Faecal Microbiota Transplant in Inflammatory Bowel Disease

Robert Bryant
Translational Gastroenterology Unit
John Radcliffe Hospital Oxford
Faecal Microbiota Transplant
Age Old Therapy

Animal Kingdom
  • Coprophagia

Veterinary Medicine
  • Transfaunation
    • Fabricius Aquapendente 17th Century

FMT in Human Beings
  • Traditional Chinese Medicine
    • Dong-jin dynasty 4th Century China
    • Ming dynasty 16th Century China
  • Bedouin of northern Africa

## Microbiota Alterations and Disease

### Gastrointestinal Disorders
- Infection: Clostridium difficile
- Inflammatory bowel disease
- Irritable bowel syndrome
- Colorectal cancer

### Non-gastrointestinal disorders
- Atopy and asthma
- Obesity and metabolic syndrome
- Neurological and mood disorders: MS, PD, CFS
- Autoimmunity: Rheumatoid arthritis, ITP, sacroiliitis

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**Defining Dysbiosis**

Quantitative and qualitative changes in composition of gut microbial communities.

Reduced diversity, decreased stability, and variable expression of certain bacterial species.

Faecal Microbiota Transplant
Ultimate Probiotic: Recurrent C. difficile infection

Recurrent C. Difficile infection (CDI)
- Example of dysbiosis

FMT for Recurrent CDI
- >300 patients
- 90% resolution of symptoms

Microbiota in IBD
Lines of Evidence

- Candidate Microorganism

References:

- Genetics: NOD2 risk locus
- Encodes bacterial recognition proteins
- Diversion surgery
  - Faecal diversion in Crohn's disease improves inflammation
- Probiotics
  - VSL#3 in induction and maintenance of UC remission
- Antibiotics
  - Decrease in mucosal inflammation in active UC

Colitis does not occur in IL-10 knockout mice without the presence of bacteria.
Faecal Microbiota Transplant in IBD
The Evidence

First Reported in the Literature...

- Bennet and Brinkman
- The Lancet January 1989
  - One of us (J. D. B.)...
  - Severe UC for 7 years
  - Refractory to prednisolone (unable to wean <30mg) and sulfasalazine
  - Faecal retention enemas over 1 week
  - Symptom free for 6 months

TREATMENT OF ULCERATIVE COLITIS BY IMPLANTATION OF NORMAL COLONIC FLORA

Sir,—One of us (J. D. B.) has proposed that bacterial metabolites of bile acids or cholesterol are involved in the aetiology of ulcerative colitis. Using himself as a subject he found that alphatocopherolquinone (\(\alpha\)-TQ) suppressed disease activity in ulcerative colitis, possibly due to its ability to interfere with bacterial oxidation of bile acids by an anti-vitamin K activity. He report a further experiment implicating colonic flora in the pathogenesis of ulcerative colitis.

J. D. B. had continuously active, severe ulcerative colitis for 7 years, confirmed endoscopically and histologically. The condition was refractory to standard management including steroids and sulphasalazine and every time daily prednisolone dosage was reduced below 30 mg severe symptoms (bloody diarrhoea, cramping, tenesmus, skin lesions, and arthritis) recurred. For the past 4 years disease activity has been well controlled with \(\alpha\)-TQ (4-2 g per day) and a very low fat diet. Although this regimen was effective at reducing the severity of symptoms the underlying disease process remained active—when \(\alpha\)-TQ was discontinued or reduced in dosage severe symptoms recurred in 1–2 days.

6 months ago we undertook an experiment designed to replace his colonic flora with that of a disease-free donor. With a protocol developed to “sterilise” the bowel before surgery his flora was greatly reduced. The donor flora was introduced by large-volume retention enemas. 1 week later \(\alpha\)-TQ was discontinued without any recurrence of symptoms. It has now been six months since this implantation of “normal” flora, and J. D. B. has been symptom-free for the first time in 11 years without any medication. Biopsy specimens of the colonic mucosa taken at flexible sigmoidoscopy 3 months after implantation of the donor flora revealed long-standing chronic inflammation (branching of the colonic glands) but no active inflammation. Before implantation, when symptoms were well controlled by \(\alpha\)-TQ, biopsy revealed prominent mononuclear cell infiltration in the lamina propria.

Faecal Microbiota Transplant in IBD

The Evidence

Literature to date

- 19 case reports/series
- 65 patients with IBD received FMT
  - 43 Ulcerative colitis
    - 24 treatment refractory UC
    - 10 mild to moderately active UC
    - 9 for C. difficile infection complicating UC
  - 12 Crohn’s Disease
    - 6 refractory to standard management
    - 6 for C. difficile infection complicating CD
  - 2 Not classified
  - 8 Pouchitis

FMT for IBD
- Ages 11-78 years
- Majority lower GIT administration
- Majority multiple infusions
- Follow-up 2 weeks to 12 years
- No published Randomised Controlled Trials on FMT in IBD

# Faecal Microbiota Transplant in IBD
## The Evidence

<table>
<thead>
<tr>
<th>Reference</th>
<th>Patient Number</th>
<th>Disease</th>
<th>Route</th>
<th>Resolution Symptoms</th>
<th>Resolution Disease</th>
<th>Followup</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bennet et al 1989</td>
<td></td>
<td>UC</td>
<td>Enema</td>
<td>Resolution</td>
<td>No resolution</td>
<td>6 months</td>
</tr>
<tr>
<td>Borody et al 1989</td>
<td></td>
<td>1UC/1C</td>
<td></td>
<td>NR</td>
<td>No resolution</td>
<td>3 months</td>
</tr>
<tr>
<td>Borody et al 2011</td>
<td>3</td>
<td>UC</td>
<td>Enema</td>
<td>Resolution</td>
<td>No resolution</td>
<td>8-16 months</td>
</tr>
<tr>
<td>Borody et al 2003</td>
<td>6</td>
<td>UC</td>
<td>Enema</td>
<td>Resolution</td>
<td>No resolution</td>
<td>1-12 years</td>
</tr>
<tr>
<td>Grehan et al 2010</td>
<td>1</td>
<td>CD</td>
<td>Colon</td>
<td>NR</td>
<td>No resolution</td>
<td>6/12 weeks</td>
</tr>
<tr>
<td>Borody et al 2011</td>
<td>3</td>
<td>1UC/2U</td>
<td>Colon</td>
<td>Resolution</td>
<td>No resolution</td>
<td>1-4 years</td>
</tr>
<tr>
<td>Vermeire et al 2012</td>
<td>4</td>
<td>CD</td>
<td>Nasojej</td>
<td>No resolution</td>
<td>No resolution</td>
<td>8 weeks</td>
</tr>
<tr>
<td>Angelberger et al 2013</td>
<td>5</td>
<td>UC</td>
<td>Nasojej</td>
<td>NR</td>
<td>No resolution</td>
<td>12 weeks</td>
</tr>
<tr>
<td>Kunde et al 2013</td>
<td>10</td>
<td>UC</td>
<td>Enemas</td>
<td>7/9 Response</td>
<td>NR</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Kump et al 2013</td>
<td>6</td>
<td>UC</td>
<td>Colon</td>
<td>Response</td>
<td>NR</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Landy et al 2013</td>
<td>8</td>
<td>Pouch</td>
<td>Enema</td>
<td>No resolution</td>
<td>No resolution</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

FMT for Management of IBD
- Resolution or Response in ALL cases
- No objective disease indices
- No consistent objective confirmation active disease
- Outcome variables poorly described
- No standardised criteria for disease phenotype
- No reproducible protocol for FMT described
## Angelberger et al. ECCO abstract 2012

**Methods**
- n=5, refractory moderate to severely active UC.
- FMT nasojejunal tube and enema over 3 days, 12/52 follow-up

**Results**
- 2 patients deteriorated. 3 patients: median Mayo 11→9

## Kunde et al. JPGN June 2013;56:597-601

**Methods**
- n=10 (paediatric), PUCAI 15-65 (mild- moderate),
- FMT enemas over 5 days, no lavage or pre-treatment
- 4/52 follow-up

**Results**
- 6/9 clinical response (PUCAI decrease by 15)
- 3/9 clinical remission (PUCAI <10)

Methods
- n=6, non-responsive to standard medical therapy
- FMT colonoscopic administration
- Changes in microbiota by 16s rRNA sequencing

Results
- Short term clinical improvement within 2 weeks
- None of the patients achieved clinical remission
- In 3 patients, microbiota changed towards that of the donor, but did not correlate with clinical response

**Vermeire et al. DDW Abstract 2012**

- **Methods**
  - n=4, ileocolonic or colonic disease
  - Refractory to biologics/immunomodulators
  - FMT nasojejunal over 2 days, bowel lavage prep.

- **Results**
  - No clinical, biologic or endoscopic benefit at 8 weeks.
  - Transient effects on recipient’s microbial composition, disappeared by week 8.

**Conclusion in Crohn’s Disease:**

- No evidence for benefit in small trial group.
Faecal Microbiota Transplant in Pouchitis Evidence for Efficacy?

Landy J et al. ECCO Abstract 2013

- **Methods**
  - n=8, UC pouch procedure, refractory pouchitis (PDAI>7)
  - FMT nasogastric administration
  - Stool collected for analysis of coliform sensitivities

- **Results**
  - No significant improvement in disease activity at 4 weeks (median PDAI 12→11)
  - No improvement in Cleveland global QoL score
  - 2 of 3 patients with resistant coliforms developed sensitivity to ciprofloxacin.

References: 1 Landy J et al. JCC 2013;7(S1):P591.
Faecal Microbiota Transplant Challenges

Fecal Microbiota Transplantation: Are We Opening a Can of Worms?

Faecal Microbiota Transplant Challenges

Safety: Adverse Reactions

- Transient Symptoms
  - Fevers, diarrhoea, nausea, abdominal cramps and bloating common within 48 hours

- IBS symptoms and constipation

- No mortality directly attributable to FMT
  - Perforation, peritonitis and death related to NJ delivery

- Emerging reports of Major ADRs...

Faecal Microbiota Transplant
Challenges

Safety: Adverse reactions

- Risk of flare of IBD
  - “Transient Flare of Ulcerative Colitis after Fecal Microbiota Transplantation for Recurrent Clostridium Difficile Infection”
    - 40% (2/5) clinical deterioration of UC patients after FMT
      - Angelberger et al ECCO Abstract 2012

- Risk of infectious exposure
  - “Norovirus Gastroenteritis after Fecal Microbiota Transplantation for Treatment of Clostridium Difficile Infection despite asymptomatic donors and lack of sick contacts”
    - Schwartz et al AJG 2013
# Faecal Microbiota Transplant Challenges

## Safety: Donor Selection and Screening

<table>
<thead>
<tr>
<th>FMT Working Group Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infectious agent</strong></td>
</tr>
<tr>
<td>Known HIV, HBV, HCV or exposure</td>
</tr>
<tr>
<td>High risk sexual practices</td>
</tr>
<tr>
<td>Illicit drugs</td>
</tr>
<tr>
<td>Tattoos/piercings 6/12</td>
</tr>
<tr>
<td>Incarceration</td>
</tr>
<tr>
<td>Current communicable illness</td>
</tr>
<tr>
<td>Risk of Creutzfeldt Jakob</td>
</tr>
<tr>
<td>Travel to endemic area</td>
</tr>
</tbody>
</table>

# Faecal Microbiota Transplant Challenges

## Safety: Donor Selection and Screening

<table>
<thead>
<tr>
<th>Serologic Testing</th>
<th>Stool Testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV</td>
<td>Clostridium difficile (toxin B PCR)</td>
</tr>
<tr>
<td>HAV IgM</td>
<td>MC&amp;S</td>
</tr>
<tr>
<td>HBsAg, HBCAb, HBsAb, HCV Ab</td>
<td>Faecal Giardia antigen</td>
</tr>
<tr>
<td>HTLV 1&amp;2</td>
<td>Faecal Cryptosporidium antigen</td>
</tr>
<tr>
<td>RPR, FTA (Syphilis)</td>
<td>Acid fast stain for cyclospora, Isospora</td>
</tr>
<tr>
<td>CMV, EBV IgM/IgG</td>
<td>Ova, Parasites</td>
</tr>
<tr>
<td>Strongyloides stercoralis</td>
<td>Helicobacter pylori faecal antigen</td>
</tr>
</tbody>
</table>

Faecal Microbiota Transplant Challenges

Safety: Unknown Risks

- Transplanting donor traits
  - Metabolic Syndrome
  - Atopic disease and allergy
  - Neurological disease and Depression
  - Autoimmune disease
  - Gender related hormonal changes

- Long-Term follow-up...
  - Lacking data

- Recipient factors
  - Immunosuppression?
  - Case reports suggest safety

Faecal Microbiota Transplant
Technical Issues and Optimisation

Selecting the Optimal Donor

- **Related vs ‘Universal’ donor**
  - Systematic Review FMT for C. difficile infection: related donor resolution rate of 93% vs unrelated donor stool 84%
  - Risk of shared dysbiosis in related donors

  Dysbiosis of the faecal microbiota in patients with Crohn’s disease and their unaffected relatives

  Marie Joossens,1 Geert Huys,2,3 Margo Cnockaert,2 Vicky De Preter,1 Kristin Verbeke,1 Paul Rutgeerts,1 Peter Vandamme,2 Severine Vermeire1

- **Donor ‘Enterotype’**

Faecal Microbiota Transplant
Technical Issues and Optimisation

Route Administration
- Lower GIT
  - Enema
  - Colonoscopic
- Upper GIT
  - Nasojejunal

Schedule of Administration
- Single
- Sequential
- Intermittent

Durability?

References:

- Lower GIT found to be more effective than UGIT in C. difficile infection (>85% vs 76.4%).
- Risks of colonoscopy in severe colitis.
- Many Firmicutes species form spores and require germination factors in the UGIT tract for viability, though Bacterioidetes may be denatured by stomach acid.
- Disease distribution

Durable alteration of the colonic microbiota by the administration of donor fecal flora.
Grehan MJ, Borody TJ, Leis SM, Campbell J, Mitchell H, Wettstein A.
Department of Gastroenterology, Nepean Hospital, Penrith, New South Wales, Australia. mgrehan@connexus.net.au
Faecal Microbiota Transplant Technical Issues and Optimisation

Patient Preparation
- Bowel lavage
- Antibiotics
- Probiotics

Stool Preparation
- Stool volume
  - 10-200gm
- Solution and Volume
  - 20-500mL, saline or milk
- Collection interval
  - Within 6 hours
  - Frozen

References:
Faecal Microbiota Transplant Calls for Standardisation

Should We Standardize the 1,700-Year-Old Fecal Microbiota Transplantation?

NICE Guidelines
- FMT for C. difficile due Autumn 2013

US Food and Drug Administration (FDA)
- 5/2013: Requires an investigational new drug application for use
- 7/2013: ‘Enforcement discretion’ announced
  - FMT for CDI without IND

Faecal Microbiota Transplant Patients are Ready

Ulcerative colitis patient survey data:

Fecal Bacteriotherapy for Ulcerative Colitis: Patients Are Ready, Are We?

Stacy A. Kahn, MD,* Rita Gorawara-Bhat, PhD,† and David T. Rubin, MD‡

- Participants compared FMT to probiotics and felt it was “natural”

Uncontrolled use in the community...

Faecal Microbiota Transplant for IBD
Future Directions

Understanding
- Microbiome
  - Characterisation of beneficial enterotypes and strains?
- Derived molecules
  - Intestinal inflammation

Clinical Trials
- Well-designed clinical trials and complimentary animal studies
  - Patient preparation
  - Transplant delivery method
  - Optimal donor
  - Collaborative

Standardisation and Regulatory Aspects

References:
Faecal Microbiota Transplant for IBD
Future Directions

Toward Artificial Stool...

- Targeted restoration of intestinal microbiota

References:
Toward Artificial Stool...

- Encapsulated, enteric coated capsules...
Thank you
Questions?