Recurrent *Clostridium difficile* : The Role of Faecal Microbiota Transplants

Dr Jonathan Sutton, Ysbyty Gwynedd, Betsi Cadwaladr University Health Board

Broadcast live from 2015 Infection Prevention Society conference (www.ips.org.uk)

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The Power of Poop

From me ... to poo

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Overview

- Case history
- Recurrent CDI
- Why FMT?
- History of FMT
- Our journey
- The future?

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Case history

- Mr MW 76 year old man
- Admitted to local hospital July 2014
  - Severe CAP - managed in ITU
  - Cardiac arrest on ITU
  - Coronary angioplasty
  - Developed ARF
  - Haemodialysis
- Developed C diff
  - Metronidazole 14 days
  - Vancomycin 14 days
  - Vancomycin + metronidazole 28 days
  - Fidaxomicin 10 days

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Referral

Sent: Tuesday, December 23, 2014 10:41 AM
To: Jonathan Sutton (BCUHB - Medical)
Subject: Stool transplant

Hi,

I am trying to get hold of the gastroenterologist who does stool transplants. Is that you?

We have a patient I would like to discuss.

Thanks

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MW

- Wife – post splenectomy on long term antibiotics
- Daughter – recent tonsillitis
- 2 grandsons aged 8 and 12
- Opted to treat with frozen material
- 8 months later no recurrence

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**Clostridium difficile**

- Difficult or obstinate
- Gram positive, spore forming organism
- Can be a minor part of normal colonic microbiota
- Causes disease when competing bacteria are wiped out following antibiotic use

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Recurrent CDI

- Complete abatement of symptoms whilst on appropriate treatment followed by reappearance of diarrhoea after treatment stopped
- Molecular methods suggest up to 50% are reinfections rather than relapses.

Recurrent CDI

- Most patients respond to initial antimicrobial therapy
- Approximately 25% have recurrence
- Second recurrence in 35-45%
- Subsequent recurrence rates higher than 50%
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Management of recurrence

• Tapered or pulsed dose vancomycin
  – Persistent spores
  – Recurrence rates 31% compared with 45%

• Fidaxomicin narrow spectrum antibiotic – less damaging to background microbiota.
  – Similar efficacy to vancomycin but less recurrence

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Why does C. diff recur?

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Emma Allen-Vercoe, Univ Guelph, Canada

Incidence of "Microbiome" in Scientific Papers

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Faecal Therapy

- First described in 4th Century - Ge Hong described using human faecal suspension for food poisoning and diarrhoea
- Li Shizhen described using ‘yellow soup’ to cure many abdominal symptoms C16th

Fast forward......

- Denver 1958
- Data limited to case reports and case series
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*The NEW ENGLAND JOURNAL OF MEDICINE*

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D.,
Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D.,
Joep F.W.M. Bartelsman, M.D., Jan G. P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D.,
Marcel G.W. Dijkstraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

- Open labelled, RCT
- 3 treatment arms
  - Vancomycin, bowel lavage, FMT
  - Standard vancomycin regimen
  - Standard vancomycin +bowel lavage

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Cure without relapse at 10 weeks

Microbiota Diversity
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- Trial stopped early as almost all the patients in the 2 control arms had recurrence
- Success rate for FMT 80% consistent with case series data

Acceptable to patients?
- Clinicians often state no patient would ever agree to this procedure
- No patient (in YG) who has been considered for procedure has refused it.


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Patient Attitudes

• Study in healthy volunteers
• 192 people attending OPD clinics
• 2 hypothetical scenarios

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• Scenario 1
  – Suffering with recurrent CDI, two treatment options
  1. Another antibiotic course with a 65% success rate
  2. Antibiotics plus ‘floral reconstitution’ with 90% success rate

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• Scenario 2  
  – Same clinical scenario but detailed information about what FR is including potential routes of administration

Results

• Scenario 1  
  – 85% chose antibiotics plus FR

• Scenario 2  
  – 81% chose antibiotics plus FR  
  – Increased to 94% if recommended by their doctor

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Safety of FMT

• Most current data is retrospective

• Minor
  – Abdominal symptoms immediately post FMT are common

• Serious
  – Related to mode of administration
  – Transmission of infection

• Potential
  – Transmission of infective agent
  – Induction of chronic disease by altering the microbiome
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FMT AT YSBYT Gwynedd

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Multidisciplinary

• Interested in the concept
• Lack of effective treatment for recurrent disease
• Discussed with local microbiologists
• Discussed with gastroenterology colleagues
• RCT was trigger to look at developing a service

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**Discussions**

- Good evidence (better than anything else)
- How?
  - Enema
  - NJT
  - Colonoscopy
- Who prepares donation?
- Where is it done?
- Who do we ask?
  - D&T
  - CPG

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**Who, where and how?**

- Must have had 2 relapses – tapered vancomycin
- Opted to use colonoscopy as preferred method
- Preferred to use relatives as donor
  - Screening confirmed

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Donor selection

- Pt relative
- BMI < 30
- No bowel symptoms (IBS/IBD)
- No autoimmune disease
- No antibiotic use for 3 months prior to transplant

Screening of Donors

Table S1. Screening of blood and feces from candidate donors.

<table>
<thead>
<tr>
<th>Blood tests:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytomegalovirus (IgG and IgM)</td>
<td></td>
</tr>
<tr>
<td>Epstein-Barr Virus (VCA IgM, VCA IgG, VCA, antiEBNA)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis A (total antibodies, and if positive also Hepatitis A IgM)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B (HBsAg, antiHBsAg)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C (anti HCV)</td>
<td></td>
</tr>
<tr>
<td>HIV-1 and HIV-2 (Combined HIV Antigen/Abodogy test)</td>
<td></td>
</tr>
<tr>
<td>Human T-lymphotropic virus types 1 and II (HTLV) (antibodies)</td>
<td></td>
</tr>
<tr>
<td>Treponema pallidum (TPHIA)</td>
<td></td>
</tr>
<tr>
<td>Entamoeba histolytica (agglutination and dipstick test)</td>
<td></td>
</tr>
<tr>
<td>Strongyloides stercoralis (ELISA)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Fecal tests:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriological evaluation by local standards</td>
<td></td>
</tr>
<tr>
<td>Parasitological evaluation by local standards (triple feces test)</td>
<td></td>
</tr>
<tr>
<td>Test for Clostridium difficile (tests ELISA and culture)</td>
<td></td>
</tr>
</tbody>
</table>
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Transplant

- Procedure performed in endoscopy unit
- Donor provides sample on arrival
- Material processed
  - 2 staff masked and gowned
  - Mixed with N/saline in household blender
  - Homogenised
  - Drawn in 50ml syringes and capped

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Patient

- Vancomycin continued until 48 hours prior to transplant
- Full bowel prep given
- Colonoscopy performed to terminal ileum
  - 10 x 50mls donor material given through the scope.
- Loperamide given immediately
- Bed rest for 6 hours
- Loperamide repeated at 6 hours

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Problems with suitable donors

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Problems

• Can be difficult to find donors who fulfil criteria

• Takes time to perform screening

• Messy to prepare stool!

The solution?

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Openbiome

- Non profit making company in Boston USA
- Mission statement to make FMT:
  - Easier
  - Cheaper
  - Safer
  - Widely available

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Easier?

- Material provided screened, mixed, filtered and frozen
- 6 months shelf life in a -20°C freezer
- No more donor finding or screening
- Allows patients to be treated quickly

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Cheaper?

• Much more extensively screened than we would do locally
• Screened at least twice in a 60 day windows
• Equivalent testing is £150 per screen i.e. £300 per sample.
• Cost to buy £200

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How can they do it?

<table>
<thead>
<tr>
<th>size of poop</th>
<th># of people treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 g</td>
<td></td>
</tr>
<tr>
<td>100 g</td>
<td></td>
</tr>
<tr>
<td>150 g</td>
<td></td>
</tr>
<tr>
<td>200 g</td>
<td></td>
</tr>
<tr>
<td>250 g</td>
<td></td>
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<tr>
<td>300 g</td>
<td></td>
</tr>
<tr>
<td>350 g</td>
<td></td>
</tr>
<tr>
<td>400 g</td>
<td></td>
</tr>
<tr>
<td>450 g</td>
<td></td>
</tr>
</tbody>
</table>

THE MOST IMPORTANT THING YOU'LL DO ALL DAY!

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Payment by results

- $40 per sample
- If they donate 5 days in a week $50 bonus
- Earn prizes
  - Biggest single donation of the month
  - Most donations in a month

Safer?

- More extensively screened
- Better quality control
- Traceability
  - Tracker codes
  - Deep frozen reference samples
- Established adverse event reporting system
- Reduced hazard of processing locally
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**Methods**

3-step process to determine stool donation eligibility

1) **Donor Registry**
   - Potential donors answered a 10-question, pre-screen survey
   - Assess for most common reasons for exclusion:
     - Logistics
     - Commitment
     - Age
     - BMI > 30
     - Birth country
     - Travel history
     - Antibiotic use
     - Smoking
     - Recent vaccination

2) **Clinical Assessment**
   - Qualified individuals completed an on-site 109-question clinical assessment
   - Transmissible diseases
   - Gastrointestinal conditions
   - Atopic conditions
   - Autoimmune conditions
   - Chronic pain syndromes
   - Metabolic conditions
   - Neurological conditions
   - Psychiatric conditions
   - Malignancy history
   - Medications
   - Diet
   - Family history

3) **Laboratory Investigation**
   - Those who passed completed a comprehensive stool and serological screening panel
   - Stool: Bacteria
     - Helicobacter pylori, EIA
     - Vibrio, Culture-based assay
     - Salmonella/Campylobacter/Shigella, Culture-based assay
     - Clostridium Difficile, PCR
     - VRE, Culture-based assay
   - Stool: Parasites
     - Cryptosporidium, EIA
     - Cyclospora/Isospora, Acid fast stain
     - Ova & Parasites, Microscopic exam
     - Microsporidia, Microscopic exam
   - Stool: Viruses
     - Norovirus, PCR
     - Adenovirus, EIA
     - Rotavirus, EIA
   - Serological:
     - HIV antibody, type 1 and 2
     - Hepatitis A (IgM)
     - Hepatitis B panel (HBsAg, anti-HBc [IgM and Total])
     - Hepatitis C (HCV antibody)
     - Treponema palladium, EIA
     - HTLV I and 2
   - CBC with differential
   - Hepatic function panel (AST, ALT, ALP, bilirubin, albumin)

**Updated Results** (as of 5/15/15)

5.0% donor enrollment rate

Starting: 6157
Excluded: 4572
Donors Enrolled: 148

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OPENBIOME IN YG

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So far..

- 15 patients treated
  - 8 with Openbiome
  - 7 ‘blender’
- No non-responders
- 2 relapses following antibiotic treatment
  - 1 treated with repeat FMT
  - 1 with Fidaxomicin
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### The future

![Image of an iceberg with the ocean and ice above the waterline.](image_url)

Table 1: Disorders associated with an altered intestinal microbiome

<table>
<thead>
<tr>
<th>Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastritis</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>Peptic ulcer</td>
</tr>
<tr>
<td>Ischemic colitis</td>
</tr>
<tr>
<td>IBD</td>
</tr>
<tr>
<td>IBD</td>
</tr>
<tr>
<td>Familial Mediterranean Fever</td>
</tr>
<tr>
<td>Gastric carcinoma or lymphoma</td>
</tr>
<tr>
<td>Recurrent Clostridium difficile infection</td>
</tr>
<tr>
<td>Autoimmunological disease</td>
</tr>
<tr>
<td>Asthma</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Autoimmune disorders</td>
</tr>
<tr>
<td>Chronic fatigue syndrome</td>
</tr>
<tr>
<td>Diabetes mellitus and insulin resistance</td>
</tr>
<tr>
<td>Eczema</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Fibromyalgia</td>
</tr>
<tr>
<td>Hepatic fibrosis</td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td>H pylori</td>
</tr>
<tr>
<td>Inflammatory bowel disease</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
</tr>
<tr>
<td>Neuropathy</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>Neuropsychiatric disorder</td>
</tr>
<tr>
<td>Chorea</td>
</tr>
<tr>
<td>Deafness and kidney stones</td>
</tr>
<tr>
<td>Parkinson's disease</td>
</tr>
</tbody>
</table>

*(IBD: inflammatory bowel disease; IBD: irritable bowel syndrome. Includes some reports as treated or long-term implemented or cure with faecal microbiota transplantation.)*

---

### Improving FMT

![Image of a gun aiming at a target.](image_url)

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‘Artificial’ Microbiota?

- Cultured microbiota in capsules
- ‘RePOOPulate’

Summary

- FMT is a very effective treatment for recurrent CDI
- More long-term safety data is needed especially if indications expand
- Stool banks may improve availability and safety
- Optimisation of therapy
  - More focused therapy
  - Cultured material
  - Best route
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Diolch Yn fawr iawn - Thank you very much
Email jonathan.sutton@wales.nhs.uk
Twitter @DrJGSutton

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