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SYMPOSIUM

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Fecal Microbiota Transplantation Update

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Background

Fecal Microbiota Transplant

- Infusion of healthy donor stool into diseased recipient
- 4th century in China, Ge Hong used fecal suspension for treatment of severe diarrhea.
- 17th century, Italian anatomist Fabricius Aquapendente described use of fecal transplantation for rumination disorders in COWS
- Eiseman 1958

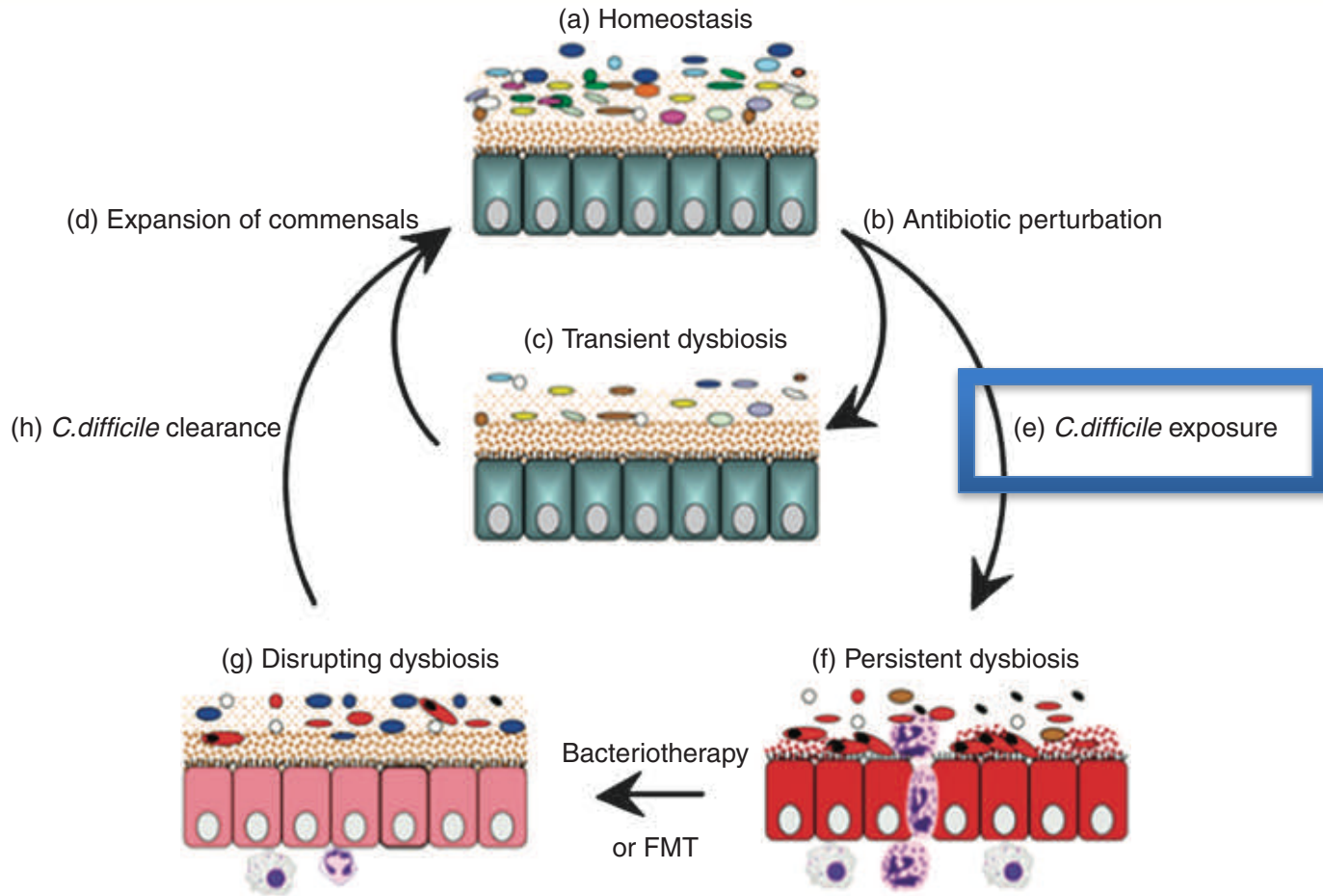
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"YES I'M AFRAID THAT ROOM IS BUBBED, BUT DON'T WORRY, IT'S JUST CLOSTRIDIUM DIFFICILE."

Rationale for FMT in *C. diff*



Early studies on FMT for Recurrent *Clostridium Difficile* Infection (rCDI)

- 2011 Systematic Review in CID
 - 27 titles: 2/3 case series, remainder case reports
 - 92% resolution; 89% after 1 treatment
- 2012 Retrospective Multicenter study published in Gastroenterology
 - 70 patients, 5 different hospitals in Finland
 - 34/34 non-027 CDI and 32/36 (89%) 027 CDI had resolution of symptoms at 12 weeks
- 2012 Multicenter US study, 77 patients
 - 91% had resolution of diarrhea within 90 days

Standardized Frozen Preparation for Transplantation of Fecal Microbiota for Recurrent *Clostridium difficile* Infection

Matthew J. Hamilton, PhD¹, Alexa R. Weingarden¹, Michael J. Sadowsky, PhD^{1,3} and Alexander Khoruts, MD^{2,3}

- 43 patients with recurrent CDI, treated with colonoscopic FMT
- At least 2 recurrences
- Overall 86% cure rate as evidenced by resolution of symptoms AND negative PCR at 2 months

Donor Material	# Relapses	Success Rate
Individual (n=10)	6.2	7/10 (70%)
Standard fresh (n=12)	6.4	11/12 (92%)
Standard frozen (n=21)	5.2	19/21 (90%)
Overall (n=43)	5.9	37/43 (86%)

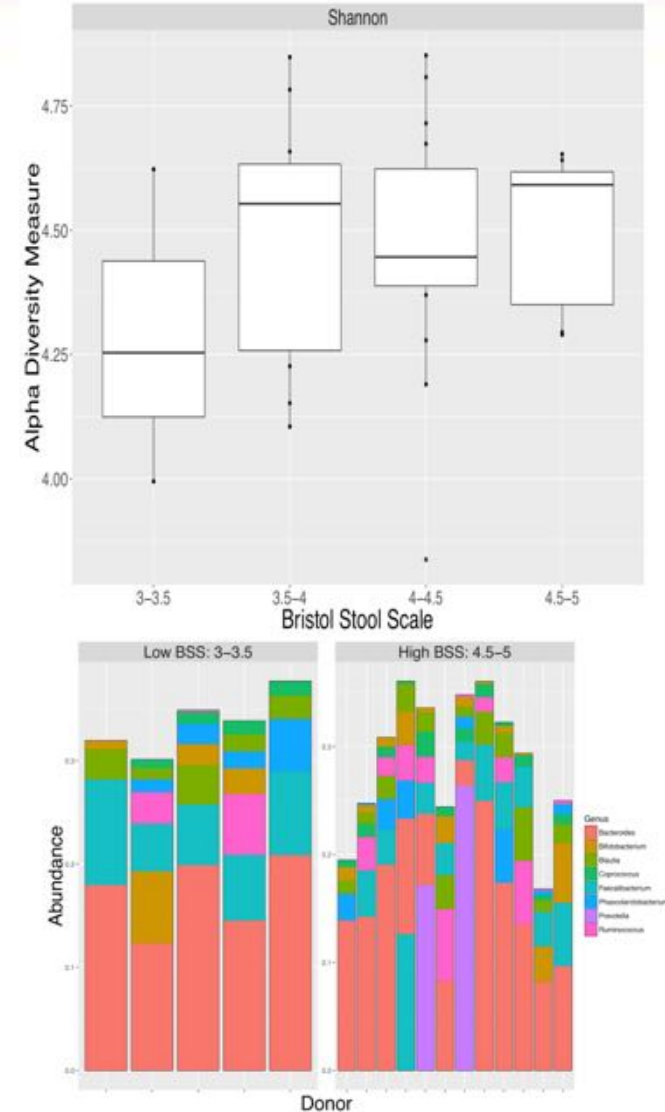
Randomized Controlled Trials Evaluating FMT for rCDI

Study	# patients	Comparator group	Route of administration	Result
Van Nood NEJM 2013	43	17 FMT 13 vanco 13 vanco + bowel lavage	Nasoduodenal	81% cure after 1 st infusion 93.8% cure after 2 nd infusion
Cammarota APT 2015	39	20 FMT 19 vancomycin	Colonoscopy	18/20 (90%) resolution in FMT group v. 5/19 (26%) in vanco group
Kelly Annals 2016	46	22 donor FMT 24 autologous FMT	Colonoscopy	91% v. 62.5%
Hota CID 2017	30	16 FMT 12 vancomycin	Enema	56% v. 42%

Updates from DDW

What makes a good donor?

- To evaluate whether patterns in stool consistency impact donor microbial profile and clinical outcomes.
 - 59 donors
 - 1413 CDI patients treated (mean cure 84.9%)
- Donor-specific clinical cure rate was extracted from physician reported outcomes.
- Across normal BSS (3-5), donor stool consistency is not associated with clinical cure rate.
- A higher BSS trends towards an increased microbial diversity; however, this relationship was not statistically significant.



The Association of Stool Donor Diet on Microbial Profile and Clinical Outcomes in FMT for rCDI

Dietary data were collected using the Willett Harvard Food Frequency Questionnaires (FFQ) to provide quantitative measures of long-term trends in dietary components

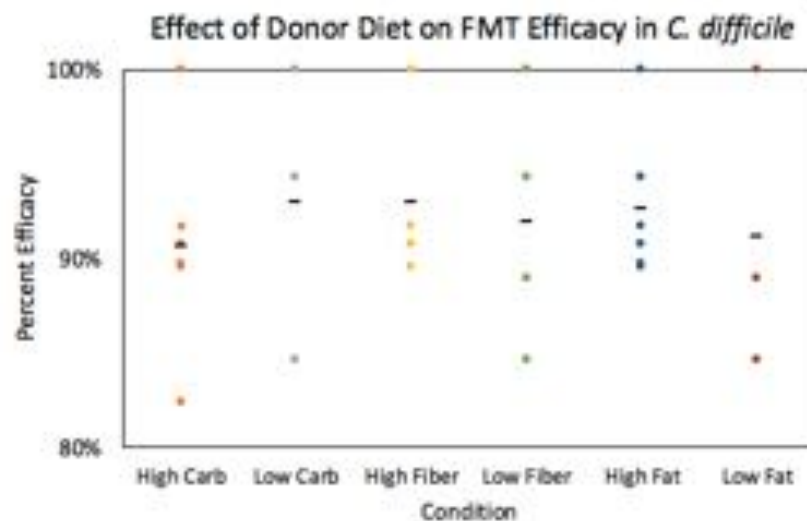
Donor specific clinical cure rate was determined using physician reported cure for each treatment at standard follow-up.

-35 donors

-353 CDI patients (89% cure)

Consumption of fiber, fat, calories or carbohydrate did not significantly impact the microbial alpha diversity of donors

Variations in diet was not associated with clinical cure rate in CDI.



FMT for rCDI and BMI

- Retrospective chart analysis of patients with rCDI treated with FMT between 2014 and 2016
- Mean BMI pre-FMT= 28.9, 1-3 months post-FMT= 27.4; mean change -1.48 (p=0.025)
- 12 months post-FMT, if BMI>25 had mean decrease 3.4 (p=0.05)
- Two patients with BMI<17 increased post-FMT

Patient Demographics

Variables	No.(%) of Patients
Total number of Patients	15
Mean Age	62
Gender (Male/Female)	6(40)/9(60)

Pre FMT (BMI)

>30	5(33)
>25	4(26)
<25	6(40)

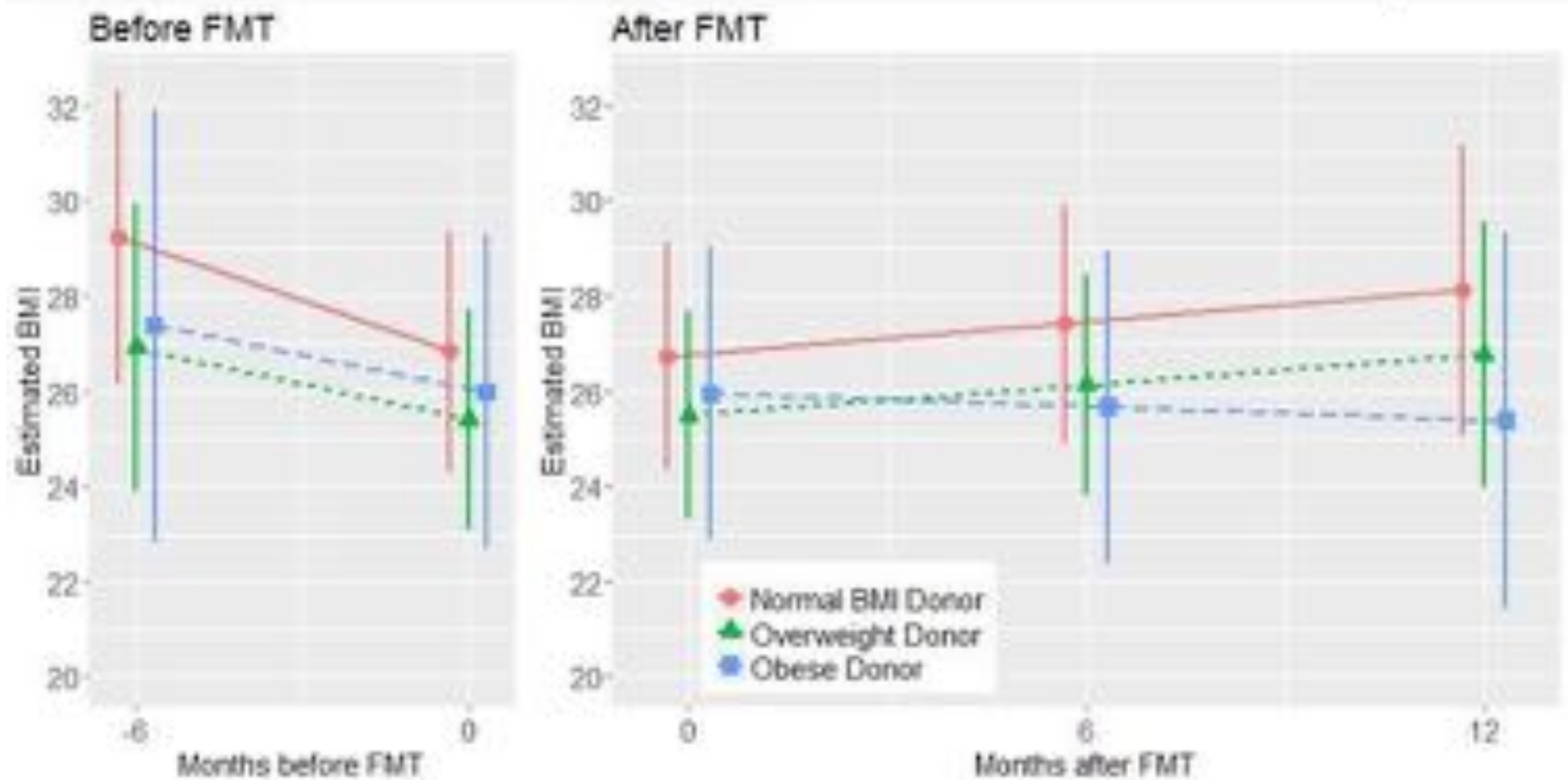
1-3 Months Post FMT

>30	4(26)
>25	3(21)
<25	8(53)

Does FMT from an Obese Donor Lead to Weight Gain? A Case Series of 70 Recipients

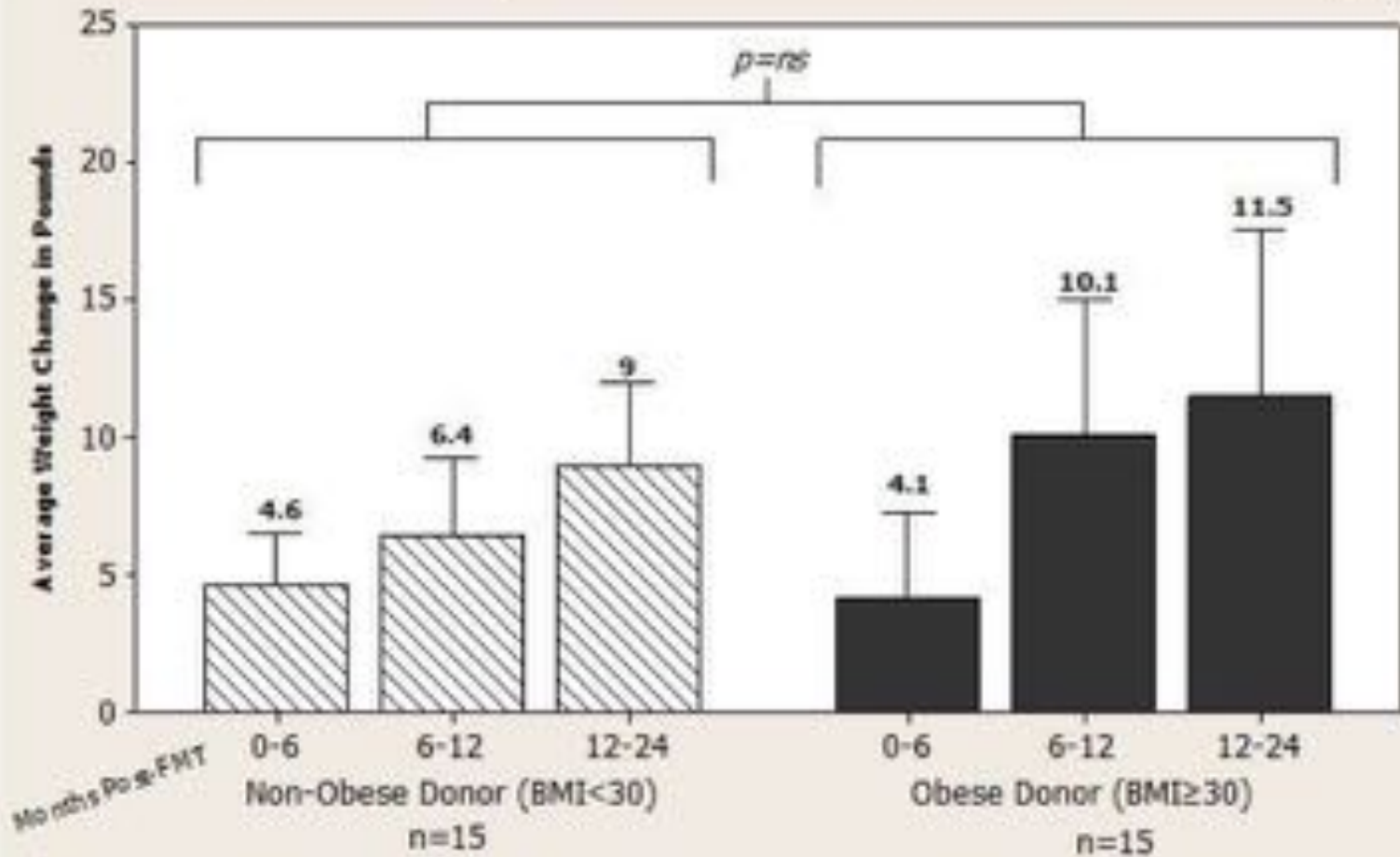
- Retrospective chart review of rCDI who underwent FMT at 2 academic centers were reviewed.
- Medically assessed BMI at 6 months pre-FMT and up to 12 months post-FMT were collected.
- 70 patients were included; 39 different donors
- Overall, BMI change post-FMT were not different among the 3 groups

FMT for rCDI and BMI

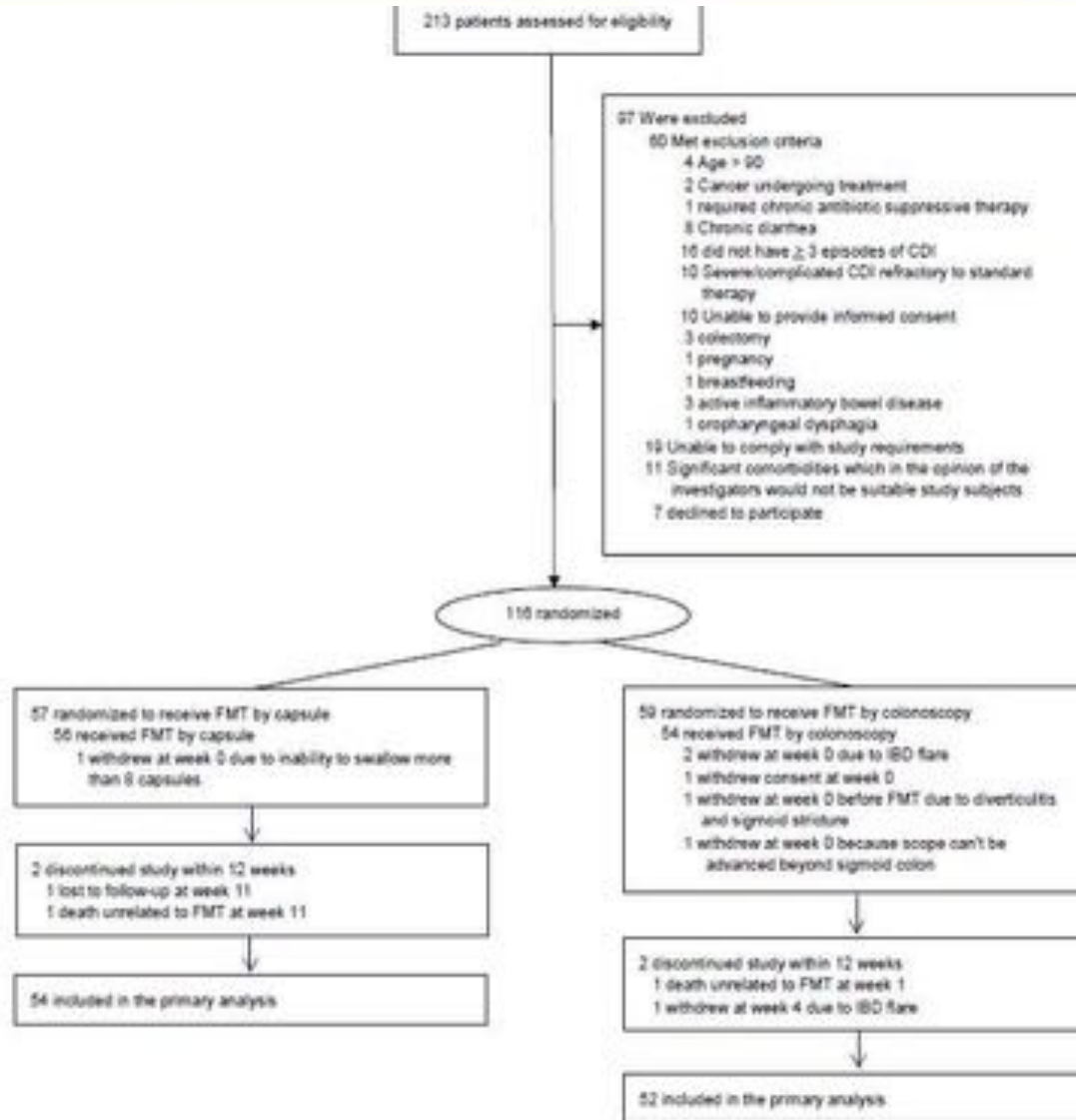


Obese Stool Donors In FMT: Not Associated with Recipient Weight Gain

No Difference in Mean Weight Gain over Time Based on Stool Donor BMI Category



Prospective, Non-Inferiority, Multi-Center, RCT Comparing Colonoscopy vs. Oral Capsule for rCDI



FMT Capsule Results

Outcome	Capsule	Colonoscopy
Number of patients	57	59
CDI Cure	96.3%	96.2%
Major AE, #	1	1
Minor AE, %	5.4%	12.5%
“Not at all unpleasant”	67%	44%

Successful Resolution of rCDI Using Freeze-Dried, Encapsulated Fecal Microbiota

- Lyophilization protocol that preserved the viability of bacteria across the taxonomic spectrum found in fecal microbiota.
- Treated a cohort of rCDI patients with a range of doses of encapsulated microbiota and analyzed the associated changes in the fecal microbiome of the recipients.
- Administered to 49 patients; 88% (43/49) achieved clinical success.
- Analysis of fecal microbiome demonstrated near normalization of fecal microbial community one month post-FMT.
- Simplest protocol using the lowest dose (2-3 capsules) without any colon purgative performed equally well.

Should We Recommend Anti-Clostridium Difficile Antibiotic or Probiotic Prophylaxis?: Risk of CDI with Systemic Antimicrobial Therapy Following Successful FMT

- Multinational, retrospective study at 3 FMT referral centers
- 426 patients included; mean follow-up 73 +/- 52 weeks
- 28% used a non-CDI abx during follow-up period
- Post-FMT CDI reinfection rate was 10.3%.
 - Those who used non-CDI antibiotics had a rate of 18.3% compared to 7.2% (22/306) among those who did not use non-CDI antibiotics.
- Highest reinfection rate fluoroquinolones>cephalosporins>amoxicillin
- Among patients who received non-CDI antibiotics, the concomitant prophylactic antibiotics group had higher CDI rates compared to no prophylaxis 27.8% v. 14.3% p=0.12
- Patients who used prophylactic probiotics also had a higher CDI rate compared to non-users 27.5% v. 13.8% p=0.08
- Patients who used dual prophylaxis (abx + probiotics) had a higher CDI rate compared to non-users (46.7% v. 14.3% p=0.007)
- Prophylactic anti-CDI antibiotics or probiotics in these patients who were re-exposed to antibiotics post-FMT did not decrease the risk of CDI

FMT for rCDI in IBD

Institution	# patients	Eradication of CDI	Flare post-FMT	Late relapse of CDI
University of Minnesota	56	86%	50% of UC, No significant increase flare in CD	17%
Mt. Sinai	38	76%	31%	24%

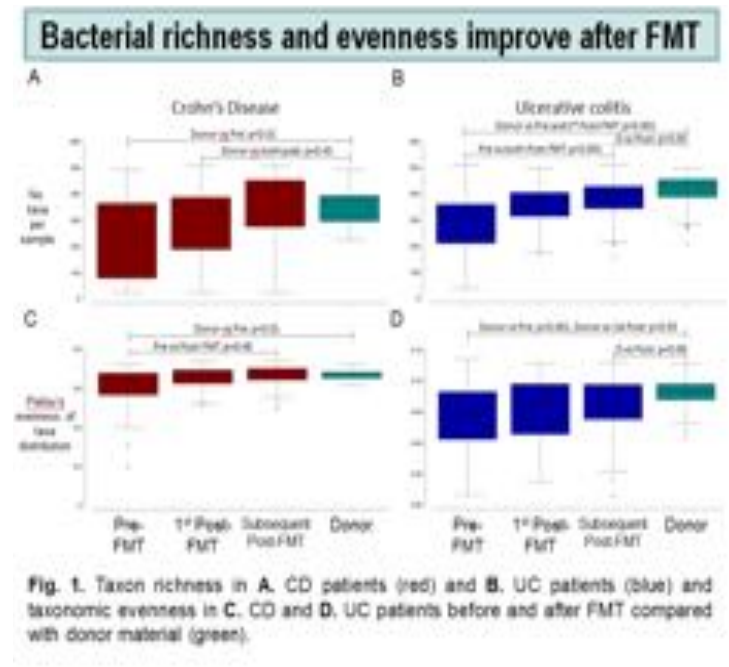
FMT for Other Indications

FMT in Ulcerative Colitis

Author	# patients	Mode and frequency of delivery	Primary Outcome	Adverse Events
Rossen Gastro 2015	37	Nasoduodenal x 2	30% v. 20% clinical remission (SCAI \leq 2 + \geq 1 decrease in Mayo endo)	4 (2 in FMT group but not felt to be related to FMT)
Moayyedi Gastro 2015	70	Enema q week x 6 weeks	24% v. 5% remission (Mayo score \leq 2, endo=0)	No difference in adverse events
Paramsothy Lancet 2017	85	Enema q day (M-F) x 8 weeks	27% v. 8% steroid-free clinical remission (Mayo \leq 2, all subscores \leq 1, endo \geq 1 point)	3 (2 FMT, 1 required colectomy)

FMT in IBD

- Open Label prospective parallel study
- FMT administered by colonoscopy
- *All Patients Combined*
 - Abdominal pain improved post-FMT (2.7 to 1.9 on scale of 10, $p=0.06$)
 - Bowel frequency declined from 5.8 BM/day to 4.9 BM/day, $p=0.05$
 - No significant change in bleeding ($p=0.38$), urgency ($p=0.48$), CRP ($p=0.49$) or fecal calprotectin ($p=0.55$)
- *Ulcerative Colitis Arm*
 - 28% had improvement in Mayo score ≥ 3 and 68% had some decrease in Mayo score (5.5 to 4.5, $p=0.05$)
 - BM frequency decreased (6.2 BM/day to 4.6 BM/day, $p=0.01$) Abdominal pain improved (3.3 to 2.3 on scale of 10, $p=0.05$)
 - No significant improvement in fecal calprotectin, slight decrease in CRP (6.5 to 4.3, $p=0.04$)
- *Crohn's Disease Arm*
 - No meaningful change in all parameters examined



FMT in Pouchitis

- 15 pouchitis patients received FMT; follow-up PDAI score available for 10 patients.
- No adverse events were reported post-FMT
- No escalation of therapy reported post-FMT
- 50% had decrease of PDAI score ≥ 3 ; average PDAI pre FMT=8.8, post-FMT= 6.3 (mean decrease 2.5, 95% CI 1.4-3.6, $p=0.0002$)
- Abdominal pain decreased post-FMT (decrease of 1.3 on scale of 10, $p=0.03$)
- Average frequency decreased post-FMT (9.1 BM/day to 7.6 BM/day, $p=0.05$)
- Bleeding, urgency, fecal calprotectin and CRP did not significantly change post-FMT.

FMT in IBS: A Randomized Placebo-Controlled Trial

- Double-blinded placebo-controlled trial
- 16 IBS patients
 - 8 FMT
 - 8 placebo (autologous FMT)
- Outcome: Symptoms and Quality of Life
 - Symptoms: IBS-SSS, GSRS-IBS
 - QoL: IBS-QoL, SF-36
- All parameters significantly improved from baseline, but no significant difference between intervention groups.

Summary

- FMT is effective for rCDI
 - No stool consistency or food pattern in donor is predictive of response
 - Obesity does not seem to be significant risk of FMT
- Patients with IBD with rCDI may flare post-FMT
- Capsules are on the horizon for FMT
- Other indications such as IBS, IBD still require further studies but look promising for UC

Questions