Fecal Transplantation in IBD: McMaster RCT and CAG Position Statement

John K. Marshall
Division of Gastroenterology
McMaster University
• 27 patients with CDI underwent FMT by retention enema
  • Clinical resolution in 25/27 (22/27 within 24 hours)
  • 5 patients required second FMT
• No relapse with mean follow-up 427 days
RCT of Fecal Microbiota Transplantation in Active Ulcerative Colitis

• Moayyedi (PI), Marshall, Armstrong, Surette, Lee
• Funding: CCFC
• Subjects: active ulcerative colitis (N=130)
  – Mayo >3 with endoscopy sub-score ≥1
• Intervention: weekly FMT vs. placebo for 6 weeks
  – Unrelated healthy donor
  – 6 additional weeks “open label” available to non-responders
• Primary outcome: remission (Mayo<3) with endoscopic subscore 0
  – Endoscopy at weeks 3 and 6
  – Roche 454 pyrosequencing and Illumina sequencing to characterize microbiome

Moayyedi P et al. [submitted]
RCT of Fecal Microbiota Transplantation in Active Ulcerative Colitis

- Healthy unrelated donors
  - No medications for 3d prior to collection
  - Detailed health questionnaire
  - Negative tests for: HIV, HAV, HBV, HCV, syphilis, HTLV I/II, VRE, MRSA,

- Stool specimen analyzed
  - No visible blood, mucus, urine
  - Negative tests for: O&P, C. difficile, Salmonella, Shigella, E. coli 0157:H7, Yersinia, Campylobacter, norovirus, adenovirus, rotavirus

Moayyedi P et al. [submitted]
RCT of Fecal Microbiota Transplantation in Active Ulcerative Colitis

• Stool processed within 5h of collection
  – 50g of stool mixed with 300ml water
  – Emulsified with spatula and allowed to settle
  – Supernatant (150ml) decanted and filtered
  – Refrigerated at 2-8°C for up to 24 hours

• Delivered as retention enema

Moayyedi P et al. [submitted]
RCT of Fecal Microbiota Transplantation in Active Ulcerative Colitis

- **Interim analysis:** 63 randomized, 53 completed
  - 45% pancolitis
  - 42% on steroids, 19% on IMM, 9% on biologics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HBT (n=27)</th>
<th>Placebo (n=26)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 week Mayo score (mean ± sd)</td>
<td>6.81 ± 3.72</td>
<td>6.19 ± 3.36</td>
<td>0.52</td>
</tr>
<tr>
<td>6 week IBDQ (mean ± sd)</td>
<td>148.4 ± 41.9</td>
<td>146.4 ± 33.28</td>
<td>0.19</td>
</tr>
<tr>
<td>6 week EQ5D (mean ± sd)</td>
<td>61.5 ± 21.4</td>
<td>66.2 ± 16.2</td>
<td>0.39</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Yes</em></td>
<td>4 (15%)</td>
<td>2 (8%)</td>
<td>0.67</td>
</tr>
<tr>
<td><em>No</em></td>
<td>23</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>30% improvement in Mayo score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>Yes</em></td>
<td>7 (26%)</td>
<td>8 (31%)</td>
<td>0.77</td>
</tr>
<tr>
<td><em>No</em></td>
<td>20</td>
<td>18</td>
<td></td>
</tr>
</tbody>
</table>

- Partial responders on HBT offered additional 6 weeks of “open-label” therapy with overall remission rate of 9/27 (33%)

- **Conclusion:** no evidence from this RCT that FMT effective
- **DSMB advised that recruitment be halted!**

Moayyedi P et al. DDW 2014
RCT of FMT for UC

Primary Endpoint:
Week 7 Remission (Mayo ≤2 with Endoscopic Subscore 0)

Moayyedi P et al. [submitted]
• Systematic literature review
• Antibiotic-resistant C. difficile infection
• Inflammatory bowel disease
• Safety
• Disclaimer
Antibiotic-resistant *C. difficile* infection

- One RCT
- 16 case series
- 88% pooled response rate
Antibiotic-resistant *C. difficile* infection

- Published rates likely to be an overestimate but effect dramatic
- FMT is likely effective in *C. difficile* infection
- FMT is a viable option for patients who experience a relapse after two courses of antibiotics

Inflammatory bowel disease

- Limited observational data available in ulcerative colitis and even more limited data for Crohn’s disease
- Impossible to make any recommendation about efficacy without properly designed controlled trials
- FMT should only be performed for IBD in the setting of a clinical trial
- Six clinical trials underway: NCT01793831, NCT01896635, NCT01961492, NCT01790061, NCT01650038, NCT01545908
Safety

• Few prospective data on safety
• No formal study in immunosuppressed populations
• No standardized screening protocols for donors
• Patients must be counseled on known and unknown risks
• All groups performing FMT should set up prospective registries to follow patients in the short and long term
• FMT should only be performed by experienced health-care practitioners using donors who are healthy and screened extensively for communicable disease
Summary:

- Reasonable evidence to use FMT for refractory *C. difficile* infection
- FMT should only be used for other indications (such as IBD) in the setting of a clinical trial
- Stay tuned for final results of McMaster’s RCT
- We still have much to learn about the efficacy and safety of FMT
Thank You