Managing FMT Non-responders and Adverse Events

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Conflict of Interest Disclosures

• Openbiome
  Research consultant and collaborator, DSMB member

• Finch Therapeutics Group
  Research consultant

• Abbvie
  Consultant
Definition of FMT failure

• 10%-30% fail a single FMT
• 5% fail multiple FMTs
• **FMT failure** = diarrhea + positive *C. diff* stool test (PCR/toxin) within 8 weeks post FMT
• The suggested 8-week follow-up is arbitrary; extrapolated from data treating CDI with antibiotics
• ~ 90% of FMT failures occur ≤ 4 weeks
  • 25% fails before week 1
  • 60% fails between week 1-4
  • Mean time to failure=2 weeks

Surawicz AJG 2013, Fischer AJG 2016, Allegretti CGH 2017
Classification of FMT failure

Long-term outcome - beyond 8 weeks post-FMT
- 10% chance of CDI recurrence in 1 year following successful FMT
- 6% chance when antibiotics can be avoided

Causes of treatment FMT failure for therapy of CDI

✓ Donor features

✓ FMT procedural methods

✓ Patient characteristics

✓ CDI characteristics

Donor characteristics do not affect treatment outcome of FMT for CDI

- 59 donors, 1,413 patient with CDI, 85% cure rate
  - Stool consistency (BSS 3-5)
  - Diet (calorie, fat, fiber, carbohydrate intake)
  - Microbial profile (diversity or specific bacterial taxa)
  - Metabolome (butyrate, acetate, SCFA level)

Budree DDW 2017 Sa 1793, Su2018, Su 2017
Variable failure rates depending on route of delivery

**Colonoscopy:** Fresh FMT vs placebo

- Overall: 91% Cure with Donor FMT, 63% Cure with Placebo (P=0.024)
- Rhode Island: 90% Cure with Donor FMT, 43% Cure with Placebo (P=0.019)
- New York: 92% Cure with Donor FMT, 90% Cure with Placebo (P=0.89)

*Kelly 2016*

**Duodenal:** Fresh FMT vs vancomycin

- First Infusion of Donor Feces (N=16): 81.3% Cure, 91.8% Cure (P=0.001)
- Infusion of Donor Feces Overall (N=16): 81.3% Cure, 91.8% Cure (P=0.008)
- Vancomycin (N=13): 30.8% Cure
- Vancomycin with Bowel Lavage (N=13): 23.1% Cure

*Nood 2013*

**Enema:** Fresh vs Frozen FMT

<table>
<thead>
<tr>
<th>No. of FMTs</th>
<th>Per-Protocol Population</th>
<th>Frozen (n = 91)</th>
<th>Fresh (n = 87)</th>
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</thead>
<tbody>
<tr>
<td></td>
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<td>(n = 91)</td>
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<tr>
<td>1</td>
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<td>19 (83.5)</td>
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<td>84/87 (96.6)</td>
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*Lee 2016*

**Oral capsules:**

- Fresh (Louie 2013)
- Frozen (Youngster 2014 and Kao 2017)
- Microbial Emulsion Matrix 10-30 caps (Allegretti/Fischer 2015)
- Lyophilized 2-3 caps (Khoruts 2017)
Variable failure rates based on stool preparation
Frozen stool is not inferior to fresh

- Colonoscopic delivery to same point
- RTC of 72 patients
- Success rates:
  - Fresh 100%
  - Frozen 83% (p=0.233 vs. fresh)
  - Lyophilized 78% (p=0.022 vs. fresh)
- Restoration of microbial diversity
  - within 7 days in fresh and frozen stool groups
  - within 30 days of lyophilized group

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Jiang and Dupont AP&T 2017
Lee JAMA 2016
Low failure rate with freeze-dried capsules

- 49 patients with rCDI
- As low as 2-3 capsules containing $2 \times 10^{11}$ CFU
- No bowel prep needed
- 12% failure rate at 8 weeks
- Normalization of gut microbiota in 1 months

Staley, Sadowsky, Khoruts AJG 2017
Failure rates impacted most by patient characteristics and CDI characteristics

- Inpatient with multiple comorbidities – 40%
- IBD – 19-25%
- Immunocompromised – 22%
  - SOT recipients – 38%
- Recurrent CDI - 10-20%
- Severe/complicated CDI – 50-75%
  - Pseudomembranous colitis

Risk prediction model for early FMT failure (4 weeks)

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<tr>
<th>Risk Factor</th>
<th>Odds Ratio</th>
<th>Risk Points</th>
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<td>Severe or severe/complicated CDI</td>
<td>5.95</td>
<td>5</td>
</tr>
<tr>
<td>Inpatient FMT</td>
<td>3.78</td>
<td>4</td>
</tr>
<tr>
<td># of previous CDI-related hospitalization</td>
<td>1.43</td>
<td>1</td>
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Risk category/points | Risk of failure
--- | ---
Low = 0 | ≤5%
Intermediate = 1-2 | 15%
High ≥ 3 | >35%

AUC = 0.84

Fischer, Kao, Kelly AJG 2016
Management of FMT non-responders

FMT indication: Recurrent CDI
Steps of FMT non-responder management

1. Assess risk of failure and counsel patient on likelihood and timing of failure
2. Close follow-up
3. Confirm FMT failure
4. Repeat FMT
5. Alternative therapies
6. Recurrence prevention
Step 1: Patient counseling

- At FMT counsel patients on...
  - The patient’s estimated risk for FMT failure
  - Diarrhea may persist or temporarily worsen within 1\textsuperscript{st} week of FMT
  - In general, symptoms should resolve by \textbf{week 1}
    - If diarrhea persists beyond week 1....
    Or if symptoms initially resolve but later recur.....Test stool
  - Alert to symptoms of rCDI in the \textbf{first 4 weeks}
Step 2: Close Post-FMT follow-up

- 1° Non-responder
- Early 2° Non-responder
- Late 2° Non-responder

FMT

Week 1

Week 4

Week 8

Month 6-12

Majority of failures (86%)

Allegretti CGH 2017
Step 3: Confirm FMT failure

• >=3 loose stools defined as BSS type 6-7 within 24 hours
• 2-step testing approach
  • Infection vs. colonization
• Consider alternative diagnosis when...
  • Prior to FMT negative stool testing while patient is still symptomatic
  • < 50% improvement on vancomycin/fidaxomicin
    • 25% referred for FMT don’t have C. diff
    • 26% post-FMT have IBS symptoms (11% pre-existing IBS)

• Alternative causes of chronic diarrhea
  ✓ IBS
  ✓ IBD
  ✓ Microscopic colitis
  ✓ Bile salt malabsorption
  ✓ Celiac disease
  ✓ Chronic pancreatitis
  ✓ Alternate infection
  ✓ Factitious diarrhea

Jackson JCGH 2016, Khoruts CGH 2016, Allegretti DDW 2017
Step 4: Repeat FMT
Success rate increases with repeat FMT

• Success rates after 2 FMTs
  • delivery route
    ➢ Colonoscopy 90% → 100%
    ➢ Via enema: 62% → 85%
    ➢ Duodenal 81% → 94%
  • patient or CDI characteristics
    ➢ Immunocompromised 78% → 89%
    ➢ IBD 75% → 90%
    ➢ Severe CDI and/or complicated CDI 50% → 70-91%

Step 4: Management of multiple FMT failures

• Repeat FMT (3rd)
  Options:
  • Via colonoscopy (if the first 2 were delivered via alternative routes)
  • Upper + lower route (100% success)
  • Fresh stool (if prior FMT with frozen)

• Or... consider alternative therapy
Step 5: Alternative/Adjunctive therapies

- Treat underlying IBD, if applies

- Vancomycin taper
- Vancomycin taper + fidaxomicin chaser
- Fidaxomicin taper
- Vancomycin taper (8 weeks) + Kefir tid

- Elderly, frail patient, limited life-expectancy, pregnancy, or needing ongoing antibiotic therapy
  - Suppressive, low dose vancomycin
    - 125 mg qd - q3d indefinitely

Soriano Open Forum ID 2014, Bakken CID 2015
Step 5: Alternative/adjunctive therapies

Bezlotoxumab: 10% ARR in CDI recurrence
6% ARR in CDI-related 30-day readmission rate
Step 6: Recurrence Prevention

Do not resume vancomycin after FMT for recurrent CDI

Home disinfection
- Spores survive > 5 months
- Clean high-touch surface areas
- EPA approved sporicidal agents

Do not “test for cure”

Antibiotic stewardship
- Gut-sparing Abx
- ? benefit from prophylactic probiotics or vancomycin

Khoruts JAC 2017, Fischer DDW 2017 Tu1914, Allegretti CDI 2017
Management of FMT non-responders

FMT indication: Severe/complicated CDI
Severe CDI/Pseudomembranous colitis

- Dramatically different phenotype
- Unsustained response to single FMT
- Repeat FMT is often needed for cure

- FMTs in rapid cycles (q3 days) (Cammarota trial)
  - 100% cured (5/5)
  - On average # 3 FMTs given

- FMT plus selected use of vancomycin (IU protocol)
  - 91% cure (52/57)
  - On average # 1.5 FMTs given

Severe and Severe/Complicated CDI

Vancomycin po/rectal ± metronidazole ≥ 5 days

Colonoscopy / Sigmoidoscopy

Pseudomembranes present
Vancomycin 125 mg orally four times a day for 5 days

Pseudomembranes absent
Clinical observation with no further intervention

Symptomatic resolution
Vancomycin for 5 additional days (10 days total)
Optional FMT as outpatient

Still symptomatic
Non-Serious Adverse events

• In general FMT is very safe
• SER of 50 studies/1,089 pts
• Non-serious AEs more common with upper routes 44% >> Lower routes 18%
• 1/3 of patients report mild AE within the first week
• Usually transient, no treatment required
  • abdominal discomfort
  • bloating
  • borborygmi
  • increased stool frequency
  • constipation
  • nausea/emesis
  • low-grade fever

Wang PLOS 2016
Serious Adverse Events

- Possibly related SAEs: 0.2-2% of FMTs
- Lower >> Upper
  - due to procedural complications
  - death due to infection
    - *E. coli, Proteus mirabilis, Citrobacter, Enterococcus faecium, CMV, norovirus*
    - No SAEs have been attributed to fecal material itself
  - new autoimmune disease
  - IBD flare
- Biobanks quarantine (~6 weeks) before shipment and keep aliquots (~2 years), making stool traceable to donor

Wang PLOS 2016, Osman ID week 2016
Universal donor: What can go wrong?
A donor with latent Crohn's disease

- 28 yo healthy donor, no PMH or FH
- dx with ileocolonic Crohn’s soon after donation
- Among the 31 recipients
  - 5 had pre-existing IBD
    - (3 UC, 2 Crohn’s disease)
    - 7 were immunocompromised

- None of the recipients developed any symptoms suggestive of IBD over 20 months f/u
- 3 patients with pre-existing IBD improved, 2 unchanged

- When using universal donor: quarantining stool is good idea
- Long-term safety of FMT is unknown....
- AGA FMT registry
Take home points

• 10-30 % of patients will fail after the first FMT
• Majority of failures occur within 4 weeks
• Follow-up phone call at 1 week to assess for 1° non-responder
• Follow-up phone call/clinic visit at week 4 to assess for early 2° non-responder
• Severe CDI, inpatient status, previous CDI related hospitalizations increase the risk of failure
  • Should plan on repeat FMTs
• Simple failure risk prediction tool is available
• Repeat FMT as many times as you deem reasonable if the patient is willing or consider alternative therapy
And if nothing works.....

My secret recipe... made in Indiana
Thank you

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