

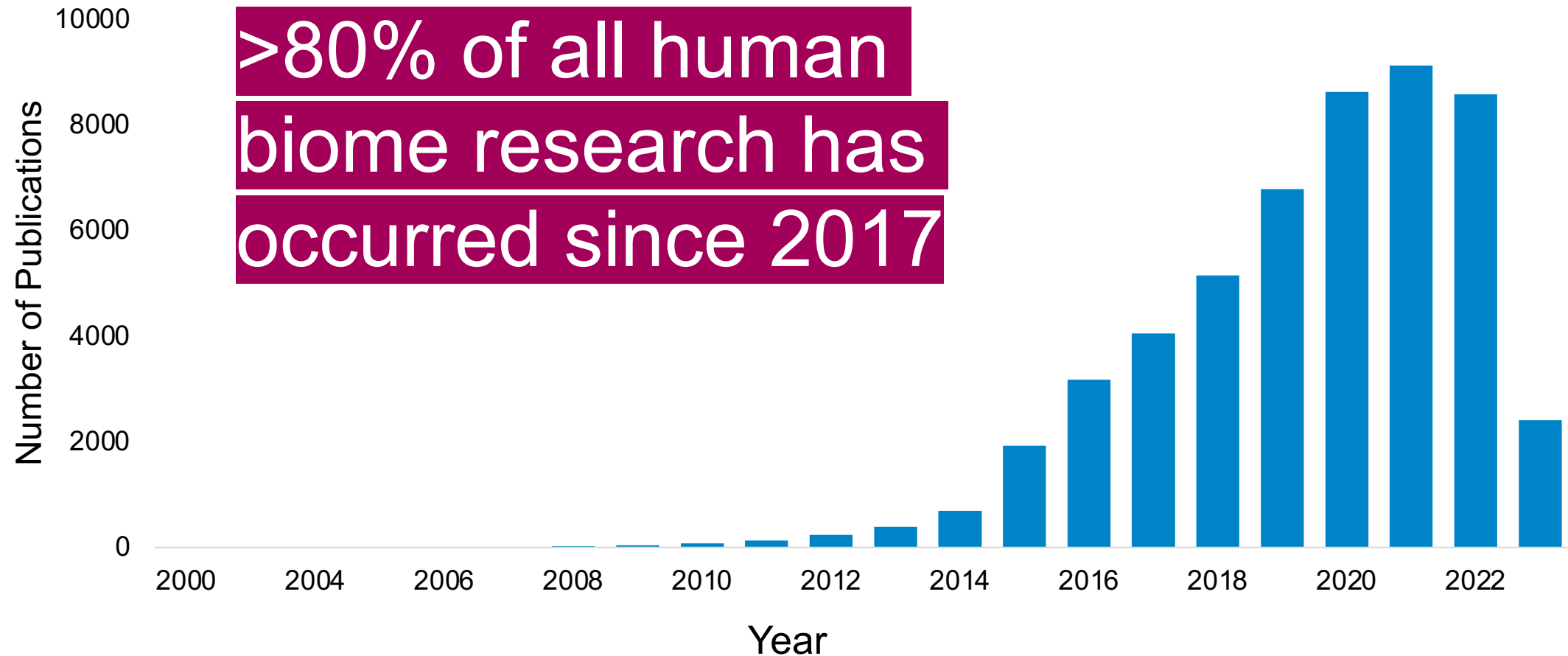


2023 NCSCG
20TH ANNUAL
3 GI SYMPOSIUM

Update in *C diff*, FMT and the Microbiome: the New World of LBPs

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The New New (research) Thing.....





#6 MICROBIOMANIA #7

(J. Eisen PhD UCD)



YOUR BABY'S MICROBIOME

The Critical Role of Vaginal Birth and Breastfeeding for Lifelong Health



TONI HARMAN and ALEX WAKEFORD

From the Directors of the Award-Winning Documentary MICROBIRTH

The Microbiome Solution

a radical new way to heal your body from the inside out



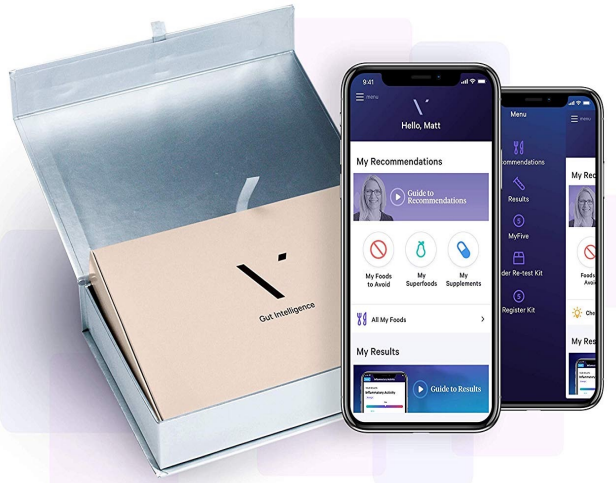
Robynne Chutkan MD, author of GUTBLISS

THE WHOLE-BODY MICROBIOME

How to Harness Microbes—Inside and Out—for Lifelong Health

A NEW DEFENSE AGAINST CANCER, HEART DISEASE, OBESITY & MORE

B. BRETT FINLAY, PhD
coauthor of Let Them Eat Dirt: How Microbes Can Make Your Child Healthier
JESSICA M. FINLAY, PhD



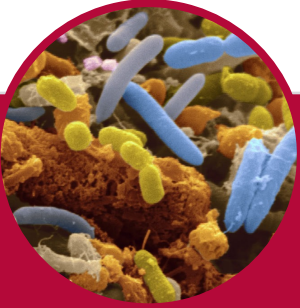
Feel better from the inside out.

We'll detect the nutrients and toxins in your gut and personally recommend foods and nutrients to keep your microbiome balanced.

VIOOME

DOCTOR MICROBIOME
OPTIMIZE YOUR GUT, OPTIMIZE YOUR LIFE

Important Definitions:



Microbiota:

The microorganisms that live in an established environment



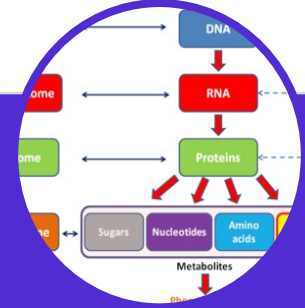
Microbiome:

The combined genetic material of the microorganisms in a particular environment



Dysbiosis:

A derangement in the microbiota



Metabolome:

Functional properties of the gut microbiota

And It's Not One Organism → One Outcome

Co-dependency rules, with symbiotic metabolic support from multiple community members to each other (and to the host)

Bacteria:

help digest nutrients, prevent colonization by pathogens, aid immune system development

Host:

provides nutrients and a mobile home with a view

Yep!!



Nope!!

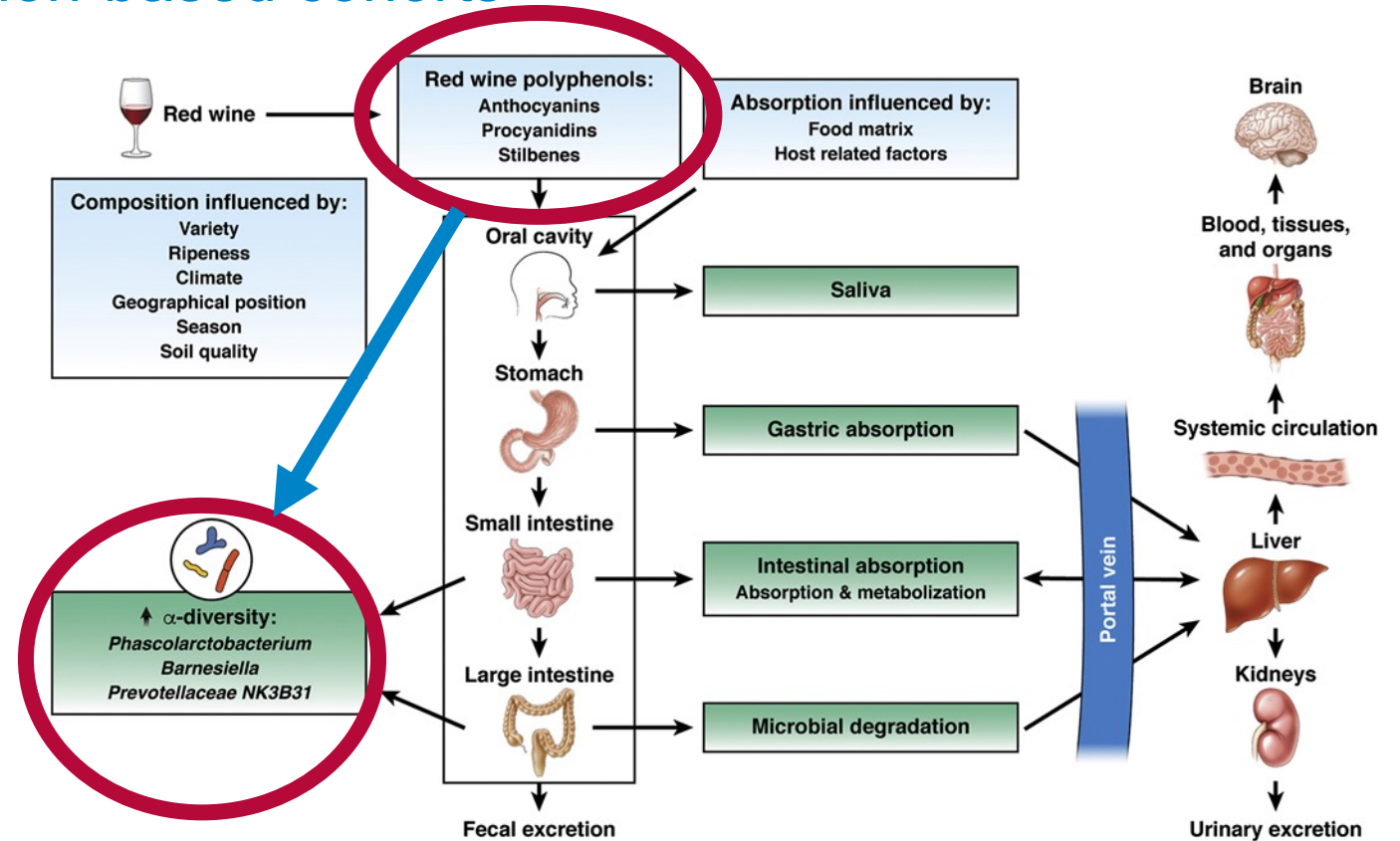


Wine → Increased Diversity!

Evaluated in 3 independent population-based cohorts

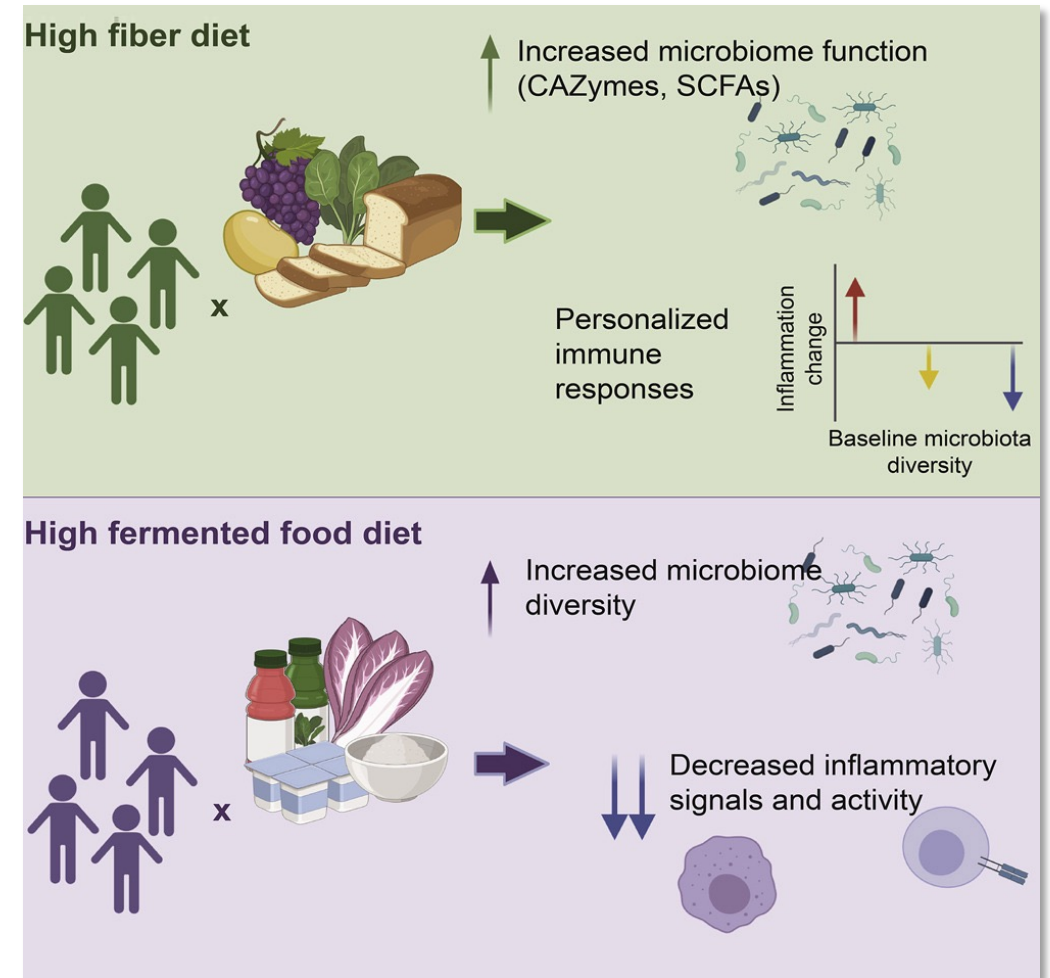
Red wine consumption positively associated with α -diversity

- Even rare consumption had effect
- White wine a lesser but suggestive association with α -diversity
- No associations with other alcohol categories.



Can Fiber or Fermented Foods Improve Our Biome?

- 17-week RCT (n=18/arm) healthy adults
- **Plant based high fiber diet** (22→45 g/day): no change in diversity or cytokine response scores
- **High fermented food diet** (yogurt, kimchi, kombucha 6 servings/d): ↑ microbiota diversity and ↓ inflammatory markers
- “Fermented foods may be valuable in countering the decreased microbiome diversity and increased inflammation pervasive in industrialized society”





FMT for rCDI: Bacteriotherapy's Proof of Concept

CLOSTRIDIoidES DIFFICILE

THREAT LEVEL **URGENT**



223,900

Estimated cases
in hospitalized
patients in 2017



12,800

Estimated
deaths in 2017



\$1B

Estimated attributable
healthcare costs in 2017

Anti-CDI Antibiotics



\$10



\$150



\$4400

Non-Severe: Initial Episode

- Stop offending antibiotics if possible
- Avoid anti-peristaltic agents
- Empiric Rx appropriate when high suspicion

Vancomycin 125 mg PO QID x 10d
Strong recommendation, low quality of evidence

Or

Fidaxomicin 200 mg PO BID x 10d
Strong recommendation, moderate quality of evidence

Metronidazole 500 mg PO TID x 10 days may be considered for initial treatment in low-risk patients (young, outpatient, no comorbidities)

Strong recommendation, moderate quality of evidence

Severe: Initial Episode

Vancomycin 125 mg PO QID x 10 days

Strong recommendation, low quality of evidence

Or

Fidaxomicin 200 mg PO BID x 10 days

Conditional recommendation, very low quality of evidence

Fulminant Infection

Volume resuscitation, early surgical consultation, imaging for ileus, megacolon

Vancomycin 500 mg PO Q6h for the first 48-72 hours

- *Strong recommendation, very low quality of evidence*

and **Metronidazole** 500 mg IV Q8h

(especially beneficial with paralytic ileus)

- *Conditional recommendation, very low quality of evidence*

Ileus: The addition of vancomycin enemas (500 mg Q6h) may be beneficial.

- *Conditional recommendation, very low quality of evidence*

FMT for Severe and Fulminant CDI

“Consider with severe and fulminant CDI refractory to antibiotics, particularly poor surgical candidates”

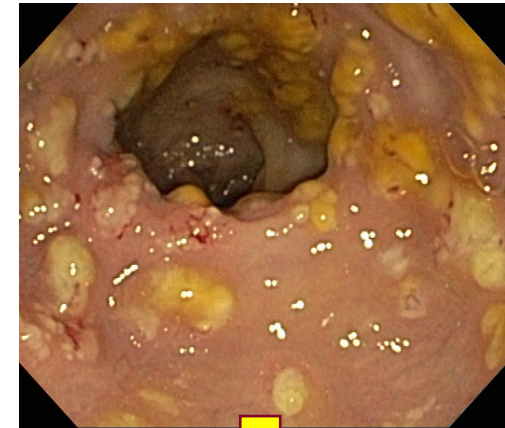
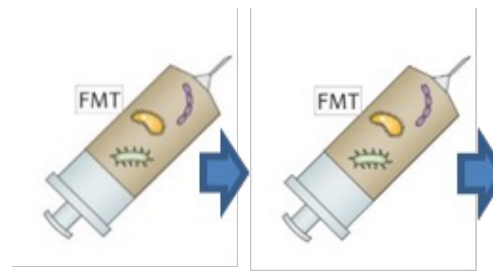
- *Strong recommendation, low quality of evidence*

FMT plus selected use of vancomycin in severe and fulminant CDI inpatients (including 7 toxic megacolon)

- 91% (52/57) cure at one month
- No serious AEs
- 30 day survival 95%

Single vs multiple FMTs in addition to vancomycin in severe CDI refractory to antibiotics

- FMT-S 75% cured (21/28)
- FMT-M 100% cured (28/28)
- On average # 3 FMTs given



RECURRENT DISEASE (rCDI)

20% after initial Rx

40% after 1st recurrence

60% after 2 or more recurrences

Mechanisms of recurrence:

- ? Persistent spores
- ? Impaired host immune response (lower anti-toxin IgG antibody levels in patients with rCDI)
- ? Decreased biome diversity
- ? Reinfection from environment

Treatment of Recurrent Infection

Fidaxomicin for patients experiencing a first recurrence after an initial course of vancomycin or metronidazole

- *Strong recommendation, moderate quality of evidence*

OR tapering/pulsed-dose vancomycin for patients experiencing a first recurrence after an initial course of fidaxomicin, vancomycin, or metronidazole

- *Strong recommendation, very low quality of evidence*

Suppressive and Prophylactic Vancomycin

For patients with rCDI who are not candidates for FMT, who relapsed after FMT, or who require ongoing or frequent courses of antibiotics, long-term suppressive oral vancomycin may be used to prevent further recurrences (125mg PO QD-TID)

- *Conditional recommendation, very low quality of evidence*

Oral vancomycin prophylaxis (OVP) may be considered during subsequent systemic antibiotic use in patients with a history of CDI who are at high risk of recurrence to prevent further recurrence

- *Conditional recommendation, low quality of evidence*

Fecal Microbiota Transplantation (FMT)

Administration of feces containing the entire gut microbial community from one human to another, with intent to favorably affect the recipient's microbiota

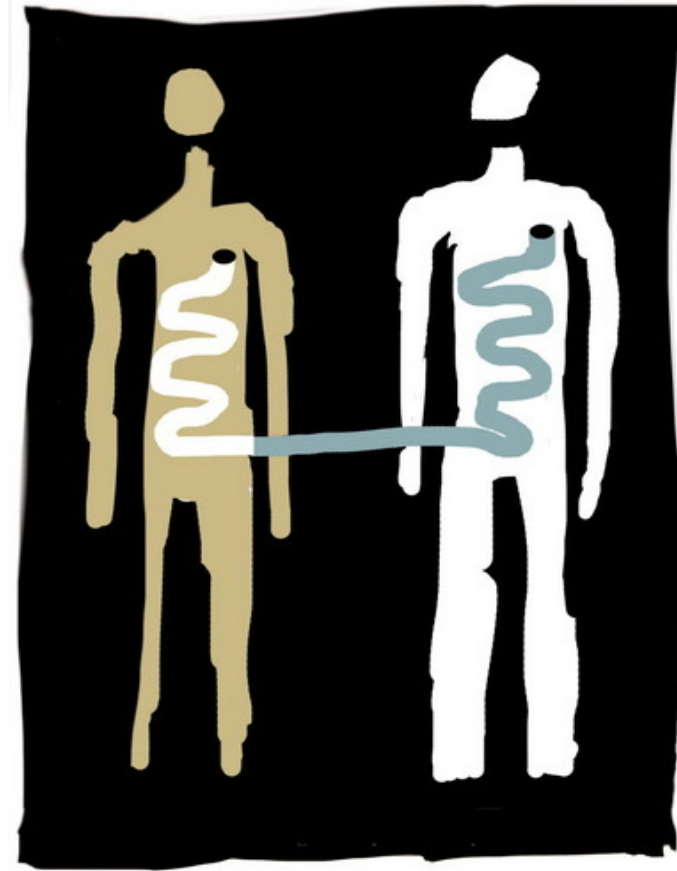
Described in 4th C. Chinese medicine texts

'Transfaunation' in veterinary literature

Eiseman (1958): fecal enemas in 4 PMC pts (presumed CDI)

FDA adopts "enforcement discretion" (2013), still in place

"Recommended for patients experiencing their second or further recurrence of CDI" (strong recommendation, moderate quality of evidence 2021)



FMT Delivery

Nasogastric or nasoduodenal tube

- Uncomfortable, ? increased risk
- X-ray or EGD placement

Retention enemas

- Variable patient ability to tolerate
- Logistics of administration (and -70 freezer)

Lower endoscopy

- Enables examination of mucosa
- Likely more effective (90% vs 75%)
- \$\$\$, sedation risks

Encapsulation

- Likely decreased risk & cost, if equal efficacy



When FMT Actually Arrived According to My Son....



Cochrane Review 2013

11 studies

273 CDI patients

Overall cure 90%

- Upper: 82%
- Lower: 91%
- No reported AEs

Systematic Review 2015

12 case-series, 2 RCTs

516 patients (rCDI)

Overall cure 85%

- Upper: 77%
- Lower: 90%
- Enema: 78%
- 'Few short term AEs'

Overall cure: 85-92%

Lower: 90-95%

Upper: 77-88%

Systematic Review 2019

- 108 studies, 7 RCTs
- 4609 patients
- Primary cure 88%
- Final cure 96%
 - AEs 'infrequent and mostly self-limited'

Do-it-Yourself FMT?

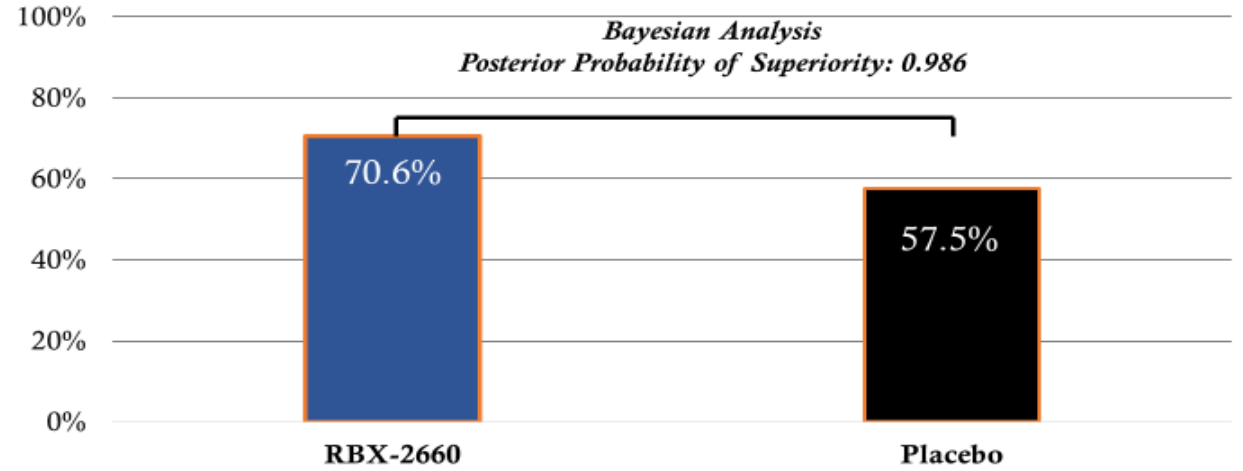
Online survey 2018-2019

- 84 respondents (71% female, 92% white, mostly US west coast)
 - 80% did it on themselves (12% a child, 2% a spouse)
 - 87% used the internet for guidance
 - 64% done 'because other treatments didn't work'
 - 92% knew their stool donor, 65% screened the donor in some way
 - 95% via enema, 43% had 'performed >10 FMTs'
- Indications: IBD 35%, food allergies 30%, IBS 29%, SIBO 11%, ASD 2%
- 12% reported adverse events (abdominal pain, gas/bloat, mood changes)
- 82% improved, 96% 'would do it again', but 57% would 'prefer a clinical setting'

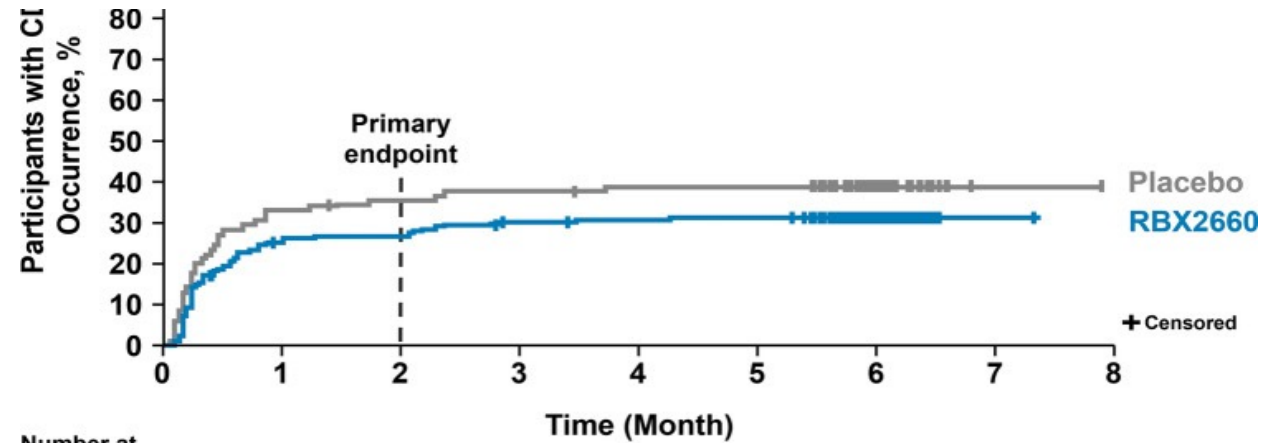


PUNCH CD3 REBYOTA™

PUNCH-CD3: Phase 3 RBX-2660 Superior to Placebo



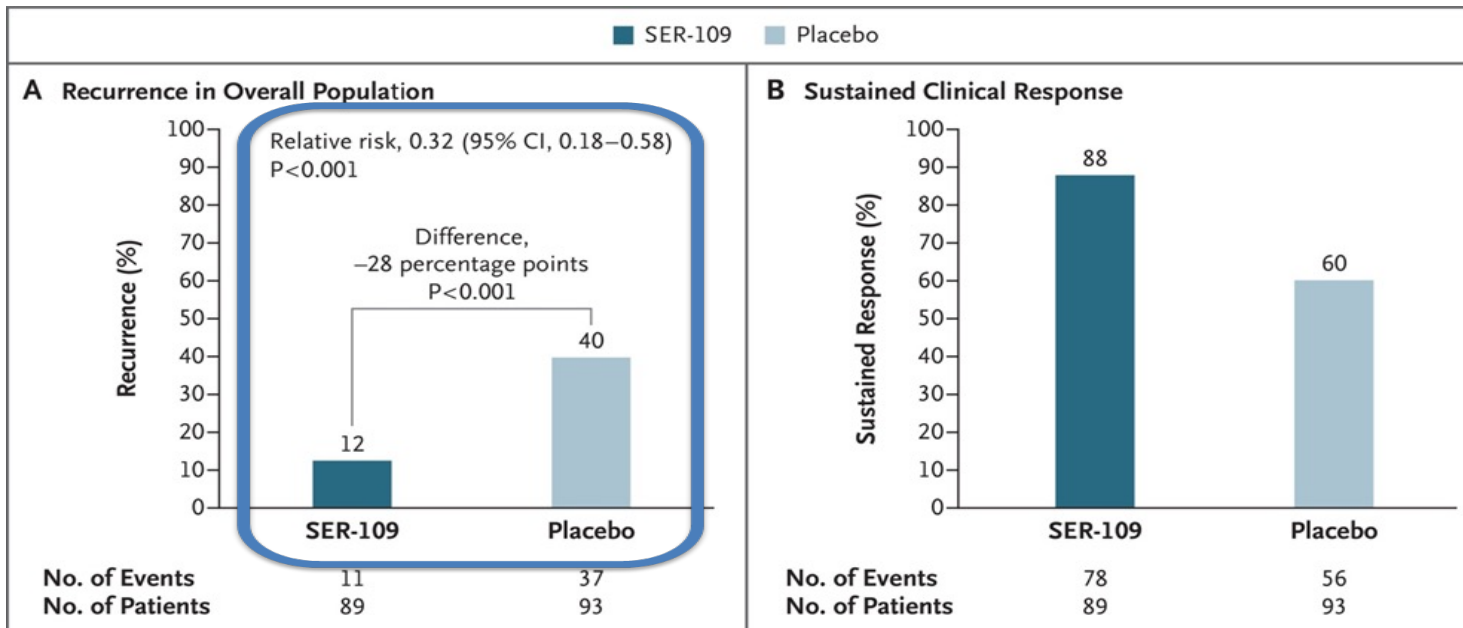
Khanna et al. Drugs. 2022 Oct;82(15):1527-1538



Number at risk	0	1	2	3	4	5	6	7	8
RBX2660	177	131	128	120	118	117	52	1	0
Placebo	85	57	54	52	49	49	22	1	0

SER 109 ECOSPOR (VOWST™)

- Live purified *Firmicutes* spores
- 182 pts with ≥ 3 CDIs / one year, responsive to Abx
- 4 capsules/d x3d vs PBO after vanco or fidax
- Primary outcome rCDI at 8 weeks



RESEARCH SUMMARY

SER-109, an Oral Microbiome Therapy for Recurrent *Clostridioides difficile* Infection
Feuerstadt P et al. DOI: 10.1056/NEJMoa2106516

CLINICAL PROBLEM
Antibiotics for *Clostridioides difficile* infection can induce microbiome disruption that enables germination of *C. difficile* spores, which can then lead to recurrent infections. A treatment approach that can prevent recurrent infection is needed.

CLINICAL TRIAL
Design: A phase 3, double-blind, placebo-controlled trial assessed the efficacy of SER-109 — an investigational oral microbiome therapeutic made up of live purified Firmicutes bacterial spores that could limit *C. difficile* spore germination — in patients with three or more *C. difficile* infections in the previous year.
Intervention: 182 adults who had symptom resolution after antibiotic treatment for *C. difficile* infection and were at high risk for recurrence were assigned to receive either SER-109 or placebo, given as four capsules once daily over 3 days. The primary end point was recurrence of *C. difficile* infection within 8 weeks.

RESULTS
Efficacy: At 8 weeks, SER-109 was superior to placebo in lowering rates of *C. difficile* recurrence. The benefit was seen in patients 65 years of age or older and in those younger than 65 years of age, as well as in those initially treated with vancomycin or fidaxomicin.
Safety: The percentages of patients with adverse events were similar in the two groups; most symptoms were gastrointestinal and mild to moderate in nature.

LIMITATIONS

- Minority groups were underrepresented.
- Stool specimens were not obtained before antibiotic treatment, so the full effect of SER-109 on the pre-antibiotic microbiome is unknown.

Links: Full Article | NEJM Quick Take

Primary Efficacy End Point
Recurrence of *C. difficile* Infection up to 8 Weeks After Treatment

Relative risk, 0.32; 95% CI, 0.18 to 0.58; P<0.001
Difference, -28 percentage points

Group	No. of Events	No. of Patients	Recurrence (%)
SER-109	11	89	12%
Placebo	37	93	40%

Adverse Events through 8 Weeks

Adverse Event	SER-109 (N = 90)	Placebo (N = 92)
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)
Gastrointestinal disorders	79 (88)	80 (87)

CONCLUSIONS
In patients with recurrent *C. difficile* infection, a two-pronged treatment approach of standard-of-care antibiotics followed by a microbiome-replacement therapy can reduce the risk of recurrence.

Live Biotherapeutic Products in Development

	Composition	Bowel Prep	Dosing	Delivery	FDA Status
Ferring¹ <i>RBX-2660</i>	Broad-spectrum	✗	1 dose 150 mL	Rectal	REBYOTA — Indicated for the prevention of rCDI in adults ≥18 years of age, following antibiotic treatment for recurrent CDI ¹
Seres² <i>SER-109</i>	Narrow-spectrum	✓	3 doses 4 capsules/day x 3 days	Oral	VOWST — Indicated to prevent rCDI in individuals 18 years of age and older following antibacterial treatment for recurrent CDI ²
Finch <i>CP101</i>	Broad-spectrum	✗	10 capsules x 1 day	Oral	Phase 3 trial discontinued
Destiny pharma <i>NTCD-M3</i>	Spores of a single nontoxigenic <i>C. difficile</i> strain	✗	1 capsule/day x 7 days	Oral	Fast track status
Vedanta <i>VE303</i>	Narrow-spectrum	✗	10 capsules/day x 14 days	Oral	Orphan Drug

1. REBYOTA Prescribing Information. Available at: <https://www.fda.gov/media/163587/download>. Last accessed April, 2023;

2. VOWST Prescribing Information. Available at: https://www.serestherapeutics.com/our-products/VOWST_PI.pdf. Last accessed April, 2023.



FMT for Other Diagnoses: Ongoing Trials (>300)

- *C. difficile* infection
- Crohn's
- Ulcerative Colitis
- Pouchitis
- IBS
- ICI resistance
- NAFLD/NASH
- PSC
- Intestinal pseudo-obstruction
- CNS diseases (and SDAT)
- Graft vs host disease
- Obesity/metabolic syndrome
- HIV
- DM-II
- Pancreatitis
- Hepatitis B
- MRSA enterocolitis
- MDROs
- Hepatic encephalopathy
- Post-stem cell transplant
- Autologous FMT (preventative)
- Autism spectrum disorders

FMT: unanswered questions, future directions

- Route: NG/ND vs F/S vs colonoscopy vs pills
- Random healthy donors vs 'rational' or 'super-donors'
- Full-spectrum stool vs narrow consortia products
- Non-bacterial FMT? Role of virome, fungome, metabolome
- FDA: tick, tick, tick.....
- Indications beyond *C difficile* still TBD
- We're literally at the beginning of the LBP era