Fecal Microbiota Transplantation (FMT)

Tatiana Bogdanovich, MD, PhD
Medical Director, FMT Program
Division of Infectious Diseases
University of Pittsburgh Medical Center
Disclosures

- I have no financial conflicts of interest

- I do not intent to discuss unapproved/ investigative use of commercial product(s)/device(s)
Outline

- Burden of *Clostridium difficile* infections
- Overview of FMT for recurrent *C. difficile* (methodology, safety)
- FMT Program at UPMC
- Future areas of research involving FMT
**Clostridium difficile Burden**

- **2011 CDC estimates**\(^1\)
  - 453,000 new cases/year (95% CI 397,000-508,000)
  - 83,000 first recurrences/year (95% CI 57,000-108,900)
  - 29,300 deaths/year (95% CI 16,500-42,100)

- **CDI among UPMC SOT (2011-2012)**\(^2\)

<table>
<thead>
<tr>
<th>Transplant type(^1)</th>
<th>Number of transplants</th>
<th>Positive pre-transplant (%)</th>
<th>Positive post-transplant (%)</th>
<th>Total positive (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>205</td>
<td>1 (0.5)</td>
<td>35 (17.1)</td>
<td>36 (17.6)</td>
</tr>
<tr>
<td>Heart</td>
<td>50</td>
<td>3 (6.0)</td>
<td>5 (10.0)</td>
<td>8 (16.0)</td>
</tr>
<tr>
<td>Kidney</td>
<td>261</td>
<td>4 (1.5)</td>
<td>13 (5.0)</td>
<td>17 (6.5)</td>
</tr>
<tr>
<td>Liver</td>
<td>134</td>
<td>3 (2.2)</td>
<td>16 (11.9)</td>
<td>19 (14.2)</td>
</tr>
<tr>
<td>Intestinal</td>
<td>15</td>
<td>0 (0)</td>
<td>2 (13.3)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Total</td>
<td>665</td>
<td>11 (1.7)</td>
<td>71 (10.7)</td>
<td>82 (12.3)</td>
</tr>
</tbody>
</table>

\(^2\)Unpublished data courtesy Minh Hong Nguyen and Lloyd Clarke
25% of patients with a single episode of *C. difficile* will get it again!

50% of patients with 2 episodes of *C. difficile* will get it again!

After >4 episodes, recurrence risk is almost 100%!

Recurrences between 2 days – 3 months after stopping *C. difficile* therapy
Risk Factors for recurrent *C. difficile*

**Clinical factors**
- Age >65 y
- Ongoing or recurrent abx exposures
- Prolonged hospitalization(s)
- Number of previous recurrences
- Immunosuppression
- Use of acid suppression medications
- Inflammatory bowel disease

**Physiologic factors**
- Persistent impairment of colonization resistance by dysbiosis
- Impaired adaptive immune response to toxins A/B or virulence factors of *C. difficile*
- Retained endogenous or newly acquired spores in the setting of a dysbiotic state
Management of recurrent *C. difficile*

- Extended courses of vancomycin (>14 days)
  - Observed to be superior vs. 10-14 days; no RCTs done
  - Pulse doses observed to be as effective as tapering

- Fidaxomicin
  - Reduced recurrence rate observed in clinical trials
  - Price set at $2800 for 10-day course

- Home disinfection with 10% bleach

- Bezlotoxumab

- FMT
Intact microbiota converts primary bile acids into secondary -> detergent-induced toxicity to vegetative C. difficile

Commensals consume SCFAs produced by other fermenting bacteria competing with C. difficile for nutrients

Antibiotic-mediated microbiota disruption leads to ↓primary bile acid converters and ↓competing sialic acid & succinate consumers
FMT Premise

- FMT involves delivery of specially prepared stool material from a healthy donor to a patient recipient.

- FMT repopulates the patient’s microbiome with diverse microorganisms and alleviates disease symptoms.
History of FMT

- **4th century**: Ancient Rome, China
  - “yellow soup” for food poisoning and severe diarrhea

- **17th century**: Italian Fabricius Aquapendente used FMT for ruminal disorders

- **1958**: Fecal enemas for antibiotic-associated colitis in 4 patients (Eiseman et al)

- **1983**: FMT for confirmed *C. difficile* (Schwan et al)

- **09/23/2017**: 883 articles in PubMed on FMT
  - 856 in the last 5 years
  - 283 reviews
FMT for recurrent *C. difficile*

- Recommended by US and international guidelines for recurrent CDI

- FMT is considered a “biological product” and a “drug” by the FDA
  - 07/2013: “enforcement discretion” for CDI use. **Physician must obtain informed consent.**
Results of Donor Screening

- 77 donors completed questionnaires:
  - 7 excluded: healthcare workers (2), age >60 (1), “riskful” sexual behavior (2), recent visit to a tropical country (2)

- 33 failed screening tests:
  - C. difficile (2)
  - Blastocystis hominis (23)
  - Dientamoeba fragilis (4)
  - B. hominis + D. fragilis (1)
  - Strongyloides (1)
## Key FMT trials since van Nood

<table>
<thead>
<tr>
<th>Ref</th>
<th>N=</th>
<th>Design</th>
<th>Dose</th>
<th>Follow-up</th>
<th>Success</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20</td>
<td>Open label</td>
<td>48 g (30 frozen capsules)</td>
<td>8 weeks</td>
<td>14/20 1X</td>
<td>15 capsules x 2 days</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>19/20 2X</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>Randomized NGT vs. colonoscopy</td>
<td>41g</td>
<td>8 weeks</td>
<td>8/10 Cscope</td>
<td>All unrelated donors</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6/10 NGT</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>Retrospective, multicenter, case series</td>
<td>varied</td>
<td>12 weeks</td>
<td>62/80 (78) single 70/80 (89) multiple</td>
<td>mostly C-scope, <strong>Immunocompromised</strong> (SOT=19, HIV=3)</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>Case series, single center</td>
<td>50 g</td>
<td>8 weeks</td>
<td>7/10 directed 30/33 stool bank p=0.12</td>
<td>30% IBD</td>
</tr>
</tbody>
</table>

Sources of FMT Doses

- **Patient directed donation**
  - spouses, partners, close relatives, or household members
  - **Pros**: presumably similar intestinal microbiota (common shared environment and/or genetics)
  - **Cons**: costs of donor’s screening not covered by insurance; not “as healthy microbiota”; increase time to FMT procedure

- **Commercial (“non-for-profit”) stool banks (OpenBiome, MA; Advancing Bio, CA)**
  - **Pros**: commercially available; standardized; “works out of the box”
  - **Cons**: no detailed info about donor; paid donations may result in false medical/social/sexual history reporting; cost to patient/institution

- **Institutional (internal) stool banks**
  - **Pros**: customized donor selection and screening; access to donor medical records, social/sexual histories, etc.; donor-recipient “matching”; flexible protocols; relatively inexpensive
  - **Cons**: need for continual recruitment of healthy donors
Safety and Tolerability of FMT

- Usually **very well** tolerated
  - common short-term AE: belching, feeling bloated, diarrhea, cramps (especially after colonoscopic route)

- Safely used in **immunocompromized** (solid organ and bone marrow transplant recipients, HIV, IBD patients on immunosuppression) and **pediatric populations**

- **Unusual** reported complications:
  - primary CMV colitis following home-administration of FMT\(^1\)
  - norovirus gastroenteritis, presumably from sick GI lab employee\(^2\)
  - diverticulitis\(^3\)
  - fatal aspiration PNA after enteroscopic FMT (during 3rd 50 ml infusion)\(^4\)
  - peripheral neuropathy after FMT for CDI\(^5\)

---

\(^5\)Didesch et al. *PM&R.* 2016 Jan; available on line.
Obesity post FMT

- 32 yo woman successfully treated with FMT for CDI and developed new onset obesity
  - Donor: 16 year old daughter (BMI=26.3)
- Recipient BMI increase: 26 → 33 → 34.5
- Donor BMI increased as well

Unclear causality!
## UPMC FMT Program

<table>
<thead>
<tr>
<th>Date</th>
<th>Milestone</th>
</tr>
</thead>
<tbody>
<tr>
<td>October 2013</td>
<td>ID founds FMT Program</td>
</tr>
<tr>
<td>July 2014</td>
<td>UPMC secures lab space for FMT</td>
</tr>
<tr>
<td></td>
<td>IRB approval for FMT registry</td>
</tr>
<tr>
<td></td>
<td>C.diff/FMT Clinic opened</td>
</tr>
<tr>
<td>October 2014</td>
<td>PA DoH approves FMT lab</td>
</tr>
<tr>
<td>December 2014</td>
<td>First colonoscopic FMT</td>
</tr>
<tr>
<td>February 2015</td>
<td>First ND tube FMT performed</td>
</tr>
<tr>
<td>April 2016</td>
<td>Creation of Volunteer Stool Donor (VSD) bank</td>
</tr>
<tr>
<td>November 2016</td>
<td>First FMT utilizing VSD</td>
</tr>
<tr>
<td>December 2016</td>
<td>First FMT by freeze-dried capsules</td>
</tr>
</tbody>
</table>
# UPMC FMT: Inclusion and exclusion criteria for recipient

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. At least three episodes of documented CDI and failure of standard therapy with extended vancomycin</strong> (6-8 week taper with vancomycin or 30-90-day pulsed dosing of vancomycin following standard therapy) with or without an alternative antibiotic (e.g., rifaximin, nitazoxanide, fidaxomicin).</td>
<td><strong>1. Unable to sign informed consent</strong></td>
</tr>
<tr>
<td><strong>OR</strong></td>
<td><strong>2. Life expectancy less than six months</strong></td>
</tr>
<tr>
<td><strong>2. CDI with at least one episode (either first or subsequent) of severe CDI resulting in hospitalization</strong></td>
<td><strong>3. No documentation of CDI within prior six months</strong></td>
</tr>
</tbody>
</table>

**Exclusion criteria:**
- Unable/unwilling to discontinue vancomycin/other CDI therapy after transplant
- Age <18 years
- Pregnancy

**Inclusion criteria:**
- Unable to sign informed consent
- Life expectancy less than six months
- No documentation of CDI within prior six months
- Unable/unwilling to discontinue vancomycin/other CDI therapy after transplant
- Age <18 years
- Pregnancy
**Exclusion Criteria for UPMC Volunteer Stool Donor**

<table>
<thead>
<tr>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unable to provide informed consent</td>
</tr>
<tr>
<td>Age &lt;18</td>
</tr>
<tr>
<td>Chronic medical conditions requiring use of <strong>prescription medications</strong> (diabetes, emphysema, hypertension, etc.)</td>
</tr>
<tr>
<td>History of malignancy (except non-melanoma skin cancer)</td>
</tr>
<tr>
<td>Chronic diarrheal disorder (IBS, IBD, celiac disease) or constipation (&lt; 1 BM daily)</td>
</tr>
<tr>
<td>Autoimmune/atopic diseases except mild seasonal allergies</td>
</tr>
<tr>
<td><strong>Obesity, defined as BMI &gt;30 OR underweight, defined as BMI&lt;18.5</strong></td>
</tr>
<tr>
<td><strong>Overweight, defined as body mass index &gt;25 kg/m²</strong></td>
</tr>
<tr>
<td>Neurologic disorders, chronic pain syndromes</td>
</tr>
<tr>
<td>HIV, hepatitis B surface antigen, hepatitis C antibody, HTLV, <strong>Strongyloides</strong>, or syphilis antibody positive</td>
</tr>
<tr>
<td>Positive for latent infections (CMV, EBV, HSV, JC virus, HHV-6) for which the recipient is seronegative</td>
</tr>
<tr>
<td>Prior deferral from blood donation (other than MSM), h/o imprisonment &gt;72 hours, tattoos, high-risk sexual behaviors</td>
</tr>
<tr>
<td><strong>Use of antibiotics (current or expected) in 90 days prior to procedure</strong></td>
</tr>
<tr>
<td>Prior history of <em>C. difficile</em> or donor testing positive for <em>C. difficile</em> by broth enrichment culture</td>
</tr>
<tr>
<td>Inability to refrain from eating food items to which recipient is allergic in 7 days prior to FMT</td>
</tr>
<tr>
<td>Unable to present for donor testing within 90 days of procedure or unwilling to have blood drawn.</td>
</tr>
<tr>
<td>Diarrheal illness, emesis, or “food poisoning” in 90 days prior to procedure.</td>
</tr>
<tr>
<td>History of travel outside US (excluding Canada, Australia, and Western Europe) in past year</td>
</tr>
<tr>
<td>History of or screening tests positive for MRSA, VRE or MDRO carriage/infection</td>
</tr>
<tr>
<td>Febrile illness in 90 days prior to procedure</td>
</tr>
<tr>
<td>Patients with family history of 1st degree relatives with colon cancer, breast cancer, or cervical cancer who are overdue for age-appropriate malignancy screening or who have had prior abnormal age-appropriate malignancy screening who are overdue for follow-up</td>
</tr>
<tr>
<td>History of transplant or skin graft</td>
</tr>
<tr>
<td>Risk factors for variant Creutzfeldt-Jakob disease</td>
</tr>
</tbody>
</table>
Pre-FMT Process at UPMC

- Evaluation in the dedicated FMT clinic
  - Meet inclusion/exclusion criteria for FMT
  - Determine source of FMT dose, delivery method
  - Obtain pre-FMT labs to “match” with a (volunteer stool) donor
- Continue anti-C. difficile therapy until 3-5 days prior to FMT
- FMT via freeze-dried capsules:
  - Fasting for 4 hrs pre and 1-2 hrs post FMT
  - PPI pre-FMT
FMT Procedures at UPMC

- Sample donation in labeled, sealed stool “hat”
- All manipulations in the type II biological safety cabinet with laminar flow
- Trained personal wearing PPE (disposable cap, face shield/mask, gloves, lab coat)
- All labware is sterile single use or steam-sterilized
- Commercial stainless steel blenders and analytical filters; pharmaceutical grade sterile saline for stool homogenization
FMT Procedures at UPMC

- Fecal homogenate is stored in sterile bottles at -80°C until use:
  - via colonoscopy (loaded into Luer-tipped syringes)
  - via naso-duodenal tube (loaded into enteral feeding bag)

OR

- Fecal homogenate is freeze-dried and encapsulated
Volunteer Stool Donor (VSD) Bank

- Recruitment of “elite” healthy donors
  - screening via questionnaire
  - collection of 3-4 stool samples
  - PE and extensive blood/stool testing prior to “clearance”

- >45 VSD doses prepared
  - various serologic profiles for latent viruses (e.g. CMV/EBV/HSV1&2)

- 24 patients treated with VSDs
  - colonoscopy (4), enteroscopy (1) and freeze-dried capsules (19)
  - success rate ~85%
Post-FMT Follow Up at UPMC

- FMT registry and FMT stool repository
  - Collect pre- and post-FMT stool samples

- Avoidance of unnecessary systemic antibiotics (asymptomatic bacteriuria, before dental cleaning in patients with prosthetic joints, etc) and complimentary antimicrobial stewardship
  - No prophylactic antibiotics for *C. difficile* in case of systemic antimicrobial therapy post FMT

- Potential for post-infectious IBS (up to 30%)
  - 2-step testing in case of persistent diarrhea (GDH EIA/PCR with reflex to toxin A/B EIA)
  - No need to test for *C. difficile* as “test of cure”
FMT for Other Microbiome-Associated Diseases

- Metabolic disorders/obesity
- Inflammatory bowel disease, IBS
- Neuropsychiatric diseases (MS, autism)
- NASH, alcoholic hepatitis
- Enhancement of immunotherapy response (melanoma, head and neck cancer)
- Sepsis/MDRO colonization

“All Disease Begins in the Gut!”
-Hippocrates
Knowledge Gaps for FMT
(= opportunities for research)

- Use in severe or primary *C. difficile* infections
- NO “head-to-head” comparison of different administration routes
  - all appear fairly effective (80-95%)
- NO standardization of safe and effective FMT dose for *C. difficile*
  - protocols based on initial stool weight/dose (“the more the better” approach)
  - unknown characteristics for optimal donors (donor/recipient matching?)
- Unknown FMT dose for non-*C. difficile* indications
- Lacking long term (decades) safety data
  - national FMT registry under development
Summary

- FMT is currently the most efficacious and cost-effective treatment for recurrent *C. difficile* not responsive to antibiotics
  - Experimental procedure requiring informed consent
  - FMT for non-*C. difficile* indications requires IND application to FDA
- FMT has potential for infectious adverse events and limited long-term safety data
  - Need infrastructure and protocols for donor screening, dose preparation/characterization, post-FMT monitoring (FMT registry, microbiota analysis, etc)
- Many knowledge gaps despite rapid and widespread adoption (focus of intense research)
- Bridge to more defined microbial therapeutics (e.g. SER-109, RBX2660, MET-1)?
Acknowledgments

**ID Division**
- John Mellors
- Scott Curry
- Yohei Doi
- Lee Harrison

**Clinical Micro Lab**
- A. William Pasculle

**GI Division**
- David Binion
- Marc Schwartz

**CMM**
- Alison Morris
- Barbara Methé