Fecal Microbiota Transplant for Crohn’s Disease, Ulcerative Colitis and Pouchitis

Najwa El-Nachef, MD

No relevant financial disclosures
Pathophysiology of Inflammatory Bowel Disease (IBD)

**GENETICS**
- NOD2
- IBD5
- IL23R
- ATG16L1...

**IMMUNOLOGY**
- Impaired epithelial barrier function
- Immunodysregulation
- Over-reactive response to autophagy

**ENVIRONMENT**
- Diet
- Smoking
- Antibiotics
- Latitude

**MICROBIOME**
- Enterobacteriaceae
- Pasteurellaceae
- Veillonellaceae
- Fusobacteriaceae
- Erysipelotrichales
- Bacteroidales
- Clostridiales
Fecal Microbiota Transplant for IBD?
Fecal Microbiota Transplant (FMT) in IBD

- Crohn’s Disease
- Ulcerative Colitis
- Pouchitis
FMT in Crohn’s Disease

- Data limited to case reports and case series
# FMT in Crohn’s Disease

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of Patients</th>
<th>Disease Phenotype</th>
<th>Route of FMT Administration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui</td>
<td>30</td>
<td>Refractory CD, HBI &gt;= 7</td>
<td>mid gut per gastroscope</td>
<td>26/30 clinical improvement (HBI decrease &gt;3); 23/30 remission (HBI&lt;=4)</td>
</tr>
<tr>
<td>Suskind</td>
<td>9, pediatric</td>
<td>PCDAI 10-29, no fistula, no abscess, no stricture</td>
<td>Nasogastric tube</td>
<td>7/9 in clinical remission at 2 weeks; 5/9 in remission at 6 and 12 weeks</td>
</tr>
<tr>
<td>Vermeire</td>
<td>6</td>
<td>Refractory CD, extensive involvement of ileum and/or colon</td>
<td>Colonoscopy or Nasojejunal tube</td>
<td>no significant improvement based on clinical score (SES-CD) and endoscopic score (CDEIS)</td>
</tr>
<tr>
<td>Wei</td>
<td>3</td>
<td>unspecified, CDAI 150-400.</td>
<td>Colonoscopy or Nasojejunal tube</td>
<td>Decrease in CDAI from 345.00 ± 77.78 to 135.00 ± 7.07 (P = 0.082); Increase in QoL IBDQ from 107.33 ± 9.45 to 149.00 ± 20.07 (P = 0.024)</td>
</tr>
<tr>
<td>Vaughn</td>
<td>19</td>
<td>Colitis or colitis and ileitis, HBI&gt;=5</td>
<td>Colonoscopy (single)</td>
<td>11/19 responded (HBI decrease &gt; 3)</td>
</tr>
<tr>
<td>Goyal</td>
<td>2, pediatric</td>
<td>unspecified</td>
<td>Duodenoscopy/Jejunoscopy, Colonoscopy</td>
<td>1 Remission, 1 no response</td>
</tr>
</tbody>
</table>
# FMT in Crohn’s Disease

## FMT in Crohn’s Disease Cohort Studies - Clinical Remission

<table>
<thead>
<tr>
<th>Study name</th>
<th>Event rate</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cui</td>
<td>0.767</td>
<td>0.585</td>
<td>0.884</td>
<td>23 / 30</td>
</tr>
<tr>
<td>Suskind</td>
<td>0.556</td>
<td>0.251</td>
<td>0.823</td>
<td>5 / 9</td>
</tr>
<tr>
<td>Vermeire</td>
<td>0.071</td>
<td>0.004</td>
<td>0.577</td>
<td>0 / 6</td>
</tr>
<tr>
<td>Wei</td>
<td>0.125</td>
<td>0.007</td>
<td>0.734</td>
<td>0 / 3</td>
</tr>
<tr>
<td>Vaughn</td>
<td>0.526</td>
<td>0.311</td>
<td>0.732</td>
<td>10 / 19</td>
</tr>
<tr>
<td>Goyal</td>
<td>0.500</td>
<td>0.123</td>
<td>0.877</td>
<td>2 / 4</td>
</tr>
<tr>
<td>Random</td>
<td>0.518</td>
<td>0.311</td>
<td>0.719</td>
<td></td>
</tr>
</tbody>
</table>

Event rate and 95% CI

Single Center Open Label Study
FMT in Crohn’s Disease

- 15 CD patients; FMT delivered by colonoscopy.
- 27% achieved primary endpoint of improvement Harvey Bradshaw Index ≥ 3.
- 18% had a decrease in fecal calprotectin.
- 3 adverse events (flare of IBD) occurred post-FMT.
FMT in Ulcerative Colitis
Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis

Noortje G. Rossen,1 Susana Fuentes,2 Mirjam J. van der Spek,1 Jan G. Tijssen,2 Jorn H. A. Hartman,2 Ann Duflou,1 Mark Löwenberg,1 Gijs R. van den Brink,1 Elisabeth M. H. Mathus-Vliegen,1 Willem M. de Vos,2,4 Erwin G. Zoetendal,2 Geert and Cyriel Y. Ponsioen1

• 50 pts with mild to moderate UC
  – 37 completed primary end point assessment
  – clinical remission with ≥1 decrease Mayo endoscopic score at week 12.

• Randomized to FMT v. placebo via nasoduodenal administration x 2

Gastroenterology. 2015 Jul;149(1):110-118
Concomitant treatments (mesalamine, immunomodulators, anti-TNF) were allowed if at stable dose for at least 12 weeks.

Glucocorticoids allowed if stable dose for 4 weeks.
Methods

• Randomized to 50ml FMT v. placebo (water enema) once weekly for 6 weeks.

• Primary outcome: remission of UC (Mayo score ≤2 with endoscopic subscore 0) at week 7.

• Secondary outcomes: improvement in UC symptoms, change in IBDQ, EQ-5D scores.

• Discontinued early for futility
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Placebo (n = 37)</th>
<th>FMT (n = 38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission, n (%)</td>
<td>2 (5)</td>
<td>9 (24)</td>
<td>.03</td>
</tr>
<tr>
<td>Clinical response, n (%)</td>
<td>9 (24)</td>
<td>15 (39)</td>
<td>.16</td>
</tr>
<tr>
<td>Full Mayo score</td>
<td>6.34</td>
<td>6.09</td>
<td>.42</td>
</tr>
<tr>
<td>IBDQ score</td>
<td>149.38</td>
<td>152.13</td>
<td>.44</td>
</tr>
<tr>
<td>EQ-5D score</td>
<td>70.07</td>
<td>68.52</td>
<td>.99</td>
</tr>
<tr>
<td>CRP, mg/L (n = 17 placebo, n = 15 FMT)</td>
<td>3.3 ± 3.4</td>
<td>4.9 ± 5.9</td>
<td>.38</td>
</tr>
<tr>
<td>ESR, mm/h (n = 17 placebo, n = 15 FMT)</td>
<td>13.1 ± 11.2</td>
<td>15.9 ± 17.0</td>
<td>.59</td>
</tr>
<tr>
<td>Proportion with high ESR, n (%)</td>
<td>4 (24)</td>
<td>3 (20)</td>
<td>1.0</td>
</tr>
<tr>
<td>Proportion with high CRP, n (%)</td>
<td>5 (29)</td>
<td>2 (13)</td>
<td>.40</td>
</tr>
<tr>
<td>Patients with serious adverse events n (%)</td>
<td>2 (5)</td>
<td>3 (8)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Predictors of Success

• Trend toward those taking immunosuppressant therapy to have greater benefit from FMT
  – 5/11 (46%) v. 4/27 (15%), p=0.09

• Recent diagnosis of UC (≤1 year)
  – 3/4 (75%) v. 6/34 (18%), p=0.04
Donor Predicted Success
Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial

Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakoush, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody

- Multicenter Study in Australia
- Total Mayo score 4-10
- Pooled donors
- Colonoscopy + enema 5 days per week x 8 weeks
Multi-donor, Intensive FMT

Prednisone ≤20, mandatory taper

Continue 5ASAs, thiopurines, mtx

Biologics washed out 12 weeks

63 included in final follow-up 8 weeks after completing FMT (week 16 blinded FMT, week 24 open-label FMT)

Lancet 2017; 389 (1218-1228)
<table>
<thead>
<tr>
<th></th>
<th>Faecal microbiota transplantation (n=41)</th>
<th>Placebo ratio (n=40)</th>
<th>Risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-free clinical remission and endoscopic remission or response</td>
<td>11 (27%)</td>
<td>3 (8%)</td>
<td>3.6 (1.1-11.9)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid-free clinical remission</td>
<td>18 (44%)</td>
<td>8 (20%)</td>
<td>2.2 (1.1-4.5)</td>
<td>0.021</td>
</tr>
<tr>
<td>Steroid-free clinical response</td>
<td>22 (54%)</td>
<td>9 (23%)</td>
<td>2.4 (1.3-4.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Steroid-free endoscopic remission</td>
<td>5 (12%)</td>
<td>3 (8%)</td>
<td>1.6 (0.4-6.4)</td>
<td>0.48</td>
</tr>
<tr>
<td>Steroid-free endoscopic response</td>
<td>13 (32%)</td>
<td>4 (10%)</td>
<td>3.2 (1.1-8.9)</td>
<td>0.016</td>
</tr>
</tbody>
</table>
Post-hoc Exploratory Analyses

• No relation noted between primary outcome and anatomical disease extent (p=0.16).

• Endoscopic severity inversely associated with primary outcome (p=0.02).

• No patient who entered study while on corticosteroids achieved primary outcome at the end of masked treatment.

• No individual donor or batch as associated significantly with the primary outcome but donor D054 seemed to be associated with benefit.
  – 37% of patients treated from this donor met criteria for primary outcome (p=0.054)
Multi-center RCT, 73 mild to moderate UC

38 received donor FMT and 35 received autologous FMT

Anaerobically prepared donor stool, pooled donors

Colonoscopy via FMT + enema x 2 by day 7

32% FMT achieved the primary end point compared 9% who received autologous FMT (p=0.02)
# Adverse Events in FMT studies in Ulcerative Colitis

<table>
<thead>
<tr>
<th>Author</th>
<th># patients</th>
<th>Mode and frequency of delivery</th>
<th>Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossen Gastro 2015</td>
<td>37</td>
<td>Nasoduodenal x 2</td>
<td>4 (2 in FMT group but not felt to be related to FMT)</td>
</tr>
<tr>
<td>Moayyedi Gastro 2015</td>
<td>70</td>
<td>Enema q week x 6 weeks</td>
<td>No difference in adverse events</td>
</tr>
<tr>
<td>Paramsothy Lancet 2017</td>
<td>85</td>
<td>Enema q day (M-F) x 8 weeks</td>
<td>3 (2 FMT, 1 required colectomy)</td>
</tr>
<tr>
<td>Costello ECCO 2017</td>
<td>73</td>
<td>Colonoscopy + enema x 2</td>
<td>1 worsening colitis, 1 c diff req colectomy, 1 pneumonia</td>
</tr>
</tbody>
</table>
FMT in Pouchitis
Microbiota in Pouchitis

• Decreased bacterial diversity
  – Higher levels of aerobes and lower level of anaerobes in patients with pouchitis compared with controls without pouchitis

• Antibiotic responsive

• Probiotics may be beneficial

# FMT in Pouchitis

<table>
<thead>
<tr>
<th>Author</th>
<th># patients</th>
<th>Route</th>
<th>Outcome</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Landy et al 2015</td>
<td>8 chronic pouchitis (PDAI ≥7)</td>
<td>Nasogastric x 1</td>
<td>2 had reduction PDAI ≥3 at 4 weeks post FMT</td>
<td>None achieved clinical remission</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>None achieved clinical remission</td>
<td>No major adverse events</td>
</tr>
<tr>
<td>Lan et al 2017</td>
<td>13 pts with CDI and pouchitis</td>
<td>EGD, pouchoscopy, enema</td>
<td>All negative C diff</td>
<td>7/12 (58%) had symptomatic improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3/11 (27%) had improvement in PDAI</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No major adverse events</td>
</tr>
</tbody>
</table>
FMT in Pouchitis

- 15 pouchitis patients received FMT delivered by pouchoscopy; follow-up PDAI score available for 10 patients.

- No adverse events were reported post-FMT

- 50% had decrease of PDAI score ≥ 3 (mean decrease 2.5, 95% CI 1.4-3.6, p=0.0002)

- Abdominal pain decreased post-FMT (decrease of 1.3 on scale of 10, p=0.03)

- Average frequency decreased post-FMT (9.1 BM/day to 7.6 BM/day, p=0.05)

El-Nachef, Piceno, Kassam
DDW 2017 Presentation Tu1925
Summary of FMT Studies in IBD

• Methods are variable
  – Route of administration
  – Dose/duration of therapy
  – Type and number of donors
  – Preparation of FMT

• Data most robust for Ulcerative Colitis

• No RCTs in Crohn’s or Pouchitis to date
Future Directions in FMT for IBD
GOOD NEWS EVERYONE

YOU CAN NOW TAKE YOUR FECAL TRANSPLANT ORALLY
Pretreatment Antibiotics and FMT

- Intact microbial community may serve as a barrier to successful FMT by resisting or competitively excluding the introduced microbiota.
- Disruption of the host’s intrinsic abnormal microbiota may open niche space for the healthy bacterial community to colonize.

Dose Finding Study for FMT in Ulcerative Colitis

• Optimal method for FMT therapy in patients with mild to moderate Ulcerative Colitis

• Investigate the role of pretreatment antibiotics

• Compare engraftment of FMT by enema v. capsule
40 patients randomized

Arm 1
Antibiotics
FMT delivered via Colonoscopy
FMT Capsules
Follow-up Colonoscopy

Arm 2
No Antibiotics
FMT Capsules

Arm 3
Antibiotics
FMT Enema

Arm 4
No Antibiotics
FMT Enema
Summary

• FMT shows promise in treatment of IBD

• Further controlled studies are needed, especially in Crohn’s disease and Pouchitis

• Optimal method of delivery, preparation, etc is still to be determined

• Ultimate goal is to develop a rationally designed cocktail to manipulate microbiome in IBD
Thank you!

- Susan Lynch lab
- OpenBiome and Finch Therapeutics
- Martin Zydek and Vivian Deng