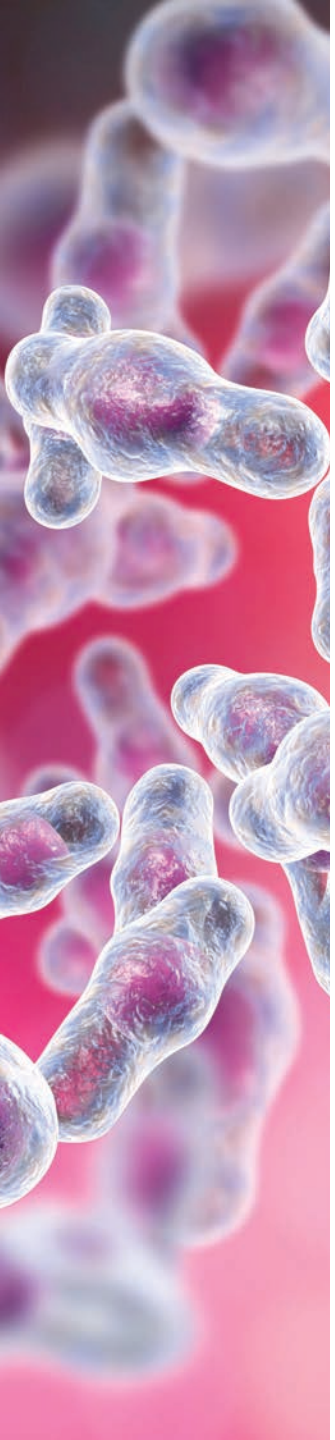


Risk factors for recurrence

- Age ≥65 y
- History of CDI in previous 6 mo
- Immunocompromised
- Severe CDI
- Infection with CDI ribotype 027, 078, or 244

*P<0.05.

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



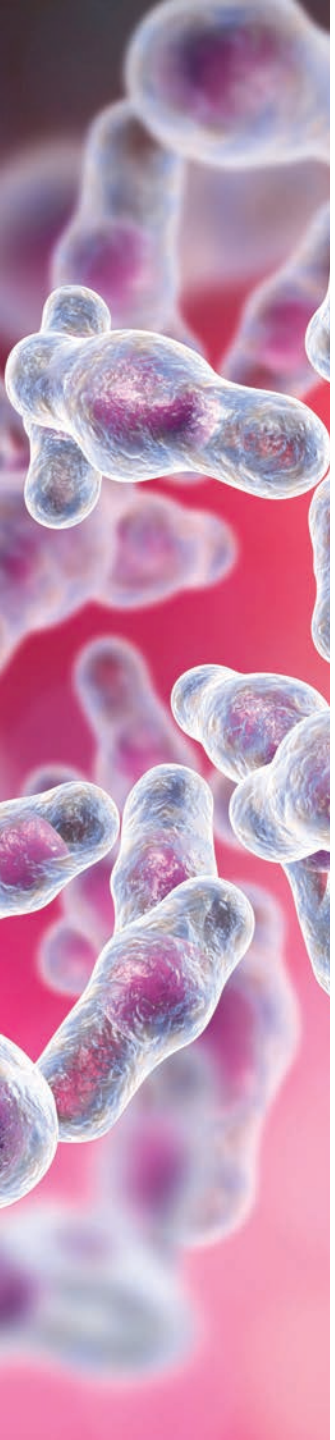
Key Ways to Optimize Antibiotics for CDI

Minimize unnecessary antibiotic exposure, *including* to CDI-directed antibiotics

- Use minimal necessary treatment duration for efficacy
- Avoid combination therapy unless treating fulminant disease
- Think hard about using vancomycin prophylaxis

Use most narrow-spectrum antibiotic as early as possible to preserve host microbiota

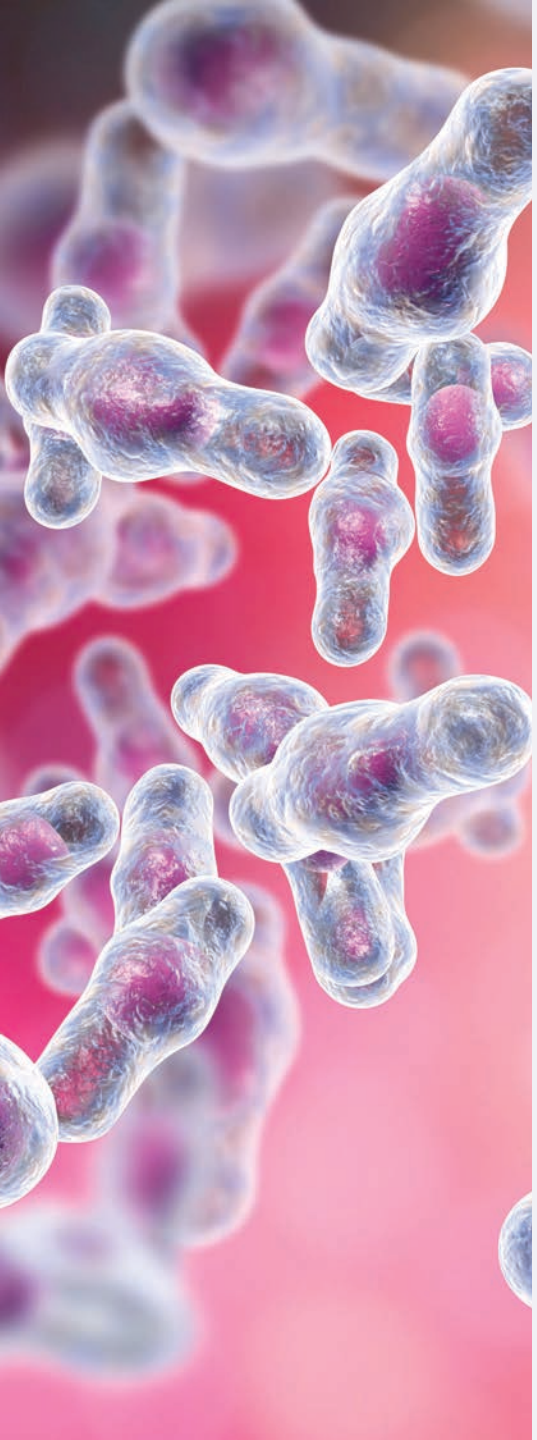
- Increases likelihood of sustained clinical cure
- Advantage of narrow-spectrum antibiotics lessened when used for later treatment courses or after broad spectrum antibiotics



Parting Thoughts

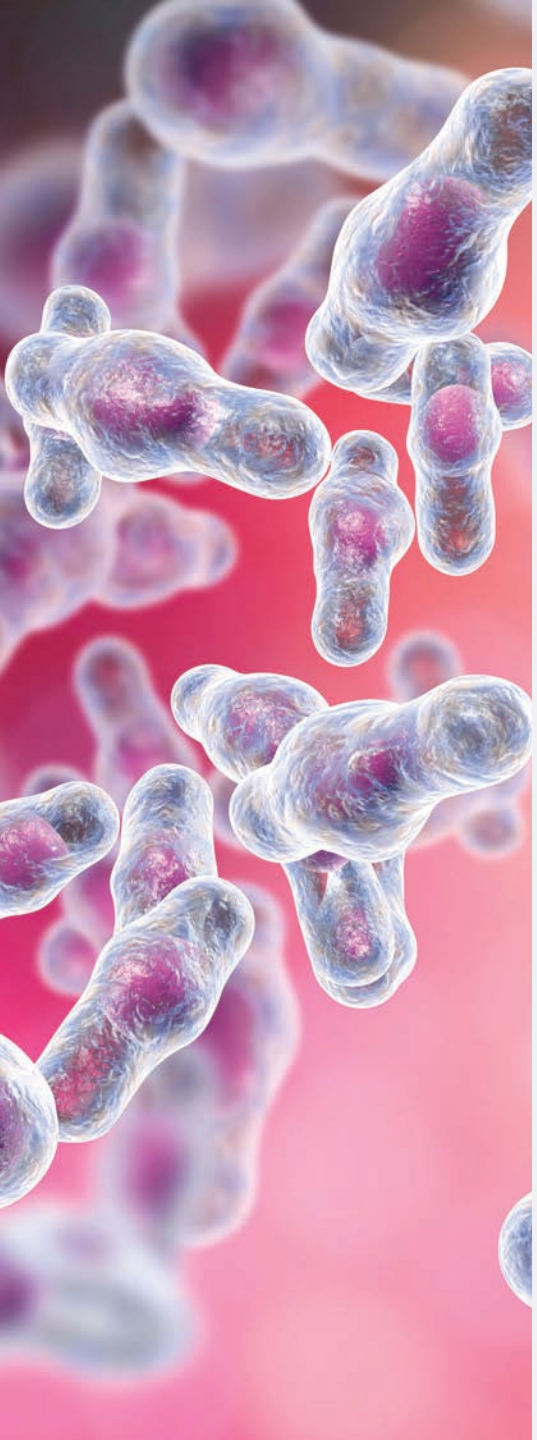
- We tend to think of antibiotics that cause CDI differently than antibiotics that treat CDI
- All CDI-directed antibiotics cause some collateral damage to the host microbiota, furthering dysbiosis
  - More narrow-spectrum CDI antibiotics minimize these disruptions and preserve more of the remaining host microbiota …

… but still do nothing to **restore** microbiota diversity



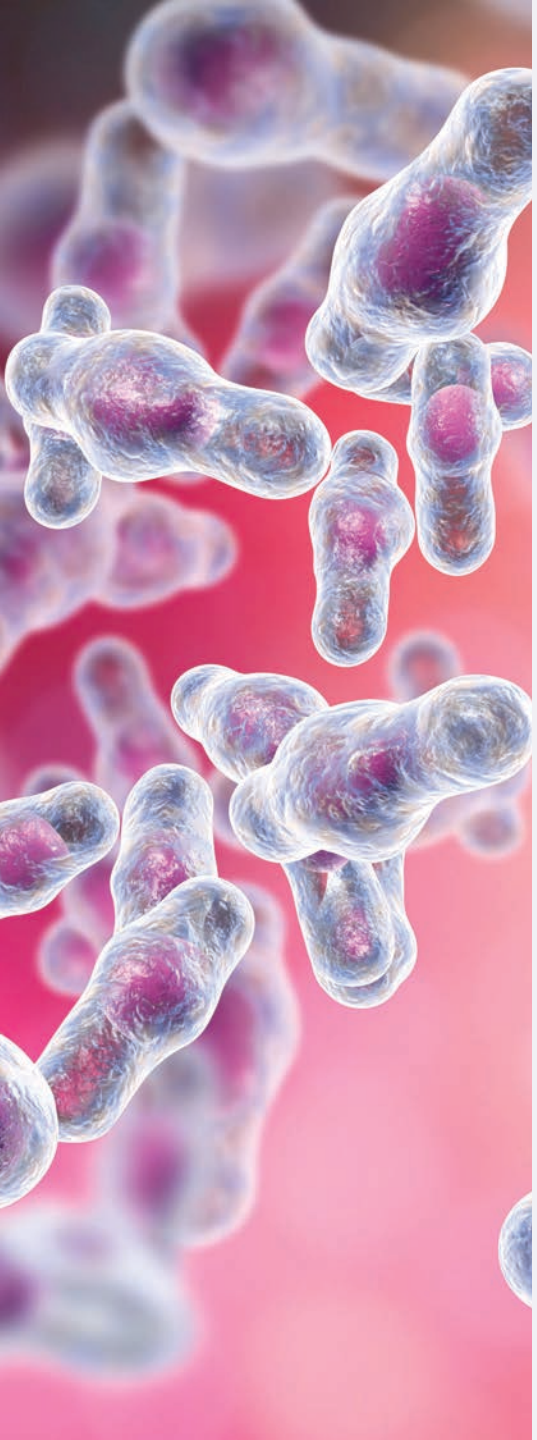
Case: Recalling Lorraine

- Woman with hypertension, diabetes, GERD, and history of appendectomy
- Presentation 2 mo after initial *C. difficile* infection: diarrhea, cramping, abdominal pain; elevated WBC/Cr
- No apparent risk for new infection
- **Lorraine is treated with vancomycin 125 mg PO 4 times daily for 10 d and responds**



Case: Familiar Symptoms Return

- 4 weeks later, Lorraine experiences abdominal pain with 6 to 9 liquid stools per day
- She calls her primary care MD and is referred to your office for further assessment
- Blood work results
  - WBC: 9000×10^3/mL
  - Cr: 0.9 mg/dL



Case: Treatment for Lorraine's Recurrence

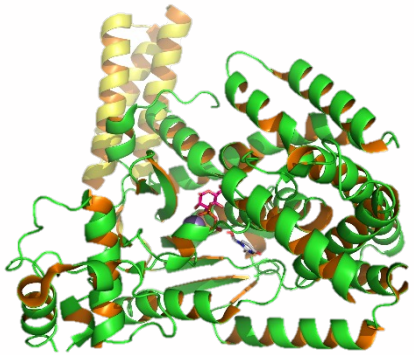
- What would be the best treatment for Lorraine's recurrence?
  - A. Vancomycin 125 mg PO 4 times daily for 10 d
  - B. Vancomycin in a taper pulse >6 wk
  - C. Fidaxomicin 200 mg twice daily for 5 d, followed by 200 mg every other day for days 7 to 25
  - D. Vancomycin 125 mg PO 4 times daily for 10 d, followed by rifaximin 550 mg PO 3 times daily for 20 d

New and Emerging Microbiota-Based Biotherapies for rCDI

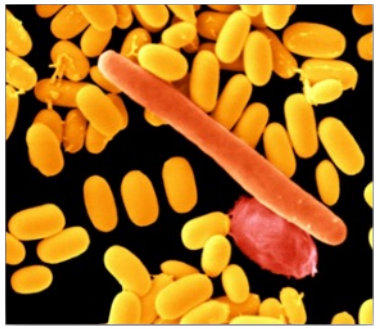
Paul Feuerstadt, MD, FACG, AGAF
Assistant Clinical Professor of Medicine
Yale University School of Medicine
Attending Gastroenterologist
PACT-Gastroenterology Center
Hamden, CT

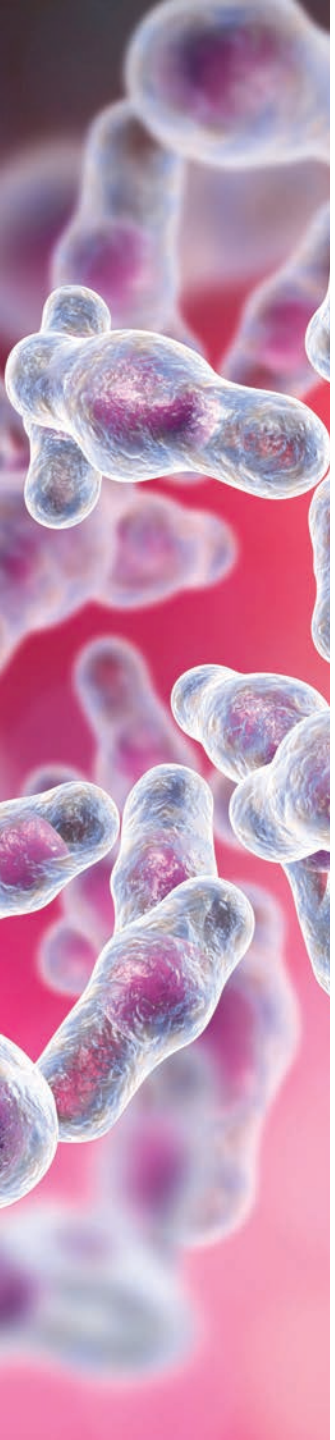
Multimodal Approach to Therapy

Bezlotoxumab



FMT



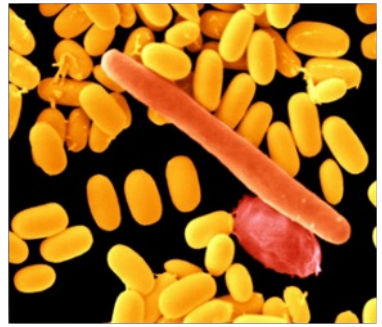


Goals of CDI Treatment

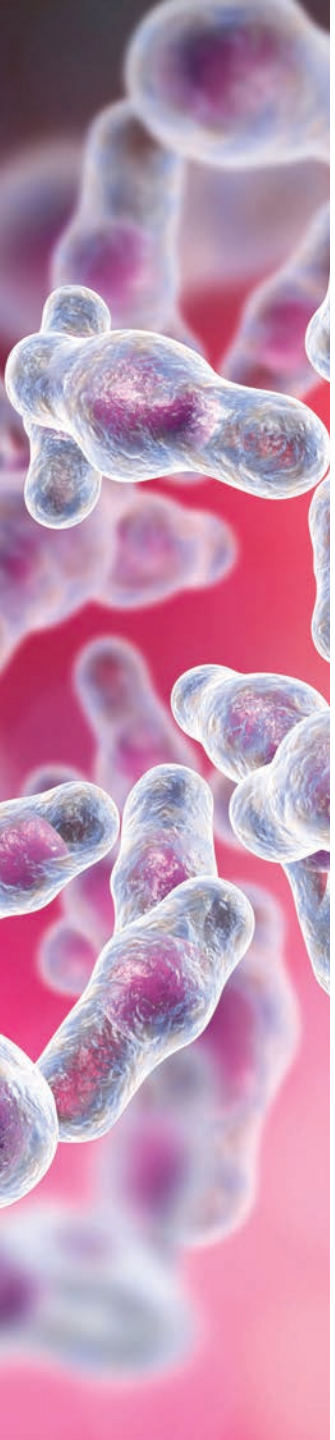
Fidaxomicin
Vancomycin
Metronidazole

Vegetative phase

Spore phase



Healthy, diverse microbiota



FMT for CDI: 2021 Guidelines

Group	Recurrence	Recommendation/ Opinion	Strength
ACG[1]	≥2 recurrences (ie, 3 episodes)	FMT to prevent further recurrence	• Strong recommendation • Moderate quality of evidence
	Recurrence in ≤8 wk of initial FMT	Repeat FMT for patients	• Conditional recommendation • Very low quality of evidence
	Severe/Fulminant CDI refractory to antimicrobial therapy, particularly in patients deemed poor surgical candidates	Consider FMT	• Strong recommendation • Low quality of evidence
IDSA, SHEA[2]	≥2 recurrences (ie, 3 episodes): should be tried	Appropriate antibiotic treatment before offering FMT	n/a

IDSA, Infectious Diseases Society of America; **SHEA,** Society for Healthcare Epidemiology of America.

1. Kelly CR, et al. *Am J Gastroenterol*. 2021;116(6):1124-1147; 2. Johnson S, et al. *Clin Infect Dis*. 2021:73:e1029-1044.

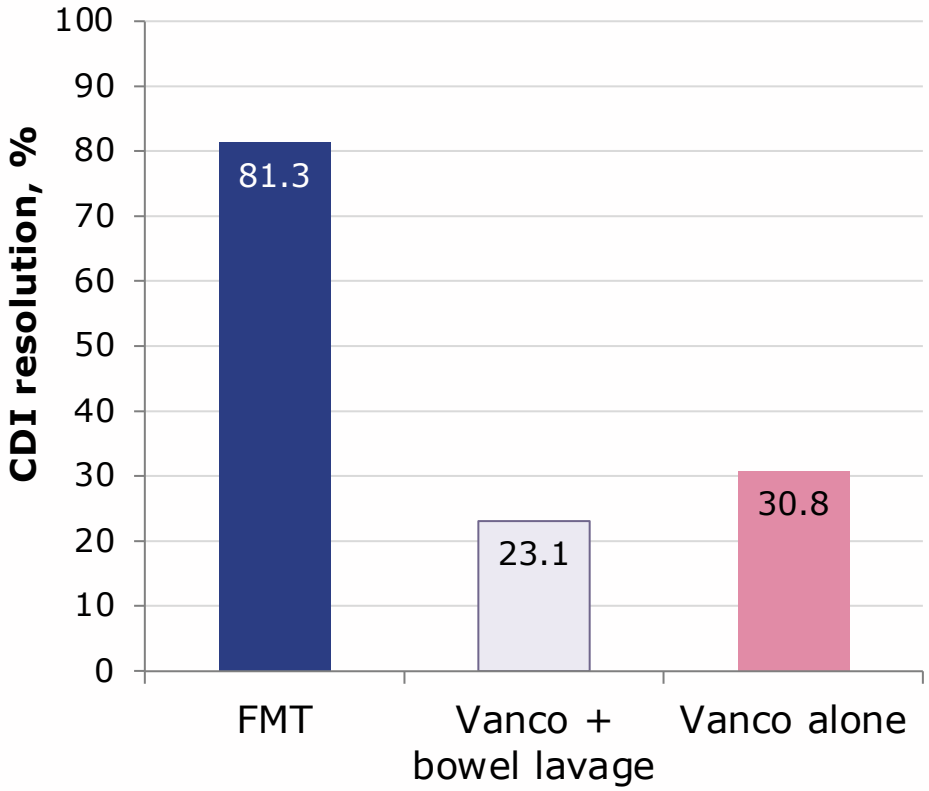
Acronyms Galore

FMT
- Fecal microbiota transplantation

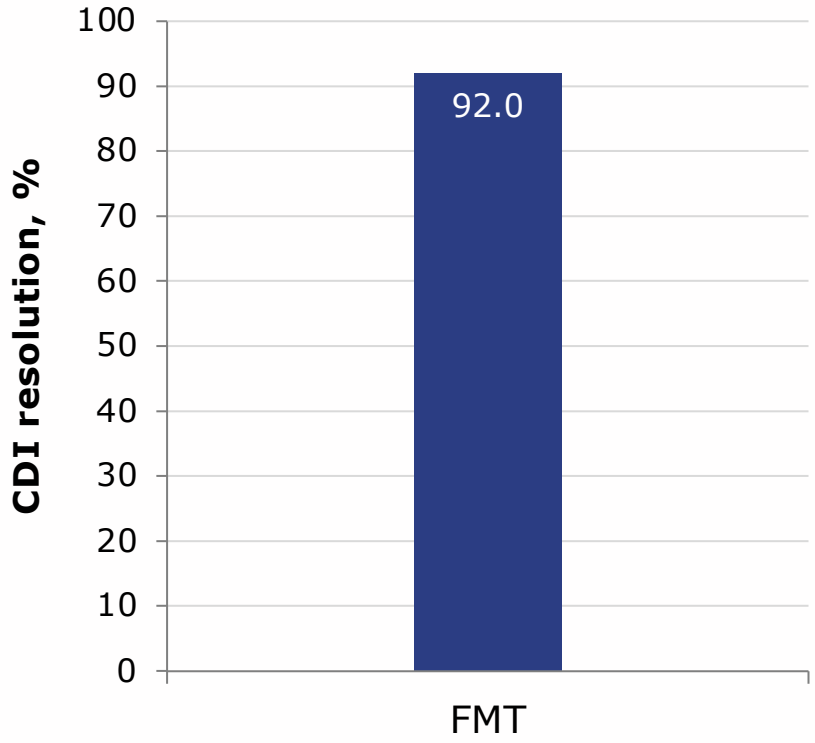
MRT
- Microbiota replacement therapy

LBP
- Live biotherapeutic product

Evolution of Outcomes for FMT in CDI



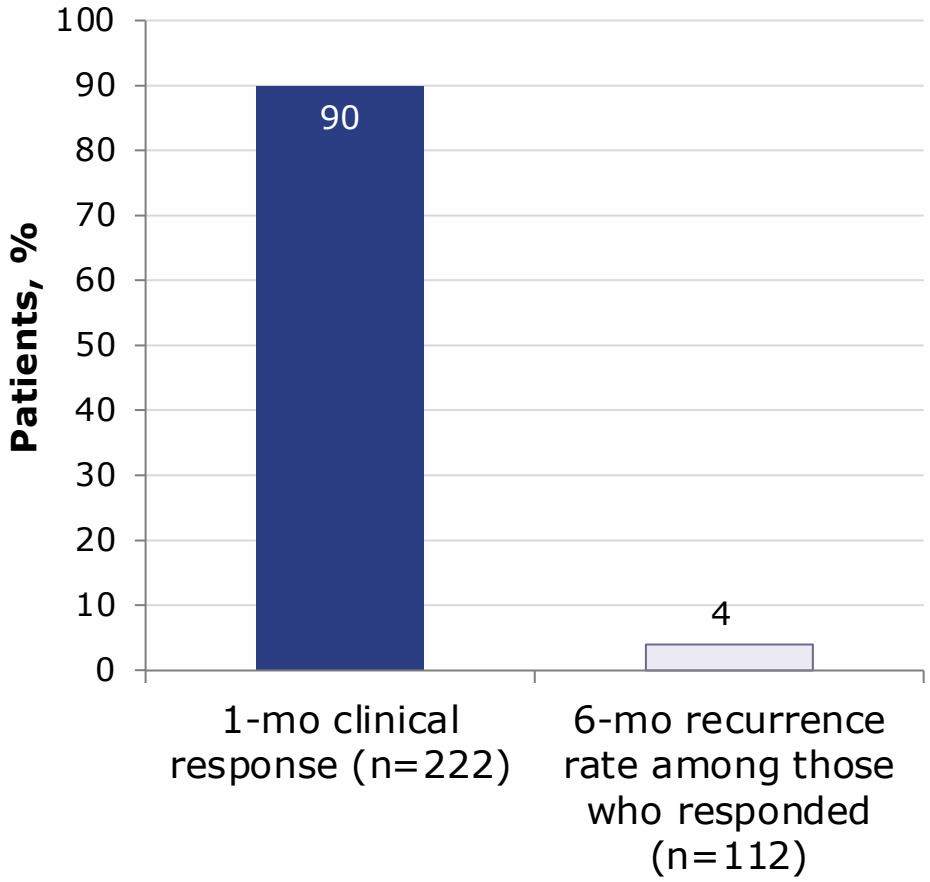
Van Nood et al., 2013



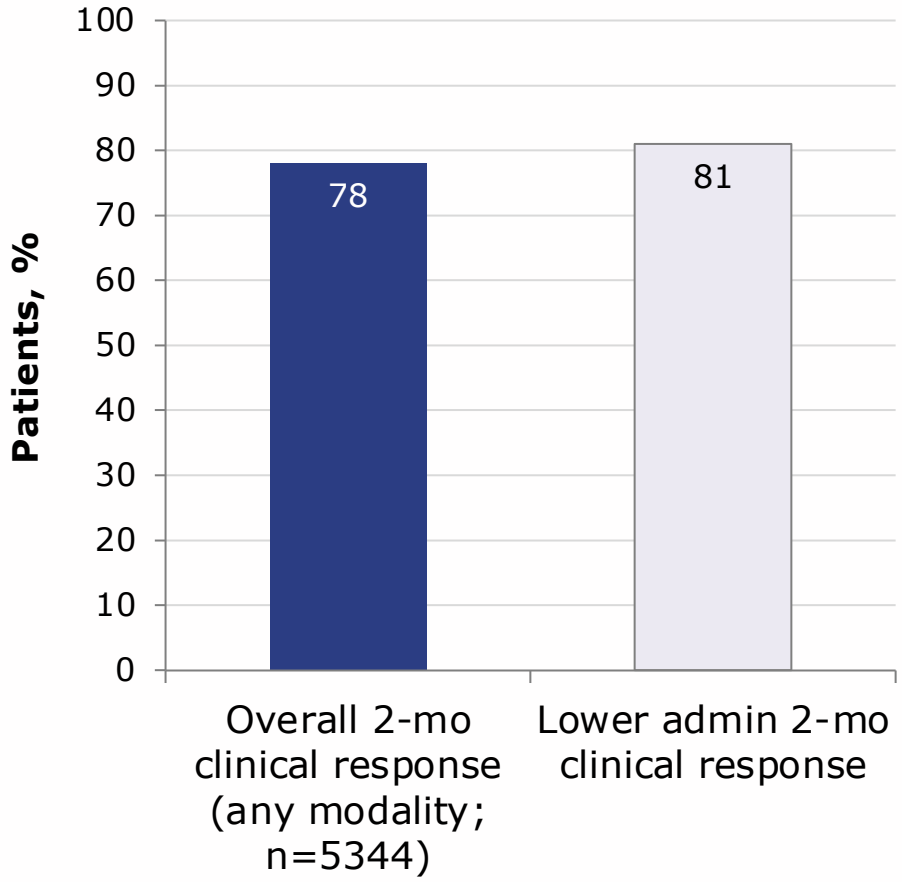
Quraishi et al., 2017

Quraishi MN, et al. *Aliment Pharmacol Ther*. 2017;46(5):479-493; van Nood E, et al. *N Engl J Med*. 2013;368:407-415.

Foundational Data for FMT in CDI



Kelly et al., 2021
AGA FMT Registry

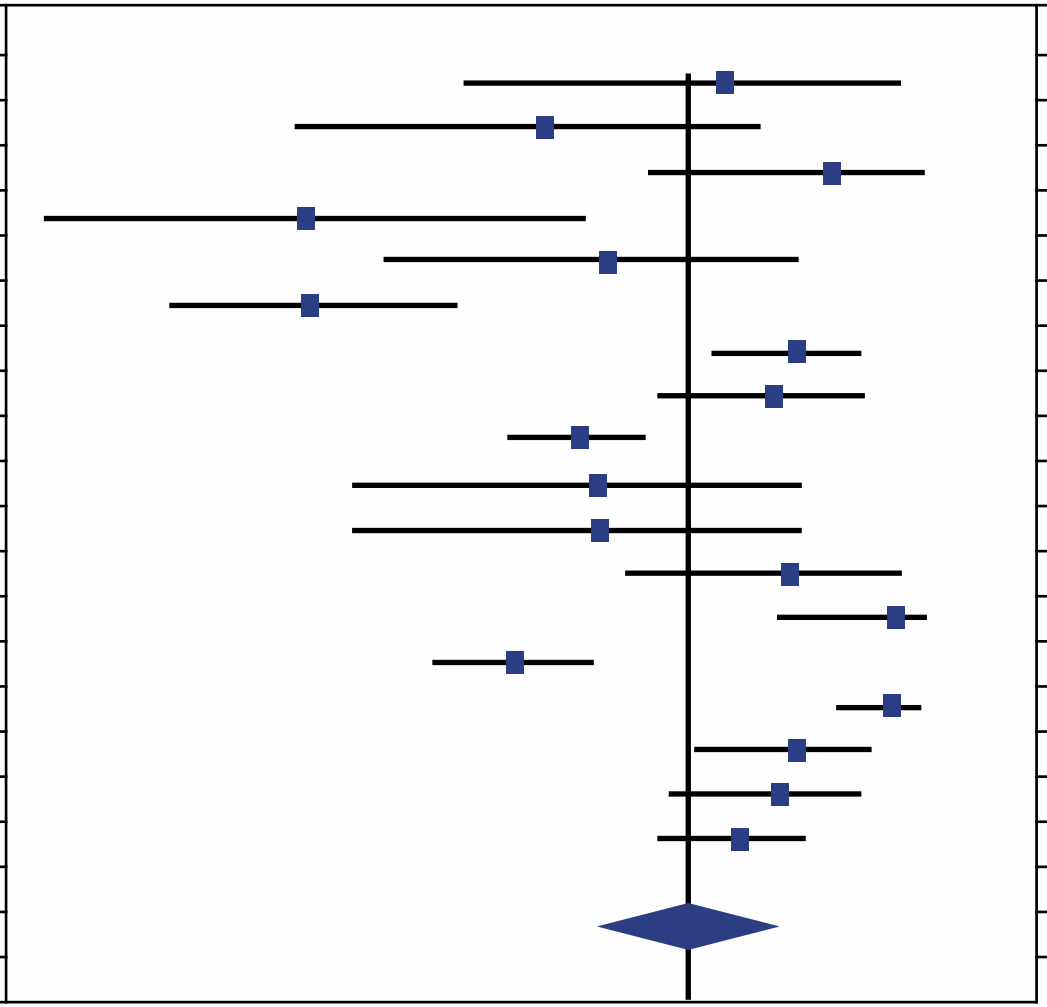


Osman et al., 2022
Stool bank

Kelly CR, et al. *Gastroenterology.* 2021;160(1):183-192; Osman M, et al. *Gastroenterology*. 2022;163(1):319-322.

Resolution of rCDI with FMT/MRT

- All clinical trials (N=1176; 19 trials, 18 studies); efficacy: 78% (95% CI, 71-85)



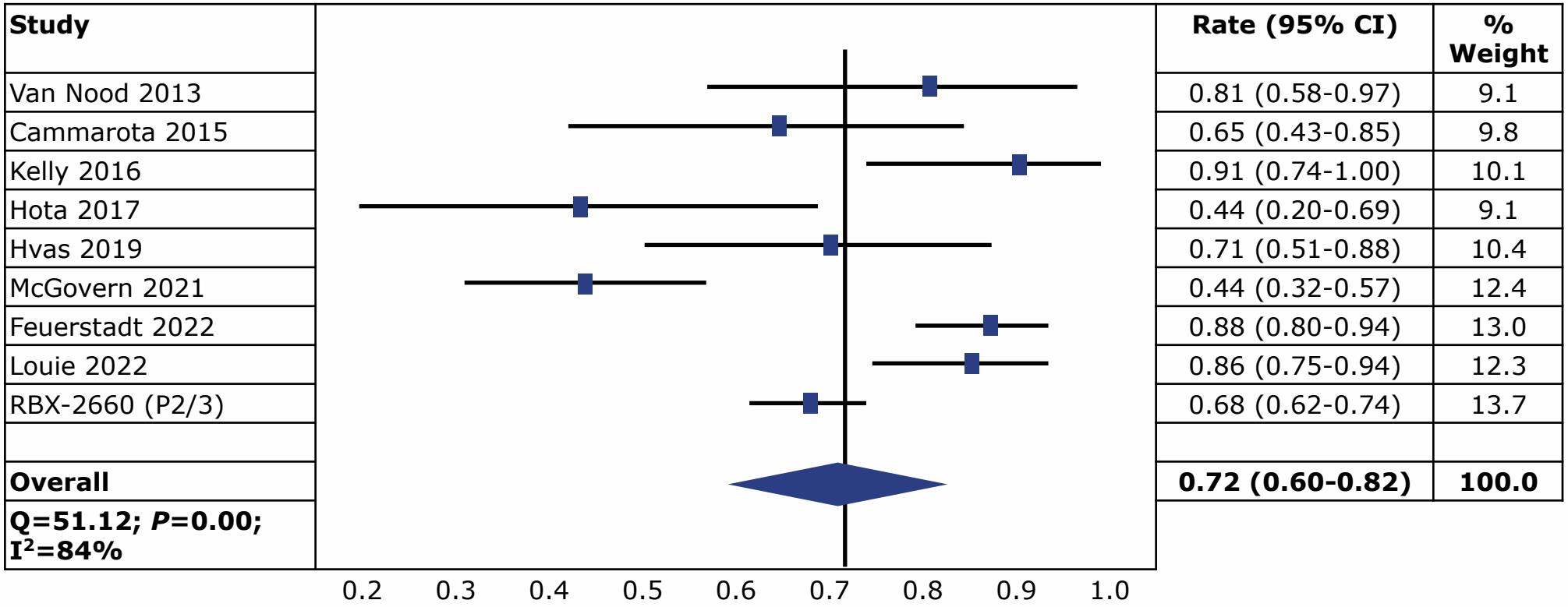
Study	Rate (95% CI)	% Weight
Van Nood 2013	0.81 (0.58-0.97)	4.4
Cammarota 2015	0.65 (0.43-0.85)	4.8
Kelly 2016	0.91 (0.74-1.00)	4.9
Hota 2017	0.44 (0.20-0.69)	4.4
Hvas 2019	0.71 (0.51-0.88)	5.0
McGowan 2021	0.44 (0.32-0.57)	6.0
Feuerstadt 2022	0.88 (0.80-0.94)	6.2
Louie 2022	0.86 (0.75-0.94)	5.9
RBX-2660 (P2/3)	0.68 (0.62-0.74)	6.6
Youngster 2014 (a)	0.70 (0.48-0.88)	4.8
Youngster 2014 (b)	0.70 (0.48-0.88)	4.8
Orenstein 2016	0.87 (0.73-0.97)	5.3
Khanna 2016	0.97 0.86-1.00)	5.3
Lee 2016	0.62 (0.55-0.69)	6.5
Kao 2017	0.96 (0.92-0.99)	6.3
Jiang 2017	0.88 (0.79-0.94)	6.1
Jian 2018	0.86 (0.77-0.94)	6.0
Allegreti 2022	0.83 (0.76-0.89)	6.4
Overall	**0.78 (0.71-0.85)**	**100.0**
Q=136.10; *P*=0.00; I^2=88%		

0.2 0.4 0.6 0.8 1.0

Tariq R, et al. *Therap Adv Gastroenterol*. 2023;16:17562848231174293.

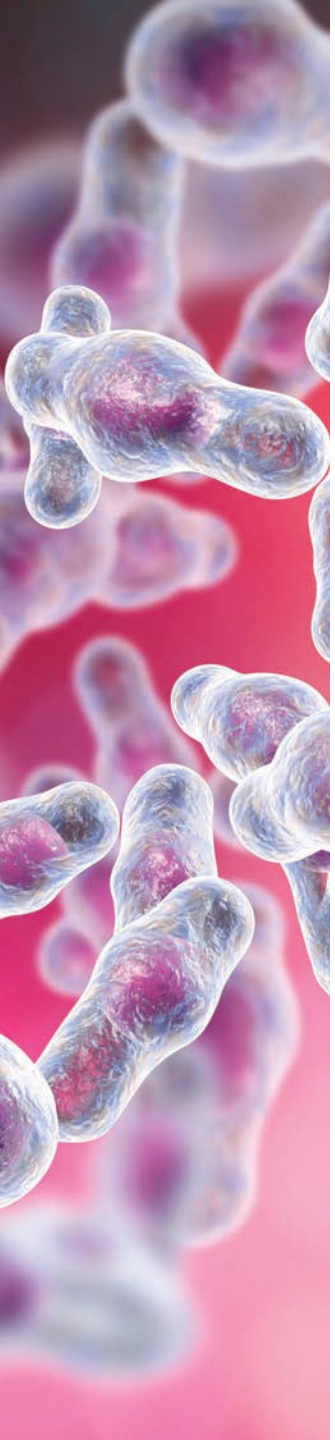
Resolution of rCDI With FMT/MRT

- Trials with a control arm (N=523; 10 trials, 9 studies); efficacy: 72% (95% CI, 60-82)



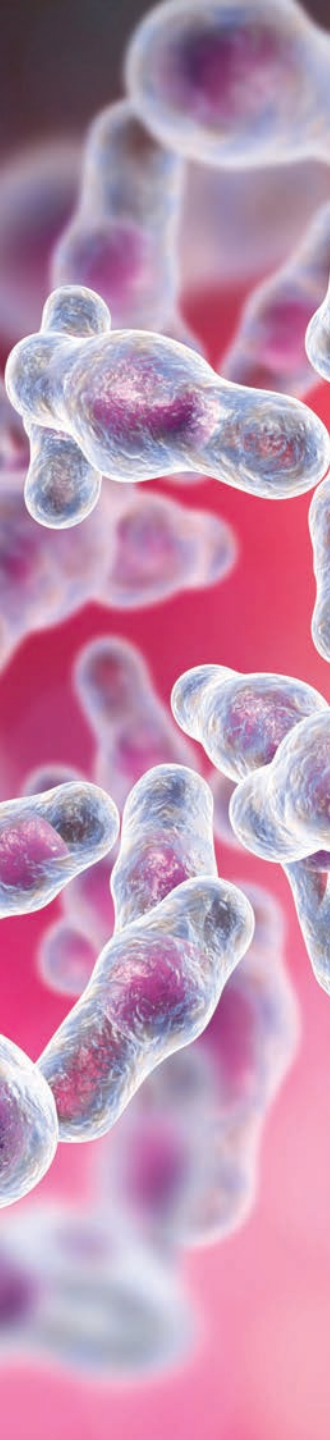
Study	Rate (95% CI)	% Weight
Van Nood 2013	0.81 (0.58-0.97)	9.1
Cammarota 2015	0.65 (0.43-0.85)	9.8
Kelly 2016	0.91 (0.74-1.00)	10.1
Hota 2017	0.44 (0.20-0.69)	9.1
Hvas 2019	0.71 (0.51-0.88)	10.4
McGovern 2021	0.44 (0.32-0.57)	12.4
Feuerstadt 2022	0.88 (0.80-0.94)	13.0
Louie 2022	0.86 (0.75-0.94)	12.3
RBX-2660 (P2/3)	0.68 (0.62-0.74)	13.7
Overall	**0.72 (0.60-0.82)**	**100.0**
Q=51.12; *P*=0.00; I^2=84%		

Tariq R, et al. *Therap Adv Gastroenterol*. 2023;16:17562848231174293.



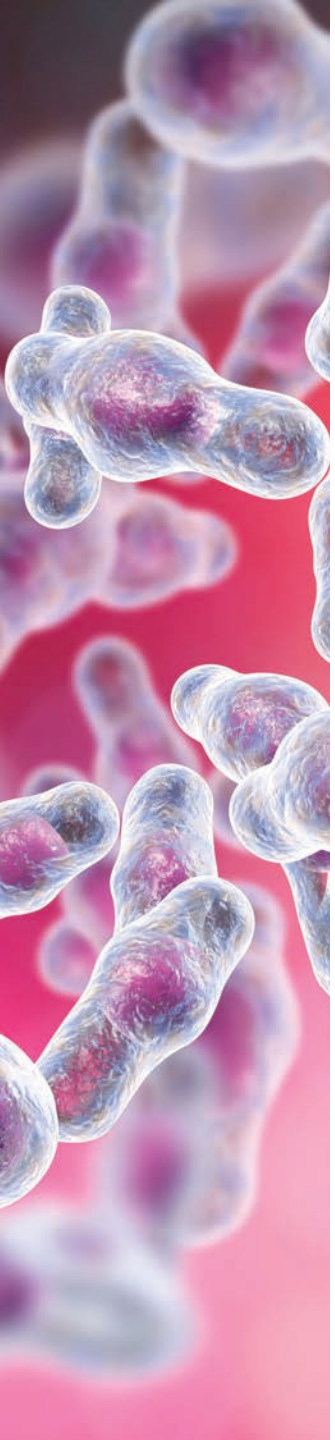
FMT vs LBP

	FMT	LBP
Donor screening	💩 💩	💩 💩 💩



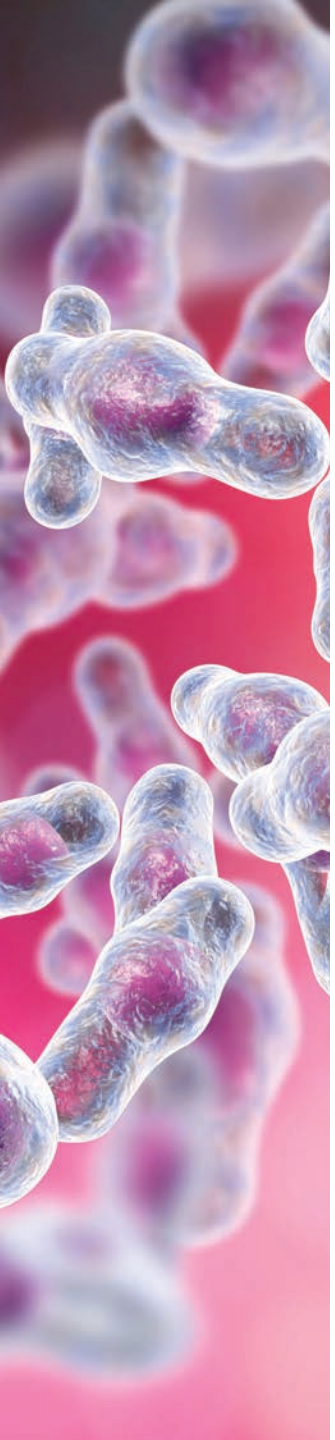
FMT vs LBP

	FMT	LBP
Donor screening	💩 💩	💩 💩 💩
Sample screening	?	💩 💩 💩



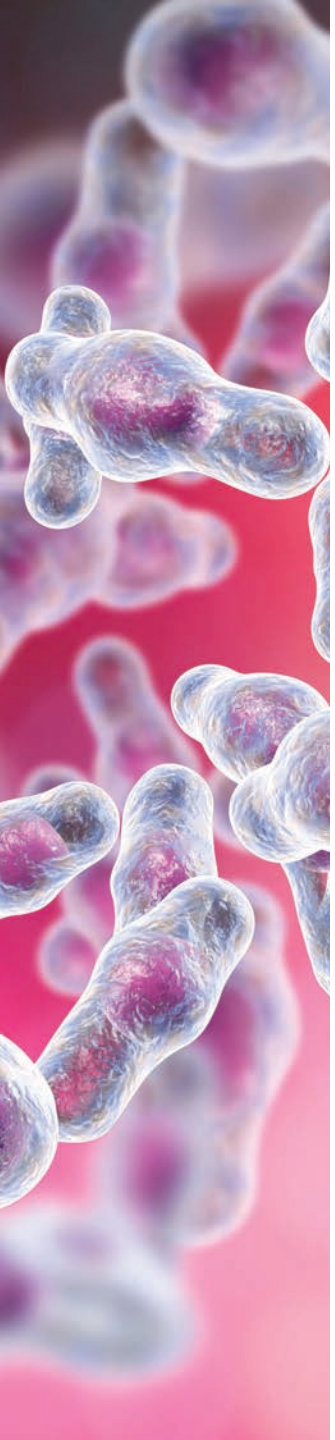
FMT vs LBP

	FMT	LBP
Donor screening	💩 💩	💩 💩 💩
Sample screening	?	💩 💩 💩
Good manufacturing practices	?	💩 💩 💩



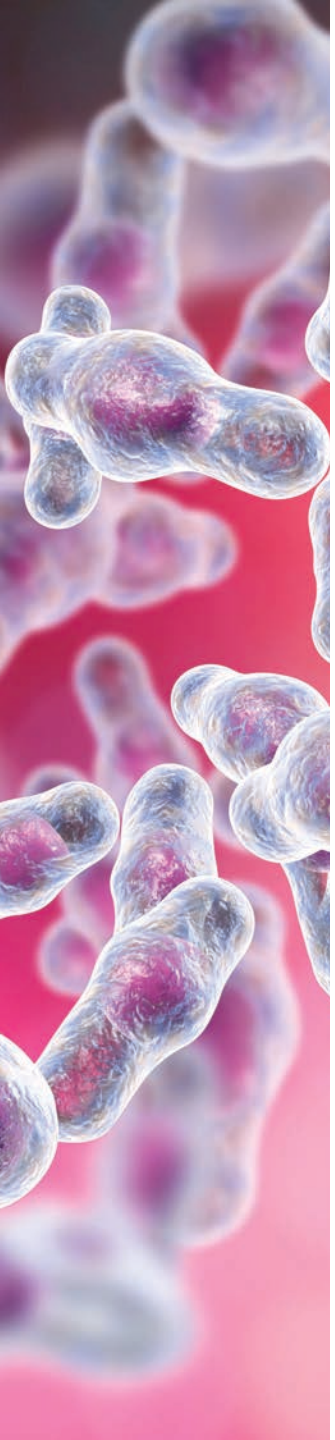
FMT vs LBP

	FMT	LBP
Donor screening	💩 💩	💩 💩 💩
Sample screening	?	💩 💩 💩
Good manufacturing practices	?	💩 💩 💩
Clinical trial data	💩	💩 💩 💩



FMT vs LBP

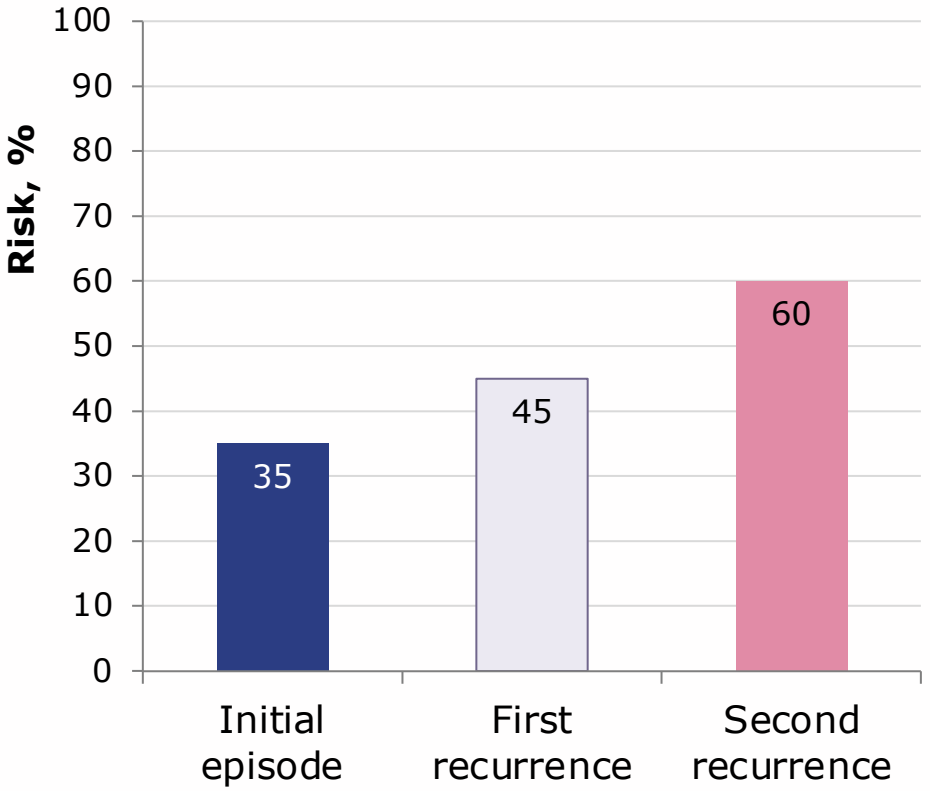
	FMT	LBP
Donor screening	💩 💩	💩 💩 💩
Sample screening	?	💩 💩 💩
Good manufacturing practices	?	💩 💩 💩
Clinical trial data	💩	💩 💩 💩
Safety data	💩 / 💩	💩 💩 💩



FMT vs LBP

	FMT	LBP
Donor screening	💩 💩	💩 💩 💩
Sample screening	?	💩 💩 💩
Good manufacturing practices	?	💩 💩 💩
Clinical trial data	💩	💩 💩 💩
Safety data	💩 / 💩	💩 💩 💩
Ease of access	?	💩

Episodes of CDI

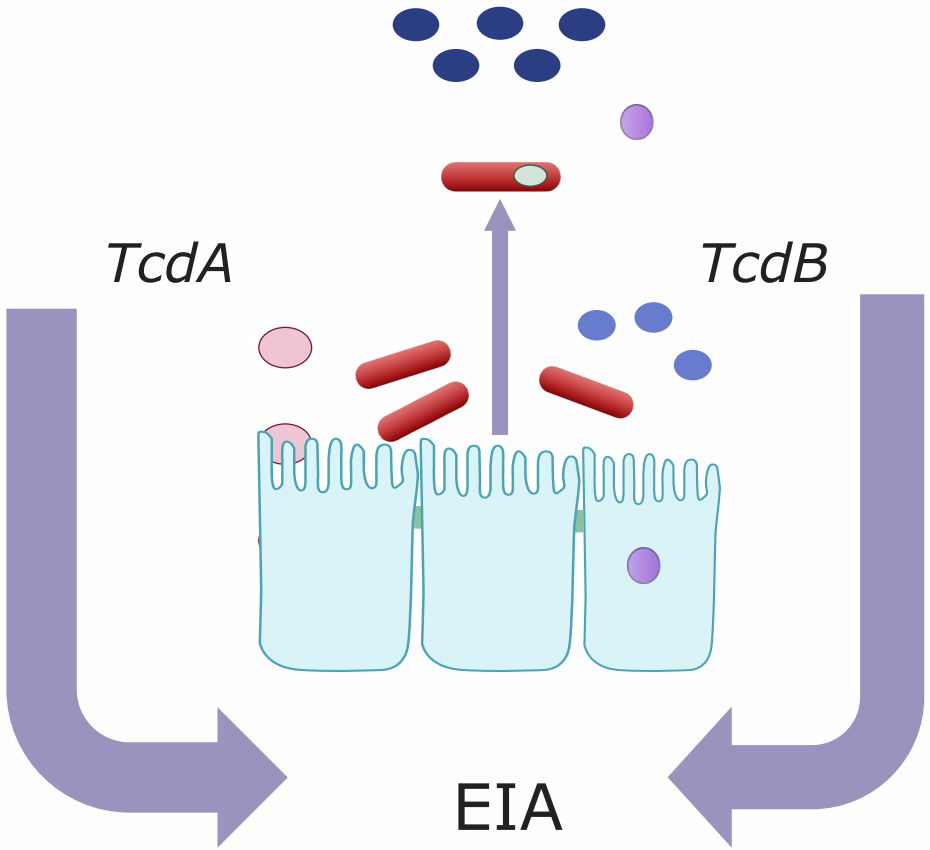


Risk for recurrence

- More episodes → more likely to recur in the future
- Does that translate to more difficulty restoring the microbiota?
- Is earlier restoration of the microbiota preferable?

McDonald LC, et al. *Clin Infec Dis*. 2018;66(7)e1-e48; McFarland LV, et al. *Am J Gastroenterol*. 2002;97(7):1769-1775; Pépin J, et al. *Clin Infect Dis*. 2005;40(11):1591-1597.

Why Is Diagnosis Important?

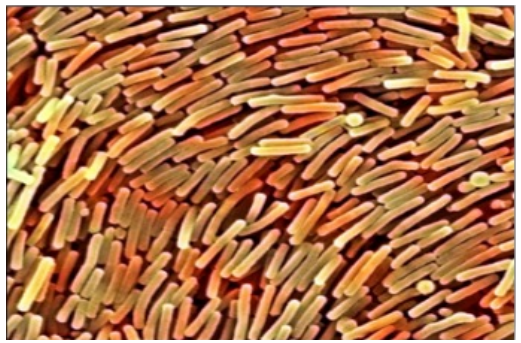


- EIA detects toxins but can have false-negative results
- PCR detects the genes coding for toxins but not toxin production
- PCR is the most commonly used test in the United States, accounting for ~80% of all tests
- **Issue:** PCR frequently over-diagnoses CDI and, if not combined with other clinical considerations, can result in patients with other diagnoses being treated and not responding

EIA, enzyme-linked immunoassay.

Duration of SOC Antimicrobial

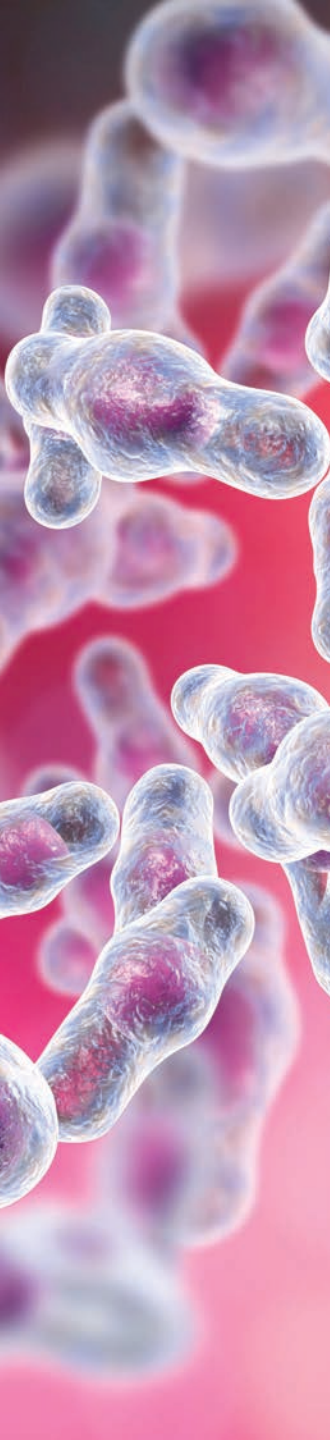
Fidaxomicin
Vancomycin
Metronidazole



Vegetative phase

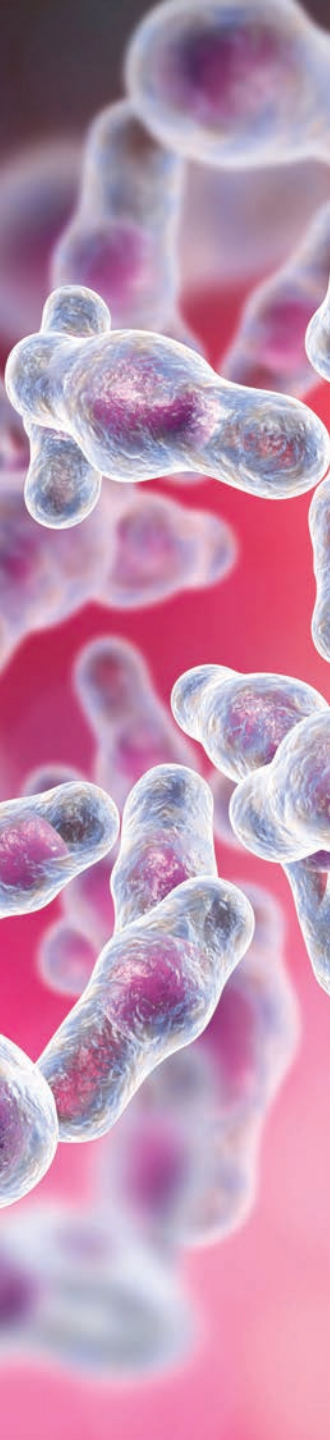
- Longer is not necessarily better
- Optimal duration before intervention is unclear, but standard treatment of ≥10 d is believed to be the minimum
- **Goal:** Suppress the vegetative phase sufficiently to:
  - Control symptoms
  - Offer the body the opportunity to replenish the microbiota to suppress the spore phase
  - Restore the microbiota rapidly to prevent recurrence

SOC, standard of care.



Washout Period

- Time from completion of SOC antimicrobial to administration of LBP
- Minimize effects of SOC antimicrobial on the administrated microbial species
- Goals
  - Clear as much of the antimicrobial from the patient's system as possible
  - Do not offer *C. difficile* the opportunity to regerminate and recur
- Optimal timing is unclear



Trial Design Overview

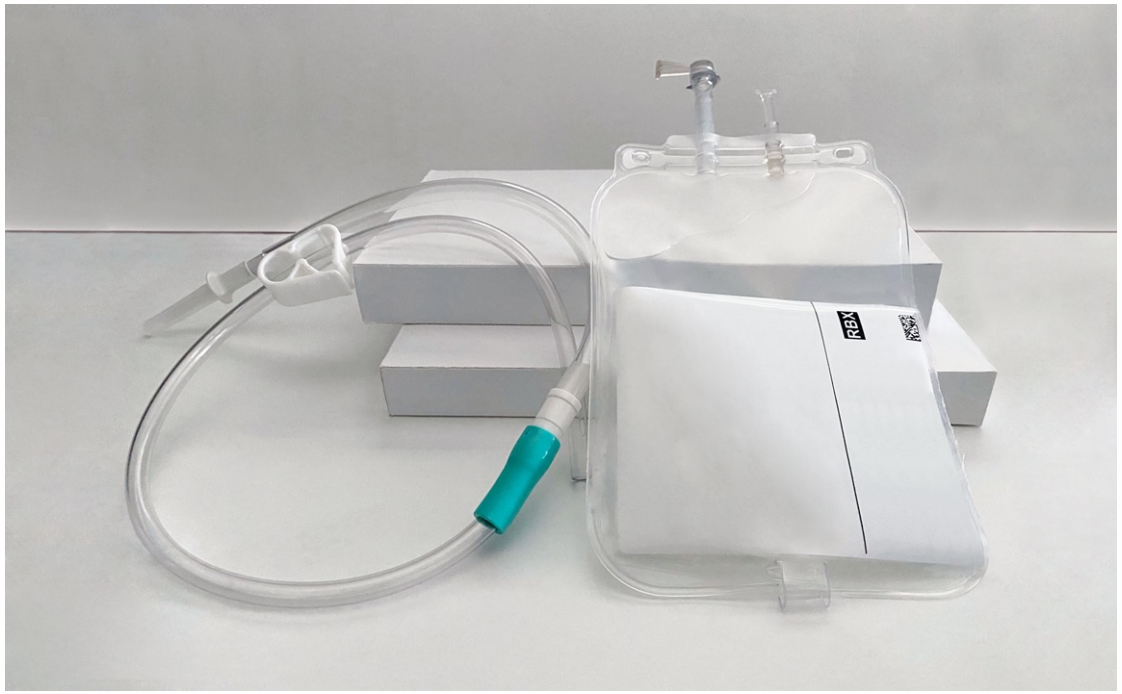
SOC Antimicrobial

Intervention

Placebo

Fecal Microbiota, Live-jslm (Rebyota™, [RBL])

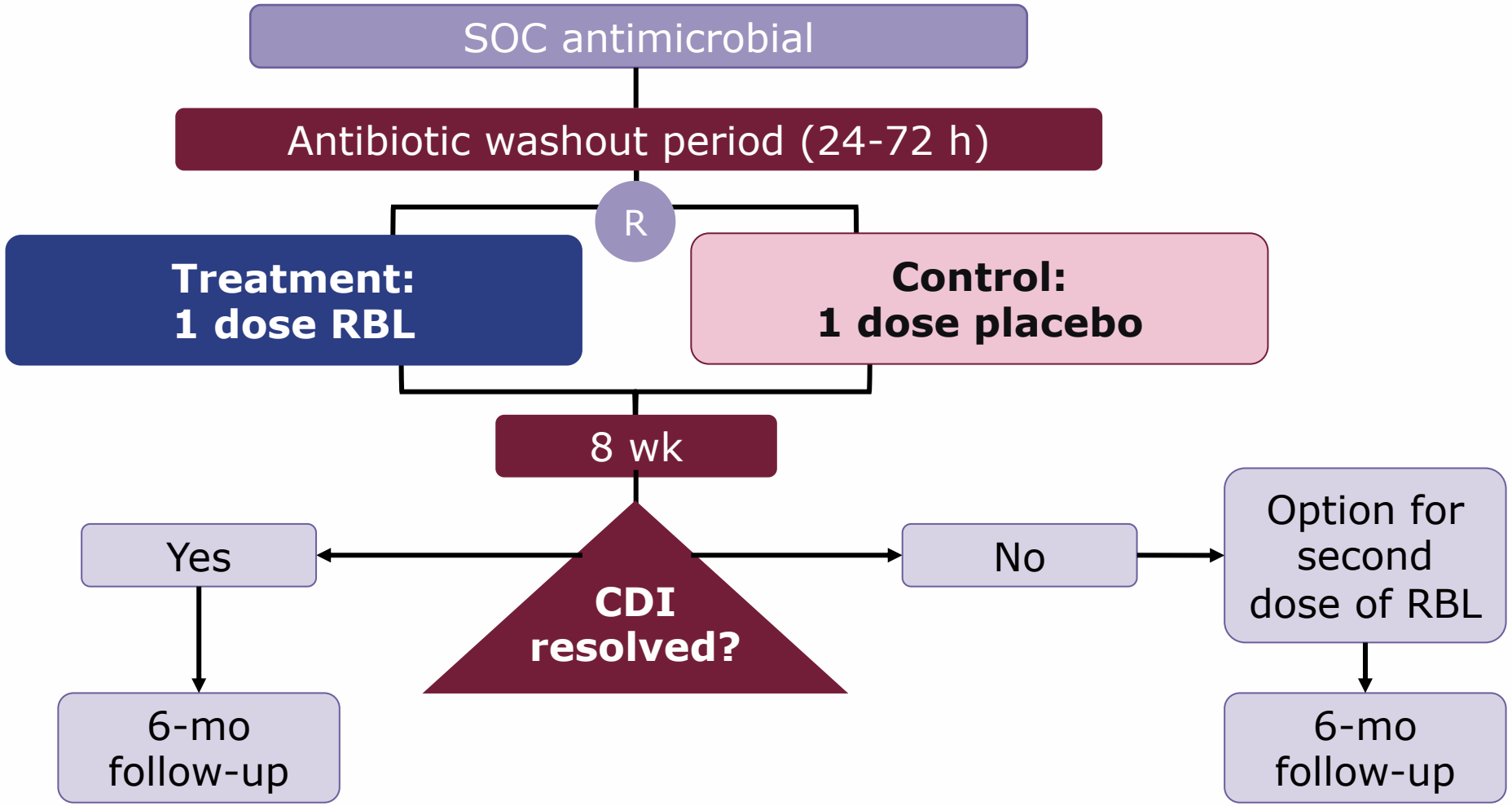
- Single-dose, microbiota-based LBP
- Rectally administered
- 150 mL of therapeutic material
- 10^7 microbes/mL or 15×10^8 microbes per treatment
- Broad consortium



- Proprietary manufacturing process preserves diverse spore-forming and non–spore-forming bacteria, including *Bacteroides*

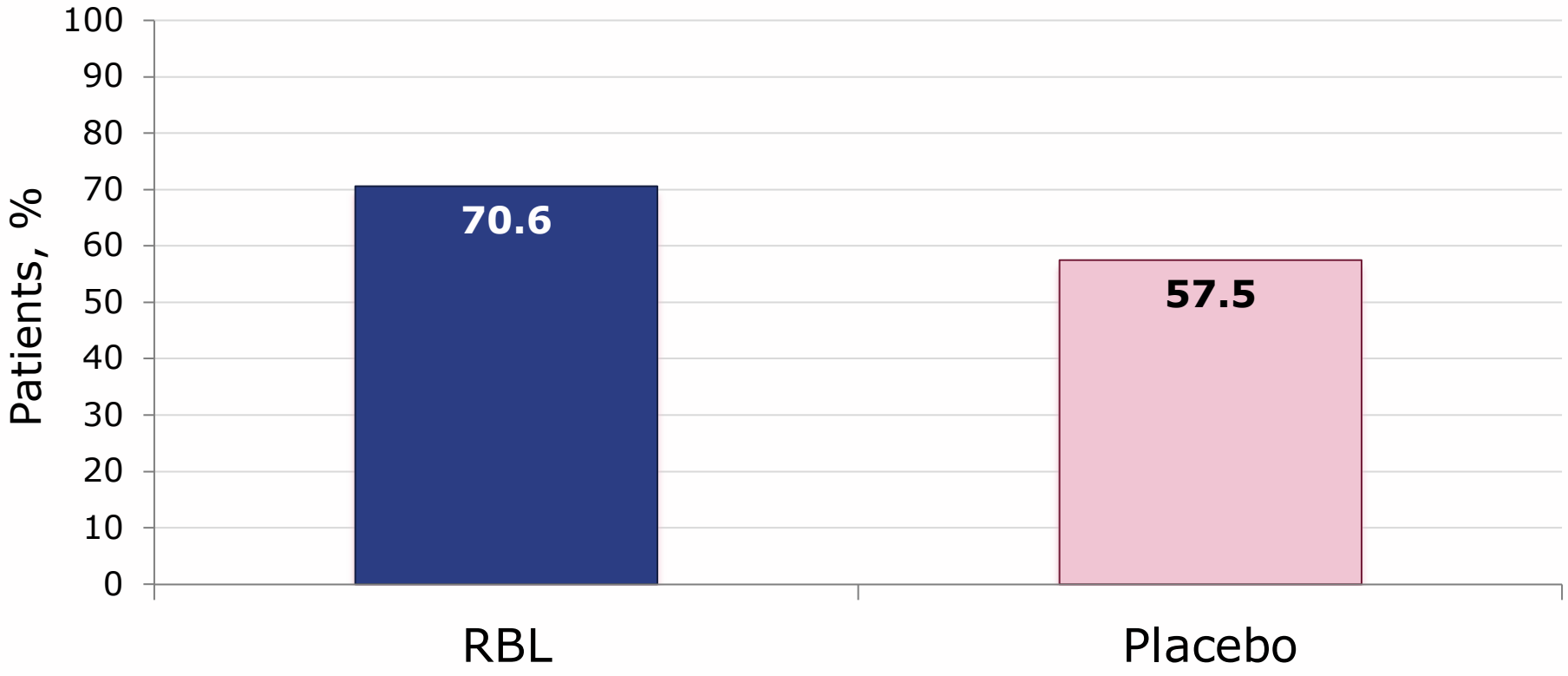
Rebyota (donor human stool suspension) prescribing information. Roseville, MN: Ferring Pharmaceuticals; Nov 2022; Blount KF, et al. *Open Forum Infect Dis*. 2019;6(4):ofz095; Orenstein R, et al. *Clin Infect Dis*. 2016;62(5):596-602; Ray A, Jones C. *Future Microbiol*. 2016;11:611-616.

PUNCH-CD3: Phase 3 Trial Design



Rebyota (donor human stool suspension) prescribing information. Roseville, MN: Ferring Pharmaceuticals; Nov 2022;
Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

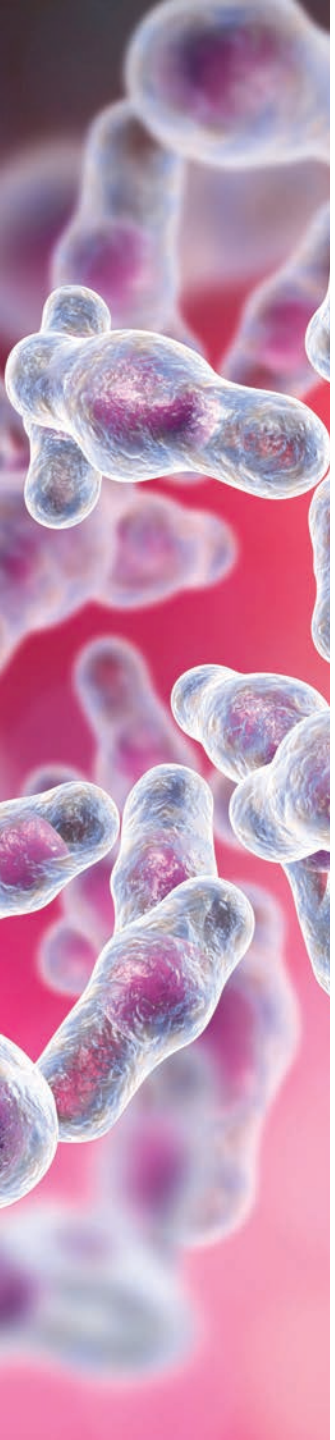
PUNCH-CD3: RBL Superior to Placebo



Bayesian analysis

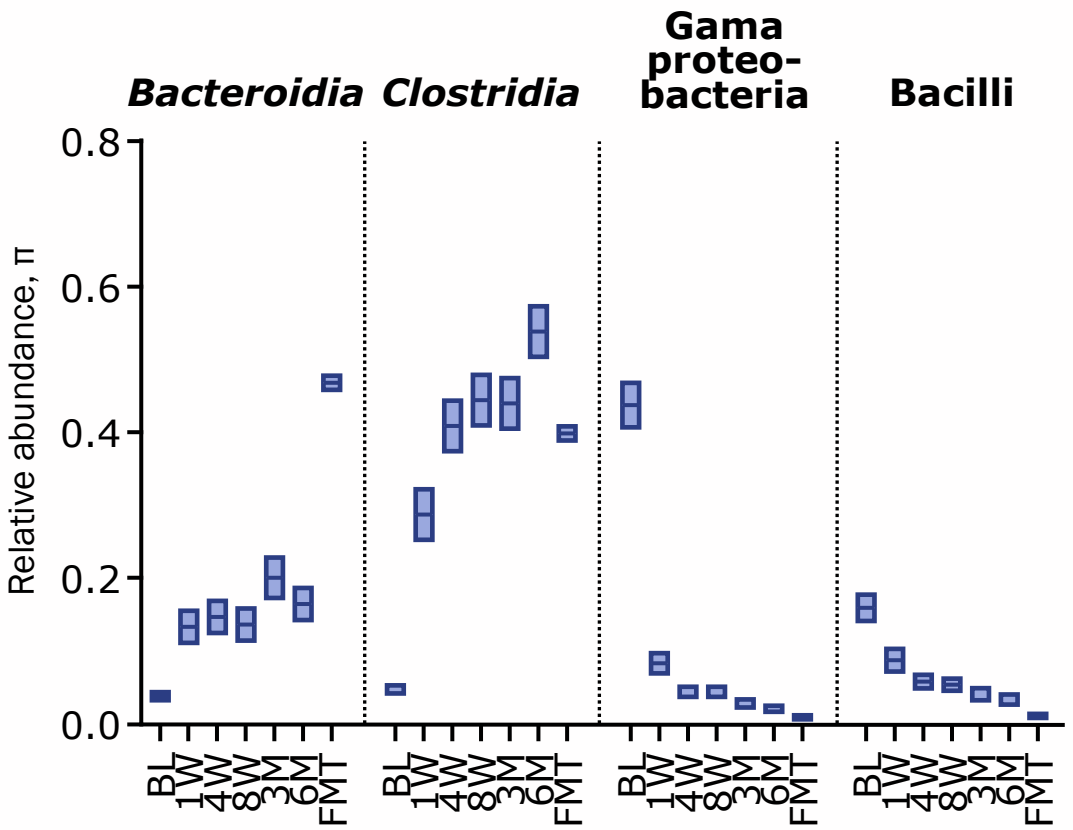
Posterior probability of superiority: 0.991

Rebyota (donor human stool suspension) prescribing information. Roseville, MN: Ferring Pharmaceuticals; Nov 2022;
Khanna S, et al. *Drugs*. 2022;82(15):1527-1538.

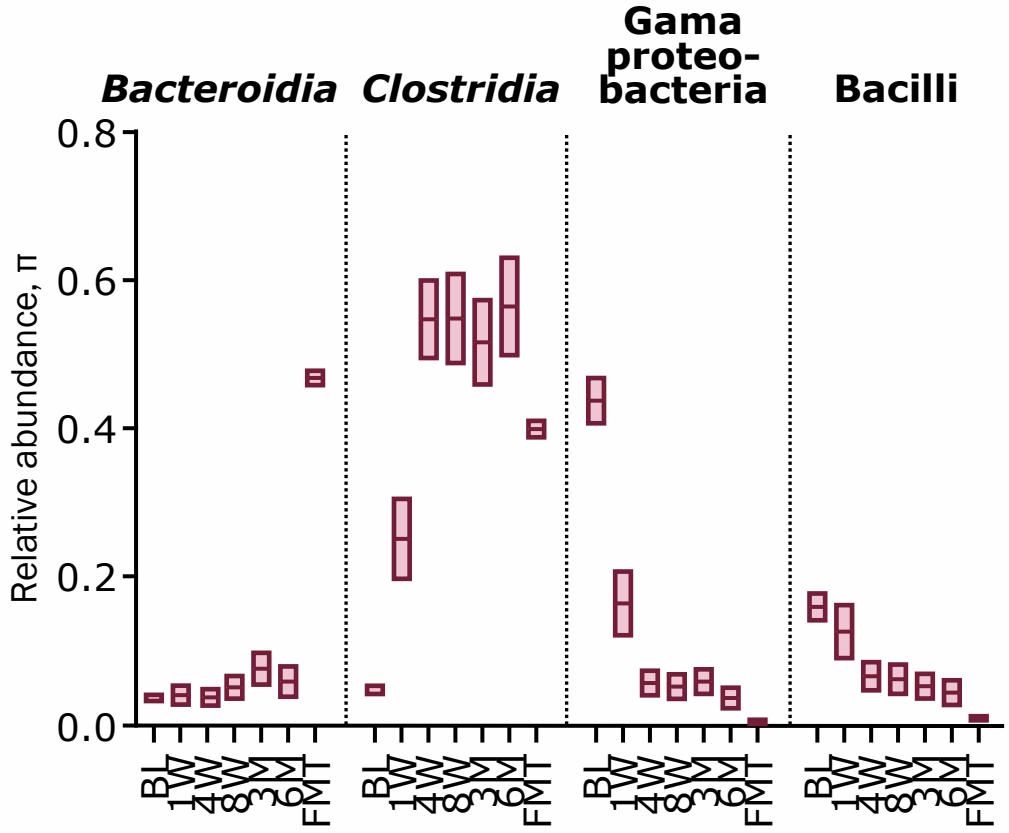


PUNCH-CD3: Microbiota Response

RBL-treated responders

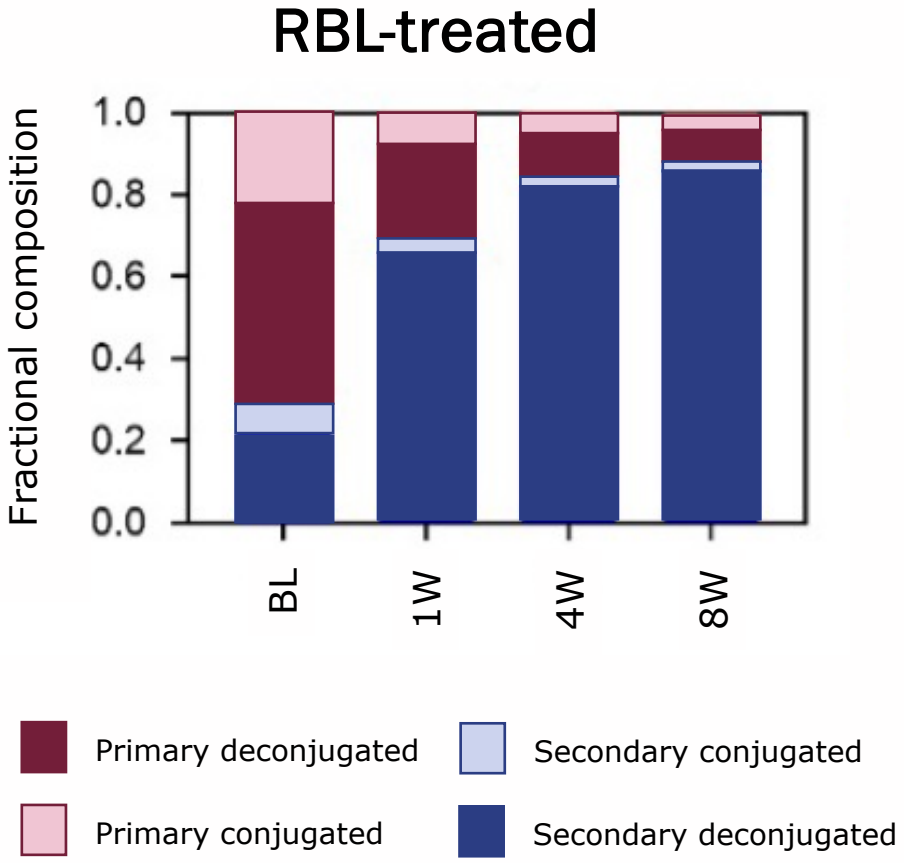


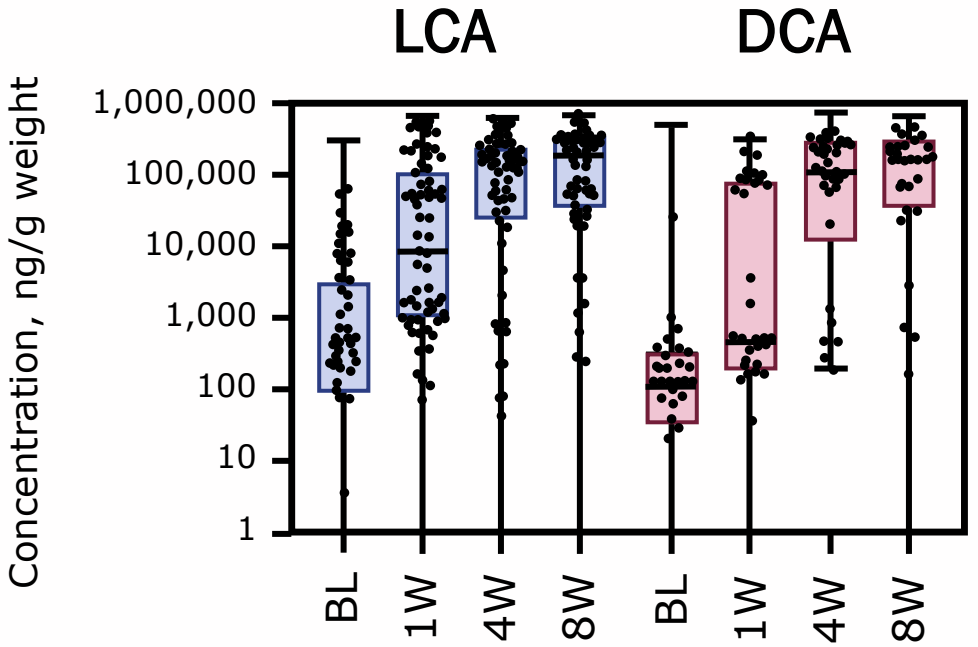
Placebo-treated responders



Lee C, et al. Presented at: DDW 2021; session 2155; Blount K, et al. Presented at: IDSA 2021; abstract 1064.

RBL Restoration of Bile Salt Milieu

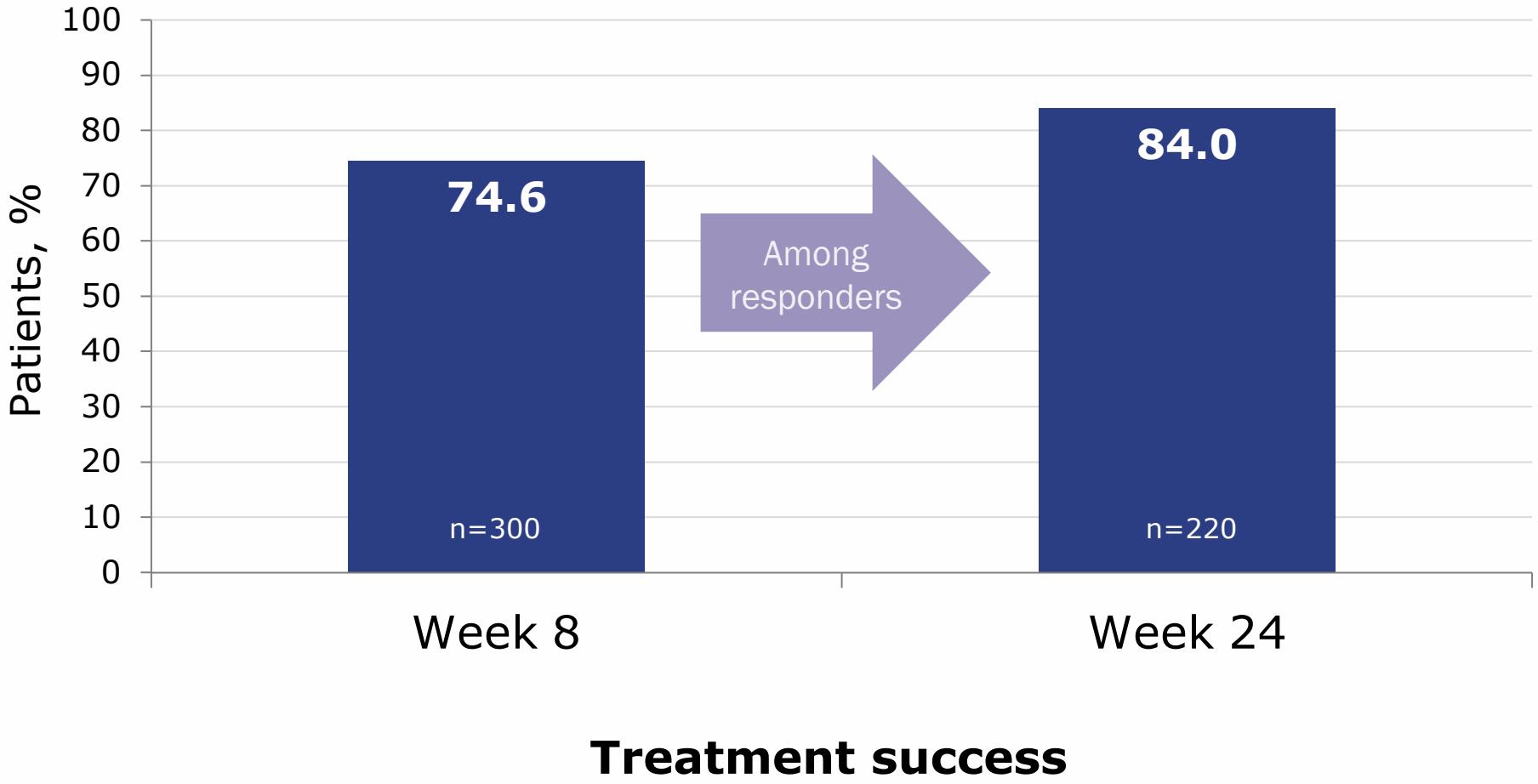




DCA, deoxycholic acid; **LCA,** lithocholic acid.

Papazyan R, et al. Presented at: ID Week 2021; abstract 1039.

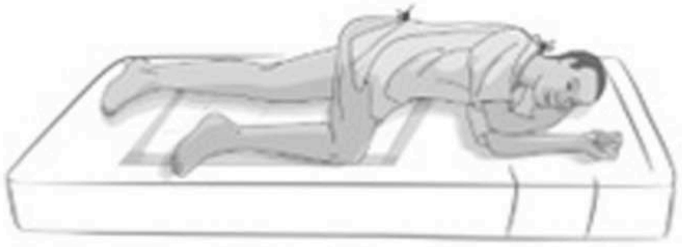
RBL Open-Label Study



Khanna S, et al. Presented at: ACG 2022; abstract 56.

RBL Administration

2 patient positions

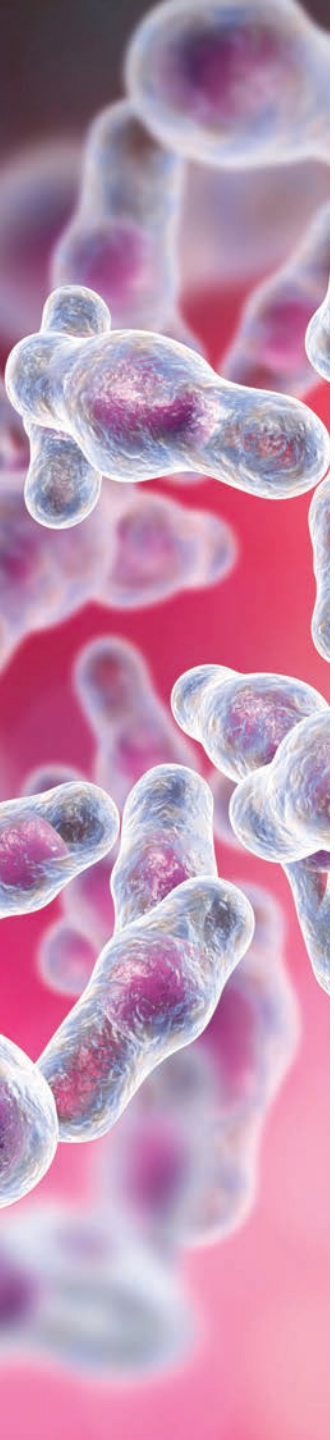


Left-side position: Lie on left side with knee bent and arms resting comfortably

OR

Knee-chest position: Kneel, then lower head and chest forward until left side of face is resting on surface with left arm folded comfortably

Rebyota (donor human stool suspension) prescribing information. Roseville, MN: Ferring Pharmaceuticals; Nov 2022.



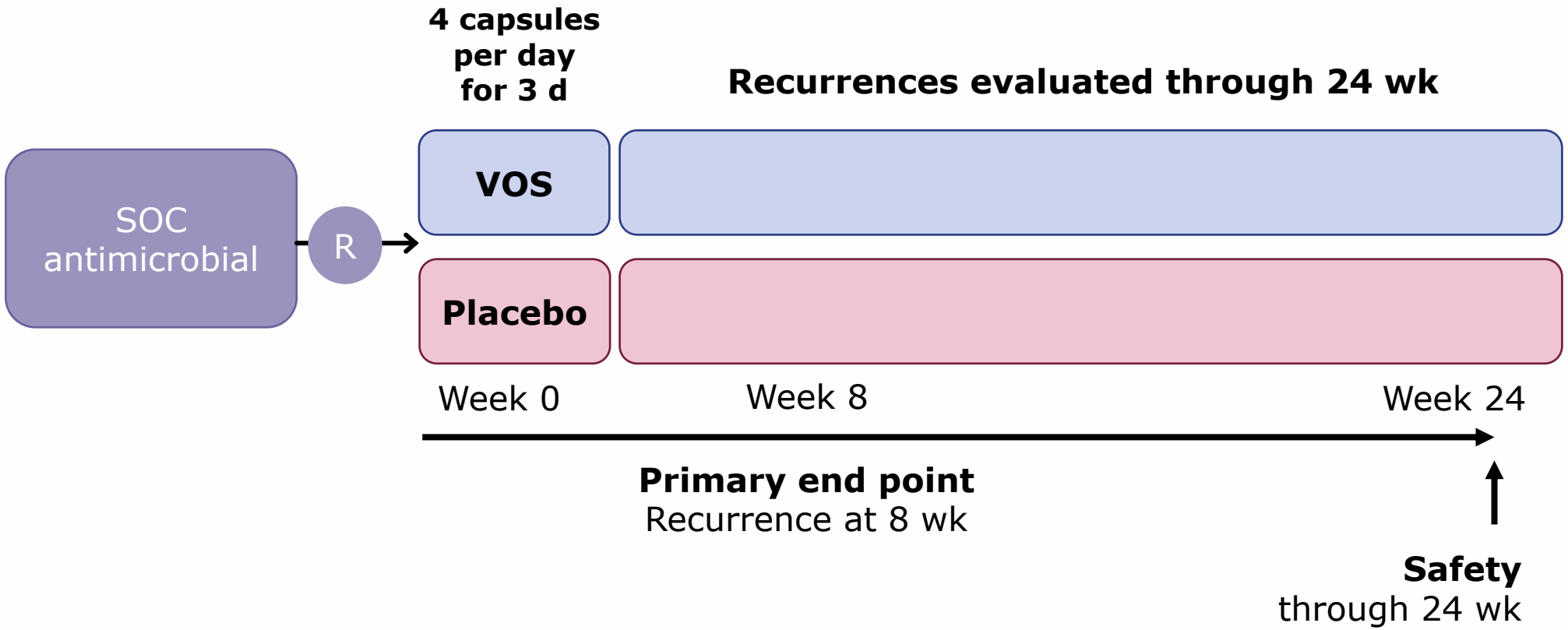
Fecal Microbiota Spores, Live-brpk (Vowst™, [VOS])

- Microbiota-based LBP
- PO administration
  - 4 capsules per day for 3 d
- 3×10^7 CFU per full treatment
- Narrow consortium
- Proprietary manufacturing process
  - Removes most fungi, parasites, viruses, and non–spore-forming bacteria
  - Results in predominantly *Firmicutes* spores

CFU, colony-forming unit.

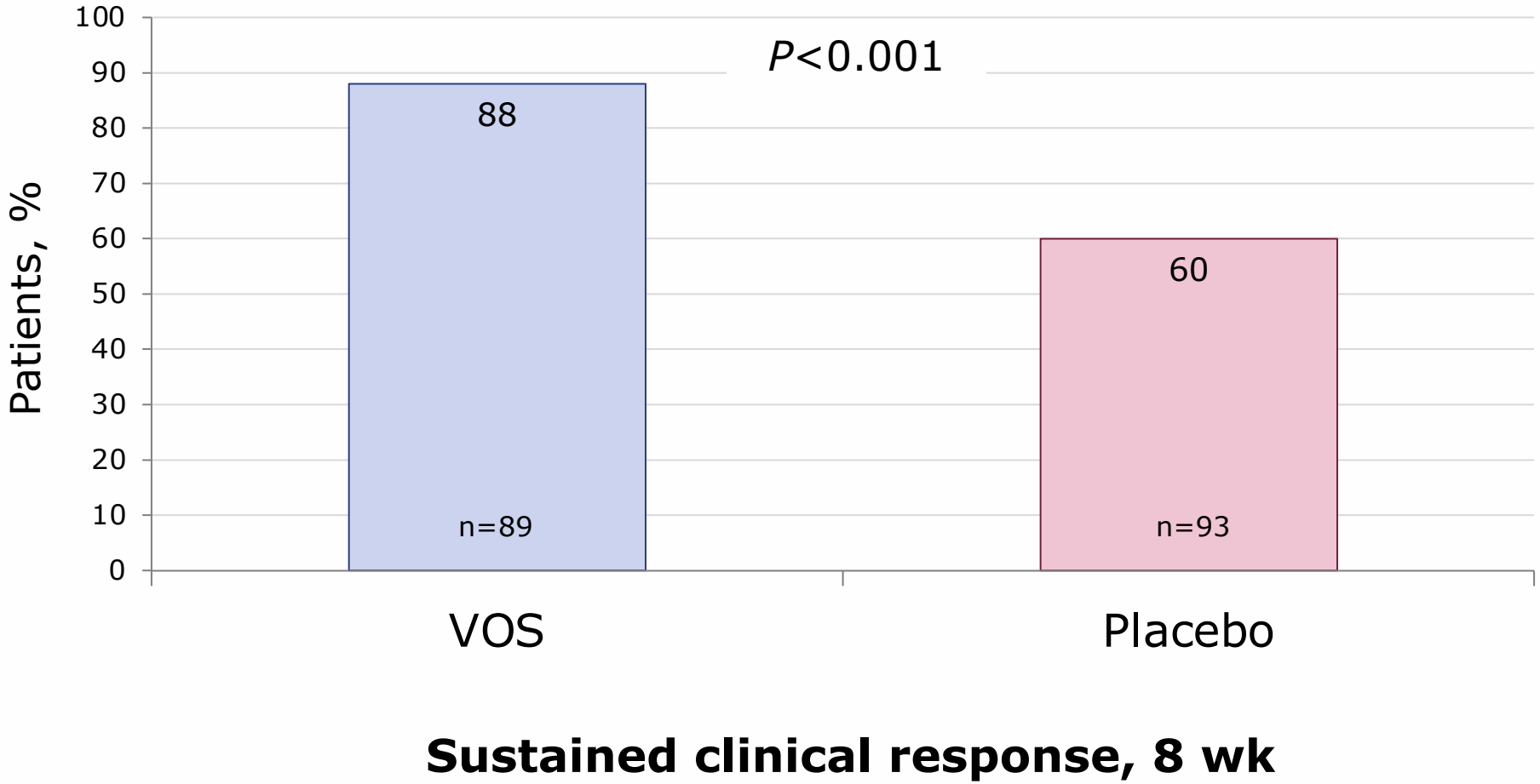
Vowst (fecal microbiota spores, live-brpk) prescribing information. Cambridge, MA: Seres Therapeutics; Apr 2023.
Feuerstadt P, et al. *N Engl J Med*. 2022;386(3):220-229.

ECOSPOR-III: Phase 3 Trial Design



Feuerstadt P, et al. *N Engl J Med*. 2022;386(3):220-229; Korman L, et al. Presented at: AGA 2021; abstract Fr572.

ECOSPOR-III: VOS superior to Placebo

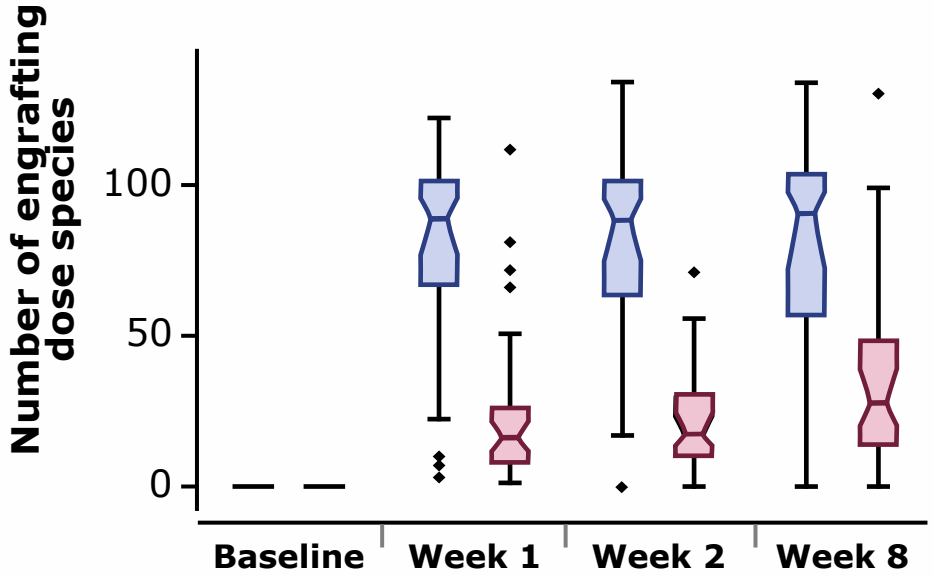


Sustained clinical response, 8 wk

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

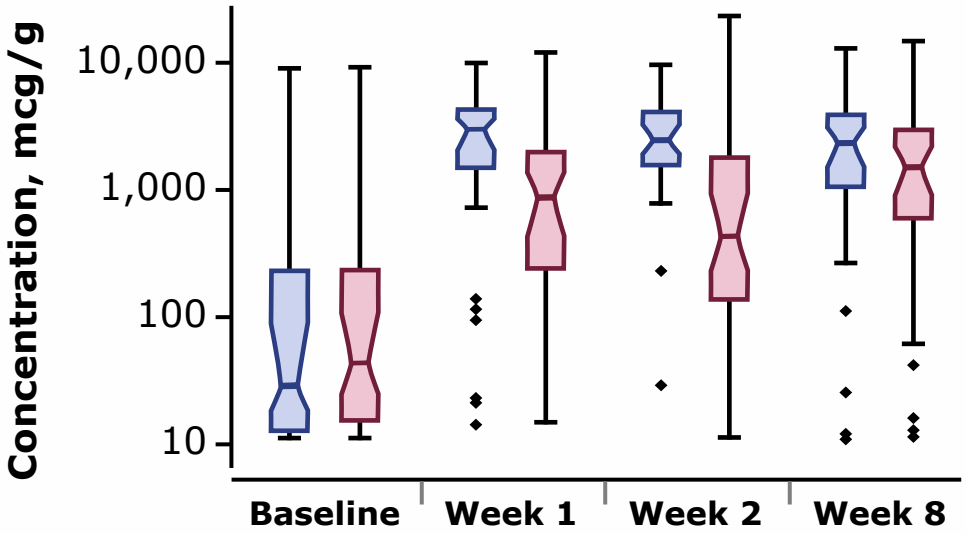
ECOSPOR-III: Compositional and Metabolomic Changes

Engraftment of VOS species



	Baseline	Week 1	Week 2	Week 8
VOS (n)	74	66	60	66
Placebo (n)	79	69	64	56

Concentration of secondary BAs



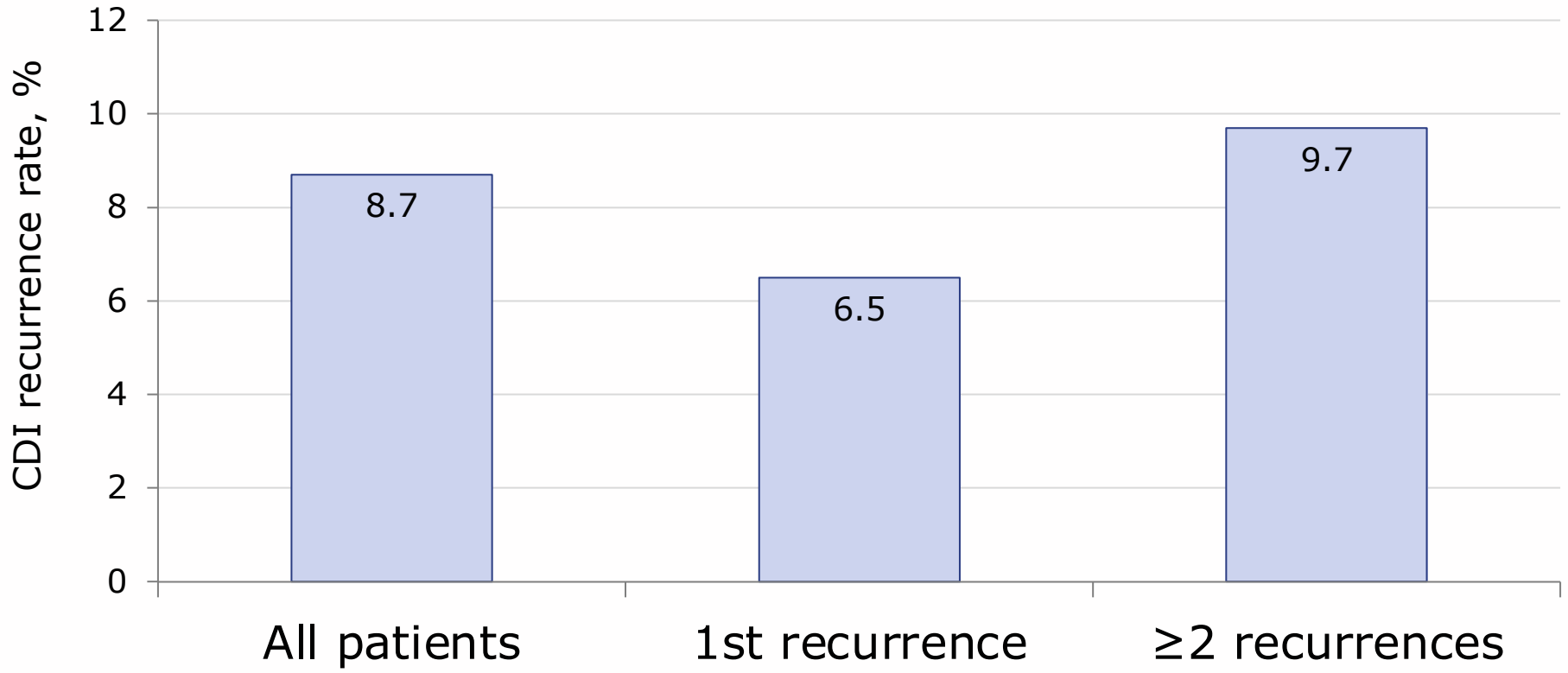
	Baseline	Week 1	Week 2	Week 8
VOS (n)	76	69	62	65
Placebo (n)	77	67	64	55

VOS

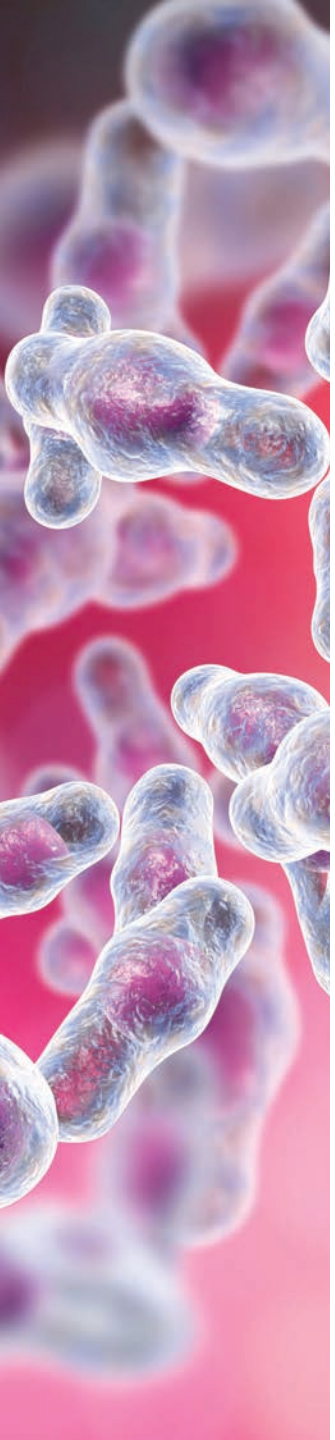
Placebo

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

ECOSPOR IV: 8-Wk, Open-Label Study



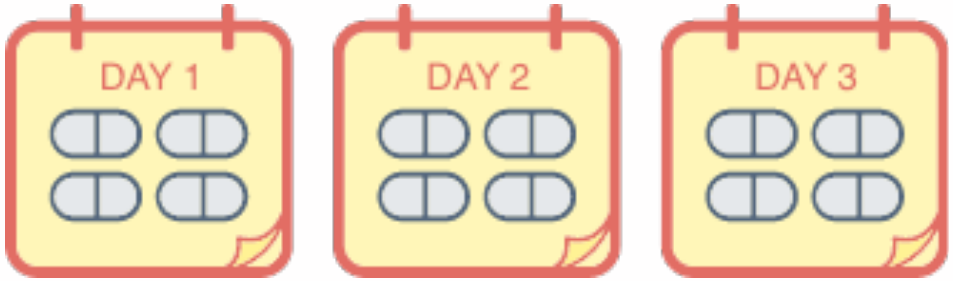
Sims MD, et al. *JAMA Netw Open*. 2023;6(2):e2255758.



VOS Administration

- Before dosing
  - Finish antimicrobials for CDI 2-4 d before starting
  - Patient should drink 10 oz magnesium citrate 1 d or ≥8 h before taking first dose
  - Consider 250 mL PEG-based bowel cleansing product for patients with renal impairment

- Dosing
  - Taken on empty stomach before first meal of day
  - 4 capsules daily for 3 d
  - No refrigeration needed

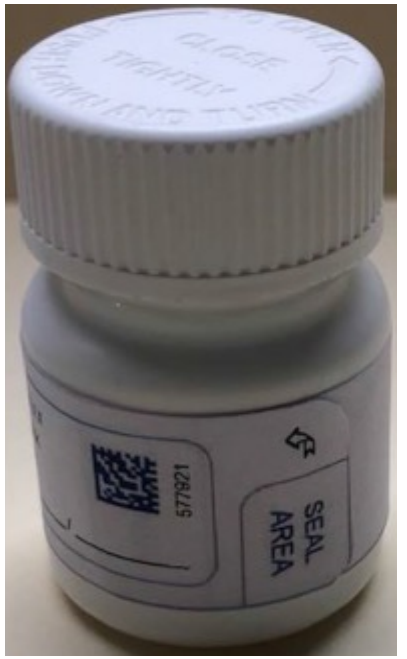


PEG, polyethylene glycol.

Vowst (fecal microbiota spores, live-brpk) prescribing information. Cambridge, MA: Seres Therapeutics; Apr 2023.

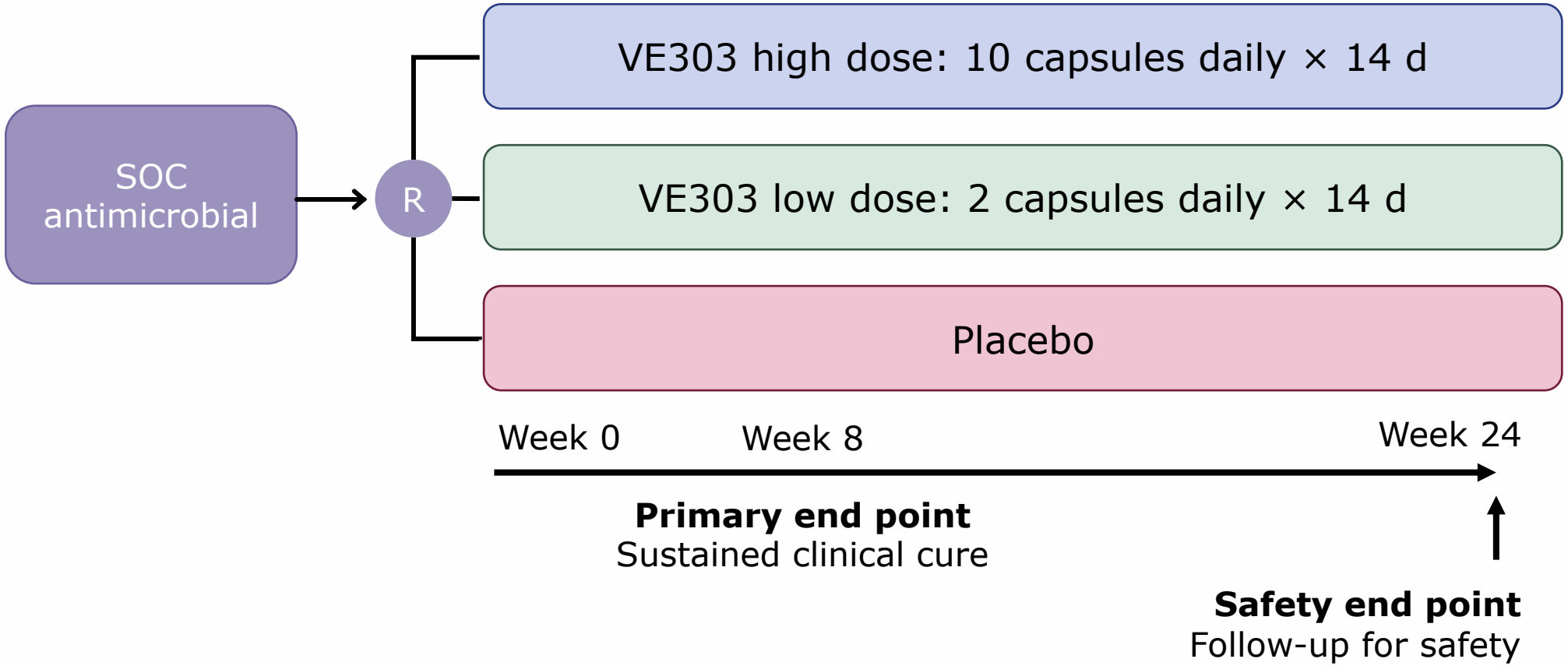
VE303

- PO
- High dose: 10 capsules daily for 14 d
- 1.1×10^{11} CFU total
- Defined consortium with 8 specific bacterial species originally derived from healthy human intestinal microbiomes



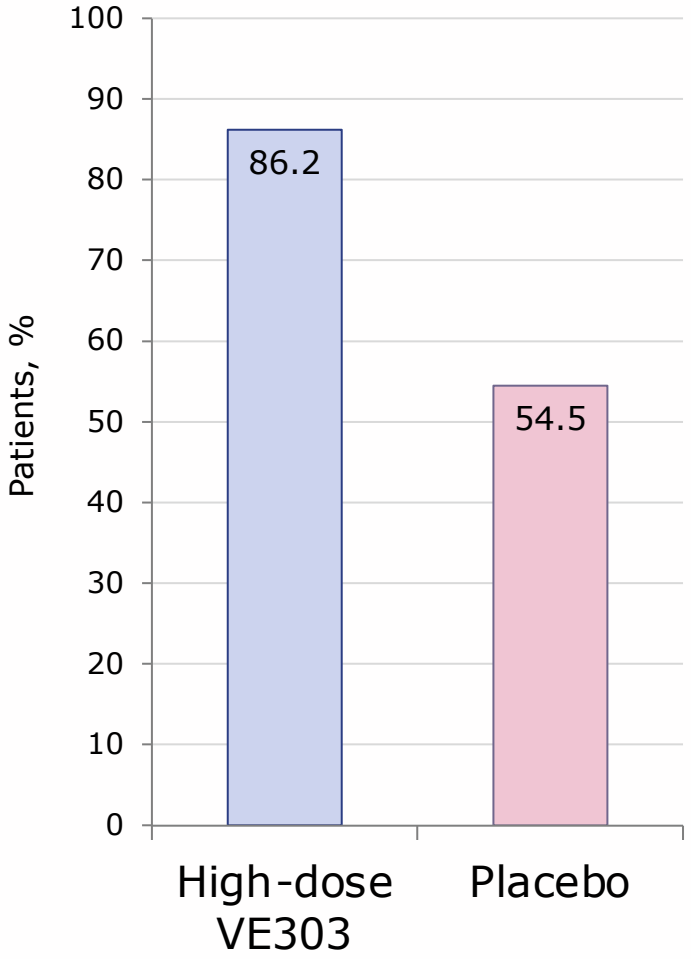
Louie T, et al. *JAMA*. 2023;329(16):1356-1366.

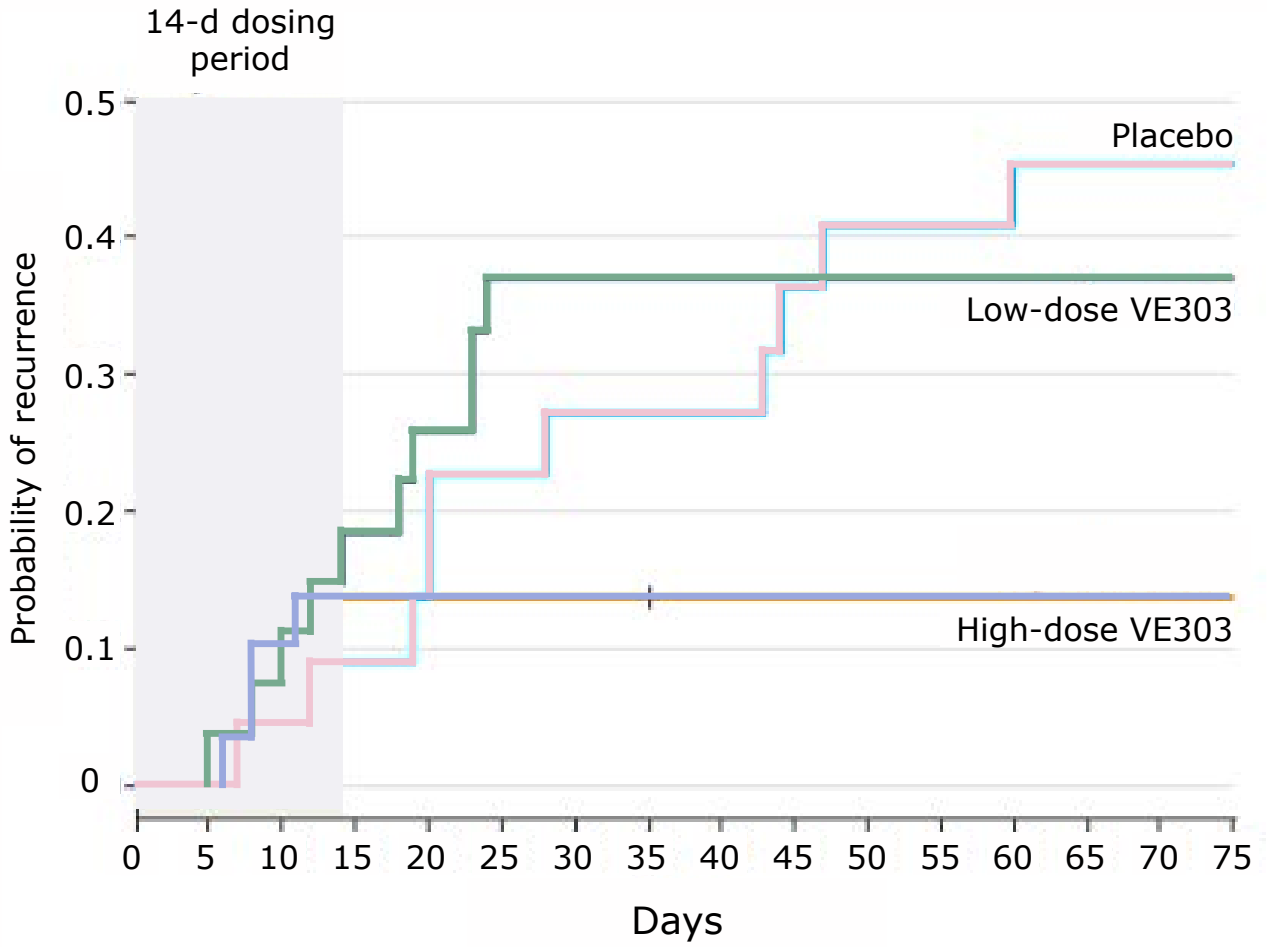
CONSORTIUM: Phase 2 Trial Design



Louie T, et al. *JAMA*. 2023;329(16):1356-1366.

Consortium: High-Dose VE303 vs Placebo, 8 wk



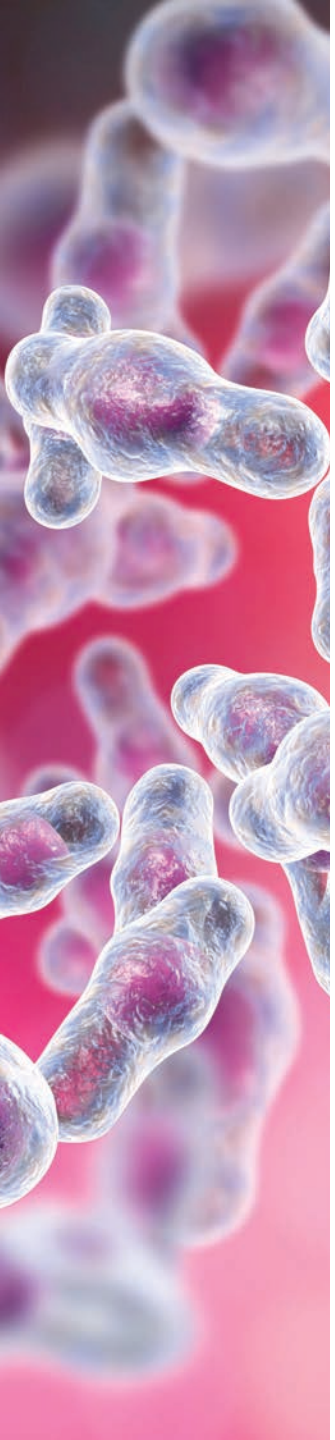


Louie T, et al. *JAMA*. 2023;329(16):1356-1366.

Conversation About LBPs

- **Introduce** MRT
  - What it is
  - Why it helps decrease recurrence
- **Describe** both LBPs
  - RBL and VOS
  - Different administration
  - No formal informed consent required
- **Discuss** potential side effects
  - Diarrhea, distension, flatulence, bloating, abdominal pain

MRT, microbiome rejuvenation therapy.



Treatment Algorithm

1st episode

- Vancomycin 125 mg PO 4 times daily × 10-14 d
- Fidaxomicin 200 mg PO twice daily × 10 d

2nd episode

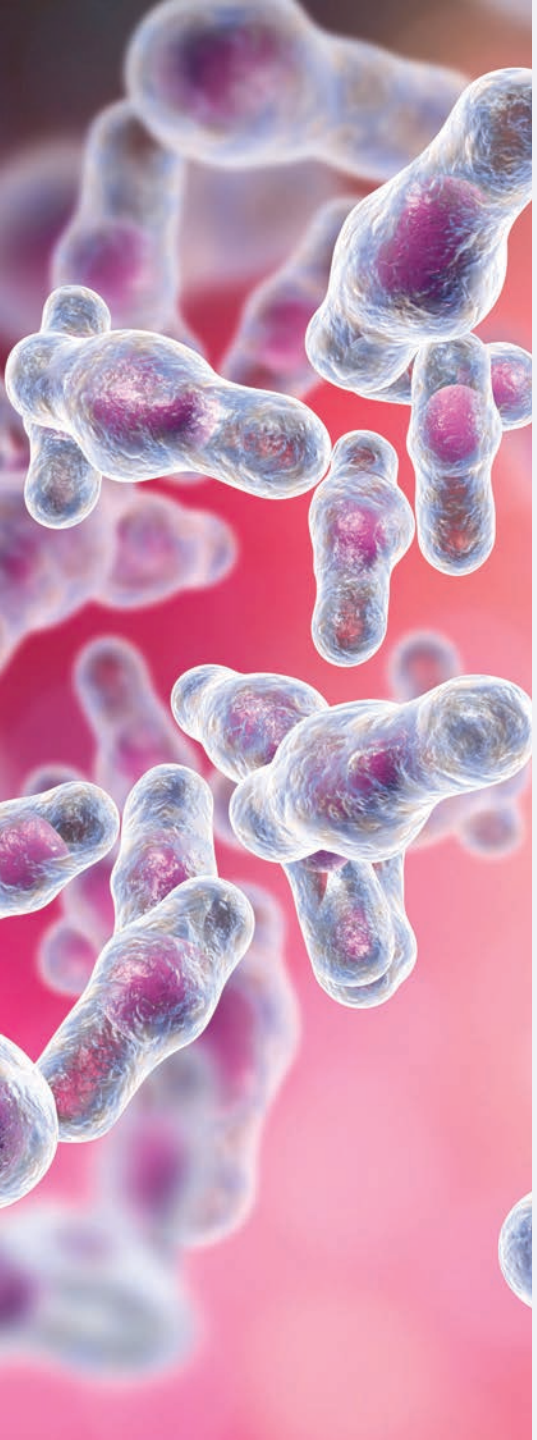
Vancomycin taper >6 wk with either pulse of vancomycin or fidaxomicin "chaser"
or fidaxomicin 200 mg PO twice daily × 10 d
or fidaxomicin 200 mg PO twice daily × 5 d
followed by once daily on days 7-25

3rd episode

Standard antimicrobial course + LBP

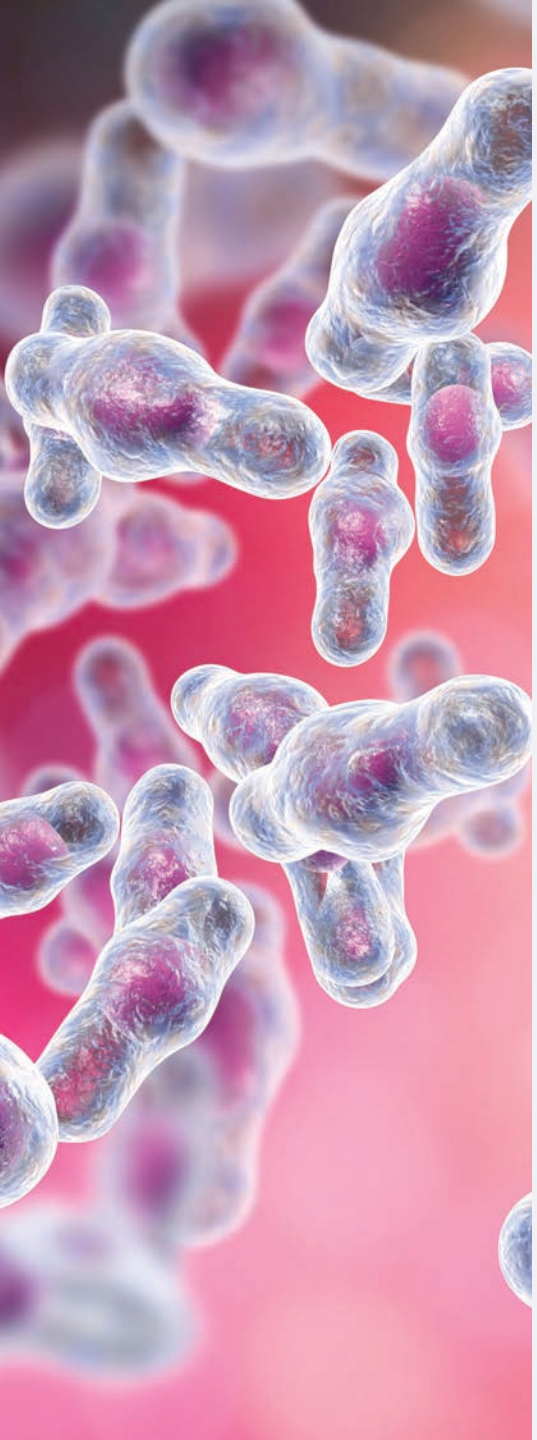
>2 risk factors for recurrence

- Bezlotoxumab
- Bezlotoxumab or LBP
- LBP



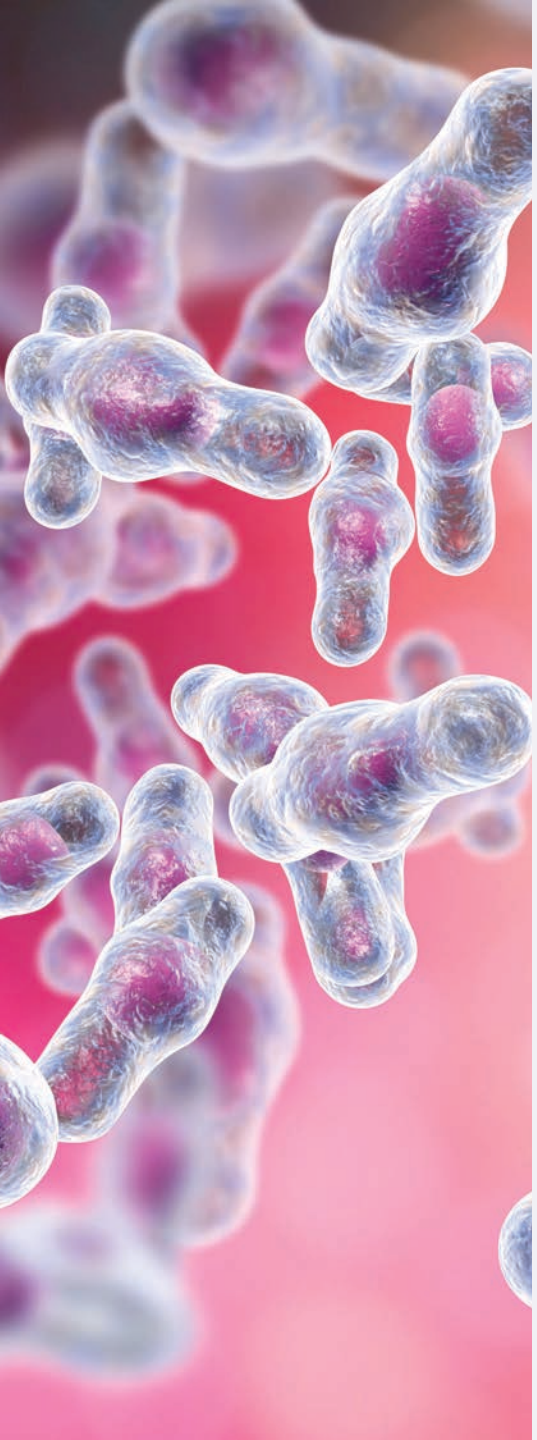
Case: Lorraine Returns

- Recall Loraine's case
  - First recurrence 2 mo after initial CDI, treated with **vancomycin** 125 mg PO daily for 10 d
  - Second recurrence 1 mo later, treated with **fidaxomicin** 200 mg PO twice daily for 10 d
- Lorraine responds initially, but 6 wk later, her symptoms return: 6 liquid (Bristol 7) bowel movements daily
  - No recent travel
  - No recent sick contacts
  - No eating of new foods
  - No recent other medications/antimicrobials



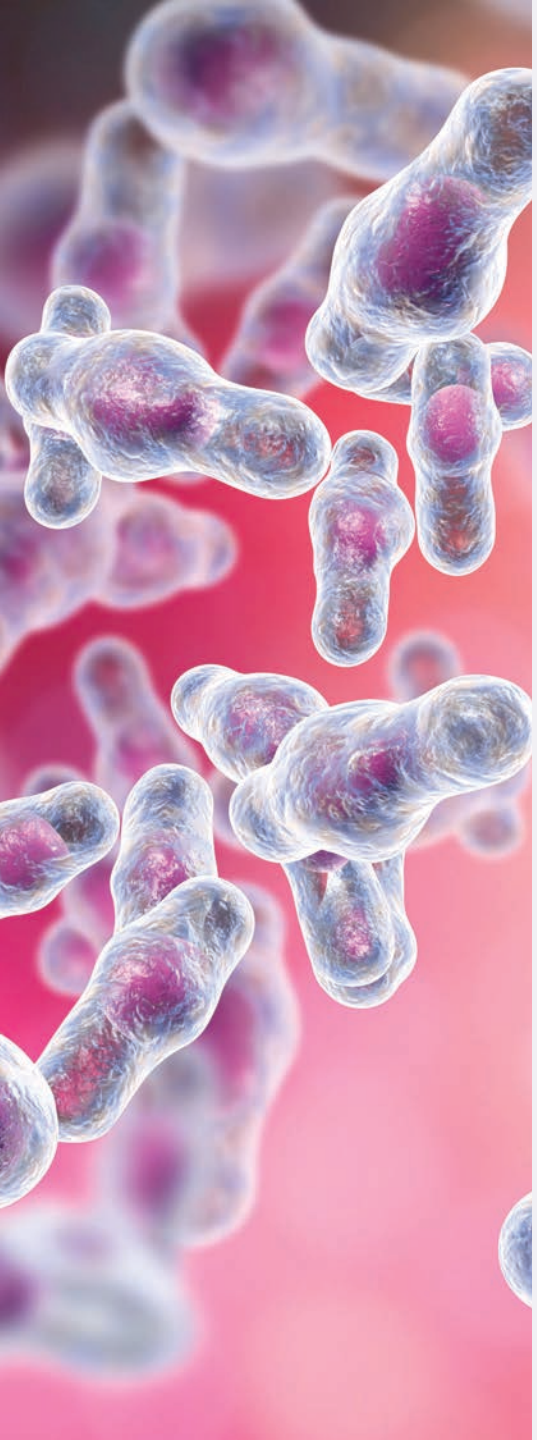
Case: Treatment for rCDI

- How would you consider treating Lorraine?
  - A. Vancomycin in a taper-and-pulse regimen for >6 wk
  - B. Fidaxomicin 200 mg twice daily for 5 d, followed by 200 mg every other day on days 7-25
  - C. LBP alone
  - D. Fidaxomicin 200 mg twice daily for 10 d, followed by LBP



Case 2: Sheila

- 58-year-old woman with Crohn's disease, well controlled on vedolizumab, presents with >10 watery stools (Bristol, 6/7) per day for 4 d
  - Normally has 3-4 Bristol 4-5 stools per day
  - Recently given amoxicillin-clavulanate for a presumed flare of diverticulitis
- GI pathogen PCR panel is positive for *C. difficile* toxin B
- You prescribe PO vancomycin 125 mg 4 times daily for 10 d



Case 2: Sheila's Risk for Recurrence

- Sheila worries that the *C. difficile* diarrhea will return; she has friends who ended up in the ICU with recurrent disease. Which of the following would you tell Sheila about her risk for rCDI?

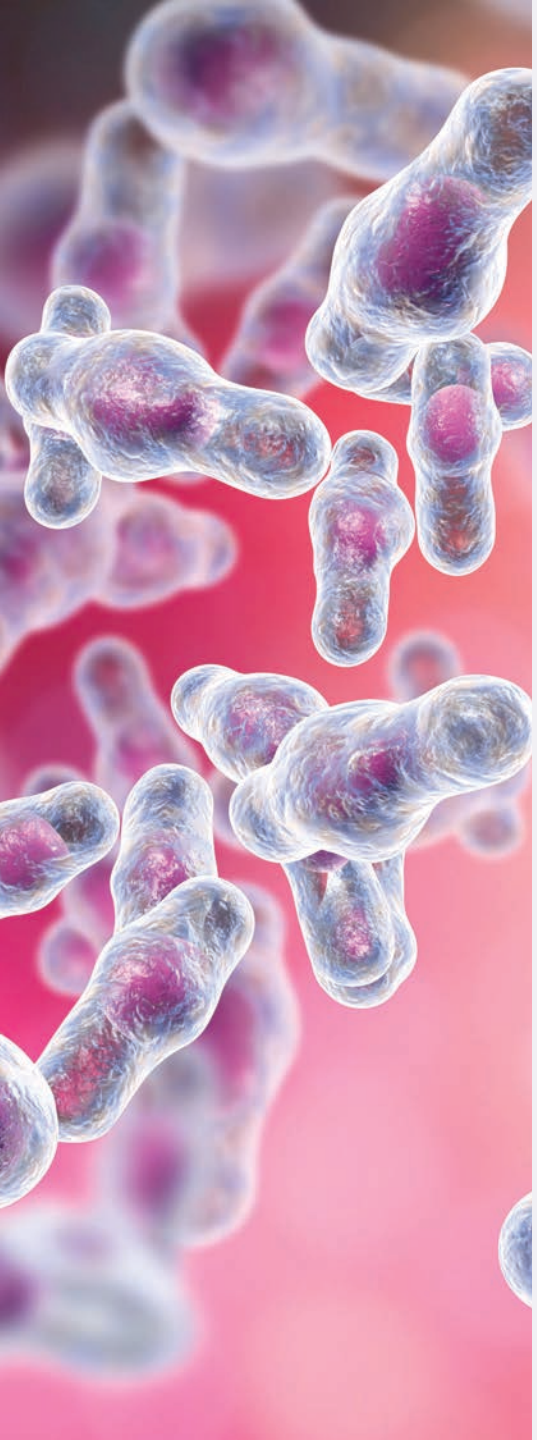
  A. Her risk for recurrence can be reduced by taking a probiotic

  B. The window for vulnerability to recurrence is ~21 d

  C. The vancomycin she has taken will reduce her risk for recurrence

  D. A microbiome stool analysis will show predominately Firmicutes

POST-TEST



Post-Test Question 1 (of 4)

Which of the following most affects the microbiota, leaving patients at the greatest risk for CDI and rCDI?

A. Advanced age

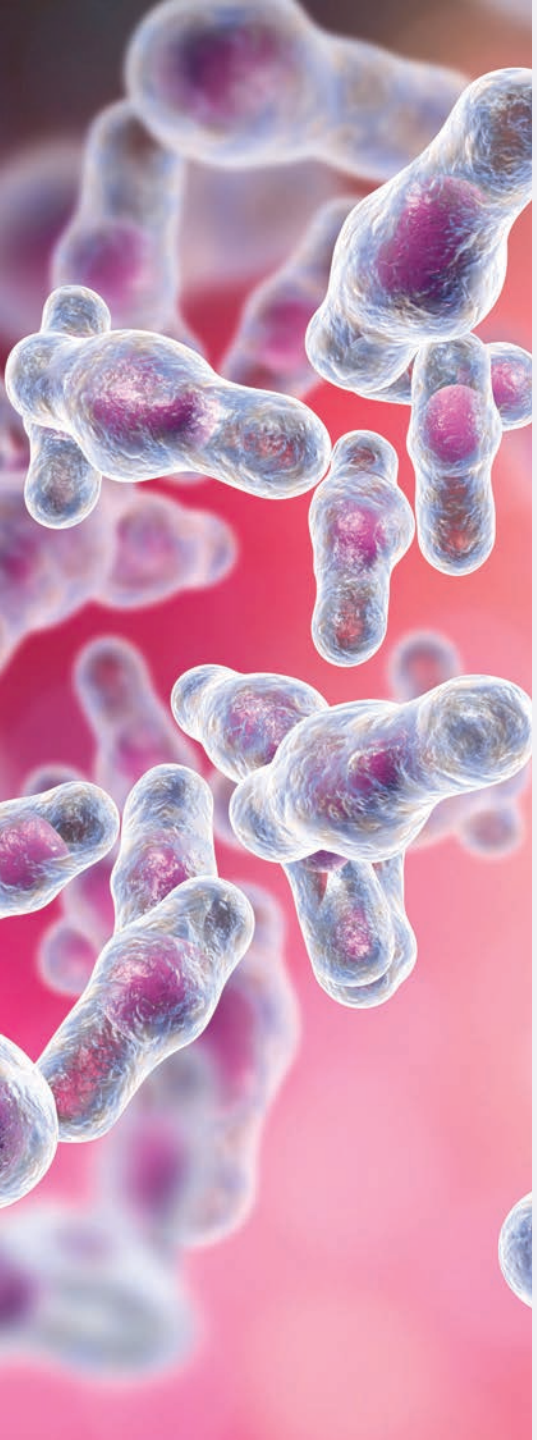
B. Recent CDI

C. Antibiotic exposure

D. Gastric acid suppression

E. Contact with an infected person

rCDI, recurrent *Clostridioides difficile* infection.



Post-Test Question 2 (of 4)

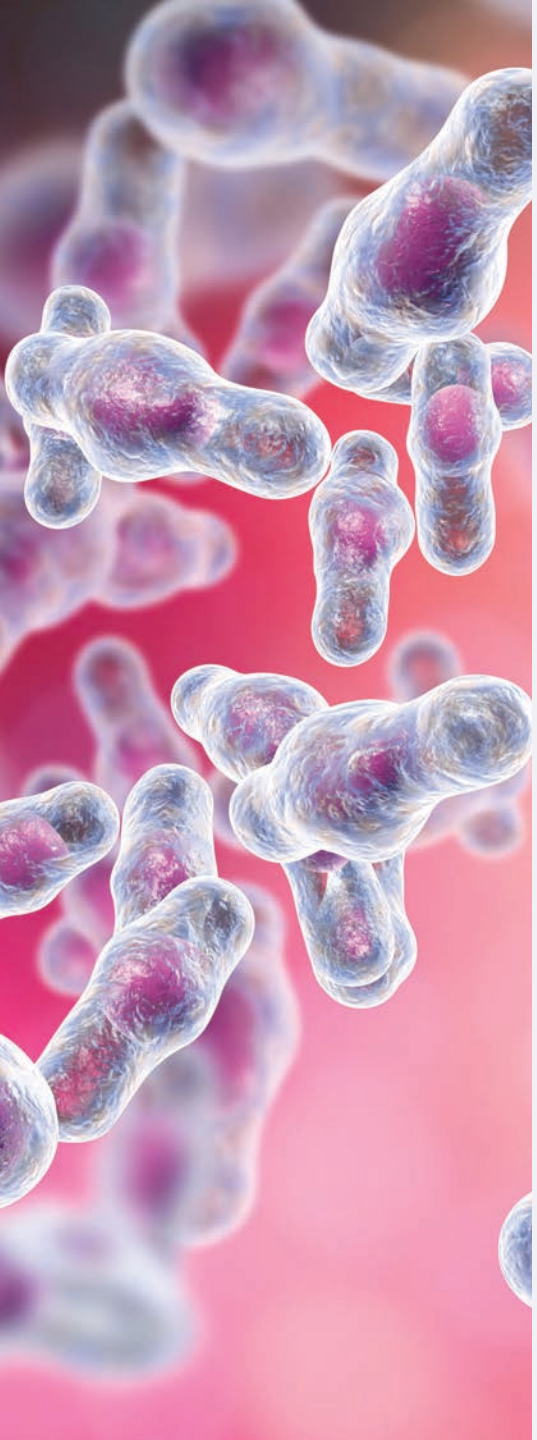
Which of the following are the most important bacterial phyla to prevent CDI?

A. Bacteroidetes and Verrucomicrobia

B. Actinobacteria and Verrucomicrobia

C. Firmicutes and Bacteroidetes

D. Firmicutes and Proteobacteria



Post-Test Question 3 (of 4)

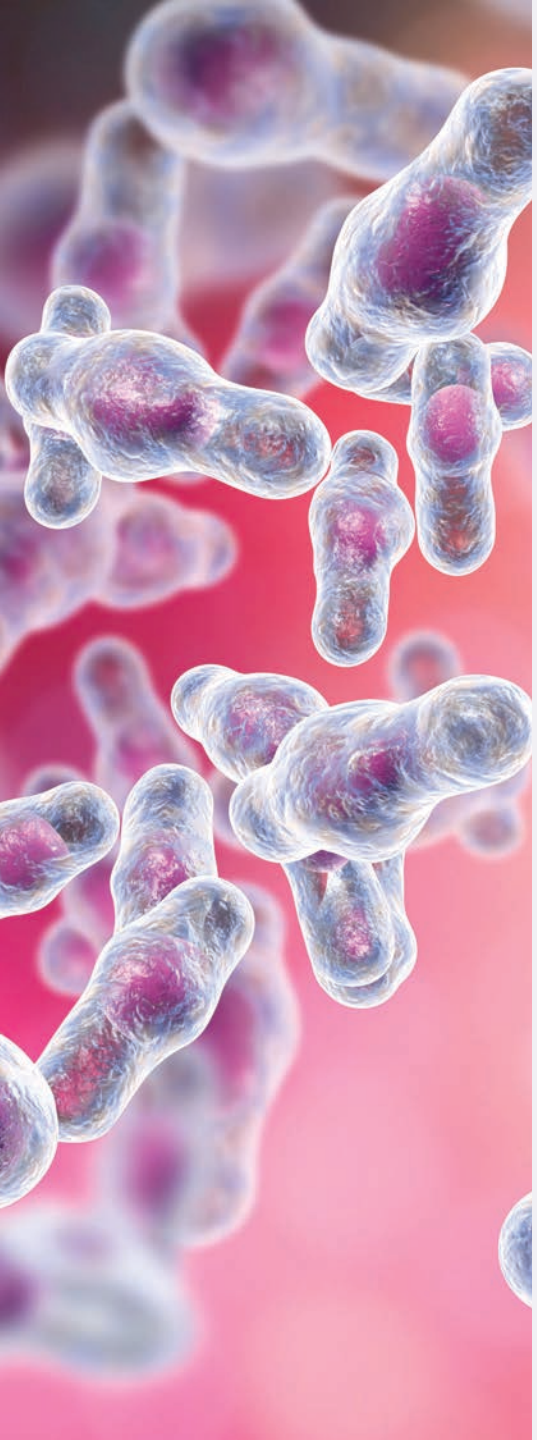
After 2 recurrences (3 episodes) of CDI despite standard antimicrobial treatment, your patient is a candidate for a live biotherapeutic product. She asks why she has to wait to receive the new product. What should you tell her about why the washout period is important?

A. It allows the microbiota time to stabilize before supplementation

B. It purges the microbiota of excess Bacteroidetes

C. It purges the microbiota of residual antimicrobial

D. It allows the microbiota time to restore before supplementation



Post-Test Question 4 (of 4)

The FDA approved the first LBP in November 2022. Which of the following statements is most accurate regarding FMT vs LBP?

A. FMT has better structured studies than LBP

B. LBPs have a defined consortium of microorganisms, whereas FMT is non-defined consortia

C. Safety assessments are less stringent for LBPs than for FMT

D. Donor screening is more comprehensive for FMT than LBP

LBP, live biotherapeutic product; **FMT,** fecal microbiota transplantation.

Managing Recurrent *Clostridioides Difficile* Infection

Advancing the Science of Microbiome-Based Therapies

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