Yale University
School of Medicine

physicians alliance of connecticut

C. difficile: Spore to Vegetative to Spore and Everything in Between

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

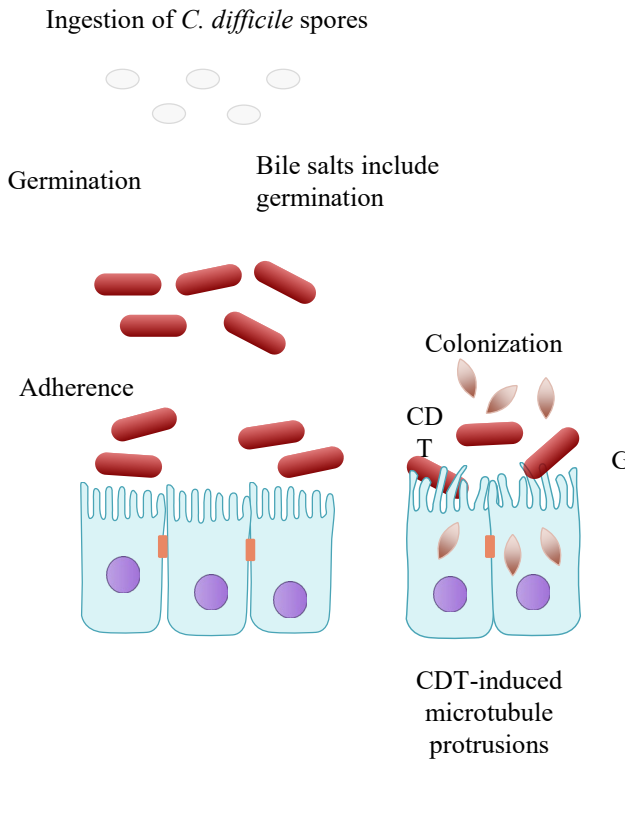
Overview of the World of *C. difficile* Infection

The Discussion Ahead

Epidemiology

Pathophysiology

Diagnosis

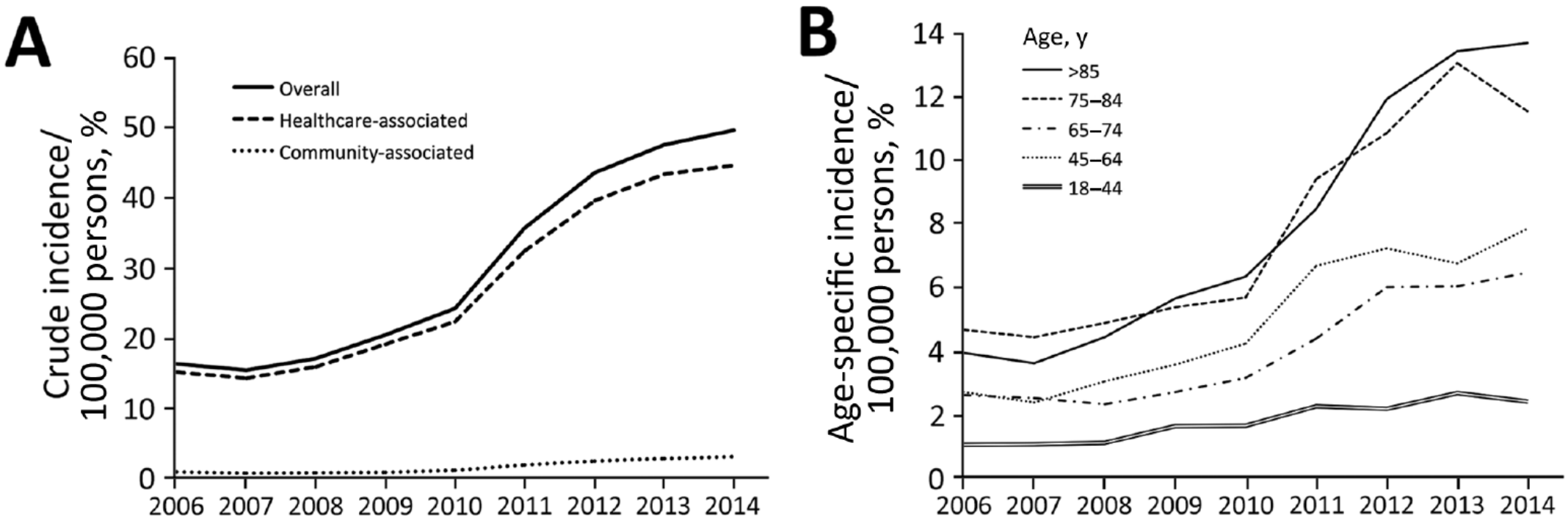


Prevention of Recurrence

Treatment

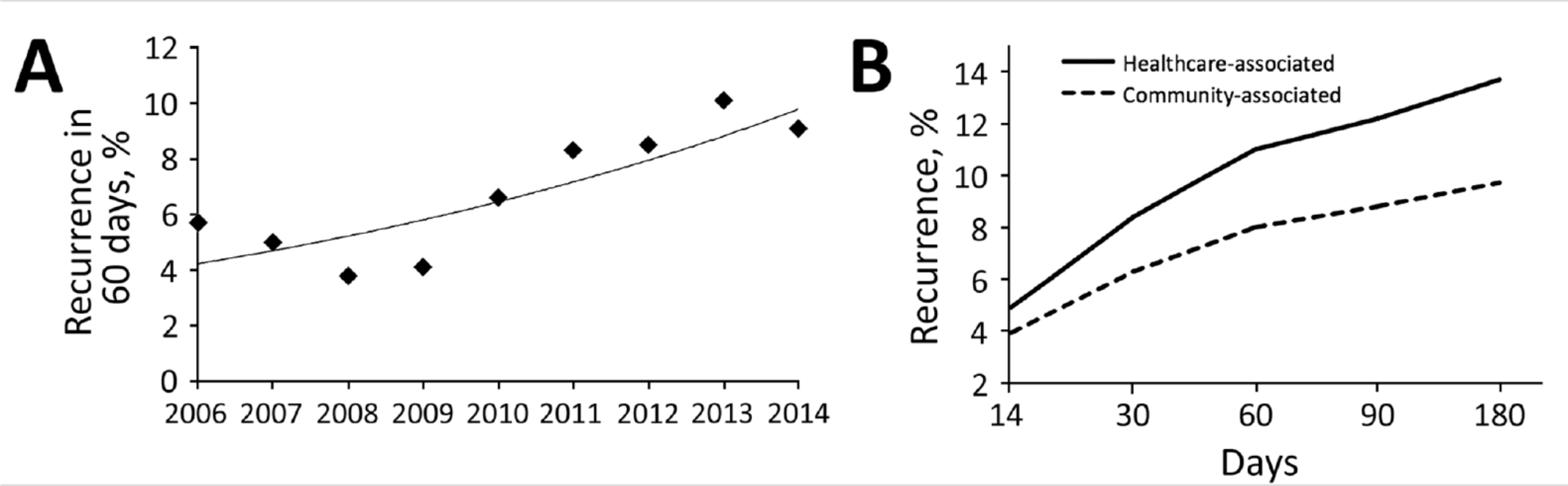
Adapted from: Shen J. *Innate Immun*. 2012;4:149-158.

Incidence of CDI in Hong Kong, 2006-2014



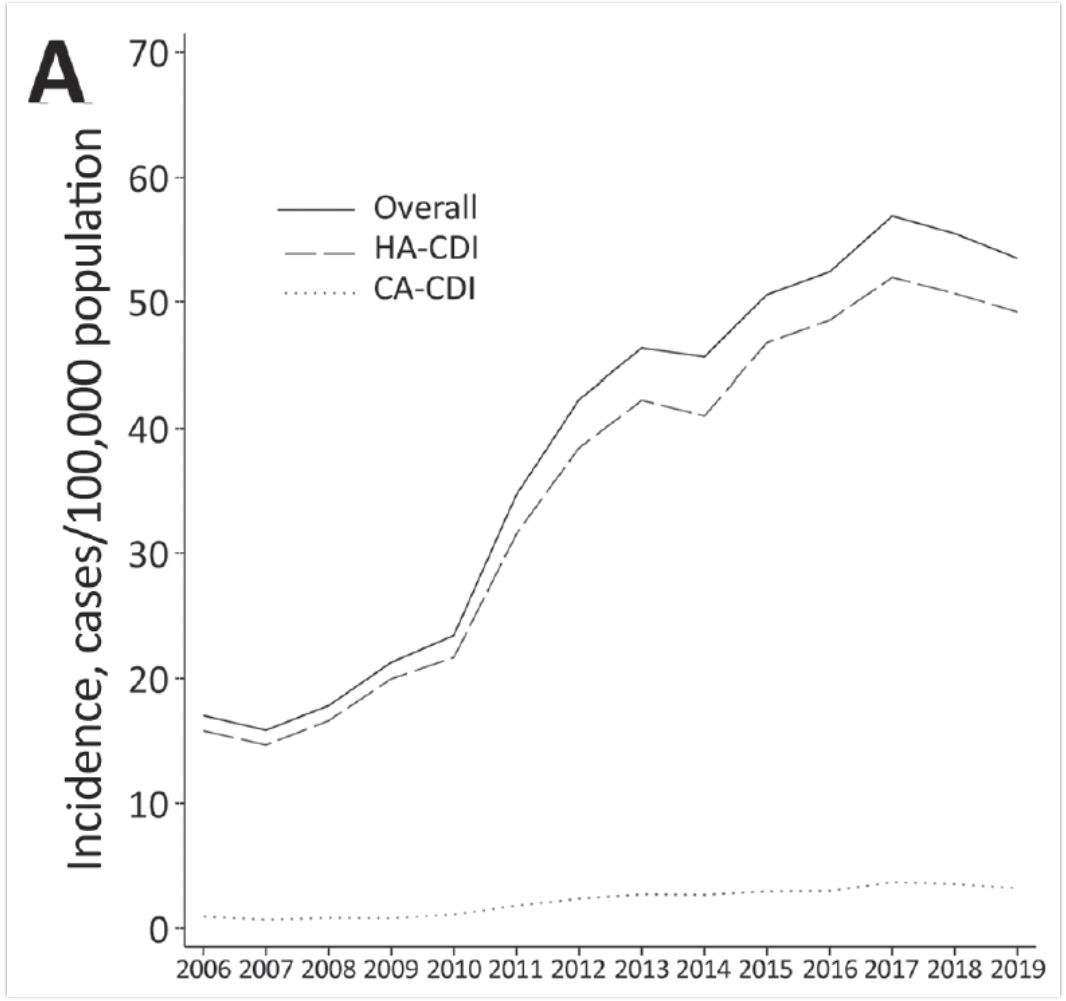
Ho et al. *Em Inf Dis* 23(10). 1671-1679

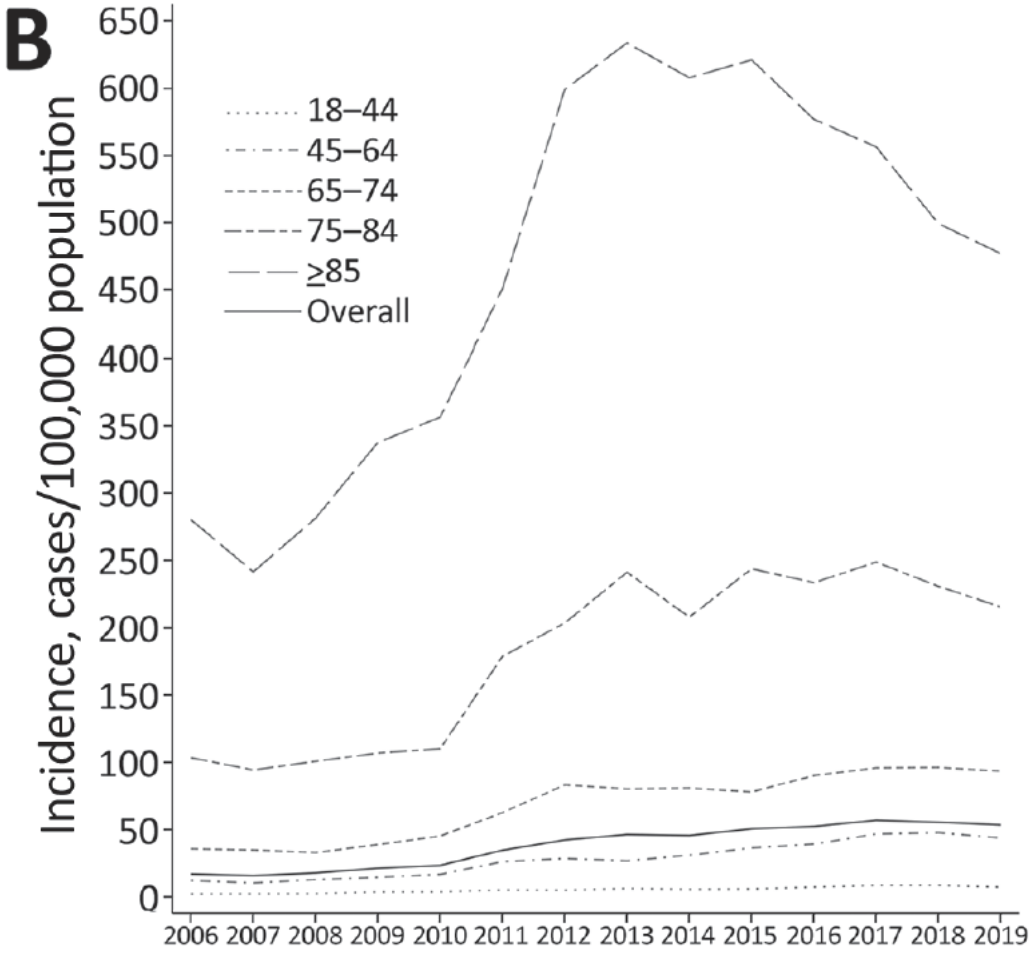
Incidence of CDI in Hong Kong, 2006-2014



Ho et al. *Em Inf Dis* 23(10). 1671-1679

Incidence of CDI in Hong Kong, 2006-2019





Guo et al. *Em Inf Dis* 27(12). 3036-3044

Risk Factors for *C. difficile* Infection

Demographics

- Age older than 65
- Female gender
- Immunocompromised
  - Diabetes
  - HIV
  - Chronic Kidney Disease
  - IBD on biologic
- Prior episode of CDI

Exposures

- Exposure to antimicrobial agents
- Chemotherapy
- Gastrointestinal surgery
- Acid suppression medications

Environment

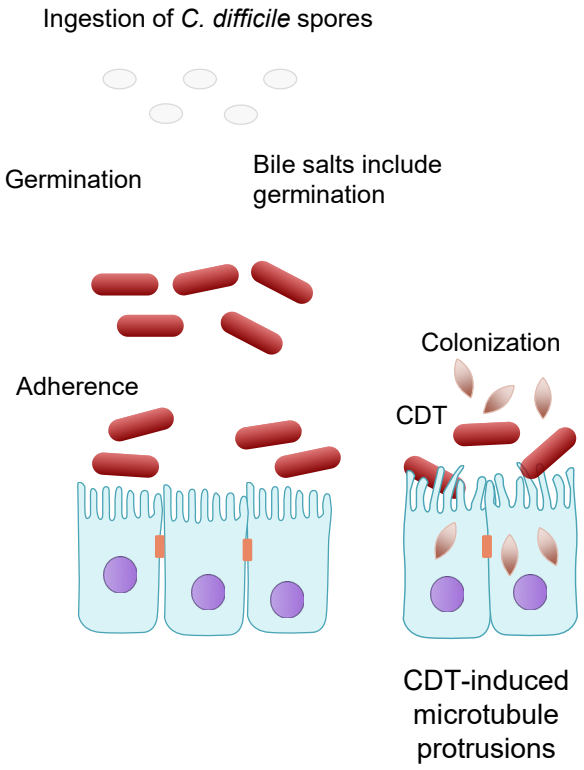
- Extended stay at a hospital and/or residence in a long-term care facility
- Contact with contaminated environment and/or health worker hand colonization
- Direct contact with a patient with CDI

Cohen SH, et al. *Infect Control Hosp Epidemiol*. 2010;31(5):431-455;
Fekety R, et al. Clin Infect Dis. 1997; 24(3): 324-333
Shakov R, et al. *Am J Infect Control*. 2011;39(3):194-198.

Epidemiology

Pathophysiology

Diagnosis

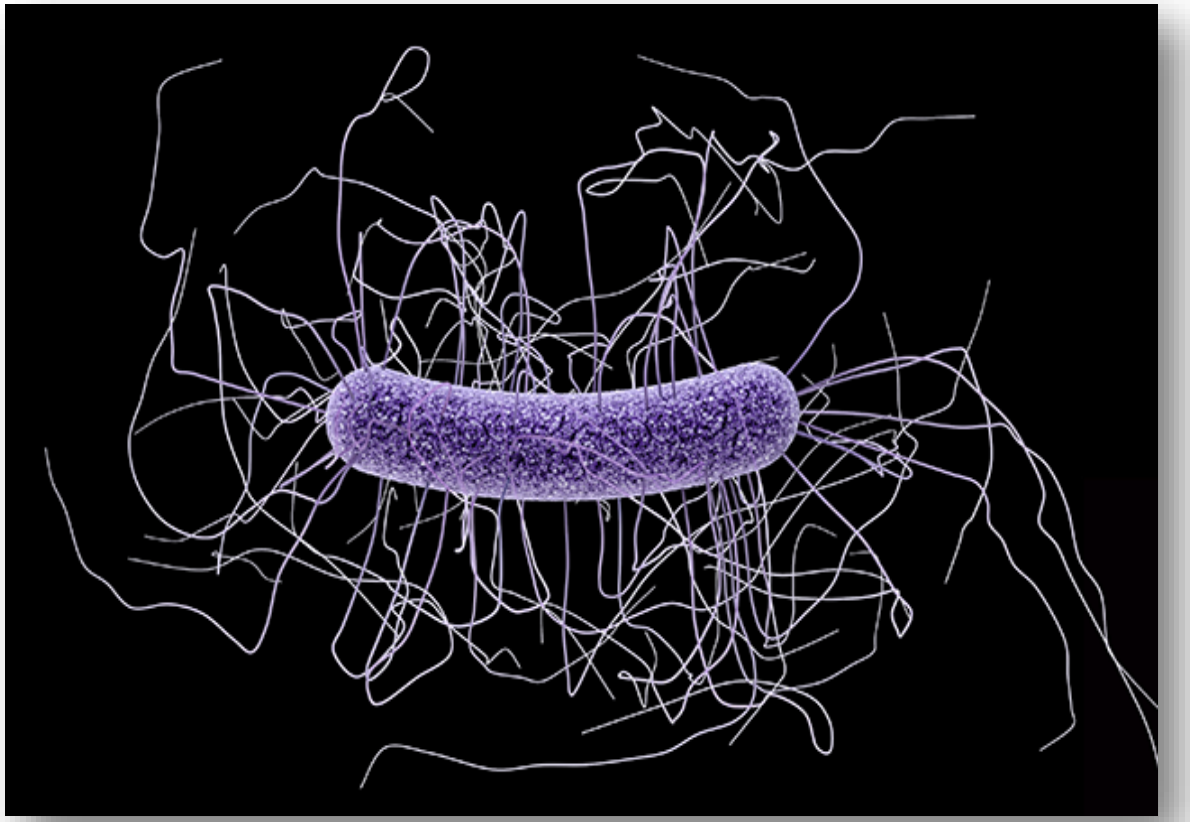


Prevention of Recurrence

Treatment

Adapted from: Shen J. *Innate Immun*. 2012;4:149-158.

What is *Clostridioides difficile*?



- Gram positive
- Spore forming
- Anaerobic
- Rod

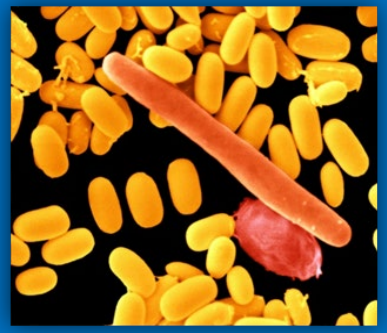
Microbiology

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]

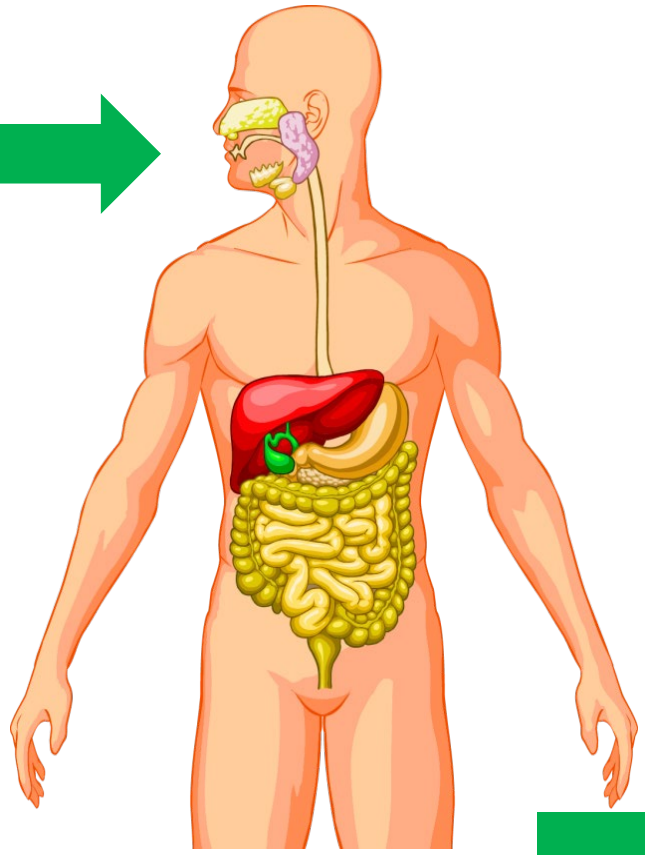
Survives on surfaces for months

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

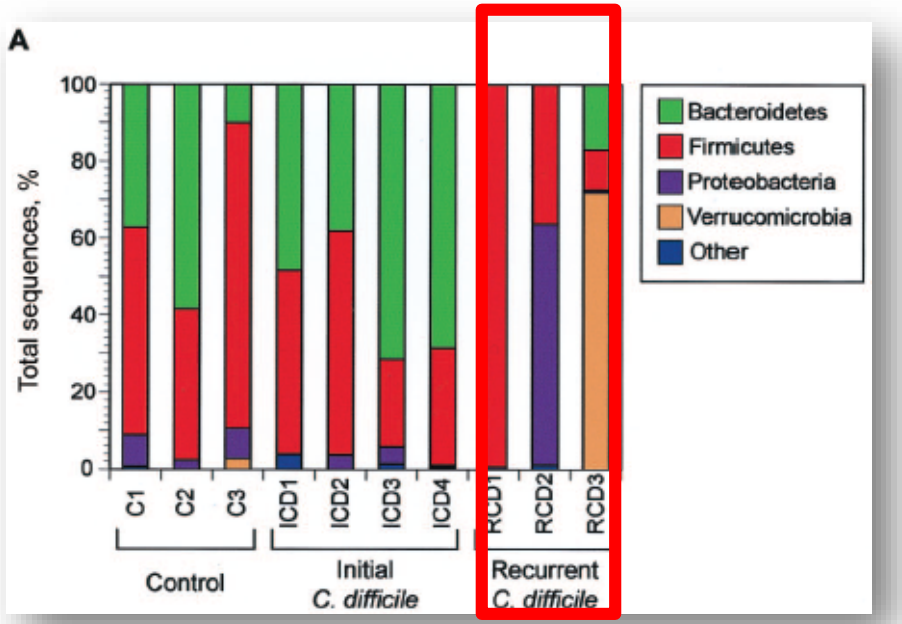


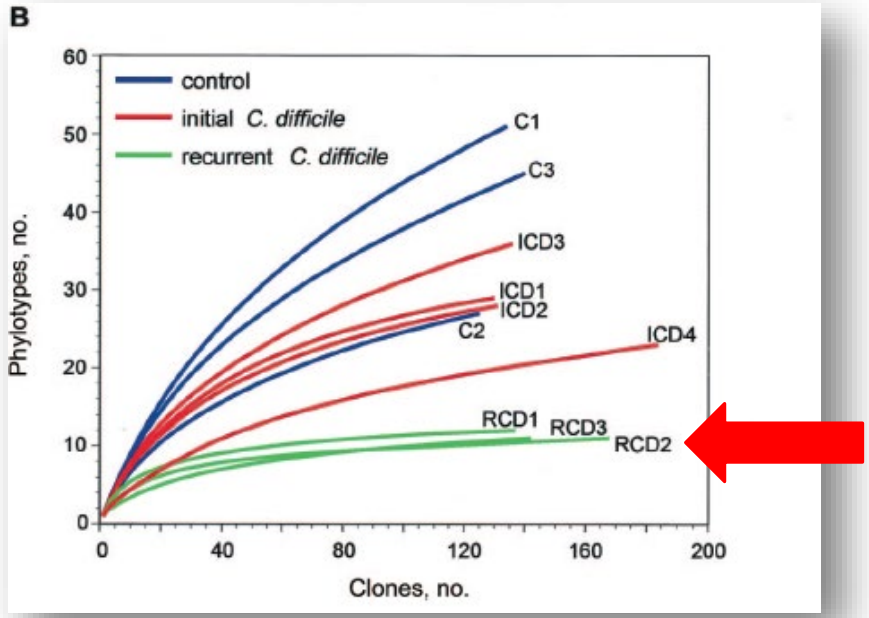
Symptoms

- Diarrhea
- Constipation
- Ileus
- Megacolon

To best understand the modern treatments, we have to understand the pathophysiology of this infection and the targets of those treatments

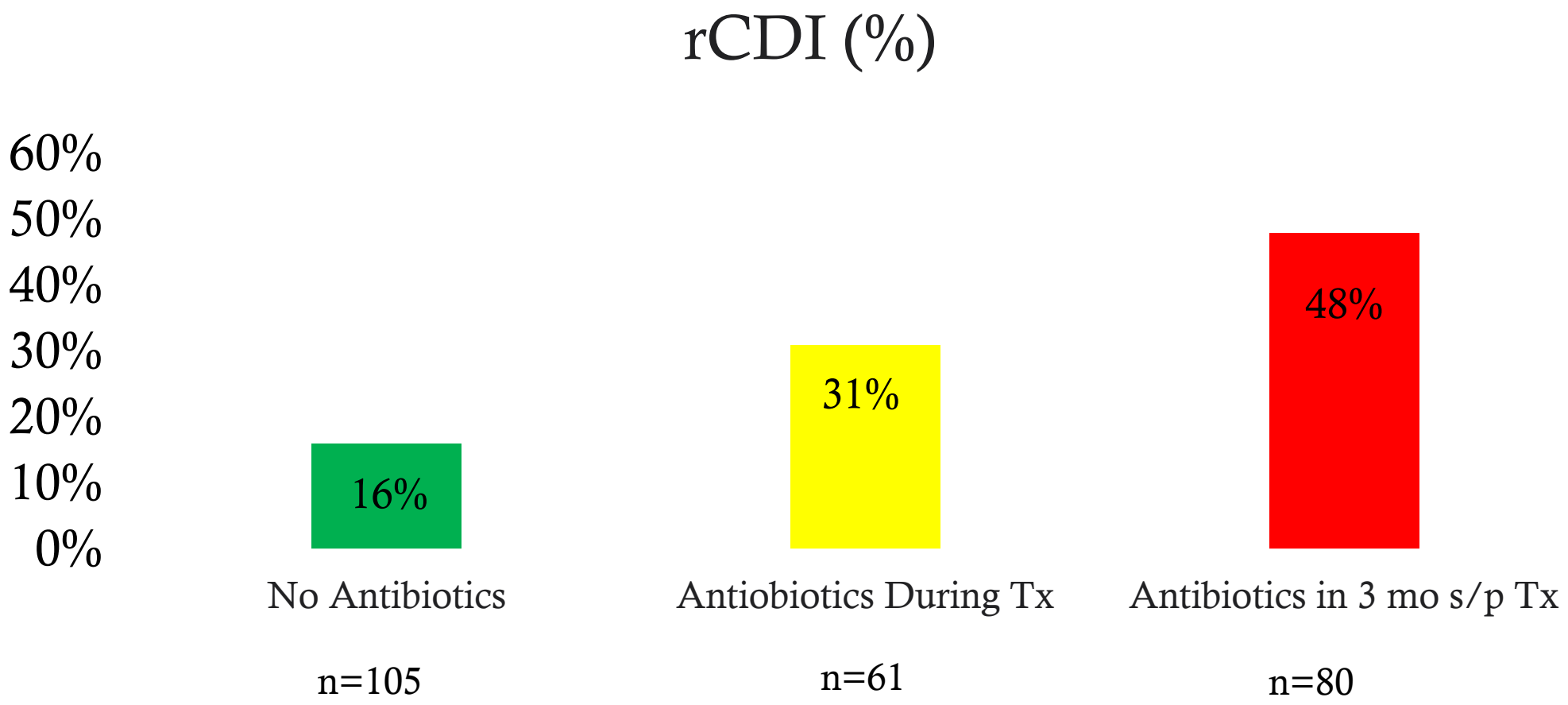
Diversity of Microbiome in Initial and Recurrent CDI





Chang JY et al. *J Infect Dis*. 2008;197(3):435-8.

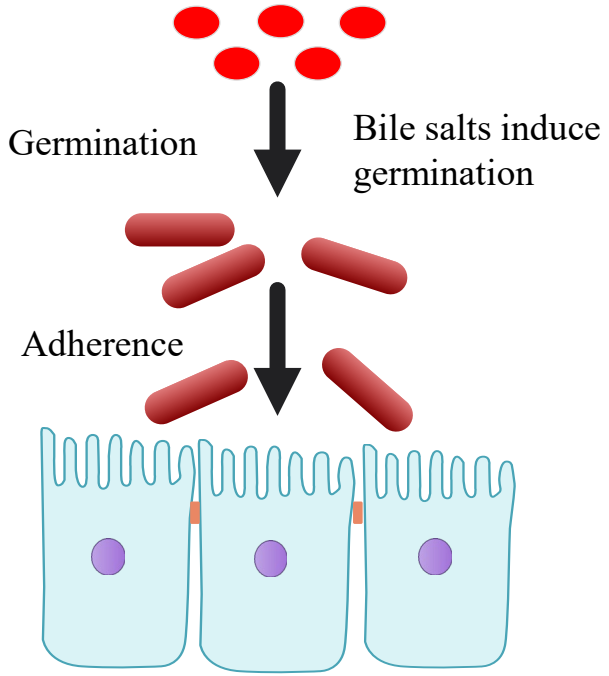
Impact of Antibiotics Post-rCDI



rCDI, recurrent *Clostridioides difficile* infection; Tx, treatment.
Drekonja et al. *Am J Med*. 2011. 124 (11) 1081-1088.

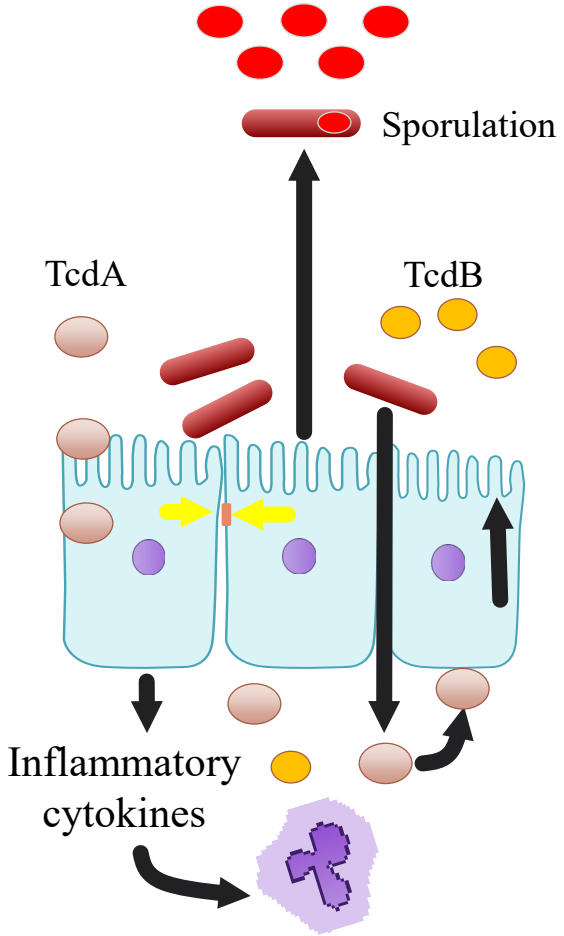
Pathophysiology

Ingestion of *C. difficile* spores

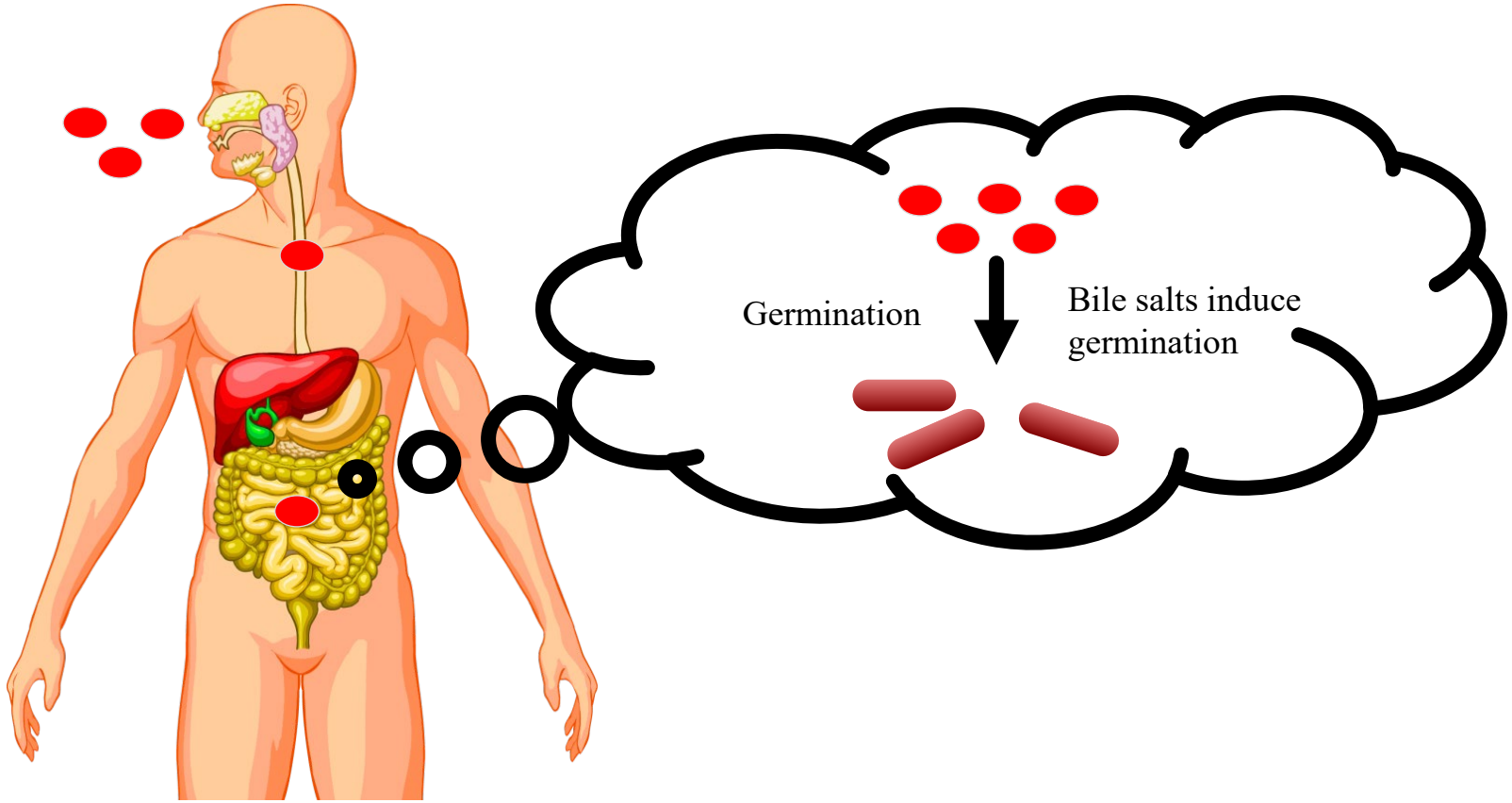


Glucosylating toxin production

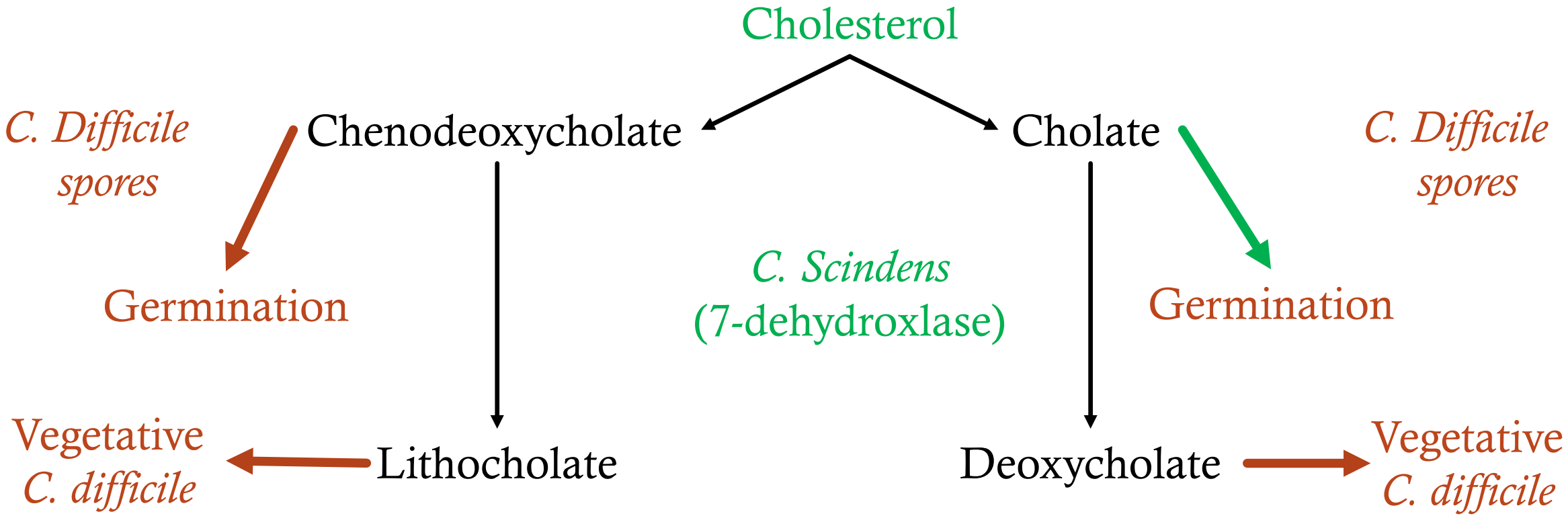
Transmission of spores



Pathophysiology: Ingestion of *C. difficile* Spores

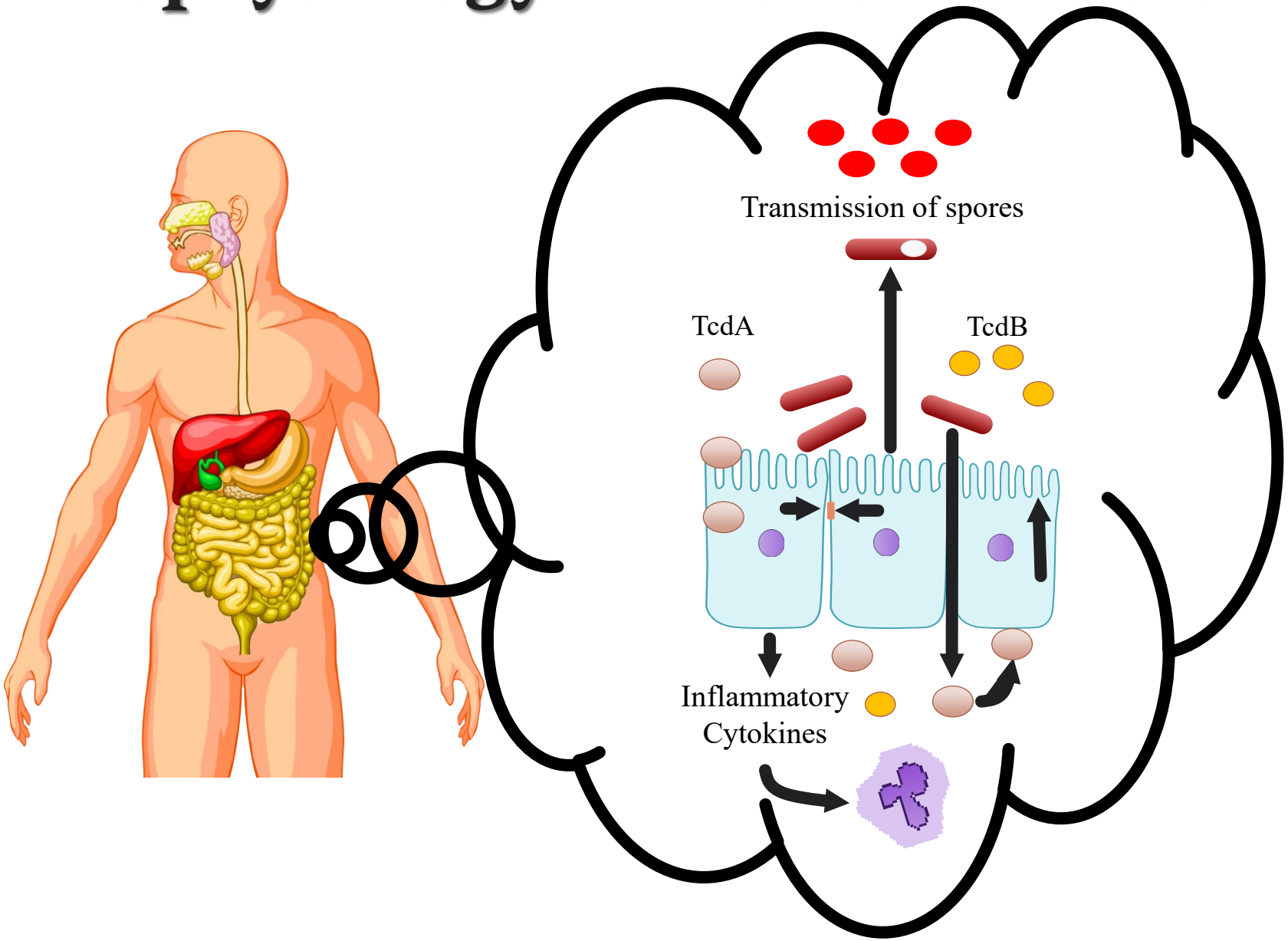


Effect of Bile Acid Metabolism on *C. difficile* Life Cycle



Shen et al. *PLOS Pathog* 2015. 10; 1-7

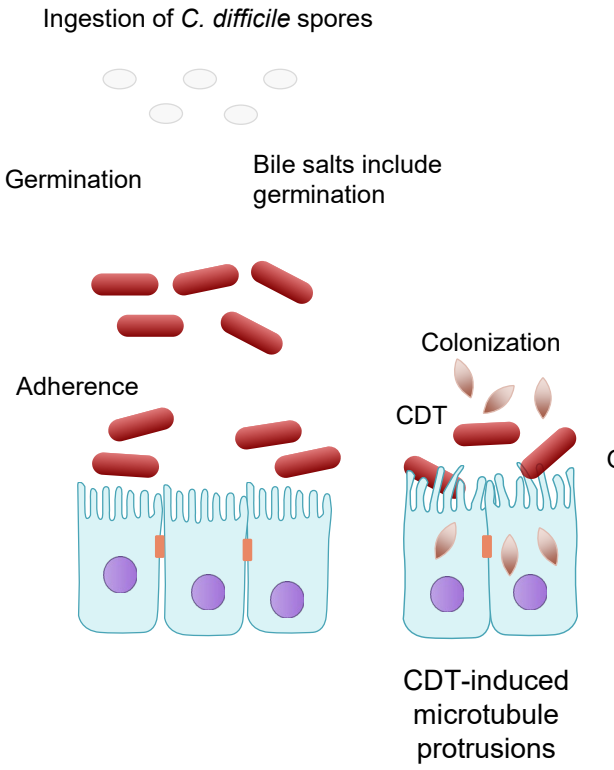
Pathophysiology: Infection of Colon



Epidemiology

Pathophysiology

Diagnosis

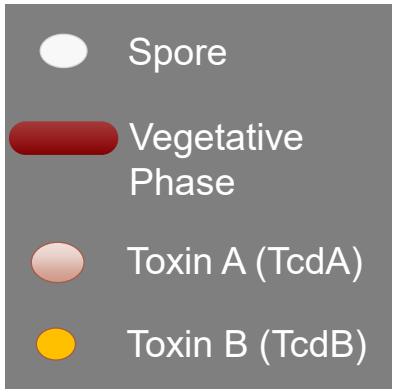


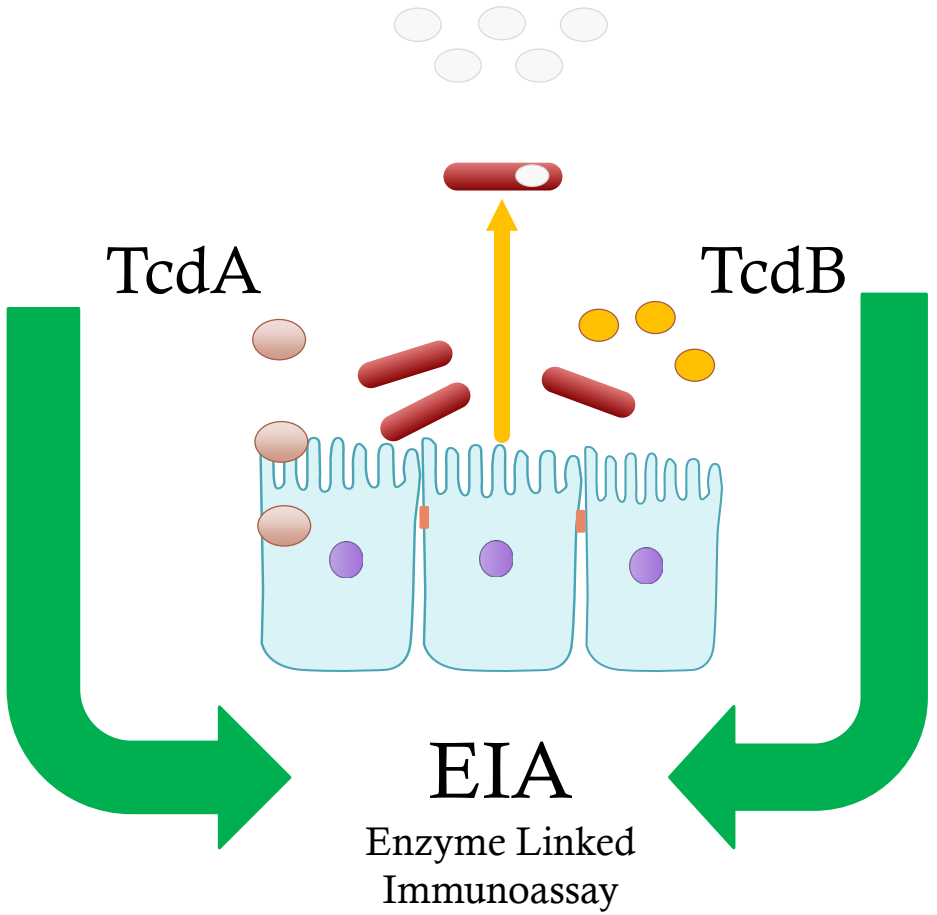
Prevention of Recurrence

Treatment

Adapted from: Shen J. *Innate Immun*. 2012;4:149-158.

Diagnostic Tool: Toxin Detection

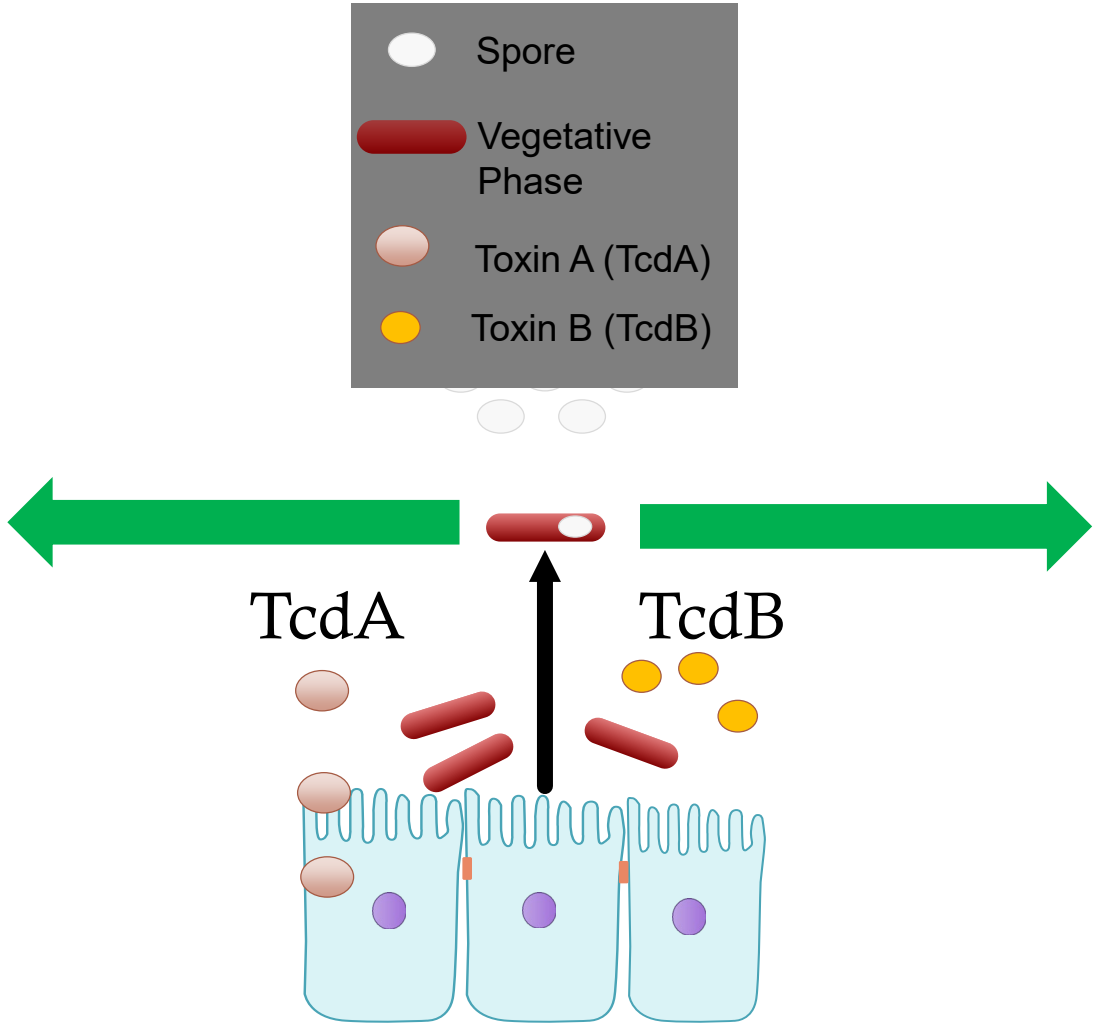




Sensitivity: Low
Specificity: Moderate

McDonald et al. *Clin Infec Dis 2018. 66 (7) e1-e48*

Diagnosis: Organism Detection



GDH
(Glutamate Dehydrodense)

Detects: Enzyme release by *Clostridioides*

Sensitivity: High

Specificity: Low

PCR
(Polymerase Chain Reaction)

Detects: Toxin Genes

Sensitivity: High

Specificity: Mod

McDonald et al. *Clin Infec Dis 2018. 66 (7) e1-e48*

Noah

- 50 year old man
- Past Medical History:
  - Hypertension
  - Diabetes
  - GERD
  - Obesity
- Past Surgical History
  - Appendectomy
- Presented with the sudden onset of 10-12 liquid bowel movements daily
- Cramping abdominal pains (6/10) relieved with bowel movement
- Subjective fevers
- No recent travel, sick contacts or antimicrobial exposures
- Initial:
  - WBC: 16,000 x 10^3/mL
  - Cr: 0.9 mg/dL

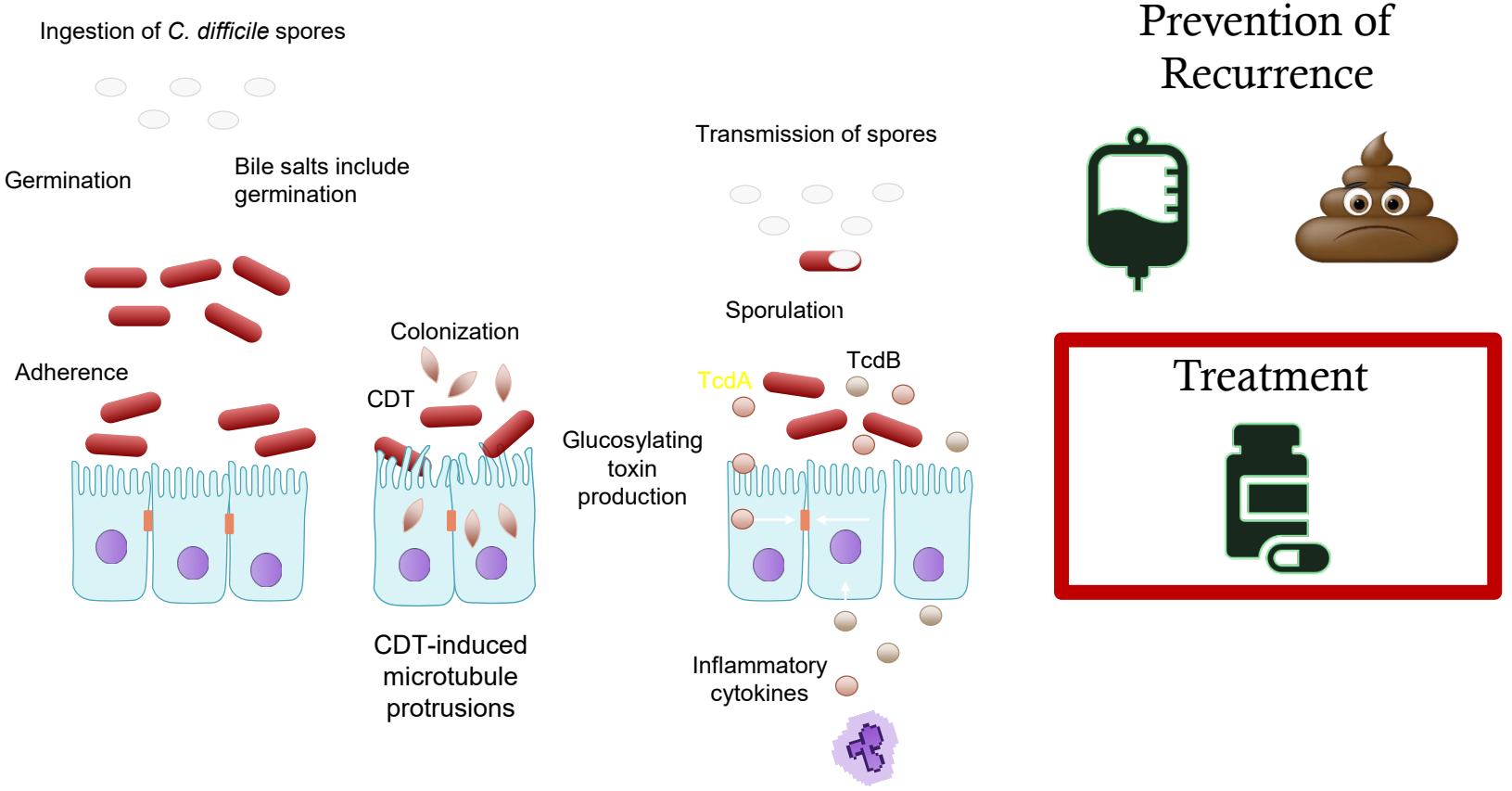
Noah

What would be the most data driven treatment for Noah?

Epidemiology

Pathophysiology

Diagnosis



Prevention of Recurrence

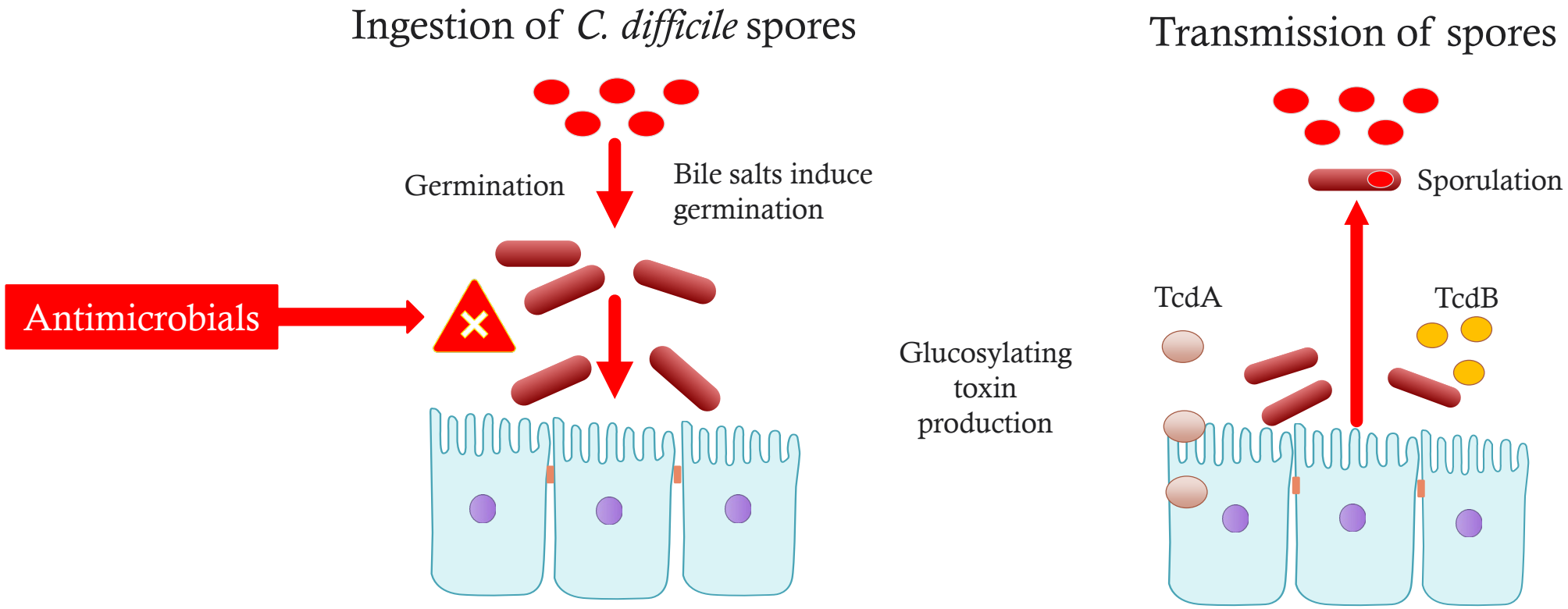
Treatment

Adapted from: Shen J. *Innate Immun*. 2012;4:149-158.

Treatment: What are we targeting?

Attack the Vegetative Phase

Boost Immune Response



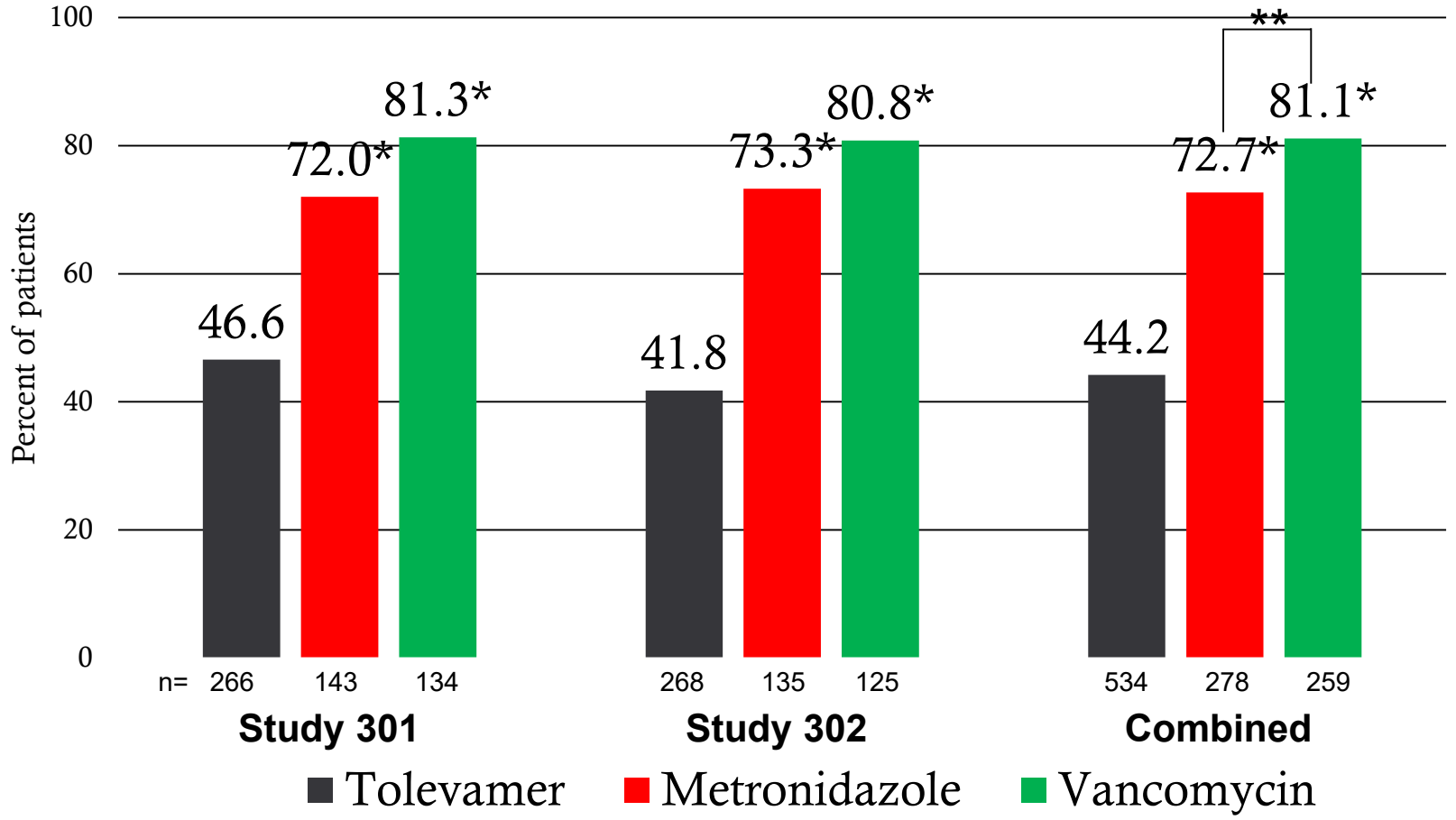
Adapted from: Shen J. *Innate Immun*. 2012;4:149-158.

Guideline Recommendations for Primary CDI Episode

Recommendation	IDSA/SHEA[1,2]	ESCMID[3]	ACG[4]
Preferred	Fidaxomicin 200 mg PO BID x 10 days	Fidaxomicin 200 mg PO BID x 10 days	Fidaxomicin 200 mg PO BID x 10 days Vancomycin 125 mg PO 4x/day x 10 days
Alternative	Vancomycin 125 mg PO 4x/day x 10 days *If no other available agents (nonsevere):* Metronidazole 500 mg PO 3x/day x 10-14 days	Vancomycin 125 mg PO 4x/day x 10 days *If no other available agents:* Metronidazole 500 mg PO 3x/day x 10 days	*If no other available agents (nonsevere):* Metronidazole 500 mg PO 3x/day x 10 days
Comments	In settings where logistics are not an issue, consider addition of bezlotoxumab in high risk of recurrence	Risk stratify for recurrence with selective use of fidaxomicin in limited access/resources Consider addition of bezlotoxumab in high risk of recurrence	Consider addition of bezlotoxumab in high risk of recurrence Consider FMT on case-by-case basis in severe CDI unresponsive to standard therapy

1. McDonald. Clin Infect Dis. 2018;66:e1. 2. Johnson. Clin Infect Dis. 2021;73:e1029.
3. van Prehn. Clin Microbiol Infect. 2021;27:S1. 4. Kelly. Am J Gastroenterol. 2021;116:1124.

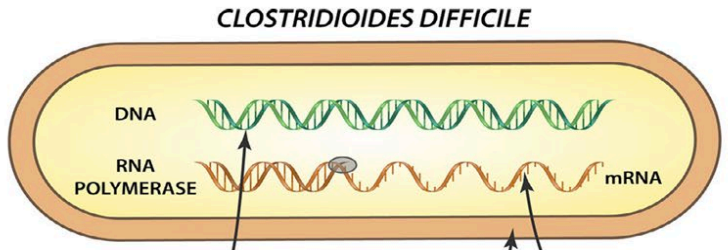
Tolevamer vs. Metronidazole vs. Vancomycin
Clinical Success-Overall Cohort



*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.

CDI Antimicrobial Comparison

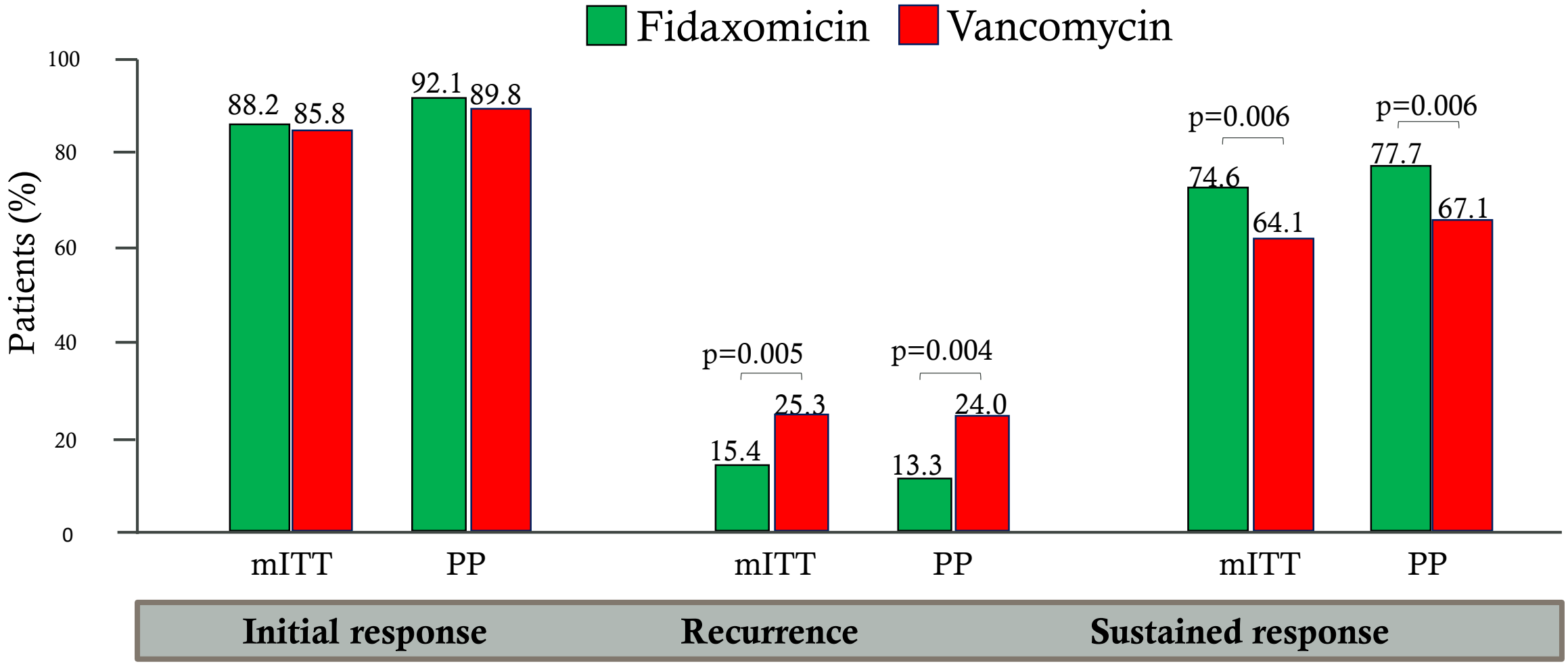


	METRONIDAZOLE	VANCOMYCIN	FIDAXOMICIN
SYSTEMIC ABSORPTION	HIGH	LOW	LOW
STOOL CONCENTRATION	LOW	HIGH	HIGH
REDUCTION OF BIOACTIVITY BY FAECES	HIGHEST	LOWER	LOWER
EFFECT ON DIVERSITY OF MICROBIOTA	REDUCTION	REDUCTION	PRESERVATION
STOOL SHEDDING DECLINE	SLOW	RAPID	RAPID
ENVIRONMENTAL CONTAMINATION	HIGHEST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

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

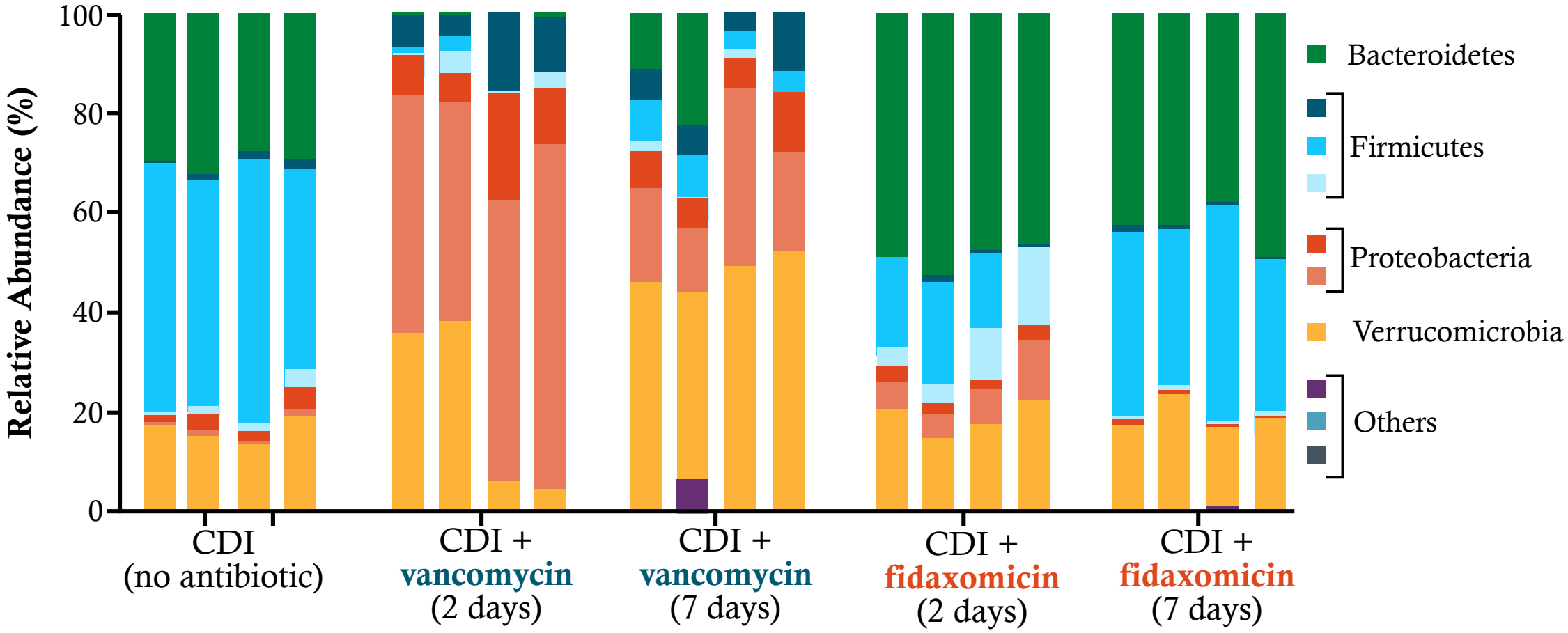
Krutova M, et al. *Int J Infect Dis*. 2022;124:118-123.

Fidaxomicin and Vancomycin for Initial *C. difficile* Infection



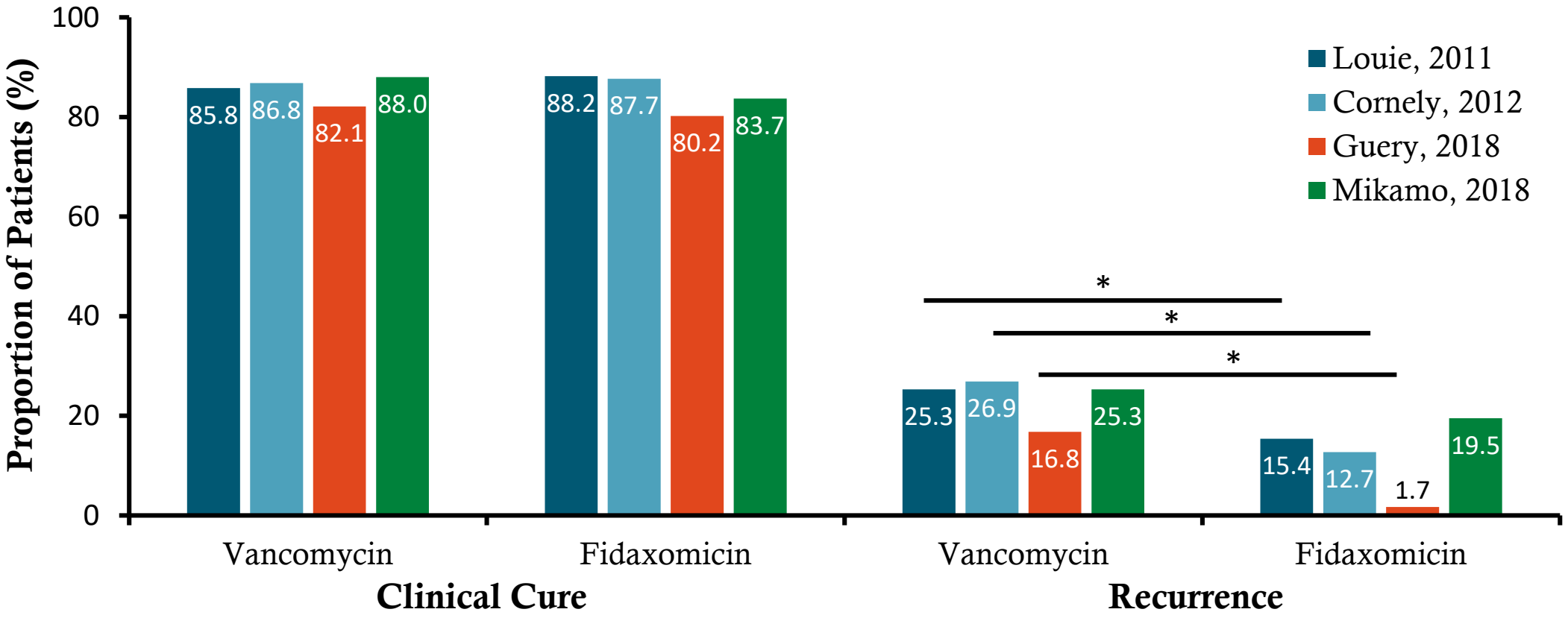
Louie et al. *N Engl J Med*. 2011;364(5):422-431.

CDI Dysbiosis by Antibiotic in Mice



Yamaguchi. J Infect Chemother. 2020;26:483.

CDI Antibiotic-associated Recurrence



*Difference was statistically significant

1. Louie. NEJM. 2011;364:422. 2. Cornely. Lancet Infect Dis. 2012;12:281. 3. Guery. Lancet Infect Dis. 2018;18:296.
4. Mikamo. J Infect Chemother. 2018;24:744.

Noah

- Treated with vancomycin 125 mg PO Qid for 14-days and responds
- 4 weeks later he has the return of abdominal pains with 6-8 numerous liquid stools per day. He calls his primary care MD and is referred to a gastroenterologist for further assessment

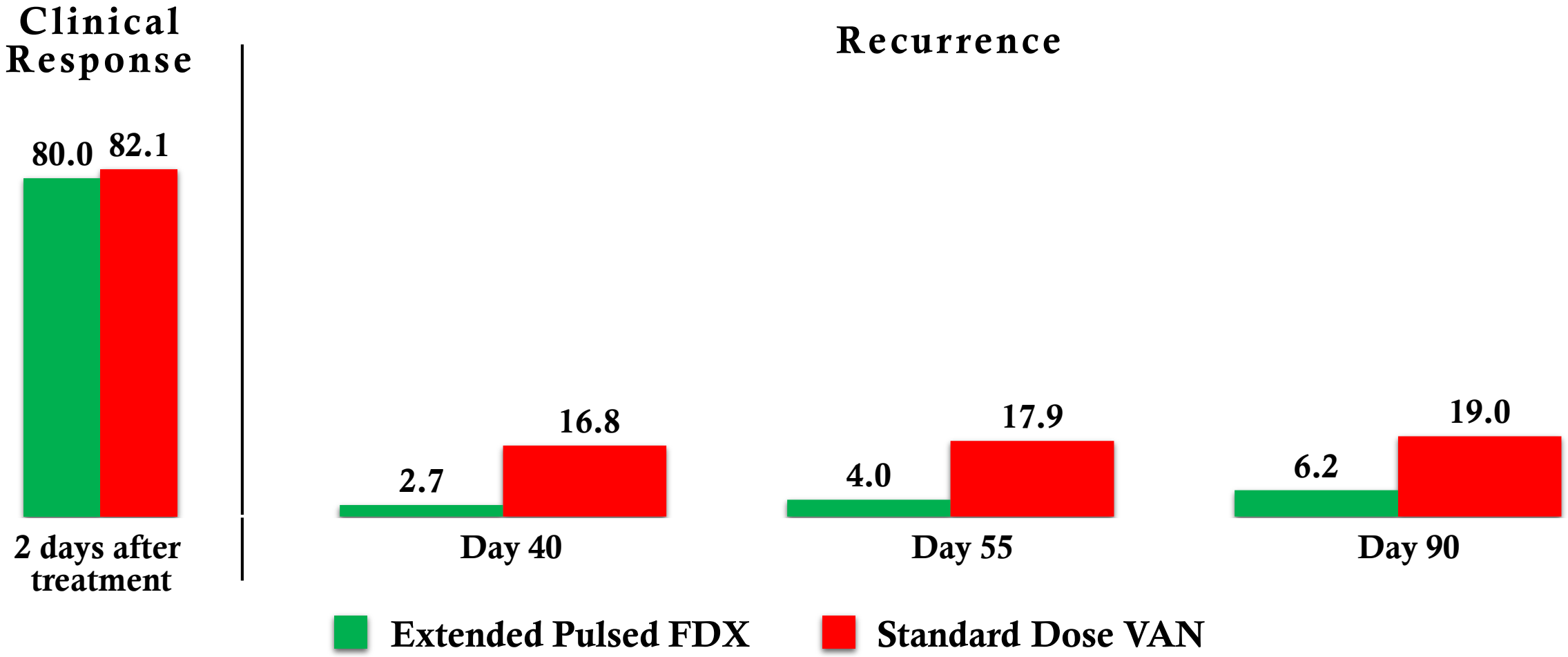
What can we use next to treat Noah's recurrence?

2021 IDSA/SHEA Treatment Recommendations for CDI in Adults: First Recurrence

Clinical Presentation	Recommendation	Comments
First Recurrence	**Preferred** **Fidaxomicin** standard or extended dosing	
	Alternative **Vancomycin in tapered and pulsed regimen**	**Vancomycin tapered/pulsed example regimen: 125 mg 4x/day x 10-14 days, 2x/day x 7 days, 1x/day x 7 days, then every 2-3 days x 2-8 wk**
	Vancomycin standard dosing	Consider if metronidazole was used for treatment of first episode
	Adjunctive **Bezlotoxumab 10 mg/kg IV once during administration of SoC antibiotics**	May be considered during first episode if other **risks for CDI recurrence** are present

Johnson. Clin Infect Dis. 2021;73:e1029.

Extended Pulsed Fidaxomicin vs 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

Vancomycin Taper *and* Pulse

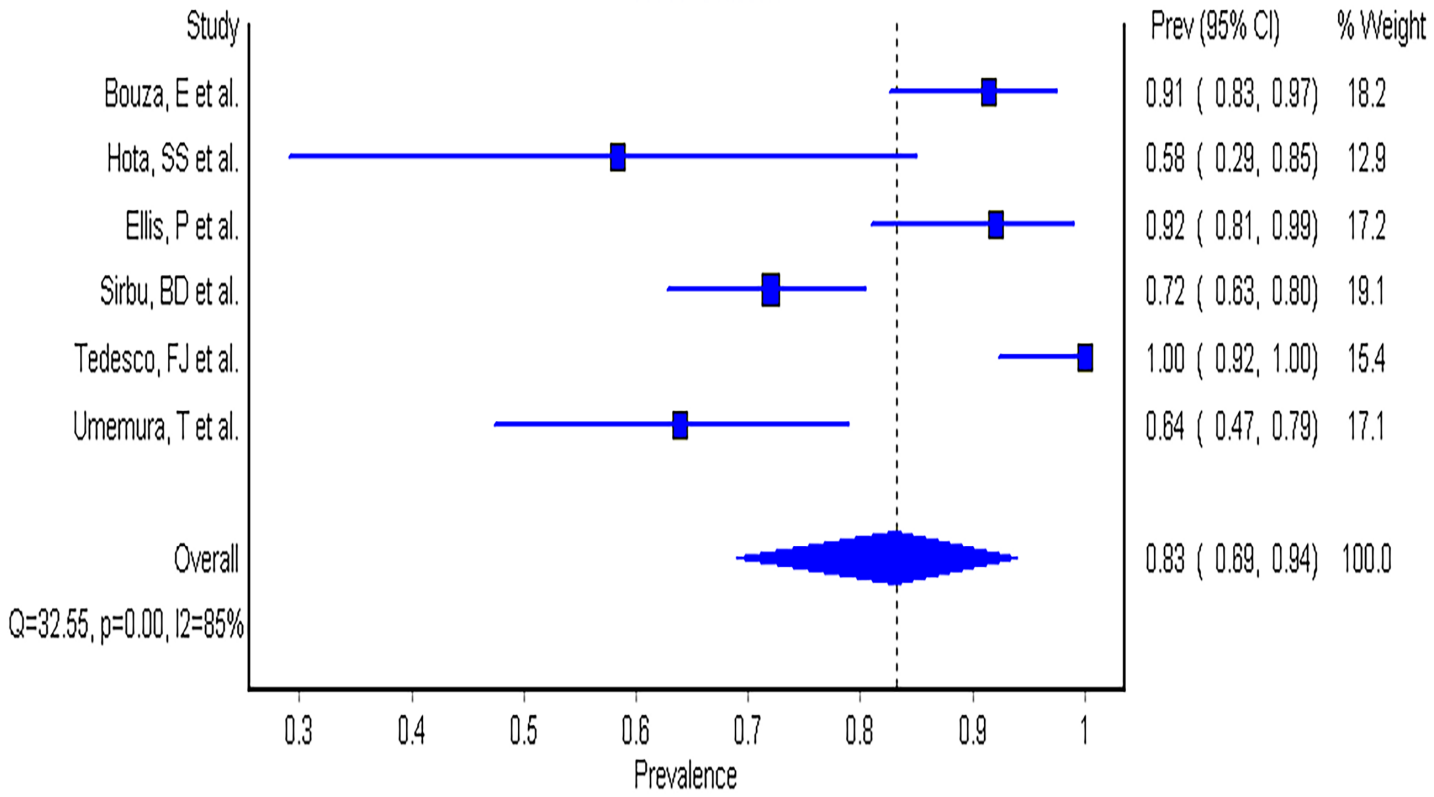
Taper and pulse

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)

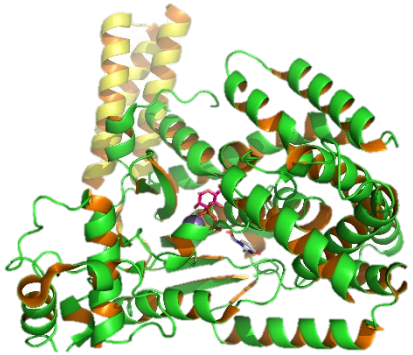
Sehgal et al. Expert Rev Anti Infect Ther 2022 20 (4):577-583

Noah

What else can be done to minimize Noah's future risks for recurrence?

Multimodal Approach to Therapy

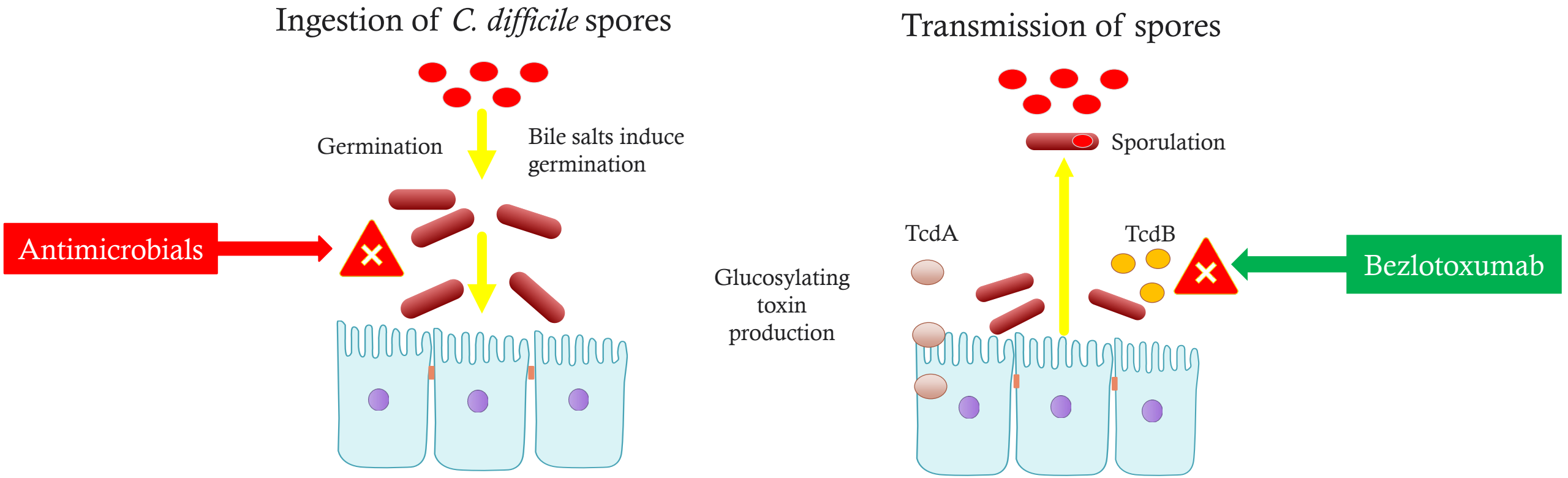
Bezlotoxumab



Treatment: What are we doing?

Attack the Vegetative Phase

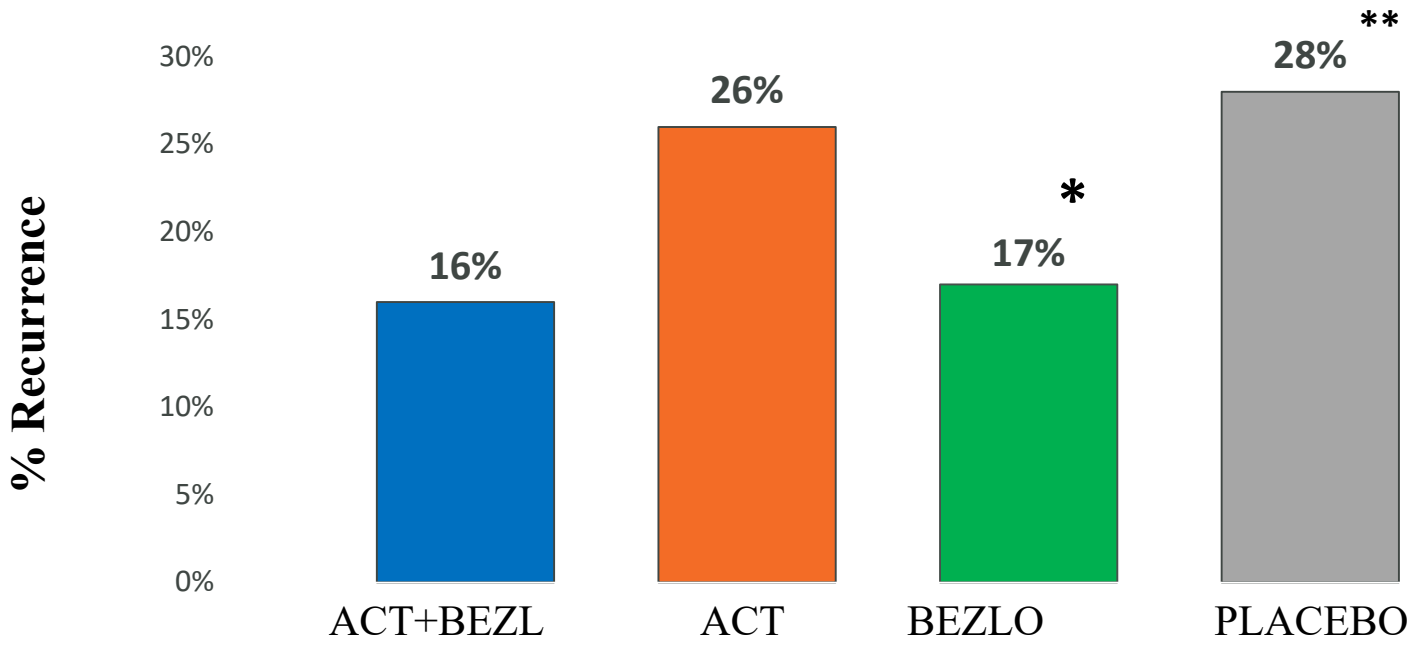
Boost Immune Response



Adapted from: Shen J. *Innate Immun*. 2012;4:149-158.

Bezlotoxumab RCT: MODIFY 1 and MODIFY 2

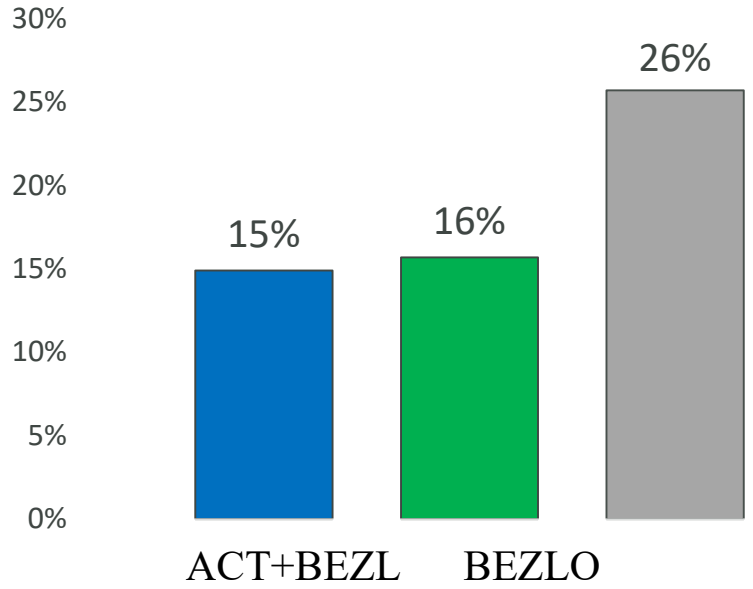
MODIFY 1



* ACT+BEZLO vs Pbo: p<0.0001

** BEZLO vs Pbo: p=0.0003

MODIFY 2



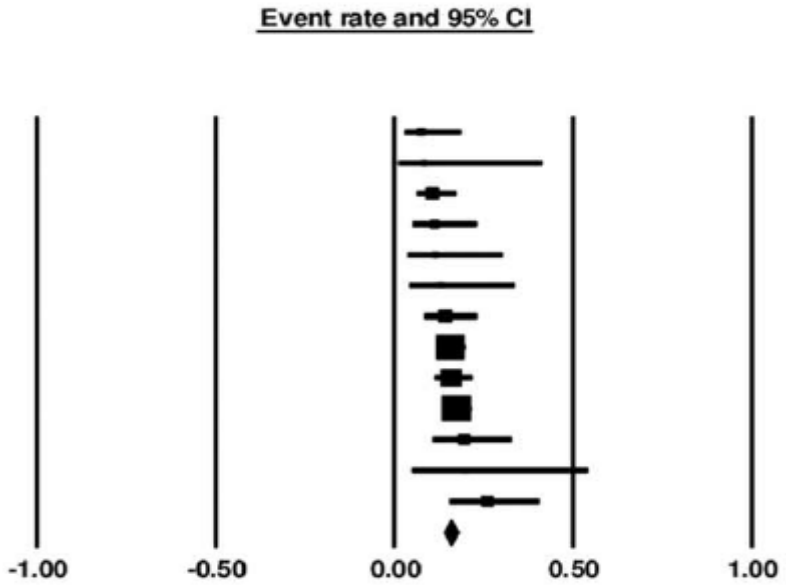
* ACT+BEZLO vs Placebo: p<0.0001

** BEZLO vs Placebo: p=0.0003

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

Efficacy of Bezlotoxumab-Metanalysis

Study name	Event rate	Lower limit	Upper limit	Z-Value	p-Value	Total	Relative weight
Lopez R.S. 2022	0.075	0.029	0.184	-4.818	0.000	4 / 53	1.94
Kerr 2019	0.083	0.012	0.413	-2.296	0.022	1 / 12	0.48
Pena 2022	0.107	0.064	0.172	-7.507	0.000	14 / 131	6.54
Johnson 2022	0.113	0.052	0.230	-4.748	0.000	6 / 53	2.78
Perreault 2020	0.115	0.038	0.303	-3.318	0.001	3 / 26	1.39
Askar 2022	0.130	0.043	0.335	-3.064	0.002	3 / 23	1.37
Escudero-Sánchez 2020	0.143	0.085	0.231	-5.981	0.000	13 / 91	5.83
Wilcox/ MODIFY II 2017	0.157	0.124	0.196	-12.153	0.000	62 / 395	27.36
Hengel 2020	0.159	0.114	0.217	-8.506	0.000	31 / 195	13.65
Wilcox/ MODIFY I 2017	0.174	0.139	0.215	-11.612	0.000	67 / 386	28.98
De La Villa 2023	0.196	0.109	0.327	-4.001	0.000	10 / 51	4.21
Bradely 2022	0.200	0.050	0.541	-1.754	0.080	2 / 10	0.84
Oksi 2019	0.261	0.155	0.405	-3.102	0.002	12 / 46	4.64
	0.158	0.140	0.178	-23.135	0.000	228 / 1472	



P-value: **0.00**; Q-value: **12**; I^2**0%**; Tau Squared: **0.00**

- 13 studies, 2 randomized controlled trials, 11 observational trials
- 2,337 patients in total
- **rCDI receiving SOC followed by Bezlo: 15.8%, SOC alone: 28.9%**

Mohamed MFH et al. J Clin Gastro 2023. Jul 3

Lorraine

- 61 year old woman
- Past Medical History:
  - Hypertension
  - Diabetes
  - GERD
  - *C. difficile* infection (3/22)
- Past Surgical History
  - Appendectomy

Lorraine, May 2023

- Presented in 5/23 with the sudden onset of 6-8 liquid bowel movements daily
- Cramping abdominal pains (3/10), diffuse and relieved with bowel movement
- Occasional sweats
- No recent travel, sick contacts or antimicrobial exposures
- Initial:
  - WBC: 11,000 x 10^3/mL
  - Cr: 1.1 mg/dL

Lorraine, June 2023

- Treated with Vancomycin 125 mg PO Qid for 14-days and responds
- 4 weeks later she has the return of her abdominal pains with 6-9 liquid stools per day. She calls her primary care MD and is referred to your office for further assessment
- Initial:
  - WBC: 9,000 x 10^3/mL
  - Cr: 0.9 mg/dL

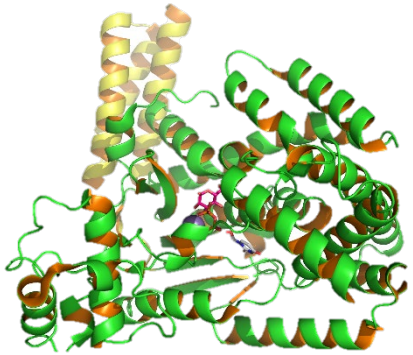
Lorraine, June 2023

What would be the best treatment for Lorraine's recurrence?

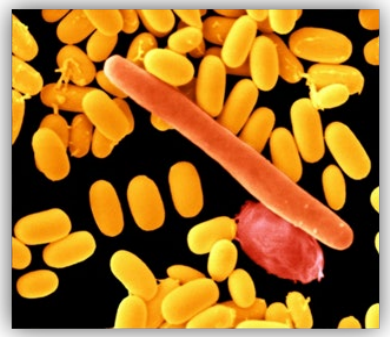
Is there anything we can do in the future to prevent another recurrence?

Multimodal Approach to Therapy

Bezlotoxumab

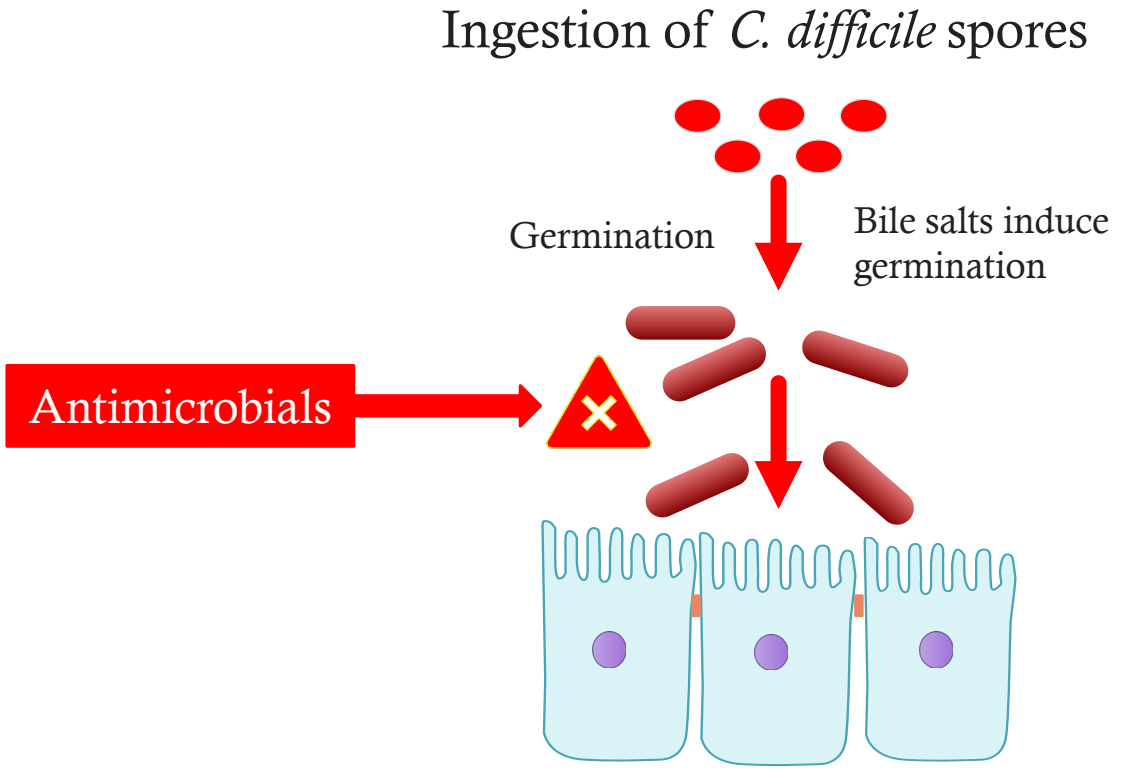


Fecal Microbiota Transplantation

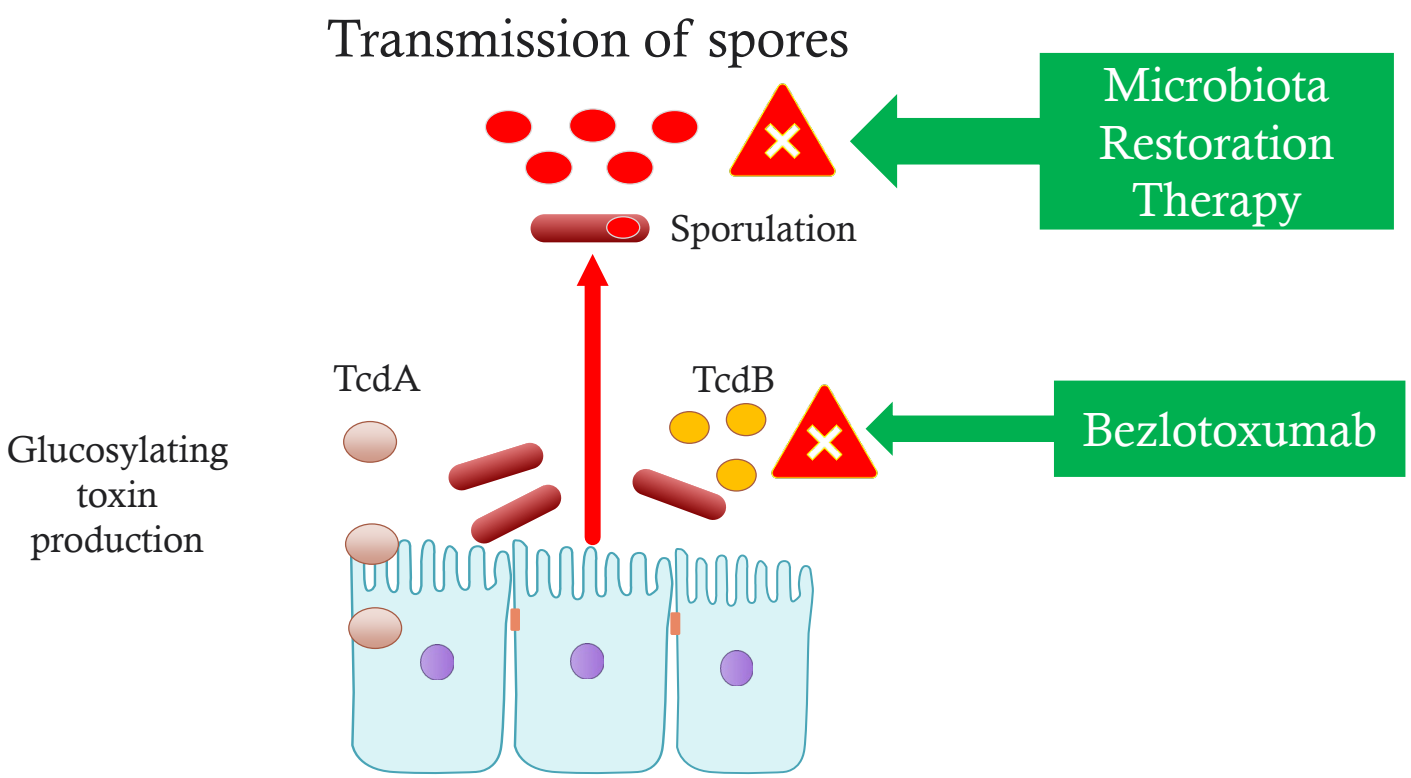


Treatment: What are we doing?

Attack the Bacteria



Boost Immune Response



Adapted from: Shen J. *Innate Immun*. 2012;4:149-158.

Guideline Recommendations: FMT for Recurrent CDI

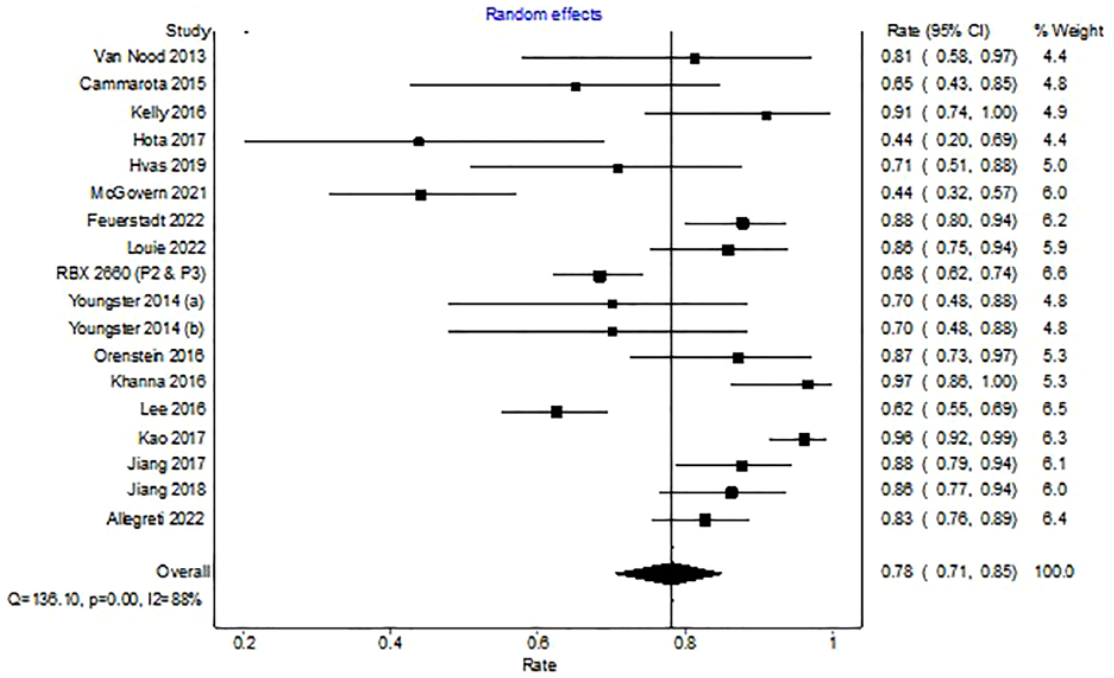
	IDSA/SHEA[1,2]	ESCMID[3]	ACG[4]
Recommendation	**FMT** may be used for patients experiencing a **2nd or subsequent CDI recurrence**	**FMT** after SOC antibiotics is an option for a **2nd or further CDI recurrence**	Recommend **FMT** for patients experiencing a **2nd or further CDI recurrence**
Comments	Appropriate antibiotic treatment for **at least 2 recurrences (3rd episode)** should be tried prior to offering FMT	An adequate multidisciplinary risk assessment and surgical consult is mandatory and FMT products should be available with standardized preparation and screening	Recommend delivery of FMT by colonoscopy or capsules, or enema if other methods are unavailable Suggest repeating FMT if patient experiences a recurrence within 8 wk of initial FMT

1. McDonald. Clin Infect Dis. 2018;66:e1. 2. Johnson. Clin Infect Dis. 2021;73:e1029.
3. van Prehn. Clin Microbiol Infect. 2021;27:S1. 4. Kelly. Am J Gastroenterol. 2021;116:1124.

Resolution of rCDI with FMT/MRT

All Clinical Trials

(n=19 trials, 18 studies)

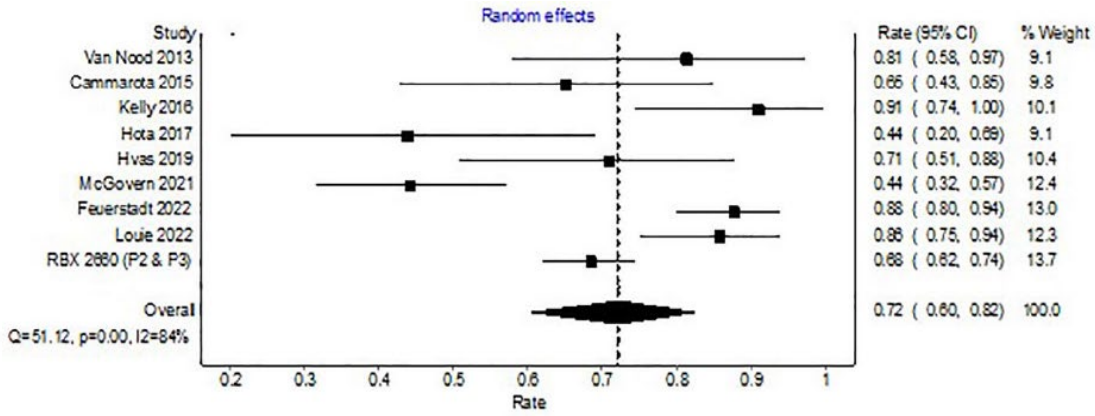


1,176 patients

Efficacy: 78% (95% CI: 71-85%)

Trials with a Control Arm

(n=10 trials, 9 studies)



523 patients

Efficacy: 72% (95% CI: 60-82%)

Tariq et al. Ther Adv Gastro 2023 Vol 16:1-9

Acronyms Galore

- FMT: Fecal microbiota transplantation
- MRT: Microbiota replacement therapy
- LBP: Live biotherapeutic product

Fecal Microbiota Transplant vs. Live Biotherapeutic Product

	FMT	LBP
Donor Screening		
Sample Screening		
Good Manufacturing Procedure		
Clinical Trial Data		
Safety Data		
Ease of access		

Fecal Microbiota Transplant vs. Live Biotherapeutic Product

	FMT	LBP
Donor Screening		
Sample Screening	?	
Good Manufacturing Procedure		
Clinical Trial Data		
Safety Data		
Ease of access		

Fecal Microbiota Transplant vs. Live Biotherapeutic Product

	FMT	LBP
Donor Screening	💩💩	💩💩💩
Sample Screening	?	💩💩💩
Good Manufacturing Procedure	?	💩💩💩
Clinical Trial Data		
Safety Data		
Ease of access		

Fecal Microbiota Transplant vs. Live Biotherapeutic Product

	FMT	LBP
Donor Screening	💩💩	💩💩💩
Sample Screening	?	💩💩💩
Good Manufacturing Procedure	?	💩💩💩
Clinical Trial Data	💩	💩💩💩
Safety Data		
Ease of access		

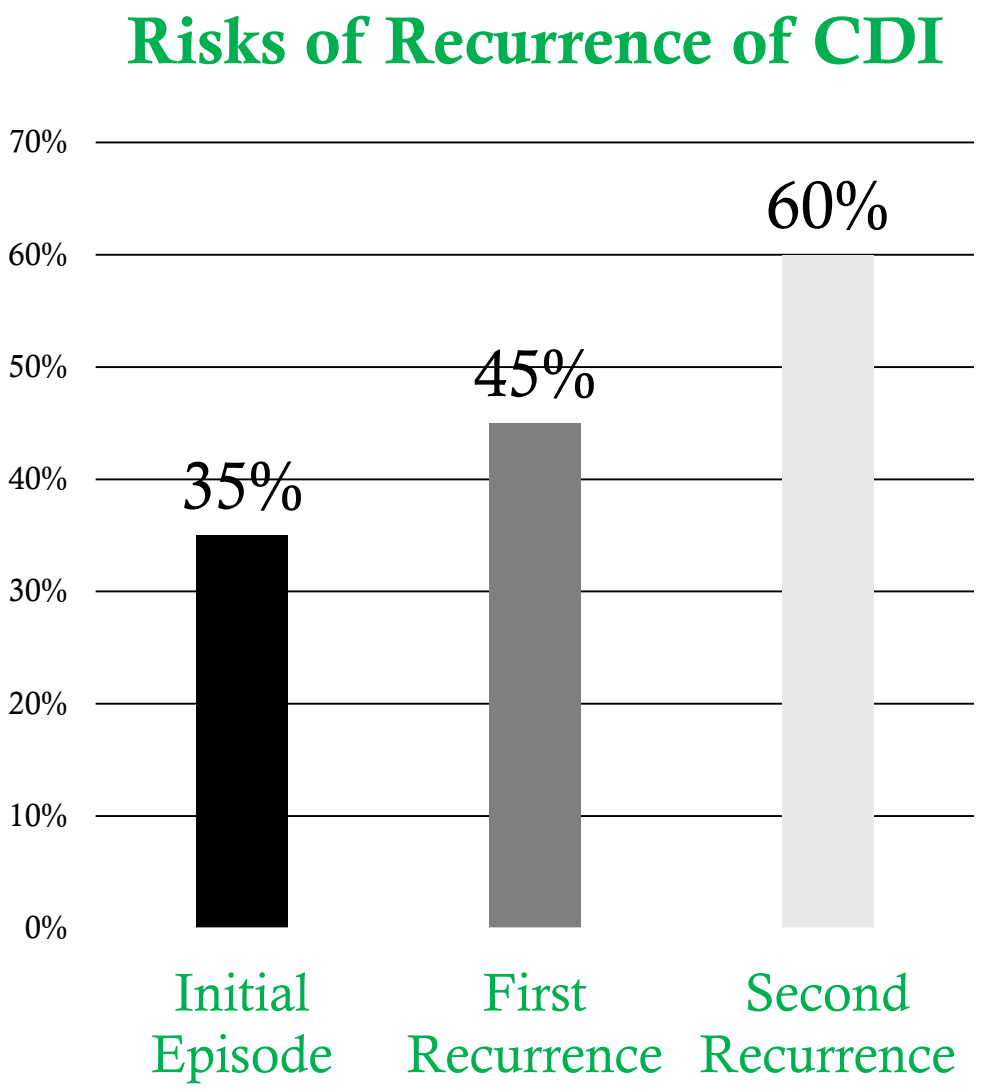
Fecal Microbiota Transplant vs. Live Biotherapeutic Product

	FMT	LBP
Donor Screening	💩 💩	💩 💩 💩
Sample Screening	?	💩 💩 💩
Good Manufacturing Procedure	?	💩 💩 💩
Clinical Trial Data	💩	💩 💩 💩
Safety Data	💩 / 💩	💩 💩 💩
Ease of access		

Fecal Microbiota Transplant vs. Live Biotherapeutic Product

	FMT	LBP
Donor Screening	💩 💩	💩 💩 💩
Sample Screening	?	💩 💩 💩
Good Manufacturing Procedure	?	💩 💩 💩
Clinical Trial Data	💩	💩 💩 💩
Safety Data	💩 / 💩	💩 💩 💩
Ease of access	?	💩

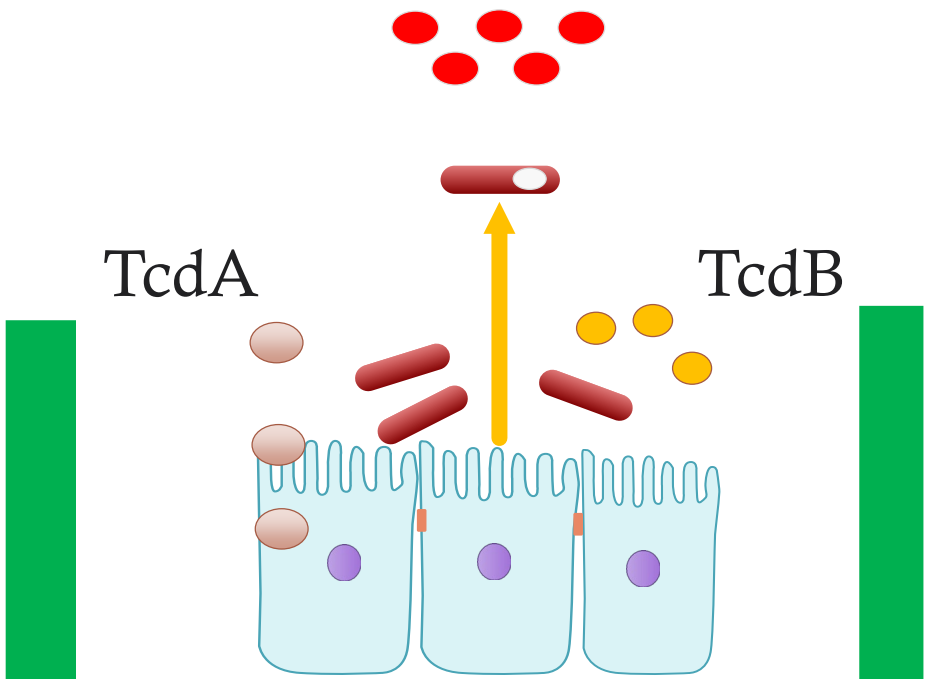
Episodes of *C. difficile* Infection



- ✓ More episodes of CDI, more likely to recur in the future
- ✓ Does that translate to it being more challenging to restore the microbiota?
- ✓ Is earlier restoration of the microbiota better?

Pépin et al. *Clin Infect Dis.* 2005;40:1591–7
McFarland et al. *Am J Gastroenterol.* 2002;97:1769–75
McDonald et al. *Clin Infec Dis 2018. 66 (7) e1-e48*

Diagnosis: Why is this Important?



EIA

Enzyme Linked Immunoassay

Sensitivity: Low
Specificity: Moderate

- ✓ EIA detects toxin but has challenges with false negative tests
- ✓ PCR accurately detects the genes coding for the 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

Duration of Standard of Care Antimicrobial

Fidaxomicin
Vancomycin
Metronidazole

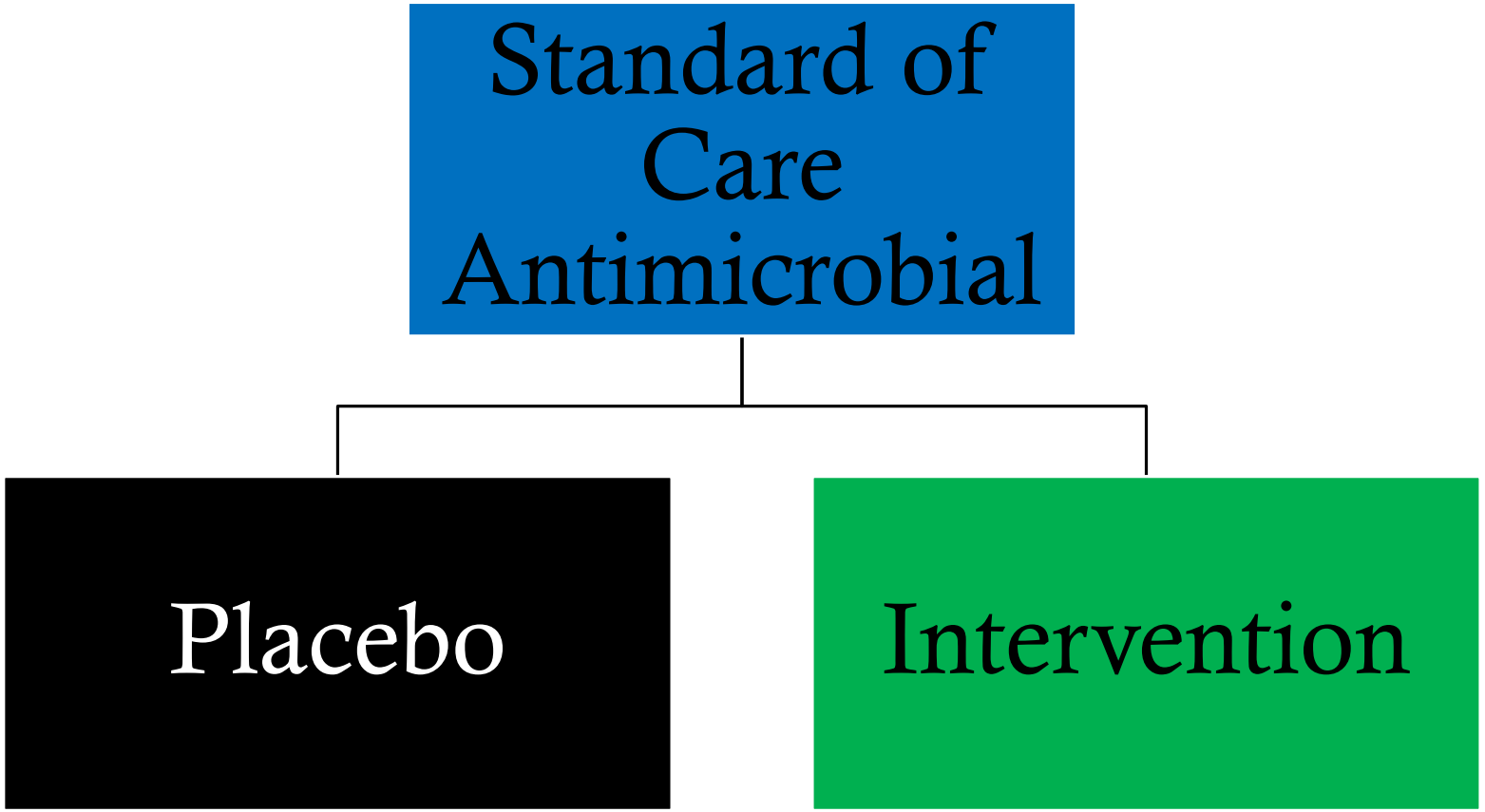
Vegetative phase

- ✓ Longer is not necessarily better
- ✓ Optimal duration prior to intervention is unclear, but standard treatment of at least 10 days is believe to be minimum
- ✓ **Goal:** Suppress the vegetative phase sufficiently to control symptoms and offer either the body the opportunity to replenish the microbiota to suppress the spore phase or restore the microbiota rapidly to prevent recurrence

Washout Period

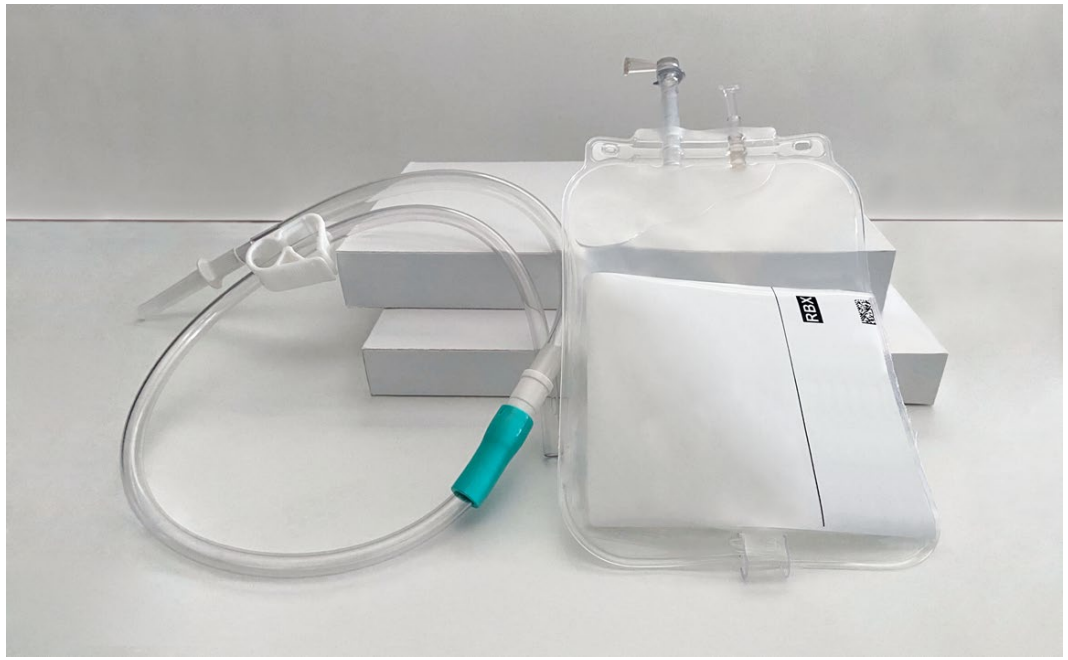
- ✓ Time from completion of standard of care antimicrobial to administration of LBP
- ✓ Minimize the impact of the standard of care antimicrobial on the administrated microbial species
- ✓ Goal: Clear as much of the antimicrobial from the patients system but also don't offer *C. difficile* the opportunity to re-germinate and recur
- ✓ Optimal timing unclear

Trial Design Overview



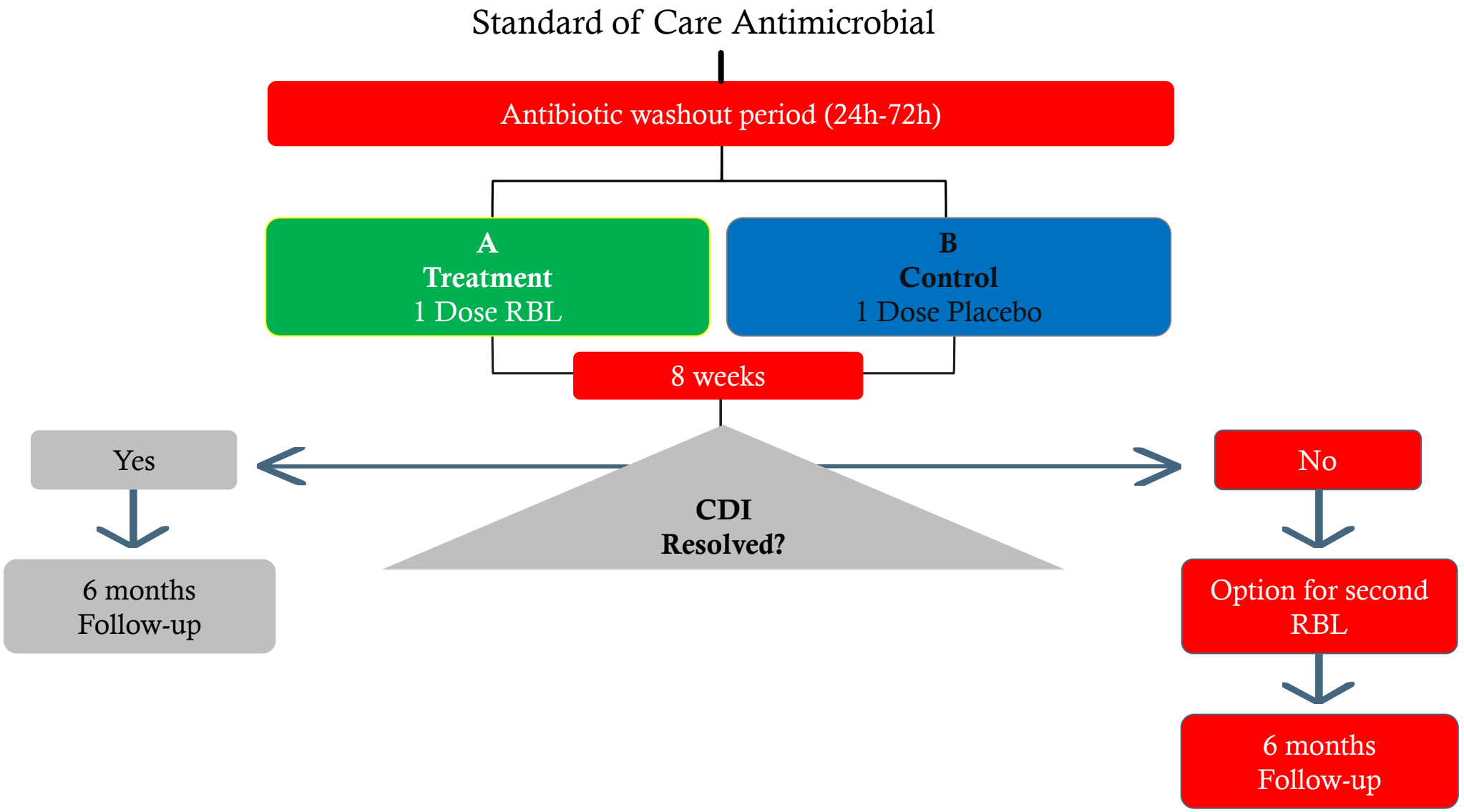
Fecal Microbiota Live-JSLM (Rebyota™, RBL)

- 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*

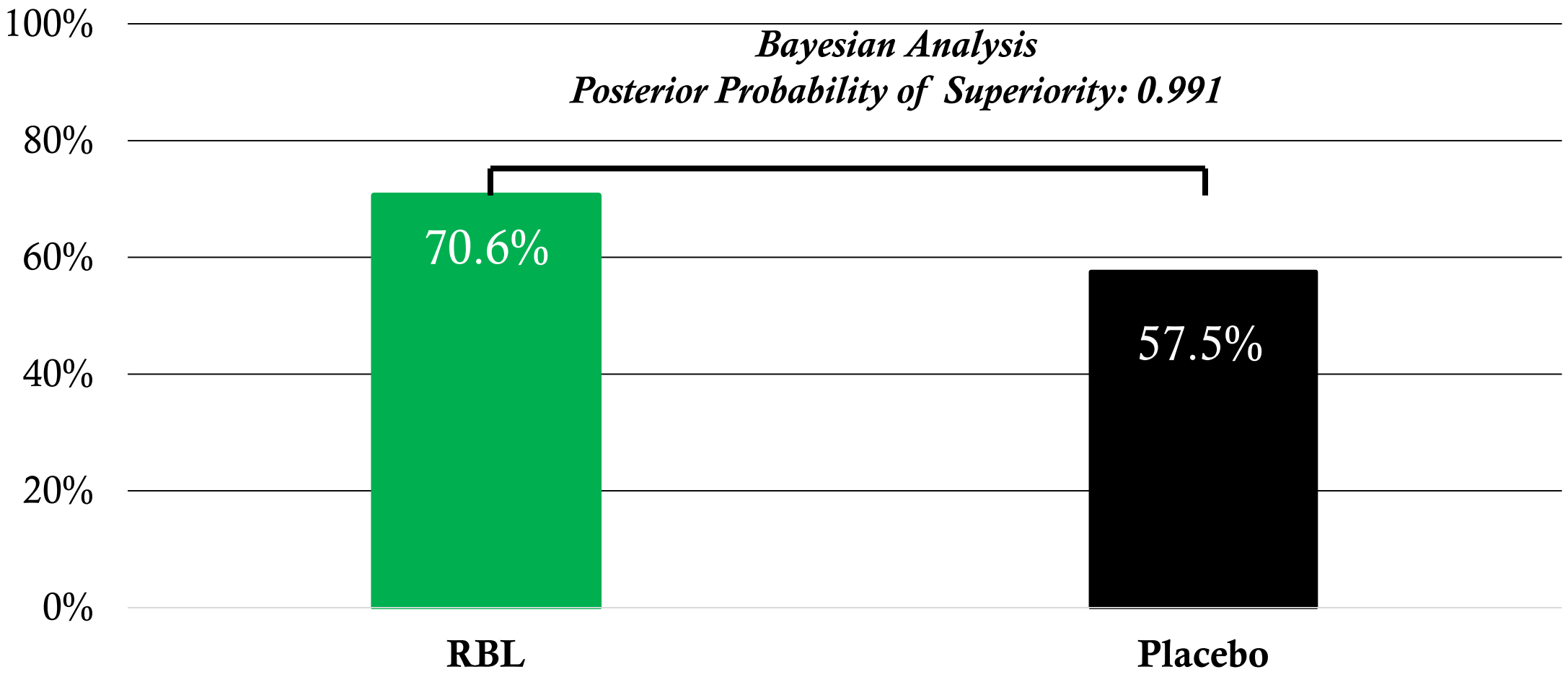


Orenstein R et al. *Clin Infect Dis*. 2016;62:596-602.
Blount KF et al. *Open Forum Infect Dis*. 2019;6:ofz095
Ray A, Jones C. *Future Microbiol*. 2016;11:611-616.

PUNCH-CD3: Phase 3 Trial Design



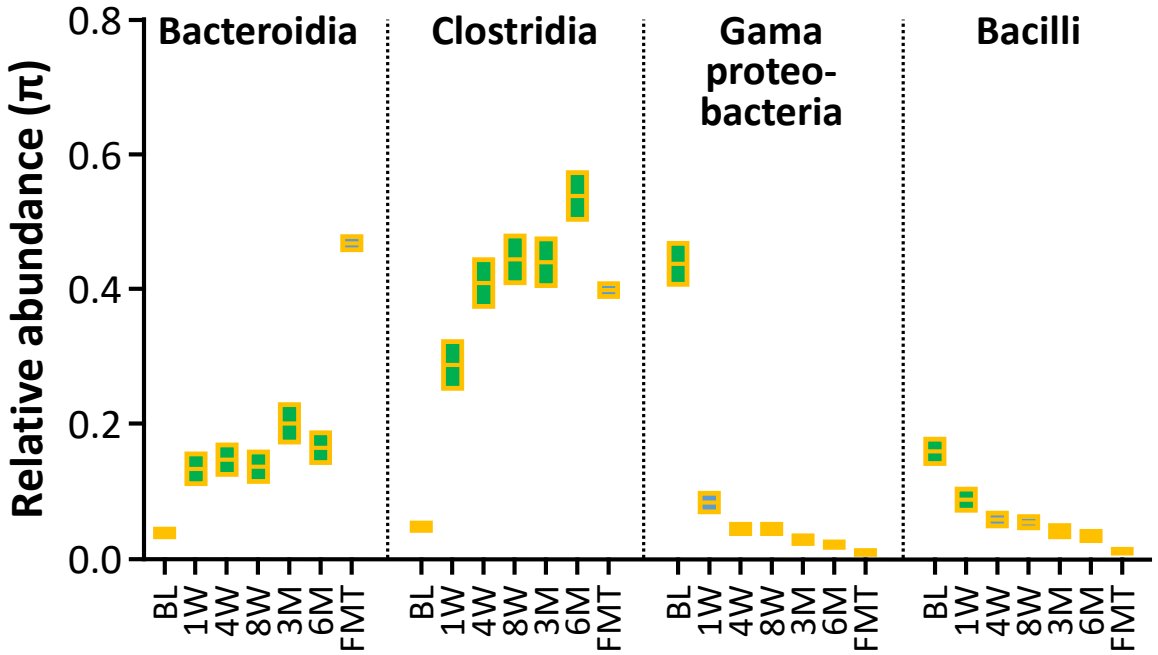
PUNCH-CD3: Phase 3
RBL Superior to Placebo



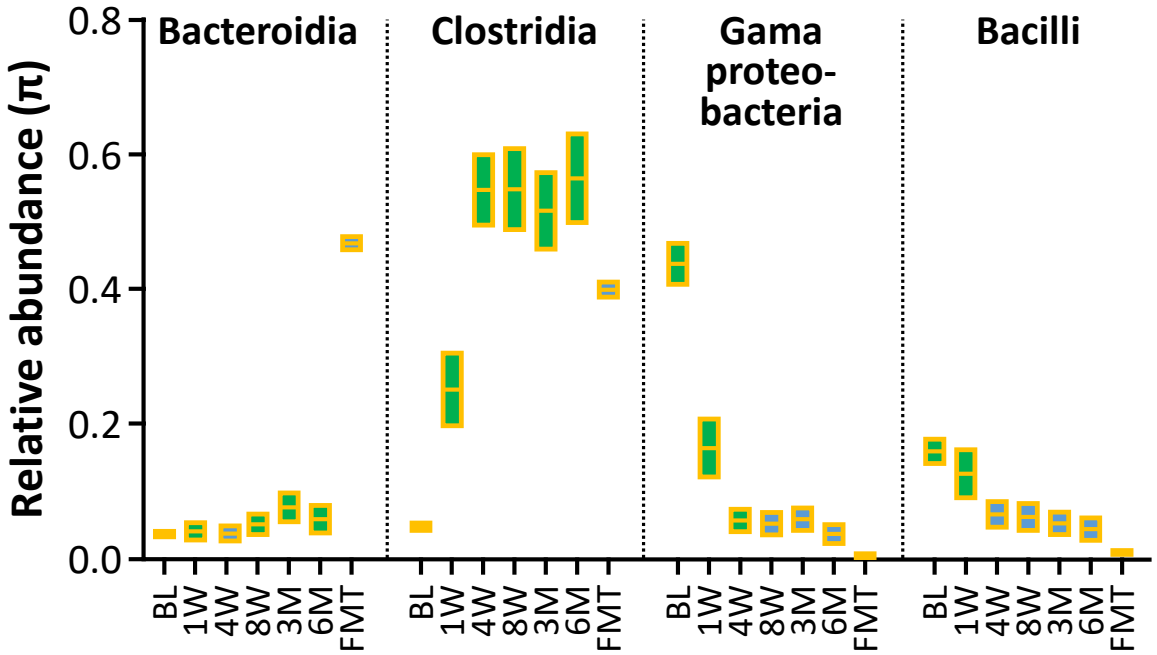
Khanna et al. Drugs. 2022 Oct;82(15):1527-1538

RBL PUNCHCD3: Microbiota Response

RBL Treated Responders



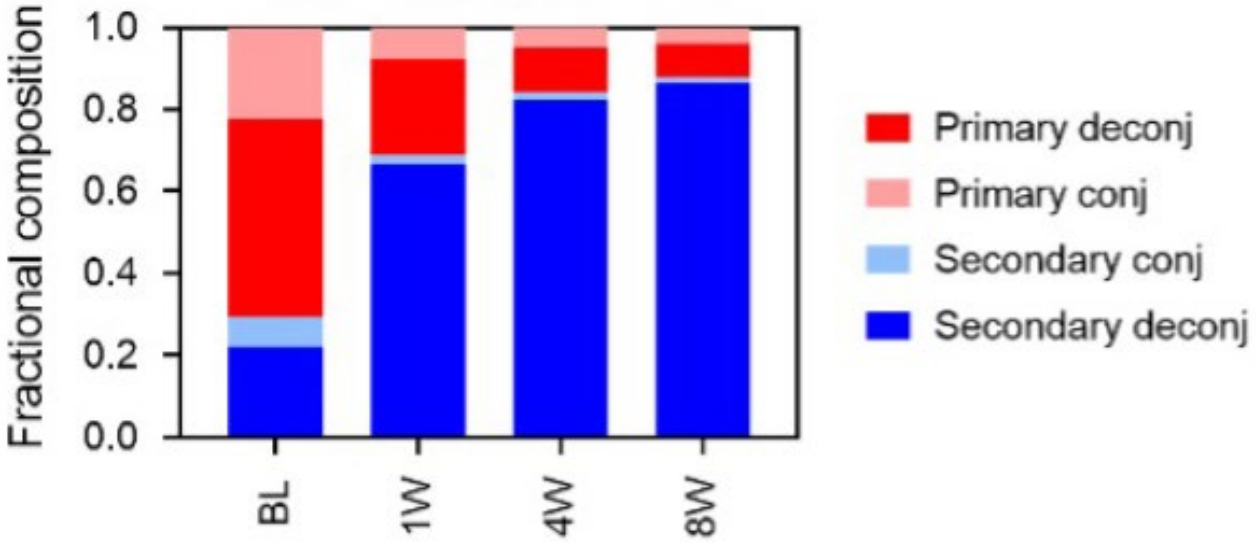
Placebo Treated Responders

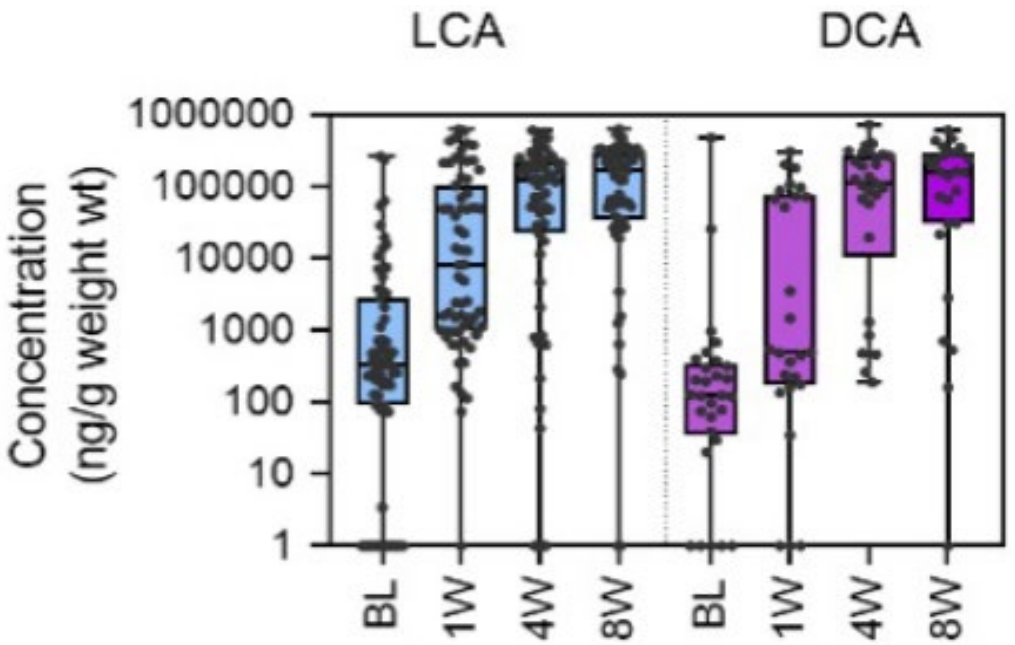


Lee C et al DDW 2021 Meeting, Blount et al IDSA 2021 Meeting

RBL Restoration of Bile Salt Milieu

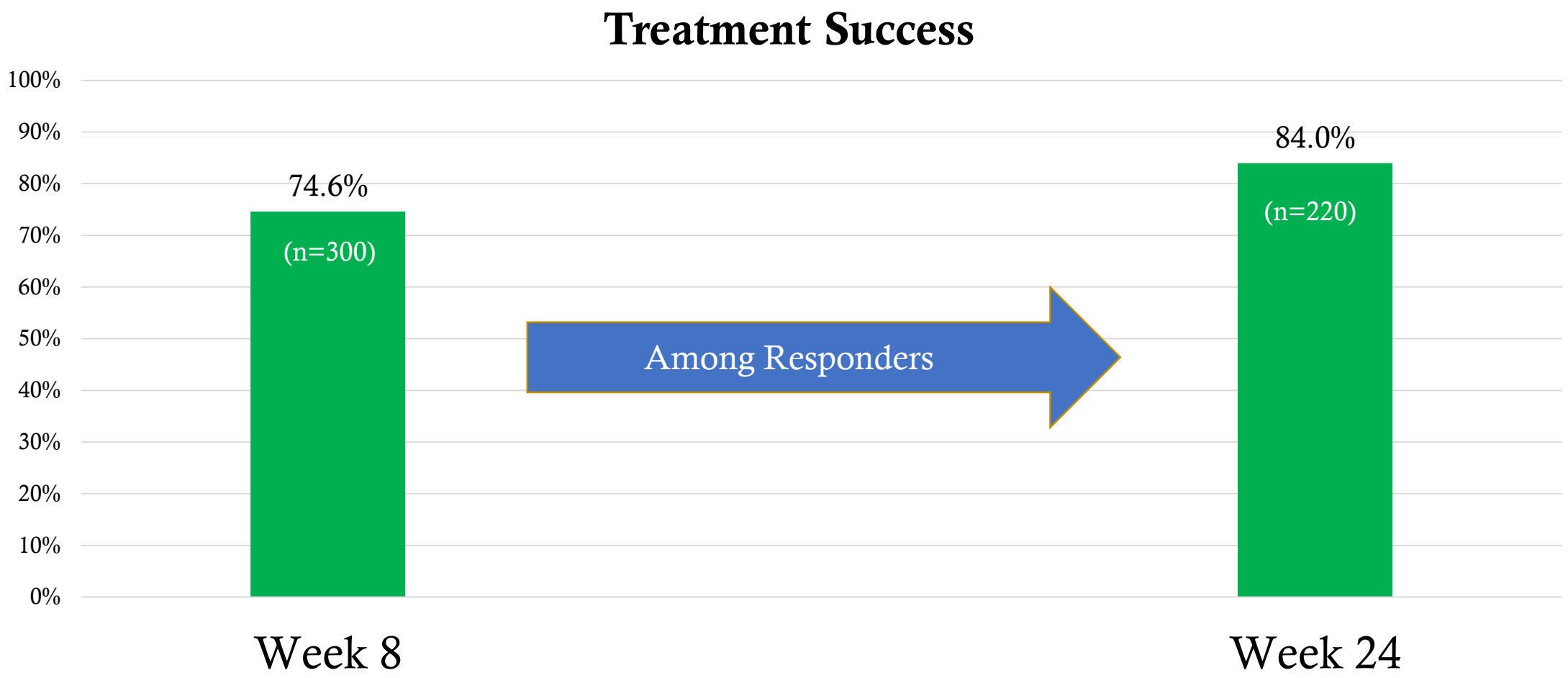
RBL Treated





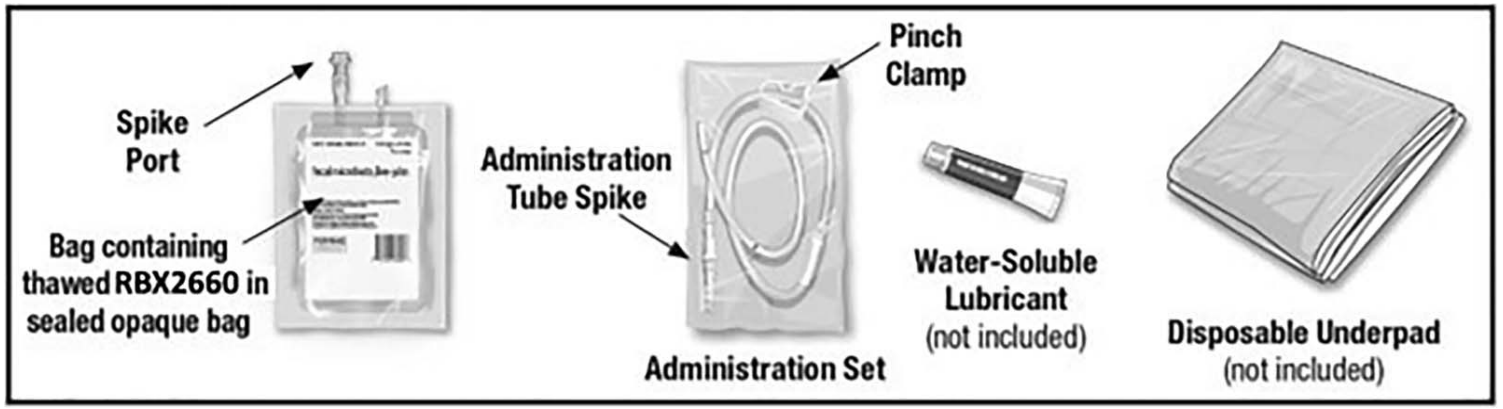
Papazyan R, et al. ID Week Presentation 2021. Abstract 1039.

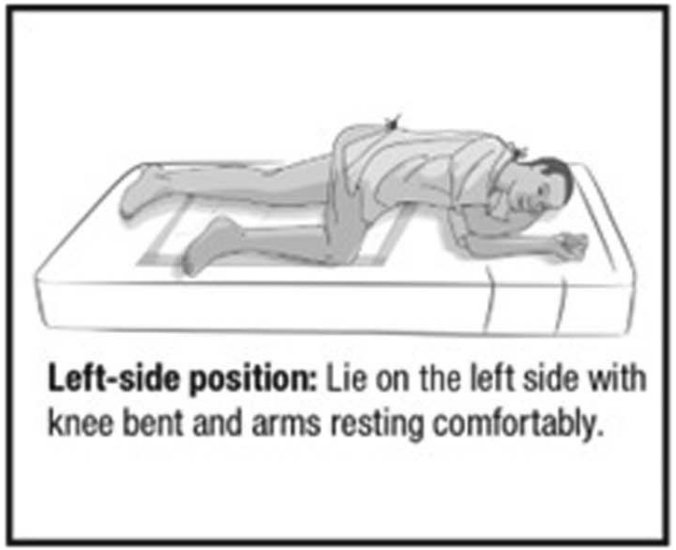
RBL Open Label Study



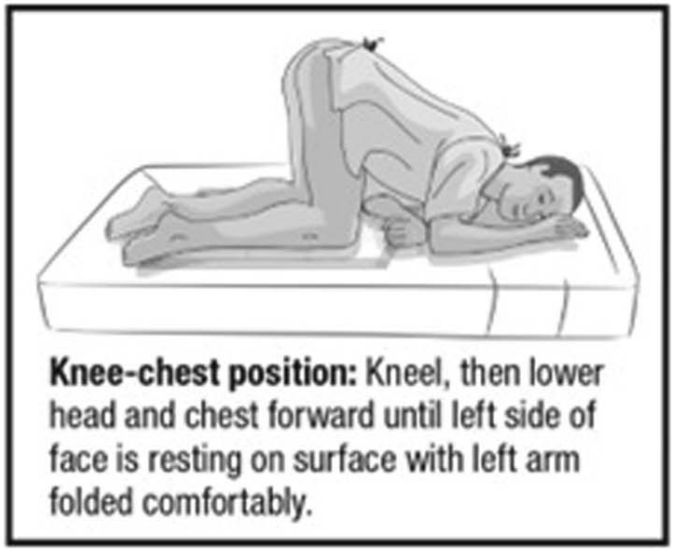
Khanna et al. ACG 2022 Oral Presentation

How Do I do it…RBL





OR



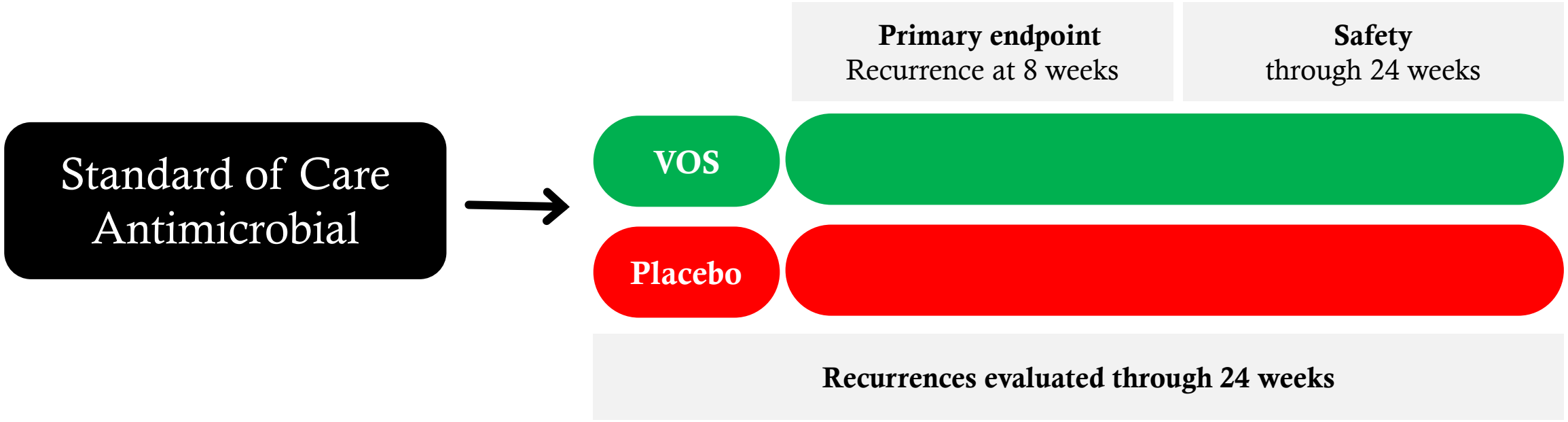
Feuerstadt et al. Am J Gastro. 2023 Mar 27

Fecal Microbiota Spores, Live-BRPK (Vowst™, VOS)

- 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

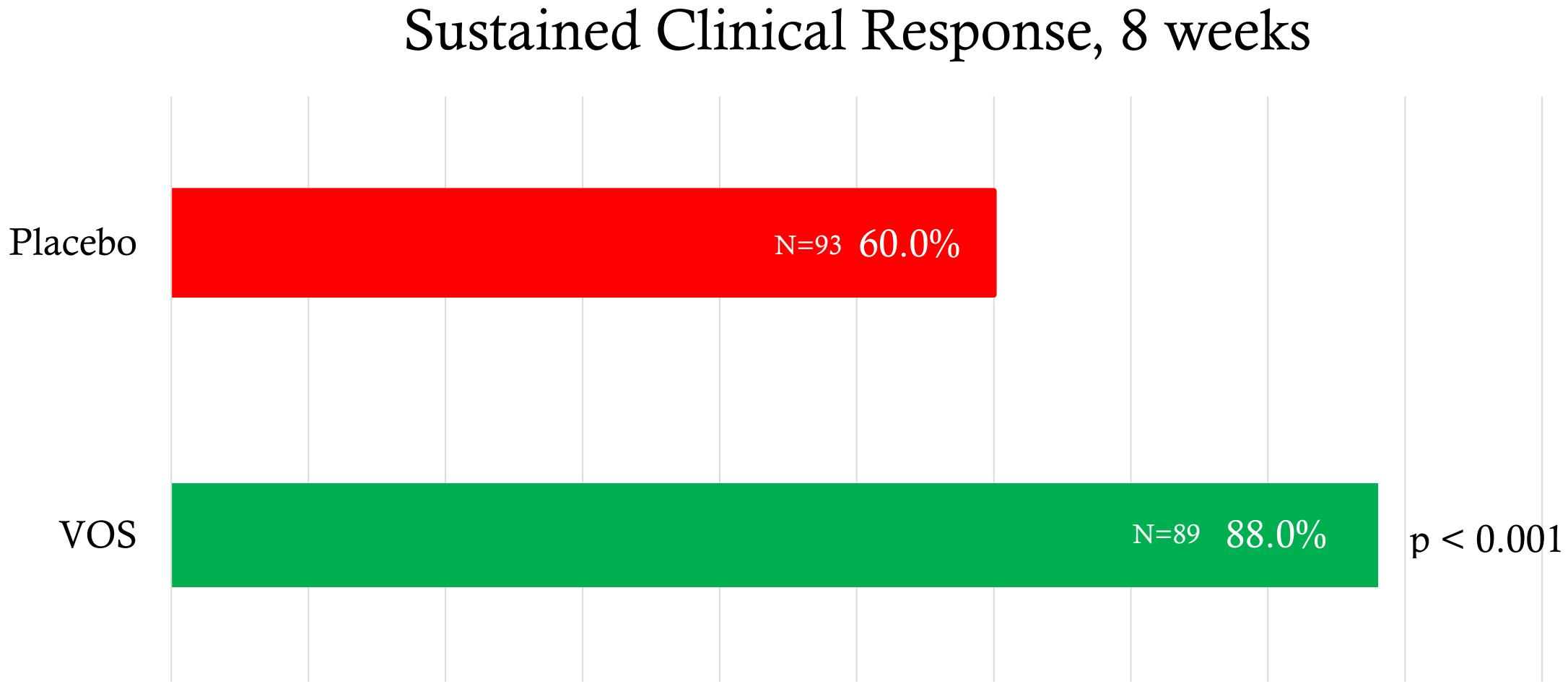
Korman L et al. Gastroenterology 2021;6:S-368.
Feuerstadt et al. N Engl J Med. 2022 Jan 20;386(3):220-229c

ECOSPOR-III: Phase 3 Trial Design



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

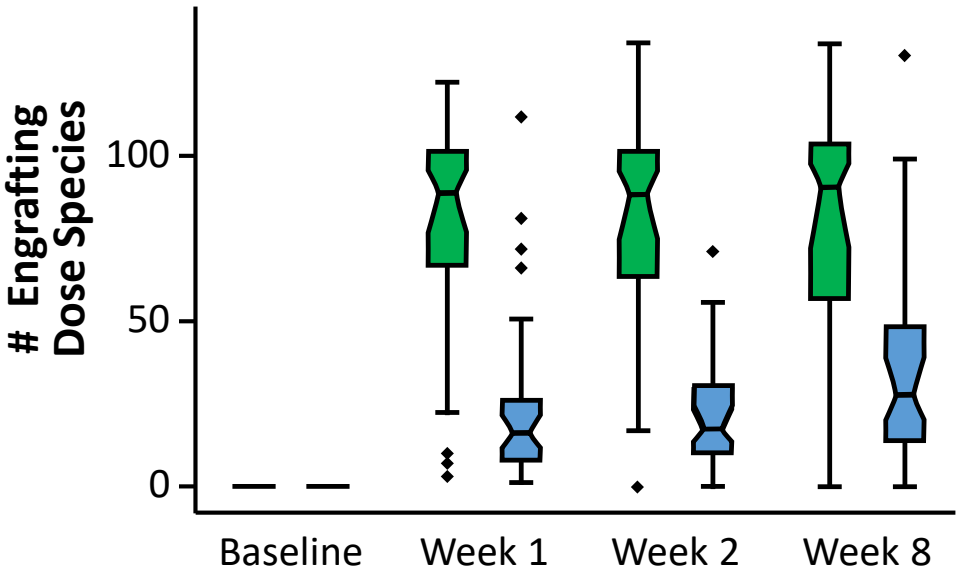
ECOSPOR-III: Phase 3
VOS superior to Placebo



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

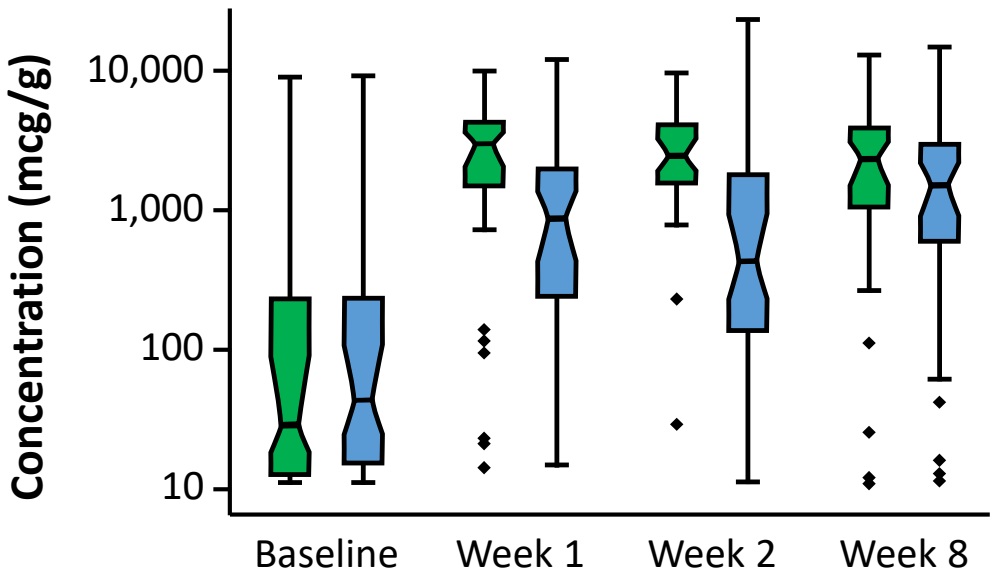
Compositional and Metabolomic Changes Following VOS vs. Placebo

Engraftment of Oral FMT Species



Oral FMT (no.)	74	66	60	66
Placebo (no.)	79	69	64	56

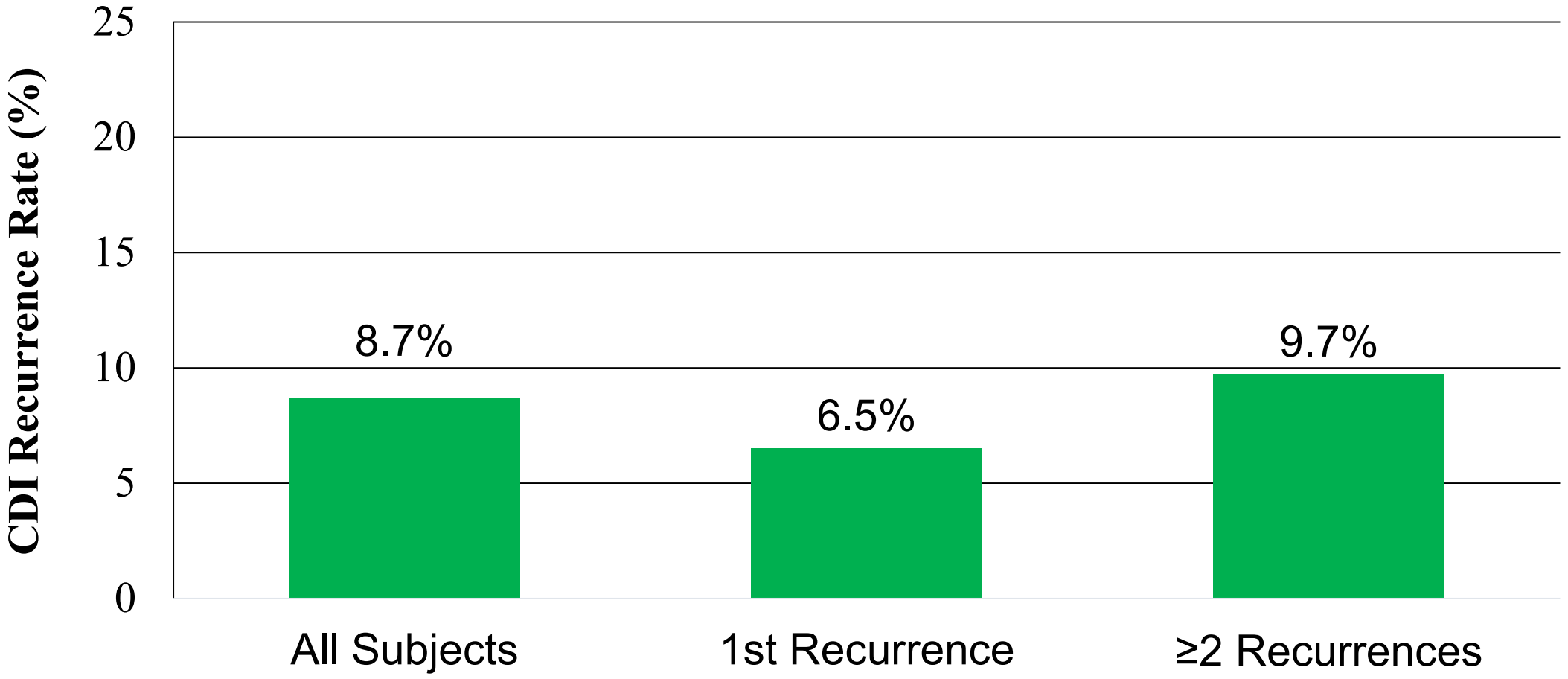
Concentration of Secondary Bile Acids



Oral FMT (no.)	76	69	62	65
Placebo (no.)	77	67	64	55

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

ECOSPOR IV: Open Label Study



Simms et al. JAMA Netw Open. 2023 Feb 1;6(2)

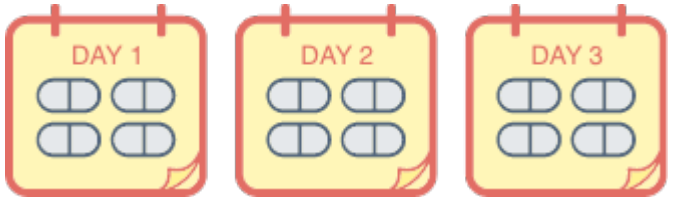
How I do it…VOS

Before Dosing

- Finish Antimicrobials for CDI 2-4 days prior to starting VOS
- The day prior, or at least 8 hours prior to administering the first dose, patient should drink 10 oz of magnesium citrate.
  - For those with renal impairment consider 250 mL of polyethylene glycol

Dosing

- Taken on an empty stomach prior to the first meal of the day
- 4 capsules administered daily for 3 days
- When not being taken, capsules are heat stable and can be left out until administered



Fecal Microbiota Spores, Live-BRPK Package Insert

Lorraine, June 2023

Lorraine received 10-days of vancomycin followed by an LBP and she now remains symptom free

Treatment Algorithm

> 2 Risk Factors for Recurrence

1st Episode

Vancomycin 125 mg PO Qid x 10-14 days

Fidaxomicin 200 mg PO Bid x 10 days

Bezlotoxumab

2nd Episode

Vancomycin Taper > 6 weeks with either pulse of Vancomycin or Fidaxomicin "Chaser"
or Fidaxomicin 200 mg PO Bid x 10 days/Fidaxomicin 200 mg PO bid for 5 days followed by qOD days 7-25

Bezlotoxumab
or
Live Biotherapeutic Product

3rd Episode

Standard Antimicrobial Course + Live Biotherapeutic Product

Live Biotherapeutic Product