9TH ANNUAL
DIGESTIVE DISEASES: NEW ADVANCES

September 16–17, 2022

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C Difficult…

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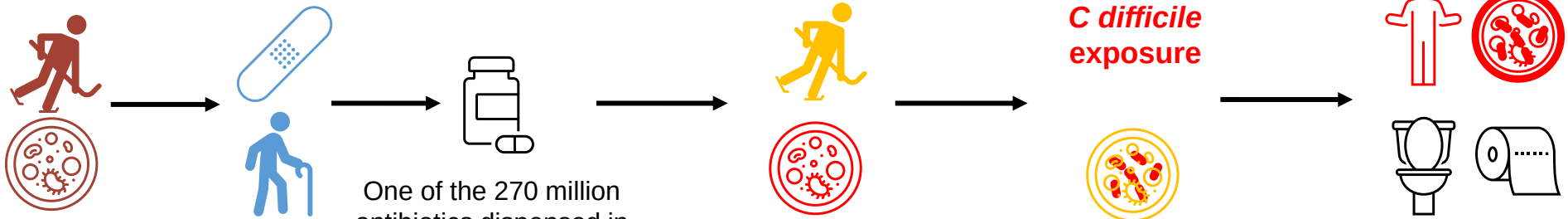
Disclosures

- **Sahil Khanna, MBBS, MS, FACG, AGAF**
  - **Research Support**: Rebioitx / Ferring, Vedanta, Finch, Seres and Pfizer.
  - **Consulting**: ProbioTech, Shire / Takeda, Niche and Immuron.

Outline

- Changing Epidemiology of *C difficile*
- Testing paradigms
- Treatment landscape for *C difficile*
  - *What's new in the guidelines?*
- Microbiome-based therapies

A Few Days in the Life of Mr. CD



One of the 270 million antibiotics dispensed in the US yearly

Recovering injury
Disrupted microbiome

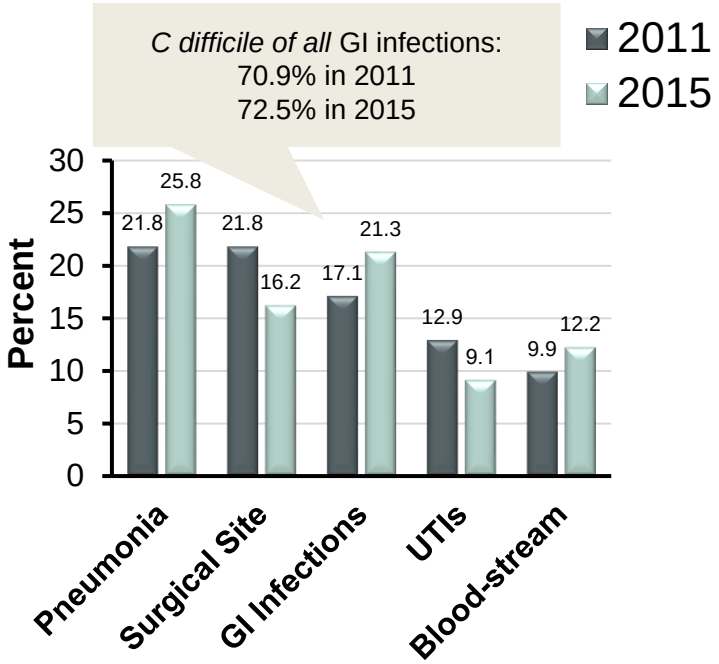
***C difficile* exposure**

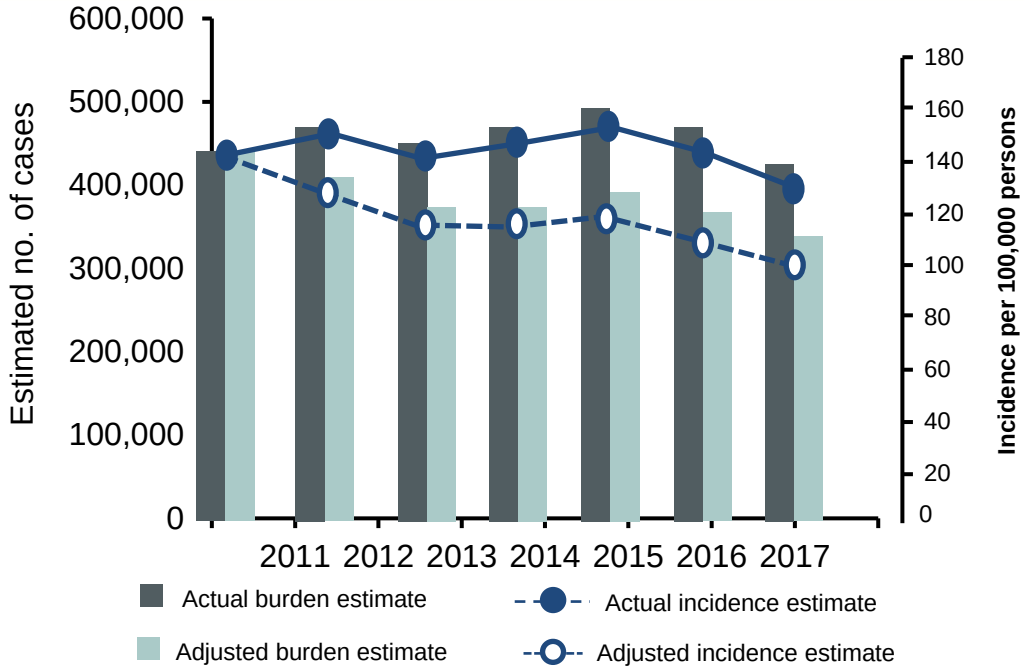
Recovering microbiome

Diarrhea, dehydration, abdominal pain
Disrupted microbiome

>9/10 times:
No discussion of adverse events including *C difficile*

CDI: Both in Healthcare & Community



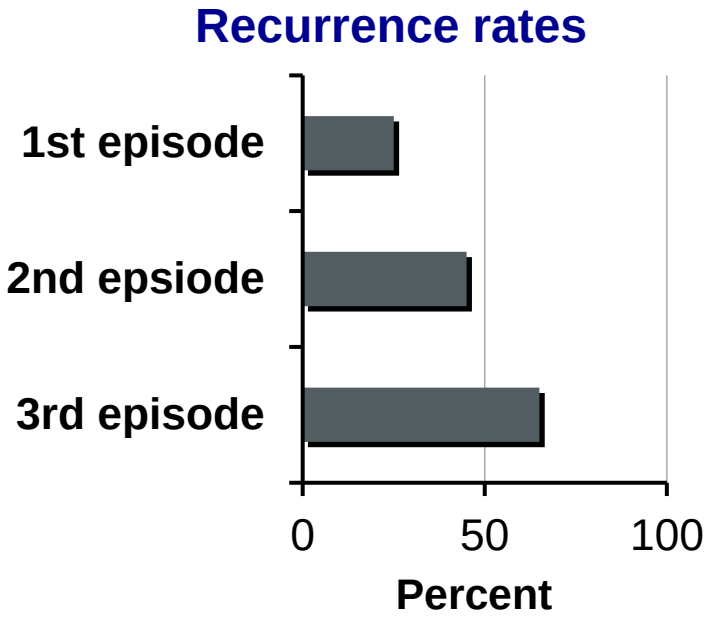


Magill SS et al. *N Engl J Med*. 2015;370:1198-208.
Magill SS et al. *N Engl J Med*. 2018;379:1732-44.
Guh AY et al. *N Engl J Med*. 2020;382(14):1320-30.

C. difficile: **Most commonly reported pathogen:**
12.1% of HAIs in 2011
15.5% of HAIs in 2015

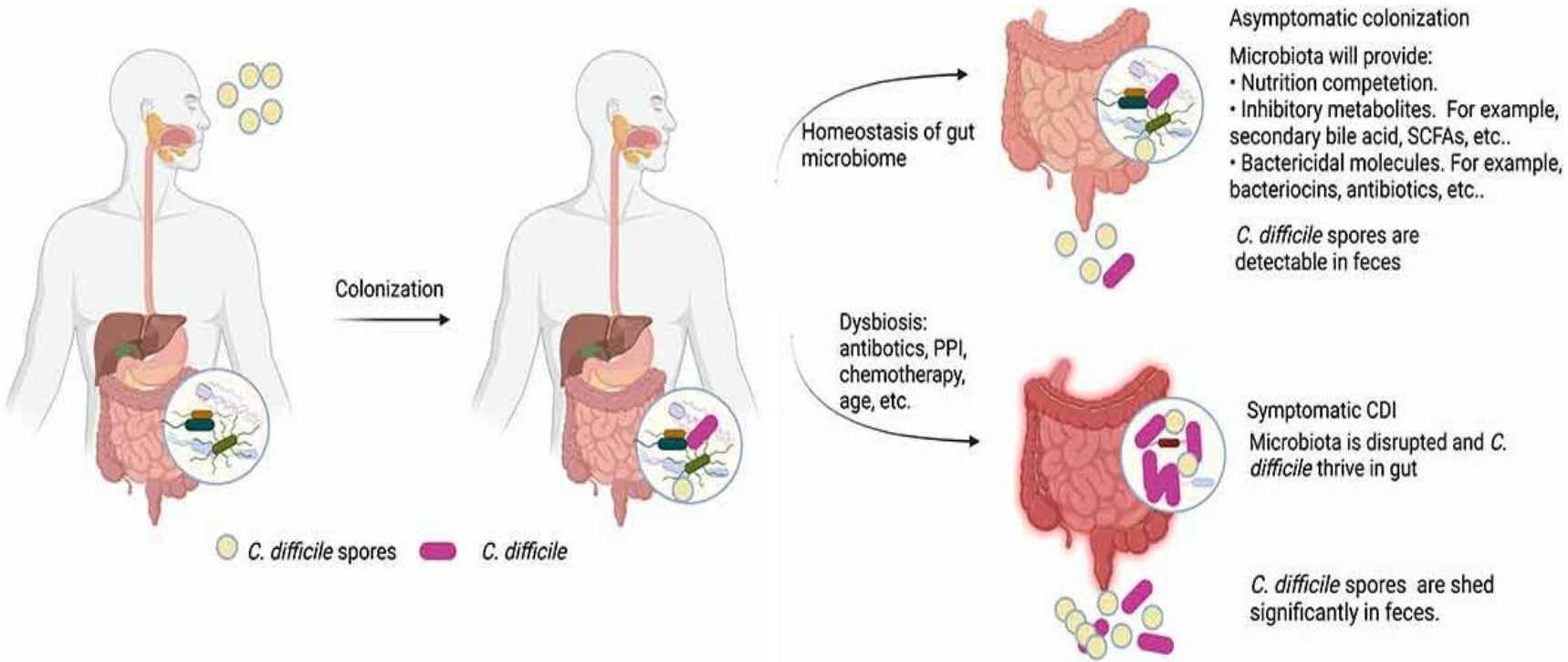
Risk Factors for Recurrent *C Difficile*

- Advanced age (> 65 years)
  - Younger people also have C difficile infection
- Antibiotic exposure
  - A key modifiable risk factor for infection
- Comorbid conditions and immunosuppression
  - ie, inflammatory bowel disease, malignancy, kidney disease
- Hospitalization and residence in skilled nursing facility
  - Prolonged length of hospital stay
- Gastric acid suppression (PPI use)
- Contact with active carriers or those actively infected
- Recent *C difficile* infection



Khanna S et al. *Mayo Clin ProC*. 2012;87:1106-1117; Khanna S. *J Int Med*. 2021;290:294-309.

Pathogenesis of *C Difficile*



Zhang Y et al. *Gut Microbes*. 2022.

How Do We Make a Diagnosis?

High pre-test probability for CDI

- Risk factors
- Unexplained diarrhea
- 3 or more watery stools a day
- Not on laxatives

Nucleic acid based test such as PCR for *tcdA or tcdB*

Low - intermediate pre-test probability for CDI

- Questionable risk factors
- Multiple causes of diarrhea

A stool toxin test obtained as part of a multistep testing strategy

Think Twice Before Testing
Low pre-test probability

McDonald LC et al. *Clin Inf Dis*. 66 (7), e1–e48.

Putting CDI Tests Into Context

PCR

Advantages

- High sensitivity
- Rapid
- Inexpensive

Advantages

Doesn't distinguish cases From carriers Overdiagnosis

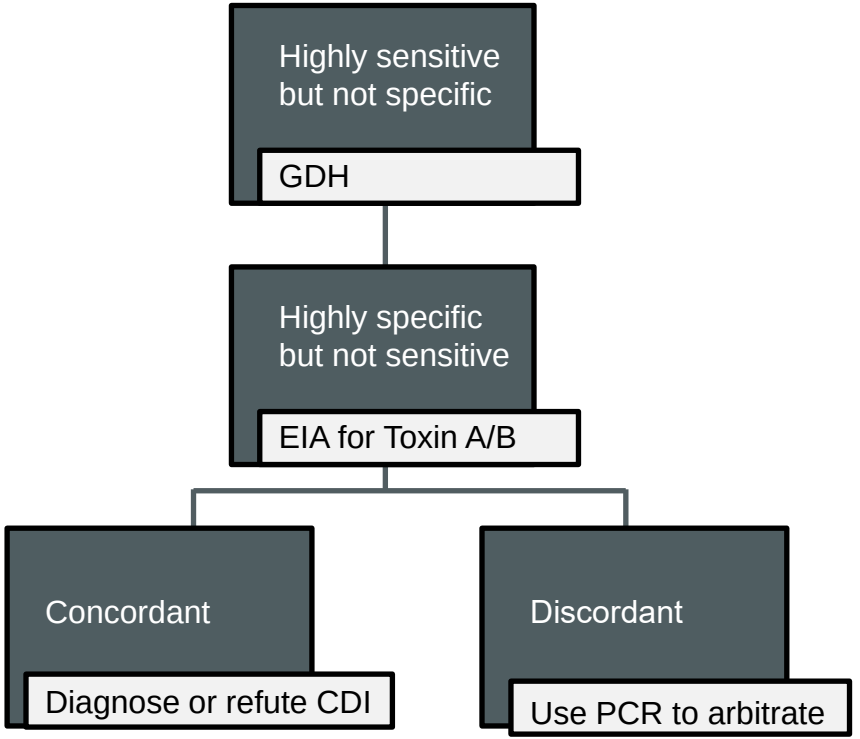
EIA for Toxin A/B

Advantages

- Detects toxin
- Rapid
- Inexpensive

Advantages

- Low sensitivity
- Missed cases



Make an Accurate Diagnosis in Practice

Assess risk factors for *C difficile Infection*

Assess for presence of symptoms

- Diarrhea, abdominal pain, dehydration, fever

A positive test for *C difficile infection*

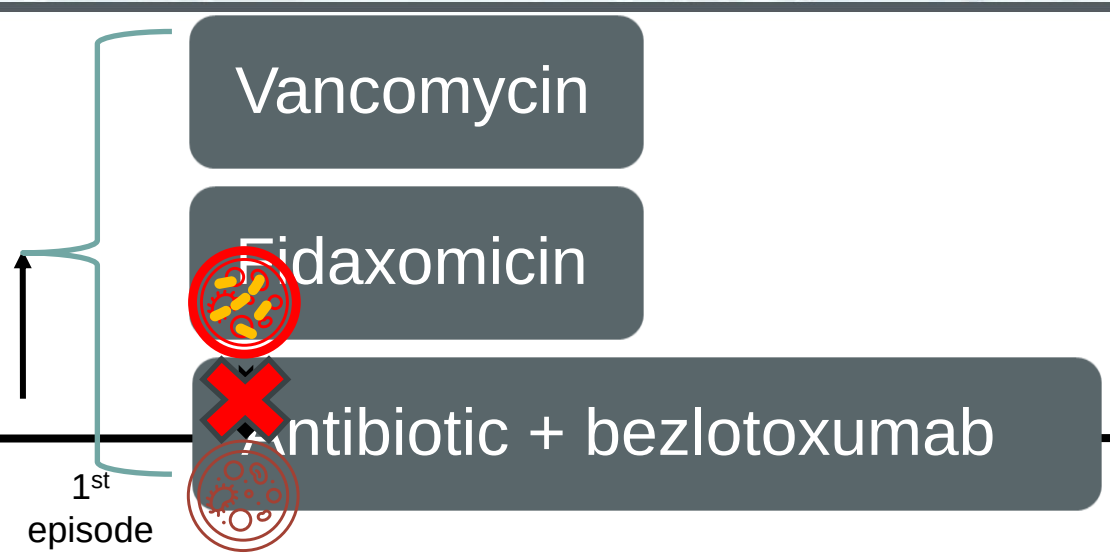
- PCR or toxin-based assay

Assess response to treatment

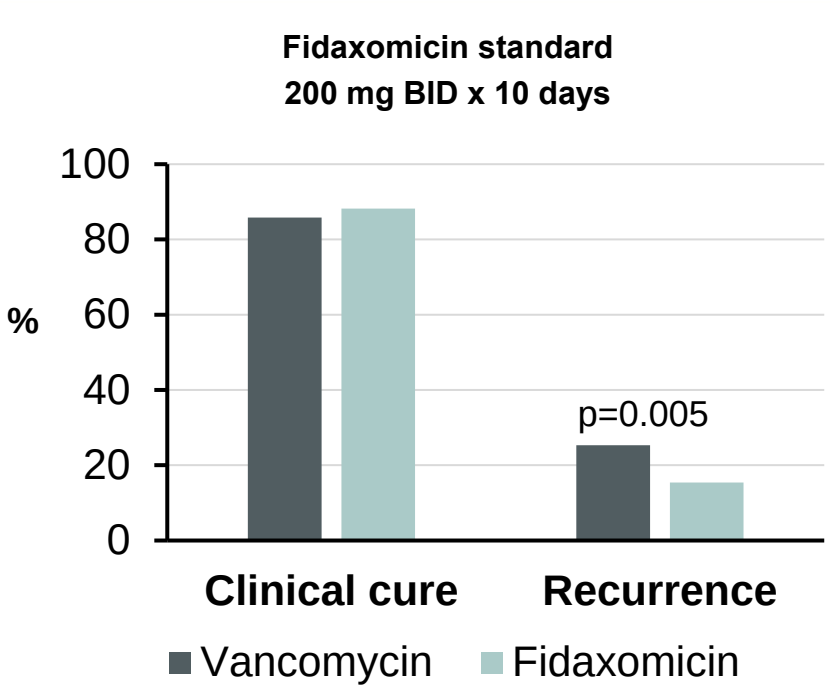
- Non-response to vancomycin / fidaxomicin is rare and suggests alternate diagnoses

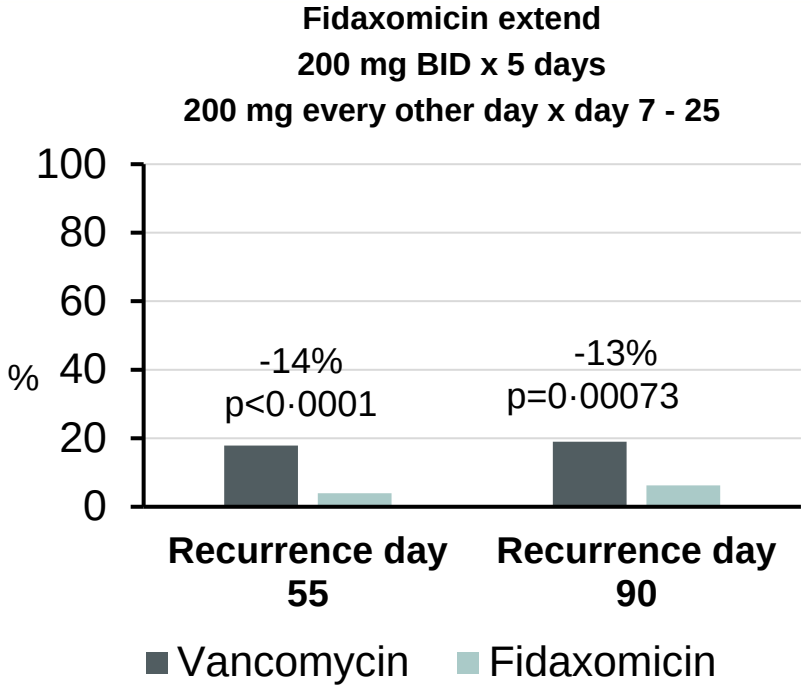
Khanna S, Pardi DS. *Am J. Gastroenterol*. 2020 Jul;115(7):971-974.

How Was Mr. CD Treated?



Fidaxomicin: As Effective as Vancomycin but Fewer Recurrences





NEJM. 2011;364:422-31; *Lancet Infect Dis*. 2018; 18: 296-307.

The First Ever *C Difficile* Infection

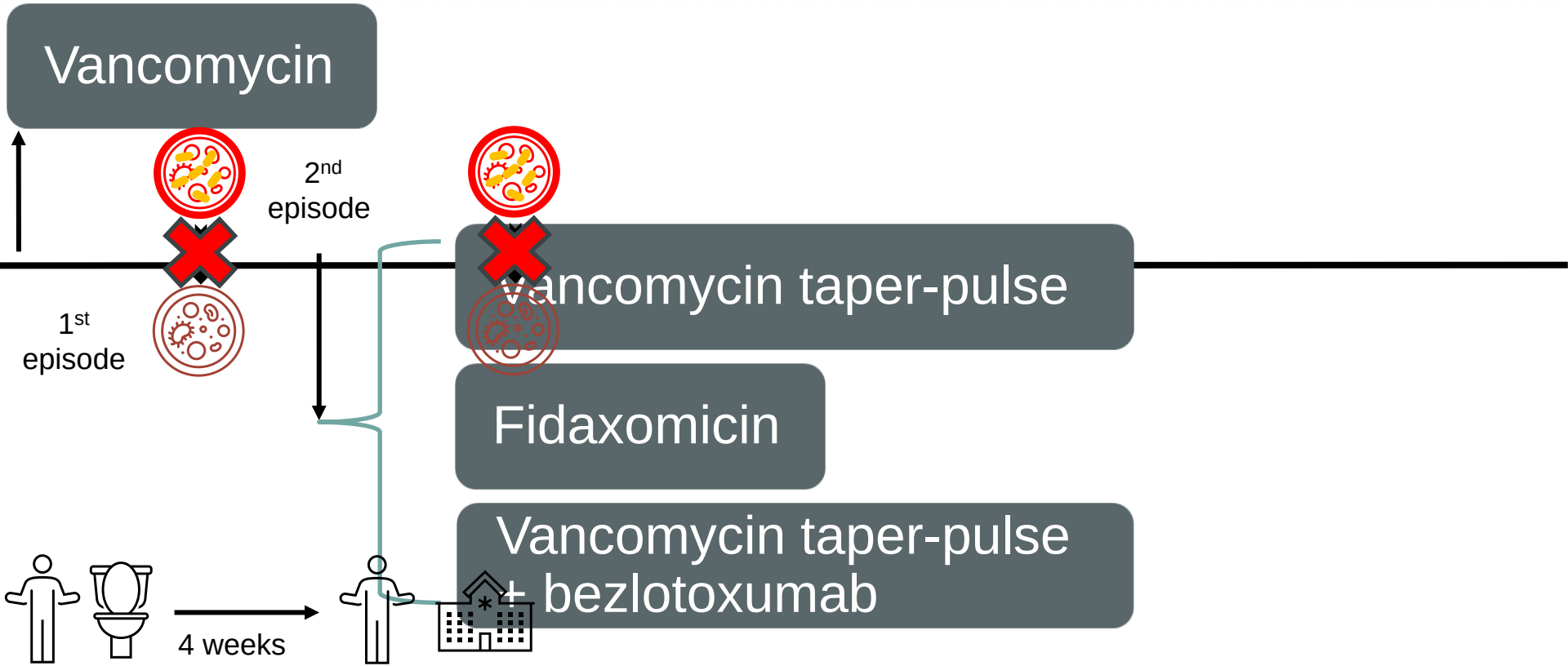
ACG	IDSA	ESCMID
Vancomycin or fidaxomicin Metronidazole alternate in low-risk	Fidaxomicin preferred over vancomycin Metronidazole if above are unavailable	Fidaxomicin* preferred over vancomycin Metronidazole if above are unavailable

* High risk of recurrence: Age >65 years + one or more of: Healthcare-associated CDI, hospitalization in the last 3 months, concomitant antibiotics, PPIs (and prior CDI)

Bezlotoxumab for recurrence prevention in those at high risk of recurrence

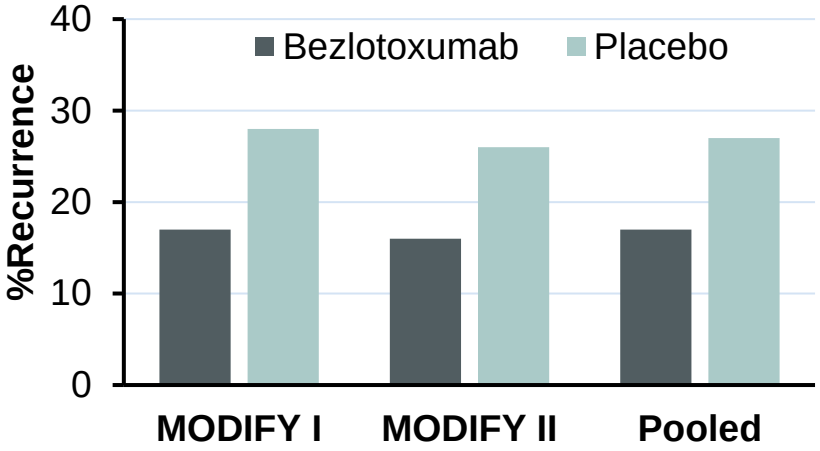
Kelly C et al. *Am J Gastro*. 116(6):1124-1147; Johnson S et al. *Clin Infect Dis*. 2021;73:e1029-1044;
Van Prehn J. *Clin Micro Inf*. Oct 2021.

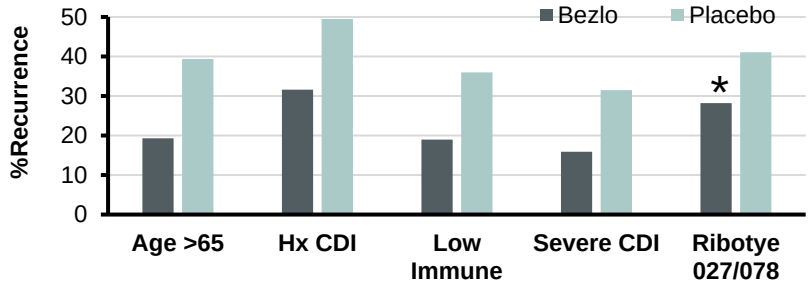
How Was Mr. CD Treated the 2nd Time?

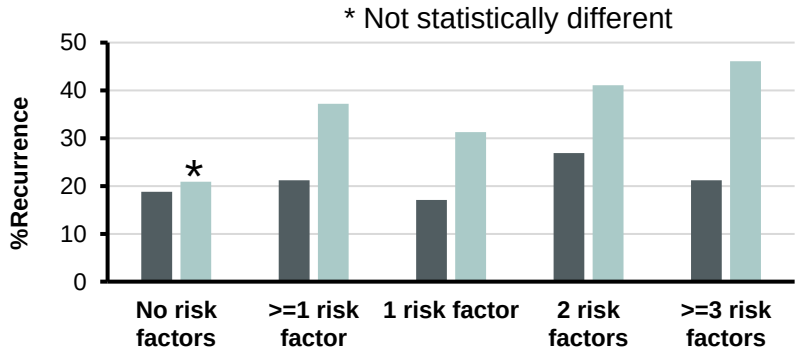


Bezlotoxumab Reduces Recurrent CDI

- Patients with 1 or 2 episodes
- Infusion of monoclonal antibody in addition to antibiotics
- Primary endpoint: Recurrent infection within 12 weeks







Wilcox MH et al. *N Engl J Med*. 2017; 376:305-317; Gerding D et al. *Clin Infect Dis*. (67)5: 649–56.

Acute Management of Fulminant CDI

Evaluation: Frequent abdominal examination

Testing: WBC, Creatinine, CRP, X-ray / CT scan

Consultations: CRS, Gastroenterology, Infectious diseases. Discuss Surgery and FMT

Medications: Vancomycin 500 mg PO QID +/- PR vancomycin and Metronidazole 500 mg IV TID

The First Recurrent *C Difficile* Infection

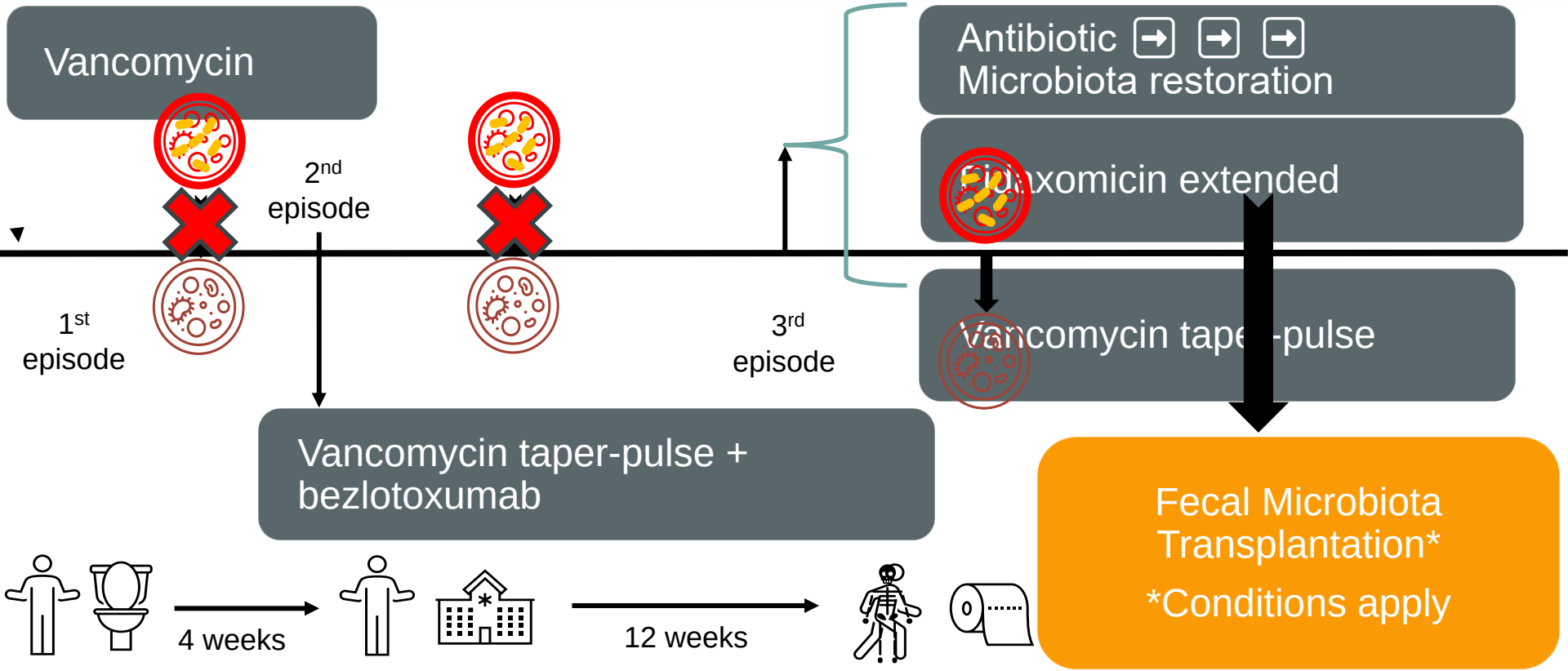
ACG	IDSA Infectious Diseases Society of America	ESCMID
Fidaxomicin or vancomycin taper-pulse	Fidaxomicin* over vancomycin taper-pulse	Fidaxomicin* over vancomycin taper-pulse

* Consider fidaxomicin extend regimen

Bezlotoxumab for prevention of CDI recurrence

Kelly C et al. *Am J Gastro*. 116(6):1124-1147; Johnson S et al. *Clin Infect Dis*. 2021;73:e1029-1044;
Van Prehn J. *Clin Micro Inf*. Oct 2021.

How Would Mr. CD Be Treated Now?



The Multiply Recurrent *C Difficile* Infection

ACG	IDSA Infectious Diseases Society of Americ	ESCMID
Abx → FMT Over antibiotic regimens	Abx → FMT Over antibiotic regimens	Abx → FMT Over antibiotic regimens

Consider Bezlotoxumab for prevention of CDI recurrence (If no FMT)

Kelly C et al. *Am J Gastro*. 116(6):1124-1147; Johnson S et al. *Clin Infect Dis*. 2021;73:e1029-1044;
Van Prehn J. *Clin Micro Inf*. Oct 2021.

Microbiota Restoration for CDI

- Efficacy >85% to prevent recurrence
- Superior to oral vancomycin
- Fresh or freeze-thawed has similar efficacy
- No donor effect on efficacy
  - Screening and recruitment standardization needed
- More adverse events are being reported
- FDA guidance on FMT is still in draft phase
- Standardized therapies are being developed

Khanna S. *J Int Med*. 2021 Aug;290(2):294-309.

Preparing / Managing Before FMT

Treat

Step1: Start an antibiotic to bring active symptoms under control

- Diarrhea improves in 3-5 days
- Risk of recurrence after 3 episodes is ~60%

Discuss

Step2: Discuss recurrence prevention: Restore microbiome

- Initiate referral to a center performing microbiome restoration
- Majority of patients will be discharged prior to getting FMT

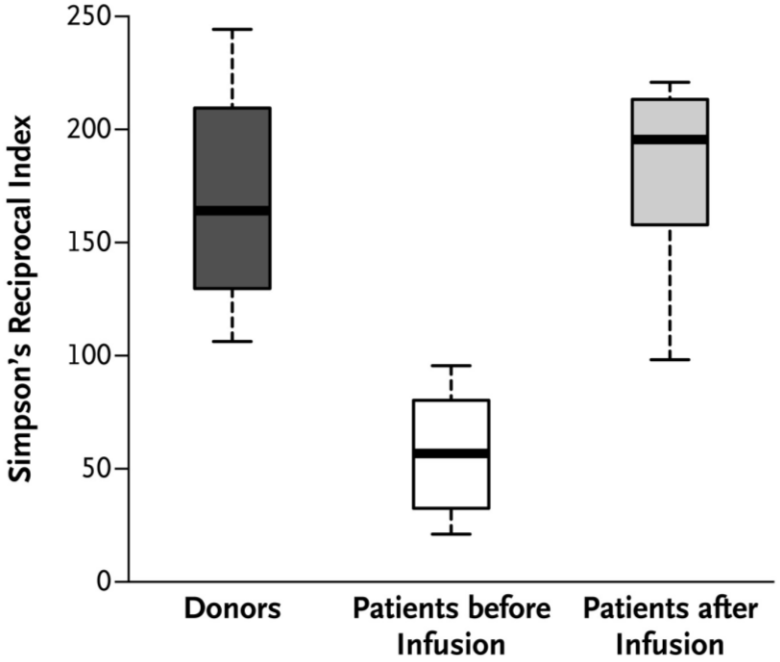
Prescribe

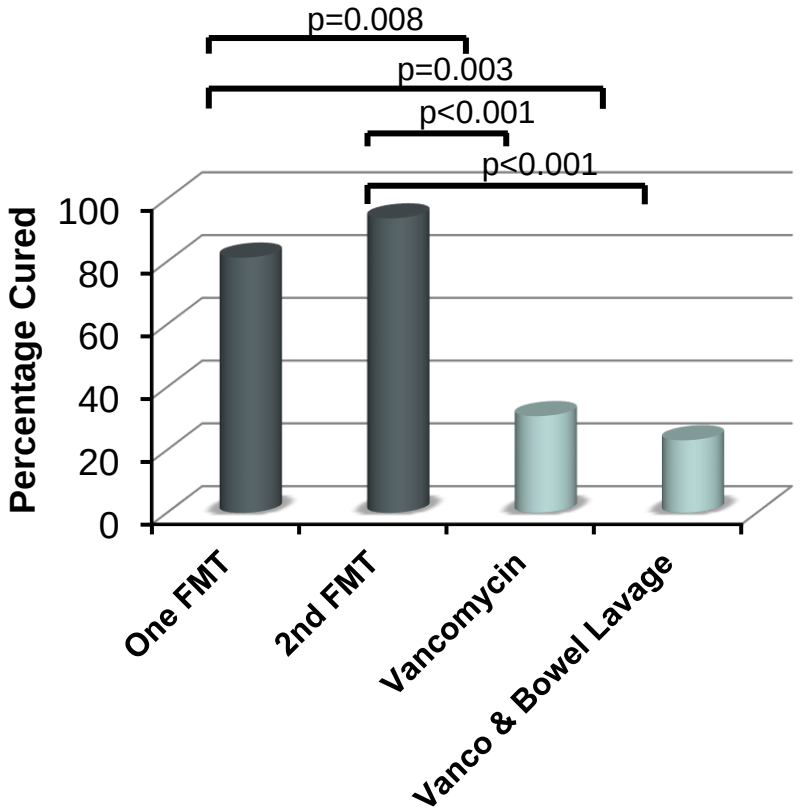
Step3: Prescribe enough antibiotic until specialist appointment

- Vancomycin 4 times a day for 10-14 days
- Taper down vancomycin to lowest effective dose

Voth E, Khanna S. *Expert Rev Anti Infect Ther*. 2020 Apr; 12:1-8.

FMT: Higher Cure Rates Than Vancomycin

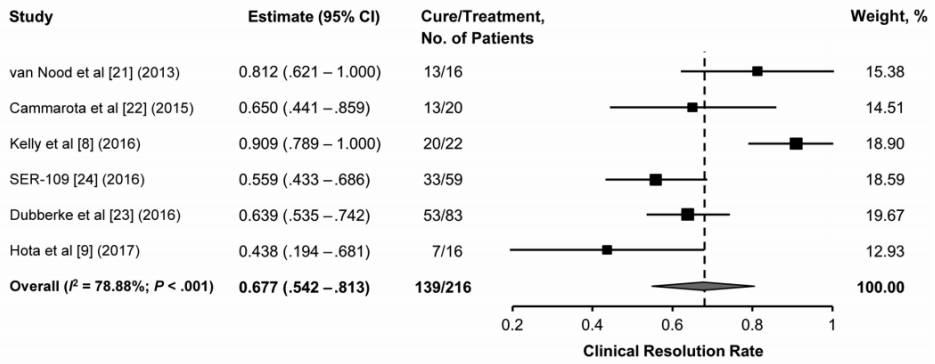




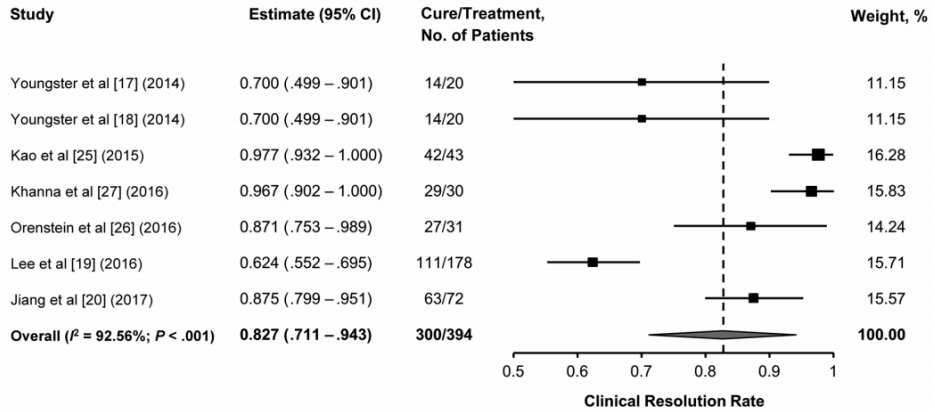
Van Nood et al. *NEJM*. 2013;368:407-15.

FMT: Lower Efficacy in Controlled Trials

Trials with a non-FMT comparator group
Cure rate: 67.7%



Open-label trials
Cure rate: 82.7%



Tariq R et al. *Clin Inf Dis*. 2019; 68:1351-1358.

FMT Has Many Many Challenges

Exclude Donors with:

Microbiome associated diseases

- Obesity, IBS, IBD, neuropsychiatric, etc

Stool infections

- Enteric pathogens, viruses, parasites
- Multi-drug resistant organisms

Blood infections

- HIV, viral Hepatitis, syphilis, others

Emerging pathogens

- SARS-CoV-2

FDA Alerts

Infection Transmission

- ESBL *E. coli* bacteremia
- *E. coli* (STEC / EPEC) infection

Screening for COVID-19

FMT remains a heterogeneous practice

Donor screening

Stool Processing

Administration

Follow up

Khanna S. *J Intern Med*. 2021 Aug;290(2); Khanna S, Pardi DS. *Am J. Gastro*. 2020; 115(7); Khanna S, Craft K. *Clin Infect Dis*. 2021 Jun 1;72(11).

Logistics of Donor Screening

Known donors

- May be screened by primary care under guidance from physician performing FMT

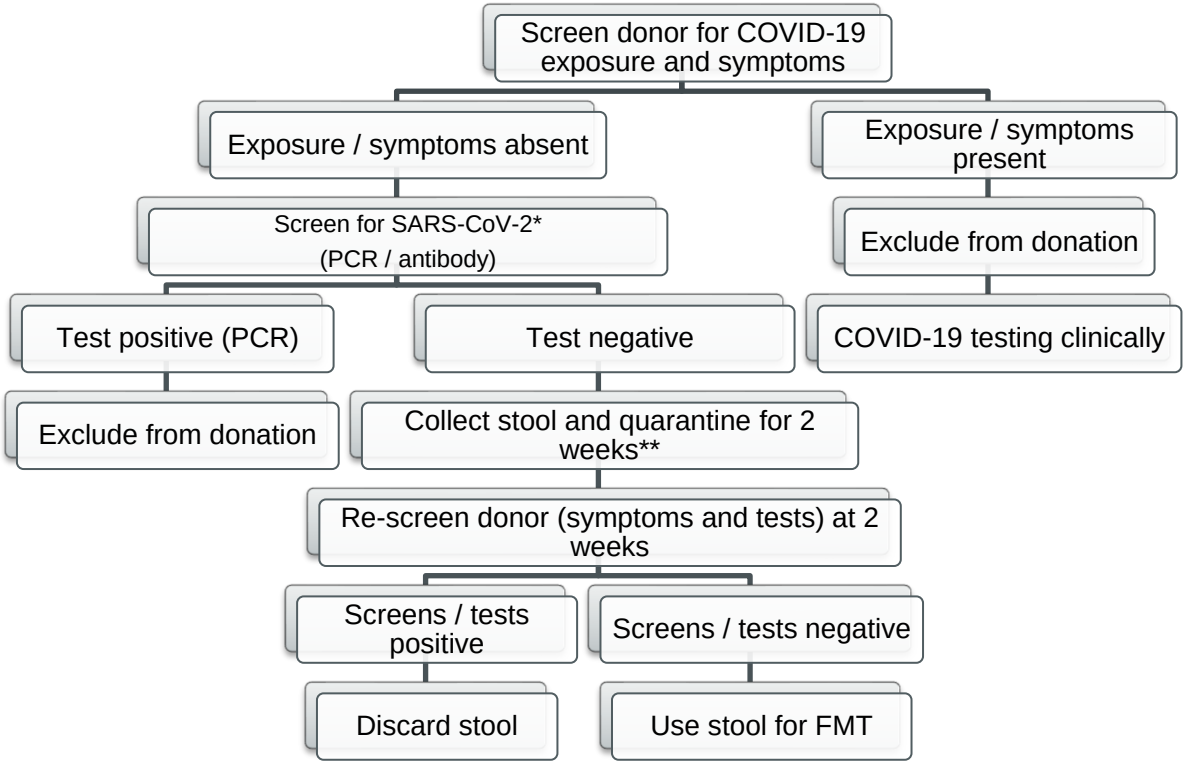
Insurance may not cover donor screening

Standard donors screened by physician performing FMT

- Cost borne by the performing institution
- Standard donors kept anonymous to patients

Screening process is iterative

Screening for COVID-19

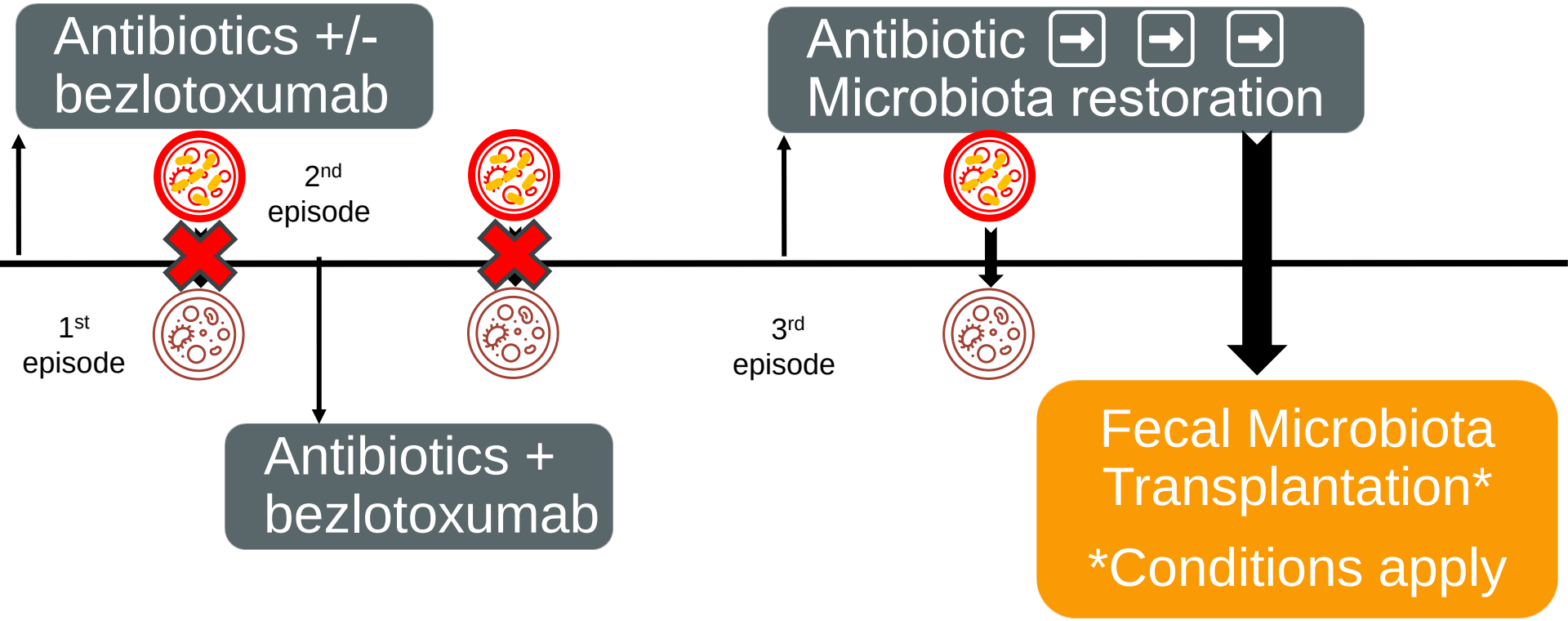


*Most places have a naso-pharyngeal PCR available, and stool assays are rare with questionable reliability

**Screen at every donation. If stool PCR is available, screen every sample and use

Khanna S, Pardi DS Am J. *Gastroenterol*. 2020 Jul;115(7):971-974.

Unmet Need in Current Rx Paradigm



RBX2660: PHASE III

Product and Study design

- 50g stool in 150mL diluent: ≥10^7 organisms/ml
- Randomized double-blinded, 2 arms in a 2:1 ratio
  - 1 active versus placebo enema

Key inclusion

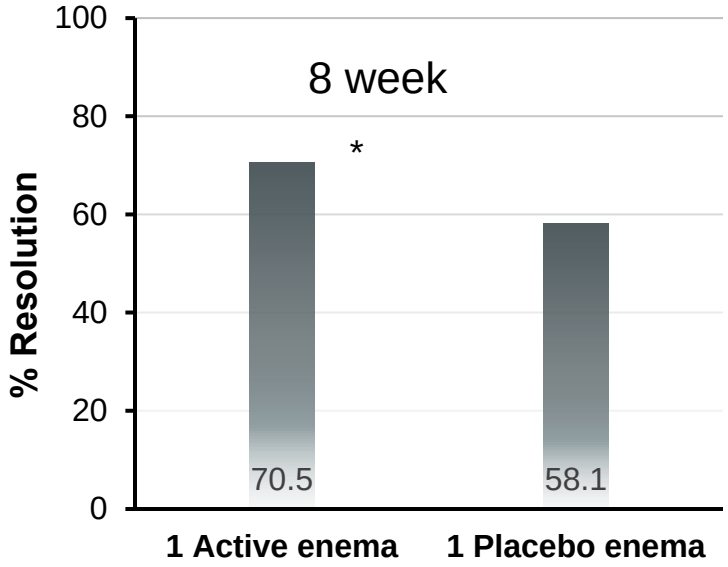
- Two or more episodes
- Any stool test, clinical response to antibiotics

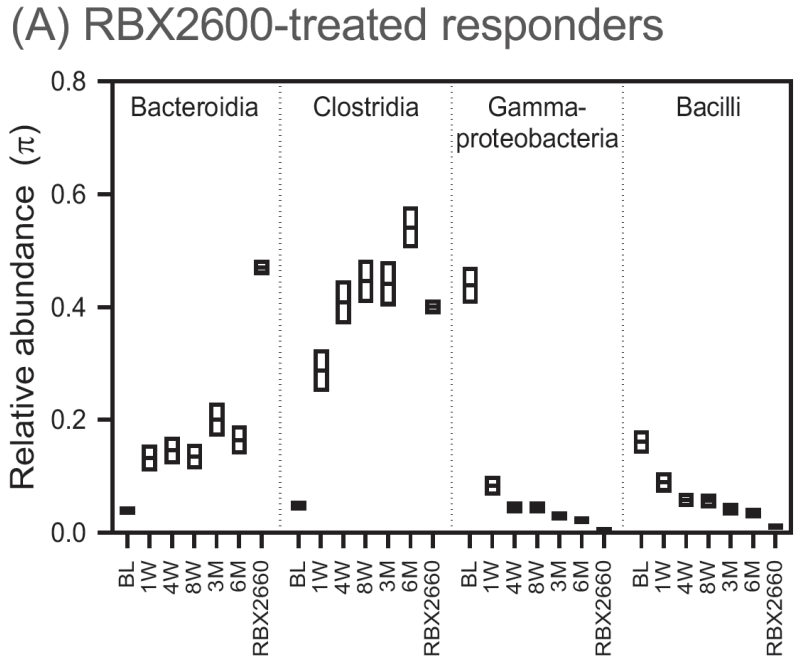
Endpoints

- Efficacy at 8 weeks (Bayesian analysis incorporating phase II data)
- Safety

Lee C et al. *DDW*. 2021 Meeting.

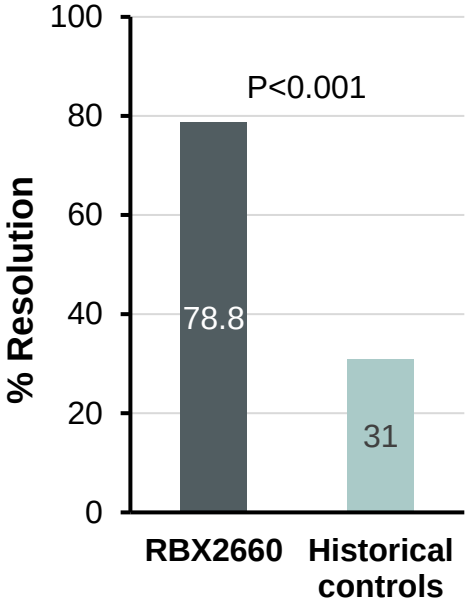
RBX2660 – PHASE III: Key Results

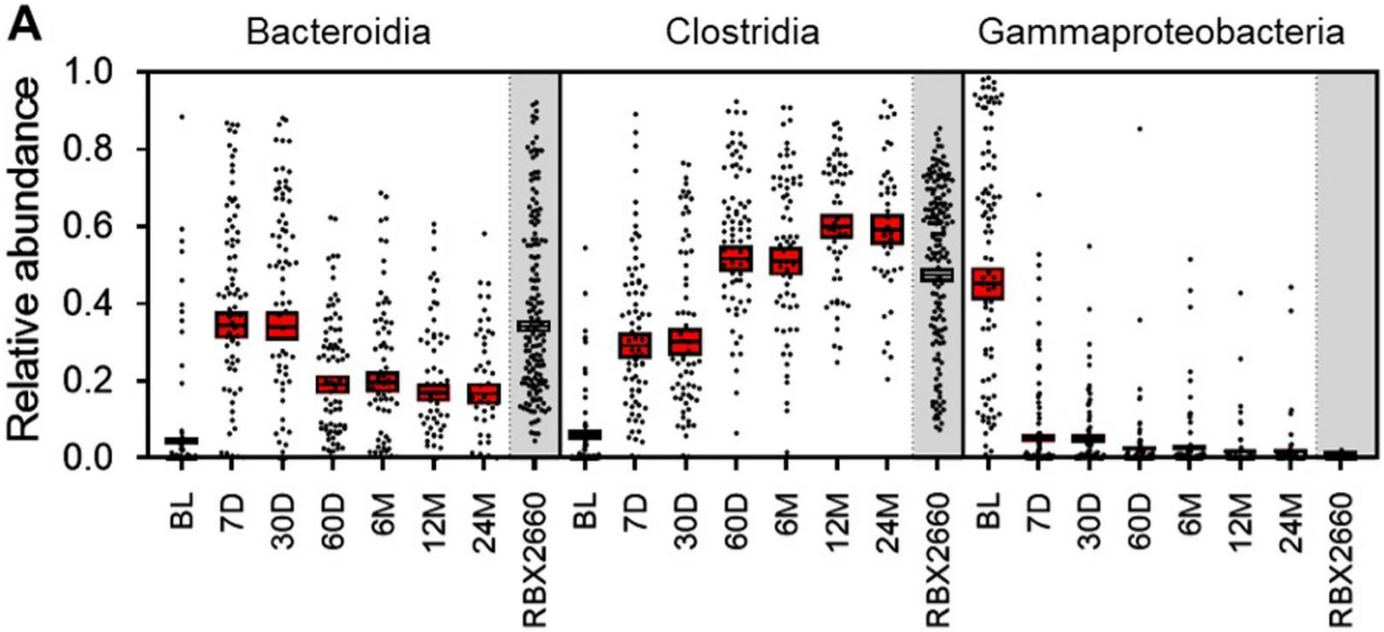




* Statistically significant difference.
98.6% posterior probability of superiority on Bayesian Analysis.
Lee C et al. *DDW*. 2021 Meeting, Blount et al. *IDSA*. 2021 Meeting.

RBX2660: PHASE II Open Label





Orenstein R et al. *BMC Infect Dis*. 2022 Mar 12;22(1):245.

SER-109: PHASE III

Composition

- ~50 species of Firmicutes spores, from donor stool, treated with ethanol
- Capsules after bowel prep, Higher dose than phase II

Study design

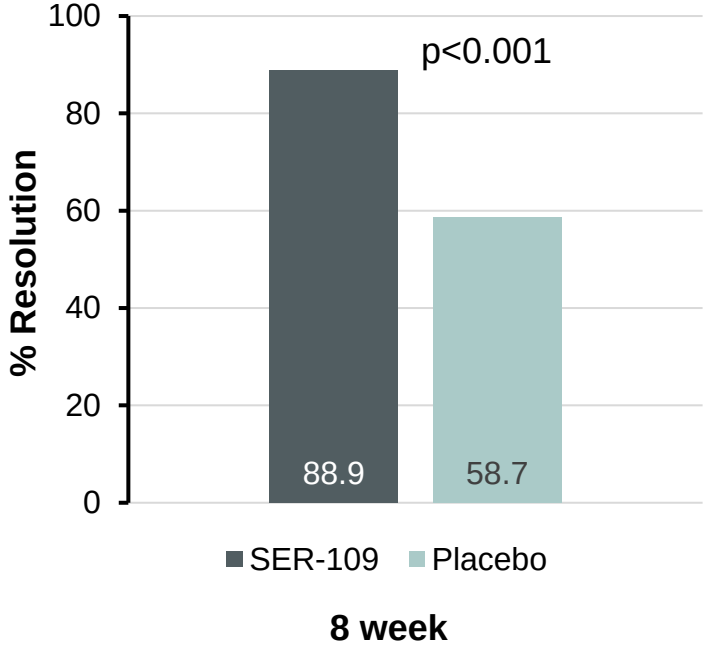
- Randomized double blinded, 2 arms in a 1:1 ratio
- Active or placebo

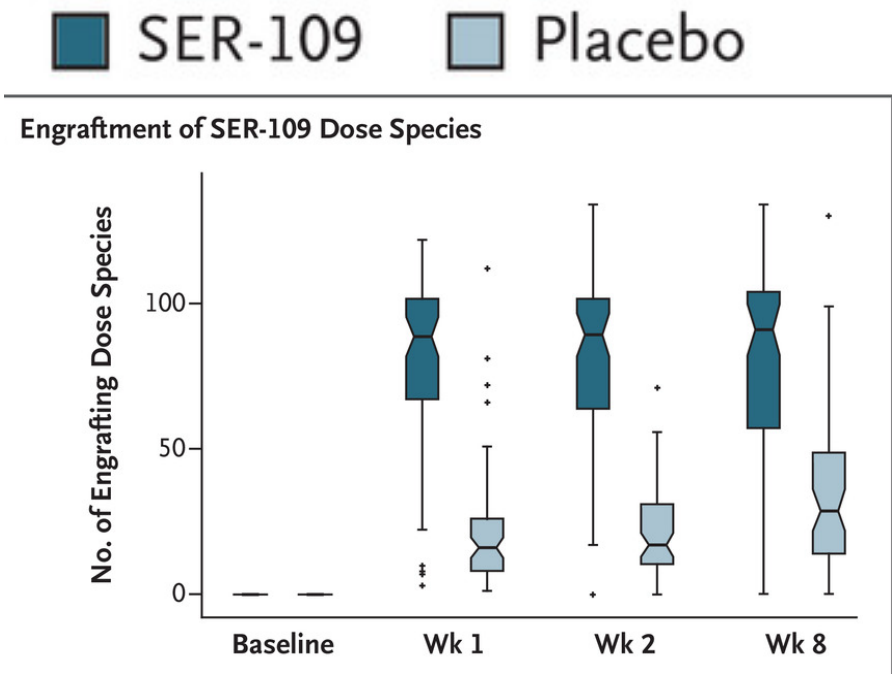
Key inclusion

- 3 or more episodes within 9 months
- Diagnosed by toxin, clinical response to antibiotics

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

SER-109 – PHASE III: Key Results



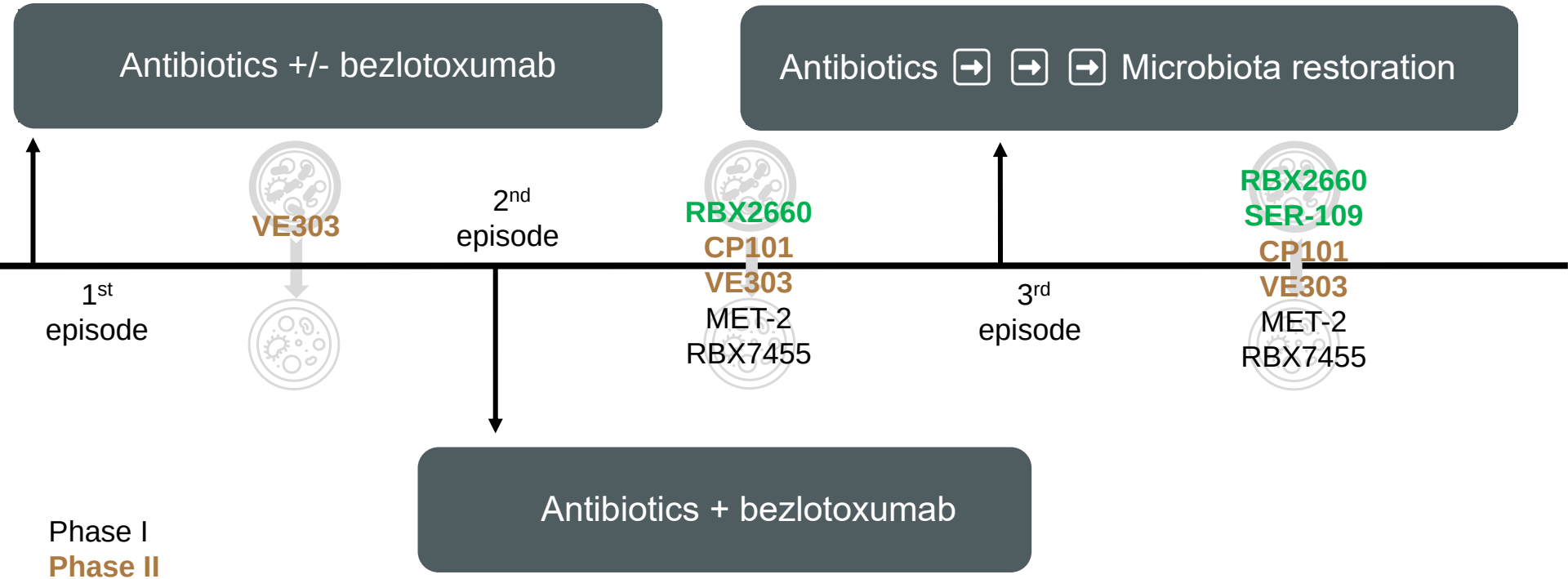


Feuerstadt P et al. *N Engl J Med*. 2022 Jan 20;386(3):220-229.

Where Are Standardized Therapies At?

	# Episodes	Diagnostics	Ph I	Ph II	Ph III	Open label only	Next Step
CP101	>=2 (age>65) >=3 otherwise	Any					Phase III
MET-2	>=2	Any					Phase II
RBX2660	>=2	Any					FDA approval
RBX7455	>=2	Any					Phase III
SER-109	>=3	Toxin					FDA approval
VE303	>=1 (high risk) >=2 otherwise	Any					Phase III

How Far Have We Come?



Phase I
Phase II
Phase III

Take Home Points

- Microbiome alterations are key to the pathogenesis of CDI
- Antibiotic recommendations for primary & recurrent CDI
  - Fidaxomicin or vancomycin but not metronidazole
  - Recurrent CDI: fidaxomicin, vancomycin taper, fidaxomicin, bezlotoxumab
- Microbiome restoration is the key to manage recurrent CDI
- FMT is effective & safe for recurrent CDI: **Has many challenges**
- Standardized microbiota-based therapies are in trials
  - RBX2660, SER-109, CP101, VE303, RBX7455, MET-2