When To Do Fecal Microbiota Transplant (FMT) For \textit{C. difficile}

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Disclosures

- Research support
  - OpenBiome

- Scientific Advisory Boards
  - Salix Therapeutics, Inc
  - Seres Therapeutics, Inc
  - Crestovo
CDI Incidence

~500,000 cases
~$5 billion in excess costs
~30,000 deaths per year

C. difficile: risk factors

Host factors
- Older age (>65 years)
- Co-morbid disease (e.g., renal disease, IBD [UC], cirrhosis)
- Immunosuppression
- Hypoalbuminemia
- Altered microbiome
  - antibiotics (↑ risk with ↑ duration)
  - acid suppression (PPI>H₂B)
  - non-surgical GI procedures (e.g., NG tube)

Exposure to C. difficile spores
- Hospitalization (↑ risk with ↑ duration)
- ICU stay
Recurrent *C. difficile* Infection

- 15-20% of patients
  - relapse vs re-infection
  - *post-C. difficile* IBS (~25%)
- 2nd recurrence: 30-45%; 3rd recurrence: 45-60%
- Rx failure before 2003 <10%; after 2003 ~20%
- Relapses can continue for years
- No universal Rx algorithm
- Rx recommendations are not evidence-based

Recurrent *C. difficile* Infection
Why Do We Get It?

- Impaired host-response
- Altered intestinal microbiome
Decreased Diversity of the Fecal microbiome in Recurrent *C. difficile*

- Patients with R-CDI have decreased phylogenetic richness
- *Bacteroidetes* and *Firmicutes* are reduced in patients with R-CDI; not in patients with just one episode of CDI

Treatment of *C. difficile* Infection

- Conventional Antibiotics
  - metronidazole, vancomycin, fidaxomicin, rifaximin, others
- Biotherapy
  - *Fecal Microbiota Transplant*, non-toxigenic *C. difficile*
- Vaccines and Monoclonal Antibodies
  - bezlotoxumab
FMT Rx of Recurrent *C. difficile*: Rationale

- Avoid prolonged, repeated courses of antibiotics, which maintain "intestinal dysbiosis"
- Rapidly re-establish normal diversity of the intestinal biome, thus restoring "colonization resistance"
  - deterrence to colonization
  - colonic "niche" occupation
  - anti-microbial peptides
  - pathogen-specific mucosal IgA
  - bacterial predation by phage
  - metabolic regulation by bile salts

Diversity in Donor, Pre-FMT and Post-FMT Samples

Seekatz et al. mBio 2014; doi:10.1128/mBio.00893-14
ACG Guidelines (2013) for Rx of Recurrent *C. difficile* Infection*

1st: can use same Rx as for initial episode; if severe, use vanco
2nd: pulsed vanco regimen
   ♦ Cond recommend, low qual evid
3rd: pulsed-tapered vanco; consider FMT
   ♦ Cond recommend, low qual evid
   ♦ Mod recommend, mod quality evid

*In more recent guidelines, FMT is recommended as equal to (WSES, ASID) or higher (ESCMID) than vanco or fidaxomicin


When to do FMT for *C. difficile* Infection

- ≥ 3 recurrences of mild/moderate CDI and failure to respond to standard Rx
- ≥ 2 episodes of CDI resulting in hospitalization and significant morbidity
- Moderate CDI with no response to standard therapy for at least 1 week
- Severe CDI with no response to standard therapy for 48 hours
FMT: A Perspective on the Evolution of Treatment

“Doc, I have diarrhea”

2000 BC. Here, eat this root
1000 BC. That root is heathen; say this prayer
1850 AD. Prayer is superstition; drink this potion
1930. That potion is snake oil; swallow this pill
1970. That pill is ineffective; take this antibiotic
2000. That antibiotic is artificial; here, eat this root

Modified from “History of Medicine” (anon)
Kassam et al. Am J Gastroenterol, 2013

Meta-analysis of Clinical Resolution Rates (11 of 2709 reports, 273 patients)

Resolution rate
- 90% overall
- lower: 91%
- upper: 82%
- No AEs
Randomized, Placebo-Controlled, Double Blind Study: Efficacy and Safety of FMT for R-CDI (44 pts)

Rates of Clinical Cure (ITT)

- 10/11 pts with CDI recurrence given open-label donor FMT remained symptom-free

Clinical Features by Site

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>RI (n=24)</th>
<th>NY (n=22)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean duration CDI (range, mos)</td>
<td>5.7 (3-11)</td>
<td>16 (3-48)</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean # CDI recurrences (range)</td>
<td>3.6 (2-6)</td>
<td>5 (3-10)</td>
<td>0.00</td>
</tr>
<tr>
<td>Prior Lactobacillus GG: # (%)</td>
<td>7 (29)</td>
<td>1 (5)</td>
<td>0.03</td>
</tr>
<tr>
<td>Prior fidaxomicin: # (%)</td>
<td>4 (17)</td>
<td>10 (45)</td>
<td>0.03</td>
</tr>
<tr>
<td>Use of PPI: # (%)</td>
<td>0 (0)</td>
<td>4 (18)</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Donor Autologous FMT Open-label FMT

RI patients cured by A-FMT had greater abundances of Clostridium XIV A and Holdemania, genera capable of 7-α dihydroxylation of bile salts

How does FMT Work to Cure Recurrent C. difficile?

- Re-establishment of a richly diverse intestinal microbiome population
- Restoration of a normal fecal bile acid profile
  1° bile acids: stimulate C. difficile germination
  2° bile acids: inhibit

Many commensal bacteria known to have 7-α dehydroxylase activity belong to Clostridial clusters XIVA and IV, e.g., C. scindens

- The microbiota and their metabolomic activities likely determine the results of FMT
Predictors of Failure after FMT for Recurrent CDI

- In-patient status*
- Hospital-acquisition#
- Severe CDI*
- Complicated CDI#
- Immunocompromise*
- COPD#
- Charlson Index#
- Maximum WBC during RCDI#


What is the Risk of CDI Recurrence after FMT Rx of R-CDI?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Recurrence rate</th>
<th># patients</th>
<th>Mean Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brandt, et al</td>
<td>2012</td>
<td>10%</td>
<td>8/77</td>
<td>17 months</td>
</tr>
<tr>
<td>Khanna, et al</td>
<td>2015</td>
<td>10.5%</td>
<td>25/238</td>
<td>14 months</td>
</tr>
<tr>
<td>Fischer, et al</td>
<td>2016</td>
<td>10.5%</td>
<td>16/152</td>
<td>16 months</td>
</tr>
</tbody>
</table>

10.3% 467

After FMT, long-term rates of rCDI with antibiotic use is low ... but not as low as without antibiotics.
Do Antibiotics Play a Role in R-CDI after Successful FMT??

152 pts followed for a mean of 62 wks (range: 12-169 wks)

CDI recurrence: 10.5% (16/152)

- 10 (63%) antibiotics
- 6 (37%) no antibiotics

58 of 152 pts (38%) took antibiotics
94 of 152 pts (62%) did not take antibiotics

CDI recurrence

- 17.2% (10/58)
- 6.4% (6/94)

FMT… The Next Steps

Courtesy, OpenBiome
Frozen Fecal Material

- Randomized non-inferiority trial: 219 patients
- 6 Canadian academic medical centers
- Frozen/thawed vs fresh stool (x2) for R-CDI

<table>
<thead>
<tr>
<th></th>
<th>Frozen</th>
<th>Fresh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per-protocol analysis</td>
<td>83.5%</td>
<td>85.1%</td>
</tr>
<tr>
<td>Intention-to-treat</td>
<td>75.0%</td>
<td>70.3%</td>
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- **Advantages of Frozen FMT**: availability, convenience, efficacy, safety, cost, data collection

Public Stool Bank*

1406 pts from 482 health care facilities; 49 states, 6 countries

<table>
<thead>
<tr>
<th>CDI</th>
<th>Clinical Cure</th>
<th>Upper (30 mls)</th>
<th>Lower (250 mls)</th>
</tr>
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<tbody>
<tr>
<td>Recurrent (910)</td>
<td>85.3 %</td>
<td>76.7 %</td>
<td>86.3 %</td>
</tr>
<tr>
<td>Severe (41)</td>
<td>80.4 %</td>
<td>81.8 %</td>
<td>80.0 %</td>
</tr>
<tr>
<td>Mixed (57)</td>
<td>72.2 %</td>
<td>64.3 %</td>
<td>73.9 %</td>
</tr>
<tr>
<td>Refractory (69)</td>
<td>67.7 %</td>
<td>72.7 %</td>
<td>66.3 %</td>
</tr>
<tr>
<td>Overall</td>
<td>82.4 %</td>
<td>75.3 %</td>
<td>83.4 %</td>
</tr>
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* OpenBiome, Medford, MA
### FMT capsules

<table>
<thead>
<tr>
<th>Author</th>
<th>Dose</th>
<th># pts</th>
<th>Cure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Louie, et al.</td>
<td>24-34 caps</td>
<td>27</td>
<td>100%</td>
</tr>
<tr>
<td>Youngster, et al.</td>
<td>15 caps</td>
<td>20</td>
<td>90% (2°)</td>
</tr>
<tr>
<td>Pardi, et al.</td>
<td>1.0x10^6, 1.5x10^9</td>
<td>15</td>
<td>93% (1°) 100%</td>
</tr>
<tr>
<td>Allegretti, et al.*</td>
<td>30 caps x1, x2</td>
<td>10</td>
<td>77% (1°) 70% (1°) 94%</td>
</tr>
</tbody>
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* After FMT, the μbiome of recipients more closely resembled donor μbiome

Seres Phase 2 trial of SER 109 to prevent recurrence in R-CDI


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**Butyrate Producers**

**SCFA Producers**

**Bile Salt Producers**

**Mucin Degraders**

**Fecal Microbial Transplant**

**Consortium**

**Single strain**

**Bioactive Molecule**

**Specificity**

**Ecosystem Effects**

Modified from Olle, B. Nature Biotechnology, 2013
Regulation of FMT

Early 2013. Fecal microbiota falls within the definition of a biologic product and a drug. Because FMT has not yet been approved by the FDA for any specific clinical indication, it constitutes an investigational agent and requires an Investigational New Drug application (IND)

March 1, 2016. FDA will continue to exercise “enforcement discretion” regarding the use of FMT products to treat C. difficile infection not responsive to standard therapies...provided

• adequate informed consent
  - use of FMT products is investigational
  - discussion of reasonably foreseeable risks

• stool donor and stool are qualified by screening and testing under the direction of the health care provider...

• the FMT product is not obtained from a stool bank

Safety OF FMT

- GI symptoms (51/213=23.9%)
  - bloating, flatulence, cramping, diarrhea, constip, nausea, GERD

- Serious Adverse Effects
  - upper route: 2.0% (4/196)
  - lower route: 6.2% (40/659)

  - Definitely or Probably Related
    - bacteremia, diverticulitis, norovirus, UC exacerbation (0.6%), CMV colitis (UC patient), weight gain

  - Possibly related
    - appendicitis, peritonitis
    - UTI, peripheral neuropathy, Sjogren’s, ITP, RA

  - Procedural
    - 1 death (aspiration), 1 bowel perforation, 1 peritonitis

**FMT: Future Areas of Investigation**

- **Indications**
  - **CDI**: 1st occurrence?
  - **other GI diseases**: IBD, IBS, constipation
  - **non-GI diseases**: diabetes, obesity, Parkinson, MS, autism?

- **Route and modality of administration; disease-specific?**

- **Safety concerns**
  - long-term: altered µbiota, new diseases?

- **Product development**
  - processed stool → spec strains ± bioactive molecules

**Take-Home Points**

- FMT is FDA-approved only for CDI (recurrent, severe, and complicated)
- FMT is highly successful in treatment of *C. difficile*
- FMT probably acts by correcting intestinal dysbiosis
- FMT can be performed via upper and lower routes; the latter is more successful
- Fresh stool, frozen fecal material or capsules from a stool bank may be used for FMT
- Anti-CDI antibiotics, but not probiotics, may be effective prophylactic agents for CDI after FMT
- Rigorous data obtained through RCTs are needed to establish a role for FMT in treating other diseases
- FMT appears safe, but long-term AEs need to be carefully monitored (AGA FMT Registry created Aug, 2016)