Indications for Fecal Transplantation: Current and Future Implications

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Objectives

- Understand indications for a fecal transplant (FMT)
- Understand the methods for an FMT
- Know the evidence for FMT and contraindications for various gastrointestinal (GI) disorders
Gut microbiome: The basics

- Distinct human organ responsible for multiple physiologic functions
- Composed of bacteria, archaea, fungi, viruses
- 1 kg of the average adult body weight
- Large scale surveys
  - Human Microbiome Project in US
  - MetaHIT in Europe

Diseases associated with alterations in the gut microbiome: When the gut microbiome is no longer healthy

- Multiple sclerosis
- Chronic fatigue syndrome
- Atherosclerosis
- Inflammatory thrombocytopenic purpura
- Non-alcoholic fatty liver disease
- Insulin resistance/ type 2 diabetes mellitus
- C difficile infection
- Irritable bowel syndrome
- Inflammatory bowel disease

**Clostridium difficile infection (CDI)**

- Best example of disease resulting from alteration of the gut microbiome.
- Gram +, anaerobic, spore-forming
- 2 large toxins: A and B
- Binary toxin: NAP1/027/BI strain: North American Pulsed Field type 1 (NAP1), restriction endonuclease analysis (REA) type BI, or polymerase-chain-reaction ribotype 027


**Pathogenesis of CDI**

Pathogenesis of CDI

McCollum D and Rodriguez JM. Clinical Gastroenterology and Hepatology 2012;10:581-592
CDI: What is the problem?

- In 2010, the yearly incidence of CDI was estimated at 500,000, with a mortality at 15,000 – 20,000.
- Increasing rates of colectomy and mortality
- Cost of managing CDI is estimated to be at least $1 billion dollars annually in the U.S. alone.
- Recurrence rates after initial episode are approximately 10-20%.
- At least 65% of patients who have one recurrence of CDI will likely have recurrent CDI after antibiotics are completed.

<table>
<thead>
<tr>
<th>Severity</th>
<th>Criteria</th>
<th>Treatment</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-to-moderate</td>
<td>Diarrhea and any sign or symptom not severe or complicated</td>
<td>Metronidazole 500 mg orally TID x 10 days, or, vancomycin 125 mg orally QID x 10 days</td>
<td>If no improvement in 5-7 days, consider changing to vancomycin standard dose</td>
</tr>
<tr>
<td>Severe</td>
<td>Serum albumin &lt; 3g/dL + ONE of the following:</td>
<td>Vancomycin 125 mg orally TID x 10 days</td>
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<tr>
<td></td>
<td>•WBC ≥ 15,000 cells/mm³</td>
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<tr>
<td></td>
<td>•Abdominal tenderness</td>
<td></td>
<td></td>
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<tr>
<td>Severe and complicated</td>
<td>Any of the following:</td>
<td>Vancomycin 500 mg orally QID and metronidazole 500 mg IV q8h, and vancomycin per rectum QID</td>
<td>Surgical consultation suggested</td>
</tr>
<tr>
<td></td>
<td>•Admission to the ICU</td>
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<tr>
<td></td>
<td>•Hypotension</td>
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<tr>
<td></td>
<td>•Fever ≥ 38.5 C</td>
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<td></td>
<td>•Ileus</td>
<td></td>
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<tr>
<td></td>
<td>•Mental status changes</td>
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<tr>
<td></td>
<td>•WBC ≥ 35,000 cells/mm³ or &lt; 2,000 cells/mm³</td>
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<tr>
<td></td>
<td>•Serum lactate &gt; 2.2 mmol/L</td>
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<td></td>
<td>•End organ failure</td>
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Fidaxomicin

- Macrocyclic antibiotic
- More active *in vitro* than vancomycin, by a factor of approximately 8, against clinical isolates of *C. difficile*, including NAP1/BI/027 strains
- Minimal systemic absorption
- High fecal concentrations

Fidaxomicin versus Vancomycin for *Clostridium difficile* Infection: Noninferiority trial

![Fidaxomicin versus Vancomycin](image)

1st end point


Cost of therapy for CDI

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Cost per dose</th>
<th>Regimen</th>
<th>Cost per 10-day regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 500 mg</td>
<td>$0.73</td>
<td>500 mg three times a day</td>
<td>$22.00</td>
</tr>
<tr>
<td>Vancomycin 125 mg pills</td>
<td>$17.00</td>
<td>125 mg four times a day</td>
<td>$680.00</td>
</tr>
<tr>
<td>Vancomycin 125 mg IV compounded for oral</td>
<td>$2.50 – $10.00</td>
<td>125 mg four times a day</td>
<td>$100.00 – $400.00</td>
</tr>
<tr>
<td>Fidaxomycin 200 mg</td>
<td>$140.00</td>
<td>200 mg twice a day</td>
<td>$2,800.00</td>
</tr>
</tbody>
</table>

Recurrent CDI (rCDI): Recurrent infection within 8 weeks of completion of therapy

- Impaired host immune response or alteration of the colonic microbiota
- No uniform effective therapy
- Recurrence rates after initial episode: 10-20%
- At least 40-65% of patients who have one recurrence of CDI will likely have recurrent CDI after antibiotics are completed

Recurrent CDI: How to treat it?

- 1<sup>st</sup> recurrence: same regimen for the initial episode can be used
- 2<sup>nd</sup> recurrence: pulsed vancomycin regimen
- Fidaxomicin: role in rCDI is not well established
- IVIG: role in rCDI unclear, retrospective data equivocal. There may be some benefit in patients with hypogammaglobulinemia. Immunologist evaluation
- Rifampin or rifaximin (“rifaximin chaser”): limited data to support efficacy. No current role in rCDI.
Vancomycin taper

- Starting dose 125 mg every 6 hours for 2 weeks
- Taper to 125 mg every 12 hours for 1 week
- Taper to 125 mg daily for 1 week
- Taper to 125 mg every other day for 1 week
- Taper to 125 mg every third day for 2 weeks
- Total of 7 weeks of therapy

Investigational and other therapies for rCDI

- Investigational
  - Monoclonal antibody to toxins A and B as an adjunct to antibiotics: phase III trials
  - Vaccine containing toxoids A and B: in trials

- Other therapies for rCDI
  - Probiotics: insufficient evidence to support routine use
    - *Saccharomyces boulardii*
    - *Lactobacillus GG*
    - Kefir
  - Bile salt binders: no evidence
  - Whole gut lavage: no evidence
Treatment of ≥3 CDI recurrences

• What to do when all else fails?

Super Poo!

Here I come...
To save the day!
Fecal Microbiota Transplantation (FMT)

• **CONCEPT:**
  - Stool from healthy individual is instilled into a sick person to cure a certain disease

• **GOAL:**
  - Reconstitute the normal microbial homeostasis and break the cycle of antibiotic agents that may further disrupt the microbiome.
FMT indications: The present

• Recurrent CDI
  • 3 or more episodes of mild to moderate CDI and failure of vancomycin taper, or
  • 2 episodes of CDI that result in hospitalization

• Moderate CDI not responding to standard therapy for at least 1 week


Clinical resolution rates of rCDI with FMT

• 245/273 patients with clinical resolution, ~90%

• Lower GI FMT delivery better than upper GI FMT delivery

• To this point no RCT’s had been published.

Duodenal Infusion of Donor Feces for Recurrent
Clostridium difficile


Duodenal infusion of FMT for rCDI

What is the process for FMT??

Recipient Screening

• Inclusion criteria for recipient
  • 3rd or greater episode of *C. difficile* infection
  • Proven by a positive *C. difficile* stool assay
  • Previous treatment with 1st line therapies for *C. difficile* infection (vancomycin, metronidazole, or fidaxomicin)
  • Previous receipt and failure of at least 1 course of a 6-8 week vancomycin taper
  • Refractory moderate to severe *C. difficile* diarrhea, failing vancomycin therapy after >1 week
  • Able to safely undergo and consent to colonoscopy
  • Able to identify potential donor and pay for donor screening – *family member / household contact* is preferred
  • Ability to stop gastric acid suppression (at least 7 days prior procedure) medications and concomitant antibiotics

• Exclusion criteria for recipient
  • Severe bowel disease precluding colonoscopy
  • Severe underlying immunosuppression
  • Decompensated liver cirrhosis
  • Severely ill ICU patients
Donor screening

- *Family member / household contact is preferred*
- Exclude those with:
  - Active communicable illness (HIV, HBV, HAV, HCV)
  - Metabolic syndrome or an autoimmune disorder
  - Recent or chronic diarrheal disorder
  - Irritable bowel syndrome, chronic constipation or diarrhea
  - Inflammatory bowel disease
  - Known colonic GI malignancy or polyposis syndromes
  - High risk sexual behavior (Men having sex with men, HIV, Multiple partners)
  - Illicit drug use; recent tattoos or incarceration
  - Exposure risk for hepatitis or HIV in the past 12 months
  - Travel to high risk areas for infectious diarrhea in past 6 months
  - High risk for Creutzfeldt-Jakob disease
  - History of *C. difficile* infection
  - Hospitalization within the past 3 months
  - Antibiotics within the last 3 months
  - Immunosuppressive or antineoplastic medication use
  - Fever of unknown origin or any suspected infectious disease

What do you need to perform an FMT?
FMT team

- Jamie Dozier, RN
- Brandon Lovell
- Carrie Rano, RN
- Vitaly Shchurovskiy
- Rachel Lapaille
- Cassaudra Strong, LPN
FMT in MCF

- To date 14 patients, no recurrences
- Patients who are potential candidates can be seen by:
  - Dr. Maria Vazquez Roque in GI, or
  - Dr. Lisa Brumble in ID
- Will adhere to the recipient inclusion criteria and strict donor criteria
- In the process of getting standard donor and talks for a stool biorepository ("stool bank")
- FDA: “enforcement discretion” of investigational new drug application (IND) for FMT for rCDI

FDA regulations on FMT for rCDI

<table>
<thead>
<tr>
<th>Fall 2012: Feces considered a drug</th>
<th>June 2013: “enforcement discretion”</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2013: FDA required IND for FMT</td>
<td>March 2014: “enforcement discretion”</td>
</tr>
</tbody>
</table>

Enforcement discretion based on:

1. Adequate informed consent from the patient.
   - Statement that the use of FMT products to treat CDI is investigational and a discussion of its potential risks.
2. Donor is known to either the patient or the treating health care provider.
3. The stool donor and stool are qualified by screening and testing performed under the direction of the health care provider for the purpose of providing the FMT product to treat his or her patient.
FDA regulations on FMT for rCDI

Fall 2012: Feces considered a drug
June 2013: "enforcement discretion"

FMT for any other indication that is not rCDI requires an IND

1. Adequate informed consent from the patient.
   • Statement that the use of FMT products to treat CDI is investigational and a discussion of its potential risks.
2. Donor is known to either the patient or the treating health care provider.
3. The stool donor and stool are qualified by screening and testing performed under the direction of the health care provider for the purpose of providing the FMT product to treat his or her patient.

FMT for rCDI in the immunocompromised patient

- Multicenter retrospective series
- 80 patients, outcomes within 12 weeks of FMT
- 12/80 (15%) had an SAE
  • 2 deaths
  • 4 IBD flares
  • 1 post procedure
  • No direct infection directly attributed to FMT

What about FMT in other conditions associated with alterations in the gut microbiome?
Diseases associated with alterations in the gut microbiome: When the gut microbiome is no longer healthy

<table>
<thead>
<tr>
<th>Disease or condition</th>
<th>Proposed mechanism</th>
<th>Evidence</th>
<th>Possible therapies available to alter microbiota</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDI</td>
<td>Reduced microbial diversity</td>
<td>Animal and human studies</td>
<td>FMT for treatment of recurrent CDI</td>
</tr>
<tr>
<td>IBS</td>
<td>Reduced microbial diversity and decreased Bacteroidetes</td>
<td>Animal and human studies</td>
<td>Probiotics for treatment of IBS, trials of FMT to start soon</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
<td>Reduced microbial diversity</td>
<td>Human studies</td>
<td>Probiotics (VSL #3) for treatment of pouchitis, trials of FMT ongoing</td>
</tr>
<tr>
<td>Obesity and metabolic derangements</td>
<td>Reversed Firmicutes to Bacteroides ratio</td>
<td>Animal and human studies</td>
<td>Trials of FMT ongoing</td>
</tr>
<tr>
<td>Allergic disorders</td>
<td>Reduced microbial diversity</td>
<td>Animal and human studies</td>
<td>Studies of probiotics ongoing, not for FMT</td>
</tr>
<tr>
<td>MDRO colonization</td>
<td>Reduced microbial diversity</td>
<td>Human studies</td>
<td>Studies of probiotics ongoing, not for FMT</td>
</tr>
</tbody>
</table>
What does the future hold for FMT?

A pill full of poop? Try 35 of them
Is the future bright for FMT?

• “RePOOPulate” trial
  • Stool substitute preparation, made from purified intestinal bacterial cultures derived from a single healthy donor

• Modified FMT (mFMT)
  • Encapsulated stool that has been chemically manipulated aiming to eliminate pathogenic organisms from standard healthy stool donors

SER-109 or mFMT

• Single-arm, open-label clinical trial
• About 30 capsules, divided in 2 consecutive days.
• Preliminary data from the trial demonstrates the response of rCDI in 29 of the 30 patients enrolled and no recurrences to date.
• Larger clinical trial planned for later 2014-5.
Summary

• rCDI is the best understood condition between host and disease
• FMT has been promising in restoring the healthy gut microbiome and treating rCDI.
• FMT may have other implications in treating other diseases such as obesity and IBD, but to date not enough data to support its role in these scenarios.
• Only FDA indication for FMT were enforcement discretion is applied is for rCDI

Thank you!
FMT for chronic constipation

- Bacterial species inhibit motility by secretion of toxins
- 3 patients with CC; one month after FMT all patients had daily or qod bowel movements.
- Consecutive 45 patients with CC treated with liquid culture of non-pathogenic bacteria.
  - 40/45 (89%) of patients obtained relief in defecation
  - At follow-up: 18/30 (60%) continued to have normal defecation without laxative use.


Summary of FMT for IBS

- The role of the gut microbiome and development of symptoms in IBS is currently under study.
- Ongoing clinical trials in Europe
- Not recommended clinically
FMT for inflammatory bowel disease: ulcerative colitis

- ~15 ongoing clinical trials
- Variable results across case series

Randomized trial of FMT in UC

- N = 61
- Primary endpoint: remission of UC defined by Mayo score
- 50 mL retention enema 1x/week x 6 weeks

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Transplant group n=31</th>
<th>Placebo group n=30</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remission</td>
<td>7 (23%)</td>
<td>2 (7%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mayo score</td>
<td>6.36</td>
<td>6.3</td>
<td>0.95</td>
</tr>
<tr>
<td>IBDQ score</td>
<td>148.4</td>
<td>146.4</td>
<td>0.85</td>
</tr>
<tr>
<td>EQ5D score</td>
<td>61.0</td>
<td>66.2</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Summary FMT in IBD

- Not recommended clinically
- Less response seen in Crohn’s disease
- Multiple vs. single sessions
- To do procedure in this group of patients, an IND by the FDA is necessary.

FMT and metabolic syndrome
FMT improves insulin resistance

- FMT from obese and lean mice into germ-free mice.

- Improved insulin resistance in obese humans who received FMT from lean individuals


Summary FMT in metabolic syndrome

- Causality not established
- Interaction remains to be completely defined
  - Human genetics
  - Diet
  - Human gut microbiota
- At least 2 clinical trials are starting soon to evaluate the role of FMT in obesity and diabetes
FMT for multiple sclerosis

- 3 patients with MS treated with FMT infusions for chronic constipation
- Follow up: 2-15 years
- All 3 patients had reversal of neurological symptoms
- Speculation of FMT eradicating a GI pathogen driving the MS symptoms.
- To date, no further studies evaluating the role of FMT in MS.


Reversal of Idiopathic Thrombocytopenic Purpura with FMT?

- 39 y/o female with UC and ITP
- Offered FMT to manage her UC
- Prior to FMT mean PLT 96,180 and months after FMT her mean PLT count was 190,000
- Marked reduction of UC symptoms, with 2-3 semi-formed BM daily with no bleeding
- Observational
- No larger cohort or longitudinal trial to date.