RECENT ADVANCES IN FECAL MICROBIOTA TRANSFORMATION in Inflammatory Bowel Disease

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Disclosure Statement

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• I do not intend to discuss an unapproved/investigative use of commercial products/devices.

Objectives

• Review of the fecal microbiome
• Dysbiosis and Inflammatory bowel disease
• Modulate the fecal microbiome
  • Fecal Microbial Transplants (FMT)
  • Diet
IBD Paradigm: Immune dysregulation

Human Microbiome
- 100 trillion microorganisms
- Human gut - 2lbs of bacteria
- Outnumber human cells by a factor of ten
  - Genomes encode around 3 million different genes
Fecal microbiome

Who's there?
What are they doing?

Who's they are varies: your microbiota is **plastic** and **personalized**.

What they're doing is **adapting to their environment**:
you, your body, and your environment.

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Microbiome and Human disease

- **Symbionts**
- **Commensals**
- **Pathobionts**

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Flipping the Paradigm
<table>
<thead>
<tr>
<th>Study</th>
<th>Study Type</th>
<th>IBD Type</th>
<th>IBD Severity</th>
<th>FMT</th>
<th>Dosage</th>
<th>Delivery</th>
<th>Pre-Abs/Lavage</th>
<th>Follow-Up</th>
<th>Outcome</th>
<th>Method</th>
<th>Placebo (n = 37)</th>
<th>FMT (n = 38)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borody et al. (1989)</td>
<td>Case-Control</td>
<td>Ulcerative</td>
<td>Active</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1-12 months</td>
<td></td>
<td>Clinical remission, n (%)</td>
<td>2 (5)</td>
<td>9 (24)</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td>Borody et al. (2001)</td>
<td>Case-Control</td>
<td>Ulcerative</td>
<td>Quiescent</td>
<td>Suspended in 200 ml saline</td>
<td>Enema</td>
<td>NR</td>
<td></td>
<td></td>
<td>Clinical response, n (%)</td>
<td>9 (24)</td>
<td>15 (39)</td>
<td>.16</td>
<td></td>
</tr>
<tr>
<td>Borody et al. (2003)</td>
<td>Case-Control</td>
<td>Ulcerative</td>
<td>Severe</td>
<td>200-300 g (diluted to 200-300 ml)</td>
<td>Enema</td>
<td>Vancomycin, Metronidazole, and rifampicin</td>
<td></td>
<td></td>
<td>Full Mayo score</td>
<td>6.34</td>
<td>6.09</td>
<td>.42</td>
<td></td>
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<tr>
<td>Borody et al. (2011)</td>
<td>Case-Control</td>
<td>Ulcerative</td>
<td>IBD</td>
<td>Enema</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<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>
<td></td>
</tr>
<tr>
<td>Borody et al. (2012)</td>
<td>Case-Control</td>
<td>Ulcerative</td>
<td>Medically-refractory</td>
<td>200 g feces</td>
<td>NJ infusion</td>
<td></td>
<td></td>
<td></td>
<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>
<td></td>
</tr>
<tr>
<td>Borody et al. (2013)</td>
<td>Case-Control</td>
<td>Ulcerative</td>
<td>Therapy-refractory</td>
<td>Colonoscopy, Lavage of donor</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Patients with serious adverse events n (%)</td>
<td>2 (5)</td>
<td>3 (8)</td>
<td>1.0</td>
<td></td>
</tr>
</tbody>
</table>

**FMT Induces Remission in Active Ulcerative Colitis in a DBRCT**

50 mL enema once per week x 7 week

Trial of FMT for Patients With Active Ulcerative Colitis – Study 2

- Nasoduodenal administration
- Donor versus autologous stool
- 2 administration 3 weeks apart
- Clinical remission
- Mayo endoscopic score


FMT in Crohn’s Disease: Study One

- Active disease
- Mid gut via enteroscopy.
- Mesalamine and dietary changes.
- Day 1-3, week 1, month 1, then every 3 months.
**FMT in Crohn’s disease: Study 2**

- Mild to moderate active disease
  - 9 Patients
  - 12-19 years of age
  - Medication therapy continued
- Pre-FMT antibiotics
- Nasogastric tube
- Disease activity and microbiome
  - Follow up 2, 6, and 12 weeks

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**Pediatric Crohn’s Disease Activity Index (PCDAI)**

- Baseline PCDAI
- PCDAI at 2 week follow up
- PCDAI at 6 week follow up

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**C-Reactive Protein (mg/dL)**

- Baseline CRP (mg/dL)
- CRP (mg/dL) at 2 week follow up
- CRP (mg/dL) at 6 week follow up
Double Blind Placebo Control trial of FMT in active Crohn’s disease

- Results Pending

<table>
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<tr>
<th>Time (wk)</th>
<th>0</th>
<th>12</th>
<th>0</th>
<th>12</th>
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<tbody>
<tr>
<td>Group A:</td>
<td></td>
<td>FMT</td>
<td></td>
<td>FMT</td>
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<tr>
<td>(n=16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group B:</td>
<td></td>
<td>Placebo</td>
<td></td>
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<tr>
<td>(n=16)</td>
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</table>
| Stool and blood analysis

ClinicalTrials.gov Identifier: NCT02272868

“Let food be thy medicine and medicine be thy food”
- Hippocrates

Effects of Modifying the Diet on Microbiome

Wu, G, Science 334, 105 (2011); 105-108
 Specific Carbohydrate Diet (SCD)
- Removes
  - Removes all grains
  - Milk products except for yogurt fermented greater than 24 hours
  - Sugars except honey
- Sidney Haas MD
  - Early 1930s used to treat celiac disease
- Popularized by Elaine Gottschall
  - Breaking the Vicious Cycle

SCD at SCH
- Retrospective study
  - Children with Crohn’s disease
  - Trialed dietary therapies as sole medical treatment for their Crohn’s disease
- Seattle Children’s Hospital
  - January 2005 to December 2012

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Prior to Diet</th>
<th>3 Months After</th>
<th>6 Months After</th>
<th>12 Months After</th>
<th>15 Months After</th>
<th>18 Months After</th>
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<tbody>
<tr>
<td>One</td>
<td>20</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>30</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Four</td>
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<tr>
<td>Five</td>
<td>15</td>
<td>0</td>
<td>0</td>
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<td>Nine</td>
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<tr>
<td>Ten</td>
<td>10</td>
<td>0</td>
<td>0</td>
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</table>

Calprotectin – Prospective SCD study

ClinicalTrials.gov Identifier: NCT02213835

Microbiome Analysis

<table>
<thead>
<tr>
<th>Species</th>
<th>Baseline</th>
<th>Week 2</th>
<th>Week 6</th>
<th>Week 12</th>
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</thead>
<tbody>
<tr>
<td>Escherichia coli</td>
<td>12.3</td>
<td>0.3</td>
<td>1.8</td>
<td>0.2</td>
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<tr>
<td>Ruminococcus gnavus</td>
<td>15.0</td>
<td>4.7</td>
<td>4.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Bacteroides fragilis</td>
<td>8.2</td>
<td>1.3</td>
<td>12.1</td>
<td>1.1</td>
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<tr>
<td>Bacteroides ovatus</td>
<td>8.4</td>
<td>3.0</td>
<td>1.1</td>
<td>1.6</td>
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<tr>
<td>Akkermansia Muciniphila</td>
<td>0.114</td>
<td>5.663</td>
<td>0.583</td>
<td>20.115</td>
</tr>
<tr>
<td>Bacteroides stercoris</td>
<td>6.7</td>
<td>4.6</td>
<td>1.0</td>
<td>2.9</td>
</tr>
</tbody>
</table>

ClinicalTrials.gov Identifier: NCT02213835

Conclusion

• Fecal Microbiome is complex and biologically important in Health and Disease
• Fecal Microbiome modulates us
• We modulate our Fecal Microbiome
Division of Gastroenterology at Seattle Children’s Microbiology Lab at Seattle Children’s Clinical Research Center (CRC) at Seattle Children’s Outpatient Procedure Center (OPC) at Seattle Children’s Sam Miller Lab at University of Washington