We are what we eat: Faecal Microbiota Transplants

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THE UNIVERSITY OF SYDNEY
GESA: Gastroenterological society of Australia

September 2016: position statement on FMT

Recommendation 1

• FMT should be made available as a treatment option in Australia for patients with refractory or recurrent *C. difficile* infection (CDI).

Recommendation 2

• At this time, FMT for indications other than for CDI should be carried out in the clinical trial setting only.
Recurrent CDI is the standard indication for FMT.

Westmead Hospital In the News
FMT at a Sydney Public Hospital

David Van der Poorten, Sydney Morning Herald – late 2015
Overview

• Introduce microbiota
• Review some of evidence for recurrent CDI as standard indication
• Types of FMT preparation, application
• Regulatory, legal, logistics, financial aspects
• A holistic view?
Microbiota – cuts across individuals

Cohabiting family members share microbiota with one another and with their dogs

Se Jin Song¹, Christian Lauber², Elizabeth K Costello³, Catherine A Lozupone⁴, Gregory Humphrey⁵, Donna Berg-Lyons⁶, J Gregory Caporaso⁷, Dan Knights⁸, Jose C Clemente⁴, Sara Nakielyn⁹, Jeffrey I Gordon⁰, Noah Fierer¹, Rob Knight¹¹,¹²

Abstract Human-associated microbial communities vary across individuals: possible contributing factors include (genetic) relatedness, diet, and age. However, our surroundings, including individuals with whom we interact, also likely shape our microbial communities. To quantify this microbial exchange, we surveyed fecal, oral, and skin microbiota from 60 families (spousal units with children, dogs, both, or neither). Household members, particularly couples, shared more of their microbiota than individuals from different households, with stronger effects of co-habitation on skin than oral or fecal microbiota. Dog ownership significantly increased the shared skin microbiota in cohabiting adults, and dog-owning adults shared more ‘skin’ microbiota with their own dogs than with other dogs. Although the degree to which these shared microbes have a true niche on the human body, vs transient detection after direct contact, is unknown, these results suggest that direct and frequent contact with our cohabitants may significantly shape the composition of our microbial communities.

DOI: 10.7554/eLife.00458.001
Where we are with FMT: Westmead situation
**Occurrence**

- Environment (soil)
- Colonizing the human and animal gut
- Colon of neonates 40-80%*
- Healthy humans colonized in 10%, hospitalised patients colonized in 20-40%**
- Long-term care residents up to 50%***
- Only 1.3% with clinical manifestation

Toxigenic vs. non-toxigenic strains (PaLoc – pathogenicity locus)

**Carlene A. Muto; Asymptomatic Clostridium difficile Colonization: Is This the Tip of Another Iceberg? Clin Infect Dis. (2007) 45 (8): 999-1000.
Toxins of *C. difficile* (toxigenic strains)

PaLoc (19 kb)

- tcdR
- tcdB
- tcdE
- tcdA
- tcdC

PaLoc: encodes toxin A and toxin B

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**PaLoc**

Catalytic domain

- 102
- 286
- 288
- 365
- 516

Trp, DXD motif, enzymatic activity, Substrate specificity

Translocation domain

- 544
- 767
- 956
- 1128

Cysteine protease, Hydrophobic region

Binding domain

- 1652
- 1678

Aspartate protease

**TcdB**

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**Binary toxin**

CDT locus (4.3 kb)

- cdtR
- cdtA
- cdtB

Catalytic domain

- 18
- 1383

50 kDa

Translocation and binding domain

- 1
- 2631

100 kDa

Unrelated to TcdA and TcdB: 2 proteins CdtA and CdtB

Variant (but functional) tcdA and tcdB

May potentiate toxicity of TcdA and TcdB

Pathogenesis

*C. difficile* spores and vegetative cells are ingested

Most vegetative cells are killed in the stomach, but spores can survive the acid environment

*C. difficile* spores germinate in the small bowel upon exposure to bile acids

Flagellae facilitate *C. difficile* movement

Gut mucosa facilitates adherence to the colonic epithelium

Secretion of toxin A/B leads to diarrhoea

“Relapsing” is NOT a good word re CDI - Is Recurrence better? What does recurrence mean?

1. relapse

Further relapses

Initial episode

Relapse in up to 25%¹⁻³

~45–65% further relapses⁴,⁵

5. McFarland et al. JAMA 1994;271:1
Risk factors for recurrence

• Age $\geq 65$ y
• Prior CDI episodes
• Caused by a BI/NAP1/027 strain
• Treatment with vancomycin (as opposed to fidaxomicin)
• (Endogenous antibodies towards toxin B protect)

Future: Risk prediction score

Cornely et al. CID 2012; Cornely et al LID 2012; Johnson et al, CID 2014; Gupta et al, CID 2016
**C. difficile** Ribotype 027 - FACTS

- Produces more toxin A (16x) and toxin B (23x) (by deletion in the regulator gene)*
- Sporulation is increased
- Multidrug resistance (clindamycin, moxifloxacin, and rifampin)**
- toxin B is more virulent ***
- In 2005 already 6 % of all isolates in europe were RT027 (but only occured in Ireland, Belgiun and Netherlands) ****

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**Spread of hypervirulent PCR ribotype 027 (2010)**

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* Figures, Clostridium difficile PCR ribotype 027: assessing the risks of further worldwide spread, The Lancet Infectious Diseases Volume 10, Issue 6, June 2010, Pages 395–404
When to consider FMT

Recurrent disease

• So... if first episode was treated properly ie. Metronidazole was NOT used,
• Then consider Vancomycin failure and use fidaxomicin
• If fidaxomicin fails, use FMT (A-I evidence)

The German, European approach
Modern FMT

Tube administration, Faecal Enemas, Colonoscopy

An old Idea Revisited

*Eiseman, B., Silen, W., Bascom, G. S. & Kauvar, A. J.
Faecal enema as an adjunct in the treatment of 4 patients pseudomembranous enterocolitis.


Then........

Landmark study: van Nood *et al.* NEJM 2013
• The study employed fresh stool
  • Unrelated healthy donors < 60 years
  • Stool mixed with 500mls NS then strained
  • FMT performed within 6 hours of stool collection
  • ND tube – infusion over 30 minutes (15-20 mls/min)

patients took at least 3 liters macrogol solution before donor feces infusion. On the day of donor feces infusion, patients were sober and a nasoduodenal tube (which fitted on a 50 cc luer-lock syringe) was placed using an electromagnetic sensing device (Cortrak™), or through duodenoscopy. The position of the tube was confirmed by X-ray.

Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

Table 2. Adverse Events in 16 Patients in the Infusion Group.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>On Day of Infusion of Donor Feces</th>
<th>During Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Belching</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal cramps</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Constipation</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2 (associated with cramping)</td>
<td>0</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>2†</td>
</tr>
<tr>
<td>Hospital admission</td>
<td>NA</td>
<td>1‡</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other adverse event</td>
<td>1§</td>
<td>1‡</td>
</tr>
</tbody>
</table>

Figure 2. Rates of Cure without Relapse for Recurrent Clostridium difficile Infection.

Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Van Nood 2013 NEJM
Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

Microbiota diversity is expressed as Simpson’s Reciprocal Index of diversity in fecal samples obtained from nine patients before and 14 days after the first infusion of donor feces, as compared with their donors. The index ranges from 1 to 250, with higher values indicating more diversity. The box-and-whisker plots indicate...
FMT for CDI

• Subsequently 10 RCTs, 5 with placebo/vanc comparison and numerous case series, 1000s of cases (about 10,000 pubs.)

• Includes studies that compared frozen vs fresh stools for FMT

• Placebo controlled RCT’s
  • 284 patients
  • FMT more effective with patients 2.5x less likely to have persisting infection than placebo treated patients.

• Minimal adverse events

• Cumulative success rate about 90%

Types and Preparation and application

• Does it matter?
Frozen preparations

• Need to standardise

Fecal Microbiota Transplant for Relapsing Clostridium difficile Infection Using a Frozen Inoculum From Unrelated Donors: A Randomized, Open-Label, Controlled Pilot Study

Ilan Youngster,1,2,3 Jenny Sauk,2,4 Christina Pindar,1 Robin G. Wilson,4 Jess L. Kaplan,2,5 Mark B. Smith,6 Eric J. Alm,6 Dirk Gevers,7 George H. Russell,2,5 and Elizabeth L. Hohmann1,2

1Division of Infectious Diseases, Massachusetts General Hospital, 2Harvard Medical School, 3Division of Infectious Diseases, Boston Children’s Hospital, 4Division of Gastroenterology, Massachusetts General Hospital, and 5Department of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston; and 6Department of Biological Engineering, and 7Broad Institute, Massachusetts Institute of Technology, Cambridge, Massachusetts

Youngster et al., CID 2014
# U of M Fecal Microbiota Transplantation (FMT) program

## Fresh vs Frozen

### Table 1. Demographics of patient population compared by type of donor

<table>
<thead>
<tr>
<th>Donor material</th>
<th>Age (years) (mean±s.d.)</th>
<th>Female gender (%)</th>
<th>Duration (months) of RCDI (mean±s.d.)</th>
<th>Number of relapses (mean±s.d.)</th>
<th>History of hospitalization for CDI (%)</th>
<th>Interim antibiotics (%)</th>
<th>PPI (%)</th>
<th>CRI (%)</th>
<th>IBD (%)</th>
<th>Diverticulosis (%)</th>
<th>Success rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individual donor (n=10)</td>
<td>61±22</td>
<td>70</td>
<td>12.7±7.3</td>
<td>6.2±3.0</td>
<td>70</td>
<td>60</td>
<td>60</td>
<td>30</td>
<td>30</td>
<td>50</td>
<td>7/10 (70%)</td>
</tr>
<tr>
<td>Standard donor, fresh material (n=12)</td>
<td>55±22</td>
<td>83</td>
<td>13.1±9.8</td>
<td>6.4±3.3</td>
<td>75</td>
<td>42</td>
<td>33</td>
<td>25</td>
<td>50</td>
<td>50</td>
<td>11/12 (92%)</td>
</tr>
<tr>
<td>Standard donor, frozen material (n=21)</td>
<td>59±21</td>
<td>67</td>
<td>10.1±10.0</td>
<td>5.2±3.0</td>
<td>38</td>
<td>43</td>
<td>43</td>
<td>14</td>
<td>24</td>
<td>48</td>
<td>19/21 (90%)</td>
</tr>
<tr>
<td>Total experience (n=43)</td>
<td>59±21</td>
<td>72</td>
<td>12.2±10.3</td>
<td>5.9±3.3</td>
<td>56</td>
<td>48</td>
<td>47</td>
<td>21</td>
<td>33</td>
<td>49</td>
<td>37/43 (86%)</td>
</tr>
</tbody>
</table>

CRI, chronic renal insufficiency or failure; IBD, inflammatory bowel disease; PPI, proton pump inhibitor medication; RCDI, recurrent *C. difficile* infection.

The first 10 cases were done using patient-identified individual donors. After that, the protocol shifted to use of a standard donor. Fresh material was used in the earlier cases, and later practice shifted to use of frozen material.

*Hamilton, M., et al., 2012*

**Now 96%**
<table>
<thead>
<tr>
<th>Application</th>
<th>Jahr</th>
<th>Author</th>
<th>Journal</th>
<th>Design</th>
<th>n</th>
<th>Cum. Ansprechen</th>
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<td>Colposcopy (17), Gastroscopy (1)</td>
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<td>Lund-Tonnesen</td>
<td>Tidsskr Nor Laegeforen</td>
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<td>Nasojejunal</td>
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<td>Polak</td>
<td>Klin Mikrobiol Infekc Lek</td>
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<td>Randomisiert, Phase III</td>
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<td>89%</td>
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<td>Application</td>
<td>Studies; n*</td>
<td>Patients; n</td>
<td>Response; n</td>
<td>Cumulative response; %</td>
<td></td>
<td></td>
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<tr>
<td>------------------</td>
<td>-------------</td>
<td>-------------</td>
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<td>Stomach</td>
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<td></td>
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<td>Overall</td>
<td>34</td>
<td>957</td>
<td>852</td>
<td>89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*4 studies with different types of applications were included into the corresponding categories
SER-109
(Seres Health, Boston)

- 1 donor – 8000 capsules
- Phase I/II – ≥ 3 relapses
- 29/30 (97%) remission after 8 weeks
- 25/27 (92%) no diagnosis of *C. difficile* in stool after 8 weeks (PCR or toxin-assay)
- 2 patients with relapses during follow-up (24 weeks), both after antibiotic treatment
- No serious adverse events graded as probably associated
- Phase III trials ongoing
A Novel Microbiome Therapeutic Increases Gut Microbial Diversity and Prevents Recurrent Clostridium difficile Infection

Methods. Stool specimens from healthy donors were treated with ethanol to eliminate pathogens. The resulting spores were fractionated and encapsulated for oral delivery as SER-109. Following their response to standard-of-care antibiotics, patients in cohort 1 were treated with SER-109 on 2 consecutive days (geometric mean dose, $1.7 \times 10^9$ spores), and those in cohort 2 were treated on 1 day (geometric mean dose, $1.1 \times 10^8$ spores). The primary efficacy end point was absence of C. difficile–positive diarrhea during an 8-week follow-up period. Microbiome alterations were assessed.

30 patients; 96.7% achieved clinical resolution
Major results

B. Microbial composition (POC analysis)
Blue: donors
Red: patients, pre-Rx
Yellow: 8 weeks Rx
Orange: 24 weeks Rx

Change in Enterobacteriaceae, *E. coli* counts before and after Rx

Khanna *et al*., JID 2016 (Boston)
FMT LOWER DELIVERY
For colonoscopy, sigmoidoscopy, or enema
Item: FMP250
Price: $485 per dose (1 bottle)
Viability: 6 months at -20°C; 24 months at -80°C

FMT UPPER DELIVERY
For nasoenteric/gastric tube or EGD
Item: FMP30
Price: $485 per dose (1 bottle)
Viability: 6 months at -20°C; 24 months at -80°C

FMT CAPSULE G3
For oral administration
Orders of capsules are capped at three units
Item: FMPCapG3
Price: $635 per dose (1 bottle = 30 capsules)
Viability: 6 months at -20°C; 12 months at -80°C
*Includes 2 inert test capsules to assess patient's swallowing abilities
Fulminant Disease: FMT performed Via ND/NJ tube

Slide: David van der Poorten
83F 5 days later

Slide: David van der Poorten
Regulation by the FDA

• 2013: FDA declared that FMT was a "drug" and that all clinicians wishing to use this "drug" would require an IND (Investigational New Drug) application.

• FMT in USA largely ceased....but....

• Early 2014 FDA was convinced by the ACG to allow discretionary use of FMT for CDI if there was consent, patient told it was an investigational therapy and if donor screening performed by physician.
TGA

• Late 2016
  • “Faecal transplant/faecal microbiota are regarded as unapproved therapeutic goods (most likely medicines) under the TGA's regulatory framework.”
  • CTN exemption must be in place before it can be supplied to patients in a clinical trial setting.
  • CTN exemption applied for and given, But....
  • Wanted Investigator Brochure; 50-100 page doc same as for a brand new investigational Drug
  • Date of this policy being enforced unclear

• CTN exemption submitted late 2016 adequate
Other obstacles

- Concept is aesthetically unappealing to both patients and clinicians
- Logistical challenges in selecting and screening of donors as well as obtaining and processing material
  - Now being overcome by availability of stool banks, capsules
- Safety and ADRS
  - Short term – colonic perforation, aspiration pneumonia small risks
  - Long term – limited data,
- Potential for Tx of infection
- Available data suggests ADRs are infrequent, and minor and self limiting
Netherlands Stool Bank

- Faecal preparation provided in standardised 250ml frozen pot
- 50g stool in 198mls saline with 10% glycerol
- Donors mostly PhD students
  - Non-payed
- Stool processed immediately and frozen -80
- Thawed overnight in fridge or for 5 hours at room temperature
The Future: define risk and regulation

A proper, proportionately regulated product with proven safety record is needed to meet growing demand. Human derived vs. bioengineered source?
Spare Slides
**Treatment algorithm: CDI 1st episode, severe**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Strength of recommendation</th>
<th>Level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Vancomycin 125 mg qid for 10 days</td>
<td></td>
<td>A-I</td>
</tr>
<tr>
<td>Fidaxomicin 200 mg bid for 10 days</td>
<td></td>
<td>B-I</td>
</tr>
<tr>
<td>Vancomycin 500 mg qid for 10 days</td>
<td></td>
<td>B-III</td>
</tr>
<tr>
<td>Metronidazole 500 mg tid for 10-14 days</td>
<td></td>
<td>D-I</td>
</tr>
</tbody>
</table>

*Westmead Protocol*

From Dr. van der Porten
What to do after the FMT?

- Test stools at day 0, day 7, day 30
- And then One year

- Re-Test donor every 4 months (Germany)
- Re-Test donor every 6 months (Westmead)