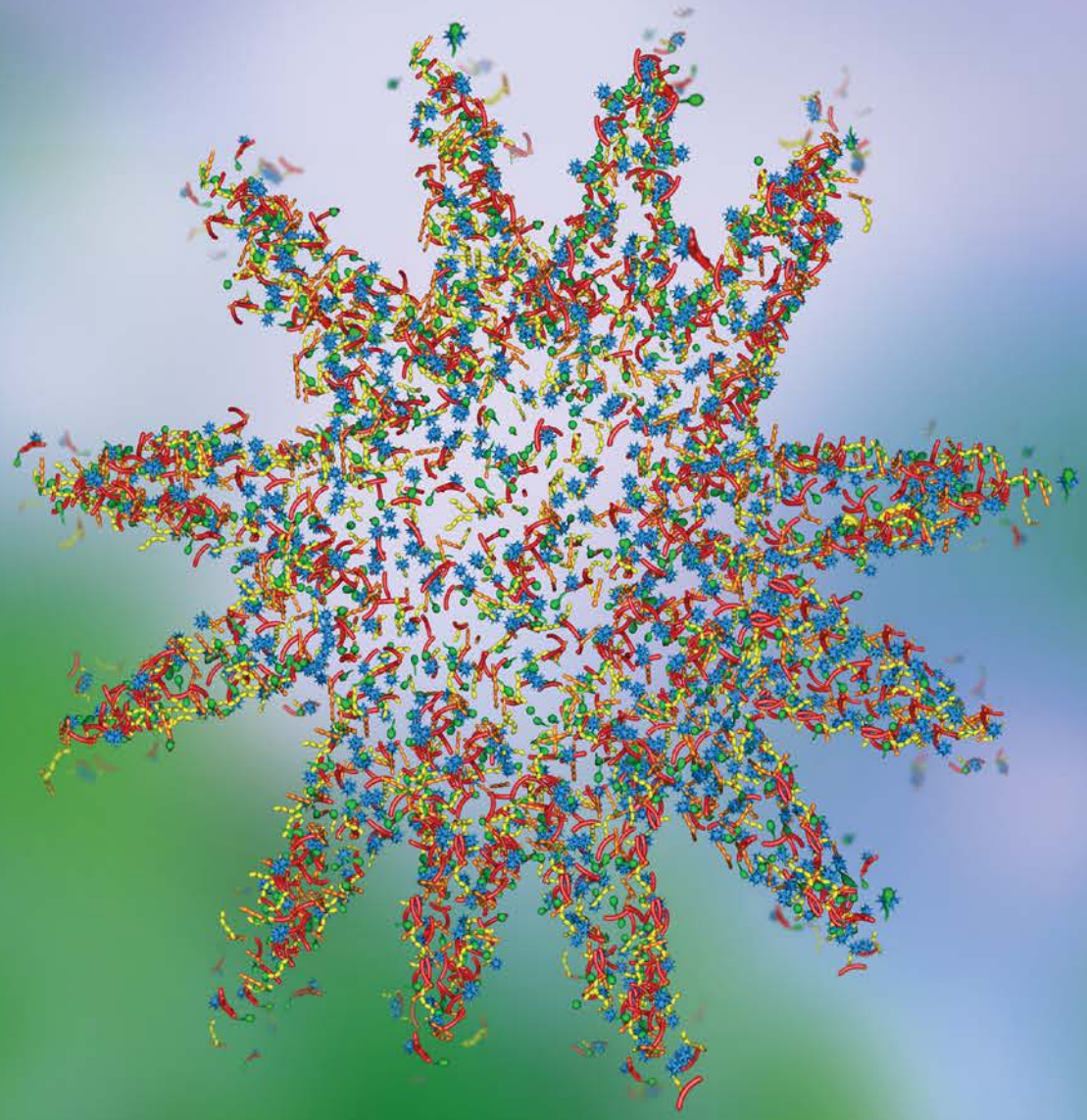
The Emerging Role of the Gut Microbiome in

Reducing Recurrence of *C. difficile* Infection



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Supported by an educational grant from Ferring Pharmaceuticals, Inc.

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Activity Description

ACTIVITY PURPOSE
This activity will review the role of the gut microbiome in *C. difficile* infection and introduce emerging approaches to restoration to reduce complications and improve clinical outcomes

TARGET AUDIENCE
This activity is intended for gastroenterologists**,** ID specialists, hospitalists, internists, physicians and other clinicians who care for patients at risk of serious gastrointestinal infection

SUPPORT
Supported by an educational grant from Ferring Pharmaceuticals, Inc

SPONSORSHIP
Sponsored by the Academy for Continued Healthcare Learning (ACHL)

Learning Objective

Upon completion of this activity, participants will be able to:

- Evaluate the role of the gut microbiome in relationship to *C. difficile* infection and approaches to reducing recurrent infection
- Discuss clinical risk factors that increase a patient's risk for recurrent and multiply recurrent *C. difficile* infection
- Review guideline recommendations for the management of first and subsequent recurrences of *C. difficile* infection
- Describe available and emerging approaches for patients with recurrent *C. difficile* who have failed appropriate antibiotic therapy

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Sahil Khanna, MBBS, MS
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Gautam Mankaney, MD
Nothing to disclose

Discussion of Off-Label, Investigational, or Experimental Drug/Device Use: Investigational approaches to treating *C. difficile* infection and reducing recurrent episodes

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Method of Participation

To receive credit, participants are required to participate in the live activity and complete the posttest, and evaluation and submit on-site. A certificate will be emailed to participants within 6 weeks. There is no fee to participate in the activity or for the generation of the certificate.

Inquiries may be directed to ACHL at (877) 444-8435, ext. 160.

The Changing Epidemiology of *C. difficile*

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Definitions

- *C. difficile* infection:
  1) diarrhea, megacolon, or severe ileus
  2) positive laboratory test or pseudomembranes

- Incident case – No episode within previous 8 weeks

- Recurrent case – Symptoms + positive test within 2-8 weeks of previous episode

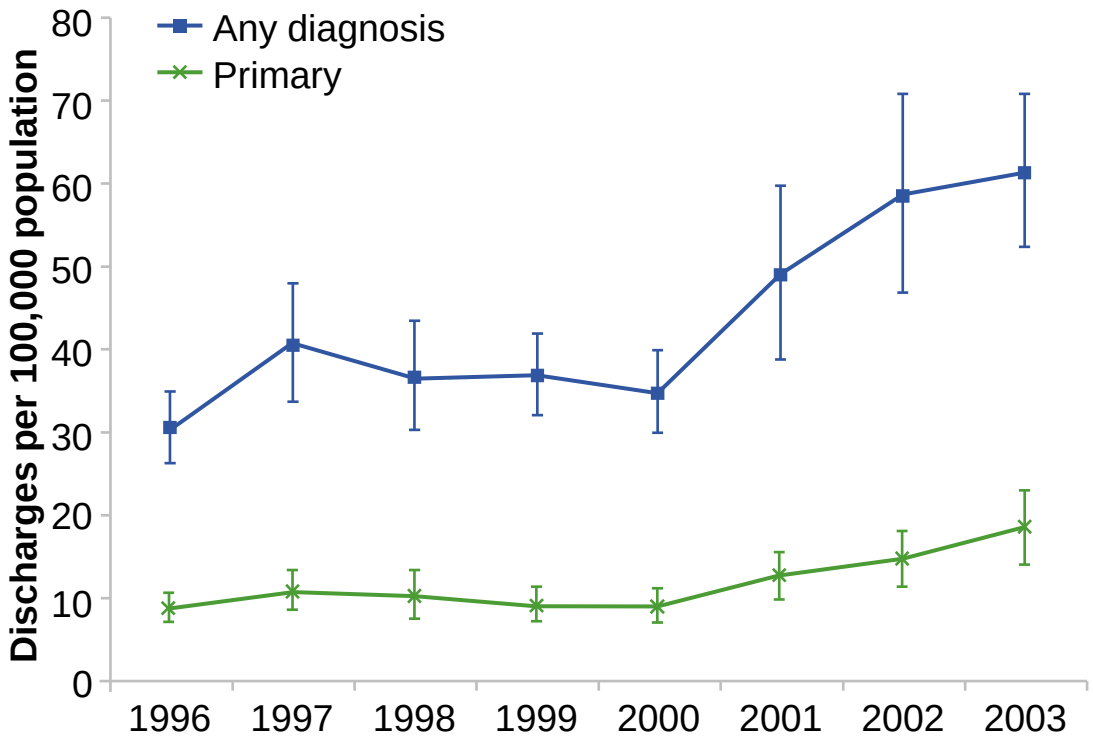
Gupta A. *JAMA*. 2016
McDonald LC. *Clin Infect Dis*. 2017

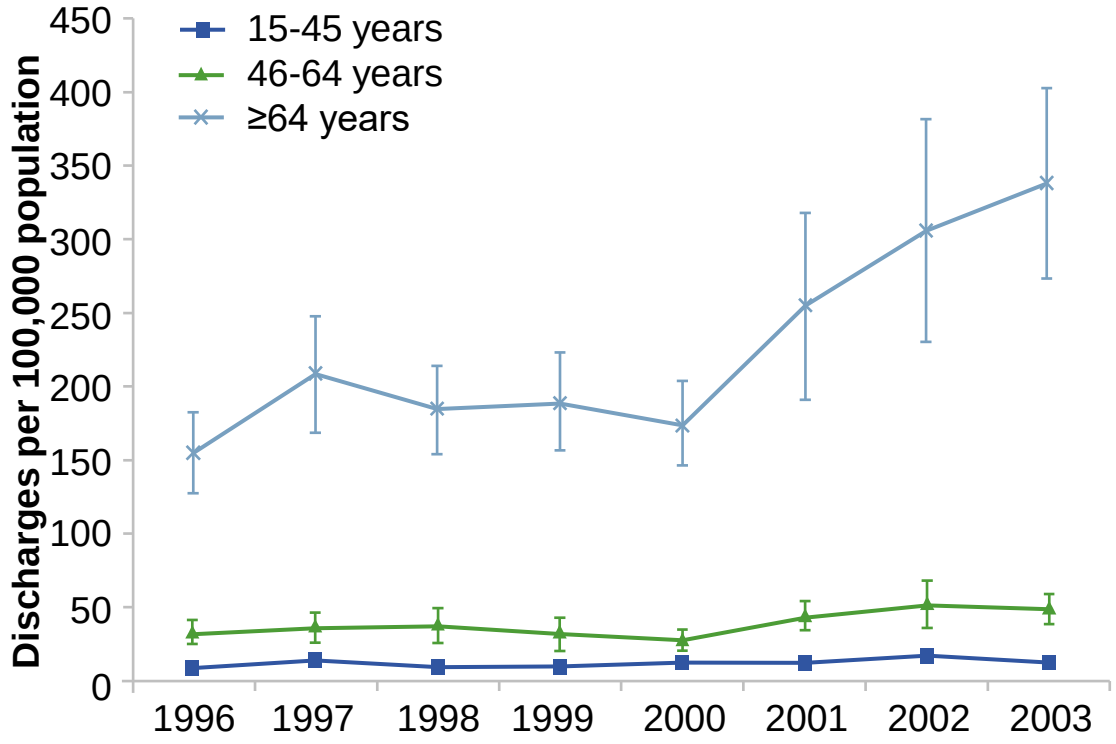
C. difficile – 1990's Background

- Nosocomial infection
- Primarily associated with antibiotic use
- Stable incidence rates ~ 30-40/100,000
- Low mortality rate ~ 2%
- Healthcare-associated diarrhea – most common cause
- *Staphylococcus aureus* most common cause of healthcare associated infection

Gerding DN. *Infect Control Hosp Epidemiol.* 1995
McDonald LC. *Clin Infect Dis*. 2006.
Lucado J. *Healthcare Cost & Utilization Project*. 2012

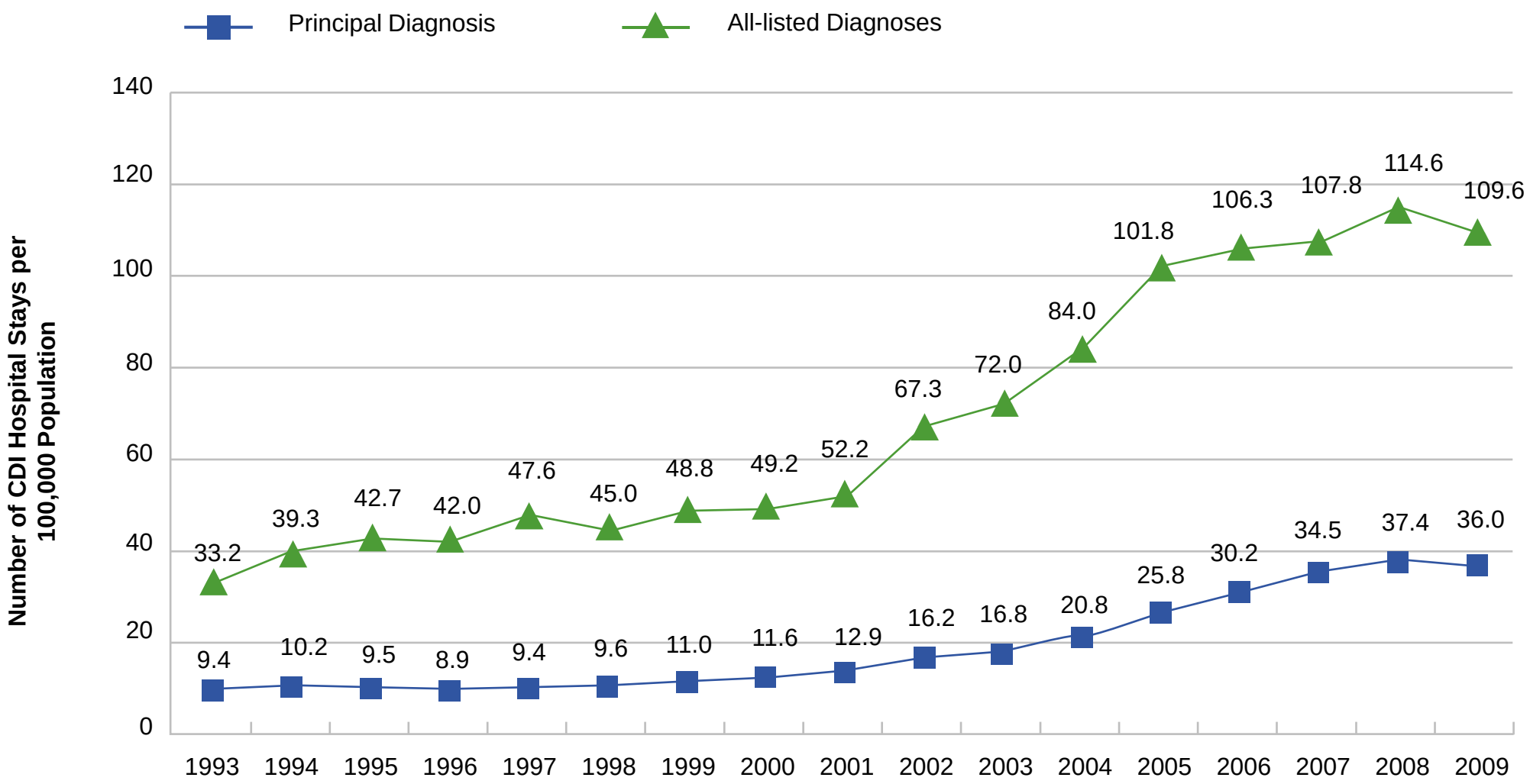
Epidemiology





McDonald LC et al. *Emerg Infect Dis*. 2006.

Trends in Hospital Stays Associated with *C. difficile*: 1993-2009



AHRQ. Center for Delivery, Organization, and Markets. Healthcare Cost and Utilization Project, Nationwide Inpatient Sample, 1993-2009

Mortality

- Prior to 2000
  - <1.5%
- After 2000
  - Endemic – 4.5-5.7%
  - Epidemic – 6.9-16.7%
- Recurrent episodes
  - 33% 6-month increased mortality risk compared to initial episode

Kwon JH. Infect Dis Clin North Am. 2015
Olsen MA. Clin Microbiol Infect. 2015

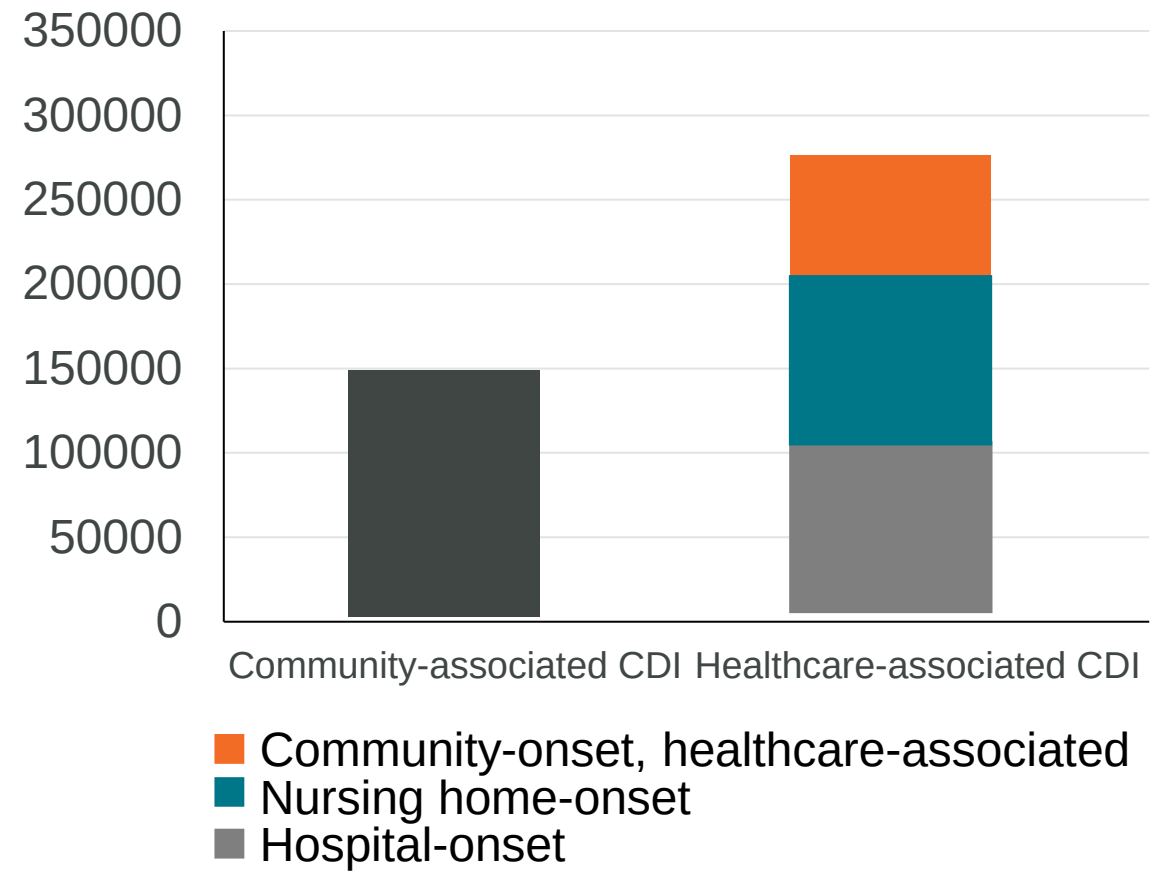
Epidemiologic Change

- Increasing age of population
- Increase in community acquired infection
  - Incidence in younger patients increasing
- Ribotype 027 (NAP1/B1) strain
  - Increased virulence and disease severity
  - Fluoroquinolone resistance
  - Community acquired infection

Miller AU. *Clin Infect Dis.* 2010
Olsen MA. Clin Microbiol Infect. 2015

Community-acquired *C. difficile*

Demographic Characteristic	Community-associated CDI		Healthcare-associated CDI		All CDI	
	Estimated No. Cases	Incidence per 100,000 Persons	Estimated No. of Cases	Incidence per 100,000 Persons	Estimated No. of Cases	Incidence per 100,000 Persons
All cases	159,700 (132,900-186,000)	51.9 (43.2-60.5)	293,300 (264,200-322,500)	95.3 (85.9-104.8)	453,000 (397,100-508,500)	147.2 (129.1-165.3)



Lessa FC. *N Engl J Med*. 2015.

Community-acquired *C. difficile*

Comparison of community-acquired and hospital-acquired CDI

Characteristic	Community-acquired (*n*=157)	Hospital-acquired (*n*=192)	*P* value
Age, median (range)	50 (0.1-102)	72 (0.1-99)	<0.001
<18, *n* (%)	21 (13)	8 (4)	
18-65, *n* (%)	87 (55)	63 (33)	
>65, *n* (%)	49 (31)	121 (63)	
Female gender, *n* (%)	119 (76)	115 (60)	0.002
Antibiotic exposure, *n* (%)	123 (78)	181 (94)	<0.001
Acid-suppression use, *n* (%)	35 (22)	90 (47)	<0.001
Mean Charlson comorbidity index	1.3	3.3	<0.0001
Inflammatory bowel disease, *n* (%)	8 (5)	5 (3)	0.22
Malignancy diagnosis, *n* (%)	26 (17)	61 (32)	<0.0001
Severe CDI[a], *n/N* (%)	32/106 (30)	60/162 (37)	0.25
Severe CDI[b], *n/N* (%)	32/157 (20)	60/192 (31)	<0.01
Severe complicated CDI, *n* (%)	7 (5)	14 (7)	0.27
Recurrent CDI, *n* (%)	44 (28)	58 (30)	0.66

Khanna S. *Am J Gastroenterol*. 2012.

CDI – Present

Factor	1990s	Today
Risk location	Nosocomial	Nosocomial + community
Etiology	Antibiotics	Do not need antibiotic exposure
Incidence	30-40/100,000	147.2/100,000
Mortality rate	<2%	Up to 16.9%
Healthcare associated diarrhea	Most common cause	Most common cause
Healthcare acquired infection – most common organism	*Staph aureus*	*C. difficile*

Gerding DN. *Infect Control Hosp Epidemiol.* 1995.
McDonald LC. *Clin Infect Dis*. 2006.
Lucado J. *Healthcare Cost & Utilization Project*. 2012.

Risk Factors

Demographics

- Age >65 years
- Female gender
- Comorbidities

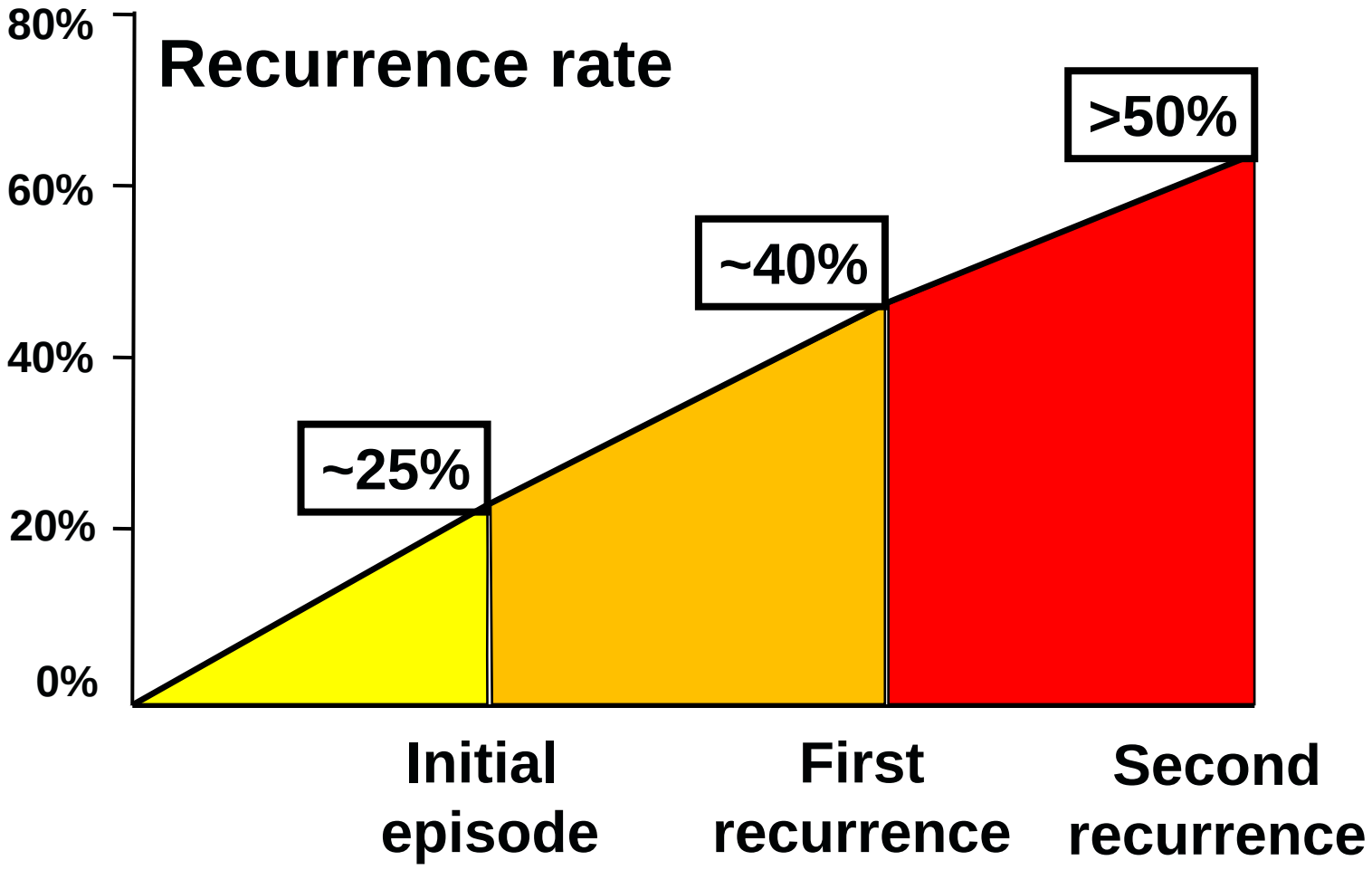
Disruption of microbiome

- Antibiotic use (clindamycin, cephalosporins, and fluoroquinolones)
- Chemotherapy
- Proton pump inhibitors
- GI surgery and manipulation

Exposure

- Hospitalization
- Stay in ICU or long-term care facility
- Direct contact with CDI patient

Recurrence Rates



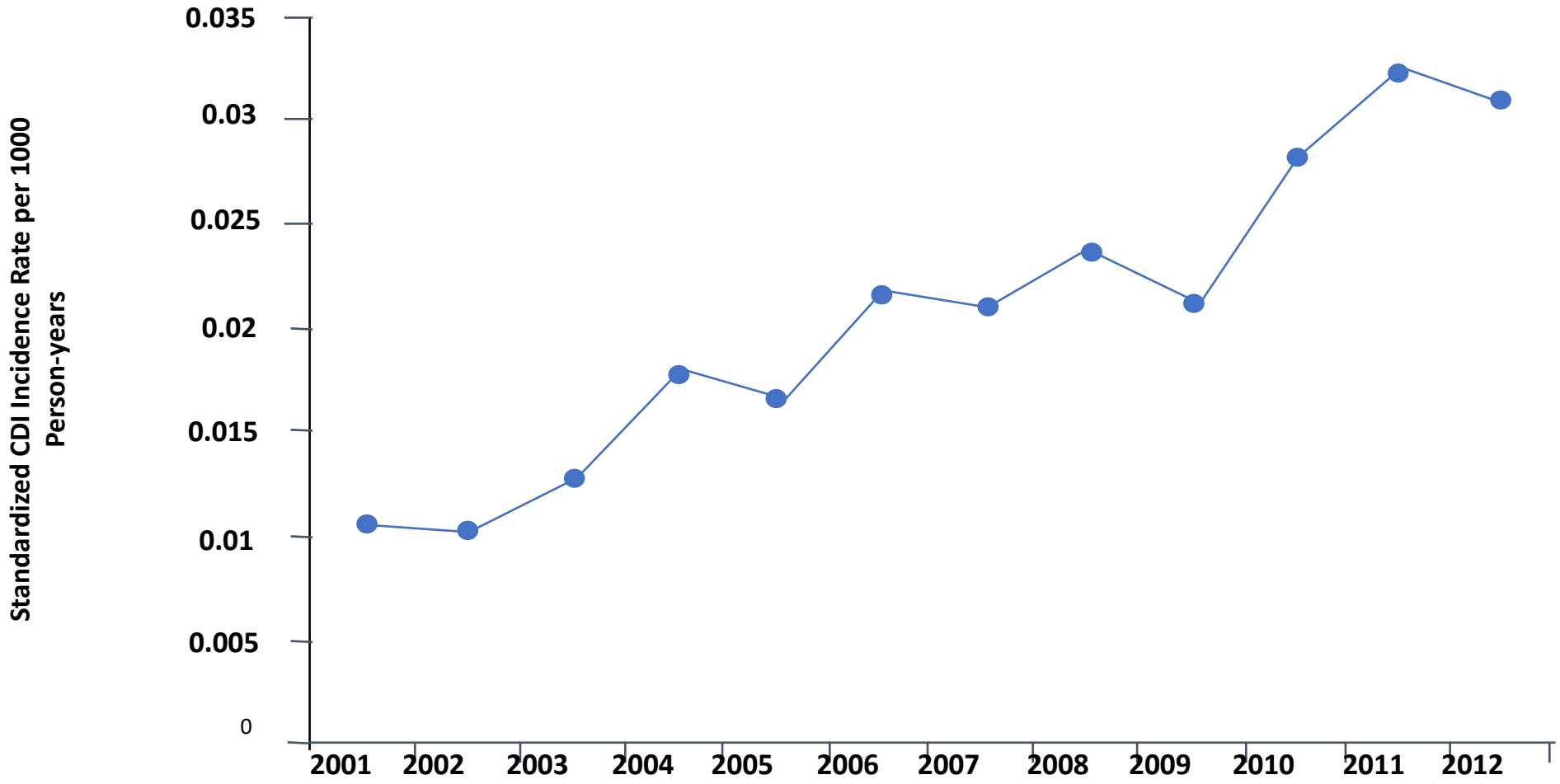
McFarland *JAMA.* 1994.
Pépin. *Clin Infect Dis.* 2005.
McFarland. *Am J Gastroenterol.* 2002.

Host Factors for Recurrent CDI

- Age ≥ 65 years
- Immunosuppression
  - recipients of organ transplants (3-11%), chemotherapy, corticosteroids, HIV, IBD, ESRD, ESLD
- PPI use ≥ 3-fold
- Hospitalization, long-term care facilities
  - After 1 week 13%, after 4 weeks > 50% colonization rate
- Previous CDI
- Antibiotics
  - Fluoroquinolones, non-CD treatment antibiotics

Hookman P. *World J Gastroenterol.* 2009
Makris AT. J *Am Med Dir Assoc*. 2007.
Goodhand JR. *Ailment Pharmacol Ther.* 2011.
Aseeri M. *Am J Gastroenterol.* 2008.
Schaier M. *Nephrol* Dial Transplant. 2004.
Deshpande A. *Infect Control Hosp Epidemiol.* 2015.

Multiply Recurrent CDI



Ma GK. *Ann Intern Med*. 2017.

Multiply Recurrent *C. difficile*

Risk Factor	OR
Age, 10 yr increments	1.25
Female	1.24
Antibiotics within 90 days	1.79
Ppi	1.14
Corticosteroids	1.15
CKD	1.49
IBD	NS
DM	NS
SNF	1.99

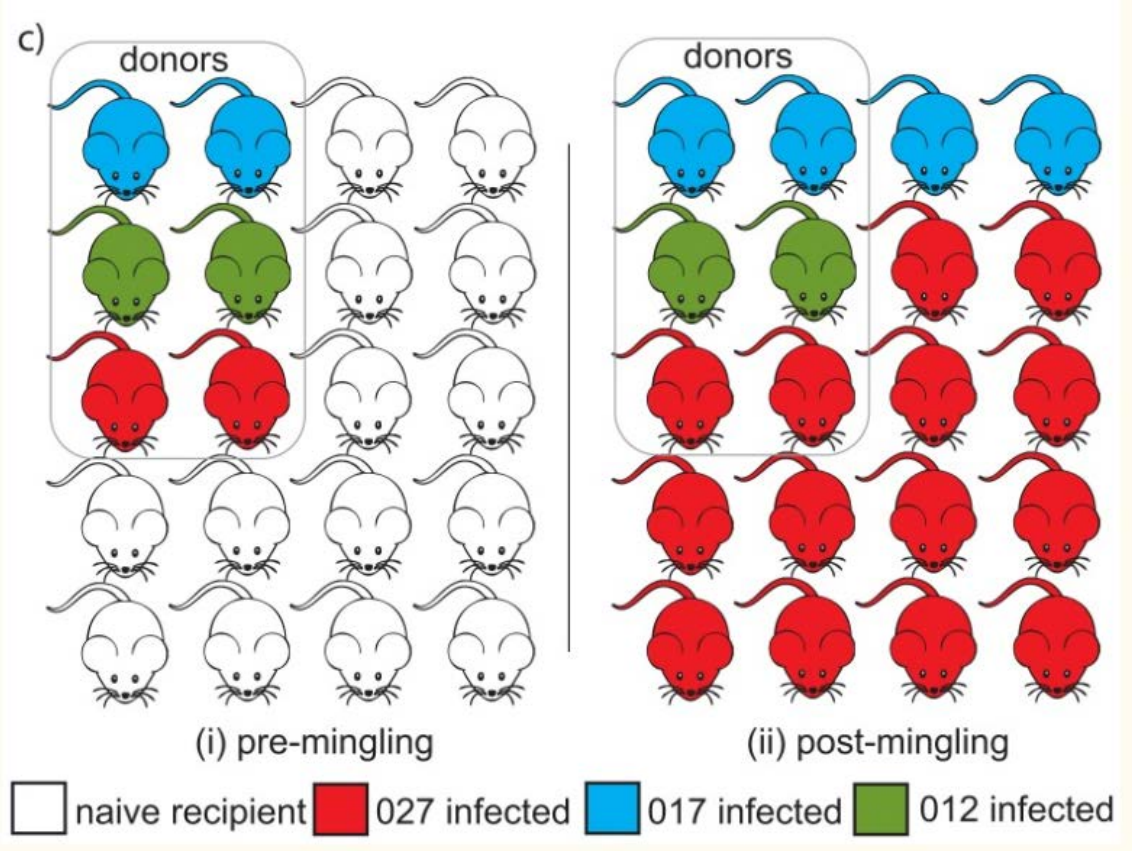
Ma GK et al. *Ann Intern Med*. 2017.

Why Do We Get Recurrent CDI ?

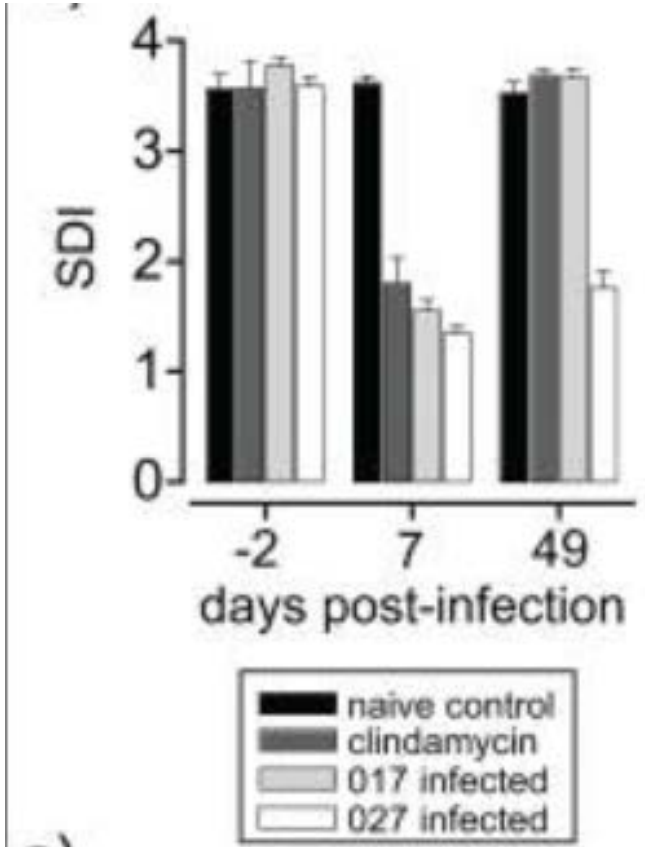
- Virulence of infection
- Impaired host-response
- Altered intestinal microbiome
  - “Dysbiosis” = decreased microbiota diversity

Dysbiosis and CDI

Virulence



Impaired Host Resposne



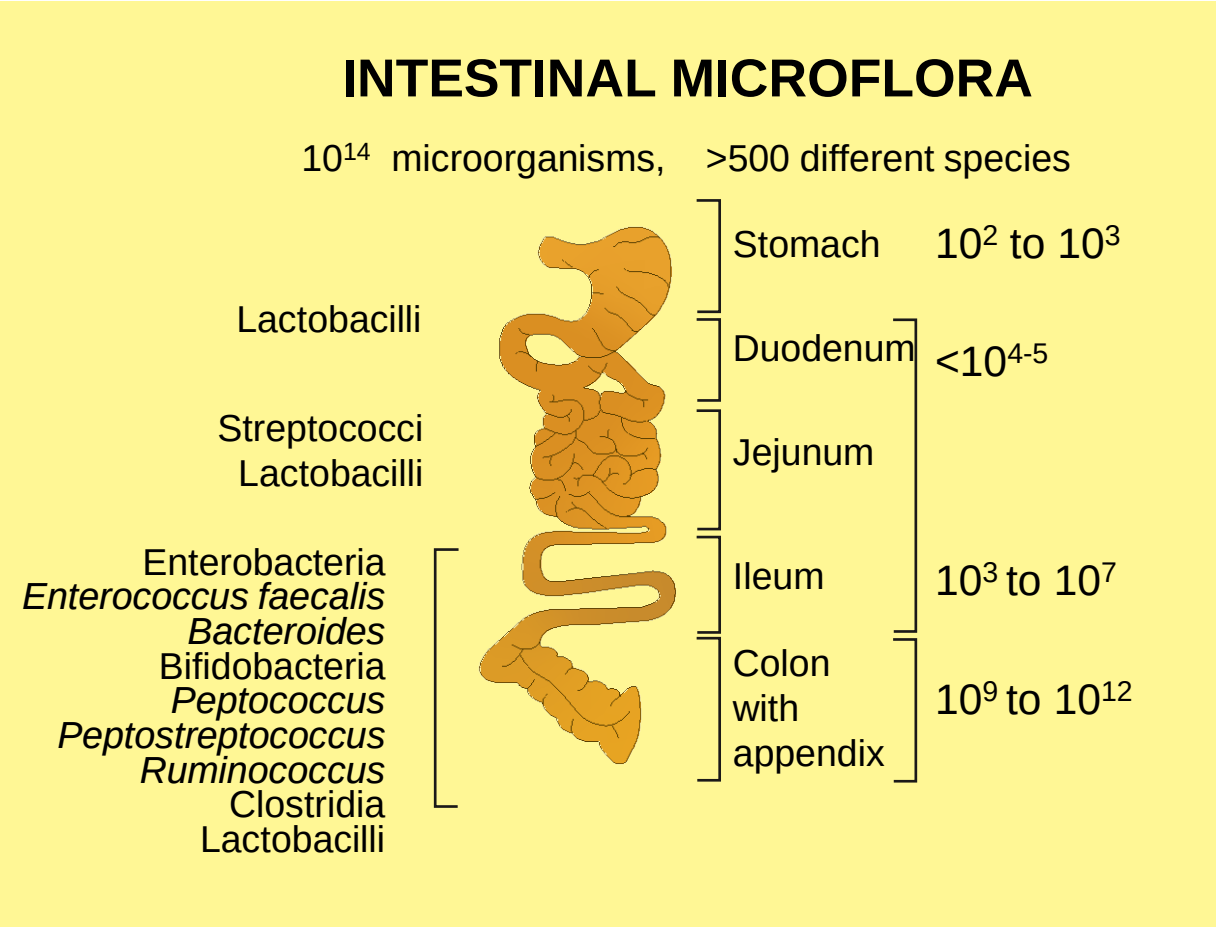
Lawley et al. *Plos Pathog*. 2012;8(10):e1002995.

Human Intestinal Microbiome

- 10^{14} bacterial cells →

  10 times > human cells in our body

- Role:
  - Protect against invasive pathogens
  - Assist in digestion
  - Produce vitamins, free fatty acids
  - Modulate colonic immune system



Eckburg PB. *Science*. 2005..

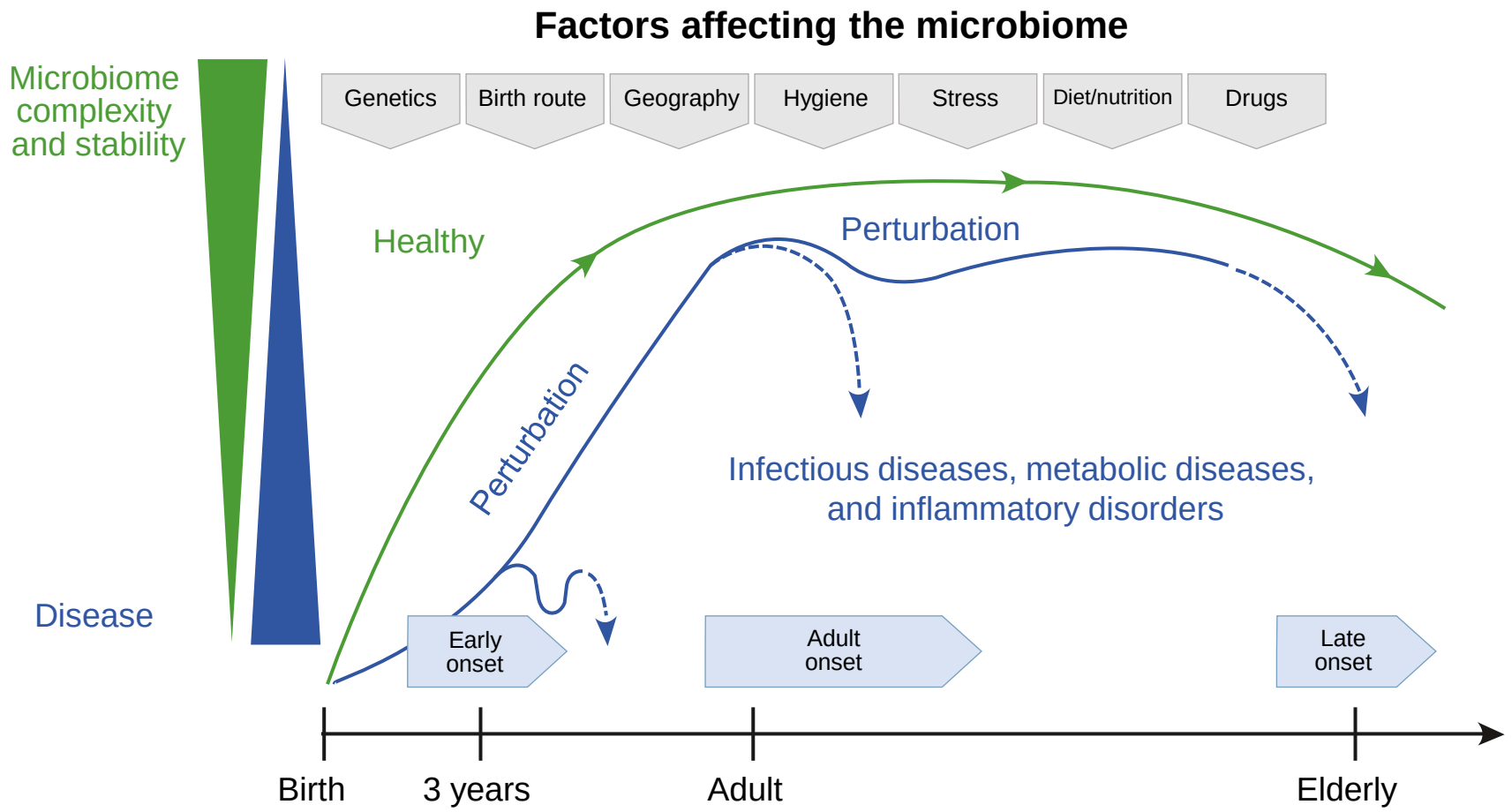
Human Intestinal Microbiome

Divisions	% sequences
Firmicutes	**69**
Bacteroidetes	**17**
Actinobacteria	6
Proteobacteria	5
Gemmatimonadetes	0.02
Defferibacteres	0.1
Verrucomicrobia	2.1
Lentisphaerae	0.08
Planctomycetes	0.08
*@CD Gut 1	0.2
*@CD Gut 2	0.01
Fusobacteria	0.9
Spirochaeates	0.7
Fibrobacteres	0.08
*Cyano Sister	0.15
Synergistes	0.12
Chloroflexi	0.01
*TM7	0.04

*: no cultured representatives
@: novel candidate division

- Firmicutes and Bacteroidetes dominate across all mammals.
- *Dietary influence*:
  - Carnivores have the fewest divisions and are most enriched in Firmicutes.
  - Humans are typical omnivores; cluster with omnivorous primates; leaf-eating primates cluster with herbivores

Human Intestinal Microbiome



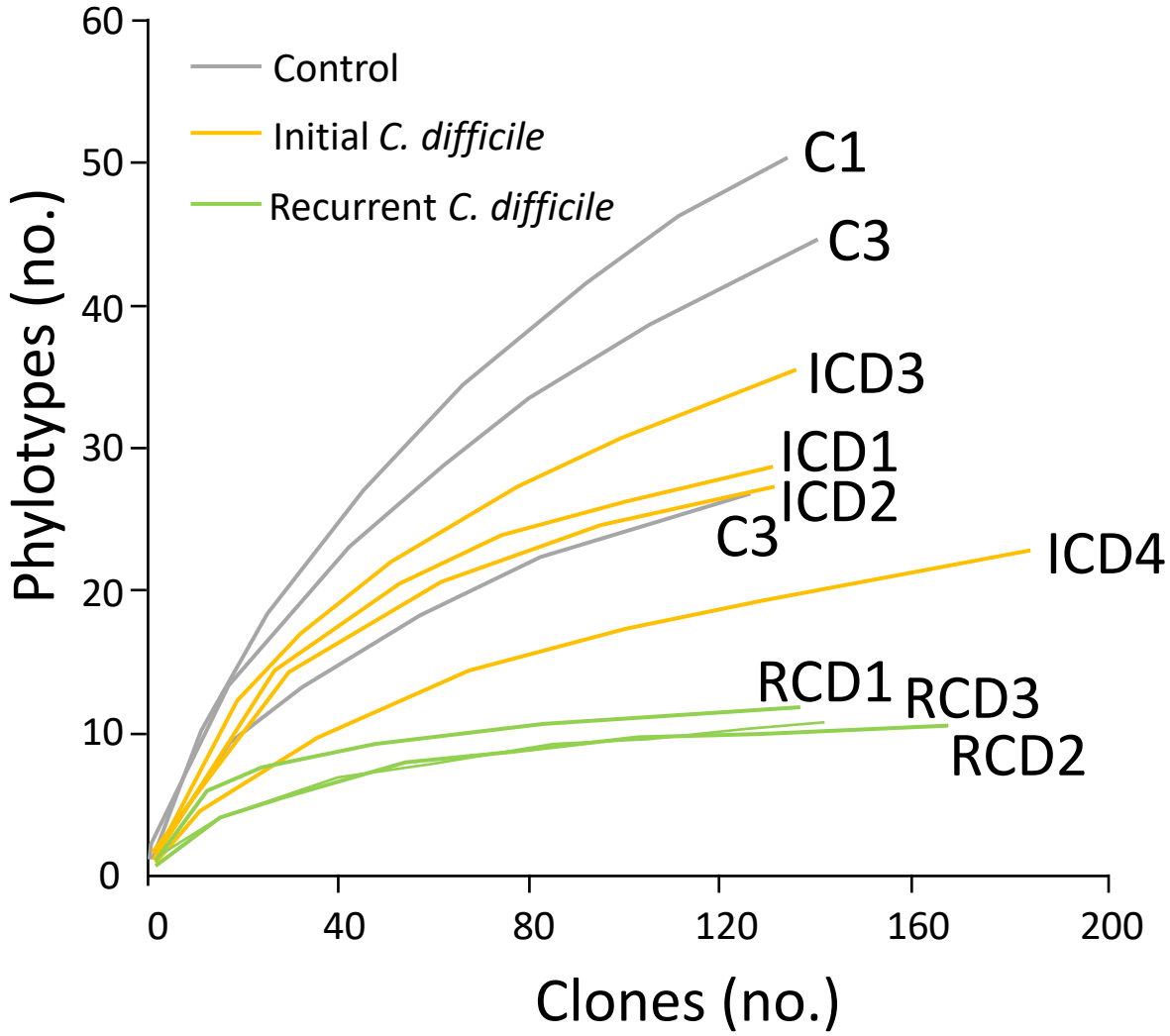
- **Protect against pathogens**
- **Train/stimulate immune function**
- **Supply nutrients, energy. vitamins, SCFA**

- **Inflammation (local > systemic)**
- **Oxidative stress**
- **Increase in Gram-negative bacteria**
- **Infection (opportunistic/ pathogenic)**
- **Altered metabolite production**

Kostic. *Gastro*. 2014..

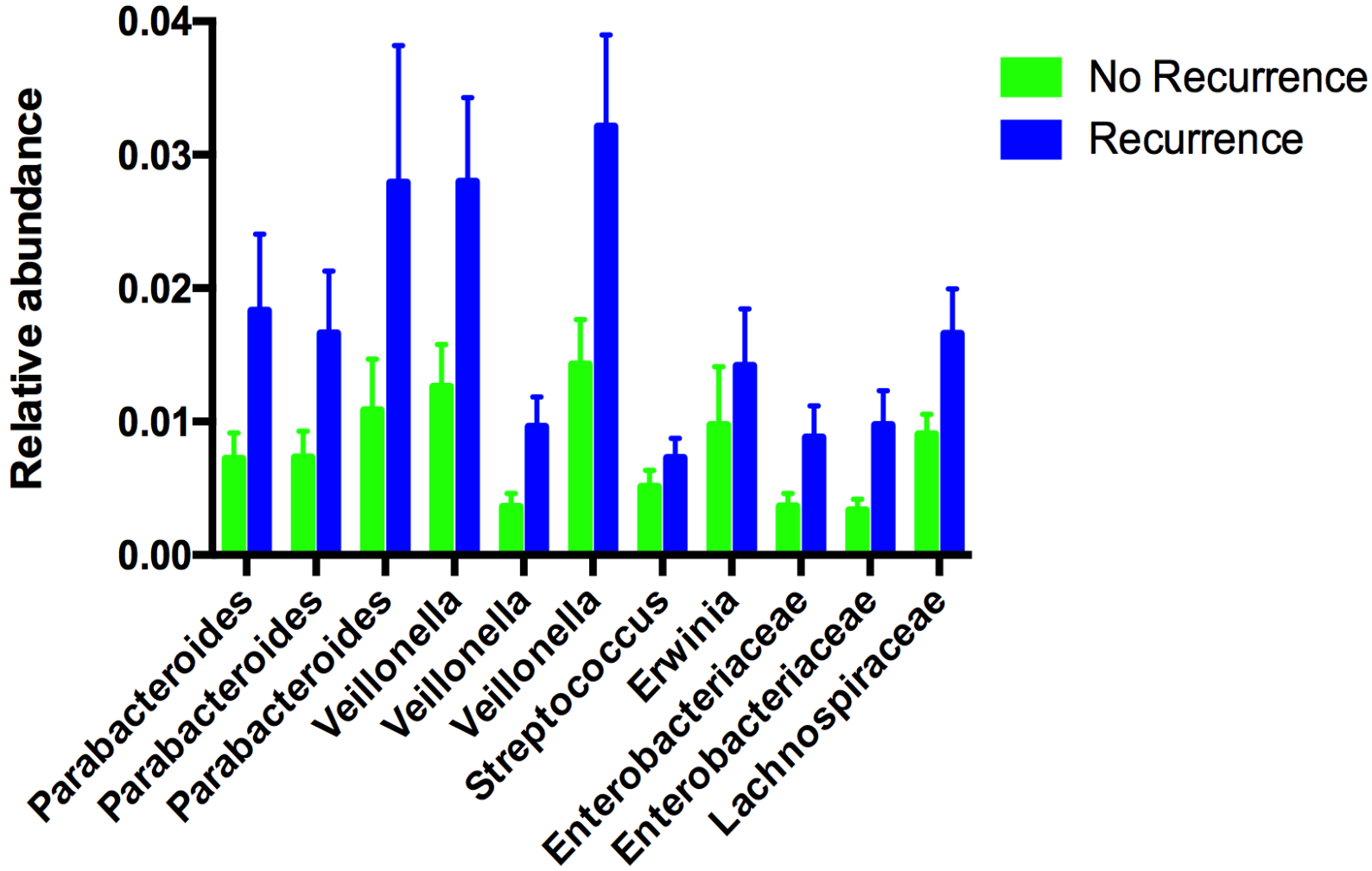
Dysbiosis in CDI

- Recurrent CDI causes loss of microbial diversity
  - Bacteroidetes and Firmicutes ⬇
  - Proteobacteria ⬆



Weingarden AR. *Am J Physiol Gastrointest Liver Physiol*. 2014.
Weingarden AR. *Microbiome*. 2015.
Chang JY *J Infect Dis*. 2008.

Higher Abundance of Parabacteroides & Enterobacteriaceae in Recurrent CDI



Khanna S. *Aliment Pharmacol Ther*. 2016.

Dysbiosis in CDI

- Decrease in secondary bile acid synthesis
- Increase in indole-producing bacteria
- Decreased production of Bacteriocins
  - Thuricin CD
    - Produced by Bacillus thuringiensis
    - Highly effective against C. difficile
  - Nisin
    - Produced by Lactococcus lactis
    - Inhibits *C. difficile* vegetative cells growth and spore germination

Khoruts. *Nat Rev Gastroenterol Hepatol*. 2016.
Darkoh C et al. *mSystems*. 2019;4(2
Rea. *Respir Med*. 2010
Lay. *J Med Microbiol*. 2016

Summary

- Increased incidence of primary and recurrent CDI
- Recurrence rate increases with subsequent recurrences
- CDI now affects young patients without any healthcare exposure
- Factors associated with epidemiologic shift
  - Virulence
  - Intestinal dysbiosis
  - Host factors

gcc Gastroenterology Center of Connecticut

pact physicians alliance of connecticut

The Evolution of Treatment Options for *C. difficile* and Recurrent Disease

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Assistant Clinical Professor of Medicine
Yale University School of Medicine
Gastroenterology Center of Connecticut

@DrPaulGastro

EverythingCdifficile.com
C. difficile education for patients and providers

Lorraine

- 66-year old woman
- Past medical history:
  - Hypertension
  - Diabetes
  - GERD
  - *C. difficile* infection (3/18)
- Past surgical history
  - Appendectomy

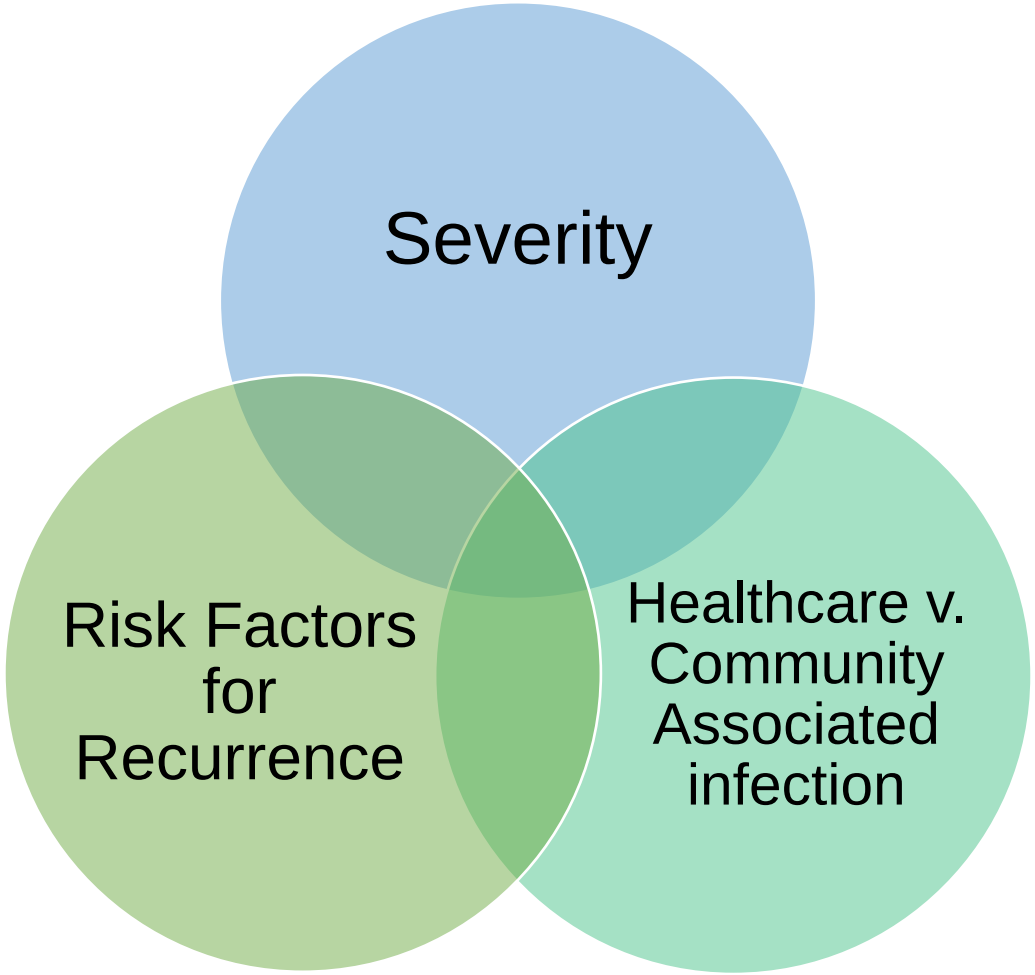
Lorraine, May 2019

- Presented 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: 16,000 x 10^3/mL
  - Cr: 1.0 mg/dL

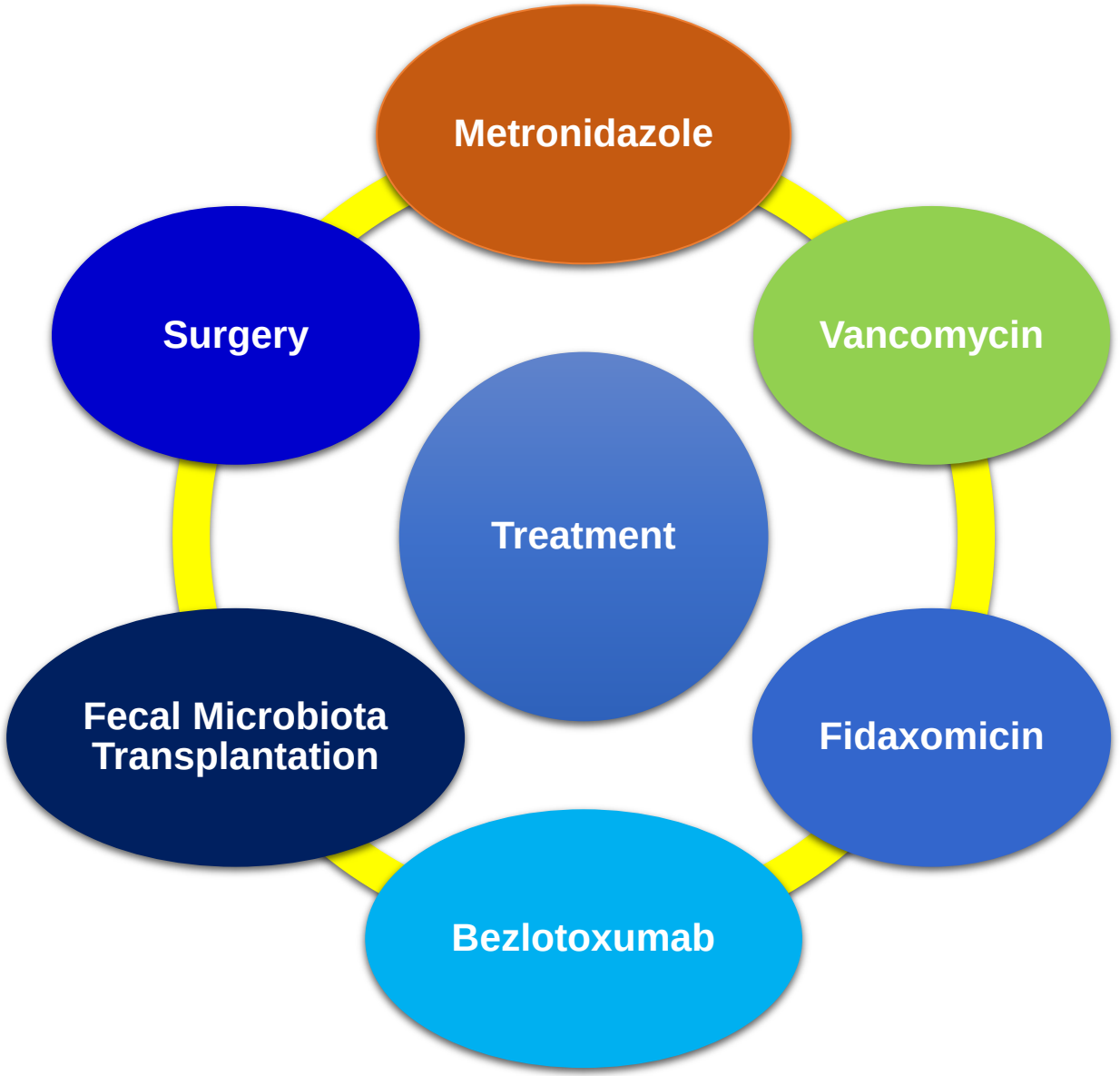
Approach to Management

Why does treating *C. difficile* illicit this response?

Factors to Consider



Treatment Options



Overall Treatment Tools

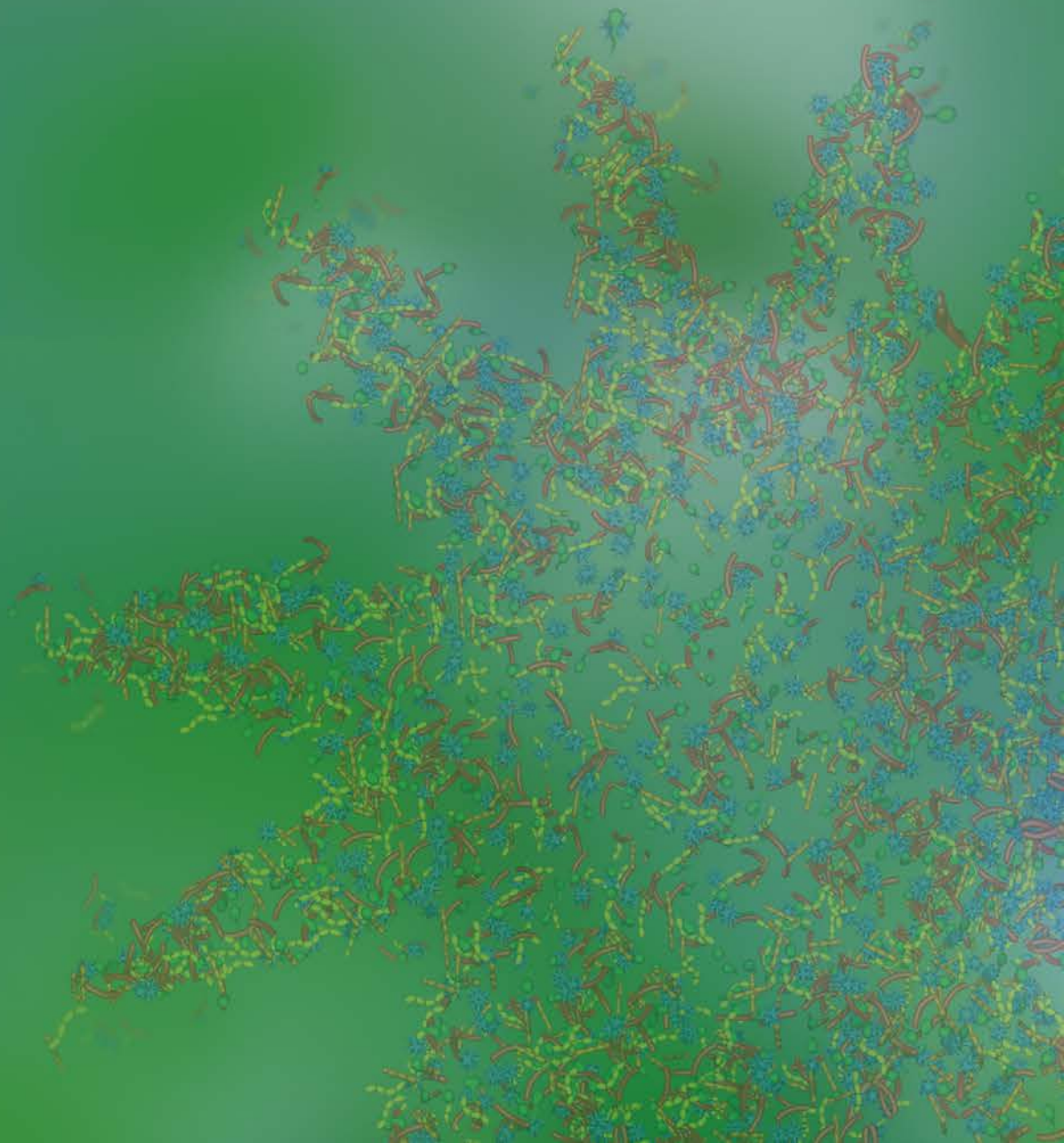
Attack the Bacteria

- Metronidazole
- Vancomycin
- Fidaxomicin

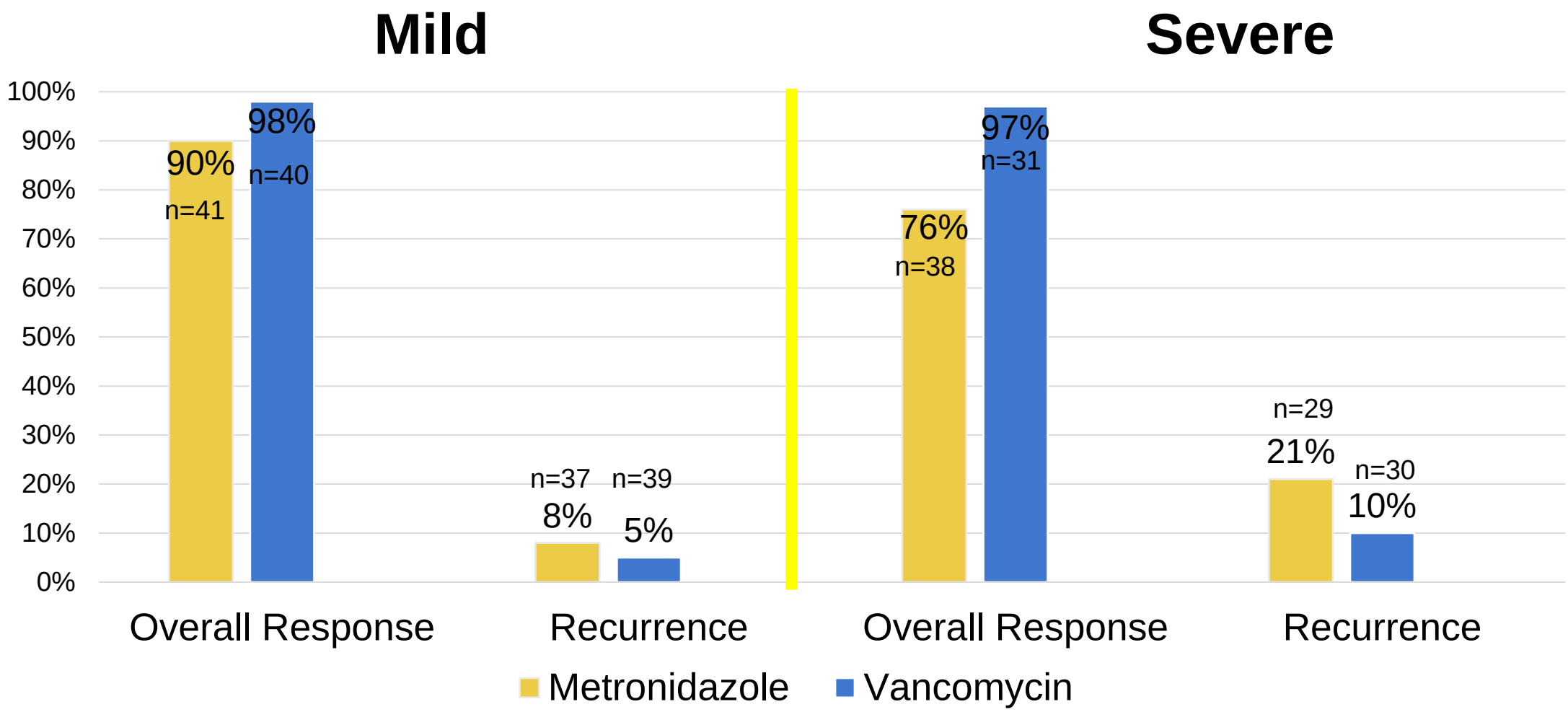
Support the Immune System

- Fecal Microbiota Transplantation
- Bezlotoxumab

Metronidazole vs. Vancomycin

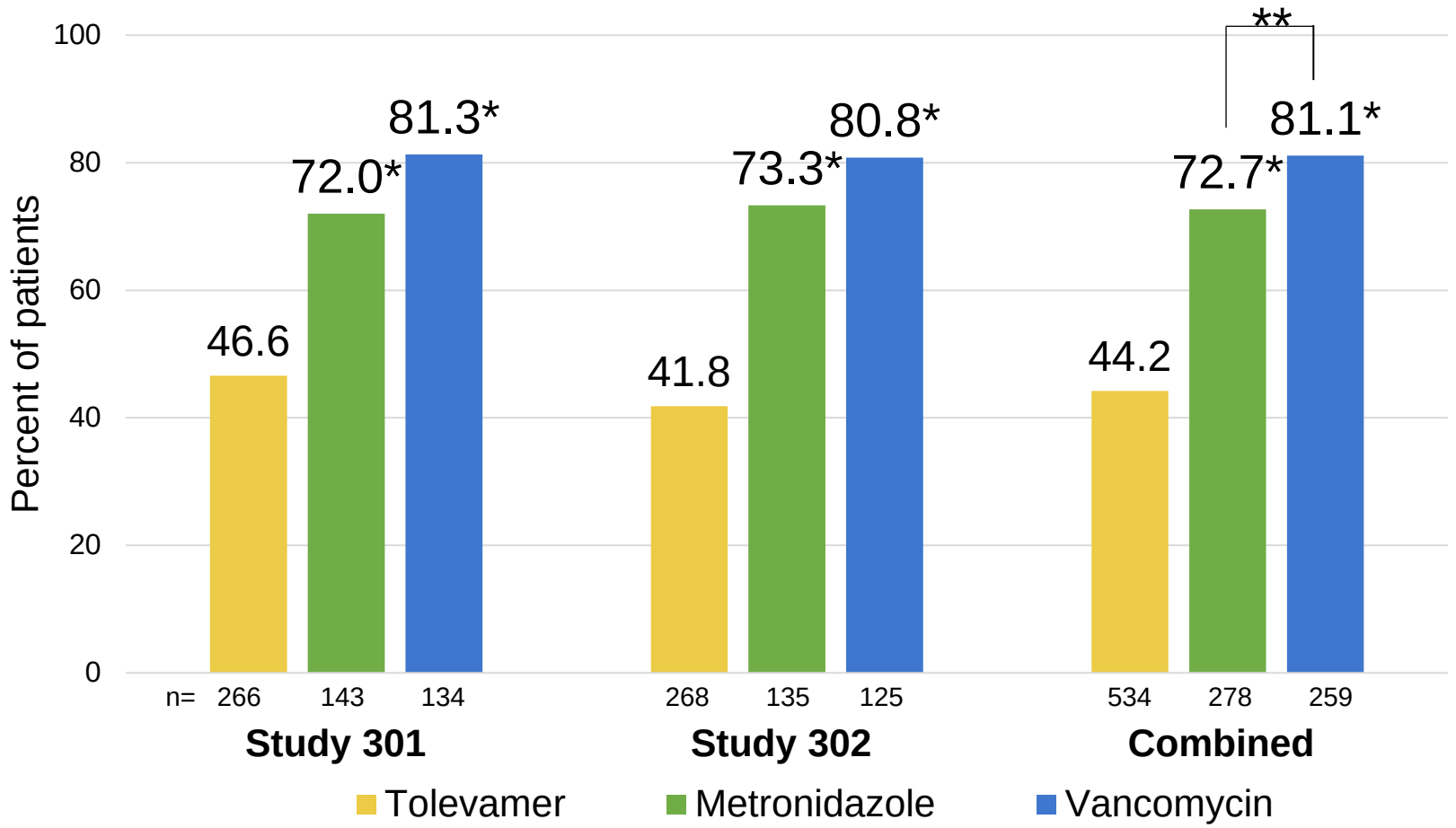


Metronidazole vs. Vancomycin



Zar et al. *Clin Infect Dis* 2007. 45 (3) 302-7.

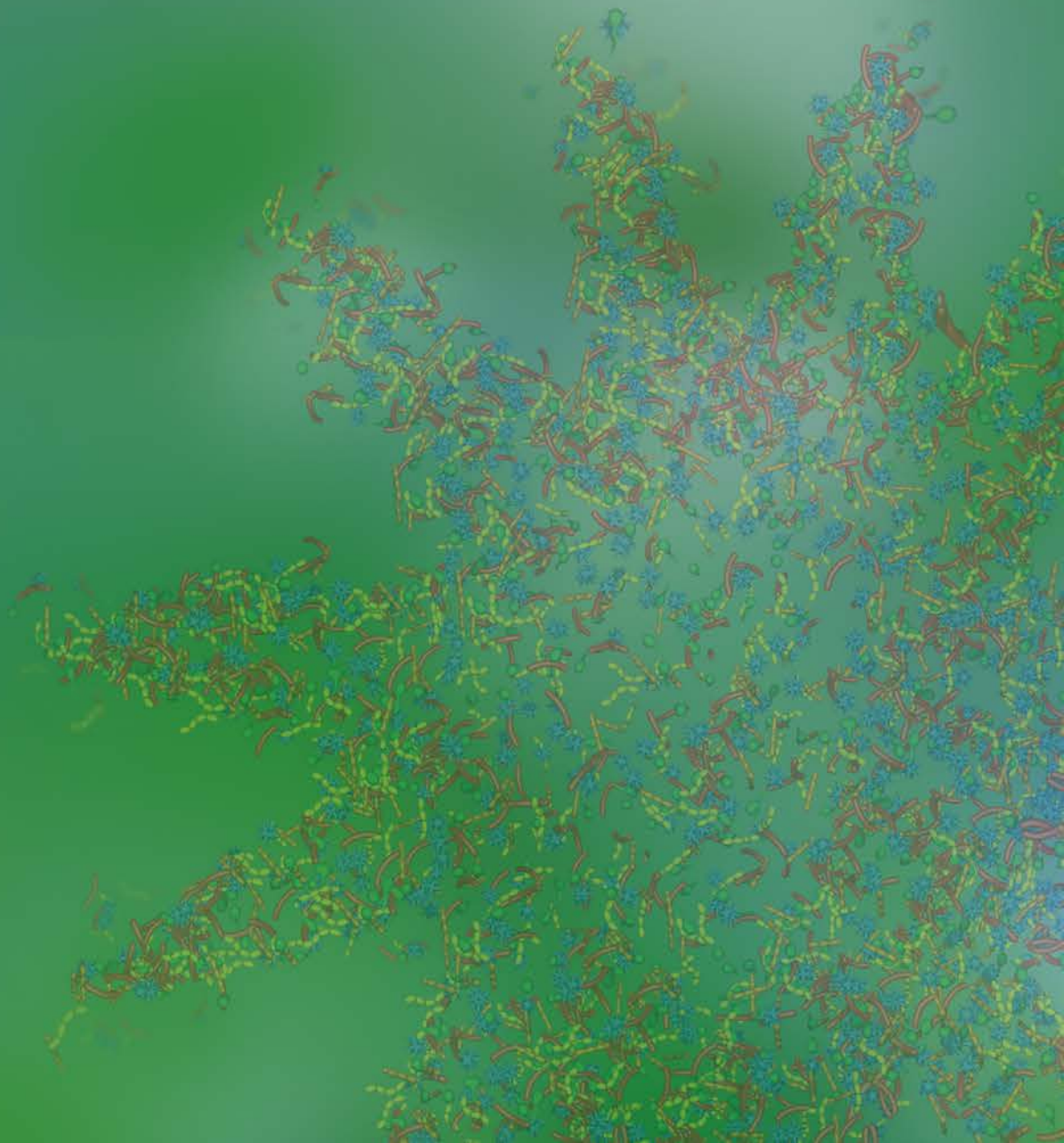
Tolevamer vs. Metronidazole vs. Vancomycin



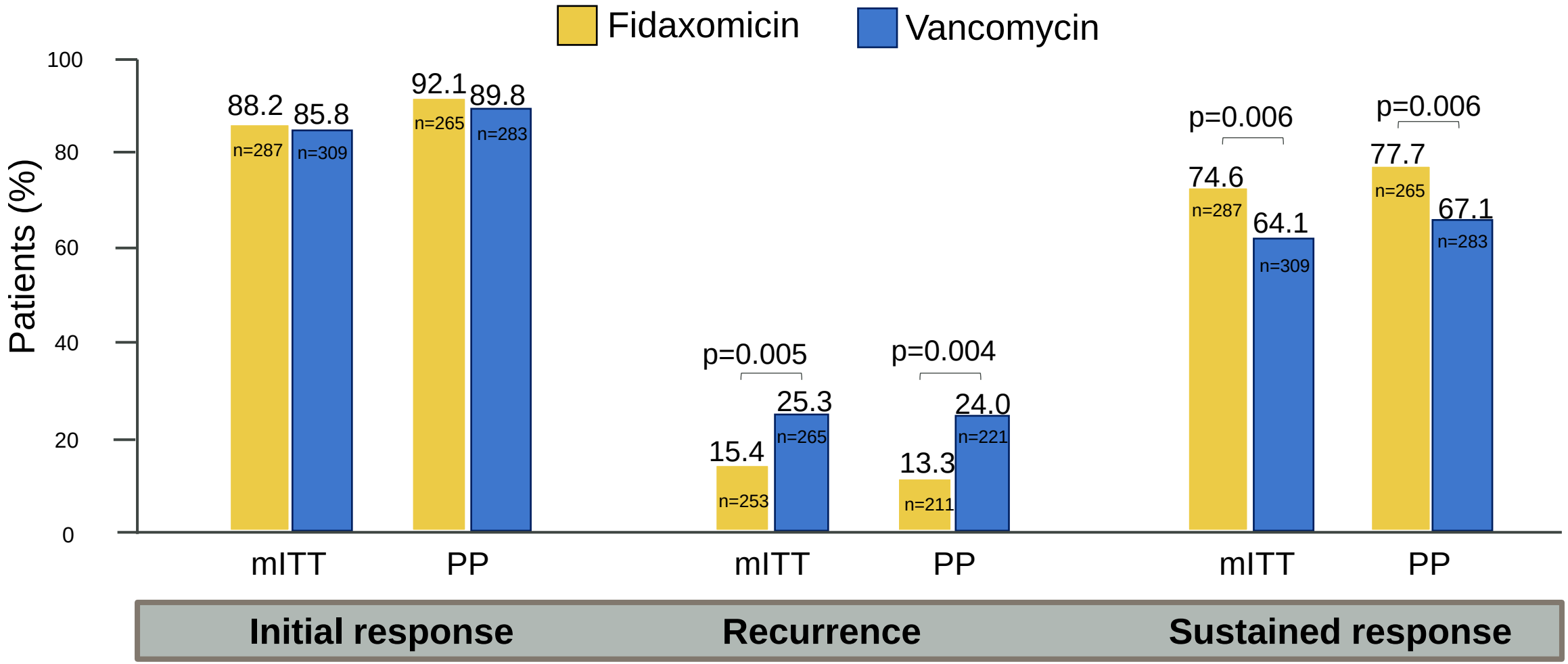
**p=0.020, M vs V

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

Fidaxomicin



Fidaxomicin and Vancomycin for Initial *C. difficile* Infection



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

IDSA/SHEA Treatment Initial Infection, 2018

Clinical Definition	Supportive Clinical Data	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
Initial episode *Non-severe*	Leukocytosis with a white blood cell count of ≤15000 cells/mL and a serum creatinine level <1.5 mg/dL	• VAN 125 mg given 4 times daily for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High
		• Alternate if above agents are unavailable: metronidazole, 500 mg 3 times per day by mouth for 10 days	Weak/High
Initial episode *Severe*	Leukocytosis with a white blood cell count of ≥15000 cells/mL or a serum creatinine level >1.5 mg/dL	• VAN, 125 mg 4 times per day by mouth for 10 days, OR	Strong/High
		• FDX 200 mg given twice daily for 10 days	Strong/High

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

IDSA/SHEA Treatment Initial Infection, 2018

Clinical Definition	Supportive Clinical Data	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
Initial episode, fulminant	Hypotension or shock, ileus, megacolon	• VAN, 500 mg 4 times per day by mouth or by nasogastric tube. If ileus, consider adding rectal instillation of VAN. Intravenously administered metronidazole (500 mg every 8 hours) should be administered together with oral or rectal VAN, particularly if ileus is present.	Strong/Moderate (oral VAN); Weak/Low (rectal VAN); Strong/Moderate (intravenous metronidazole)

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

Lorraine, May 2019

What would be an appropriate treatment for Lorraine?

Lorraine, June 2019

- Treated with vancomycin 125 mg PO Qid for 14-days and responds
- 4 weeks later she has the return of her abdominal pains with 6-8 liquid stools per day. She calls her primary care MD and is referred to your office for further assessment
- Initial:
  - WBC: 11,000 x 10^3/mL
  - Cr: 1.1 mg/dL

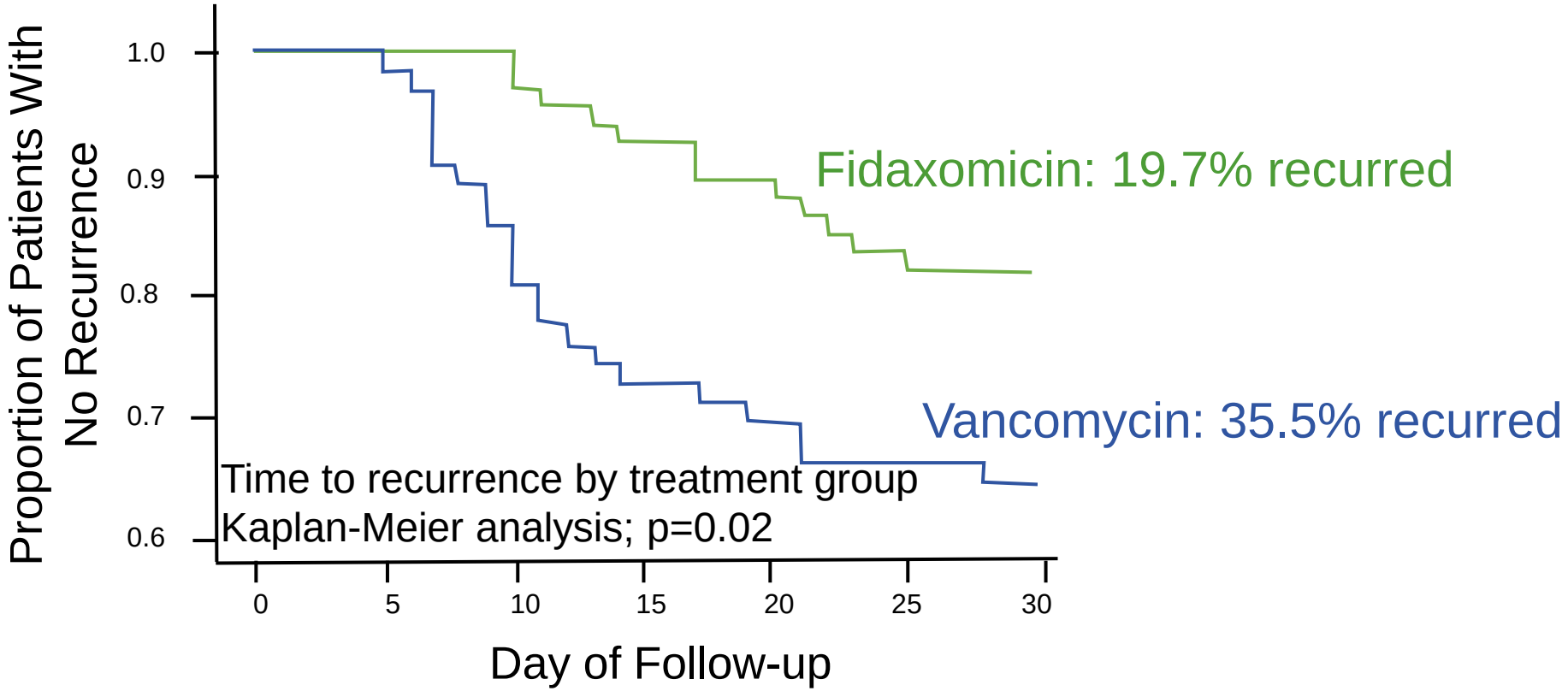
Lorraine, June 2019

What treatment options do we have for Lorraine’s recurrence?

Strategies for Managing Recurrent CDI

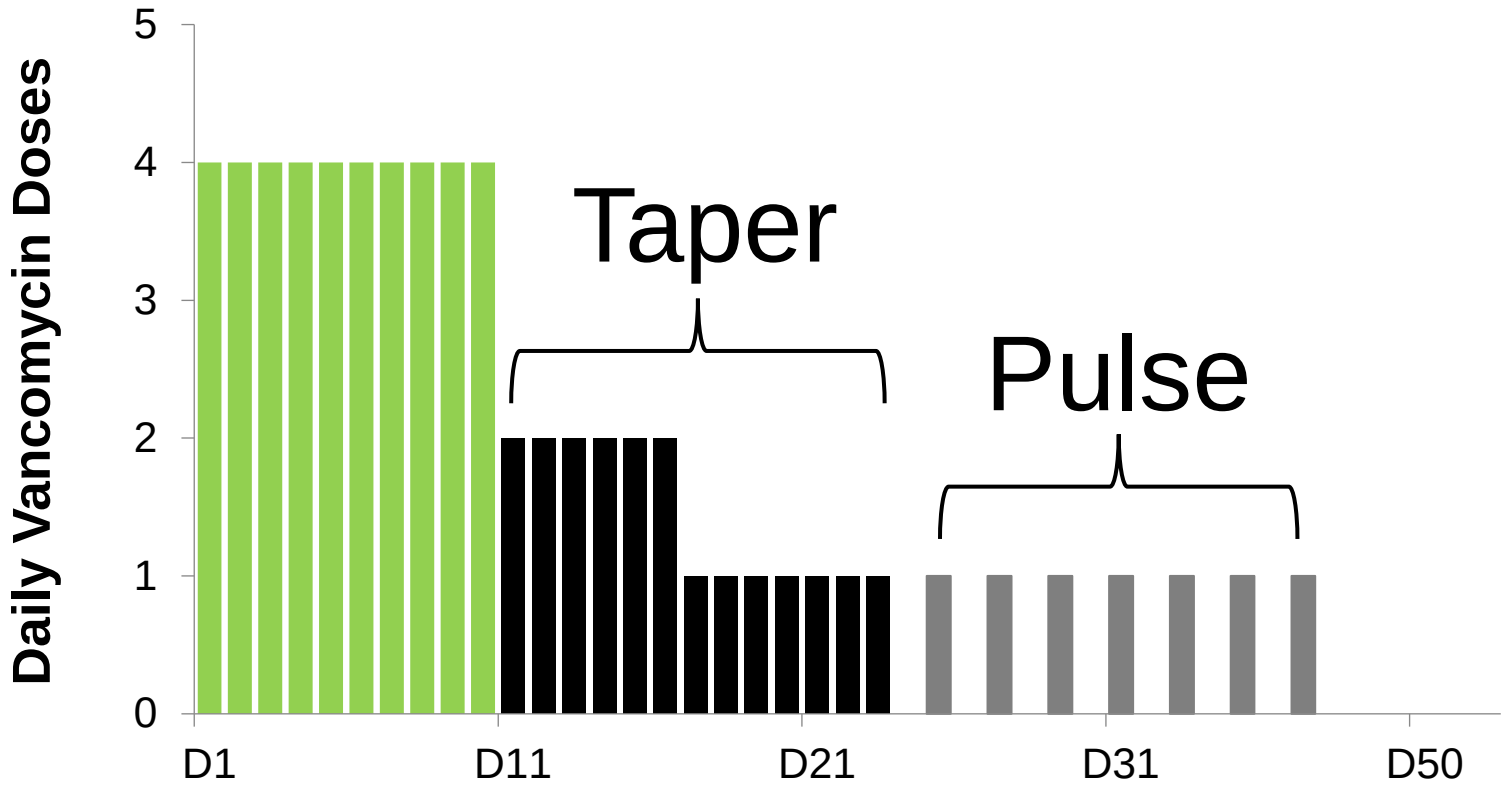
Switch Agent	• Vancomycin • Fidaxomicin
Pulsed or Tapered	• Vancomycin • Fidaxomicin
Post-Vancomycin “Chaser”	• Rifaximin • Fidaxomicin
Microbiota Replacement	• Fecal Microbiota Transplantation

Fidaxomicin Sub-Group Analysis: 1st Recurrence of CDI

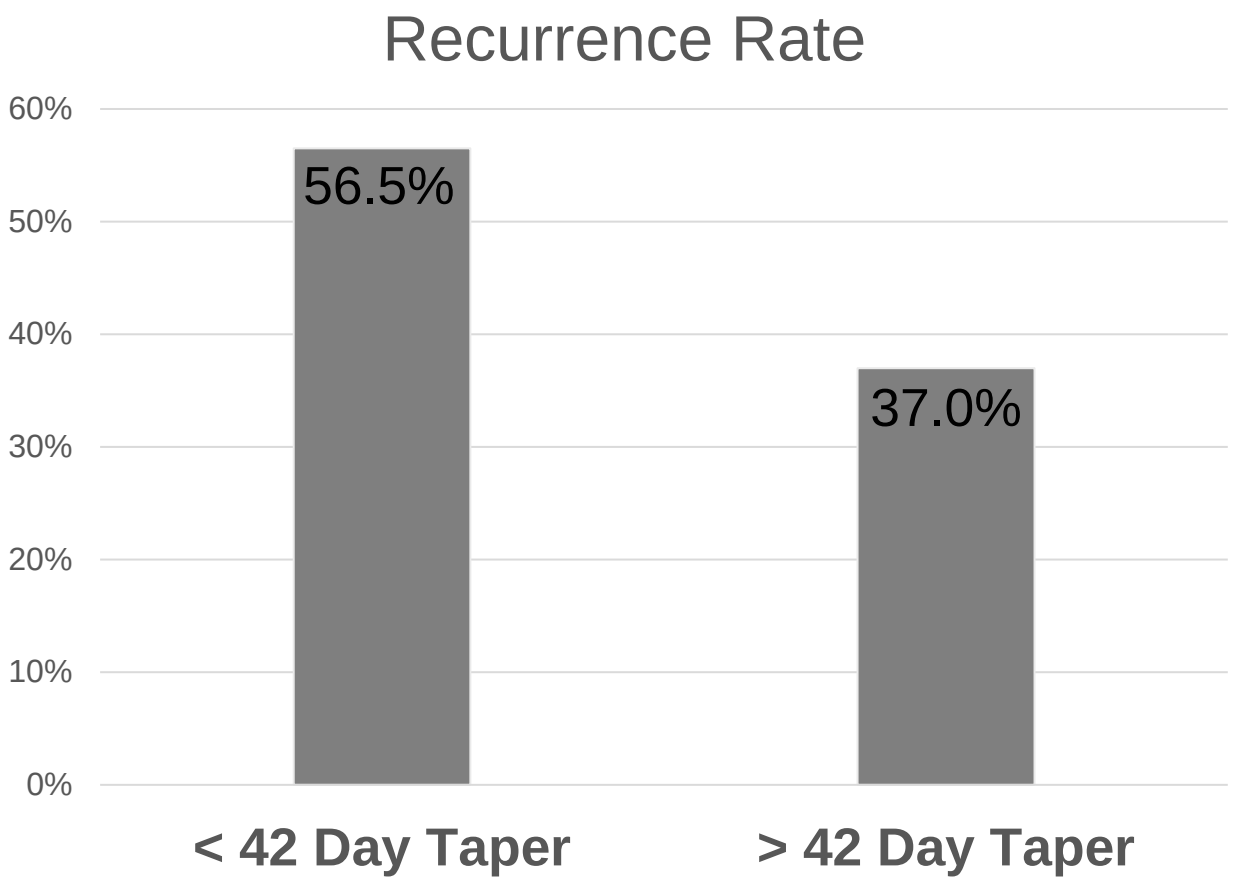


Cornely et al. *Clin Infect Dis*. 2012;(suppl 2)55:S154-61.

Vancomycin Taper and/or Pulse Regimens



Efficacy of Vancomycin Taper



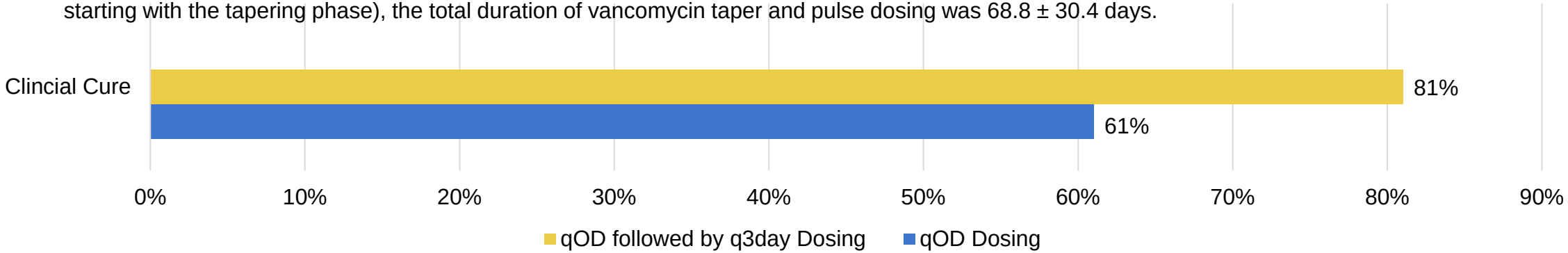
- 128 patients
- Median # Episodes: 3 (Range: 1-7)
- Median Age 60.5
- Median Duration of taper: 50.5 days
- **Overall Recurrence: 41%**
- Multivariate analysis (Recurrent CDI after completion of taper):
  - **Antibiotic use** (OR: 2.9 (95%CI 1.14-7.9) *P* value=0.025)
  - **Taper duration <42 days** (odds ratio 2.6 (95% CI 1.03- 6.88), *P* value=0.04)

Khanna S and Pardi DS. *DDW* 2017. Abstract: SA1791.

Taper vs. Taper and Pulsed Vancomycin

Taper/Pulse Phase	QOD (n = 36)	QOD + Q3D (n = 64)	*P* Value	Total; Range (N = 100)
Total duration of treatment,* d	60.3 ± 25.9	86.3 ± 27.8	0.0004	77 ± 29.9; 18–189
Taper phases				
Duration of twice daily dosing (n = 92)	8.7 ± 3.6	9.9 ± 6.9	0.39	9.4 ± 5.9; 3–43
Duration of daily dosing (n = 100)	15 ± 11.8	12.3 ± 11.1	0.26	13.3 ± 11.5; 4-76
Pulse phases				
Duration of QOD dosing (n = 100)	24.7 ± 14.0	25.5 ± 10.4	0.75	25.2 ± 11.8; 7-60
Duration of Q3D dosing (n = 64)	…	27.2 ± 11.6		27.2 ± 11.6; 12-64

Data are presented as mean days ± standard deviation.
*Total duration of vancomycin treatment prescribed in our clinic. This duration included treatment dosing (4 times daily) in approximately half of the patients (n = 58) prior to tapering vancomycin. The other patients had treatment dosing prior to referral to our clinic. Excluding treatment dosing (ie, starting with the tapering phase), the total duration of vancomycin taper and pulse dosing was 68.8 ± 30.4 days.



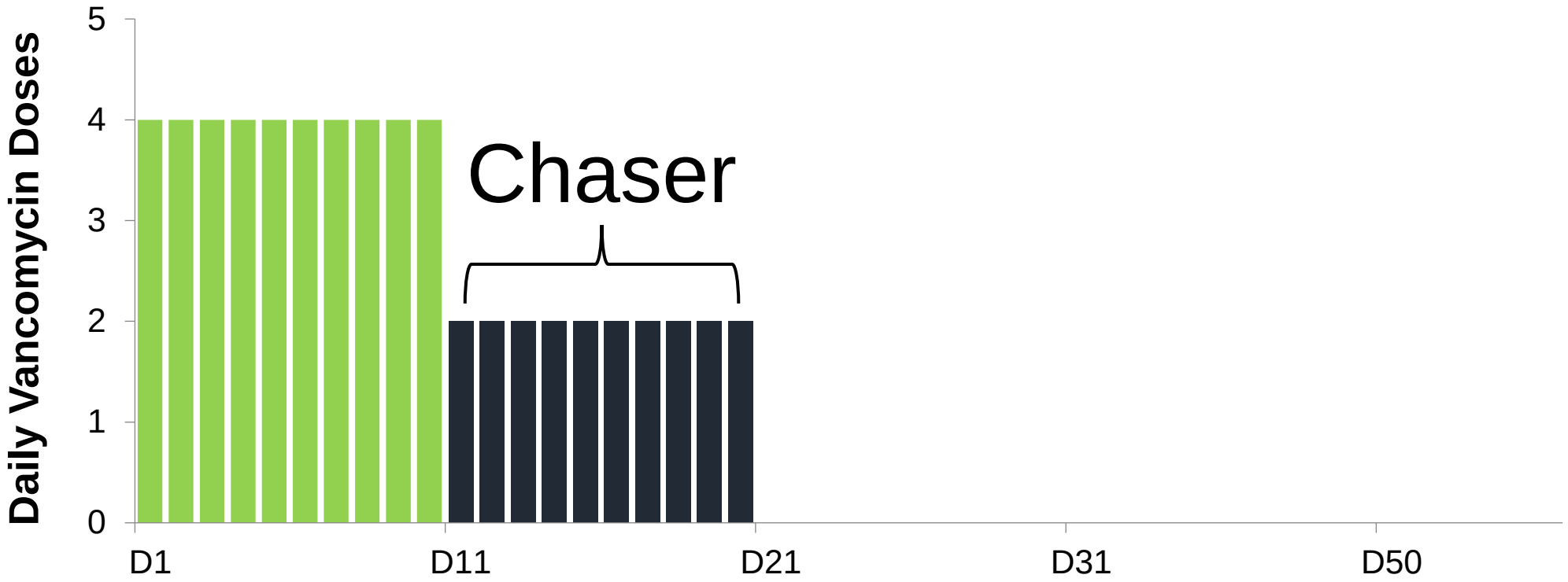
Adapted from Sirbu et al. *Clin Infect Dis.* 2017;65(8):1396-1399.

IDSA/SHEA Treatment Recurrence, 2018

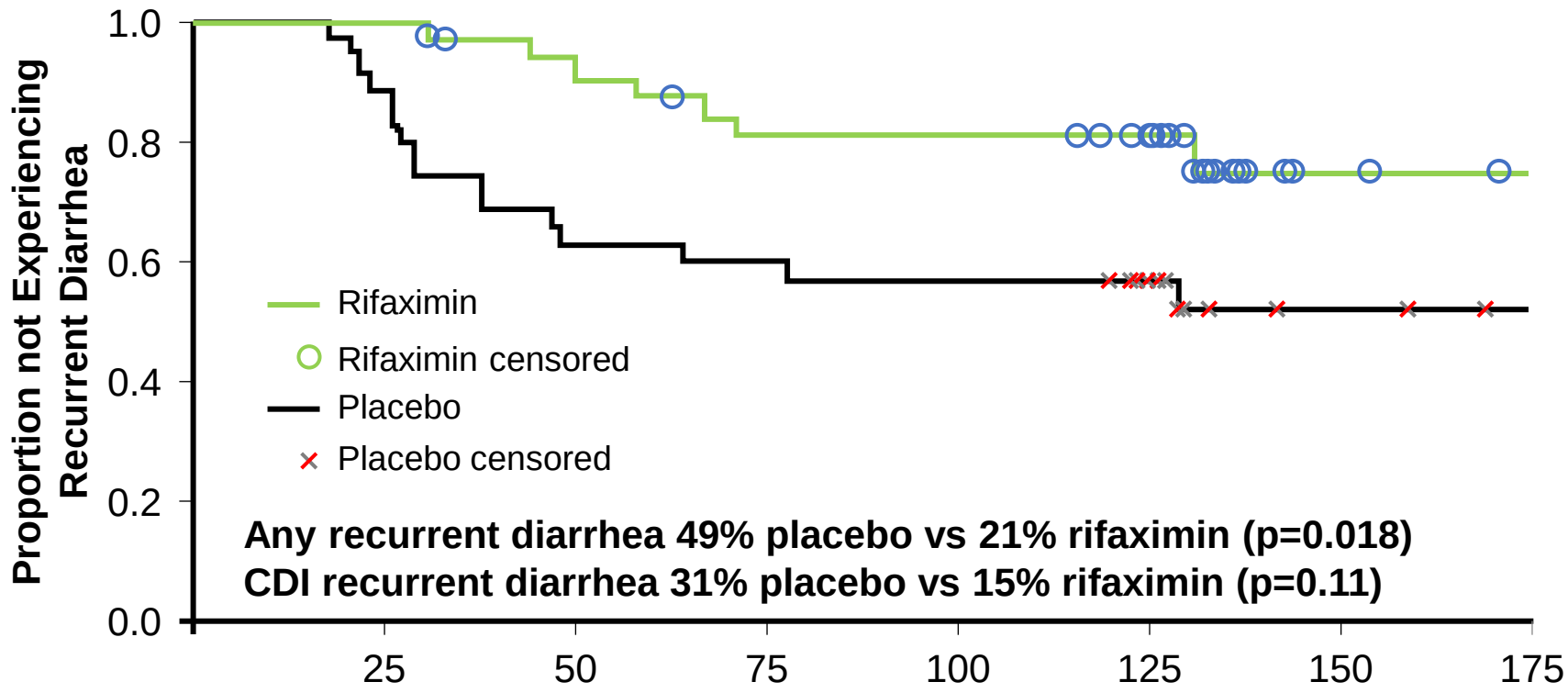
Clinical Definition	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
First recurrence	• VAN 125 mg given 4 times daily for 10 days if metronidazole was used for the initial episode, OR	Weak/Low
	• Use a prolonged tapered and pulsed VAN regimen if a standard regimen was used for the initial episode (eg, 125 mg 4 times per day for 10–14 days, 2 times per day for a week, once per day for a week, and then every 2 or 3 days for 2–8 weeks), OR	Weak/Low
	• FDX 200 mg given twice daily for 10 days if VAN was used for the initial episode	Weak/Moderate

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

Post-vancomycin, ‘chaser’ regimens



Rifaximin “Chaser”



Garey KW, et al. *J Antimicrob Chemother* 2011;66:2850−5.

Fidaxomicin "Chaser"

	n	Age, mean ± SD	Sex (f)	No. of CDI episodes, mean ± SD	Subsequent recurrence rate
Fidaxomicin 200mg PO Bid x 10 days	8	66.9 ± 19	75%	5.5 ± 2	38%
Fidaxomicin 200mg daily x 7 days followed by qOD x 14 days	12	63.6 ± 16	58%	5.1 ± 2	18%

Soriano MM et al. *Open Forum Infect Dis*. 2014;1:ofu069.

IDSA/SHEA Treatment Recurrence, 2018

Clinical Definition	Recommended Treatment	Strength of Recommendation/ Quality of Evidence
Second or subsequent recurrence	• VAN in a tapered and pulsed regimen, OR	Weak/Low
	• VAN, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days, OR	Weak/Low
	• FDX 200 mg given twice daily for 10 days, OR	Weak/Low
	• Fecal microbiota transplantation*	Strong/Moderate

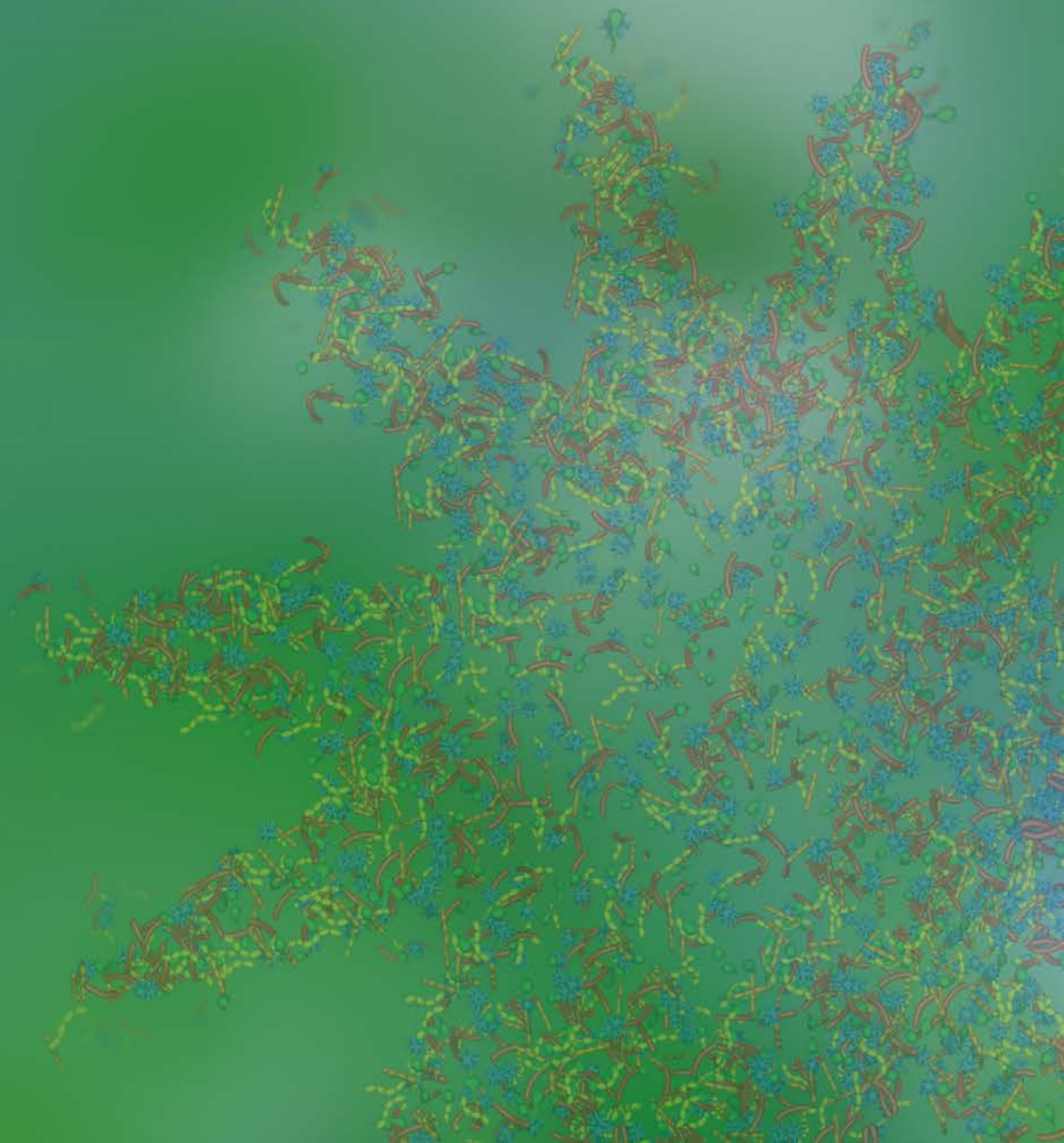
***The opinion of the panel is that appropriate antibiotic treatments for at least 2 recurrences (ie, 3 CDI episodes) should be tried prior to offering fecal microbiota transplantation**

McDonald et al. *Clin Infec Dis*. 2018.66(7)e1-e48.

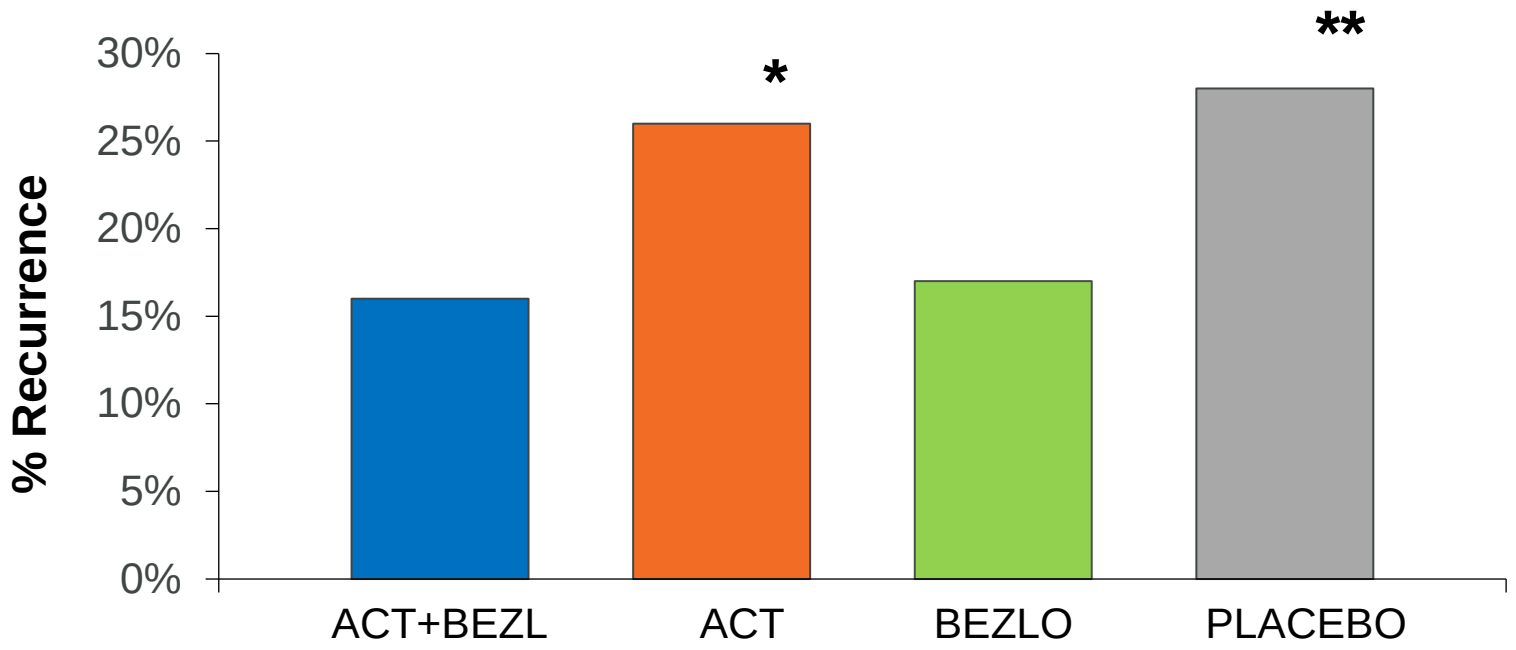
Lorraine, June 2019

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

Bezlotoxumab



Bezlotoxumab RCT: MODIFY 1

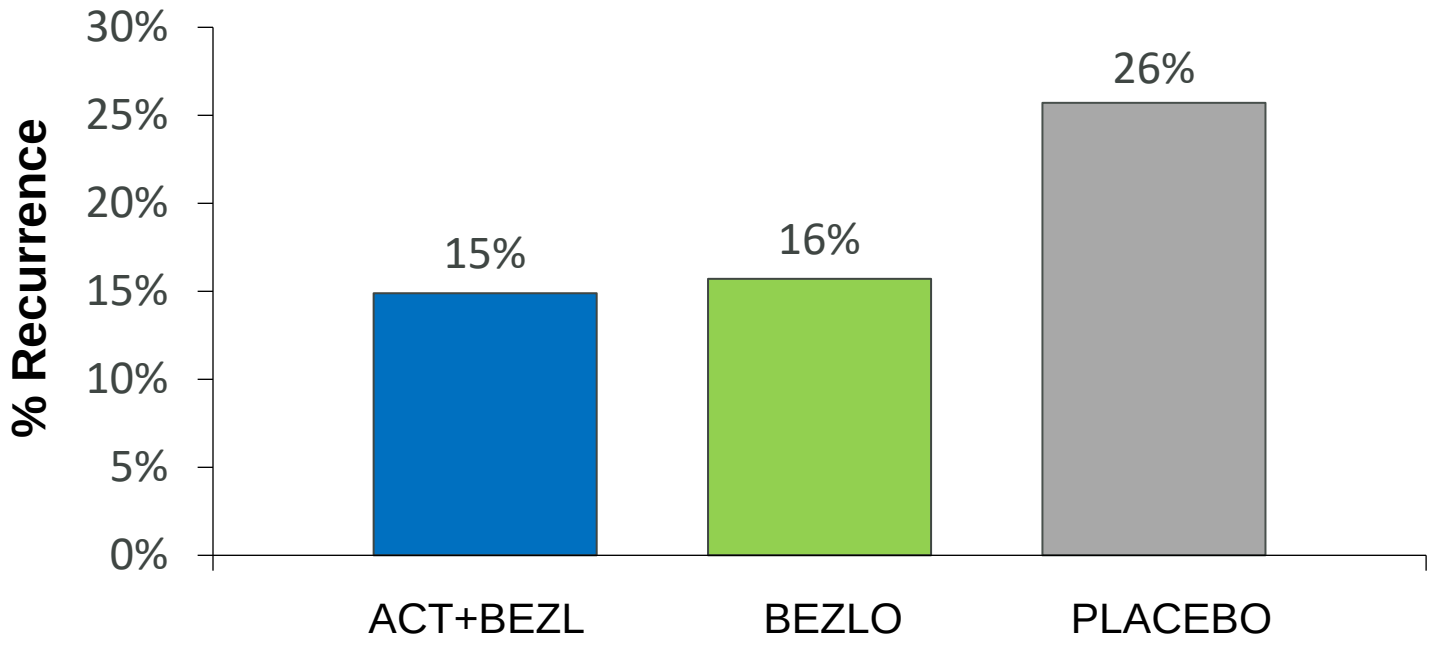


* **ACT+BEZLO vs Pbo: *P*<0.0001**

** **BEZLO vs Pbo: *P*=0.0003**

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

Bezlotoxumab RCT: MODIFY 2

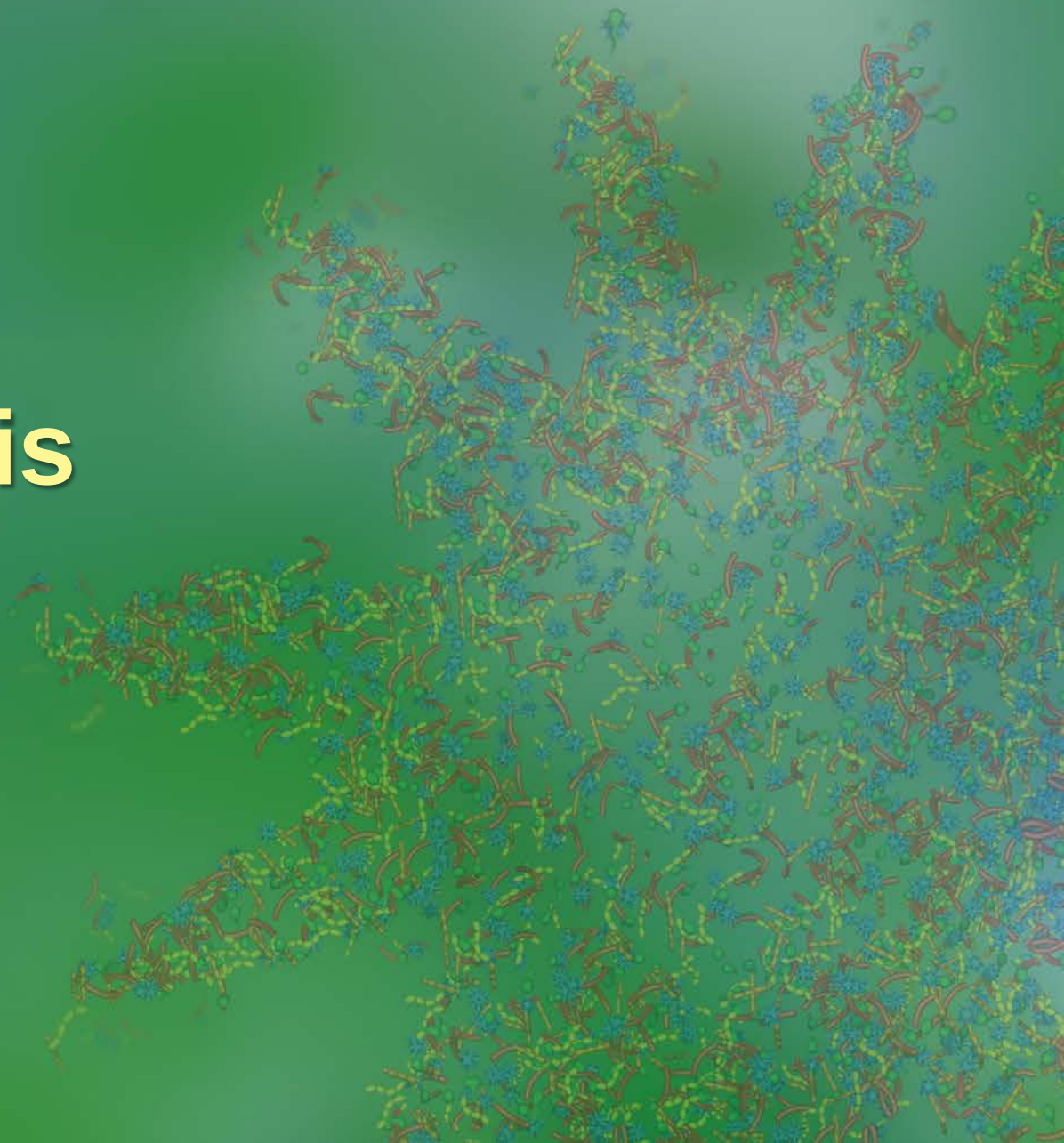


* **ACT+BEZLO vs Placebo: *P*<0.0001**

** **BEZLO vs Placebo: *P*=0.0003**

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

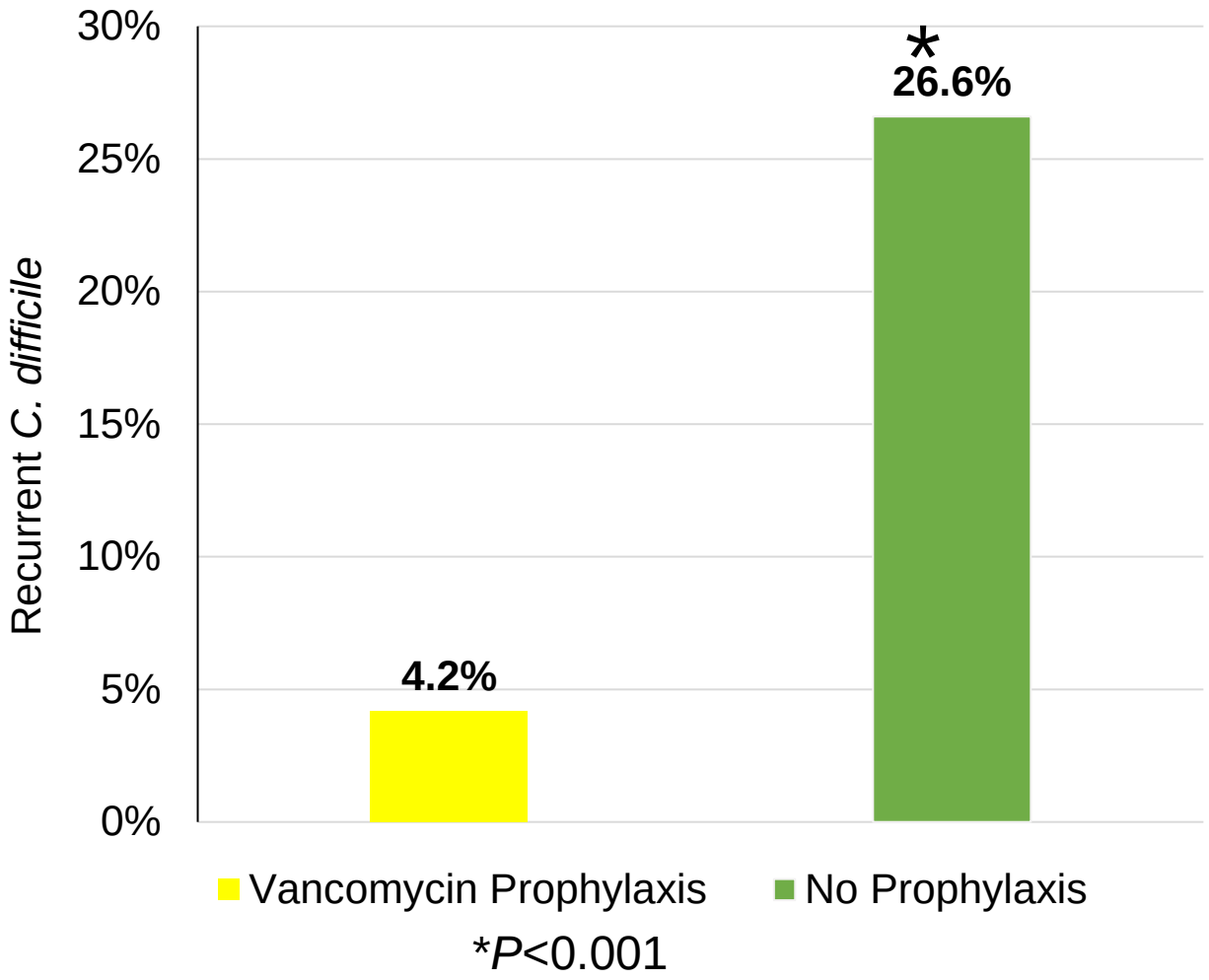
Vancomycin Prophylaxis



Vancomycin Prophylaxis to Prevent Recurrent *Clostridioides difficile* Infection

Characteristic	OVP Group (n = 71)	Control Group (n = 132)	*P* value
Male, No. (%)	36 (51)	67 (51)	>.99
Age, mean (range), y	73 (41-97)	69 (25-9)	.07
White race, No. (%)	58 (82)	105 (80)	.85
Probiotics, No (%)[a]	31 (14)	21 (16)	.84
Systemic antimicrobials, No. (%)			
Fluoroquinolones	31 (43.7)	47 (35.6)	.29
Aminopenicillins[b]	35 (49.3)	63 (47.7)	.88
Cephalosporins	25 (35.2)	59 (44.7)	.23
Carbapenems	14 (19.7)	16 (12.1)	.15
Meropenem and imipenem	12 (16.9)	10 (7.6)	.06
Ertapenem	6 (8.5)	6 (4.5)	.35
Vancomycin, piperacillin-tazobactam, and levofloxacin[c]	16 (22.5)	21 (15.9)	.26
Duration of systemic antimicrobial therapy, mean (range), d	12.5 (2-56)	11.9 (3-42)	.67
H2RA or PPI, No. (%)			
Before admission	39 (54.9)	70 (53)	.77
Inpatient	58 (81.7)	90 (68.2)	.047
Prior CDI, mean (range), mo	6.14 (1-21)	7.61 (1-22)	.16
Discharged to home, No. (%)	40 (56.3)	74 (56.1)	1.0

Abbreviations; CDI, *Clostridium difficile* infection; H2RA, histamine-2 receptor antagonist; OVP, oral vancomycin prophylaxis; PPI, proton-pump inhibitor.
[a] *Saccharomyces boulardii* administered during inpatient stay.
[b] Ampicillin, ampicillin-sulbactam, amoxicillin, and amoxicillin-clavulanate.
[c] Intravenous vancomycin, piperacillin-tazobactam, and levofloxacin as a fixed combination.



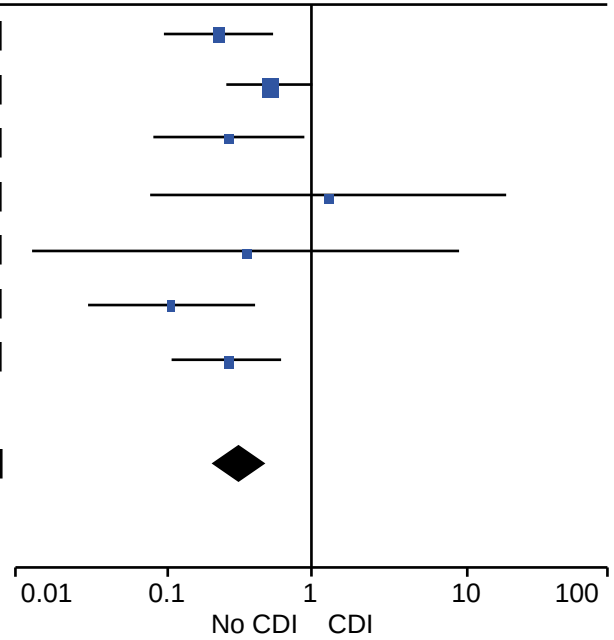
Van Hise et al. *Clin Infect Dis*. 2016;6 3(3):651-3.

Vancomycin Therapy Prophylaxis

	OVP		No OVP			Odds Ratio	Odds Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**M-H, Random, 95% CI**	**M-H, Random, 95% CI**
Bajrovic 2016	6	90	1661	7445	20.5%	0.25 [0.11, 0.57]	
Carignan 2016	49	90	57	82	33.8%	0.52 [0.28, 0.98]	
O'Connell 2017	6	80	11	55	13.0%	0.32 [0.11, 0.94]	
Pereiras 2017	2	12	1	7	2.3%	1.20 [0.09, 16.24]	
Splinter 2017	0	12	2	24	1.6%	0.36 [0.02, 8.10]	
Van Hise 2016	3	71	35	132	10.0%	0.12 [0.04, 0.41]	
Wong 2015	7	112	28	145	18.9%	0.23 [0.12, 0.66]	
Total (95% CI)		**467**		**7890**	**100.0%**	**0.33 [0.22, 049]**	
Total events	73		1795				

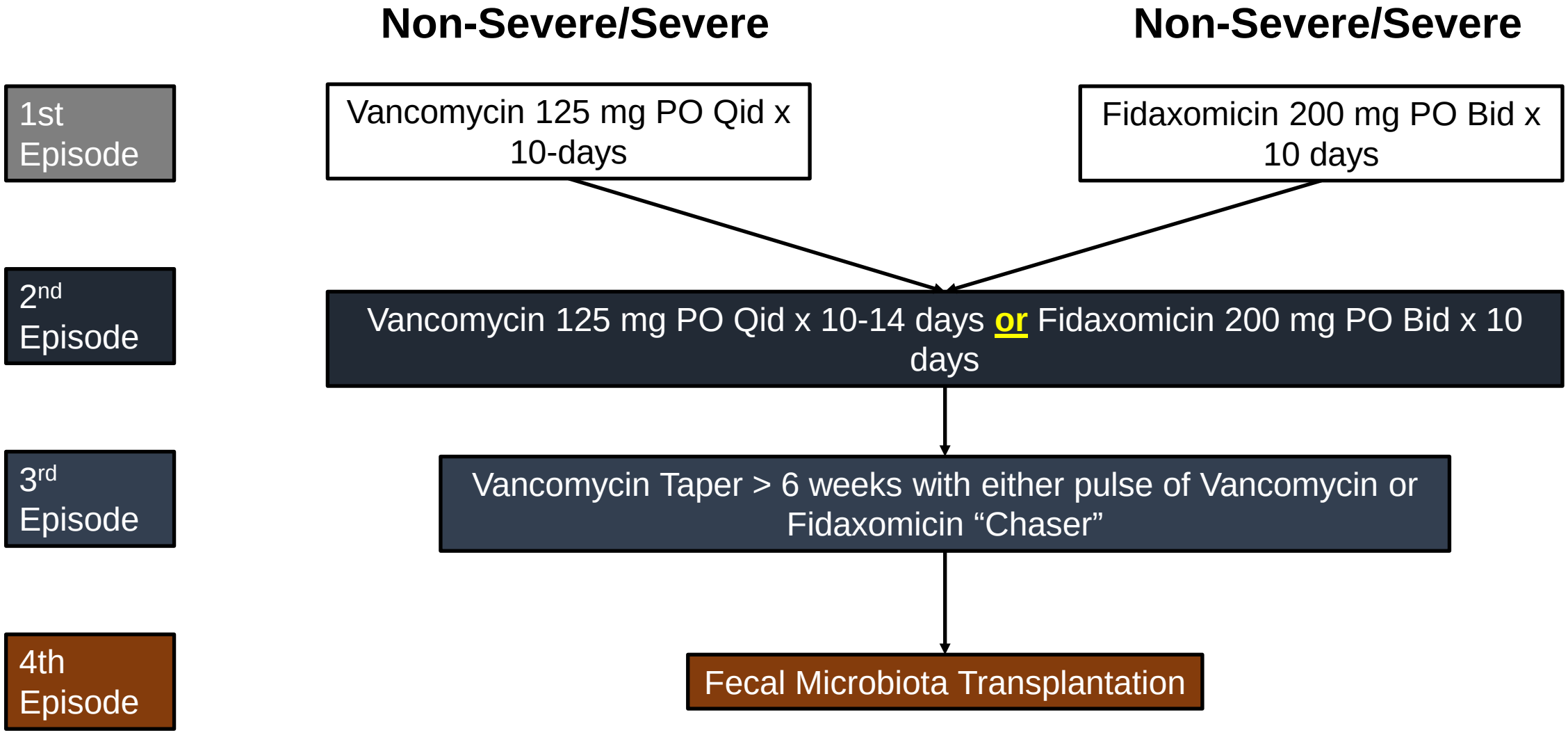
Heterogeneity: Tau^2 - 0.02; Chi^2 = 6.35, df = 6 (P = 0.38); I^2 = 6%

Test for overall effect: Z = 5.55 (*P*<0.00001)



Tariq et al. *DDW* 2019 Presentation. Mo1952.

FMT not Readily Available

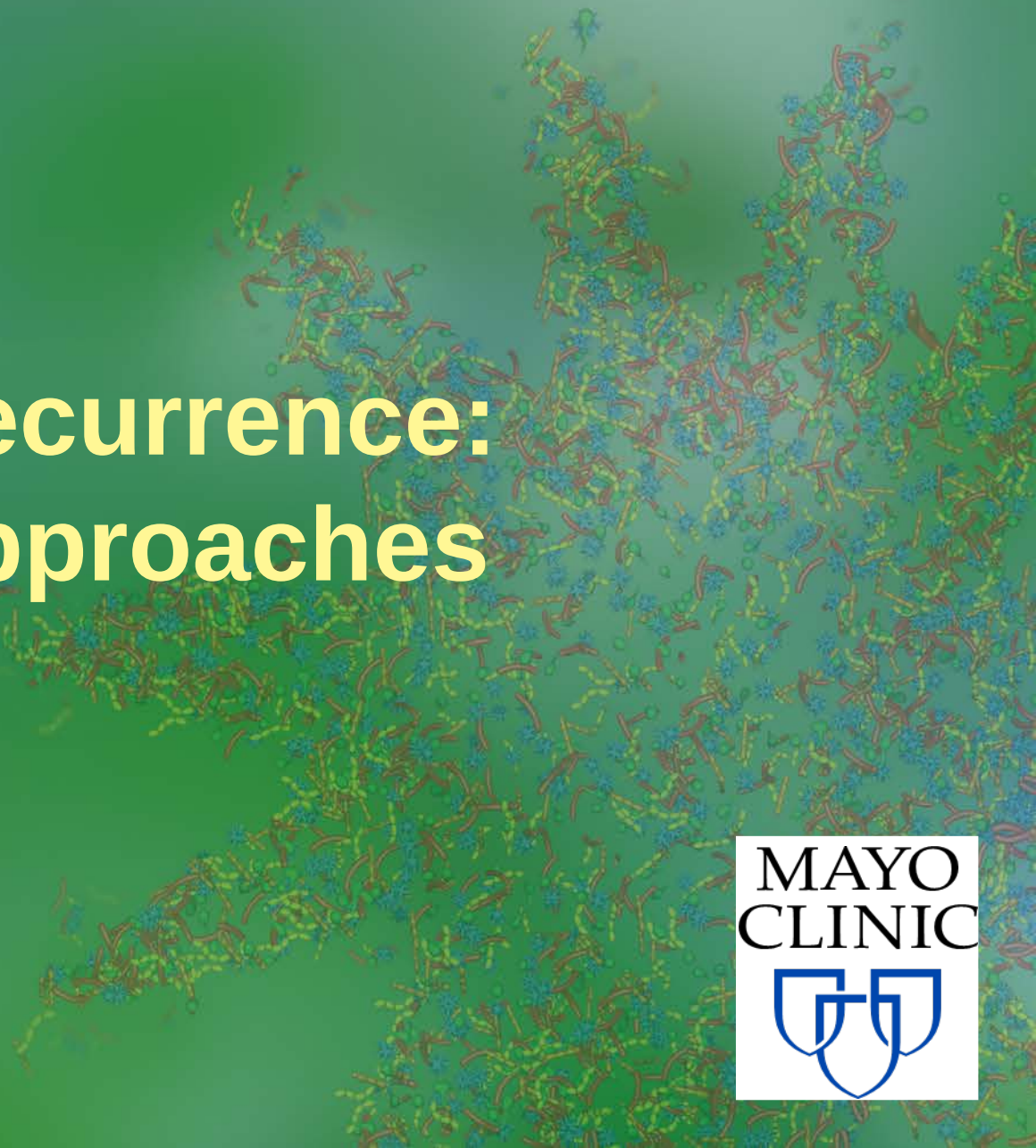


FMT *More* Readily Available

	Non-Severe/Severe	Non-Severe/Severe
1st Episode	Vancomycin 125 mg PO Qid x 10-days	Fidaxomicin 200 mg PO Bid x 10 days
2nd Episode	Vancomycin Taper > 6 weeks with either pulse of Vancomycin or Fidaxomicin "Chaser" **or** Fidaxomicin 200 mg PO Bid x 10 days	
3rd Episode	Fecal Microbiota Transplantation	

Breaking the Cycle of Recurrence: Available & Emerging Approaches Beyond Antibiotics

Sahil Khanna, MBBS, MS
Associate Professor of Medicine
Gastroenterology and Hepatology
khanna.sahil@mayo.edu



MAYO CLINIC

Learning Objectives

- FMT: available data and challenges
- Microbiota restoration therapies
  - Rationale for restoration
  - Mechanisms of emerging approaches
  - Clinical trial data on reduction of recurrence
  - Process and impact of FDA-approved microbiota restoration/transplant therapies

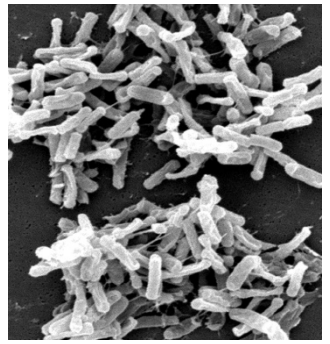


Image source: www.phil.cdc.gov

Monday Morning in the Clinic

- 69/M retired physician presents with diarrhea x 3 days
- 2 weeks ago: clindamycin x 5 days for dental work
  - Has penicillin allergy
  - No visible tooth abscess
  - Lost argument with his oral surgeon friend and took the prophylactic antibiotic
- ***C. difficile* test is positive**
- **Fidaxomicin 200 mg twice daily x 10 days**

Guidelines (2017 / 2018)

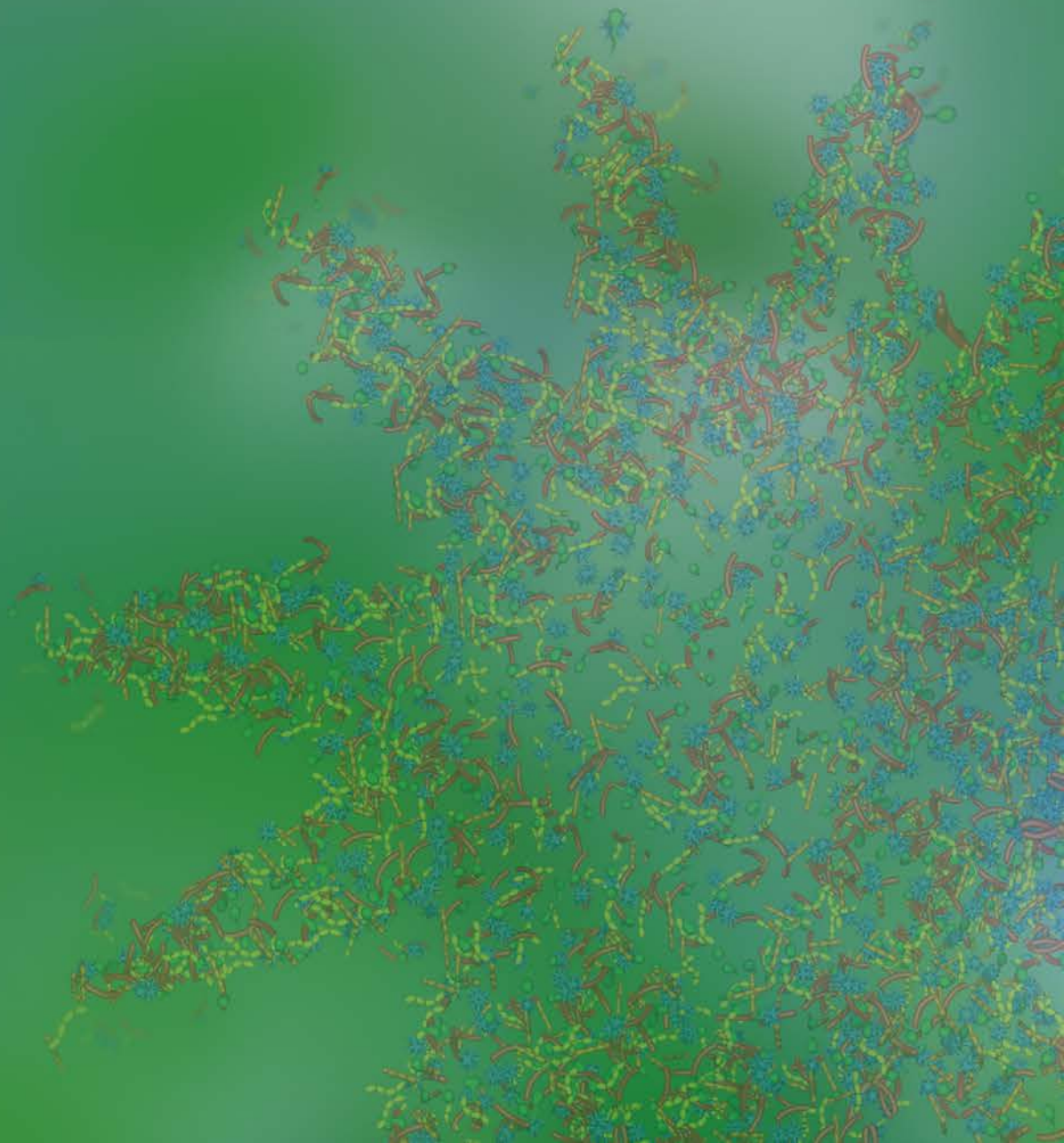
Patient Group	Recommended Treatment in Adults
Initial episode, non-severe	• **Vancomycin** 125 mg QID x 10 d OR • **Fidaxomicin** 200 mg BID x 10 d • If above agents are unavailable: metronidazole 500 mg TID x 10 d
Initial episode, severe	• **Vancomycin** 125 mg QID for 10 d OR • **Fidaxomicin** 200 mg BID for 10 d
Initial episode, fulminant	• Vancomycin 500 mg QID PO & PR QID & metronidazole 500 mg TID IV
First recurrence	• Vancomycin 125 mg QID x 10 d if metronidazole used initially • Taper-pulse vancomycin or Fidaxomicin 200 mg BID x 10 d if vancomycin was used for initial episode
Second or subsequent recurrence	• Tapered and pulsed vancomycin OR • Fidaxomicin 200 mg BID for 10 d, OR • **Vancomycin 125 mg QID or Fidaxomicin 200 mg BID x 10 d followed by Fecal microbiota transplantation** OR • Vancomycin, 125 mg 4 times per day by mouth for 10 days followed by rifaximin 400 mg 3 times daily for 20 days

McDonald LC et al. *Clin Inf Dis*. 66(7):e1-e48.

Monday Morning in the Clinic

- 69/M retired physician presents with diarrhea x 3 days
- 2 weeks ago: clindamycin x 5 days for dental work
  - Has penicillin allergy
  - No visible tooth abscess
  - Lost argument with his oral surgeon friend and took the prophylactic antibiotic
- ***C. difficile* test is positive**
- **Fidaxomicin 200 mg twice daily x 10 days**
- **1st recurrence treated with fidaxomicin 200 mg twice daily x 10 days**
- **Presents with 2nd recurrence**

Patient: Can we do something to prevent recurrence?



Of Recurrent *C. difficile:* Some Principles

- Treat primary *C. difficile* infection well
  - Use more effective antibiotics
  - Use narrow spectrum antibiotics
- Implement recurrence prevention strategies
  - Enhance the immune system
- Eliminate risk factors that cause recurrence
- Treat underlying pathophysiology of recurrence
  - Multiple medication therapies
  - **Replenish disrupted gut microbiome**

What is Fecal Microbiota Transplantation?

Instillation of processed **stool** from a healthy donor into another individual to alleviate a medical condition that may be caused by an alteration in the gut microbiome

FMT for CDI – What is Well-known?

- Efficacy >85% to prevent recurrence
- Superior to oral vancomycin
- Fresh or frozen has similar efficacy
- No donor effect on efficacy
  - Screening and recruitment standardization needed
- Few recipient contraindications
- Few adverse events
  - Long term follow up data needed
- FDA guidance on FMT is still in draft phase

Status of FMT

US FDA: The use of FMT to treat *C. difficile* is investigational

FDA In Brief: FDA warns about potential risk of serious infections caused by multi-drug resistant organisms related to the investigational use of Fecal Microbiota for Transplantation

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June 13, 2019

Media Inquiries

Megan McSeveney
240-402-4514

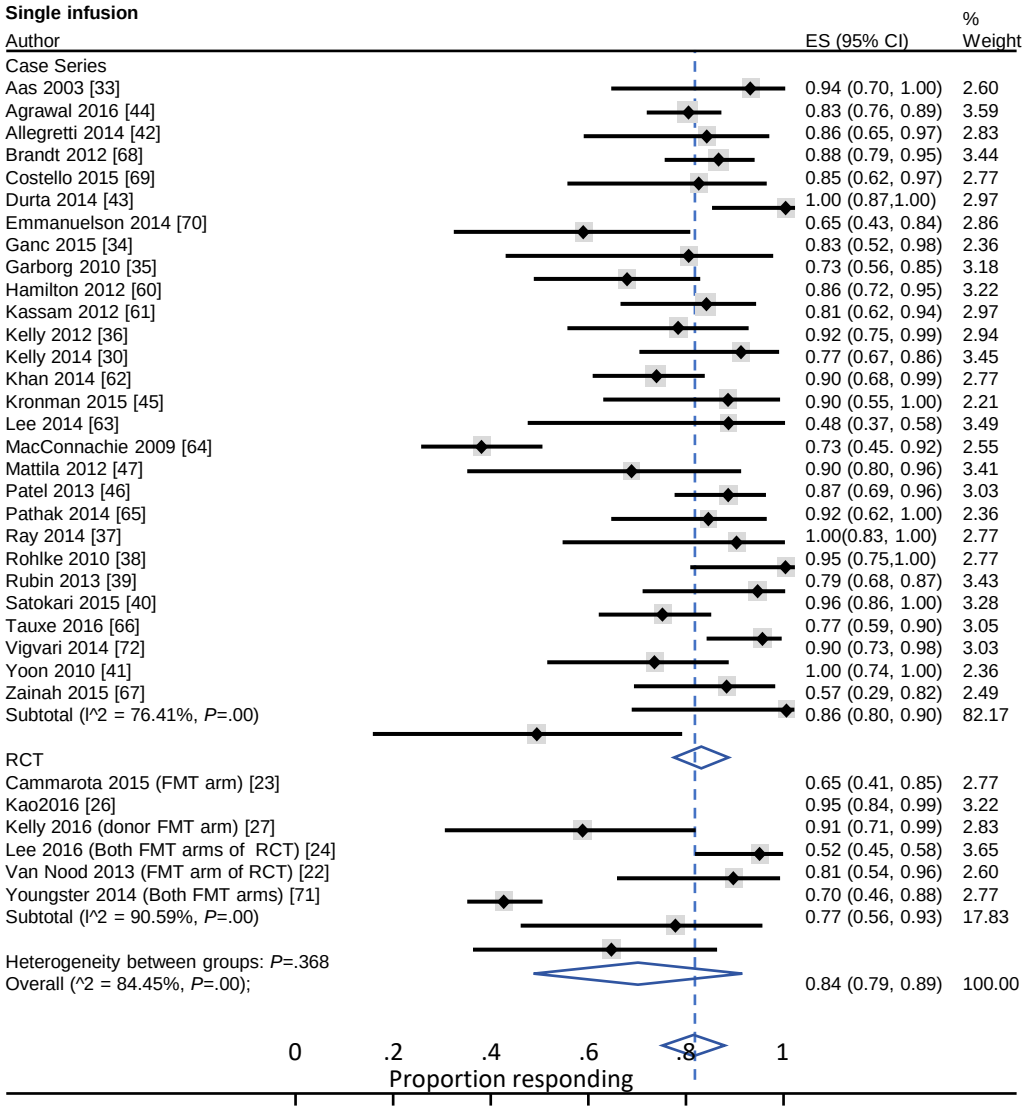
Content current as of:
06/19/2019

"The medical community is actively engaged in exploring the potential uses of Fecal Microbiota for Transplantation, or FMT. Although FMT is not approved by the FDA for any use, the agency plays a

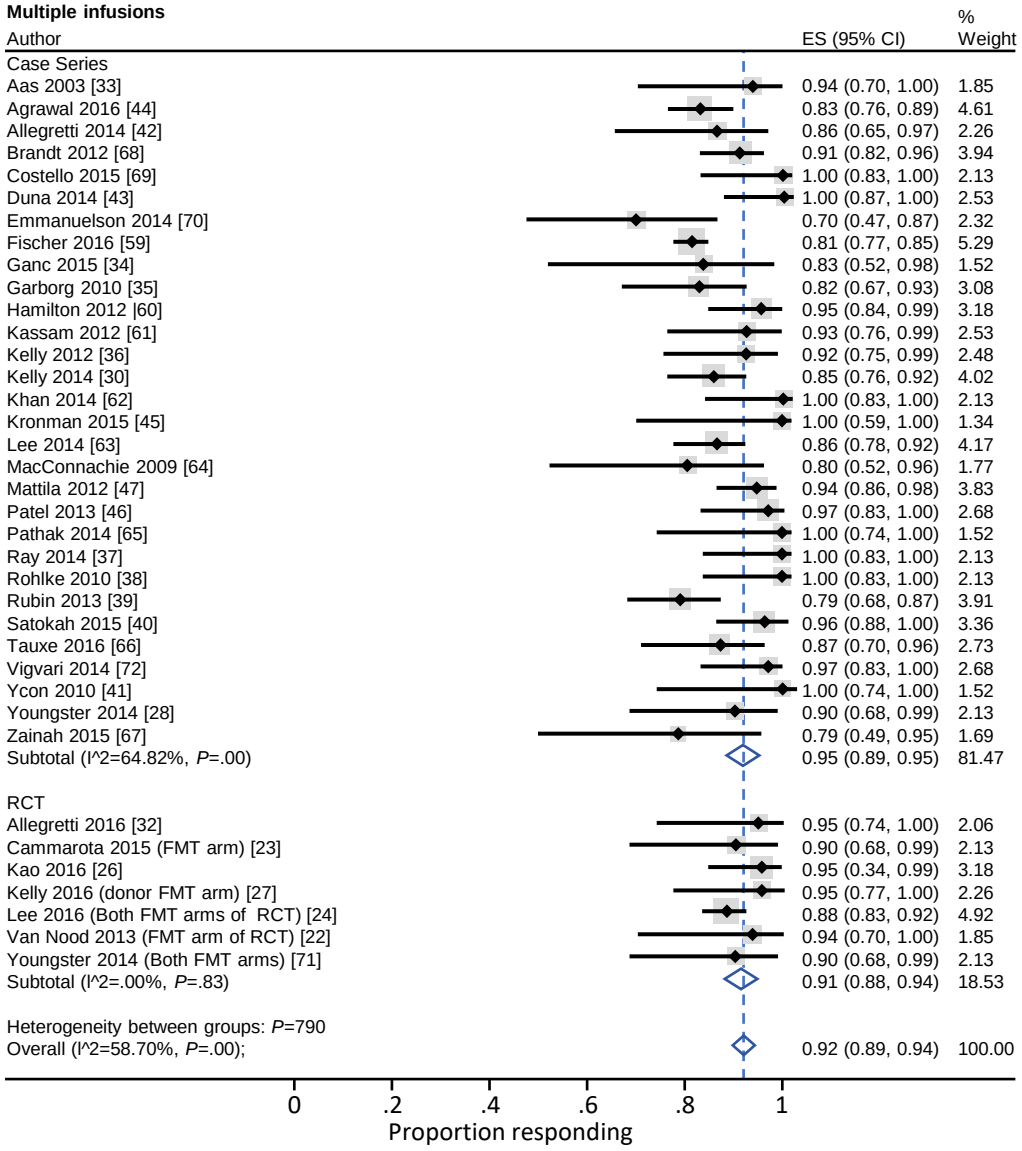
Public hearing: "Use of Fecal Microbiota for Transplantation (FMT) to Treat Clostridium difficile Infection Not Responsive to Standard Therapies"

- November 4, 2019

FMT Efficacy: >85% for Preventing rCDI



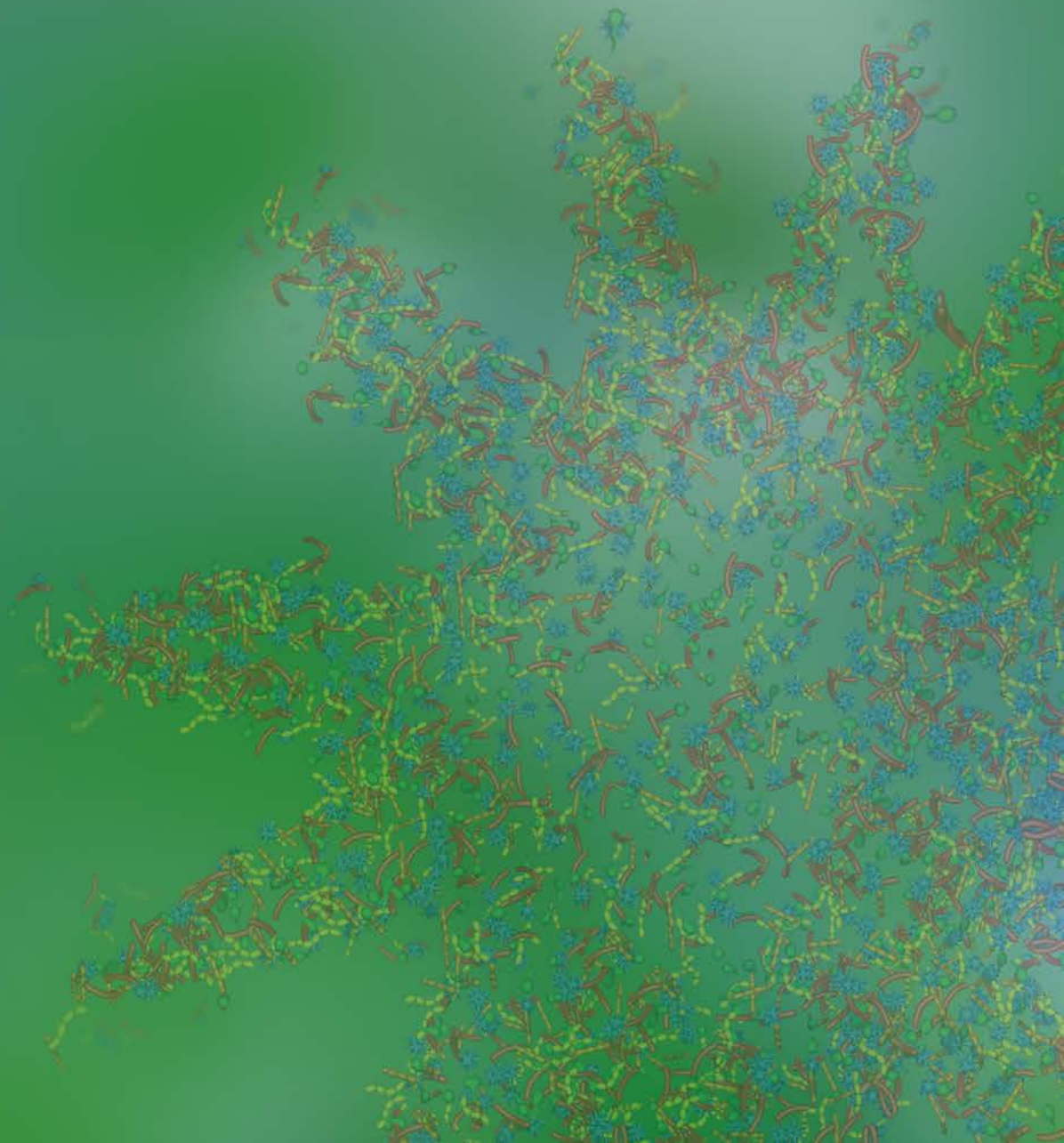
84%: Single infusion



92%: Multiple infusions

Adapted from Quraishi MN et al. *Aliment Pharmacol Ther*. 2017;46:479-93.

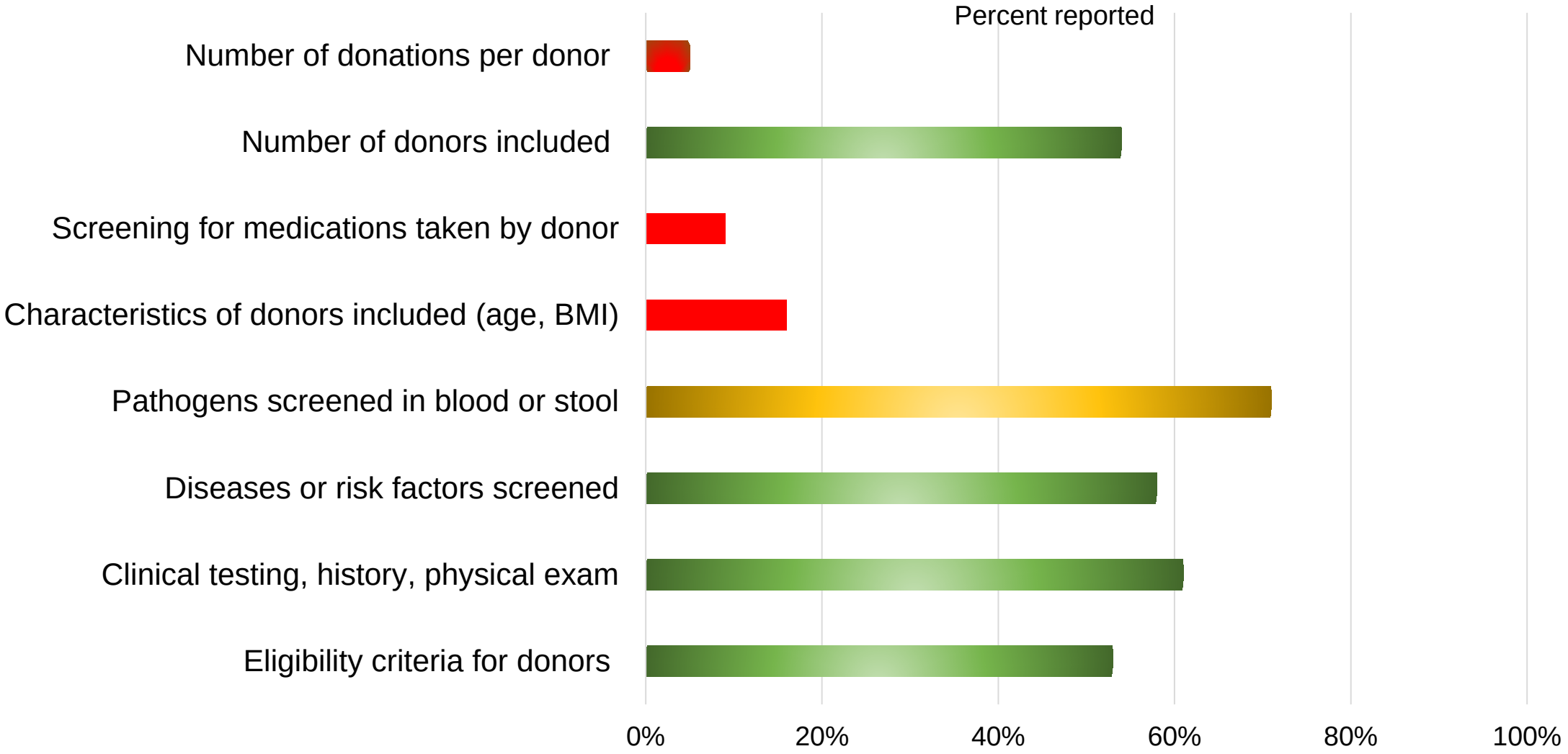
Clinical Microbiome Replacement is Heterogeneous



Non-regulation of Microbial Replacement

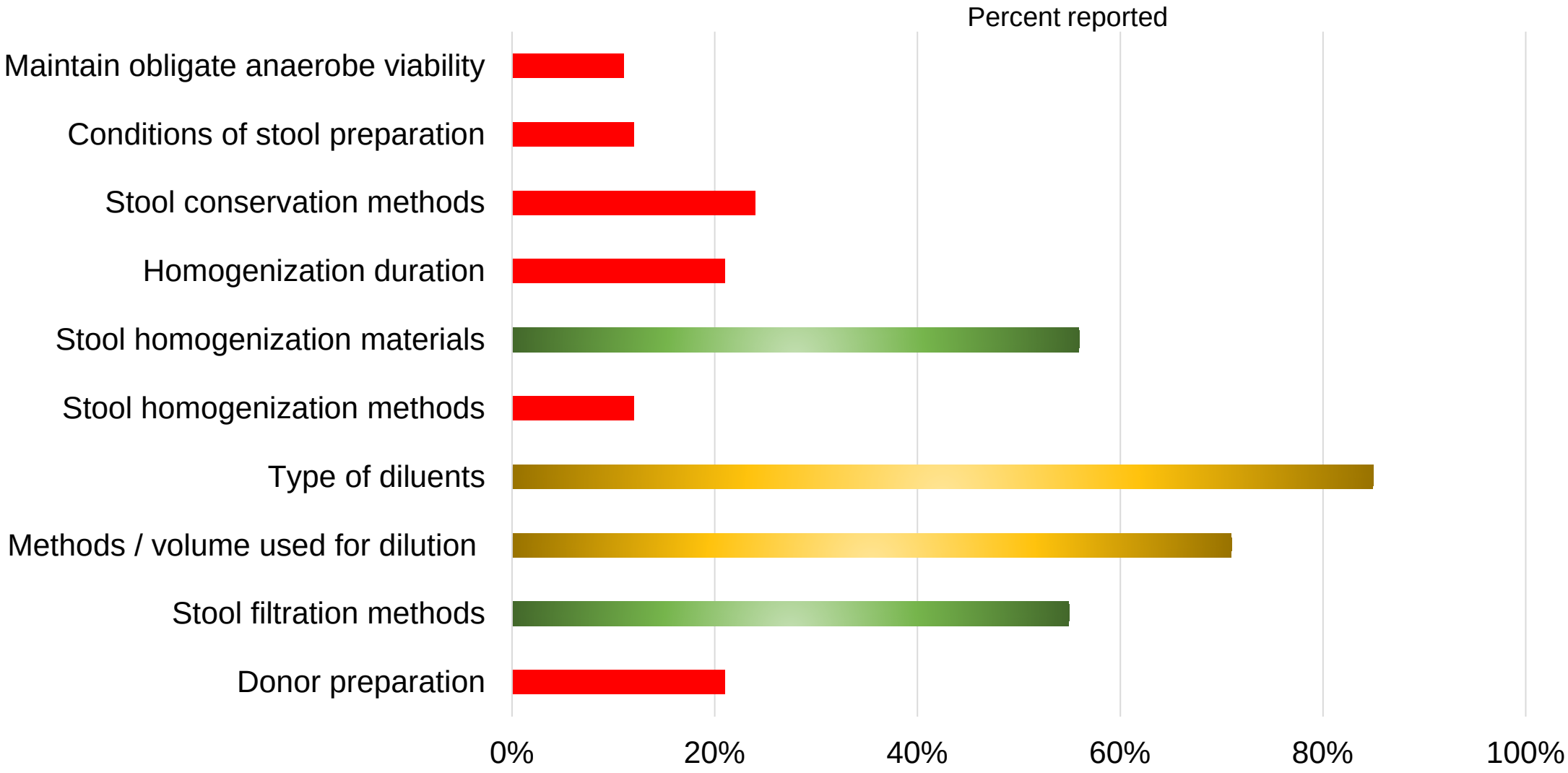
- No existing approved product
- Lack of universal consensus on methodological components
- Donor recruitment, screening and preparation
- Stool preparation & storage
- Patient preparation & instillation
- Follow up & endpoints

Donor Recruitment is Not Standardized



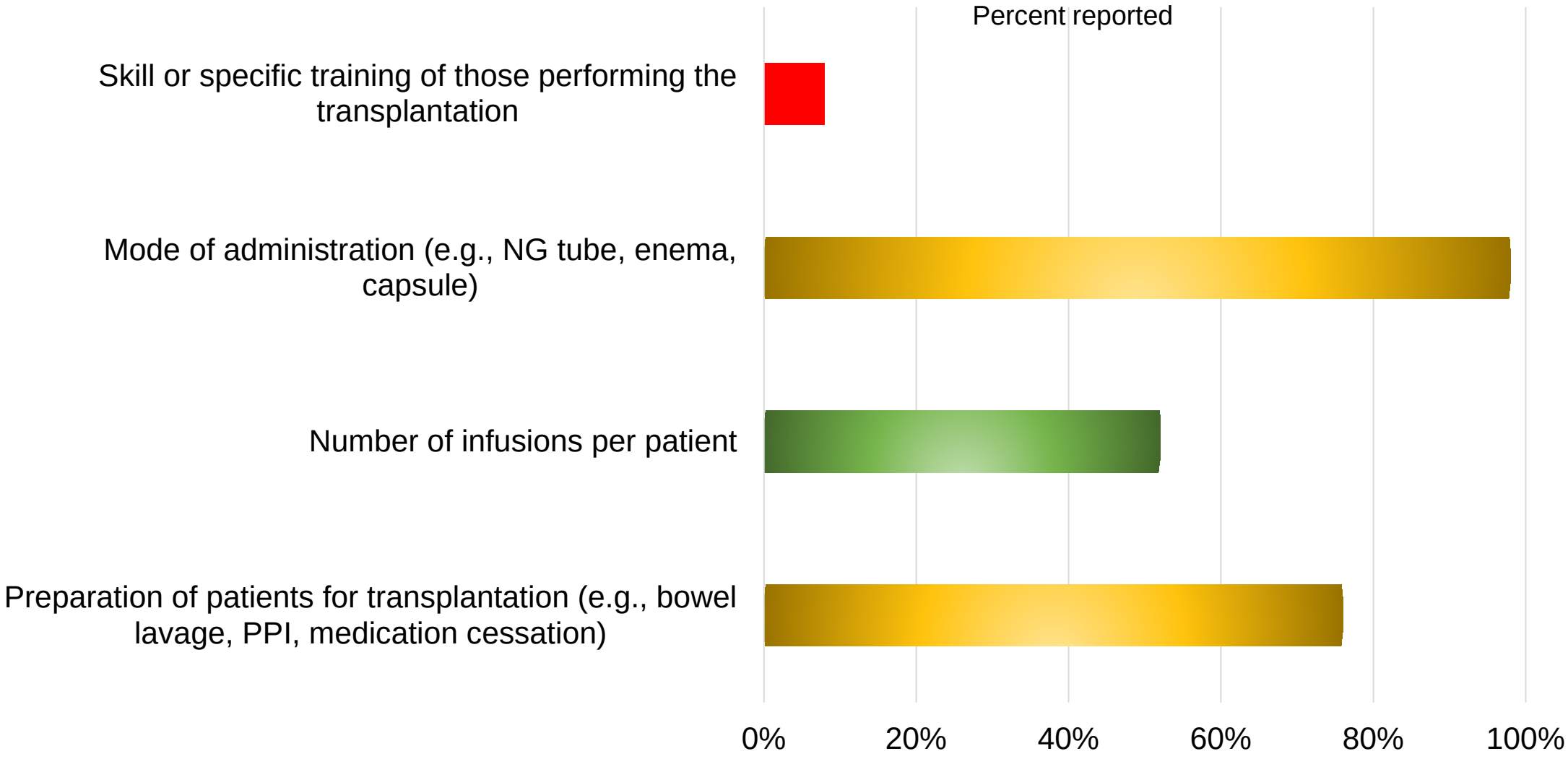
Bafeta A et al. *Ann Intern Med*. 2017;167:34-39.

Stool Collection and Processing is Non-uniform



Bafeta A et al. *Ann Intern Med*. 2017;167:34-39.

Stool Instillation is Better Reported



Bafeta A et al. *Ann Intern Med*. 2017;167:34-39.

Donors Need to be Carefully Screened

- No infectious risk, high-risk sexual behaviors or use of illicit drugs, incarceration or nursing home residence
- Travel to high risk areas for diarrhea
- Metabolic syndrome or diabetes mellitus
- Known or history of *C. difficile* infection
- Recent hospitalization / antibiotics
- Chronic diarrheal illnesses
- Malignancy or autoimmune diseases
- Immunosuppressive or anti-neoplastic medications

Khanna S, Pardi DS. *Therap Adv Gastroenterol*. 2014;7:72-86.

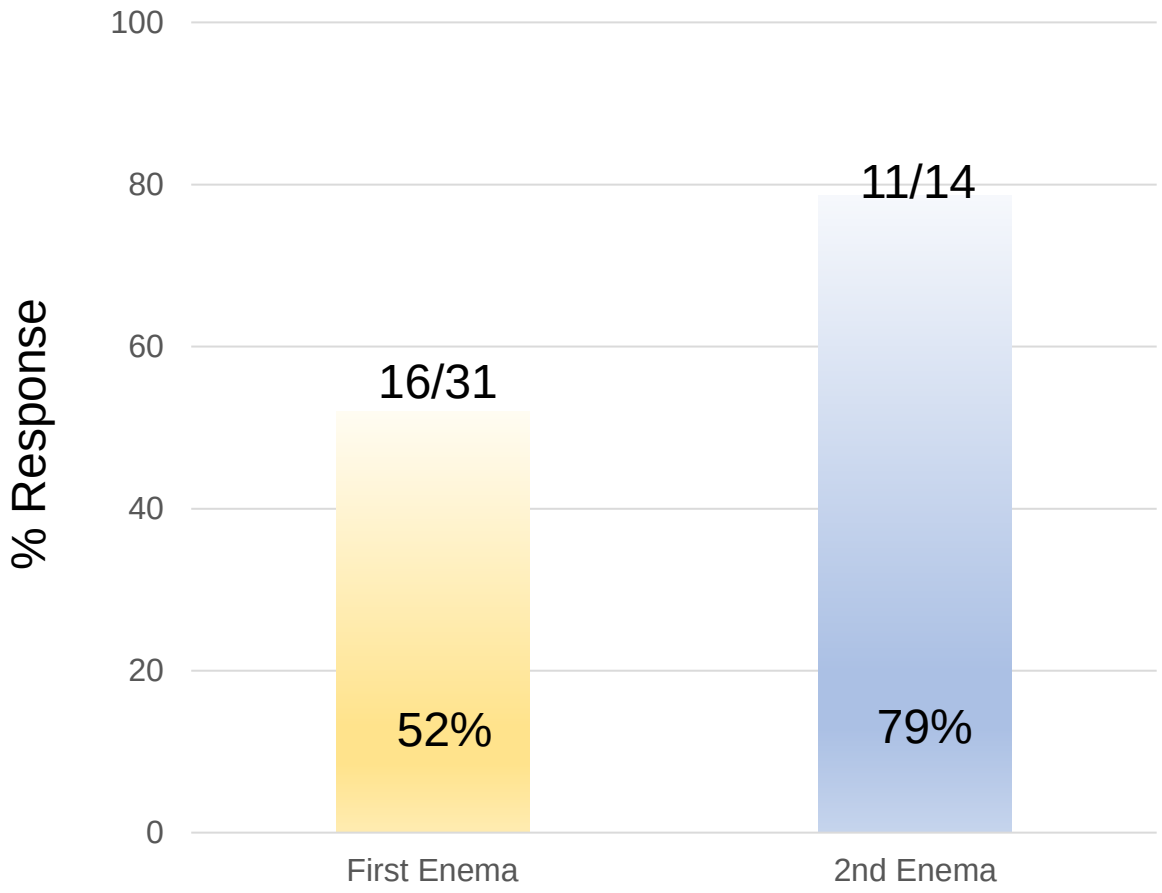
Stool and Blood Tests for Donors

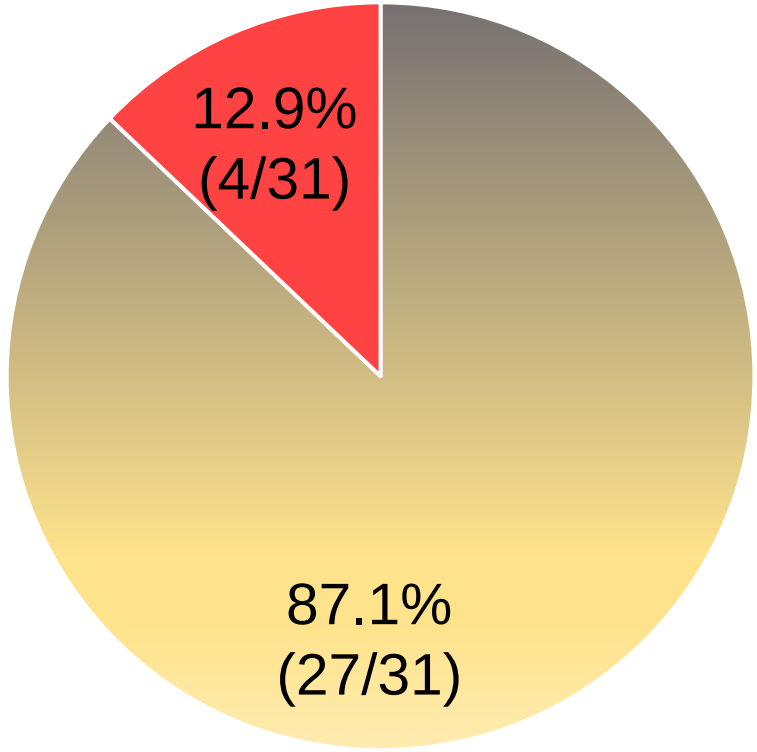
- Enteric pathogens PCR
- *C. difficile* PCR
- Vancomycin resistant *Enterococcus* PCR
- Ova and parasites
- Cryptosporidia
- Microsporidia
- Multidrug resistant organisms
- HIV
- Syphilis
- Acute & chronic hepatitis
  - Hepatitis A
  - Hepatitis B
  - Hepatitis C

Development of Standardized Microbiome Therapies

- Enema based therapies in phase III clinical trials
  - RBX2660
- Pill based therapies in phase I and III clinical trials
  - CP-101
  - RBX7455
  - SER-109
- Emerging synthetic microbiome-based therapy
  - VE-303

RBX2660 – Open-label Experience





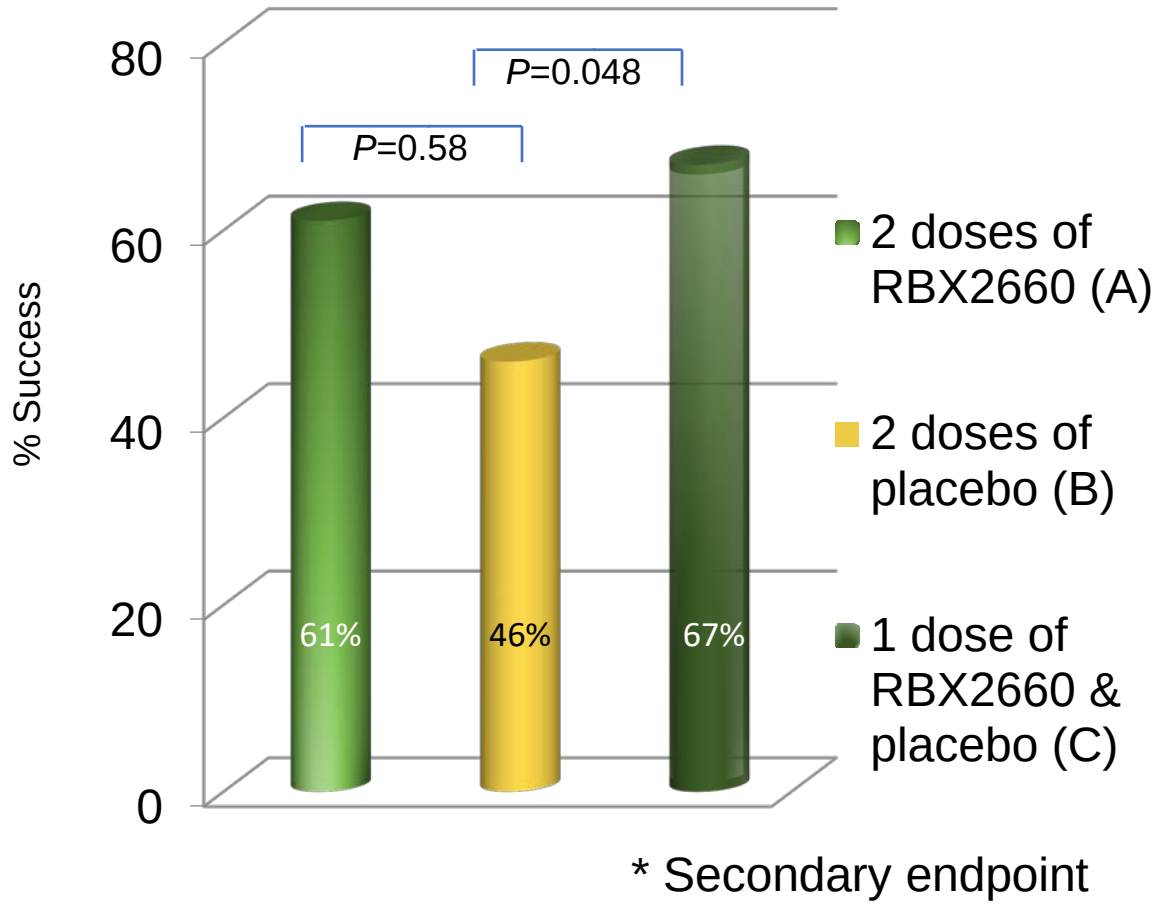
Responder ■ Non-responder

Overall satisfactory safety profile

Orenstein et al. *Clin Infect D*is. 2016;62(5):596-602.

Enema Based Therapy: RBX2660 is More Effective than Placebo*

- Microbiota suspension from donor stool as enema
- 50g stool in 150mL diluent
  ≥10^7 organisms/ml
- Double-blinded RCT: Phase II
- Patients with recurrent CDI
- Three or more episodes
- Enemas after standard antibiotic treatment

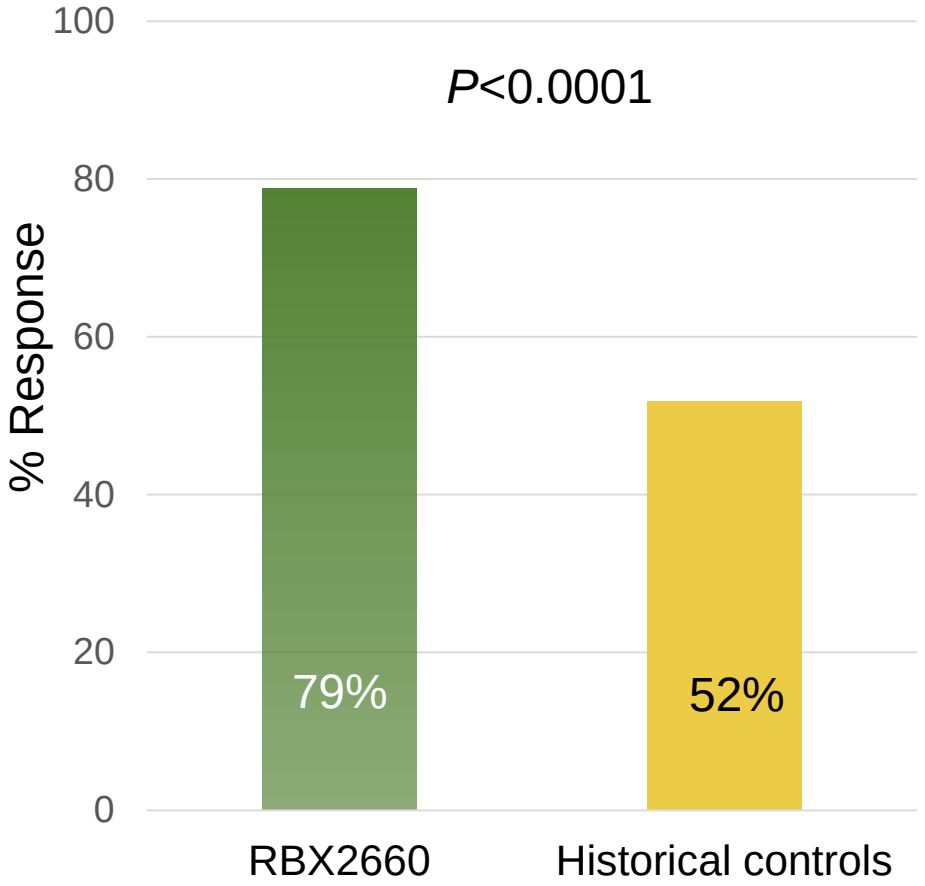


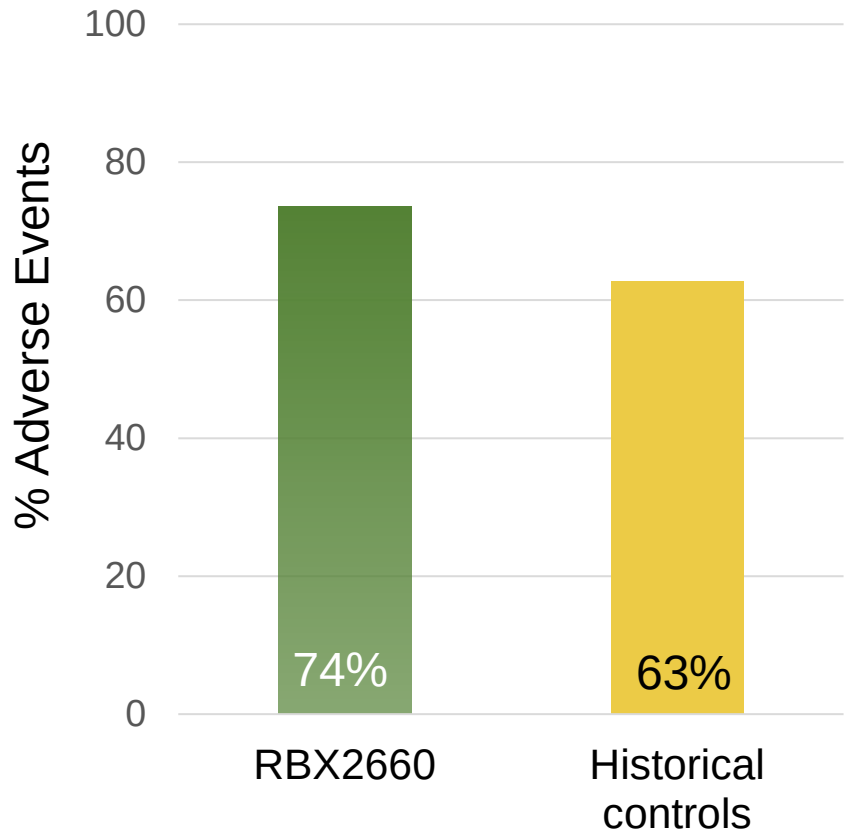
* Secondary endpoint

Dubberke E et al. *Clin Infect Dis*. 2018 Mar 29. doi: 10.1093/cid/ciy259.

RBX2660 – Open-label vs Historical Controls: Safety and Efficacy

- Prospective, multicenter, open-label Phase II
  - 132 RBX2660 at 29 & 110 controls at 4 centers





Orenstein et al. ID Week 2017.

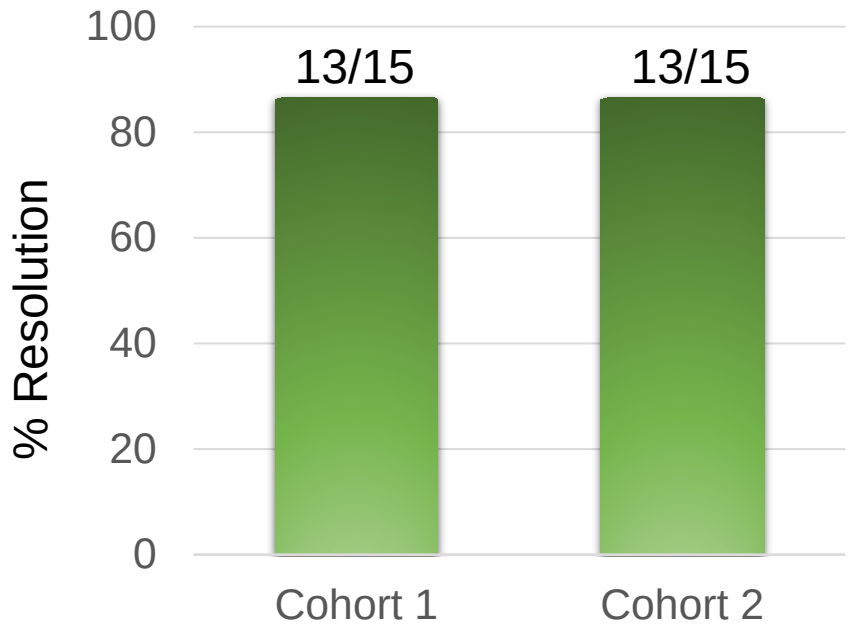
RBX2660 – Phase III trial (PUNCH CD III)

- 2 arms: Placebo vs one enema
- Patients with 2 or more episodes
- Primary outcome
  - Efficacy of RBX2660 compared to placebo at 8 wks
- Secondary outcomes
  - Adverse events
  - Quality of life

https://clinicaltrials.gov/ct2/show/NCT03244644

Ser-109: Efficacious in Phase I

- ~50 species of Firmicutes from donor stool
  - Frozen at −80°C & suspended in saline
- Ethanol treatment to eliminate vegetative forms
- Filled into capsules stored at −80°C
- Cohort 1: $1.7x10^9$ spores x 2 days
- Cohort 2: $1.1x10^8$ spores x 1 day



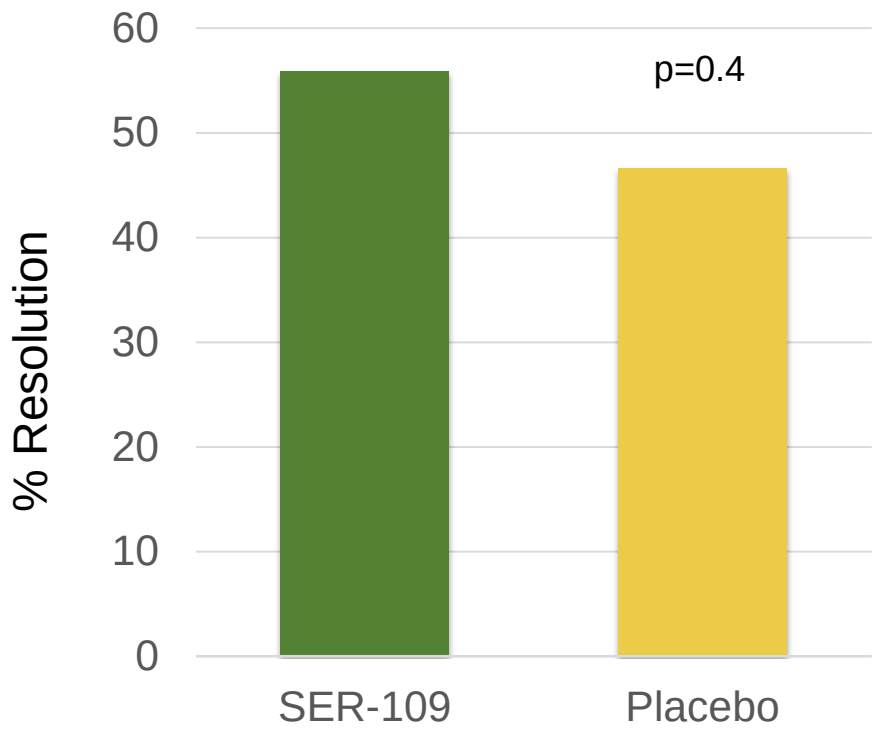
3 / 4 “failures” had self limiting diarrhea and did not require treatment

Secondary resolution rate: 96.7%

Khanna S et al. *J Inf Dis*. 2016;214:173-81.

Ser-109 – Blinded Experience (Phase II)

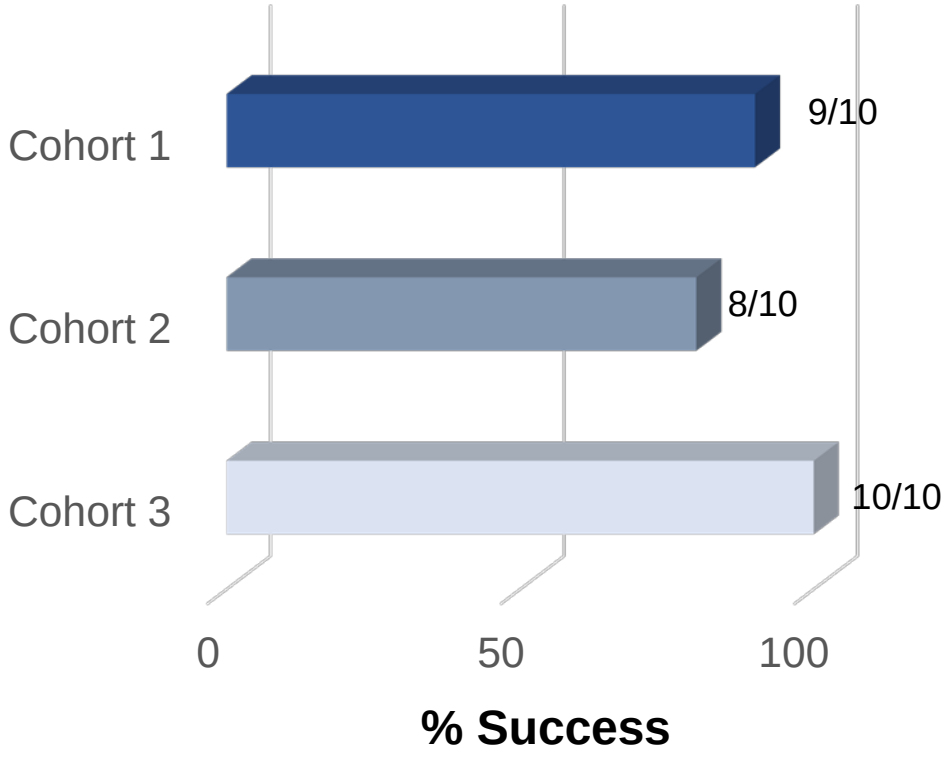
- 89 patients with 3 or more episodes
- Randomized at a 2:1 :: SER-109: Placebo
  - 59 received SER-109 & 30 received placebo
- Single dose ~10^8 bacterial spores



https://clinicaltrials.gov/ct2/show/results/NCT02437487

RBX7455 – Phase I

- Lyophilized, room temperature
- At least one recurrence after a primary episode
- Prospective, single-center, open-label phase I, dose-finding, investigator-initiated trial
  - 3 arms – 10 patients per arm
    1. 4 capsules BID x 4 days
    2. 4 capsules BID x 2 days
    3. 2 capsules BID x 2 days



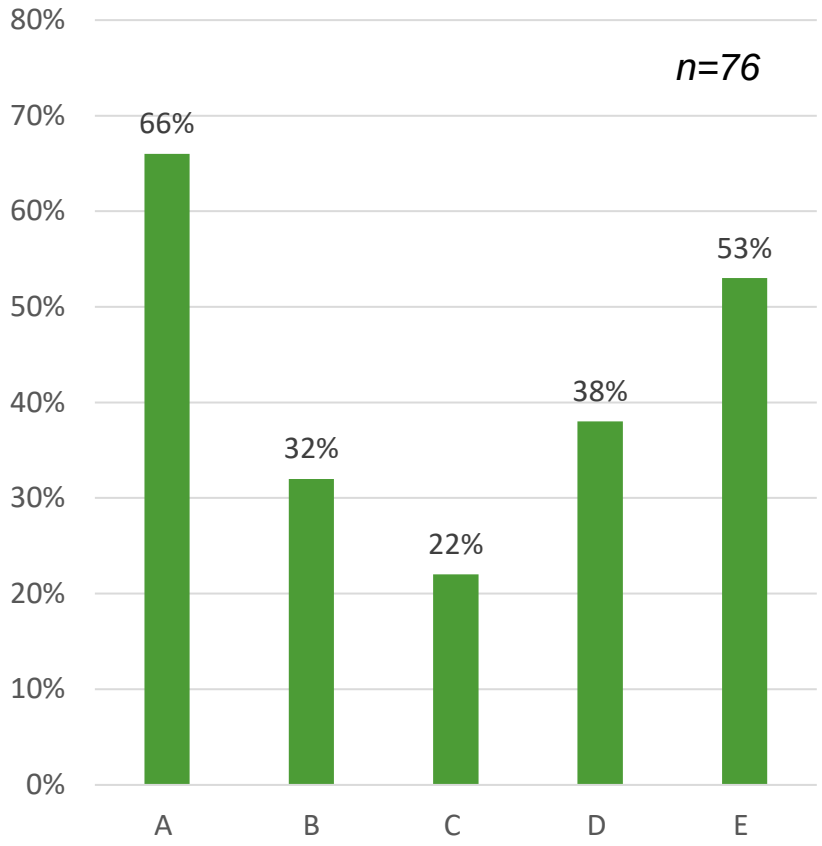
https://clinicaltrials.gov/ct2/show/NCT02981316
Khanna S et al. UEGW 2018 meeting.

Take Home Points and Future Directions

- FMT is effective & safe for recurrent *C. difficile*
- Standardized microbiome-based therapies are in clinical trials
- Microbial replacement by pill, enema
  - RBX2660, RBX7455, SER-109
- Defined microbial consortia
- Earlier microbial replacement
  - Trials ongoing for 1st or 2nd infection

Which of the following factors would make you more likely to use microbiota replacement therapy? *(Select all that apply)*

A. FDA approval
B. Additional efficacy data
C. More colleagues with experience using this approach
D. Data demonstrating safety
E. Guideline recommendations



Please identify how you will change your practice as a result of participating in this activity? *(Select all that apply)*

A. Implement processes to screen patients for risk of recurrent *C. difficile* infection

B. Change selection of therapy based on a patient's risk of recurrence

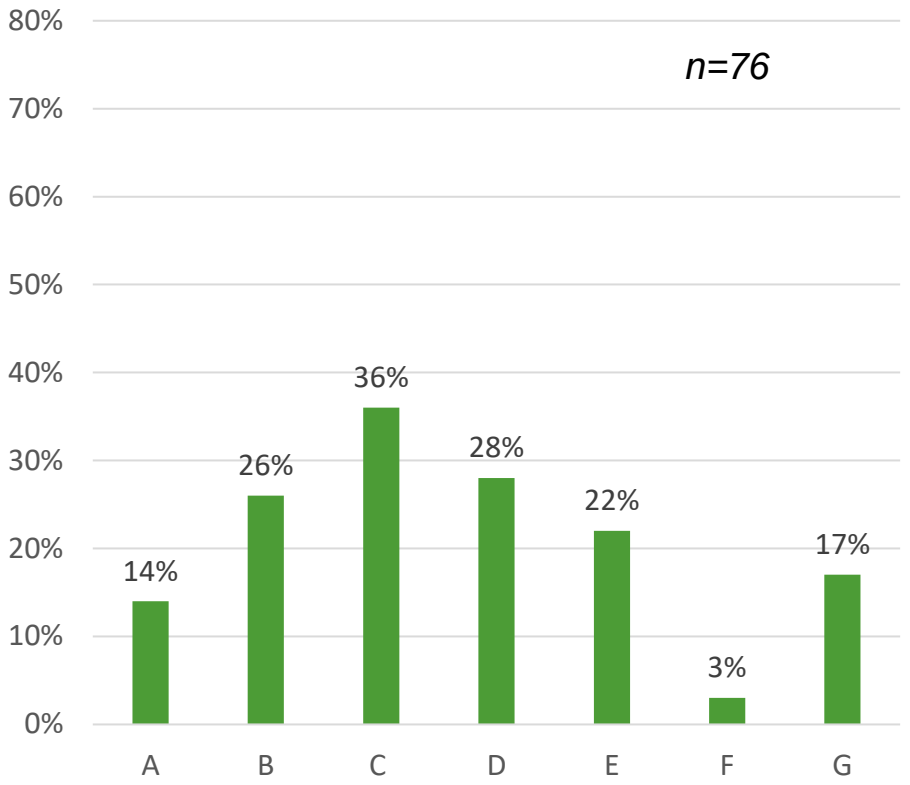
C. Refer more patients for FMT

D. Evaluate using FMT in my practice

E. Encourage my patients to participate in clinical trials of microbiota restoration therapy

F. Other

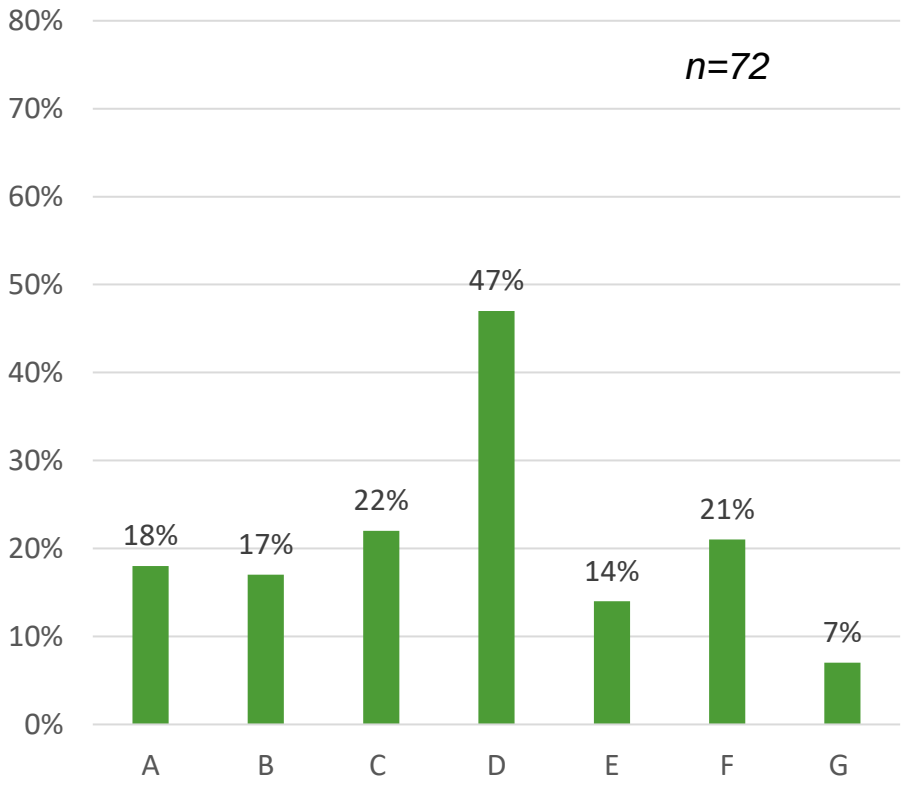
G. This activity validated my current practice; no changes will be made



Other changes include building rules into EMR for pharmacy review, noting cholecystectomy, fidaxomicin for higher risk pts, longer course of tapered therapy.

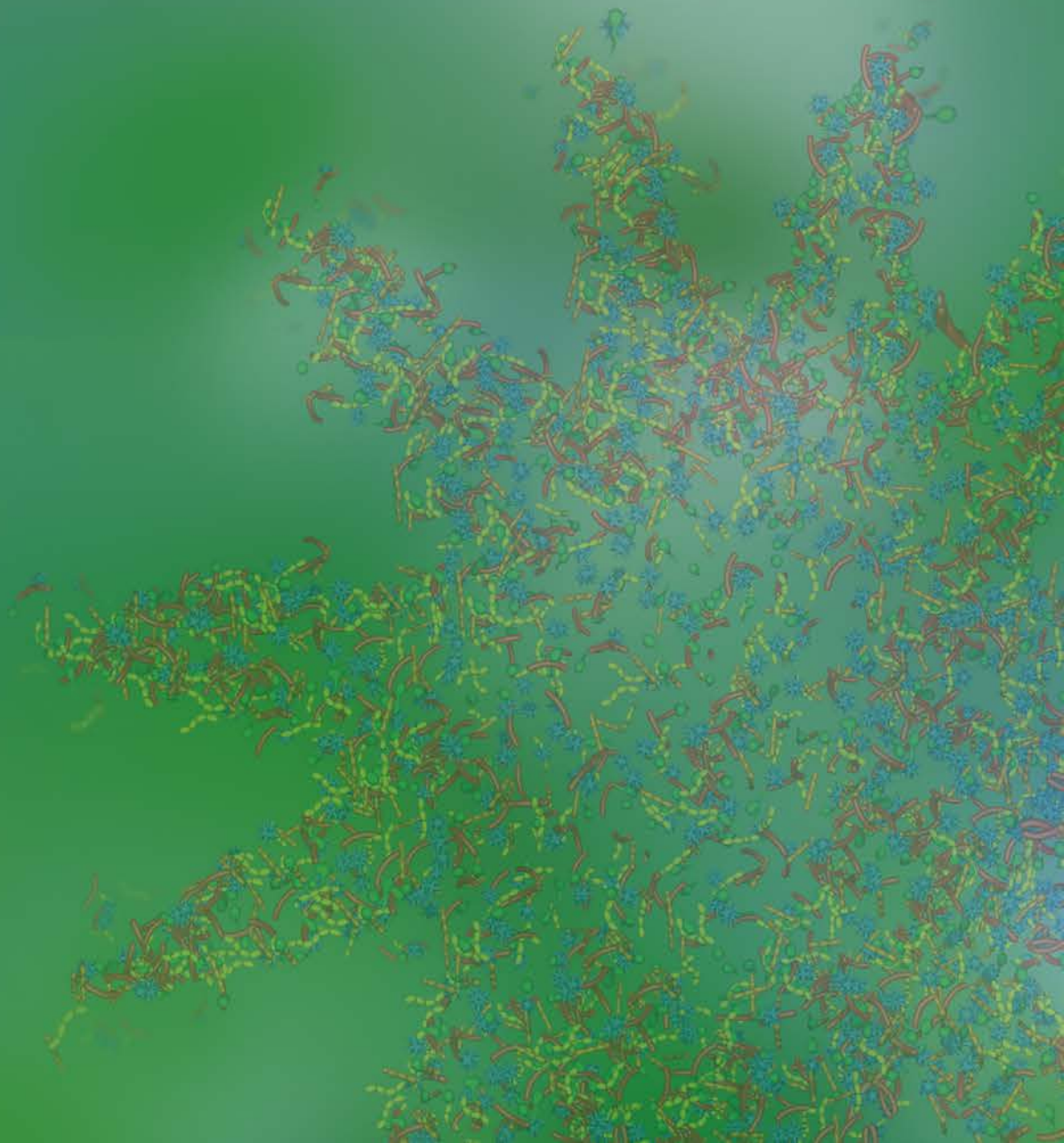
What are the current barriers to using FMT in your practice? *(Select all that apply)*

A. Patient reluctance
B. Concerns about safety
C. Cost
D. Access
E. Lack of evidence/guidance
F. Administrative support
G. Other
H. No barriers

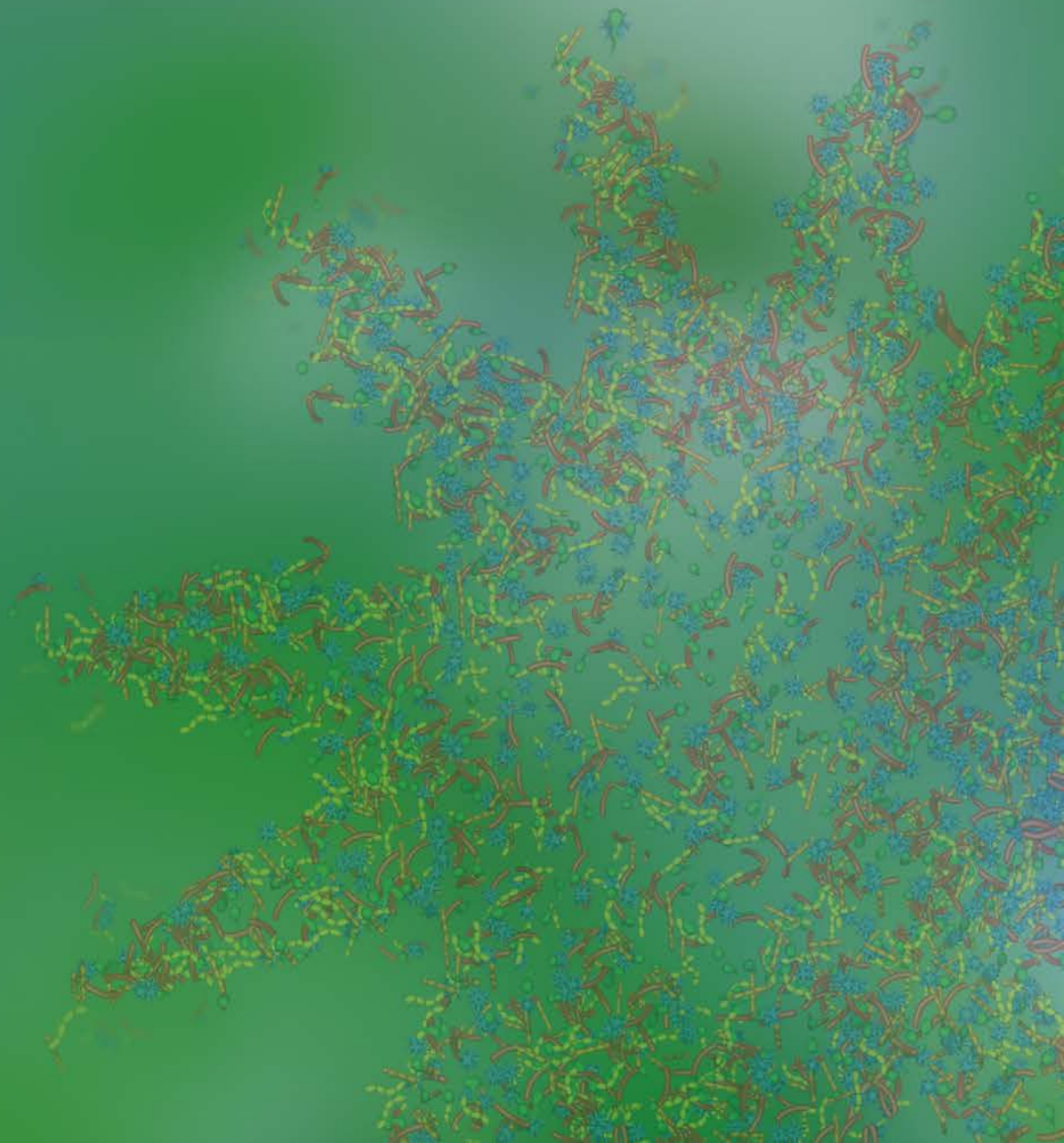


Other barriers include not FDA approved, availability, insurance coverage, not currently indicated.

Panel Discussion



Question & Answers



Please remember to turn in your evaluation to the onsite staff