All POOPed out: fecal microbiota transplant in *C. difficile*

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Talk outline

- History of trials of FMT
- Methods and Regulation
- Evolution of understanding of the microbiome

Burden and risks of recurrent disease

- 20-30% of patients with primary CDI develop recurrent CDI within 2 weeks of completion of therapy.

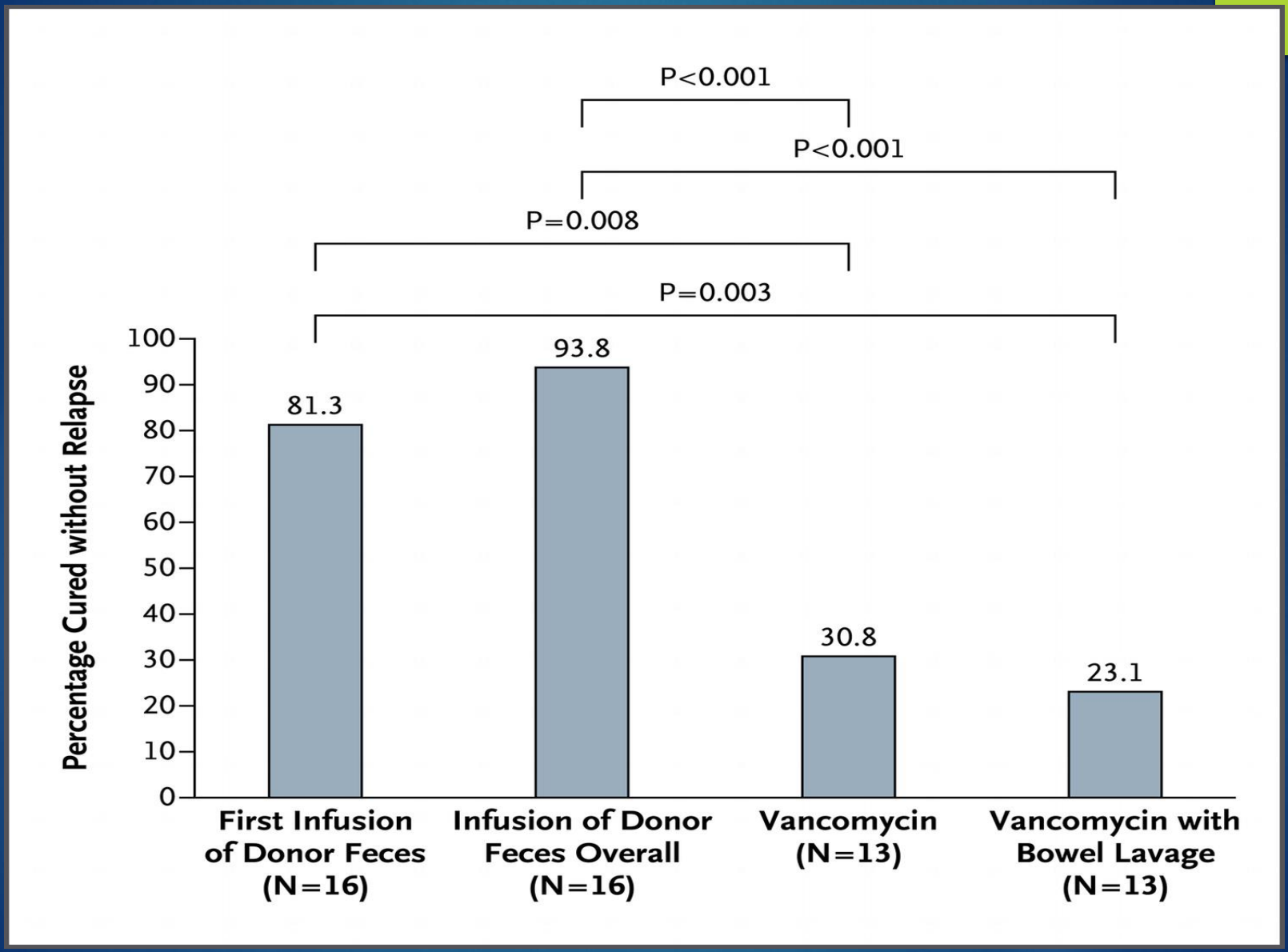
- Independent risk factors for recurrent *C. difficile*:
  - Age ≥65 years RR 1.63; 95% CI 1.24-2.14
  - additional antibiotics during follow-up RR 1.76; 95% CI, 1.52-2.05
  - use of proton-pump inhibitors RR, 1.58; 95% CI, 1.13-2.21;
  - renal insufficiency RR, 1.59; 95% CI, 1.14-2.23; P=.007.
  - patients previously on fluoroquinolones RR, 1.42; 95% CI, 1.28-1.57

    - Deshpande et al: **Risk factors for recurrent Clostridium difficile infection: a systematic review and meta-analysis.** ICHE 2015 Apr;36(4):452-60.

Conventional therapies for recurrent diseases

- Treat first recurrence with metronidazole or vancomycin as usual treatment dose
  - Fidaxomicin considered for non-NAP 1, very expensive
- Second recurrence: retreat with vancomycin plus taper
- AGA and IDSA guidelines

Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.



van Nood E et al. N Engl J Med 2013;368:407-415.

Key features of the study

- **Treatments:**
- 43 Patients were randomized to receive
- vancomycin (500 mg orally 4 times per day for 4 or 5 days), followed by bowel lavage with 4 liters of macrogol solution (Klean-Prep) on the last day of antibiotic treatment and the infusion of a suspension of donor feces through a nasoduodenal tube the next day; OR
- a standard vancomycin regimen (500 mg orally four times per day for 14 days); OR
- a standard vancomycin regimen with bowel lavage on day 4 or 5.

- Performed in the Netherlands, sponsored by government grants

What did it take?

- 77 donors (<60 years of age) were volunteers who were initially screened using a questionnaire addressing risk factors for potentially transmissible diseases.

- Donor feces were screened for parasites (including *Blastocystis hominis* and *Dientamoeba fragilis*), *C. difficile,* and enteropathogenic bacteria.

- Blood was screened for antibodies to HIV; human T-cell lymphotropic virus types 1 and 2; hepatitis A, B, and C; cytomegalovirus; Epstein–Barr virus; *Treponema pallidum*; *Strongyloides stercoralis*; and *Entamoeba histolytica*.

- A donor pool was created, and screening was repeated every 4 months. Before donation, another questionnaire was used to screen for recent illnesses.

The methodology:

- Feces were collected by the donor on the day of infusion and immediately transported to the hospital.
- Feces were diluted with 500 ml of sterile saline (0.9%). This solution was stirred, and the supernatant strained and poured in a sterile bottle.
- Within 6 hours after collection of feces by the donor, the solution was infused through a nasoduodenal tube (2 to 3 minutes per 50 ml).
- The tube was removed 30 minutes after the infusion, and patients were monitored for 2 hours.
- For patients who had been admitted at referring hospitals, the donor-feces solution was produced at the study center and immediately transported and infused by a study physician.

Table 1. Baseline Demographic and Clinical Characteristics of the Patients.*

Characteristic	Donor-Feces Infusion (N=16)	Vancomycin Only (N=13)	Vancomycin and Bowel Lavage (N=13)	P Value†
Age — yr	73±13	66±14	69±16	0.39
Body-mass index‡	22±3	22±4	24±4	0.41
Female sex — no. (%)	8 (50)	7 (54)	3 (23)	0.22
Karnofsky performance status§	50±18	50±17	56±21	0.62
Median Charlson comorbidity index (range) — score¶	3 (0–4)	1 (0–8)	1 (0–6)	0.53
Median recurrences of CDI (range) — no.	3 (1–5)	3 (1–4)	2 (1–9)	0.69
Previous failure of tapered vancomycin therapy — no. (%)	10 (62)	8 (62)	6 (46)	0.63
Reported antibiotic use before CDI — no. (%)	16 (100)	12 (92)	13 (100)	0.62
Hospital-acquired CDI infection — no. (%)	10 (62)	6 (46)	10 (77)	0.27
Admitted to a hospital at study inclusion — no. (%)	5 (31)	4 (31)	4 (31)	1.00
Days of antibiotic use for CDI since first diagnosis — no.‖	63±41	51±27	49±38	0.56
Use of proton-pump inhibitor — no. (%)	13 (81)	10 (77)	11 (85)	0.88
ICU admission in preceding month — no. (%)	1 (6)	0	1 (8)	1.00
Feeding tube present — no. (%)	3 (19)	2 (15)	2 (15)	0.96
Median stool frequency per 24 hr (range) — no.	5 (3–20)	5 (3–12)	5 (3–10)	0.72
Leukocyte count — per mm^3**				
Median	8000	8100	6500	0.39
Range	4000–15,000	4000–23,000	3000–14,000	
Albumin — g/dl**	3.7±0.7	3.8±0.7	3.9±0.8	0.66
Median creatinine (range) — mg/dl**	1.3 (0.6–10.3)	1.0 (0.5–1.8)	0.9 (0.6–5.2)	0.26
Ribotype 027 in first sample — no. (%)††	3 (23)	1 (11)	0	0.28

Dealing with the disadvantages

- Stool substitute transplant therapy for the eradication of*Clostridium difficile* infection: ‘RePOOPulating’ the gut
  - Elaine O Petrof et al *Microbiome*2013. **1**:3
- Successful treatment of two patients with a synthetic blend of organisms from the feces of a healthy 41-year-old woman infused throughout the colon

Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent *C. difficile* Infection: A Randomized Clinical Trial

JAMA. 2016;315(2):142-149. doi:10.1001/jama.2015.18098

Table 2. Number of Fecal Microbiota Transplantations and the Proportion With Clinical Resolution at 13 Weeks After Last Transplantation

	No. (%) With Clinical Resolution			
	mITT Population		Per-Protocol Population	
No. of FMTs	Frozen (n = 108)	Fresh (n = 111)	Frozen (n = 91)	Fresh (n = 87)
1	57 (52.8)	56 (50.5)	57 (62.7)	54 (62.1)
2	24 (75.0)	22 (70.3)	19 (83.5)	20 (85.1)
3-5	13 (87.0)	12 (81.1	9 (93.4)	9 (95.4)
>5	4 (90.7)	5 (85.6)	2 (95.6)	1 (96.6)
Total	**98**/108 (90.7)	**95**/111 (85.6)	**87**/91 (95.6)	**84**/87 (96.6)

Abbreviations: FMT, fecal microbiota transplantation; mITT, modified intention-to-treat.

Going commercial

- October 28, 2015: Fecal transplant pills: Large-scale production begins following successful dosing study

- The pill was created by OpenBiome, a nonprofit stool bank.
- A pilot, multi-center randomized dose-finding study with 17 patients found an initial efficacy rate of 70 percent in both low and high dose groups receiving capsules. Treatment with a high dose after an initial nonresponse yielded an aggregate clinical cure rate of 94 percent. There were no adverse events reported.

- OpenBiome's FMT Capsule G3 uses a patent-pending Microbial Emulsion Matrix (MEM) technology, which preserves the viability of complex bacterial communities while ensuring capsules' long-term physical stability.
- http://www.openbiome.org/

Total evidence to date

Oral Delivery Modality				
Fischer M, Allegretti JR et al. 2016.	Randomized, cluster dose-finding study	17	Capsules	• 94% aggregate
Youngster I et al. 2014.	Open-label cohort study	20	Capsules	• 90% aggregate
Hirsch BE et al. 2015	Open-label cohort study	19	Capsules	• 89% aggregate

What is stool?

- Per FDA, it is an investigational new drug!
- Current draft guidance for comment (May 2016)
- FDA intends to exercise enforcement discretion, provided that:
- 1) the licensed health care provider treating the patient obtains adequate consent from the patient or his or her legally authorized representative;
- 2) the FMT product is not obtained from a stool bank;
- 3) the stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product

Draft requirements

- A sponsor, typically the stool bank, must have an IND in effect before distributing the FMT product to investigators for administration to subjects in accordance with the investigational plan.

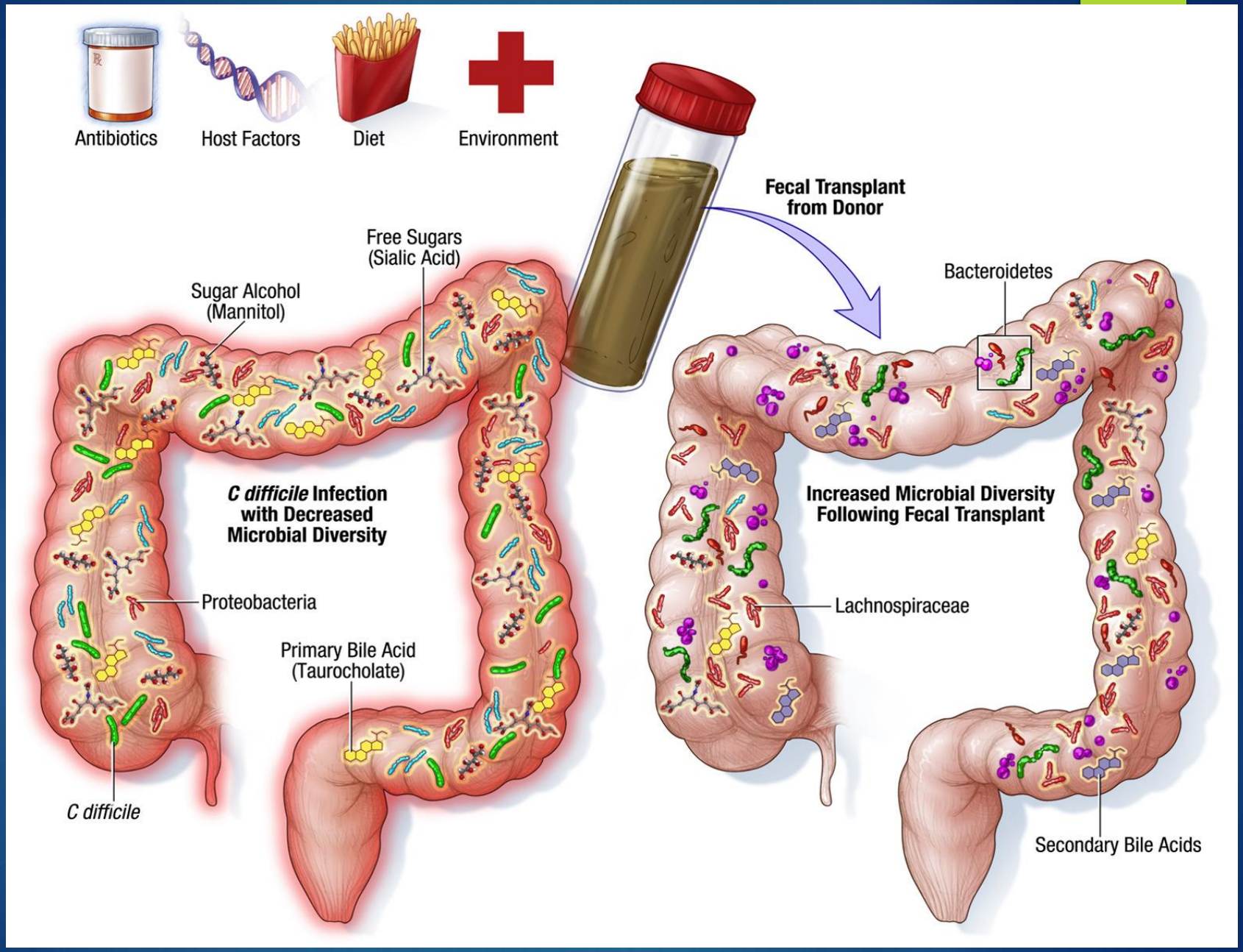
- However, as described in this guidance, an IND sponsor may request a waiver of certain IND regulations applicable to investigators for those licensed health care providers receiving FMT product to treat patients with *C. difficile* infection not responsive to standard therapies.

What are the potential hazards of FMT?

- Newly recognized potential risks of the human gut microbiome
  - Associations with malignancy, obesity, metabolic syndrome, autoimmune disease, IBD, IBS, fibromyalgia

Suggested donor exclusion criteria

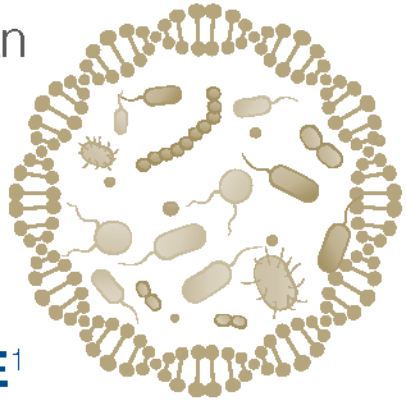
- A history of antibiotic treatment during the 3 months preceding donation
- A history of GI disease IBD, IBS, chronic constipation, GI malignancies, or major GI surgical procedures
- A history of autoimmune or atopic illnesses or ongoing immune-modulating therapy
- A history of chronic pain syndromes (fibromyalgia, chronic fatigue) or of neurological or neurodevelopmental disorders
- Metabolic syndrome, obesity , or malnutrition
- A history of malignant illnesses or ongoing oncologic therapy.



Kelly C. Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook *Gastroenterology* 2015 149, 223-237DOI: (10.1053/j.gastro.2015.05.008)

There are more than
3 MILLION
MICROBIAL GENES
in our gut microbiota

150 TIMES
more genes than in the
HUMAN GENOME[1]



APPROXIMATE
WEIGHT OF THE TOTAL GUT MICROBIOTA[1]

OUR GUT MICROBIOTA EVOLVES THROUGHOUT OUR ENTIRE LIFE
and is the result of a variety of influences:[1-2]

- GENETICS
- STRESS
- HYGEINE PRACTICES
- MODE OF DELIVERY
- DRUGS/ ANTIBIOTICS
- DIET
- INFECTIONS
- SURGERY
- ENVIRONMENT

The composition of
GUT MICROBIOTA
IS UNIQUE
to each individual,
just like our FINGERPRINTS[1]