Fecal Microbiota Transplantation (FMT) for the Treatment of Inflammatory Bowel Disease

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What is Fecal Microbiota Transplant (FMT)?

• FMT is a procedure where stool is collected from a healthy donor and administered to a patient to treat disease

• Can be delivered via colonoscopy, enema, nasoduodenal tube or capsules

• Aim is to restore a healthy microbial ecosystem in the gut

• Used primarily to treat refractory *C. difficile* infection
Donors wanted

Our research needs your poo

We are conducting research into faecal transplantation as a potential treatment for ulcerative colitis and we need healthy volunteer donors (donors will be reimbursed for their time)

If you are interested or want to find out more please contact

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Faecal donor screening questionnaire - CONFIDENTIAL

Date:

Name: Date of birth:

Address:

Email address: Telephone number:

Height (cm): Weight (kg):

Have you received antibiotic or probiotic therapy in the last 3 months? Y N
If yes What was this? When?

Place of birth:

If born outside of Australia, when did you first arrive in Australia?

Have you travelled outside of Australia for the past 6 months Y N
  o If yes, where?

Do you take medication? If so please elaborate Y N

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Do you have a history of any of these medical conditions?

☐ Inflammatory bowel disease Y N
☐ Irritable bowel syndrome Y N
☐ Colonic polyps Y N
☐ Malignancy or cancer Y N
☐ Any other gastrointestinal disorder Y N
  o If yes please elaborate:
    ☐ Obesity Y N
    ☐ High blood pressure Y N
    ☐ Diabetes Y N
    ☐ Heart disease Y N
    ☐ Stroke Y N
    ☐ Major depression Y N
    ☐ Infection with Hepatitis B or C, HIV or syphilis Y N
    ☐ Autoimmune disease (e.g rheumatoid arthritis, SLE) Y N
    ☐ Amyloid disease Y N
    ☐ Chronic pain syndrome or neurological disorder Y N

Do you have any other medical illnesses? Y N
  o If yes please elaborate:

Have you had unprotected sexual intercourse in the last 1 month outside of a long term monogamous relationship? Y N

Are you a man who has had sex with another man? Y N

Have you had sex for drugs or money? Y N

Have you had an exposure to HIV or Hepatitis in the past 12 months? Y N

Have you had a tattoo or body piercing within the last 6 months Y N

Do any household members have infectious symptoms Y N

Have you used intravenous illicit drugs? Y N

Have you been incarcerated in prison in the past? Y N

Do you have a family history of colorectal carcinoma involving 2 or more first degree relatives? Y N

Do you have any household contacts who have an active gastrointestinal infection? Y N

Donor Signature:
• Fresh stool (25%) blended with normal saline (65%) and pharmaceutical grade glycerol (10%)
• 200ml aliquot per patient
• Frozen at -80°C
FMT procedure
FMT in IBD

- Rapid rise in IBD incidence over the last century
- Evidence points to the involvement of the gut microbiome in IBD pathogenesis
- Majority of currently available therapies target the immune response
- Current therapies hampered by incomplete efficacy and significant adverse events
- First FMT for IBD reported by Dr. Justin Bennet in 1989
Cochrane Review: Fecal transplantation for the treatment of IBD

**Purpose**

• To assess the efficacy and safety of FMT for the treatment of IBD

**Databases searched**

• MEDLINE, EMBASE, Cochrane CENTRAL, Clinicaltrials.gov, Cochrane IBD Specialized register (July 5, 2017)

**Reference**

Cochrane Review: Fecal transplantation for the treatment of IBD

**Inclusion criteria**

- UC or CD patients of all ages
- Patients followed for ≥6 weeks post-FMT

**Types of studies**

- Randomized controlled trials
- Prospective cohort studies
Primary outcomes

- Clinical remission
- Clinical relapse
- Serious adverse events

Secondary outcomes

- Clinical response
- Endoscopic remission
- Endoscopic response
- Biomarkers
- Quality of life
- Adverse events
- Withdrawal due to adverse events
- Change in alpha diversity in fecal microbiome
1020 records identified

665 records after duplicates removed

665 records screened

650 records excluded

15 full text articles assessed

11 records excluded with reasons

4 studies included in meta-analysis

PRISMA flow diagram
## Included studies

<table>
<thead>
<tr>
<th>Patients enrolled (Donor/Placebo)</th>
<th>Rossen 2015</th>
<th>Moayyedi 2015</th>
<th>Paramsothy 2017</th>
<th>Costello 2017</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>50 (23/25)</td>
<td>75 (38/37)</td>
<td>81 (41/40)</td>
<td>73 (38/35)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Autologous stool</th>
<th>Water</th>
<th>Discoloured and odoured water</th>
<th>Autologous stool</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>End point (weeks)</th>
<th>12 weeks</th>
<th>6 weeks</th>
<th>8 weeks</th>
<th>8 weeks</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Disease severity</th>
<th>SCCAI 4-11 + endoscopic subscore ≥1</th>
<th>Mayo ≥4 with endoscopic subscore ≥1</th>
<th>Mayo 4-10</th>
<th>Mayo 3-10 with endoscopic subscore ≥2</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Definition remission</th>
<th>SCCAI ≤2 with ≥1 point improvement on the combined Mayo endoscopic Mayo score of sigmoid and rectum</th>
<th>Total Mayo &lt;3 with endoscopic Mayo =0</th>
<th>Total Mayo ≤2 with subscores of ≤1 for rectal bleeding, stool frequency and endoscopic appearance; and a ≥1 point reduction in endoscopic subscore</th>
<th>Total Mayo ≤2 with endoscopic Mayo ≤1</th>
</tr>
</thead>
</table>


## Study characteristics

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FMT route</strong></td>
<td>Nasoduodenal</td>
<td>Enema weekly</td>
<td>Colonoscopy (x1) and Enema (x39)</td>
<td>Colonoscopy (x1) and Enema (x2)</td>
</tr>
<tr>
<td><strong>FMT treatments during trial</strong></td>
<td>2</td>
<td>6</td>
<td>40</td>
<td>3</td>
</tr>
<tr>
<td><strong>Preparation</strong></td>
<td>Fresh</td>
<td>Fresh + Frozen</td>
<td>Frozen</td>
<td>Frozen</td>
</tr>
<tr>
<td><strong>Stool processing</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FMT stool weight (g)</td>
<td>Median 120g (85-208g)</td>
<td>8.3g</td>
<td>37.5g</td>
<td>Colon 50g, Enema 25g</td>
</tr>
<tr>
<td>Stool weight week 1</td>
<td>120g</td>
<td>8.3g</td>
<td>187.5g</td>
<td>100g</td>
</tr>
<tr>
<td>Average stool weight per week of trial</td>
<td>30g/w</td>
<td>8.3g/w</td>
<td>187.5g/w</td>
<td>12.5g/w</td>
</tr>
<tr>
<td><strong>Dilutant</strong></td>
<td>Saline (500mls)</td>
<td>Water (50mls)</td>
<td>Saline 97.5mls (65%)</td>
<td>Saline (65%)</td>
</tr>
<tr>
<td><strong>Stool additive during preparation</strong></td>
<td>Nil</td>
<td>Nil</td>
<td>Glycerol 15mls (10%)</td>
<td>Glycerol (10%)</td>
</tr>
<tr>
<td><strong>Donor stool</strong></td>
<td>Single donor</td>
<td>Single donor</td>
<td>Pooled (3-7 donors)</td>
<td>Pooled (3-4 donors)</td>
</tr>
</tbody>
</table>
Clinical remission at 8 weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costello 2017</td>
<td>19</td>
<td>38</td>
<td>6</td>
<td>35</td>
<td>28.7%</td>
<td>2.92 [1.32, 6.46]</td>
</tr>
<tr>
<td>Moayyedi 2015</td>
<td>9</td>
<td>38</td>
<td>2</td>
<td>37</td>
<td>14.0%</td>
<td>4.38 [1.01, 18.94]</td>
</tr>
<tr>
<td>Paramsothy 2017</td>
<td>18</td>
<td>41</td>
<td>8</td>
<td>40</td>
<td>31.6%</td>
<td>2.20 [1.08, 4.46]</td>
</tr>
<tr>
<td>Rossen 2015</td>
<td>6</td>
<td>23</td>
<td>8</td>
<td>25</td>
<td>25.7%</td>
<td>0.82 [0.33, 1.99]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>140</td>
<td>137</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>2.03 [1.07, 3.86]</td>
</tr>
<tr>
<td>Total events</td>
<td>52</td>
<td>24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.21; Chi² = 5.97, df = 3 (P = 0.11); I² = 50%

Test for overall effect: Z = 2.17 (P = 0.03)
Clinical remission at 12 weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FMT Events</th>
<th>Total Events</th>
<th>Control Events</th>
<th>Total Events</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossen 2015</td>
<td>7</td>
<td>23</td>
<td>8</td>
<td>25</td>
<td>100.0%</td>
<td>0.95 [0.41, 2.21]</td>
</tr>
</tbody>
</table>

Total (95% CI) events:

- FMT: 7
- Control: 8

Weight:

- 100.0%

Risk Ratio M-H, Random, 95% CI:

- 0.95 [0.41, 2.21]

Heterogeneity: Not applicable

Test for overall effect: $Z = 0.12$ (P = 0.91)
Clinical relapse at 12 weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FMT Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rossen 2015</td>
<td>0</td>
<td>23</td>
<td>2</td>
<td>25</td>
<td>100.0%</td>
<td>0.22 [0.01, 4.29]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>0</td>
<td>23</td>
<td>2</td>
<td>25</td>
<td>100.0%</td>
<td>0.22 [0.01, 4.29]</td>
</tr>
</tbody>
</table>

Total events: 0, 2

Heterogeneity: Not applicable

Test for overall effect: Z = 1.00 (P = 0.32)
Clinical and endoscopic remission at 6-12 weeks
Serious adverse events at 6-12 weeks

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>FMT Events</th>
<th>FMT Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Costello 2017</td>
<td>3</td>
<td>38</td>
<td>2</td>
<td>35</td>
<td>29.6%</td>
<td>1.38 [0.25, 7.79]</td>
</tr>
<tr>
<td>Moayedi 2015</td>
<td>3</td>
<td>38</td>
<td>2</td>
<td>37</td>
<td>29.5%</td>
<td>1.46 [0.26, 8.25]</td>
</tr>
<tr>
<td>Paramsothy 2017</td>
<td>2</td>
<td>41</td>
<td>1</td>
<td>40</td>
<td>15.9%</td>
<td>1.95 [0.18, 20.68]</td>
</tr>
<tr>
<td>Rossen 2015</td>
<td>2</td>
<td>23</td>
<td>2</td>
<td>25</td>
<td>25.1%</td>
<td>1.09 [0.17, 7.10]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>140</strong></td>
<td><strong>137</strong></td>
<td></td>
<td></td>
<td><strong>100.0%</strong></td>
<td><strong>1.40 [0.55, 3.58]</strong></td>
</tr>
</tbody>
</table>

Total events 140, 7

Heterogeneity: \( \tau^2 = 0.00; \ \chi^2 = 0.15, \ df = 3 (P = 0.99); I^2 = 0\%

Test for overall effect: \( Z = 0.70 \ (P = 0.49) \)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Time</th>
<th>No. of participants (studies)</th>
<th>GRADE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical remission</td>
<td>8 weeks</td>
<td>277 (4 RCTs)</td>
<td>⊕⊕⊝⊝ LOW</td>
</tr>
<tr>
<td>Clinical relapse</td>
<td>12 weeks</td>
<td>48 (1 RCT)</td>
<td>⊕⊝⊝⊝⊝ VERY LOW</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>6-12 weeks</td>
<td>277 (4 RCTs)</td>
<td>⊕⊕⊕⊕⊝ MODERATE</td>
</tr>
</tbody>
</table>
## Types of serious adverse events

<table>
<thead>
<tr>
<th>Type of SAE</th>
<th># of patients in control</th>
<th># of patients in treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Worsening colitis</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C. difficile requiring colectomy</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>C. difficile toxin positive</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Change from initial diagnosis</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Spontaneous hospitalization</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Primo cytomegalovirus</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Conclusions

• FMT increased rates of clinical remission at 8 weeks
• No difference in clinical remission rates at 12 weeks
• No difference in clinical relapse rates at 12 weeks
• FMT increased rates of clinical and endoscopic remission at 6-12 weeks
• No difference in serious adverse events rates at 6-12 weeks
Case 1
Fecal microbiota transplantation for the treatment of IBD

- 32 year old male
- 6-year history of ulcerative pancolitis
- Responded to 5-ASA but symptoms have recently flared
- Colonoscopy shows Mayo endoscopic subscore = 2
- Can he be treated with FMT?
- What is optimal route of administration?
- Should it be given as single treatment or as ongoing maintenance therapy?