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C. difficile and the Microbiome: All You Need to Know

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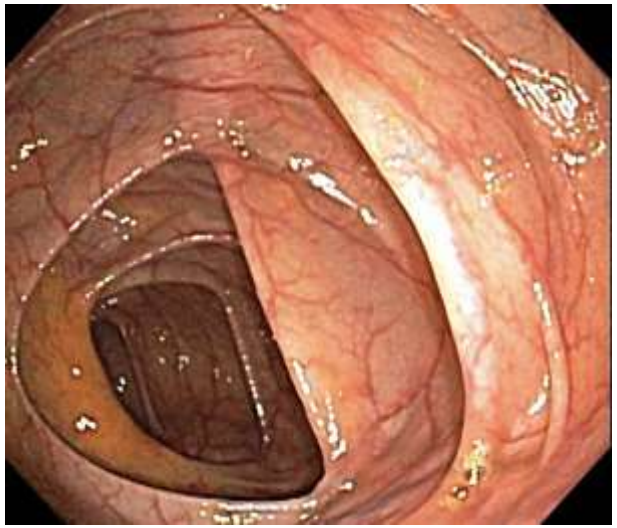
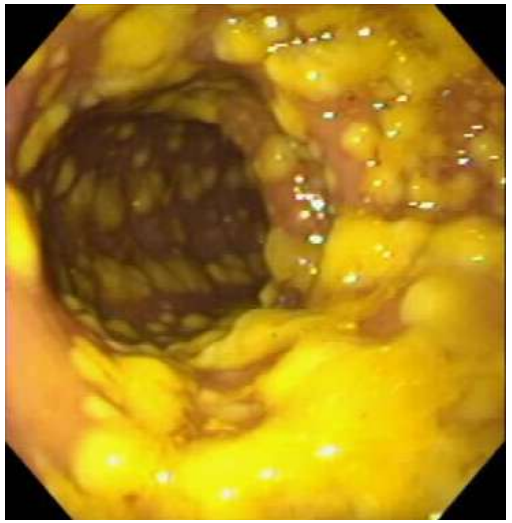
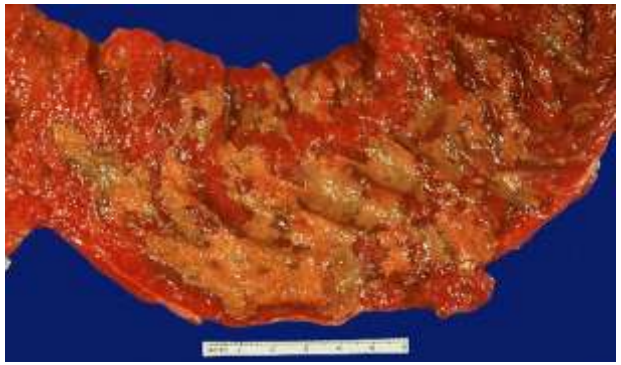
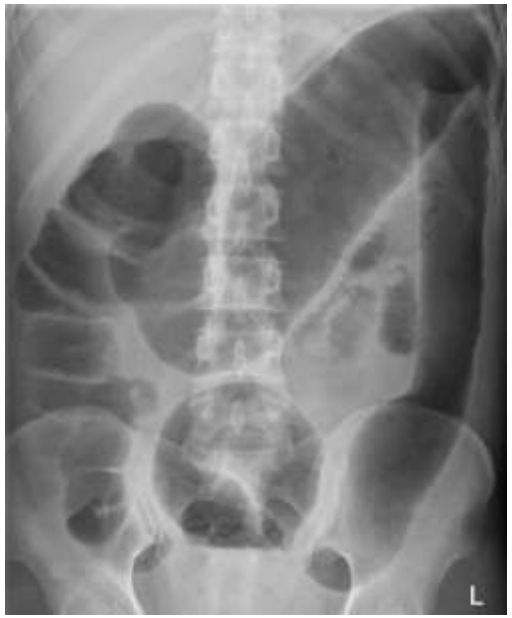
C. difficile overview

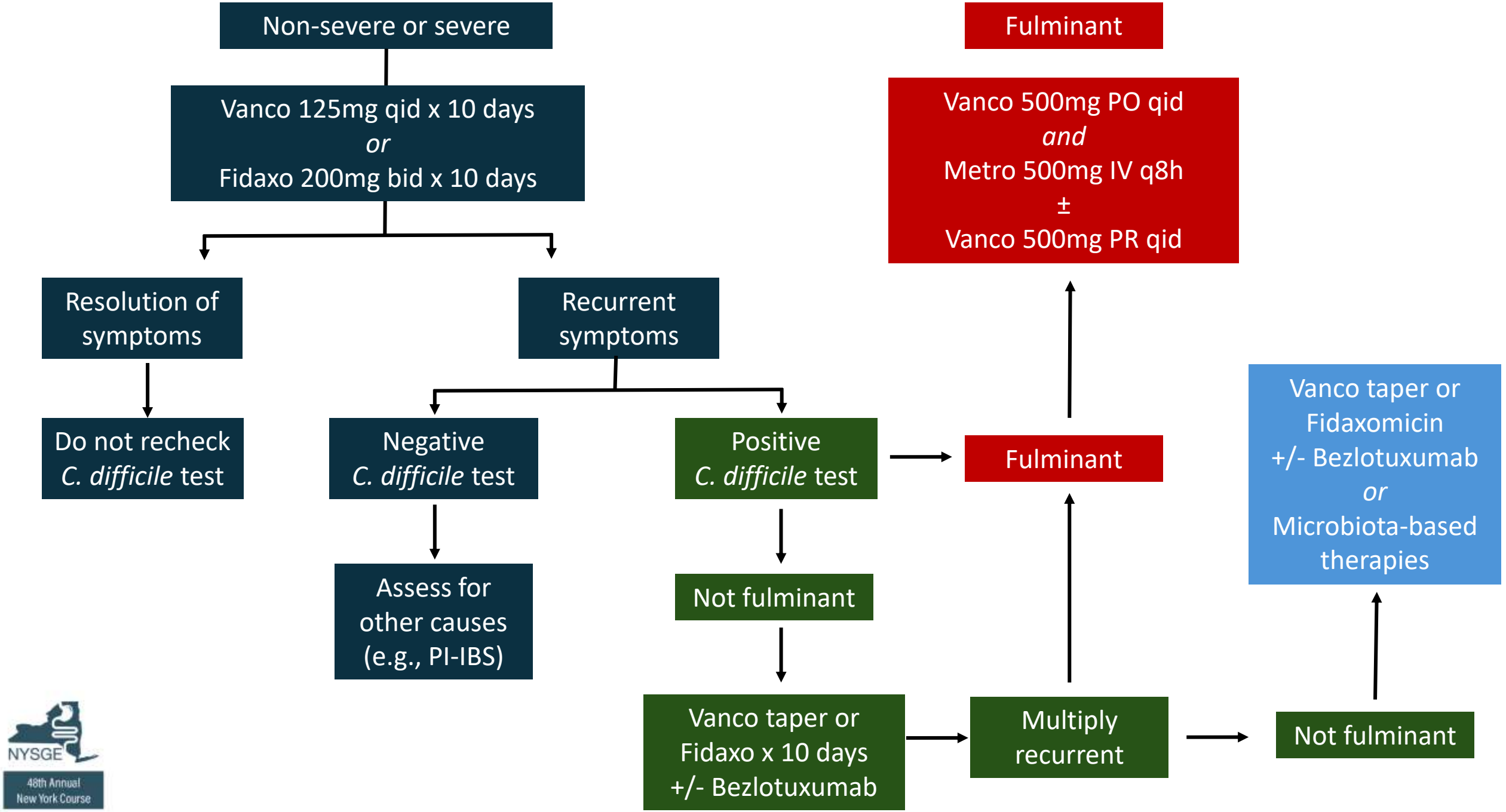
- Gram-positive, spore forming organism
- Dysbiosis → disease
- Various clinical manifestations
  - Carrier state (asymptomatic)
  - Infectious state (symptomatic)
    - *≥3 watery BMs ± abdominal pain*
- Multi-step testing algorithm











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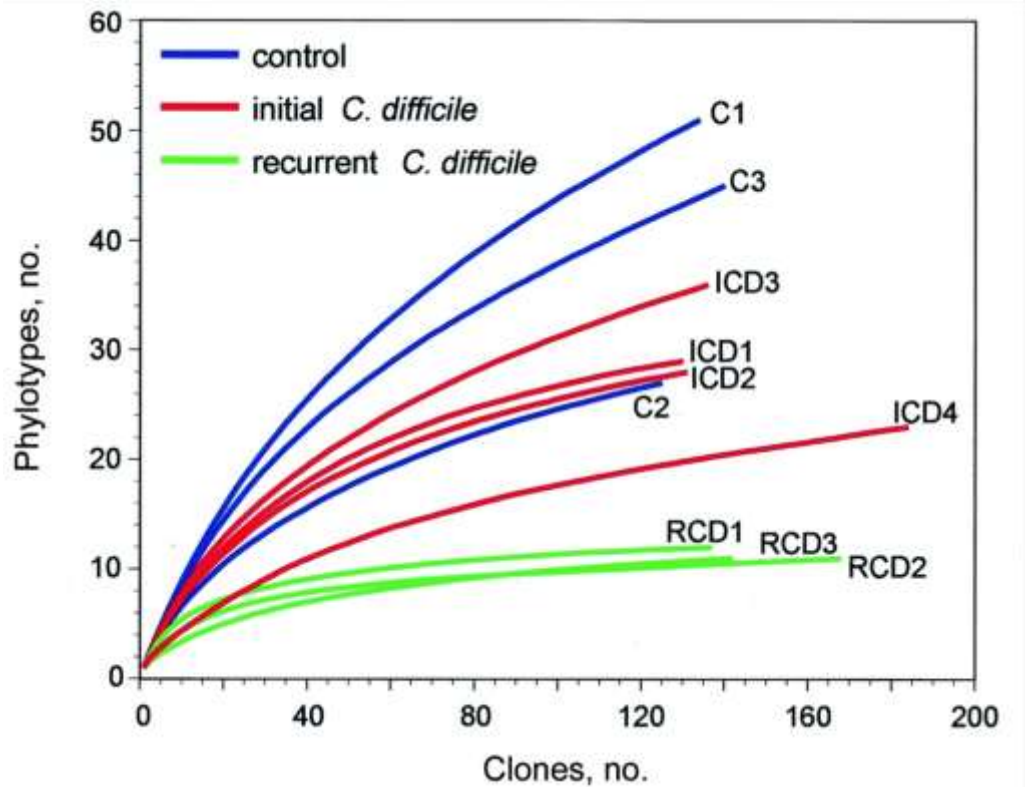
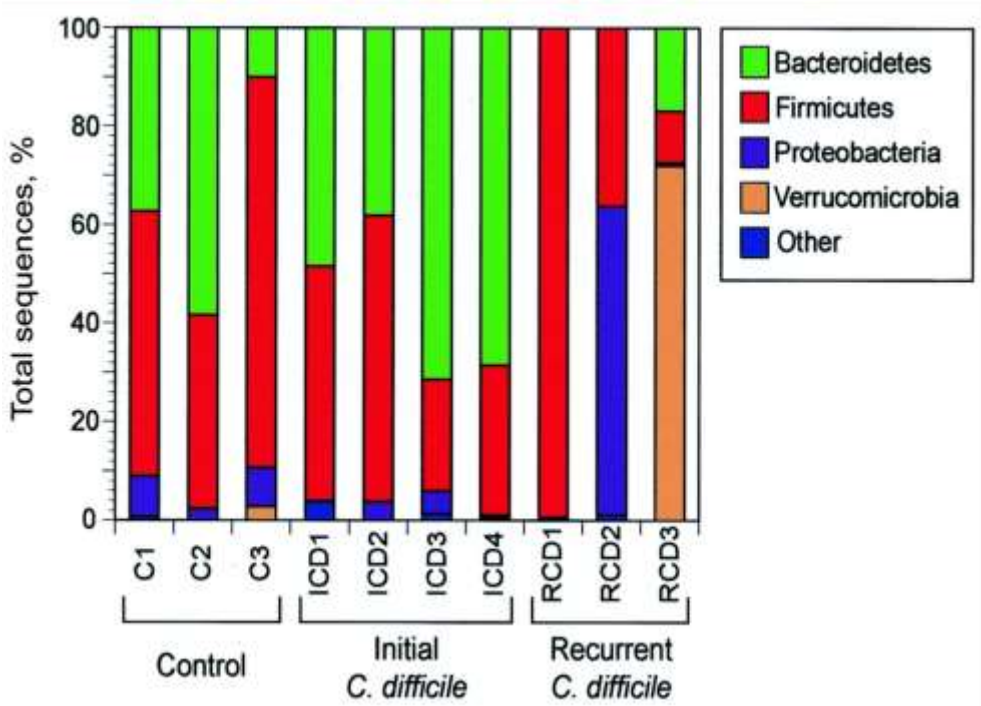
Recurrent *C. difficile* infection is characterized by dysbiosis



Patients with recurrent *C. difficile* have decreased phylogenetic richness



Bacteroidetes and *Firmicutes* are reduced in patients with recurrent *C. difficile* but not in patients with just one episode of *C. difficile* infection

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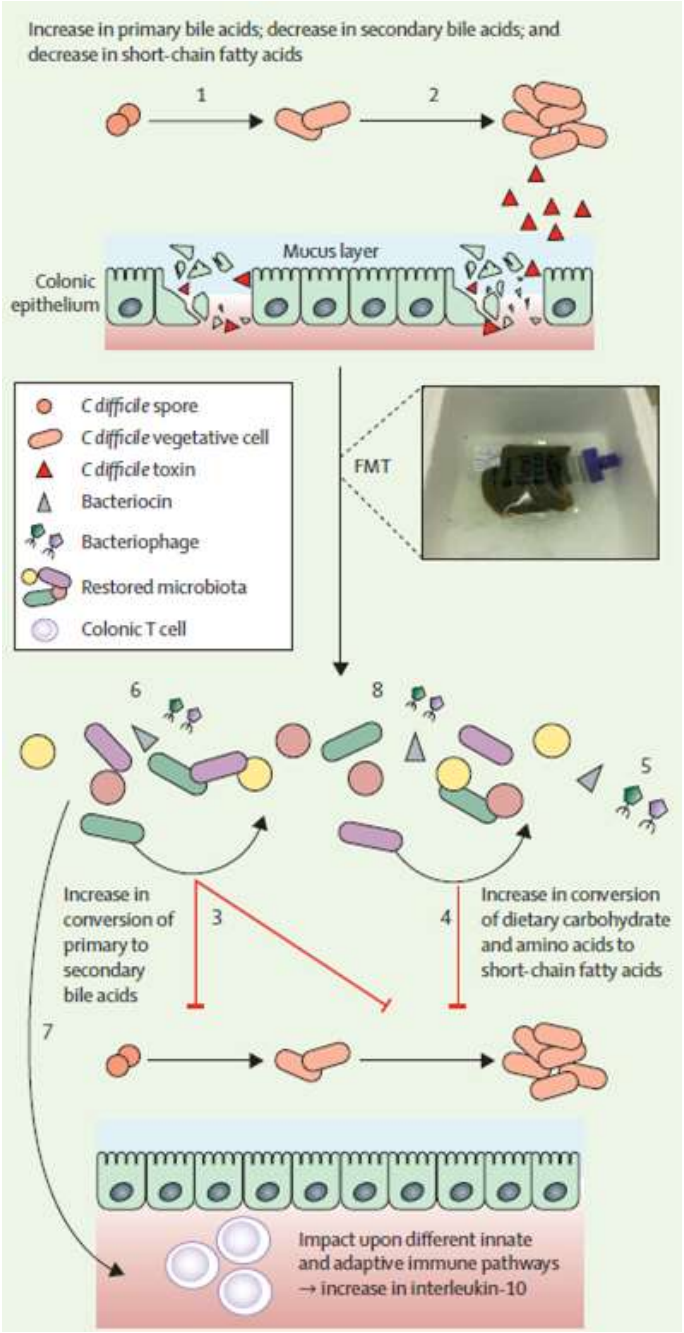
Chang, et al. J Infect Dis, 2008

Fecal Microbiota Transplantation (FMT) proposed mechanisms of action

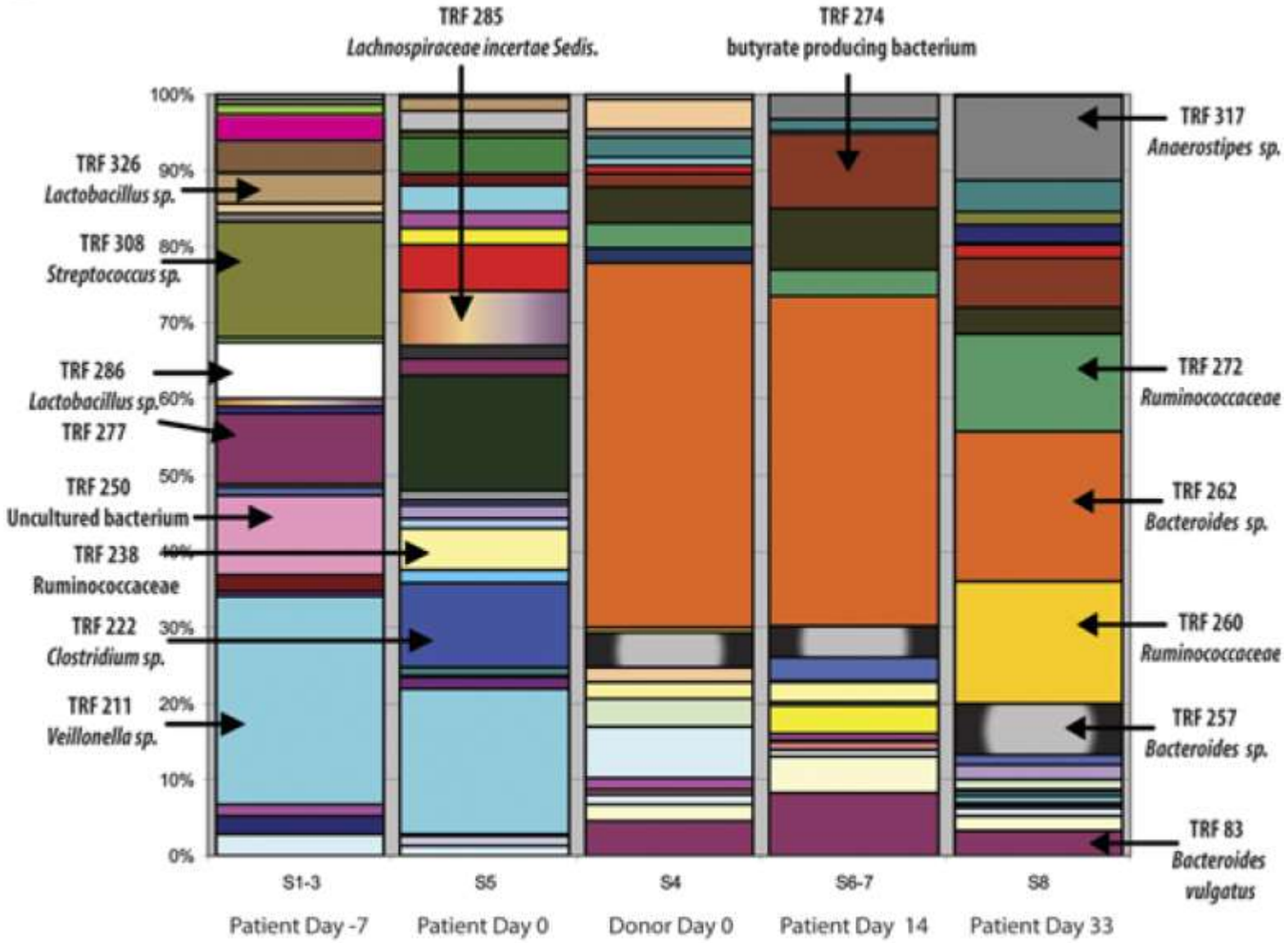
- Restoration of the host microbiome

- Metabolic output of the microbiota
  - Activation of host immune defenses
  - Restoration of barrier function
  - Inhibition of the vegetative growth of *C. difficile* as a result of increased secondary bile acids and short-chain fatty acids (SCFAs)
  - Production of anti-bacterial compounds (bacteriocins) by bacteria



Allegretti et al, Lancet 2019

Fecal microbial richness and diversity increase with fecal microbiota transplantation (FMT)



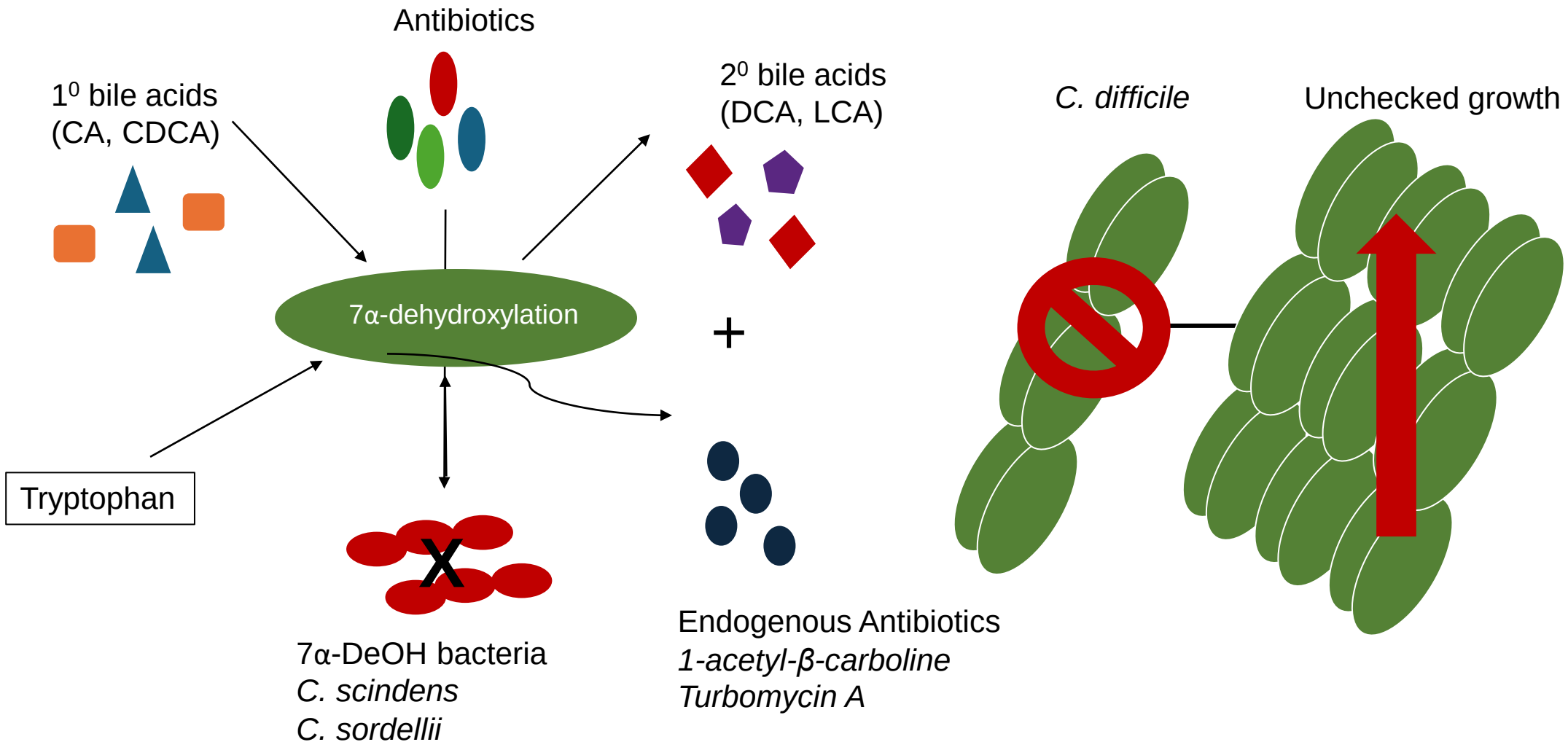
Seekatz, et al. mBio, 2014

FMT alters the gut microenvironment

	Healthy Control *"Normobiotic"*	Recurrent CDI *Dysbiosis*	FMT response
Microbiome			 **Microbiome**[1-3] Resembles donor ↑ diversity
Virome	 Donor-derived *Caudovirales*	 ***Caudovirales***[4,5] ↑ Abundance ↓ Diversity ↓ Richness	 ***Caudovirales***[4] ↑ Donor-derived ↓ Abundance Virome resembles donor after sterile fecal filtrate[6]
Fungome	 *Candida albicans*	 **Fungome**[7] ↑ Total load ↓ Diversity ↓ Richness ↑ *C. albicans*	 ***Fungome***[7] ↑ Diversity ↑ Richness ↓ *C. albicans*

[1]Khoruts et al, J Clin Gastroenterol 2010; [2]Van Nood E et al, NEJM 2013; [3]Kelly et al, Ann In 2013; [4]Zuo et al, Gut 2017; [5]Draper et al, Microbiome 2018
[6]Ott et al, Gastroenterol 2017; [7]Zuo et al, Nature Communications 2018

Antibiotics and secondary bile acids inhibit *C. difficile*



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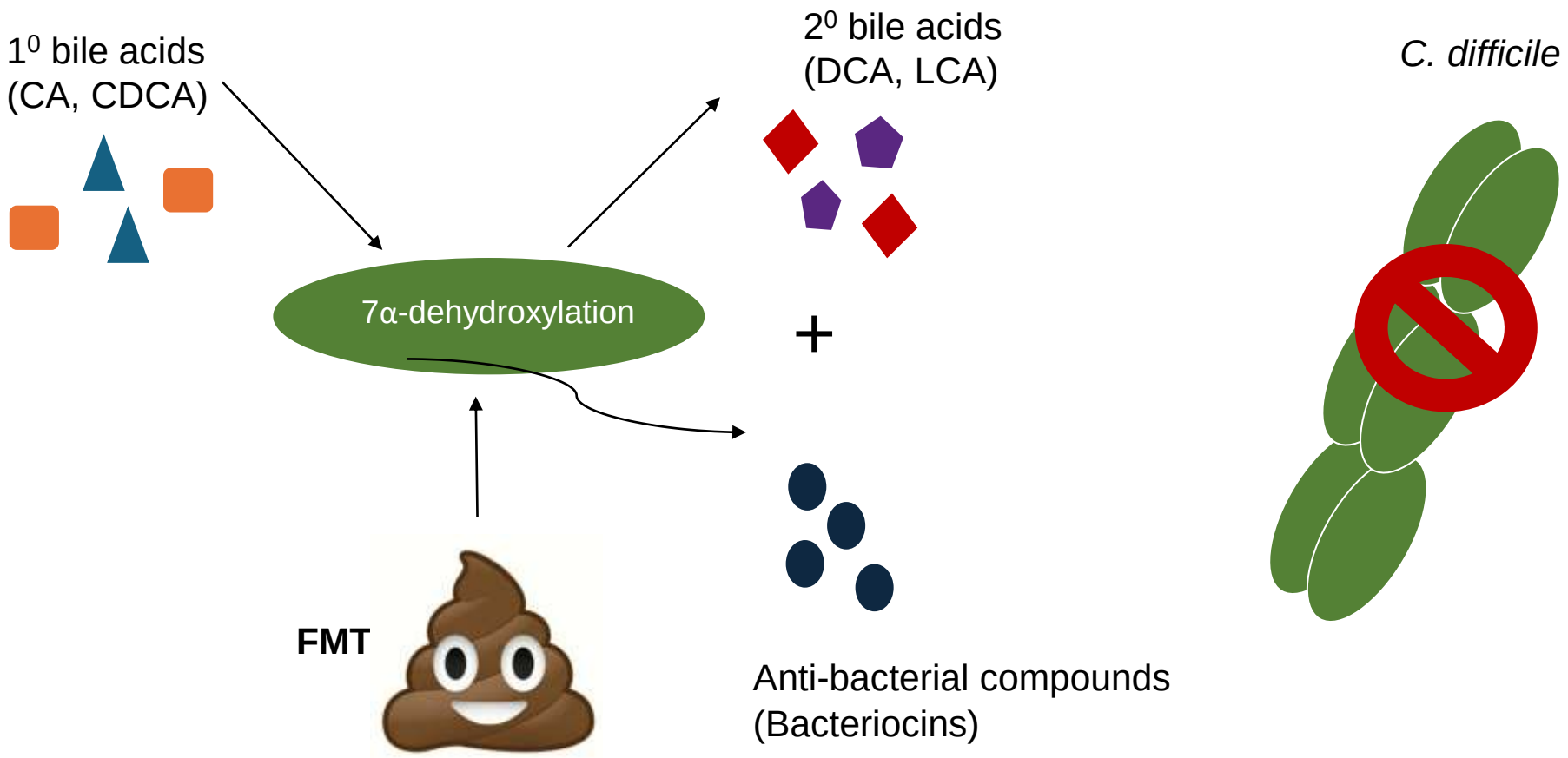
Adapted from:
Kang et al, Cell Chem Biol 2019
Savidge and Sorg, Cell Chem Biol 2019

Increase in 2^0 bile acids and bacterocins following FMT



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Kelly, et al, Gastroenterol 2015

FMT efficacy for recurrent CDI (RCDI)

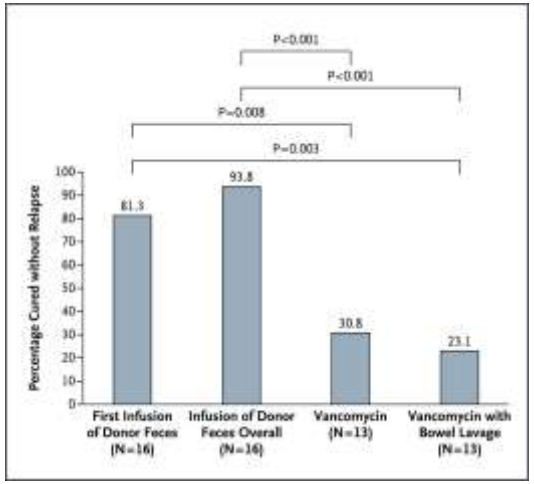
- Multiple case-reports and case-series
- Meta-analyses & systematic reviews
- >10 clinical trials

Bottom-line: FMT has been shown to be an effective treatment for halting the RCDI cycle

van Nood, et al. NEJM, 2013
Kao, et al. JAMA, 2017
Kelly, et al. Ann Int Med, 2015
Tariq, et al. CID, 2019
Ianiro, et al. United European Gastroenterol J, 2018
Quraishi, et al. Aliment Pharmacol Ther, 2017

FMT is successful via various routes of administration

FMT *vs* vancomycin - via duodenal infusion



80%

Van Nood 2013

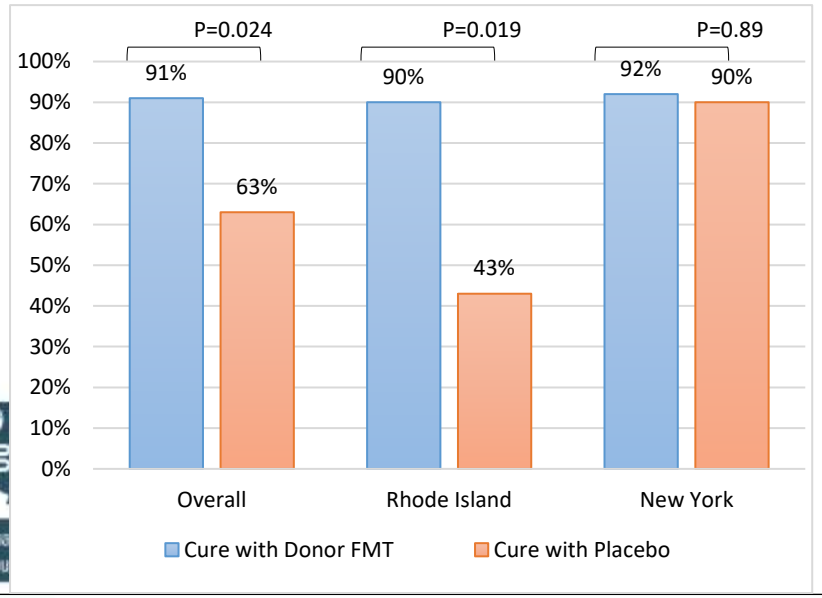
Fresh *vs* Frozen FMT- via enema

No. of FMTs	Per-Protocol Population	
	Frozen (n = 91)	Fresh (n = 87)
1	57 (62.7)	54 (62.1)
2	19 (83.5)	20 (85.1)
3-5	9 (93.4)	9 (95.4)
>5	2 (95.6)	1 (96.6)
Total	87/91 (95.6)	84/87 (96.6)

60%

Lee 2016

FMT *vs* placebo - via colonoscopy



Kelly 2016

90%

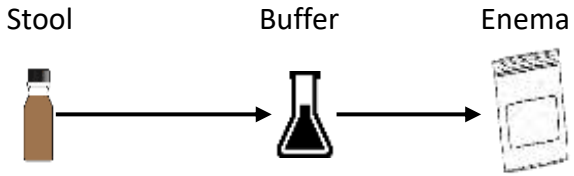
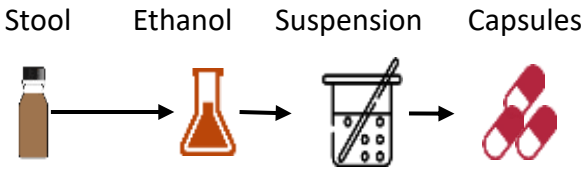
Encapsulated FMT

- Fresh (Louie 2013)
- Frozen (Youngster 2014, Kao 2017)
- Microbial Emulsion Matrix (Fischer/Openbiome 2015)
- Freeze-dried (Khoruts 2017)

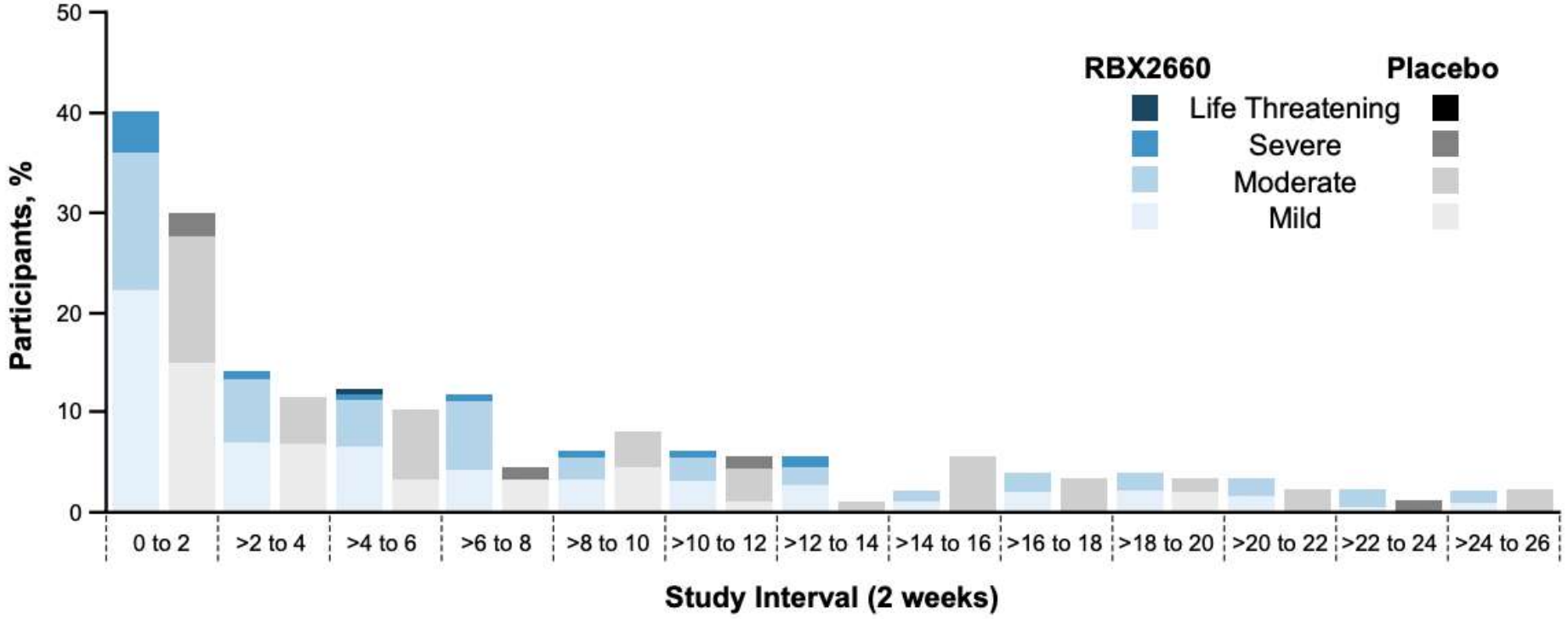
70-90%

Allegretti, DDW 2024

FDA-approved microbiota-based products

	Product Overview	Composition	Bowel Prep	Dosing	Delivery	Efficacy vs Placebo
Fecal microbiota live-jslm (Rebyota)		Full-Spectrum	✘	1 dose	Enema	70.6% vs 57.5% (PUNCH CD3)
Fecal microbiota spores live-brpk (Vowst)		Fractionated	✓	4 capsules daily for 3 consecutive days	Capsule	87.6% vs 60.2% (SER-109)

RBX2660: well tolerated, mild-moderate AEs



- Most AEs occurred within 2 weeks of treatment
- AEs ≥ 5% in both groups were GI-related
- Favorable safety profile due to rigorous donor screening

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Khanna, et al, Drugs 2022

SER 109: well tolerated, mild-moderate AEs

Table 2. Adverse Events through 8 Weeks (Safety Population).*

Adverse Event	SER-109 (N=90)	Placebo (N=92)
	no. of patients (%)	
Any adverse event	84 (93)	84 (91)
Adverse event related or possibly related to SER-109 or placebo	46 (51)	48 (52)
Serious adverse event†	7 (8)	15 (16)
Adverse event of special interest that occurred or worsened after initiation of SER-109 or placebo	1 (1)	1 (1)
Serious adverse event or an adverse event of special interest that occurred or worsened after initiation of SER-109 or placebo and was related or possibly related to SER-109 or placebo	0	0
Serious adverse event leading to withdrawal from the trial	0	1 (1)
Adverse event leading to death‡	2 (2)	0
Adverse events reported in ≥5% of patients		
Gastrointestinal disorders	79 (88)	80 (87)
Flatulence	63 (70)	70 (76)
Abdominal distension	49 (54)	49 (53)
Abdominal pain	46 (51)	56 (61)
Constipation	28 (31)	22 (24)
Diarrhea	22 (24)	20 (22)
Nausea	16 (18)	30 (33)
Vomiting	3 (3)	10 (11)

- Gastrointestinal events were most common AEs
- AEs were mild to moderate
- 3 deaths, none attributed to SER-109

Feuerstadt et al, NEJM 2022

aga American Gastroenterological Association

Gastroenterology 2024;166:409–434

GUIDELINES

AGA Clinical Practice Guideline on Fecal Microbiota–Based Therapies for Select Gastrointestinal Diseases

Anne F. Peery,[1,*] **Colleen R. Kelly,**[2,*] **Dina Kao,**[3,*] **Byron P. Vaughn,**[4,*] Benjamin Lebwohl,[5] Siddharth Singh,[6] **Aamer Imdad,**[7,§] and **Osama Altayar,**[8,§] on behalf of the AGA Clinical Guidelines Committee

- **Conventional FMT, live-jslm (Rebyota) and live-brpk (Vowst)**
  - ✓Prevention, *not treatment*, after 2nd recurrence (3rd episode) of CDI
  - ✓High risk of either recurrent CDI or a comorbid CDI recurrence
  - ✓Recovery following severe, fulminant or treatment-refractory CDI
- Alternatives include vancomycin taper, tapered-pulsed fidaxomicin, or bezlo
- Not recommended for severely immunocompromised

Microbiota-based therapies are used for prevention not treatment of recurrent CDI

- Administration of fecal microbiota-based therapies
  - After SOC antibiotics
  - Suppressive antibiotics (i.e., vancomycin) used as bridge
  - Stop antibiotics 1-3 days prior
    - Conventional FMT: multiple routes; appropriate donor screening
    - Live-jslm: fecal enema; no bowel prep
    - Live-brpk: oral capsules; requires bowel prep

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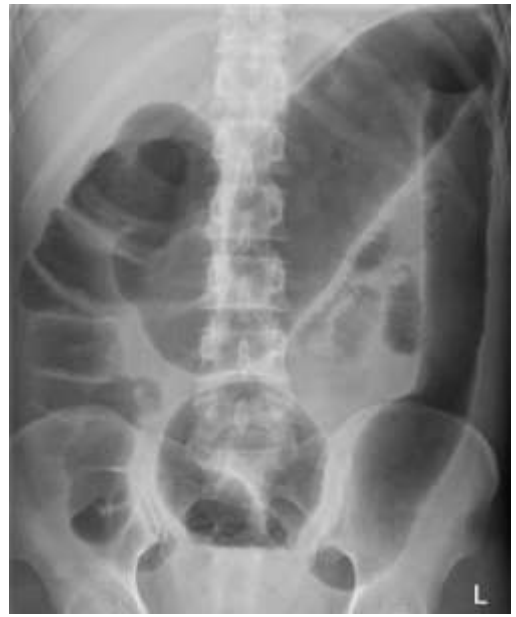
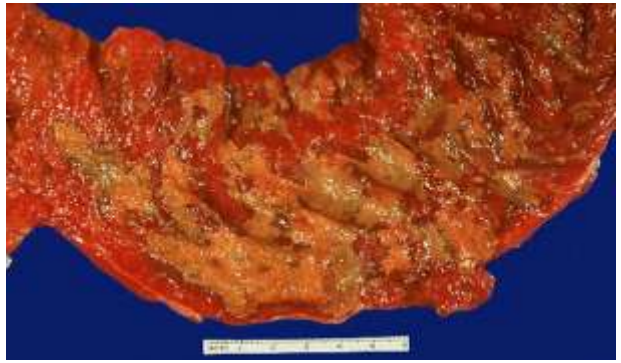
Peery, et al, Gastroenterology 2024

Fecal microbiota-based therapies may play a role in fulminant CDI not responding to antimicrobial therapy

- Consider fecal microbiota-based therapies if
  - Not responding to SOC antibiotics within 2-5 days
  - Recommend use of conventional FMT over no FMT
  - Multidisciplinary care (GI, surgery, ID)
  - *Contraindications:* bowel perforation, obstruction, severely immunocompromised
  - No evidence for FDA-approved fecal microbiota-based therapies





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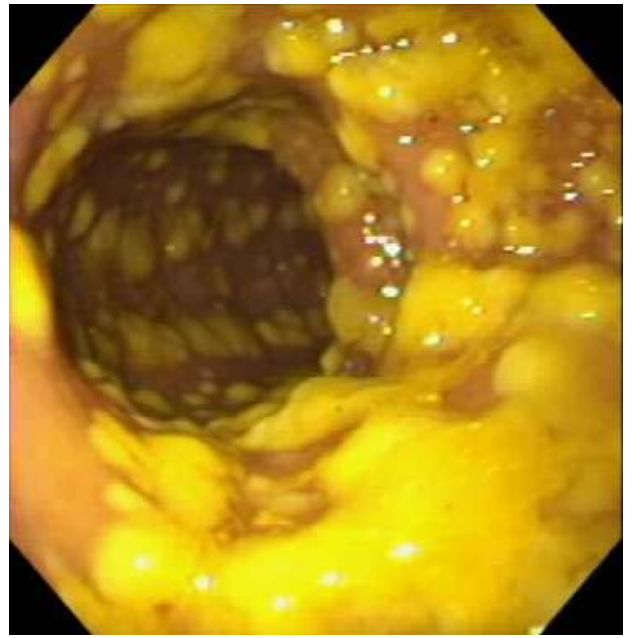
Kelly, C, DDW 2024
Peery, et al, Gastroenterology 2024

Treatment of fulminant CDI by FMT



FMT via colonosocopy or sigmoidoscopy

↓

Continue anti-CDI antibiotics
Repeat mucosal evaluation in 3-5 days

↙ Symptoms continue
Pseudomembranes

↘ Symptoms resolve
No pseudomembranes

↓

Suppressive vancomycin
Fecal microbiota-based therapy as outpatient

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Peery, et al, Gastroenterology 2024

Practical tips for using FDA approved products

- **FDA approved products**
  - Number of prior CDI episodes not specified
  - 2 or more recurrences accepted SOC
    - Potential role with fewer recurrences in select cases
  - Insurance coverage
  - In-home administration
- **Non-FDA approved products**
  - Institutional stool banks and OpenBiome
  - Fulminant CDI
  - IND not needed
- Discuss FDA approval status and safety with the patient

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Summary

- *C. difficile* infection is caused by dysbiosis
- Antibiotic therapies are used for treatment of CDI, however, recurrence is common
- Fecal microbiota-based therapies are effective for prevention of recurrent CDI
  - FMT
  - Live-jslm (Rebyota)
  - Live-brpk (Vowst)
- Fecal microbiota-based therapies restore the intestinal microenvironment
  - Microbiome, virome, fungome
  - Bile salt milieu