January 27th 2017,  
8th Gastro Foundation Weekend for Fellows; Spier Hotel & Conference Centre, Stellenbosch

Fecal Microbiota Transplantation in C. diff. colitis – Benefits and Limitations

Gerhard Rogler, Department of Gastroenterology and Hepatology, University Hospital Zürich
Case

28 year old mother of a two year old daughter

4/2013 Cystitis: Therapy with Amoxicillin/Clavulanic acid

• 5/2013 Diarrhea; Clostridium difficile toxin positive;
  Therapy with metronidazole for 2 weeks

• 6/2013 again diarrhea; Clostridium difficile toxin positive;
  Therapy with vancomycin orally

• 7/2013 again Diarrhea; C. diff toxin negative
  weight loss of 10 kg; unable to work; unable to care for the daughter
Is administration of probiotics useful when giving antibiotics?

antibiotics-associated diarrhea

<table>
<thead>
<tr>
<th>Diarrhoea</th>
<th>Probiotic</th>
<th>Control</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>7 (12%)</td>
<td>19 (34%)</td>
<td>0.007</td>
</tr>
<tr>
<td>No</td>
<td>50 (88%)</td>
<td>37 (66%)</td>
<td></td>
</tr>
<tr>
<td>No of patients</td>
<td>57†</td>
<td>56†</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C difficile toxin</th>
<th>Probiotic</th>
<th>Control</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>0</td>
<td>9 (17%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Negative</td>
<td>56 (100%)</td>
<td>44 (83%)</td>
<td></td>
</tr>
<tr>
<td>No of patients</td>
<td>56 ‡</td>
<td>53 ‡</td>
<td></td>
</tr>
</tbody>
</table>

*Fisher's exact test.
†22/135 patients lost to follow-up or withdrew.
‡4/113 patients not tested for C difficile.

Hickson, M. et al. BMJ 2007;335:80
C. diff colitis – clinical impact

- most frequent form of hospital-acquired diarrhea\(^1\)
- costs: > **1.000.000.000** $ per year in the US\(^2\)
- toxin A: enterotoxin; permeability, secretion ↑
- toxin B: cytotoxin; inflammation
- new, more virulent strains (BI/NAP1/027 & Co.), quinolon-resistance, gene-deletion: toxin-production ↑\(^3\)
- US numbers 2008 – mortality: 6x more deaths as compared to all other enteropathogens together
- increasing number of cases without antibiotic pre-treatment
- risk factors: age, co-morbidity, immunosuppression.....

3. O’Connor JR; Gastroenterology 2009
Relapsing C. diff. Infection (rCDI)

- suggested definition: recurrence of symptoms within 8 weeks after successful antibiotic therapy¹
- clinical definition: no repeated C. diff. Assay necessary
- recurrence – how frequent?
  - „only“ around 10-30%...
  - ...BUT if 1x relapse 40-60% (up to 65%) further relapses ²,³

² Kelly CP,; NEJM 2008
³ McFarland LV, JAMA 1994
# Therapy Recommendations - C. diff Colitis

| CDC practice guidelines for treating *Clostridium difficile* infection |
|----------------------------------------------------------|----------------|
| **CLINICAL DEFINITION** | **SUPPORTIVE CLINICAL DATA** | **RECOMMENDED TREATMENT** |
| Initial episode, mild or moderate | White blood cell (WBC) count  \( \leq 15,000 \text{ cells/mL} \) | Metronidazole 500 mg three times per day by mouth for 10–14 days |
| Initial episode, severe | WBC count  \( \geq 15,000 \text{ cells/mL} \) Serum creatinine  \( \geq 1.5 \text{ times baseline} \) | Vancomycin 125 mg four times per day by mouth for 10–14 days |
| Initial episode, severe, complicated, or fulminant | Severe *C difficile* infection complicated with hypotension, shock, ileus, or megacolon | Vancomycin 500 mg four times per day by mouth or nasogastric tube, **plus** metronidazole 500 mg every 8 hours intravenously If complete ileus, consider adding rectal instillation of vancomycin |
| **First recurrence** | | **Same as for initial episode** |
| **Second recurrence** | | **Vancomycin in a tapered and/or pulsed regimen** |

FMT in C. diff. colitis - Evidence

- Power calculation: randomisation of at least 118 Pat.

**Inclusion criteria:**
- a relapse after at least one course of adequate antibiotic therapy (≥10 days of vancomycin at a dose of ≥125 mg four times per day or ≥10 days of metronidazole at a dose of 500 mg three times per day).
- diarrhea and a positive stool test for C. difficile toxin.

Initially, the inclusion of 40 patients per study group was planned. Because most patients in both control groups had a relapse, the data and safety monitoring board performed the interim efficacy analysis and advised termination of the trial, as

2. Van Nood E; NEJM 2013
FMT - Procedure

- 30g of feces are sufficient!
FMT - Procedure

and then....?

Trend in favor for lower GI route? – success 91.4% vs. 82.3%¹

¹ Kassam Z; Am J Gastro 2013
FMT - Procedure
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- 7/2013 again diarrhea; C. diff toxin negative
- weight loss of 10 kg; unable to work; unable to care for the daughter

8/2013; FMT regained 8 kg of weight, fully working

(writes nice e-mails every Christmas)
Comparative success rates (~85%)
**FMT: Adverse events**

<table>
<thead>
<tr>
<th>Authors</th>
<th>No.</th>
<th>Method of delivery</th>
<th>Follow-up</th>
<th>Adverse events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Nood et al</td>
<td>16</td>
<td>Duodenal infusion</td>
<td>70 days</td>
<td>Diarrhea, 5; abdominal cramps, 5; belching, 3; nausea, 1; symptoms resolved in all within 3 hours</td>
</tr>
<tr>
<td>Youngster et al</td>
<td>20</td>
<td>Nasogastric tube or colonoscopy</td>
<td>6 mo</td>
<td>Mild abdominal discomfort/bloating, 4; transient fever (day 2), 1</td>
</tr>
<tr>
<td>Rubin et al</td>
<td>75</td>
<td>Nasogastric tube</td>
<td>60 days</td>
<td>No adverse events or deaths</td>
</tr>
<tr>
<td>MacConnachie et al</td>
<td>15</td>
<td>Nasogastric tube</td>
<td>4–24 wk</td>
<td>No adverse events “related to transplant”; upper GI bleeding during the first month after FMT</td>
</tr>
<tr>
<td>Aas et al</td>
<td>18</td>
<td>Nasogastric tube</td>
<td>90 days</td>
<td>Peritonitis in patient on peritoneal dialysis on day 3 (died “shortly thereafter”); pneumonia in patient with chronic obstructive lung disease</td>
</tr>
</tbody>
</table>

Mattila et al
Hamilton et al
Patel et al
Yoon et al
Pathak et al
Dutta et al
Lee et al
Emanuelsson et al
Silverman et al
Schwartz et al
Kelly et al

FMT associated SAE are rare
FMT: open questions

- Standardization
- Inclusion criteria for recipient and donor
- Costs
- Patient acceptance
- Risks (disease transmission, long-term effects)
- Fresh stool/frozen stool (open biome)
- Filtered supernatant may do it

### Table 1. Suggested Donor Testing

<table>
<thead>
<tr>
<th>Serological</th>
<th>Stool</th>
<th>Consider</th>
<th>Possibly</th>
</tr>
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<tbody>
<tr>
<td>Hepatitis A virus/Immunoglobulin M</td>
<td>C difficile toxin B (preferably by polymerase chain reaction)</td>
<td>Giardia</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>Hepatitis B surface antigen</td>
<td>Culture for enteric pathogens</td>
<td>Cryptosporidium</td>
<td>Human T-cell lymphoma virus</td>
</tr>
<tr>
<td>Antibody to hepatitis C virus</td>
<td>Ova and parasite examination, if travel history suggests</td>
<td>Isospora and Cyclospora</td>
<td>Epstein-Barr virus</td>
</tr>
<tr>
<td>Human immunodeficiency virus 1 and 2 enzyme immunoassay</td>
<td>E coli O157</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid plasma reagin (RPR)</td>
<td>Rotavirus</td>
<td>Dientamoeba fragilis</td>
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<tr>
<td></td>
<td>Listeria</td>
<td>Blastocystis hominis</td>
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<tr>
<td></td>
<td>Vibrio</td>
<td>Strongyloides stercoralis</td>
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<tr>
<td></td>
<td>Norovirus</td>
<td>Entamoeba histolytica</td>
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<td></td>
<td></td>
<td>H pylori</td>
<td></td>
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<td></td>
<td></td>
<td>Schistosoma</td>
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<td></td>
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<td>JC virus</td>
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<tr>
<td></td>
<td></td>
<td>Vancomycin-resistant enterococci</td>
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<tr>
<td></td>
<td></td>
<td>Meticillin-resistant</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Staphylococcus aureus</td>
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</tr>
</tbody>
</table>
FMT: open questions

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- Costs
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- Risks (disease transmission, long-term effects)
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"Stool was sterile-filtered to remove small particles and bacteria; the filtrate was transferred to patients in a single administration via nasojejunal tube. .......
A preliminary investigation of 5 patients with CDI shows that transfer of sterile filtrates from donor stool (FFT), rather than fecal microbiota, can be sufficient to restore normal stool habits and eliminate symptoms."


Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With Clostridium difficile Infection.
Ott SJ¹, Waetzig GH², Rehman A³, Moltzau-Anderson J⁴, Bharti R⁵, Grasis JA⁶, Cassidy L⁶, Tholey A⁶, Fickenscher H⁷, Seegert D², Rosenstiel P³, Schreiber S³.
FMT: messages

- In relapsing C. diff. Infections FMT with very high success rates around 90%
- Patient acceptance is high (many requests in other indications such as IBS, multiple sclerosis, depression....but we only do rCDI!!)
- Many open questions with respect to practical application, however, all application forms seem to work (even sterile filtration)
- At present no conclusive data for other indications
What’s coming next?

PharmaBiome will make microbiota therapy the new standard for the treatment of intestinal diseases.

......maybe......
Thank you for your attention