C. difficile: When to Do Fecal Microbiota Transplant (FMT)

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CDI Incidence

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

Lefler, DA. NEJM 2015; 372:1539-48
**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

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**Recurrent C. difficile Infection**

- 15-20% of patients
  - relapse vs re-infection
  - post-C. difficile IBS
- 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

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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*

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FMT Rx of Recurrent *C. difficile*: Rationale

- Avoid prolonged, repeated courses of antibiotics which maintain “intestinal dysbiosis”
- Re-establish normal diversity of the intestinal microbiome, thus restoring “colonization resistance”

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

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

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

*Surawicz et al. Am J Gastroenterol, 2013*

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)*
When to do FMT for *C. difficile* Infection

- ≥3 episodes 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

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

- Resolution rate
  - 90% overall
  - lower: 91%
  - upper: 82%
- No AEs

*Kassam et al. Am J Gastroenterol, 2013*
Multicenter, 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

Kelly C, Brandt LJ. Presented at ACG Meeting 2015

Multicenter, Randomized, Placebo-Controlled, Double Blind Study: Efficacy and Safety of FMT for R-CDI (44 patients): Clinical Features by Site

<table>
<thead>
<tr>
<th>Clinical Features</th>
<th>RI (n=24)</th>
<th>Bx (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>

Kelly C, Brandt LJ. Presented at ACG Meeting 2015
Distribution of Phyla in Fecal Samples

Kelly C, Brandt L.J. Presented at ACG Meeting 2015

FMT... The Next Steps
Lawrence J. Brandt, MD, MACG

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>
</tr>
</tbody>
</table>

Advantages of Frozen FMT: availability, convenience, efficacy, safety, cost, data collection

Lee CH, et al. JAMA 2016;315;142-149

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) n=12.4 %</th>
<th>Lower (250 mls) n=86.6 %</th>
</tr>
</thead>
<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>
</tbody>
</table>

* OpenBiome, Medford, MA

Poster: Su 1737. DDW, 2016
### 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>70% (1°)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>90% (2°)</td>
</tr>
<tr>
<td>Pardi, et al.</td>
<td>1.0x10^8</td>
<td>15</td>
<td>93%</td>
</tr>
<tr>
<td></td>
<td>1.5x10^9</td>
<td>15</td>
<td>100%</td>
</tr>
<tr>
<td>Allegretti, et al.*</td>
<td>30 caps x1</td>
<td>10</td>
<td>70% (1°)</td>
</tr>
<tr>
<td></td>
<td>30 caps x2</td>
<td>9</td>
<td>77% (1°)</td>
</tr>
<tr>
<td></td>
<td>30 caps x2</td>
<td>5 NRs</td>
<td>80% (2°)</td>
</tr>
</tbody>
</table>

* After FMT, the microbiome of recipients more closely resembled donor microbiome


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### Microbial Ecosystems

![Diagram of microbial ecosystems](image)

*Modified from Olle, B. Nature Biotechnology, 2013*
What is the Risk of 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.


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#

PPI or antibiotic use within 3 mos was *not* a predictor of failure after FMT

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
CDI recurrence 17.2% (10/58)

94 of 152 pts (62%) did not take antibiotics
CDI recurrence 6.4% (6/94)

Does Prophylaxis Work To Prevent R-CDI?

Case Scenario: A 63-year-old woman who has had rCDI and now needs antibiotic Rx for a UTI calls you to ask your advice; she is concerned about getting CDI again.

<table>
<thead>
<tr>
<th>Prophylactic Agent(s)</th>
<th>CDI Recurrence Rate</th>
<th>CDI Recurrence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>23% (4/17)</td>
<td></td>
</tr>
<tr>
<td>Probiotic only</td>
<td>21% (3/14)</td>
<td></td>
</tr>
<tr>
<td>Anti-CDI antibiotics only</td>
<td>0% (0/12)</td>
<td></td>
</tr>
<tr>
<td>Anti-CDI antibiotic + probiotic</td>
<td>20% (3/15)</td>
<td></td>
</tr>
<tr>
<td>Anti-CDI antibiotics and/or probiotic</td>
<td>15% (6/41)</td>
<td></td>
</tr>
</tbody>
</table>

Fischer M, et al. Presentation # 93 @ DDW, 2016
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 and Ethical Concerns

- Acute infections
  - bacterial, viral, parasitic
  - colonic, systemic

- Acute allergic reactions

- Long-term concerns
  - is it possible that we are predisposing the FMT recipient to diseases/conditions that the donor might develop in his/her lifetime?
FMT: Future Areas of Investigation

- **Indications**
  - **CDI**: severe, complicated disease? 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, or 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
- Rigorous data obtained through RCTs are needed to establish a role for FMT in treating other diseases
- Although FMT appears safe, long-term AEs need to be carefully monitored