Fecal Microbiota Transplantation
CDDW Small Group Session
March 5, 2017 (11:50-12:30)

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University of Alberta
Name: Dr. Nikhil Pai

**Financial Interest Disclosure**
*(over the past 24 months)*

<table>
<thead>
<tr>
<th>Commercial Interest</th>
<th>Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbvie</td>
<td>Consultant</td>
</tr>
<tr>
<td>Janssen</td>
<td>Consultant</td>
</tr>
<tr>
<td>Rebiotix</td>
<td>Research materials</td>
</tr>
</tbody>
</table>


Name: Dr. Karen Wong

Financial Interest Disclosure
(over the past 24 months)

No relevant financial relationships with any commercial interests
**CanMEDS Roles Covered**

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Expert</strong></td>
<td>(as <em>Medical Experts</em>, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. <em>Medical Expert</em> is the central physician Role in the CanMEDS Framework and defines the physician’s clinical scope of practice.)</td>
</tr>
<tr>
<td><strong>Communicator</strong></td>
<td>(as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)</td>
</tr>
<tr>
<td><strong>Collaborator</strong></td>
<td>(as <em>Collaborators</em>, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)</td>
</tr>
<tr>
<td><strong>Leader</strong></td>
<td>(as <em>Leaders</em>, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)</td>
</tr>
<tr>
<td><strong>Health Advocate</strong></td>
<td>(as <em>Health Advocates</em>, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)</td>
</tr>
<tr>
<td><strong>Scholar</strong></td>
<td>(as <em>Scholars</em>, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)</td>
</tr>
<tr>
<td><strong>Professional</strong></td>
<td>(as <em>Professionals</em>, physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)</td>
</tr>
</tbody>
</table>
Objectives

1. How is fecal microbial transplant (FMT) done and advantages/disadvantages of different FMT delivery modalities?

2. Describe indications for fecal microbial transplant (FMT) in Clostridium difficile infection in adult and pediatric patients

3. What is the approach to treatment of patients with concomitant IBD and recurrent C. difficile?

4. Discuss short and long-term safety profile of FMT
Case Presentation
Patient with 12 Year History of Ulcerative Colitis

- 61 yo male
- History of ulcerative pancolitis
- Diagnosed 2004, maintained on Asacol
  - 2006 – flare up – treated with steroids
  - 2011 – flare up – treated with steroids
- CABG in July 2015 for triple vessel disease
Recurrent Episodes of C. Difficile Colitis

<table>
<thead>
<tr>
<th>Date</th>
<th>Symptoms</th>
<th>C. Difficile Test</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sept 14</td>
<td>Watery diarrhea</td>
<td>PCR +ve</td>
<td>Flagyl x 14 days</td>
</tr>
<tr>
<td>Oct 23</td>
<td>Watery diarrhea</td>
<td>Toxin +ve</td>
<td>Vancomycin x 14 days</td>
</tr>
<tr>
<td>Nov 23</td>
<td>Watery diarrhea</td>
<td>PCR +ve</td>
<td>Vancomycin x 7 week taper</td>
</tr>
<tr>
<td>Feb 11</td>
<td>Watery diarrhea*</td>
<td>PCR +ve</td>
<td>Vancomycin</td>
</tr>
</tbody>
</table>

*Partial response only:
- 8-10 BM/d with 20% blood
- 30 pound weight loss
- No abdominal pain or fevers

Referred for FMT
Colonoscopy Performed for IBD Disease Staging

- Feb 24, 2016: colonoscopy performed
  - Persistent blood in stools after vancomycin taper
  - Scope showed moderately active pancolitis

How would you manage this patient?
Corticosteroid Treatment Initiated

- Hb 122, MCV 81, CRP 57
- C. difficile – negative

- Treated with IV solumedrol → oral prednisone
- Vancomycin continued, ↓125mg bid until FMT
- CRP normalized
Repeat Colonoscopy Performed and $\alpha_4\beta_7$ Started

• June 10, 2016: colonoscopy for FMT
  • Mild MAYO 1 disease

• July 1, 2016:
  • Started vedolizumab
  • Healthy in followup
  • No further episodes of C. difficile
Objective 1: How is fecal microbial transplant done?

Advantages/disadvantages of different FMT delivery modalities
No Standardized Methodology for FMT

• Several different methods published
• Little variation in clinical effectiveness across techniques of delivery
Step 1: Universal Donor Screening (UAH Model)

- **Initial**
  - Detailed history and physical exam
  - Donor questionnaire (to identify high risk behaviors)
  - Test negative for infections

- **Subsequent**
  - Rescreened every 4 months

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# UAH Donor Questionnaire

## Donor Questionnaire for human biotechnology/ fecal microbiota transplantation

### You

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling healthy and well today?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Currently taking an antibiotic?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Currently taking any other medication for an infection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4. Currently taking any immunosuppressant medication by mouth or injection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. History of chronic diarrhea persisting &gt; 10 days?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. History of blood in stool not related to hemorrhoid?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. History of change in bowel habit, alternating from constipation to diarrhea?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Any type of active cancer that is not cured?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9. Any active autoimmune diseases?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### the past 12 weeks have you

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>10. Had any vaccinations? (if yes, please indicate which one(s))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Had contact with someone who had a smallpox vaccination?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12. Had contact with someone who had a mycobacterium leprae infection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13. Had contact with someone who had a mycobacterium tuberculosis infection?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>14. Had shigellosis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15. Had gonorrhea?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Had a recent diagnosis of a sexual transmitted disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Had a recent diagnosis of a sexually transmitted infectious disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### the past 16 weeks have you

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>18. Had a recent diagnosis of a sexually transmitted infectious disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>19. Had Chagas’ disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20. Had malaria?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21. Had Babesiosis?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### the past 12 months have you

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>23. Had sexual contact with anyone who has hemophilia or has used clotting factor concentrates?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything not prescribed by their doctor?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### the past 3 years have you

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>30. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### you EVER

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>31. Had a positive test for the HIV/AIDS virus?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>32. Used needles to take drugs, steroids, or anything not prescribed by your doctor?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>33. Used clotting factor concentrates?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>34. Had a tattoo?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35. Had a body piercing?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36. Had an accident that resulted in a break in the skin or mucous membranes?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>38. Received a dura mater (or brain covering) graft?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>39. Had sexual contact with anyone who was born in or lived in Africa?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40. Have any of your relatives had Cretzfeldt-Jakob disease?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41. Have any of your relatives had Cretzfeldt-Jakob disease?</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

To the best of my knowledge, the above information is accurate and true.

**Donor’s Signature:**

**Date:**
Donor Screening Methods Also Show Variation

- Other models:
  - OpenBiome (publically funded stool bank) publishes screening protocol (*appendix*)
  - Rebiotix (private biotech, supporting several Canadian RCTs) publishes screening protocol

- Donor interval retesting standards common
Health Canada Offers “Guidance Document” Only

• Health Canada Guidance Document:
  • Single donor
  • Known to physician or patient
  • Screening (infections, “cancer,” medications, health/lifestyle questionnaires)
  • Record-keeping of donor ID

• No allowance for public stool banks outside of research/special exemption

Sample Published Methods for FMT Delivery

**METHOD A**
- Blend 50g of stool
- Dilute mixture with saline to 250mL
- Filter down to 0.25mm with sieves
- Administer 250mL

**METHOD B**
- Blend 100g of stool
- Emulsify with wooden spatula
- Add drinking water to 300mL
- Filter with gauze
- Administer only 50mL

**METHOD C (UAH)**
- Blend 100g in 400mL (colonoscopy)
- Blend 50g in 200mL (EGD)

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Methodological Questions Have Been Addressed

- **Fresh versus frozen FMT**
  - (2016, JAMA) Frozen product equally effective for treatment of rCDI
  - n=219 (mITT population); 75.0% vs. 70.3% (p<0.001 for noninferiority)

- **UGI versus LGI FMT administration**
  - UGI associated with rare cases of aspiration pneumonia
  - Trend towards higher resolution with LGI route
    - n=273
    - 91.2% (95% CI: 86-95%) versus 82.3% (95% CI 69–90%)

- **Oral microbial capsules versus colonoscopy similar efficacy**

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# RCT of Oral Microbial Capsules versus Colonoscopy for rCDI

Kao D, Wong K et al. 2017. Unpublished data

<table>
<thead>
<tr>
<th></th>
<th>Oral Microbial Capsule (n=56)</th>
<th>Colonoscopy (n=59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cure rate after 1 FMT</td>
<td>98%</td>
<td>95%</td>
</tr>
<tr>
<td>Cure rate after 2 FMT</td>
<td>100%</td>
<td>98%</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• FMT related infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>• Death</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>• Colonic perforation</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Adverse events</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>• Nausea</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>• Vomiting</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>• Transient fever</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>• IBD flare</td>
<td>0</td>
<td>2</td>
</tr>
</tbody>
</table>
FMT Has Several Key Practical Considerations

• Setup: supplies, handling of biohazards, cleaning precautions

• Method of delivery
  • Challenges of endoscopic administration particularly in pediatrics

• No evidence that pediatric protocols need be different than adult
Objective 2: Describe indications for fecal microbial transplant (FMT) in *Clostridium difficile* infection

In adult and pediatric patients
FMT for rCDI is Only Health Canada Approved Indications

- Recurrent *Clostridium difficile* colitis
- **Research Trials:**
  - Inflammatory bowel disease (UC/CD; adult, pediatric)
  - Metabolic syndrome (obesity, diabetes)
  - Hepatic encephalopathy
  - Multidrug resistant organism eradication
  - Chronic intestinal pseudoobstruction
  - Chronic constipation
  - Liver cirrhosis
  - NASH
  - Irritable bowel syndrome
Definition of *Recurrence* in rCDI

1. **Recurrent or relapsing CDI:**
   a) Three or more episodes of mild-moderate CDI and failure of 6-8wk taper with vancomycin with or without alternative antibiotic (ie. Rifaximin, nitazoxanide, fidaxomicin)
   b) At least two episodes of CDI resulting in hospitalization and associated with significant morbidity

2. Moderate CDI not responding to standard therapy (vancomycin or fidaxomicin) for at least a week

3. Severe (even fulminant CDI) with no response to standard therapy after 48 hours

FMT is Effective for rCDI

- 3 randomized-controlled trials, 29 case series

Fecal Microbiota Transplantation for *Clostridium difficile* Infection: Systematic Review and Meta-Analysis

| Table 3. Subgroup analysis for fecal microbiota transplantation in *Clostridium difficile* |
|-----------------------------------------------|-----------------|-------------------|------------------|------------------|
| Subgroups                                    | Unweighted rate n/N (percentage) | Weighted rate (95% CI) | Proportion difference of unweighted rate (95% CI, P value) | Proportion difference of weighted rate (95% CI, P value) |
| **Delivery modality**                        |                               |                   |                  |                  |
| Lower gastrointestinal delivery (colonoscopy, enema) | 203/222 (91.4%) | 91.2% (86.0%, 95.2%) | 9.1% (-0.1%, 22.1%), P=0.046 | 10.5% (-0.6%, 21.8%), NS |
| Upper gastrointestinal delivery (nasogastric/nasojejunal tube, gastroscopy, gastrostomy tube) | 42/51 (82.3%) | 80.6% (69.3%, 89.8%) |                  |                  |
| **Donor type**                               |                               |                   |                  |                  |
| Patients selected (related family member, partner, spouse, close friend) | 196/219 (89.5%) | 89.2% (83.2%, 94.0%) | -1.2% (-8.5%, 9.9%), NS | -0.7% (-10.5%, 9.1%), NS |
| Anonymous                                    | 49/54 (90.7%) | 89.9% (80.3%, 96.6%) |                  |                  |

FMT is Similarly Effective for rCDI in Pediatric Patients

- Pediatric data for FMT in rCDI limited
- 9 case series (n=45) show similar efficacy as adult trials
- No significant differences in technique

<table>
<thead>
<tr>
<th>Ref</th>
<th>AGE (yr)</th>
<th>n</th>
<th>FMT route</th>
<th>Response rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hourigan et al[22], 2015</td>
<td>6-17</td>
<td>8</td>
<td>Colonoscopy</td>
<td>100%</td>
</tr>
<tr>
<td>Kronman et al[35], 2015</td>
<td>6-17</td>
<td>10</td>
<td>NG</td>
<td>90%</td>
</tr>
<tr>
<td>Wang et al[58], 2015</td>
<td>1</td>
<td>1</td>
<td>NJ</td>
<td>100%</td>
</tr>
<tr>
<td>Kelly et al[10], 2014</td>
<td>6-16</td>
<td>5</td>
<td>Not specified</td>
<td>89% (whole series)</td>
</tr>
<tr>
<td>Pierog et al[54], 2014</td>
<td>1-21</td>
<td>6</td>
<td>Colonoscopy</td>
<td>100%</td>
</tr>
<tr>
<td>Russell et al[57], 2014</td>
<td>1-21</td>
<td>10</td>
<td>NG (2); Colonoscopy (8)</td>
<td>90%</td>
</tr>
<tr>
<td>Walia et al[59], 2014</td>
<td>1-2</td>
<td>2</td>
<td>Colonoscopy</td>
<td>100%</td>
</tr>
<tr>
<td>Rubin et al[60], 2013</td>
<td>6-8</td>
<td>2</td>
<td>NG (64); EGD (7); Gastrostomy (previously placed) (4)</td>
<td>50%</td>
</tr>
<tr>
<td>Kahn et al[44], 2012</td>
<td>1</td>
<td>1</td>
<td>Colonoscopy</td>
<td>100%</td>
</tr>
</tbody>
</table>

Objective 3: Approach to patients with concomitant IBD and recurrent *Clostridium difficile* infection
Patients with IBD Have Unique Bacterial Signatures

- High proportion of patients with concurrent IBD and rCDI
- Unique intestinal microbial signatures in Crohn’s and ulcerative colitis patients
- Reduced FMT treatment effectiveness for rCDI in IBD patients
Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection

Alexander Khoruts,*⁺‡ Kevin M. Rank,* Krista M. Newman,* Kimberly Viskocił,* Byron P. Vaughn,* Matthew J. Hamilton,‡ and Michael J. Sadowsky‡

<table>
<thead>
<tr>
<th></th>
<th>rCDI alone (n=229)</th>
<th>rCDI + IBD (n=43)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>60.8 ± 17.3</td>
<td>38.8 ± 17.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female gender</td>
<td>73%</td>
<td>51%</td>
<td>0.0065</td>
</tr>
<tr>
<td>IBD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BM 24hrs pre FMT</td>
<td>5.2 ± 4.6</td>
<td>8.3 ± 7.2</td>
<td>0.0044</td>
</tr>
<tr>
<td>Success after 1 FMT</td>
<td>92%</td>
<td>75%</td>
<td>0.0018</td>
</tr>
<tr>
<td>Success after ≥2 FMT</td>
<td>98.7%</td>
<td>82.9%</td>
<td></td>
</tr>
<tr>
<td>IBD flare post FMT</td>
<td></td>
<td>11 (25%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>*4/11 had left sided colitis at time of FMT</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Table 4.** Multivariate Analysis for Clinical Factors Associated With Failure of Initial FMT to Clear CDI

<table>
<thead>
<tr>
<th>Variable</th>
<th>aOR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.01 (0.99–1.04)</td>
<td>.2</td>
</tr>
<tr>
<td>Gender</td>
<td>0.9 (0.4–2.1)</td>
<td>.8</td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>0.4 (0.1–1.2)</td>
<td>.08</td>
</tr>
<tr>
<td>IBD</td>
<td>8.7 (2.4–30.8)</td>
<td>.0008</td>
</tr>
</tbody>
</table>

Fecal microbiota transplantation is safe and efficacious for recurrent or refractory *Clostridium difficile* infection in patients with inflammatory bowel disease.
FMT for Crohn’s Disease, Ulcerative Colitis Less Studied

• Systematic review of FMT in IBD (2014 JCC): 18 studies, n=122 (79 UC; 39 CD; 4 IBD-U)
  • Median f/u: 6wk (range: 1wk – 13yrs)
  • 37% clinical response for CD (I²=37%; moderate heterogeneity in results)
  • 22% clinical response for UC (I²=0%; little heterogeneity in results)

• Meta-analysis (2016 Mucos Immun): 9 UC publications, n=118
  • 30.3% clinical response for UC (95% CI: 19.3-44.2%)

3 Adult RCTs of FMT for IBD with Differing Results

- 3 RCTs have been performed in adults
- **2017: Borody et al.**
  - Colonoscopic FMT/placebo + 8wk serial enema infusion
  - Clinical + endoscopic remission/response 26.8% vs. 7.5% \(p=0.021\)
- **2015: Moayyedi et al.**
  - Enemas from anonymous healthy donors vs. normal saline placebo
  - Clinical + endoscopic remission in 23.7% vs. 5.4% \(p=0.03\)
- **2015: Rossen et al.**
  - Enemas from anonymous versus autologous
  - Clinical + endoscopic remission in 30.4% vs. 20.0% \(p=0.29\)
Pediatric FMT for IBD Data Limited; 1 Canadian RCT

- No RCTs, 4 pediatric case series:
  - n=25 patients total
  - Different protocols
  - 56% unweight pooled response (combined clinical/endoscopic outcomes)

- McMaster Children’s Hospital: 1st RCT of FMT for children
  - London Children’s Hospital (PI: Dr. Ashok Dhandapani)
  - Sainte Justine’s Children’s Hospital (PI: Dr. Kelly Grzywacz)

FMT for Patients with IBD + rCDI Involves Similar Approach

- Higher rates of 1st FMT failure for rCDI treatment in patients with IBD
  - Irrespective of whether patient is on immunosuppression

- FMT-specific adverse events does not appear to be increased with immunosuppression
  - ~ 20% risk of IBD flare

- IBD may concurrently improve after FMT
  - Best evidence for FMT in IBD involves multiple FMT administrations
  - Treatment of rCDI involves different goals than treatment of IBD

- Best order of treatment (treat IBD first or rCDI first)?
  - Not known

Objective 4: Short & Long-Term Safety Profile of FMT
Safety Data for FMT Very Good, but Limited

- Limited data
- Short-term adverse outcomes described
  - Long-term risks remain speculative, largely based on (germ-free) animal data
- Differentiate endoscopic-related adverse outcomes from those of FMT
Short-term Adverse Outcomes

• Minor
  • Abdominal discomfort, bloating, flatulence, diarrhea, constipation, borborygma, vomiting
  • Transient fevers

• Serious
  • Transmission of enteric pathogens (rare)
    • Norovirus (endoscopy staff, community acquired?)
    • 2 cases C. difficile colitis (not found in donor, activation in recipient?)
    • Peritonitis in patient on peritoneal dialysis
  • IBD flares
  • Aspiration pneumonia

FMT for rCDI Safe in Immunocompromised Patients

- Patients with rCDI often immunocompromised
- 15% had significant adverse event within 12 weeks
  - 1 death (aspiration)
  - 14% IBD patients flared

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>N</th>
<th>IC Reason</th>
<th>Day Post FMT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>SOT</td>
<td>13</td>
</tr>
<tr>
<td>Aspiration</td>
<td>1</td>
<td>SOT</td>
<td>1</td>
</tr>
<tr>
<td>Hospitalizations</td>
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<td></td>
<td></td>
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<td>Fever, diarrhea, encephalopathy</td>
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<td>Cirrhosis</td>
<td>4</td>
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<tr>
<td>Abdominal pain</td>
<td>1</td>
<td>SOT</td>
<td>0</td>
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<tr>
<td>IBD flare</td>
<td>3</td>
<td>IBD</td>
<td>≤84</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>1</td>
<td>ESRD</td>
<td>21</td>
</tr>
<tr>
<td>Colectomy</td>
<td>1</td>
<td>IBD</td>
<td>≤28</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1</td>
<td>End-stage COPD</td>
<td>84</td>
</tr>
<tr>
<td>Influenza B</td>
<td>1</td>
<td>SOT</td>
<td>3</td>
</tr>
<tr>
<td>Catheter inf'n</td>
<td>1</td>
<td>Cancer</td>
<td>14</td>
</tr>
<tr>
<td>Other adverse events</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3</td>
<td>ESRD; SOT</td>
<td>≤84</td>
</tr>
<tr>
<td>Fever</td>
<td>1</td>
<td>SOT</td>
<td>1</td>
</tr>
<tr>
<td>Bloating, Abdominal Pain</td>
<td>3</td>
<td>HIV; ESRD; IBD</td>
<td>1–2</td>
</tr>
<tr>
<td>Hip pain</td>
<td>1</td>
<td>IBD</td>
<td>≤84</td>
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<tr>
<td>Crohn's flare</td>
<td>1</td>
<td>IBD</td>
<td>≤84</td>
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<tr>
<td>Pertussis</td>
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<td>IBD</td>
<td>≤30</td>
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<tr>
<td>Nausea</td>
<td>1</td>
<td>IBD</td>
<td>30</td>
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<tr>
<td>Mucosal tear</td>
<td>1</td>
<td>SOT</td>
<td>0</td>
</tr>
</tbody>
</table>

Total number of study patients 80

- Mean adult age (years) 53 (range 20–88)
- Mean pediatric age (years) 10.9 (range 6.5–16)
- Mean follow-up (months) 11 (range 3–46)

Reason for immunocompromised state:
- Immunosuppressive agents for IBD 36
- Solid organ transplant recipients 19
- HIV/AIDS 3
- Treatment with antineoplastics 7
- Other chronic medical conditions 15

Long-term Adverse Outcomes

• Concerns largely speculative
  • Adult to pediatric FMT: age-related taxonomy
  • Transmission of infectious agents
  • Development of chronic diseases/conditions related to changes in gut microbiota
    • Obesity, diabetes, atherosclerosis, IBD, colon cancer, NAFLD, IBS, asthma, autism, neuropsychiatric conditions
    • Transmissibility of chronic conditions largely shown in *germ-free* animal models
Final Thoughts
Mechanism Behind FMT for rCDI Remains Unknown

• Significant efforts to optimize FMT for rCDI + extrapolation to other indications

• Persistent question: what are we doing?
  • rCDI FMT: recipient microbiome resembles donor microbiome initially
    • recipient microbiome reverts to baseline, CDI does not recur
  • CD/UC: no sustained microbiome difference among patients who respond to FMT, versus those who do not
Therapeutic Changes May Not be Mediated by Bacteria

• Role of bacteriophages in the intestinal microbiome
  • Bacteriophages = bacterial pathogens; modified by diet, antibiotics
  • *Promote* bacterial diversity by adapting, targeting abundant species

• Fungal diversity described in IBD
  • *Aspergillus* negatively correlated with bacterial SCFA production
  • *Candida albicans* promote inflammatory cytokine production

• Primary, secondary bile acids
  • 1° bile acids may promote germination of *C. difficile* spores
  • 2° bile acids may inhibit germination of *C. difficile* spores (2016 PLoS ONE)

Theriot CM, Bowman AA, Young VB. mSphere. 2016;1(1)
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Efficacy of Sterile Fecal Filtrates in Treating rCDI

- (2016 Gastro) Sterile fecal filtrates (devoid of fecal residue, bacteria)
  - 5 immunocompromised rCDI patients
  - Response in all 5 patients
  - Bacterial DNA stimulating host responses via PRRs

Useful Materials for Your Reference

This presentation will be available through CAG/CDDW for your reference

- Health Canada Guidance Document
- NASPGHAN Draft Pediatric Consent
- UAH Adult Consent
- UAH FMT Delivery Protocol
- UAH FMT Screening Protocol
Appendix
FMT Case Presentation: Details

- PMHx:
  - CABG July 2015
  - COPD
  - HTN

- Referred for FMT

- Meds:
  - ASA
  - Plavix
  - HCTZ
  - Olmesartan
Donor Exclusion Criteria (UAH)

- Active cancer
- Autoimmune disease (eg multiple sclerosis, connective tissue disease)
- Metabolic syndrome
- Chronic pain syndrome
- Atopic diseases
- Risk factors for acquisition of HIV, syphilis, Hepatitis B, Hepatitis C, prion or any neurological disease
- Gastrointestinal comorbidities (IBD, IBS, chronic constipation or diarrhea, GI malignancy, known polyposis)
- Tattoo or body piercing within 6 months
- History of incarceration
- Blood transfusion from a country other than Canada within 6 months
- Antibiotic, immunosuppressive, biological, antineoplastic, exogenous glucocorticoids within 3 months
- Live vaccine within 3 months
- Ingestion of nut or shellfish within 3 days if recipient has known allergies to these foods
- Any current or previous medical/psychosocial condition which, in the opinion of the investigator, may pose risk to the recipients
- Travel to areas where diarrheal illnesses or BSE/TSE are endemic within 6 months
Donor Investigations

- Blood
  - CBC, electrolytes, creatinine, AST, ALT, ALP
  - HIV 1/2
  - Hepatitis A: IgM Ab
  - Hepatitis B: HBVsAg, HBVsAb, HBVc Ab (IgM and IgG)
  - Hepatitis C: antibody
  - RPR
  - HTLV I/II

- Stool
  - *Salmonella*, *Shigella*, *E.coli* O157 H7, *Yersinia*, *Campylobacter*
  - *C. difficile* toxin by EIA
  - Ova and parasites
  - Fecal *Giardia* and *Cryptosporidium* antigen
  - *H. pylori* fecal antigen for UGI FMT

OpenBiome Quality & Safety Program (Accessed Feb 26, 2017; https://tinyurl.com/jahk858)