How to Bring FMT To Your Practice

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Learning Objectives

• To understand the purpose and procedural details of FMT
• To know regulatory considerations of FMT
• To understand how FMT can be brought into your practice
• Disclosures - none
Early History of FMT Before the FDA

- **4th Century (Ge Hong):**
  - Oral human fecal suspension ("yellow soup") for severe diarrheal illnesses, food poisoning

- **16th Century (Li Shinzen):** fermented fecal solution, dry feces - treated fever, severe diarrhea, vomiting and constipation

- **1958:** FMT enema
  - Eismann, et al. 4 patients with pseudomembranous colitis
  - "Dramatic" response within 48 hours

Yellow Soup/Cappuccino

Cleveland Plain Dealer, October 21, 2015
FMT in Veterinary Medicine Since the 17th C.
The USDA does not care

- Transfaunation
- Horses with diarrhea- infuse stool from healthy horse per rectum
- Cattle - per os as rumen


Conditions Potentially Treatable By FMT

Different ages and geographic populations have very different microbiomes

Yatsunenko et al. 2012 *Nature*
The mammalian gut microbiota (Ley et al)

<table>
<thead>
<tr>
<th>Divisions</th>
<th>% sequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Firmicutes</td>
<td>69</td>
</tr>
<tr>
<td>Bacteroidetes</td>
<td>17</td>
</tr>
<tr>
<td>Actinobacteria</td>
<td>6</td>
</tr>
<tr>
<td>Proteobacteria</td>
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</tr>
<tr>
<td>Gemmatimonadetes</td>
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<tr>
<td>Defferribacteres</td>
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<tr>
<td>Verrucomicrobia</td>
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<tr>
<td>Lentisphaerae</td>
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<tr>
<td>Planctomycetes</td>
<td>0.08</td>
</tr>
<tr>
<td>*CD Gut 1</td>
<td>0.2</td>
</tr>
<tr>
<td>*CD Gut 2</td>
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<tr>
<td>Fusobacteria</td>
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<tr>
<td>Spirochaetes</td>
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<tr>
<td>Fibrobacteres</td>
<td>0.08</td>
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<tr>
<td>*Cyano Sister</td>
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<tr>
<td>Synergistes</td>
<td>0.12</td>
</tr>
<tr>
<td>Chloroflexi</td>
<td>0.01</td>
</tr>
<tr>
<td>*TM7</td>
<td>0.04</td>
</tr>
<tr>
<td>: no cultured representatives</td>
<td></td>
</tr>
<tr>
<td>@: novel candidate division</td>
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</tr>
</tbody>
</table>

- *Firmicutes* and *Bacteroidetes* dominate across all mammals.
- **Dietary influence:**
  - Carnivores have the fewest divisions and are most enriched in *Firmicutes*.
  - Humans are typical omnivores; cluster with omnivorous primates; leaf-eating primates cluster with herbivores

Atherosclerosis and Fecal Dysbiosis

- Mechanistic link between atherosclerosis and intestinal microbial metabolism of dietary nutrients to produce trimethylamine N-oxide (TMAO)
- Specific dietary nutrients – choline, phosphatidyl choline, and carnitine – eggs, liver, meat
- Atherosclerosis-prone strain of mice were given FMT from low TMAO producing strain
- Choline-rich diet led to lower atherosclerotic plaques and lower TMAO

Gut microbiota-dependent metabolism of dietary phosphatidylcholine in atherosclerosis

ZN Wang et al. Nature 472, 57-63 (2011)

Dietary/ microbial interactions impact intestinal, hepatic and vascular inflammation

J Goldsmith and RB Sartor J. Gastroenterology 2014
FMT and the FDA: Existing Regulatory Framework

Drug and Biologic

- IND requirement
- “Enforcement discretion”
  - C. difficile only

Source: U.S. Food & Drug Administration, www.fda.gov/AboutFDA/Transparency/Basics/ucm361441.htm

Dilemmas

For regulatory agencies

For patients

For clinicians and clinical researchers

For healthcare organizations

Perfect Donor

- Lean
- No chronic diseases
- No infectious disease
- No predisposition to diabetes, or other chronic diseases like NAFLD, MS, IBD, or chronic fatigue syndrome
- Low TMAO-producing foods

Capsules for FMT

- 20 patients, open-label, relapsing *C. difficile*
- *****Healthy donor volunteers*****
- 15 capsules on 2 consecutive days
- Resolution of diarrhea – 70%
- 4/6 non-responders responded to second FMT
- Overall response rate 90%
- No adverse events

Youngster I, et al. *JAMA* 2014;312:1772-8
OpenBiome

- No IND
- Donor testing: 3% of prospective donors pass testing, retested every 60 days
- No dietary restrictions

OpenBiome

- Recommendations:
  - PPI
  - Informed Consent
  - Direct observation of capsule ingestion
- Cost
  - $385 – 30 mL upper GI or 250 mL lower GI
  - $535 – 30 capsules

We also perform high-throughput 16S rRNA sequence characterization on stool samples from each of our donors. While traditional approaches to FMT donor screening have focused on measuring what is absent, we believe that a holistic donor assessment should also evaluate what is present in an FMT donor’s microbiome.
FMT is being conducted under an enforcement discretion from FDA—as described in a Guidance issued in 2013, followed by two Draft Guidances issued in 2014 and 2016, respectively.

The draft guidances are not enforceable, but they do reflect FDA’s current opinion on the topic, and in this case it is pretty clear they would want an IND for using capsules from OpenBiome.

The changes from 2013 to 2016 have added progressively more language circumscribing third-party specimen use without an IND, while encouraging providers to obtain and bank specimens obtained and screened under their (or their colleagues’) supervision without an IND.

OpenBiome has made it clear that since the draft guidances are not enforceable, they will not obtain an IND.

You can see that this puts us in a difficult position from a regulatory standpoint.

IND Application Process for FMT/CDI

- FDA Form 1571 - 1) Product name, 2) proposed indication, 3) dosage and route of administration, 4) donor screening, 5) processing of donor stool.
- Informed consent including all potential risks to donor and recipient
- Adverse events anticipated and AE reporting system (serious AEs including infection transmission need to be reported within 7 days)
- Data entered into a secure database with periodic reporting of entire safety data, as well as failure rate to treat C. difficile. $$
- Independent DSMB $$
- FDA Form 1572 – personnel
- IRB approval
- Case report form
- Investigator brochure
Editorial

- FDA considers FMT a drug and a biologic; not approved for any indication.
- IND is required for any indication
- “Enforcement discretion” for CDI – IND encouraged, but not required
- “A sober, objective, data-driven approach is called for to protect as well as serve our patients and to ensure the most rigorous evaluations of the short-term and long-term medical benefits of microbiota manipulation.”


Protocol for FMT in Recurrent CDI at the Cleveland Clinic

- **Insurance Approval:** $4,300.
- **IRB-Approved informed consent**
- **Choose donor**
  - Spouse/partner
  - 1st degree relative
  - Household contact
- **Donor exclusions**
  - Antibiotic use within 3 months
  - Diarrhea, constipation, IBS, IBD, colorectal cancer, immunocompromised, anti-neoplastic drugs, high-risk behaviors
- **Testing**
  - Donor Stool: culture for enteric pathogens, O&P, *C. difficile*
  - Donor and Recipient Blood: Hepatitis remote panel, syphilis, HIV, HTLV
Protocol for FMT in Recurrent CDI

- **Donor**
  - Gentle laxative (e.g. MOM) evening before FMT
  - Freshly passed stool
  - Mixed with 500 mL non-bacteriostatic water/saline
  - Filtered
  - Used within 6-8 hours

- **Recipient**
  - D/C antibiotics 5 days prior to procedure
  - Large volume bowel prep evening before FMT
  - Loperamide before procedure
  - Instill up to 500 mL in the right colon

Protocol for FMT in Recurrent CDI

- **Stool Transplant**
  - Donor stool → suspension with non-bacteriostatic water
  - Filtered
  - 60 cc catheter tip syringe
  - Volume of ~ 300 mL instilled into ascending colon
  - Patient to hold stool for 4-6 hours
Cleveland Clinic Outcomes

- N >150
- Average age: 63
- Indication: *C. difficile*
- 96% success in eradicating *C. difficile*
- 1 repeat FMT successful
- 20 with repeat *C. difficile* testing - neg

Follow-up Survey

- 77 patients >3 months after FMT
- Duration of illness: 11 months
- Symptomatic response after FMT
  - <3 days in 74%
  - **Primary cure rate:** 91%
  - **Secondary cure rate:** 98.7%
- 97% of patients would have another FMT for recurrent CDI
- 58% would choose FMT as their preferred Rx

Cost-Effectiveness FMT

- Decision analytic model comparing 4 strategies for 1st episode recurrent CDI
  - Metronidazole
  - Vancomycin
  - Fidaxomicin
  - FMT-colonoscopy
- FMT most cost-effective strategy with incremental cost-effectiveness ratio of $17,016 vs vancomycin
- More cost effective than fidaxomicin and metronidazole because of higher cost and/or lower efficacy of medications
- FMT colonoscopy most cost-effective strategy with cure rate 96.4%


The Do-It-Yourself Approach

How to Bring FMT to Your Practice

• Colonoscopic approach:
  - Recurrent CDI only
  - Be in control of donor testing to avoid FDA scrutiny
  - Informed consent from donor and recipient
• At home enema approach: Strongly discourage
• FMT pills or solution from 3rd party for recurrent CDI
  - IND is necessary
• FMT for other indications besides CDI
  - IND is necessary