Practical Aspects of Faecal Microbiota Therapy (FMT) for recurrent *C. difficile* Infection (CDI)

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CDI recurrence rates

- After first episode: 20%
- After first recurrence: 40%
- After two or more recurrences: 60%

Risk factors for CDI recurrence

- Age ≥65 years\textsuperscript{1-4}
- Severe CDI\textsuperscript{1,4}
- Previous episode of CDI\textsuperscript{1,3-5}
- Co-morbidities including renal failure\textsuperscript{1,4,6,7}
- Exposure to concomitant antibiotics\textsuperscript{4}
- Infection with particular strains eg RT 027
- Exposure to PPIs / other gastric acid suppressors\textsuperscript{8}
- Previous hospital admission\textsuperscript{9}

\textsuperscript{1} Kyne et al. Lancet 2001; 357: 189-93
\textsuperscript{3} Bauer et al. Lancet 2011; 377: 63-73
\textsuperscript{4} Hu et al. Gastro 2009; 136: 1206-14
\textsuperscript{5} McFarland et al. Am J Gastroenterol 2002; 97: 1769-75
\textsuperscript{6} Do et al. CID 1998; 26: 954-9
\textsuperscript{7} Bauer et al. Clin Microbiol Infect 2011; 17: A1-4
\textsuperscript{8} Kwok et al. Am J Gastro 2012; 107: 1011-9
\textsuperscript{9} Eyre et al. CID 2012; 55: 77-88
Recurrent *C. difficile* Infection

- Impaired host-response
- Altered intestinal microbiome
The Human Microbiome

- Human gut is home to ~100 trillion bacterial cells
- Density of $10^{11}$ to $10^{12}$ per gram in the colon weighing ~2kg
- Genome size of microbiota at least 100-fold greater than human
- Large numbers species present (200-1000 species), most uncultured

Factors shaping intestinal microbial composition
Decreased Diversity of the Faecal Microbiome in Recurrent *C. difficile*

- Patients with recurrent *C. difficile* have decreased phylogenetic richness


- After antibiotics some bacteria remain disrupted for long periods:
  - Up to 2 years following treatment with clindamycin
  - Up to 4 years after H. pylori eradication therapy

  *Sadowsky et al. The Fecal Bacteria, 2011*
Faecal Microbiota Transplantation (FMT)

Instillation of stool from a healthy person into another person to cure a certain disease
Faecal Microbiota Transplantation (FMT)

Rationale: A perturbed imbalance in intestinal microbiota (dysbiosis) is associated with or causes disease and can be corrected by re-introduction of donor faeces

• Avoids prolonged, repeated courses of antibiotics
• Re-establish normal diversity of the intestinal microbiome, thus restoring “colonization resistance”
Early History of FMT

4th century: Ge Hong described use of human faecal suspension by mouth for diarrhoea and food poisoning
“Zghou Hou Bei Ji Fang”
Handy Therapy for Emergencies

16th century: Li Shizhen prescribed fermented faeces for abdominal diseases with diarrhoea, abdominal pain, fever, vomiting and constipation; “yellow dragon soup”
“Ben Cao Gang Mu”
Compendium of Materia Medica
Early History of FMT

17th century: veterinary medicine:

Transfaunation (transfer of cecal contents or fresh faeces) from healthy horses to treat horses with chronic diarrhoea

Rumen transfaunation is used to ‘refaunate’ cows that have been off-feed because of illness e.g mastitis
Later History of FMT

- 1958: Eismann et al. 4 patients with fulminant pseudomembranous colitis treated with FMT enema
- 1983: Schwann, et al. CDI treated with FMT enema

Other methods of FMT
- 1991: NG tube (Aas, Gessert, Bakken)
- 1998: gastroscopy and colonoscopy (Lund-Tønnesen, Persky, Brandt)
- 2010: self-administered enemas (Silverman, Davis, Pillai)

Eisman et al. Surgery 1958; 44: 854-9
Meta-analysis of Clinical Resolution Rates
(11 of 2709 reports, 273 patients)

Clinical resolution rate
89% overall
(95% CI = 84-93%)

No AEs

Kassam et al. AM J Gastroenterol, 2013
# FMT for Treatment of *CDI*: A Systematic Review

<table>
<thead>
<tr>
<th>Site of FMT</th>
<th># of Pts</th>
<th>Dose of FMT (mean g/mls)</th>
<th>Success Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>109</td>
<td>25/68</td>
<td>81</td>
</tr>
<tr>
<td>Duod/Jejunum</td>
<td>97</td>
<td>63/252</td>
<td>86</td>
</tr>
<tr>
<td>Caecum/Asc Colon</td>
<td>214</td>
<td>93/281</td>
<td>93</td>
</tr>
<tr>
<td>Distal Colon</td>
<td>116</td>
<td>58/272</td>
<td>84</td>
</tr>
</tbody>
</table>

102 Patients were assessed for eligibility or their treating physicians contacted the study center

49 Were excluded
  2 Were pregnant
  2 Were admitted to the intensive care unit
  2 Had life expectancy <3 mo
  3 Were immunocompromised
  8 Were not able to give informed consent
  1 Was allergic to vancomycin
  31 Did not meet criteria of both diarrhea and positive stool toxin for *Clostridium difficile*
  10 Declined to participate

43 Underwent randomization

17 Were assigned to receive donor-feces infusion
  1 Was excluded
  16 Completed evaluation

13 Were assigned to receive vancomycin
  1 Died
  12 Completed evaluation

13 Were assigned to receive vancomycin and bowel lavage
  13 Completed evaluation
Nasoduodenal FMT for Recurrent CDI: a RCT

Follow-up Survey
77 patients > 3 months after FMT

- Symptomatic response after FMT
  - mean of 6 days
  - <3 days in 74%

- Primary cure rate (Resolution within 90 days): 91 %
  Secondary cure rate (resolution after one further course of vancomycin +- FMT): 98.7%

- 97% of patients would have another FMT for recurrent CDI and 58.3 % would choose FMT as their preferred Rx

- All late recurrences occurred in setting of subsequent unrelated antibiotics

# Cure Rates and AEs in 146 Patients > 65 years of Age

<table>
<thead>
<tr>
<th>CDI (n)</th>
<th>Primary cure rate</th>
<th>Secondary cure rate</th>
<th>Transient AEs</th>
<th>Serious AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent-CDI (89)</td>
<td>82%</td>
<td>94.4%</td>
<td>11.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>Severe-CDI (45)</td>
<td>88.8%</td>
<td>97.7%</td>
<td>4.4%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Complicated-CDI (12)</td>
<td>67%</td>
<td>100%</td>
<td>0%</td>
<td>16.6%</td>
</tr>
<tr>
<td>Total (146)</td>
<td>82.8%</td>
<td>95.8%</td>
<td>7.5%</td>
<td>4.1%</td>
</tr>
</tbody>
</table>

High-throughput pyrosequencing of the 16S rRNA gene demonstrates stability of microbiota in faecal samples at seven time points during a six month storage period at -80oC.
Standardized Frozen Preparation for Transplantation of Faecal Microbiota

<table>
<thead>
<tr>
<th>Donor material</th>
<th>Mean age (years)</th>
<th>% female</th>
<th>Mean number of relapses</th>
<th>Success rate (%)</th>
<th>Symptom resolution and negative PCR @ 2 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual donor n=10</td>
<td>61</td>
<td>70%</td>
<td>6.2</td>
<td>7/10 (70%)</td>
<td></td>
</tr>
<tr>
<td>Standard donor, fresh n=12</td>
<td>55</td>
<td>83%</td>
<td>6.4</td>
<td>11/12 (92%)</td>
<td></td>
</tr>
<tr>
<td>Standard donor, frozen n=21</td>
<td>59</td>
<td>67%</td>
<td>5.2</td>
<td>19/21 (90%)</td>
<td></td>
</tr>
<tr>
<td>Total N=43</td>
<td>59</td>
<td>72%</td>
<td>5.9</td>
<td>37/42 (86%)</td>
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</tr>
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OpenBiome is a nonprofit organization dedicated to expanding safe access to fecal microbiota transplantation (FMT) therapies.

www.openbiome.org
Healthy volunteer donors screened. FMT EC capsules were generated and stored at −80°C.

Patients received 15 capsules on 2 consecutive days and were followed up for symptom resolution and adverse events. Primary endpoint: clinical resolution of diarrhoea with no relapse at 8 weeks.

Resolution of diarrhea was achieved in 14 patients (70%; 95% CI, 47%-85%) after a single capsule-based FMT.

All 6 non-responders were re-treated; 4 had resolution of diarrhoea, resulting in an overall 90% (95% CI, 68%-98%) rate of clinical resolution of diarrhoea (18/20).
For multiple recurrent CDI unresponsive to repeated antibiotic treatment, faecal transplantation in combination with oral antibiotic treatment is strongly recommended (A-I).
“This procedure should only be considered for patients with recurrent *C. difficile* infections that have failed to respond to antibiotics and other treatments.”
Updated guidance on the management and treatment of *Clostridium difficile* infection

“Consider donor stool transplant in cases of recurrent CDI”
Protocol for FMT in Recurrent CDI

**Choose donor**
- any healthy person – friend/family (donor directed),
- anonymous
- universal donor

**Questionnaire screening**
- Risk factors for BBV etc

**Donor testing**
- serum and stool
- archived aliquots
Donor Exclusions:

• Age <18 or >60
• Obesity (BMI >30)
• In receipt of any regular prescribed oral medication (except oral contraceptive pill)
• Known to be infected with HIV, HTLV, or Hepatitis A, B, C, or E
• Known exposure to HIV, HTLV, or Hepatitis A, B, C, or E in the last 12 months
• Active diarrhoea (≥3 loose or watery stools per day for at least 2 consecutive days)
• High risk sexual behaviour (sexual contact with known HIV or hepatitis patients, men who have sex with men within the past 12 months, sex workers)
• Use of recreational drugs and/or novel psychoactive substances drugs
• Tattoos or body piercing within the last 6 months
• Incarceration or history of incarceration within past 12 months
• History of inflammatory bowel disease
• History of irritable bowel syndrome
• History of gastrointestinal malignancy or known polyposis syndrome
• Use of antibiotics within last 3 months
• Major immunosuppressive agents (e.g. calcineurin inhibitors, exogenous corticosteroids, biological agents)
• Systemic antineoplastic agents
Informed consent is obtained to perform serological testing for:

- HIV 1+2 serology
- HTLV I/II Ab
- Hepatitis A IgG (and if positive IgM)
- Hepatitis B surface antigen (HBsAg)
- Hepatitis C (HCV Ab)
- Hepatitis E
- Syphilis
- CMV/EBV IgG/M
- *Strongyloides stercoralis* (ELISA)

Stool for:

- Culture (*Campylobacter, Salmonella, Shigella* and *E. coli* O:157)
- Ova, cysts and parasites by concentration x3
- *C. difficile* test, Norovirus
- Screen for gentamicin and carbapenem resistant Gram negative organisms
- Screen for MRSA
- Helicobacter pylori antigen
- *Entamoeba histolytica* PCR
“Expressions of interest” = 11

Did not attend screening appointment = 1

Excluded at screening = 3
  Polys removed, Abx in past 3 months, antidepressants

Did not submit samples for testing = 2

Issues identified after testing = 2
  H. Pylori (1), H. pylori plus Gent resistant coliform (1)

Donors accepted = 3
Protocol for Colonoscopic FMT in Recurrent CDI

**Stool Transplant Preparation**

- Donor stool >50g → suspension with non-bacteriostatic saline to make a ‘slurry’ mix by hand/blender/shaker
- Filtered through gauze into container
- Use of a biosafety hood
- Final volume (~250-300mL) adjusted with 12.5% glycerol
- Stored at -80°C for up to 6 months
Protocol for Colonoscopic FMT in Recurrent CDI

Recipient

- Recipient serum archived pre-tranplant
- Antibiotics (oral vanc) 3-5 days before procedure (stop 24 hours before)
- Large-volume colonoscopy prep the evening before procedure
- Loperamide immediately before procedure
- Approx 300mL instilled into patient (approx 2/3rd into caecum)
How Do Patients Feel About FMT?

- Hypothetical case scenarios given to clinic attendees (n=192)
  - efficacy data alone (described as Floral Reconstitution) (85%)
  - awareness of faecal nature of FR (81%)
  - FMT chosen if by pill (90%) or if physician recommended (94%)

- FMT issues found most unappealing
  - need to handle stool (65%)
  - receiving FMT by NGT (75%)
  - women: all aspects of FMT unappealing, “gross” (odour, handling stool)
  - men: concerned with safety issues
  - no signif difference in age or education level
  - older patients: FMT less unappealing

“Dear Dr Irving and Dr Goldenberg, I just thought I would drop you an email to let you know that I am feeling so much better, I am convinced the transplant has worked. In fact people have commented that I am looking so much better (little do they know what I have done) I have a lot more energy and not feeling tired. I can start re'living' my life again.”
Challenges with faecal transplants

- Risks of transmission of viruses and bacteria that are yet uncharacterised (even with careful donor screening)
- Unclear sample stability – if fresh, needs to be used within a short period of time but unclear exactly how long it is stable
- “Yuk” factor – steps involved to prepare a faecal transplant sample are unappealing
- Difficult to QC, given variability between donors and within the same donor over time
- Unclear potential for long term complications (diabetes, cancer, etc) and difficult to study (each donor and host will be different)
Weight gain following FMT: a case report

32 year old female with recurrent CDI underwent FMT – pre transplant weight stable (BMI 26)

Donor (patients 16 year old daughter) was overweight at time of transplant (~140 lbs / BMI 26.1) and later increased to 170lbs

Recipient presented 36 months after FMT with unintentional weight gain of 41 lbs (BMI 34.5) despite medically supervised diet and exercise programme

The hypothesis of FMT triggering or contributing to obesity is supported by animal models demonstrating that an obese microbiota can be transmitted

## Barriers to widespread adoption

Survey of 161 UK Infection and Gastroenterology specialists from 86 Trusts/Boards

<table>
<thead>
<tr>
<th>Factor</th>
<th>Favours use %</th>
<th>Inhibits use %</th>
<th>Neither %</th>
<th>Don’t know %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence base</td>
<td>96.4</td>
<td>0</td>
<td>1.4</td>
<td>2.2</td>
</tr>
<tr>
<td>Benefit vs risk</td>
<td>90.8</td>
<td>0.7</td>
<td>5.7</td>
<td>2.8</td>
</tr>
<tr>
<td>Overall cost</td>
<td>41.8</td>
<td>9.9</td>
<td>29.8</td>
<td>18.4</td>
</tr>
<tr>
<td>Antimicrobial resistance</td>
<td>61</td>
<td>3.5</td>
<td>29.1</td>
<td>6.4</td>
</tr>
<tr>
<td>Patient safety</td>
<td>55.3</td>
<td>12.1</td>
<td>26.2</td>
<td>6.4</td>
</tr>
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*Porter, Clin Microbiol Infect, 2015, in press*
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<tbody>
<tr>
<td>Patient acceptance</td>
<td>23.4</td>
<td>41.1</td>
<td>26.2</td>
<td>9.2</td>
</tr>
<tr>
<td>Donor selection</td>
<td>9.3</td>
<td>47.9</td>
<td>32.1</td>
<td>10.7</td>
</tr>
<tr>
<td>Cost to local laboratory</td>
<td>10</td>
<td>32.9</td>
<td>45.7</td>
<td>11.4</td>
</tr>
<tr>
<td>Availability of prepared stool</td>
<td>33.6</td>
<td>47.1</td>
<td>11.4</td>
<td>7.9</td>
</tr>
<tr>
<td>Feasibility / practicality of procedure</td>
<td>24.8</td>
<td>57.4</td>
<td>13.5</td>
<td>4.3</td>
</tr>
<tr>
<td>Local expertise</td>
<td>32.1</td>
<td>45.7</td>
<td>17.1</td>
<td>5</td>
</tr>
</tbody>
</table>

*Porter, Clin Microbiol Infect, 2015, in press*
Synthetic stool / stool substitute

“RePOOPulate”

33 strains chosen at relative ratios matching a metagenomic database of health stool donors

Final product delivered to 2 patients with recurrent CDI via colonoscopy: both remained symptom free at 6 month follow up

Petrof et al. Microbiome 2013, 1:3
Summary

- Success rate of ~90% when FMT is used to treat recurrent CDI
- Prescreening of donors is critical to prevent transmission of currently known pathogens
- Currently over 800 cases reported in the literature
- FMT is an appropriate salvage therapy for multiply recurrent CDI
  - More robust (RCTs) data are needed which include cost effectiveness analysis
  - Concern for long-term sequelae
- FMT may be replaced by bioengineered product/synthetic stool