
Virtual Grand Rounds
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2025
ACG'S FUNCTIONAL GI & MOTILITY DISORDERS SCHOOL & MIDWEST
REGIONAL POSTGRADUATE COURSE
AUGUST 22-24, 2025 | MARRIOTT INDY PLACE INDIANAPOLIS, IN
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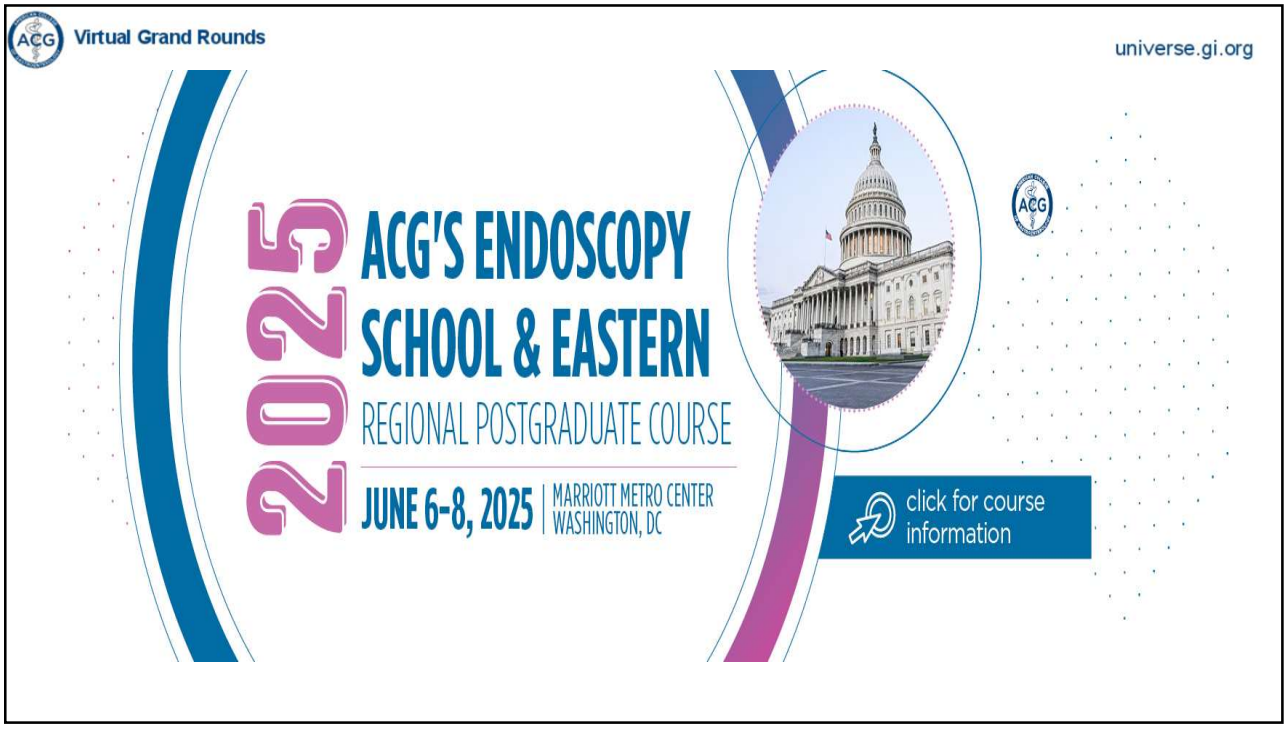
Virtual Grand Rounds
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2025
ACG'S ENDOSCOPY SCHOOL & EASTERN
REGIONAL POSTGRADUATE COURSE
JUNE 6-8, 2025 | MARRIOTT METRO CENTER WASHINGTON, DC
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It's ACG Institute Week!

June 2-6, 2025

The Center for Leadership, Ethics & Equity and other signature programs of the ACG Institute provide a transformational resource for members:

- **Visiting Scholar in Equity, Diversity and Ethical Care**
- **Leonidas Berry Health Equity Research Award**
- **Leadership programs:**
  - **The Emerging Leadership Program** (ACG members in the U.S. who are 3rd or 4th-year fellows)
  - **The Early Career Leadership Program** (ACG physician members in the U.S. who are 1-5 years post-fellowship/terminal training)
  - **The Advanced Leadership Program** (ACG physician members in the U.S. who are 10-20 years post-fellowship/terminal training)
  - **The Clinical Research Leadership Program** (ACG physician members in the U.S. who are 2-15 years post-fellowship training, with active or recent funding as a principal investigator or co-principal investigator)

Help the ACG Institute grow, uplift and transform the GI profession and become a G.U.T. Giver today!

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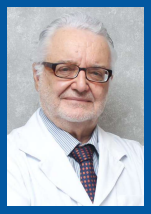
Participating in the Webinar



Moderator:
Wilson R. Catapani, MD, FACG

All attendees will be muted and will remain in "Listen Only Mode"

Type your questions here so that the moderator can see them.
Not all questions will be answered but we will get to as many as possible.

A handout with the slides and room to take notes can be downloaded from your control panel.

Exit

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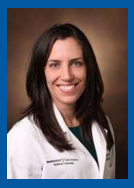
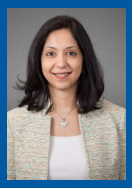
ACG Virtual Grand Rounds

Join us for upcoming Virtual Grand Rounds!

Week 23 – Thursday June 5, 2025
Small Bowel Nutrient and Fluid Absorption: Key Concepts to Manage Short Bowel Syndrome
Faculty: Carol E. Semrad, MD, FACG
Moderator: Dawn W. Adams, MD, MS, CNSC
At Noon and 8pm Eastern

Week 24 – Thursday June 12th, 2025
ACG Guidelines: H. pylori
Faculty: William D. Chey, MD, FACG
Moderator: Shilpa Grover, MD, MPH
At Noon and 8pm Eastern

Visit **gi.org/ACGVGR** to Register

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ACG 2025
OCTOBER 24 - 29, 2025 | PHOENIX, ARIZONA
REGISTER TODAY: ACGMEETINGS.GI.ORG

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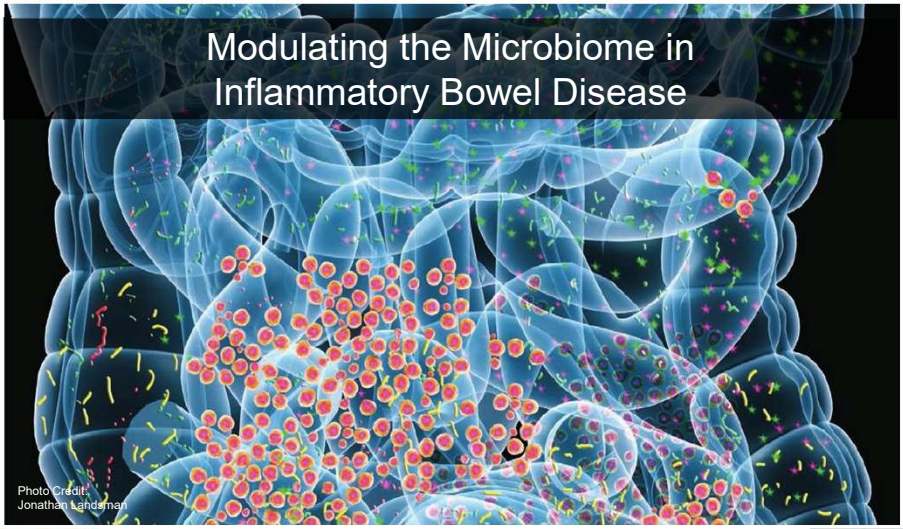
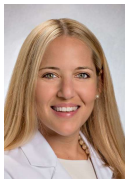
Modulating the Microbiome in Inflammatory Bowel Disease





JESSICA R. ALLEGRETTI, MD, MPH, FACG
MEDICAL DIRECTOR, CROHN'S AND COLITIS CENTER
DIRECTOR, FECAL MICROBIOTA TRANSPLANT PROGRAM
DIRECTOR, CLINICAL RESEARCH
DIVISION OF GASTROENTEROLGY, BRIGHAM AND WOMEN'S HOSPITAL
ASSOCIATE PROFESSOR OF MEDICINE, HARVARD MEDICAL SCHOOL

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Gut Microbiota

- The gut microbiota is the largest reservoir of **microbes** in the body.
- The human gut microbiota is estimated to consist of at least 10^14 bacteria and as many as 1000 to 1200 bacterial species, most of which reside in the colon.

Supply of nutrients and energy	Development of immune system
Vitamin synthesis (vitamin K and B) Short-chain fatty acids production (acetate, propionate, butyrate)	immune system development IgA production Modulation of T cell repertories Regulation of T-helper cell balance (Th1/Th2 balance, Th17, Treg) Reinforcement of barrier function

Host defense
Colonization resistance (e.g. nutrient competition) Production of anti-microbial factors (e.g. bactriocins, lactic acid, RegIIIγ)

Nishida et al. CJG 2018

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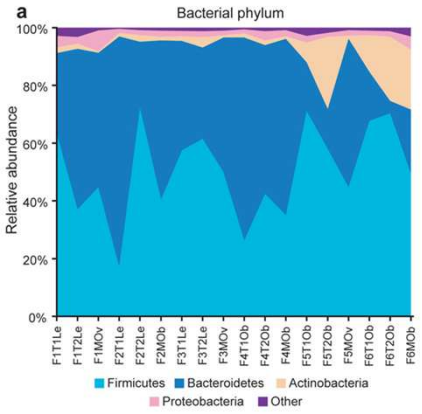
Gastrointestinal Microbiome in Health

- Types of microorganisms present
  - Bacteria: 1000 species
  - Archaea (prokaryotes)
  - Viruses/bacteriophages
  - Fungi (mycobiome)
  - Even protozoa in some places
- Unique & Dominated by 4 Phyla
  - Firmicutes (Gram +)
  - Bacteroidetes (Gram -)
  - Proteobacteria (e.g. E coli, Salmonella, Shigella, Helicobacter)
  - Actinobacteria (common in soil, e.g. Mycobacteria, Bifidobacteria)



Musso G. Diabetes Care; 2010; Qin J. Nature; 2010
Prakash, S. et al. Biologics; 2011; Turnbaugh PJ, et al. Nature; 2009

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The human gut is like a rainforest

- High diversity of species
- Healthy ecosystem
- Balance
- Resistance to disease

- Low diversity of species
- Sick ecosystem
- Imbalance
- Susceptibility to disease

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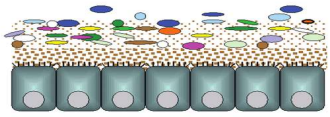
Dysbiosis Disrupts Health

- Diverse and abundant microbiota
- Firmicutes, Bacteroidetes and Actinobacteria dominant
- Healthy levels of SCFA production
- Intact mucosal barrier
- No overt inflammation

a)

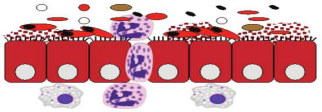


Health

Therapeutic disruption of dysbiosis
Antibiotics
Probiotics
Dietary intervention/Prebiotics
Faecal transplantation

Dysbiosis-related diseases
Chronic gastrointestinal infections
Antibiotic-associated diarrhoea
Pseudomembranous colitis
Inflammatory bowel disease
Necrotizing enterocolitis

b)



Dysbiosis

- Microbiota diversity reduced
- Elevated *Enterobacteriaceae*/opportunistic pathogens
- Skewed SCFA profile
- Disruption of mucosal barrier
- Host inflammatory response initiated

Walker AW, et al. *Pharmacol Res.* 2013;69(1):75-86.

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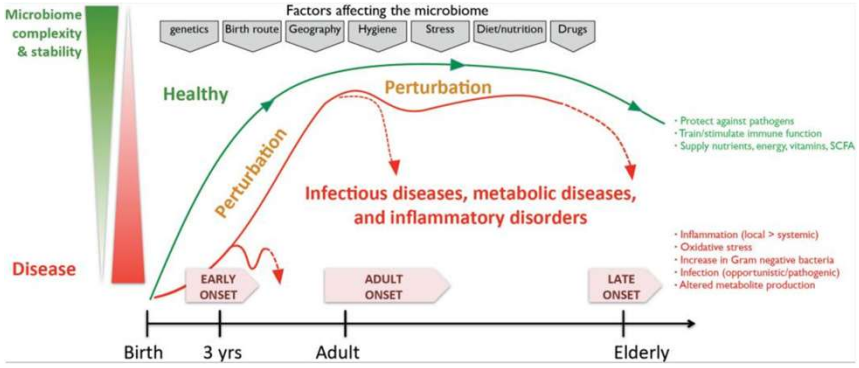
Gut Microbiota in IBD

- As infants develop, they establish a **pattern of bacteria in their intestine**. Immune cells develop in the lining of the intestine to ignore one's normal bacteria and attack potential invading organisms.



- In some individuals, the immune cells lose the ability to recognize the bacterial pattern as being one's own leading to inflammation and subsequent damage to the gut.

Kostic et al. Gastro 2014.

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Gut Microbiota in IBD

Changes in the microbiome linked to Inflammatory Bowel Disease

Microbial composition	Decrease in alpha diversity
	Decrease in Bacteroides and Firmicutes
	Increase in Gammaproteobacteria
	Presence of Escherichia coli, specifically AIEC
	Presence of Fusobacterium
	Decrease in Clostridia, Ruminococcaceae, Bifidobacterium, Lactobacillus
	Decrease in Faecalibacterium prausnitzii
Microbial function	Decrease in Short Chain Fatty Acids (SCFA), butyrate
	Decrease in butanoate and propanoate metabolism
	Decrease in amino acid biosynthesis
	Increase in auxotrophy
	Increase in amino acid transport
	Increase in sulfate transport
	Increased oxidative stress
	Increase in type II secretion system, secretion of toxins

Kostic et al. Gastro 2014.

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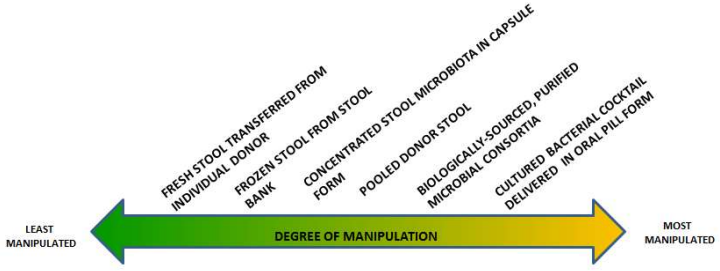
The Solution: Microbiome Restoration

- Full Spectrum Products: minimally manipulated microbial communities from stool of a healthy donor into a patient's GI tract.
- Defined consortia: are isolated microorganisms



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THE STORY BEGINS WITH CDI….

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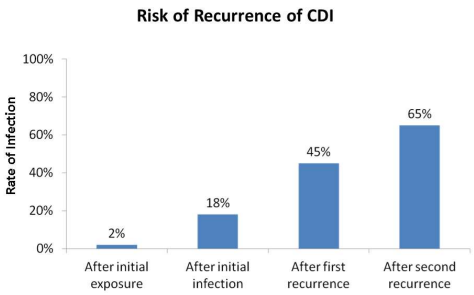
The Rationale: Recurrent CDI

- Recurrence is present when CDI re-occurs within 8 weeks
  - provided the symptoms from the previous episode resolved
  - May occurs within days



Risk of recurrent infection increases with each treatment failure. (Jiang,et. *Am J Gastroenterol* 2006; 101:112.)

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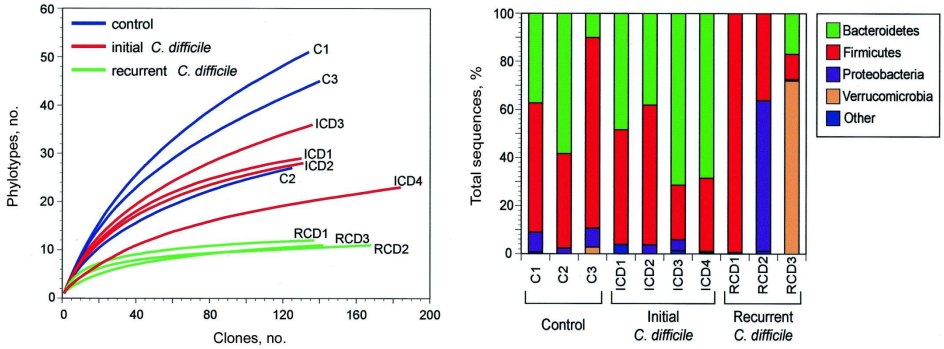
Altered Intestinal Microbiome



- Decreased phylogenic richness
- *Bacteroidetes* and *Firmicutes* are reduced in patients with recurrent *CDI,* not in patients with just one episode

Chang JY, et al. J Infect Dis 2008:197;435-8

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Current Landscape

- Non-FDA approved FMT
- FDA approved fecal microbiota products
  - Fecal microbiota, spores live-brpk (VOWST)
  - Fecal microbiota, live-jslm (Rebyota)

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Terminology	Definition	Examples
Probiotics	Live microorganisms that provide health benefits when consumed in adequate amounts.	Lactobacillus, Bifidobacterium
Prebiotics	Non-digestible food ingredients that promote the growth of beneficial bacteria.	Inulin, Fructo-oligosaccharides
Synbiotics	A combination of probiotics and prebiotics, working synergistically to enhance gut health.	Lactobacillus + Inulin
Postbiotics	Bioactive compounds produced by microorganisms during fermentation or metabolism.	Butyrate, Peptidoglycans
Unapproved Fecal Microbiota Transplantation (FMT)	Transfer of stool from a healthy donor to restore microbial balance in a recipient.	
FDA approved donor-derived microbiota therapy (FMDT)	Donor-derived microbiota therapeutic, regardless of definition of consortium to treat or prevent disease	RBL, VOS
Live Biotherapeutic Products (LBPs)	Living microorganisms designed as pharmaceutical agents to treat or prevent disease.	VE303

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Non-FDA Approved Fecal Microbiota Transplantation

- Instillation of minimally manipulated microbial communities from stool of a healthy donor into a patient's GI tract.
- FMT is distinguished from a defined consortia of microorganisms, highlighting the degree of complexity and functionality of the microbiome.
- Is considered to be both a "drug" and a "biologic or tissue"

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FDA guidance on FMT

- **May 2013: Investigational New Drug application (IND) requirement announced**
- **Fecal Microbiota = drug/biologic product**
  - Considered investigational
  - Requires randomized controlled trials, safety/efficacy data
- **July 2013: May administer FMT to treat *C. difficile* infection not responding to standard therapies**
  - Must provide informed consent
    - State that FMT is investigational
    - Discuss potential risks
  - All other applications outside of CDI require an IND
- **March 2016: Draft guidance would require directed donors; limit material from stool banks**
  - Public comments were elicited
  - April 2019 "update to the policy is immanent" and human stool does not meet definition of human tissue
- **UPDATE December 2022:** FDA enforces IND requirement for stool banks

http://www.fda.gov

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Impact of FDA enforcement discretion policy

- Allows broader access for patients with CDI to be treated with FMT
- Allowed for expansion into management of fulminant CDI
- Facilitated research into other areas outside of CDI

- ✗ Stool banks supply the majority of donor material, yet operating with no mechanism for regulation
- ✗ Efficacy and safety data not consistently collected
- ✗ Donor material costs generally not covered by insurance
- ✗ Confusion and uncertainty (patients, physicians, hospitals) around regulations
- ✗ Difficulty recruiting patients into clinical trials of microbiota-based therapeutics for CDI

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Stool Banks Facilitate FMT

- Provide (on a national, regional, or local level) ready to use, high quality donor feces
- Convenient
  - Material stored frozen until ready to use
  - Available for emergent use (Fulminant CDI)
  - Supply material for research purposes
- "Safer/cheaper"
- Openbiome closed 12/2024

Terveer et al, Clinical Microbiology and Infection 2017

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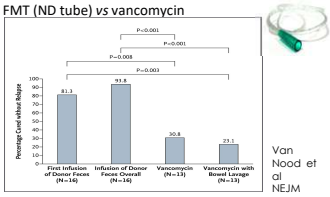
FMT has an established role for recurrent CDI

FMT (ND tube) *vs* vancomycin



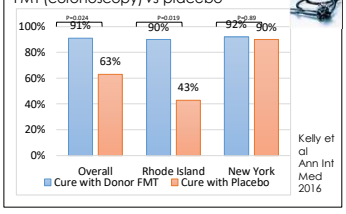
Van Nood et al NEJM 2013

Fresh *vs* Frozen FMT(enema)

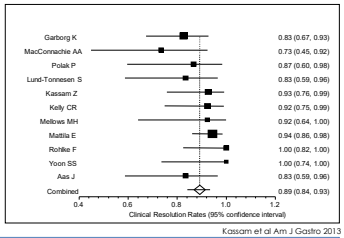
No. of FMTs	Per-Protocol Population Frozen (n = 91)	Fresh (n = 87)
1	57 (62.7)	54 (62.1)
2	19 (83.5)	20 (85.1)
3-5	9 (93.4)	9 (95.4)
>5	2 (95.6)	1 (96.6)
Total	87/91 (95.6)	84/87 (96.6)

Lee et al JAMA 2016

FMT (colonoscopy) *vs* placebo



Kelly et al Ann Int Med 2016



Kassam et al Am J Gastro 2013

ID and GI CDI clinical guidelines from US and European recommend FMT

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Fecal Microbiota, live-jslm (REbyota): Indications for Use

- Broad consortium microbiota-based therapy
- Administered as a single rectal installation following SOC antibiotics
- FDA indication: Prevention of recurrent CDI in individuals ≥ 18 years of age following antibiotic treatment for recurrent CDI

Indications for Live-jslm
Second recurrence (third episode) following standard of care antimicrobial
First recurrence in patients that are at high risk for future recurrences
Age > 65
Chronic proton pump inhibitor usage
Immunocompromised (e.g., Chronic kidney disease, Diabetes mellitus, Active chemotherapy)
Likely future concomitant antimicrobial usage
Lives in skilled nursing facility
Severe underlying illness
Spends significant amount of time as an inpatient at the hospital
Lives in skilled nursing facility
Recurs within 8-weeks of receiving an initial treatment
FDA Indication: RBX2660 is indicated for the prevention of recurrence of Clostridioides difficile infection (CDI) in individuals 18 years of age and older, following antibiotic treatment for recurrent CDI.
*The indications from this chart are based upon expert opinion and not data supporting these specific risk factors

Feuerstadt P, et al. *Am J Gastroenterol.* 2023;118(8):1303-1306. Drugs@FDA: FDA-Approved Drugs. Accessed November 27, 2023. https://www.fda.gov/media/163587/download?attachment.

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Fecal Microbiota, live-jslm: Safety

- Contraindicated in patients with history of severe allergic reaction (eg. anaphylaxis) to any known components

Adverse Reaction	FMB, Live-jslm N = 180 N (%)	Placebo N = 87 N (%)
Abdominal pain	16 (8.9)	6 (6.9)
Diarrhea	13 (7.2)	3 (3.4)
Abdominal distension	7 (3.9)	2 (2.3)
Flatulence	6 (3.3)	0
Nausea	6 (3.3)	1 (1.1)

Khanna S, et al. *Drugs.* 2022;82(15):1527-1538. Drugs@FDA: FDA-Approved Drugs. Accessed November 30, 2023. https://www.fda.gov/media/163587/download?attachment.

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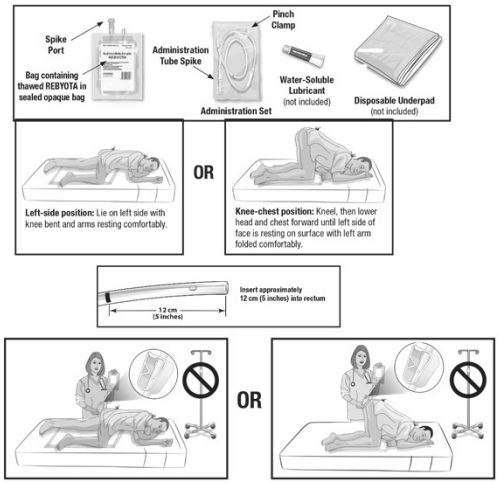
Colonoscopy Administration

Drugs@FDA: FDA-Approved Drugs. Accessed November 27, 2023. https://www.fda.gov/media/163587/download?attachment.



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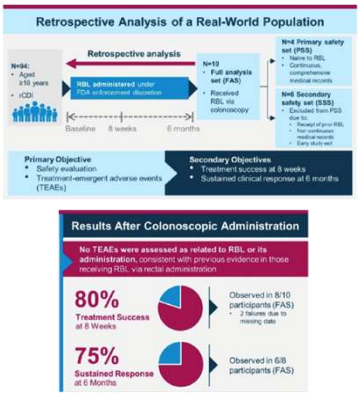

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Fecal Microbiota Spores, live-brpk (VOWST): Indications for Use

- Narrow consortium composed of live purified *Firmicutes* spores
- FDA indication: Prevention of recurrent CDI in individuals ≥ 18 years of age following antibiotic treatment for recurrent CDI
- Dosage: 4 capsules taken orally once daily for 3 consecutive days
- Antibiotic treatment should be completed 2 to 4 days before initiating therapy

Drugs@FDA: FDA-Approved Drugs. Accessed November 27, 2023. https://www.fda.gov/media/167579/download

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Fecal Microbiota Spores, live-brpk Capsules: Safety

- Contraindications: None
- Potential to cause adverse reactions due to food allergens is unknown

Adverse Reaction	FMS, Live-brpk N = 90 (%)	Placebo N = 92 (%)
Abdominal distention*	31	29
Fatigue*	22	22
Constipation*	14	11
Chills*	11	8
Diarrhea†	10	4

*Solicited adverse events: AEs that were recorded by participants in a diary for 7 days after completion of the 3-day regimen of live-brpk or placebo. Participants were monitored for unsolicited events by queries during visits for a period of 8 weeks after the first dose of study drug. †Unsolicited Investigator AEs. FDA-Approved Drugs. Accessed November 22, 2024. https://www.fda.gov/media/162570/download

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Fecal microbiota, live-jslm

- Single-dose rectal installation
- In-office administration by anyone trained in its administration (depending on state regulations)
- Refrigerate for ≥ 24 h to 5 d
  - Thaw at room temperature 1 h before patient arrives
- Administer 24 to 72 h after completion of SOC antibiotics for recurrent CDI

Fecal microbiota spores, live-brpk

- 4 capsules taken orally once daily for 3 consecutive days
- Taken 2 to 4 days after completion of SOC antibiotics for recurrent CDI
- Drink 296 mL (10 oz) of magnesium citrate on day before and ≥ 8 h before taking first dose of FMS, live-brpk capsules

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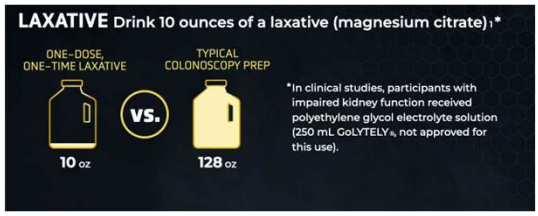

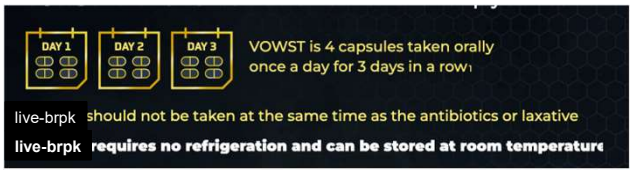

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How do you choose what is appropriate for your patient

Upper vs lower administration?

- Ability to swallow capsules
- Contraindication to a colonoscopy, or rectal administration
- Need for a mucosal assessment

Location of patient

- Is the patient traveling very far for this
  - FMS will get shipped to the patient's house for administration
- FML and non-FDA approved FMT is done in the office
  - Is this an inpatient

Speed

- How fast do you need to get product?
- Insurance approval can often takes weeks
- Non-FDA approved FMT readily available

Approval Status

- How important is FDA approval to the patient?

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FMT for rCDI in IBD patients

Does it works as well for rCDI in IBD patient as in non-IBD?

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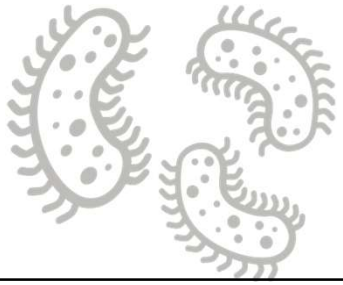
The Scope of the Problem in IBD

- Prevalence is 2.5-8 fold higher then non-IBD patients
- 10% lifetime risk
- 4.5-fold higher risk of recurrence
- Patients with colitis are at the highest risk.



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Sequela Of CDI in IBD

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- Exacerbations of IBD
- Increased hospitalizations
- Increased LOS
- Escalation in IBD therapy
- Colectomy
- Higher mortality rates
- Failure of CDI medical therapy
- More CDI recurrences
- Increased health care costs.

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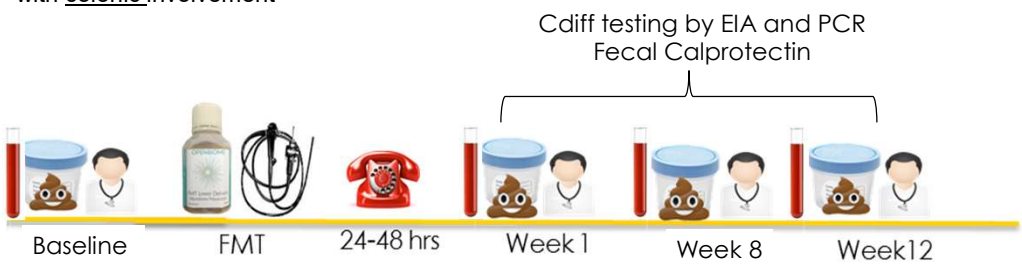
Open label trial at 4 sites around the US

Key inclusion criteria:
Confirmed recurrent CDI
(2 episodes or more)
Confirmed diagnosis of IBD
with colonic involvement



Stool Tests:
-Microbiome analysis (16S)
-Fecal Calprotectin
-Metabolomic Profiling
-Banked Samples

Blood Tests:
-CBC, CRP, albumin, Cr
-Metabolomic Profiling (LCMS)
-Banked Samples

Clinical Data:
-Diarrheal Symptoms
-IBD Activity Scores
-Changes in IBD therapy
-Need for surgery

Allegretti et al, Gastro 2019

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Outcomes

Primary Clinical Outcome:

- **Efficacy of FMT** for the treatment of recurrent CDI in patients with IBD at 8 weeks

Primary Outcome				
Symptoms	**Step 1: PCR**	**Step 2: EIA**	**FMT Failure**	**Treatment Course**
Diarrhea	+	+	Yes	Anti-CDI Abx
Secondary Outcomes				
Symptoms	**Step 1: PCR**	**Step 2: EIA**	**FMT Failure**	**Treatment Course**
Diarrhea	+	-	No	Clinical discretion
No Diarrhea	+	-	No	Asymptomatic Carriage, No tx needed
No Diarrhea	+	+	No	Clinical discretion
No Diarrhea	-	-	No	No treatment
Diarrhea	-	-	No	No CDI, evaluate for other cause and treat accordingly

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Secondary Clinical Outcomes:

- **IBD clinical outcomes** following FMT at week 12
  - ***De Novo* IBD flare** defined as a Mayo or HBI score ≥4 at week 12 in the absence of CDI if Mayo or HBI were 2 or less at baseline
  - **Worsening IBD** pertains to those with baseline active disease (Mayo or HBI score ≥ 4) and was defined as an increase in either HBI or Mayo by 2 or more at week 12
  - **IBD improvement** was defined as a decrease in Mayo or HBI score by 2 or more at week 12 compared to baseline.
- **AEs** related or possibly related to FMT
- **Microbial** and **metabolic** changes post-FMT

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CDI Outcomes
4/49 (8%) experienced CDI recurrence

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Subject ID	Week 1		Week 8		Week 12	
	Toxin	PCR	Toxin	PCR	Toxin	PCR
101	neg	pos	neg	pos	neg	pos
102	neg	neg	neg	neg	neg	neg
103	neg	neg	neg	neg	neg	neg
104	neg	neg	neg	neg	neg	neg
105	neg	neg	neg	neg	neg	neg
106	pos	pos				
106B	neg	neg	neg	neg	neg	neg
107	neg	pos	neg	pos	neg	neg
108	neg	neg	neg	neg	neg	neg
109	neg	neg	neg	neg	neg	Neg
110	pos	pos				
110B	neg	neg	neg	neg	neg	Neg
111	neg	neg	neg	pos	neg	pos
112	neg	neg	neg	neg		

Subject ID	Week 1		Week 8		Week 12	
	Toxin	PCR	Toxin	PCR	Toxin	PCR
301	neg	neg	neg	neg	neg	neg
302	pos	pos				
302B	neg	neg	neg	neg	neg	neg
303	neg	neg	neg	pos	neg	neg
304	neg	neg	neg	neg	neg	neg
305	neg	neg	neg	neg	neg	neg
306	neg	neg	neg	neg	neg	neg
307	neg	pos	neg	neg	neg	pos
308	neg	neg	neg	neg	neg	neg
309	neg	neg	neg	neg	neg	neg
310	neg	neg	neg	neg	neg	neg
311	neg	neg	n/a	n/a	n/a	n/a

Subject ID	Week 1		Week 8		Week 12	
	Toxin	PCR	Toxin	PCR	Toxin	PCR
201	neg	pos				
202	neg	neg	neg	neg	neg	neg
203	neg	neg	neg	neg	neg	neg
204	neg	neg	neg	neg	neg	neg
205	neg	neg	neg	neg	neg	neg
206	neg	neg	neg	neg	neg	neg
207	neg	neg	neg	neg	neg	neg
208	neg	pos	neg	neg	neg	neg
209	neg	Pos				
209B	neg	neg	neg	neg	neg	neg
210	neg	neg	neg	neg	neg	neg
211	neg	neg	neg	neg	neg	neg
212	pos	pos				
212B	neg	pos	neg	neg	neg	neg
213	neg	neg	neg	neg	neg	neg
214						
215	neg	neg	neg	pos	neg	Pos
216	neg	neg	neg	neg	neg	neg
217	neg	neg	neg	neg	neg	neg
218	neg	neg	neg	neg		

Subject ID	Week 1		Week 8		Week 12	
	Toxin	PCR	Toxin	PCR	Toxin	PCR
401	neg	neg			neg	pos
402	neg	neg			neg	neg
403	neg	neg	neg	neg	neg	neg
404	neg	neg	neg	neg	neg	neg
405	neg	neg	neg	neg	neg	neg
406	neg	neg	neg	neg	neg	neg
407	neg	neg				
407B	neg	neg	neg	neg	neg	neg
408	neg	neg	neg	neg	neg	neg
408B	neg	neg	neg	neg	neg	neg
409	neg	neg	neg	neg	neg	neg

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IBD Outcomes

- CD cohort:
  - 73.3% (11/15) had IBD improvement
  - 26.6% (4) had no change in clinical scores.
- UC cohort
  - 62% (22/34) had IBD improvement
  - 29.4% (11/34) had no change
  - 4% (1/34) experienced a *de novo* flare.

Allegretti et al. IBDJ 2020

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Steroid Use Post-FMT

- CD cohort, among those who improved
  - 54.5% (6/11) were able to taper off steroids by week 12.
  - 3 (27%) were safely started on a biologic after FMT.
- UC cohort among those who improved
  - 27.2% (6/22) were able to taper off steroids
  - 18% remained on a stable prednisone dose
  - 3 patients were safely started on biologics post-FMT

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Microbiome Analysis

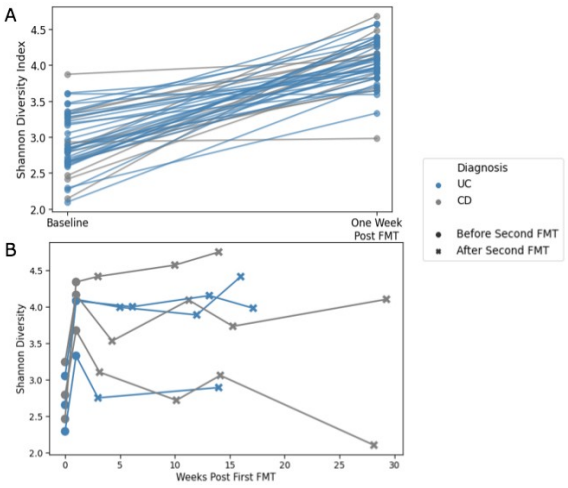

Figure 1: Alpha diversity after (A) first FMT and (B) in patients receiving second FMT. Increases were significant after first FMT for all patients pooled (p<1e-17) and when stratified by IBD subtype (UC p<1e-13, CD p<1e-5).

Allegretti et al. IBDJ 2020

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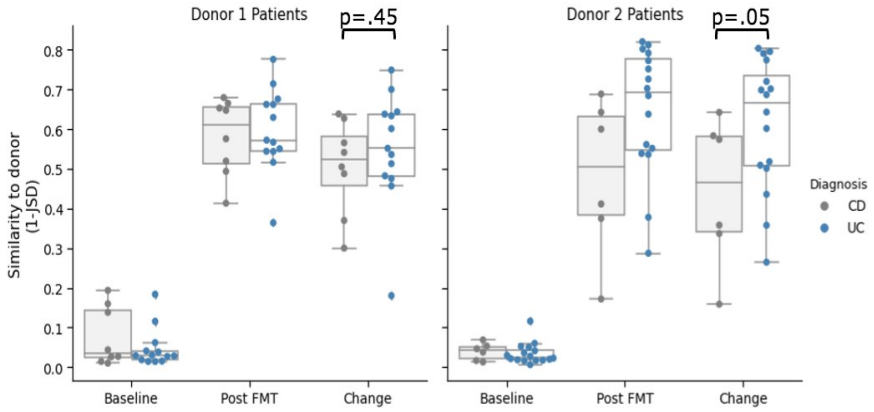

Figure 2: Similarity to the donor post-FMT measured by Jensen-Shannon Divergence, stratified by donor and IBD subtype. Data from two patients receiving other donors not shown. Change was measured as difference in similarity post-FMT vs baseline and was significantly different between UC and CD patients (all patients, p=0.040; Donor 1 and 2 only, p=0.038, two-sided t-test). Differences between the subtypes were largest among recipients of Donor 2.

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- This is the first prospective trial to assess the effect of FMT in patients with IBD-CDI.
- FMT for the treatment of recurrent CDI in patients with IBD was safer and better tolerated previously reported
- We did not appreciate IBD worsening
  - only one patient met the definition of a flare *de novo*,
  - many patients have active disease prior to FMT and will continue to have active disease post FMT.
  - Appropriate treatment with biologics post-FMT after eradication of CDI was safe and led to overall IBD improvement.

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FMT FOR IBD

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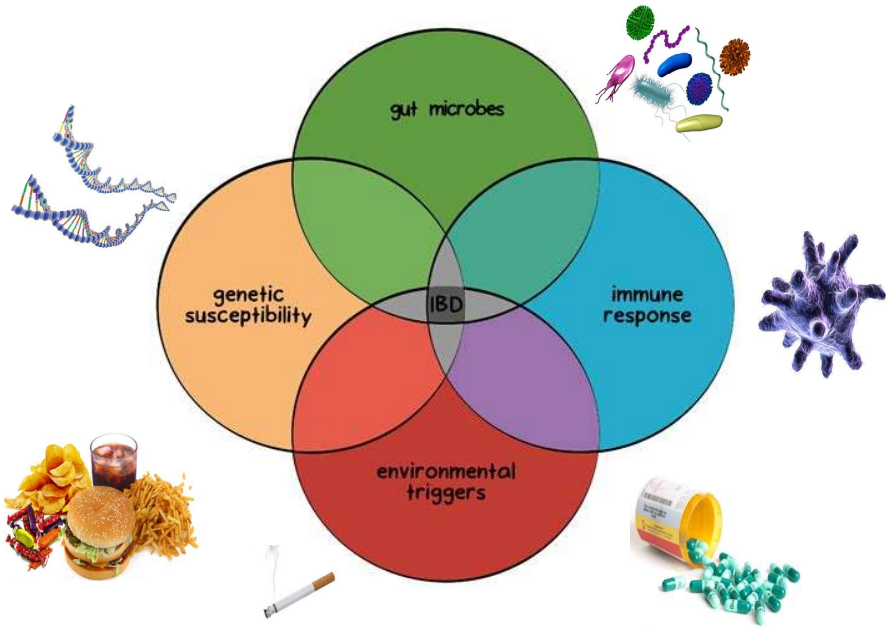
Pathogenesis of IBD



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Therapeutic Manipulations of the Microbiome in IBD

- **CD: Role seems clear**
  - Diversion of fecal stream is effective
  - Antibiotics are beneficial in subsets of patients with CD
  - Role for TPN/bowel rest
- **UC: Role less clear**
  - Diversion not effective
  - No clear role for antibiotics or TPN/bowel rest
  - Probiotics VSL #3 and *Escherichia coli* Nissle 1917 effective

CD = Crohn's disease; UC = ulcerative colitis; TPN = total parenteral nutrition.
Triantafillidis JK, et al. *Scand J Gastroenterol.* 2014;49:3-14. Kruis W, et al. *Gut.* 2004;53:1617-1623.

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Microbiome Therapeutics in IBD: Why could they work?

- Many identified IBD susceptibility genes are involved in innate and adaptive immune responses to microbes
- Transferring the gut microbiota from humans with IBD alters the balance of Th17 and T regs, and exacerbates colitis in mice
- Changes in the gut microbiome precede an IBD diagnosis
- Clinical efficacy of fecal diversion, antibiotics in Crohn's and pouchitis

Jostins et al. Nature. 2012; 491:119-124.
Raygoza et al. Gastroenterology. 2023; 165:670-681.
Britton, et al. Immunity. 2019; 50:212-224.e4.

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Conventional prebiotics and Probiotics in IBD

- **Prebiotic: Fructo-oligosaccharides (FOS)**
  - 10 patients with CD dosed with FOS for a 3-week period had a significant reduction in the HBI, increase in bifidobacteria, and modified mucosal dendritic cell function.
- **Prebiotic: Sodium-butyrate (BLM)**
  - 19 patients with CD and 30 with UC were randomized to BLM or placebo for 2 months. BLM improved QoL and increased SCFA producing bacteria in UC patients (Lachnospiraceae spp.) and the butyrogenic colonic bacteria in CD patients (Butyricicoccus).
- **Probiotics:**
  - Meta-analysis: 2- to 3-strain probiotic blends (**Lactobacillus, Bifidobacterium** strains) showed benefit for reducing UC activity
  - **VSL#3** (8 strains of *Streptococcus*, *Bifidobacterium*, *Lactobacillus*, bulgaricus) showed efficacy in inducing remission of UC compared with placebo
  - Multistrain probiotics, including **VSL#3**, prevent recurrent pouchitis

Lindsay et al. Gut 2006 Mar;55(3):348-55. Facchin et al. Neurogastroenterol Motil. 2020 Oct;32(10):e13914. Derwa et al. Aliment Pharmacol Ther. 2017; 46:389-400. Zhang et al. Eur J Nutr. 2021; 60:2855-2875. Barnes et al. Gastro. 2024; 166:59-85.

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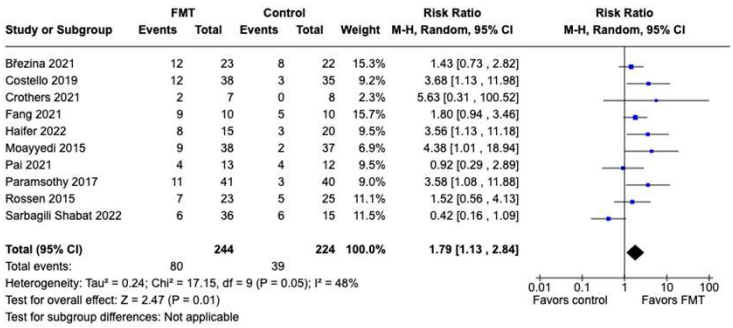
Unapproved FMT in UC

- 10 studies, 468 participants, reported induction of clinical remission in UC at longest follow up (range 6 to 12 weeks)
- 5 studies reported on induction of endoscopic remission in UC at longest follow-up (range 8 to 12 weeks)



The NNT to induce clinical remission was 7

Imdad et al. Cochrane Database Syst Rev. 2023 Apr 25;4(4):CD012774.

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Unapproved FMT in CD

- RCT of 17 patients with active CD receiving corticosteroids randomized to FMT or a sham FMT
  - At week 10, steroid-free clinical remission rates were numerically higher in the FMT group

Sokol et al. Microbiome. 2020; 8:12

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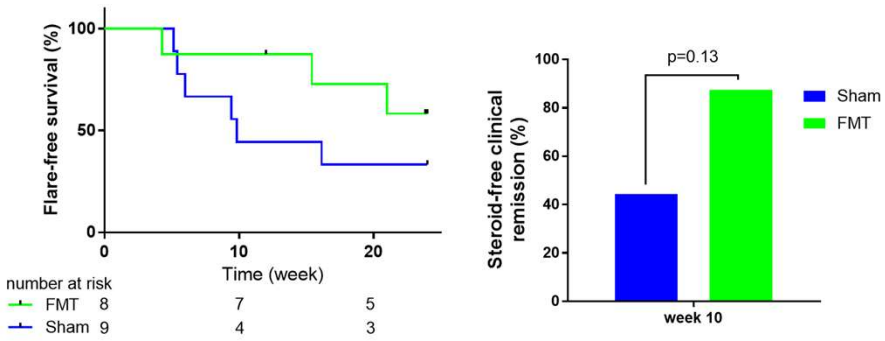
IMPACT-Crohn's Study



Sokol et al. Microbiome 2020

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RCTs FMT for UC: What have we learned?

- Factors associated with response
  - Short disease duration (≤ 1 year)
  - Mild mucosal inflammation
- The more, the better…not true
  - High-intensity treatment (40 X 37.5g!) not superior compared low intensity treatment (weekly 8g stool x6 or 100g x3 within 1 week)
- Short therapy duration (1 week) may be sufficient for induction of remission

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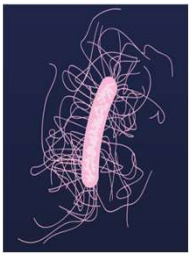
Donor characteristics do not affect outcome of FMT for *C. difficile*- *what about IBD and the "super donor"*

In Non-IBD Patients:

- 59 donors, 1,413 patient with CDI, 85% cure rate
  - Stool consistency (BSS 3-5)
  - Diet (calorie, fat, fiber, carbohydrate intake)
  - Microbial profile (diversity or specific bacterial taxa)
  - Metabolome (butyrate, acetate, SCFA level)
- Stool from any healthy person works for *C. diff*



It might be different for IBD…

- "super donor" (rich in Ruminococcus and Lachnospiraceae)

Budree DDW 2017 Sa 1793, Su 2018, Su 2017

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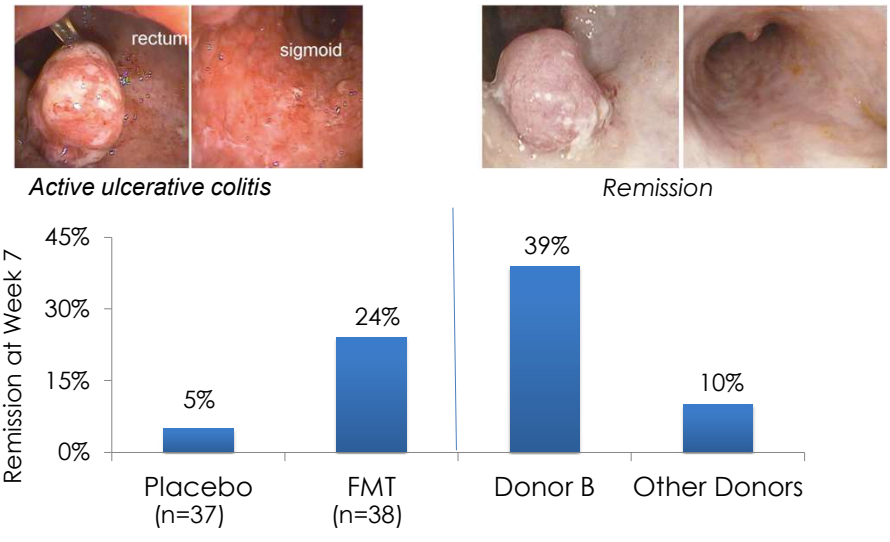
Unlike recurrent *C. difficile* – the source matters in ulcerative colitis



Moayyedi et al Gastroenterology 2015

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RCTs FMT for UC: Safety Signals

- Safety
  - No short-term safety signals
  - SAEs: 3/140 in the FMT arm (1 colectomy) and 4/137 in the placebo arm (worsening colitis)
  - 3 cases of subsequent small bowel Crohn's
  - 2 cases of C. diff
  - 79% (FMT) and 75% (placebo) reported mild, transient gastrointestinal symptoms

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Questions remaining…

- Optimal protocol or technique?
  - Upper vs. lower delivery
  - Aerobic vs. anaerobic preparation
- Pooled or single donor?
  - Pooling stool – greater chance to transfer important elements needed for response but more complicated logistics
  - "Super donor"?
- Durability of treatment results?
- Interval dosing to maintain remission?
- Long-term safety?

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Emerging Microbiome Therapeutics in IBD

What is the evidence?

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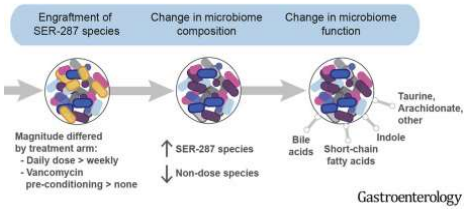
LBPs in IBD: PBO-controlled RCTs

- Phase 1 trial of **SER-287** (Firmicutes spores) following vancomycin preconditioning in mild-to-moderate UC
- Ongoing phase 2 trial of **VE202** (consortia of spore-forming Clostridia) for biologic-naïve mild-to-moderate UC (NCT05370885)

Phase 1b trial: Daily dosing had greatest engraftment and clinical remission (40% SER-287 vs 0% placebo)



Henn et al. Gastro 2021 Jan;160(1):115-127.e30.

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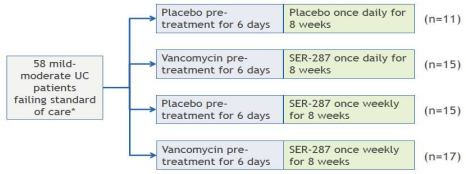
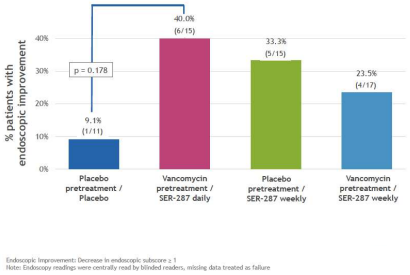
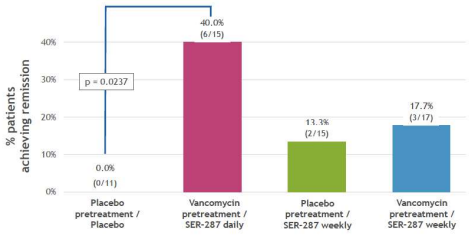
A Phase 1b Safety Study of SER-287, a Spore-Based Microbiome Therapeutic, for Active Mild to Moderate Ulcerative Colitis

SER-287 (4 capsules containing 1 × 10^7 colony-forming units) once daily or once weekly or matching placebo once daily for 8 weeks.







Endoscopic Improvement: Decrease in endoscopic subscore ≥ 1
Note: Endoscopy readings were centrally read by blinded readers, missing data treated as failure

Dose dependent response rate best with daily dosing of SER-287. Compelling data in line with efficacy seen with SOC biologics. Engraftment data and clinical outcomes supports sustained effect in long term follow up, no flares across responders on 26 week follow up.

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Phase 2b ECO-RESET evaluated SER-287

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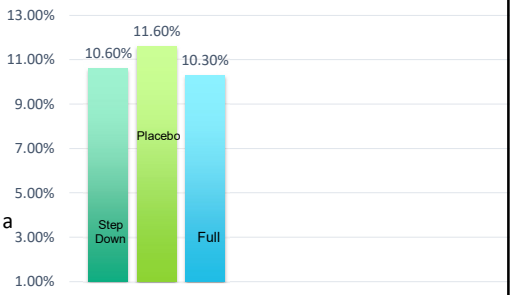
- randomized, placebo controlled, double blind, parallel group multicenter study
- mild-to-moderate ulcerative colitis (UC).
- two SER-287 cohorts (randomized 1:1:1).
  - full induction dose
  - step-down induction dose
  - placebo Clinical remission was analyzed and defined by a 3-component modified Mayo Score.
- No meaningful clinical differences were observed
- **The study did not meet its primary endpoint of improving clinical remission rates compared to placebo at 10 weeks (following vancomycin pre-conditioning)**



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- In Conclusion:
  - FMT was an effective and safe therapy for patients with IBD and recurrent CDI and was showing promise as a therapy for UC though its role in CD is evolving
  - Approved donor derived microbiome therapeutics are working well for patients with rCDI with and without IBD
  - Novel therapies for the treatment of IBD are being explored

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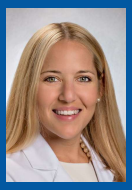
Questions



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