Fecal transplantation as a treatment option for recurrent *Clostridium difficile* infection

Josbert Keller
Department of Gastroenterology
Haga Teaching Hospital, The Hague
Case:  81 yrs, CVA, recurrent UTI, trimethoprim, Clostridium difficile

- initial episode: metronidazole
- 1st recurrence: vancomycin + tapered/pulsed
- 2nd recurrence: vancomycin & metronidazole
- Third recurrence: vanco & metronidazole & IVIG
- Fourth recurrence: ?

110 days isolation precautions
fecal transplantation

• Donor: son (screened)

• day 1-4 vancomycin orally q.i.d. 500 mg

• day 4: start bowel lavage: 4l. macrogol solution

• day 5: suspension of ~ 150 gram fresh donor feces diluted in ~400 cc 0.9% saline infused by colonoscope (right-sided colon)
After fecal transplantation:

- no diarrhea, toxine - (3x)
- stop isolation precautions
- no recurrence after antibiotics
Clostridium difficile infection

• 1935: Bacillus difficile

• 1978: Pseudomembranous colitis = Clostridium difficile infection

• Anaerobic, gram positive rod
  • Spores
  • ~ 10-25 % of antibiotic associated diarrhea

• Toxine A en B
Comment

Outbreak from a high-toxin intruder: Clostridium difficile

Robert C. Owens

Summary

Outbreaks of Clostridium difficile infection (CDI) often result from nosocomial transmission. Some outbreaks are large and sustained, and may occur in settings in which the standard precautions recommended by the Centers for Disease Control and Prevention (CDC) are implemented. A recent outbreak in a long-term care facility was characterized by unusually high-toxin-producing C. difficile organisms. This association was noted in other studies, and one outbreak was linked to a confirmed case of CDI in a long-term care resident. The clinical presentation of CDI in this outbreak differed from that in the long-term care facility, and the absence of nosocomial transmission is currently under investigation.
Chemotherapy, surgery, IBD
Prevention of *Clostridium difficile*

- Restrictive antibiotic use
- Isolation precautions / hygiene
- Probiotics?
  - RR meta analysis 0.34 (0.24-.49)
Treatment of CDI

• Selflimiting disorder
  – Stop antibiotics

• Metronidazol / Vancomycin
  – 1 placebo controlled randomised trial: Keighley et al., 1978
    • FU 5 days
    • Vancomycin 4 dd 125 mg (n=9)  
    - toxin – 8/9
    - diarrhea 2/9
    • Placebo (n=7)  
    - toxin – 5/7
    - diarrhea 6/7  
    p<0.05
Treatment of initial CDI

• Relapse: 15-30 % (< 10 weeks)
  – older age
  – co-morbidity
  – continuing hospitalization
  – Antibiotics
  – Ribotype 027 strain
Pathogenesis of recurrent CDI

- Prolonged disturbed bowel flora
  - Loss of bacteroides
  - Loss of diversity
- different strain / multiple strains
- spores
- absence of immune response (IgG)
- more virulent strains (ribotype 027)
Treatment of recurrent CDI

- **Antibiotics:**
  
  **1st relapse**
  - metronidazole 10-14 d.  response rate ~ 55%
  - vancomycin 10-14 d.  ~ 55-60%
  - fidaxomycin 10 d.  ~ 75%

  **2nd relapse**
  - vancomycin 14 d.  < 50%

  tapered pulsed regimen??

*Pepin et al. CID 2006; 42:758*  
*Tedesco et al. Am J Gastroenterol 1985*
Donor feces infusion
FECAL ENEMA AS AN ADJUNCT IN THE TREATMENT OF PSEUDOMEMBRANOUS ENTEROCOLITIS

B. EISEMAN, M.D., W. SILEN, M.D., G. S. BASCOM, M.D., AND A. J. KAUFMAN, M.D., DENVER, COLO.

(From the Departments of Surgery and Medicine, University of Colorado School of Medicine and the Veterans Administration Hospital)

THE apparent increased incidence of pseudomembranous enterocolitis has renewed interest in the pathogenesis and clinical management of this disease.2, 6, 10, 14 Even with the aid of modern supportive measures, a mean mortality of 45% was reported in 1956. Since that time, the

1958
Literature reports about fecal transplantation

• > 400 patients reported

• Different routes
  - enema
  - colonoscopy
  - nasoduodenal (gastric) tube
  - capsules

• Different protocols
  - pretreatment vancomycin
  - bowel lavage
  - amount of feces 5 - > 200 gram
Literature reports about fecal transplantation

- > 400 patients reported
- Different routes: enema, colonoscopy, nasoduodenal (gastric) tube, capsules
- Different protocols: pretreatment with vancomycin, bowel lavage, amount of feces 5-200 gram

→ Success rate consistently very high (average ~90%)
Fecal therapy to Eliminate Clostridium difficile Associated Longstanding diarrhea
Recurrent CDI after at least one course of adequate antibiotic treatment

- Vancomycine
  - N=40
- Vancomycine Kleanprep
  - N=40
- Vancomycine Kleanprep FECES
  - N=40

Follow up 10 weeks
Patients

Inclusion criteria

• male or female; over 18 years of age
• at least one proven *C. difficile* recurrence: as proved by positive toxin test (culture and ELISA)

• no other antibiotic
• no prolonged compromised immunity
• no ICU
Donors

Screening donors:
- Questionnaire (bowel habits, travel history, medication, etc)
- Feces: parasites, *Clostridium difficile*, SSYC
- Blood: Hepatitis, HIV, HTLV, CMV, EBV, *Strongyloides stercoralis*, *Treponema pallidum*
- Checklist day before treatment: recent illnesses? different sexual contact? travelling? recent antibiotics?
Figure 1. Enrollment and Outcomes.

After randomization, one patient in the infusion group required high-dose prednisolone because of a rapid decrease in renal-graft function that was noted immediately after randomization but before the study treatment was initiated. This patient was excluded from the analysis. One patient in the vancomycin-only group died before the first stool sample could be tested for the presence of *Clostridium difficile* toxin.
Early termination of the trial

Power calculation:

- Expected cure rate donor feces 90%

- Expected cure rate vancomycin 55%
  - Based on literature reports first recurrence

Included patients:

- Median number of recurrences 3 (1-9)
  - expected cure rate vancomycin < 30%

- Cure rate donor feces 94%
- Cure rate vancomycin 23-31%  \( P < 0.001 \)
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.
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></td>
<td>no. of events</td>
<td></td>
</tr>
<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>

* Adverse events that were reported on the day of donor feces infusion and those that were reported during follow-up are listed separately. NA denotes not applicable.
† During follow-up, one patient with recurrent urinary tract infections had a urinary tract infection for which antibiotics were prescribed. Another patient had fever during hemodialysis for which antibiotics were prescribed; cultures remained negative.
‡ On day 56, one patient was hospitalized for symptomatic choledocholithiasis, for which endoscopic retrograde cholangiopancreatography and stone extraction were performed.
§ One patient with autonomic dysfunction had dizziness combined with diarrhea after donor-feces infusion.
<table>
<thead>
<tr>
<th>Phylum</th>
<th>Phylum (Class) / Genus-like</th>
<th>Donor</th>
<th>Before</th>
<th>After</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteroidetes</td>
<td>Bacteroidetes</td>
<td>10.56±8.29</td>
<td>5.27±9.04</td>
<td>13.69±14.42</td>
<td>0.04</td>
</tr>
<tr>
<td>Firmicutes</td>
<td>Bacilli</td>
<td>2.69±2.71</td>
<td>41.46±27.69</td>
<td>8.11±6.54</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>Clostridium cluster IV</td>
<td>25.60±10.74</td>
<td>3.43±3.25</td>
<td>14.66±7.19</td>
<td>0.0001</td>
</tr>
<tr>
<td></td>
<td>Clostridium cluster XIVa</td>
<td>53.75±14.68</td>
<td>27.97±27.22</td>
<td>54.92±18.46</td>
<td>0.01</td>
</tr>
<tr>
<td>Proteobacteria</td>
<td>Enterobacter aerogenes et rel.</td>
<td>0.01±0.01</td>
<td>1.36±2.30</td>
<td>0.01±0.01</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae et rel.</td>
<td>0.00±0.00</td>
<td>0.96±1.26</td>
<td>0.01±0.01</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Proteus et rel.</td>
<td>0.00±0.00</td>
<td>0.19±0.36</td>
<td>0.00±0.00</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>Vibrio</td>
<td>0.00±0.00</td>
<td>0.06±0.05</td>
<td>0.00±0.00</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Yersinia et rel.</td>
<td>0.00±0.00</td>
<td>0.27±0.44</td>
<td>0.00±0.01</td>
<td>0.03</td>
</tr>
</tbody>
</table>
Conclusions

*Clostridium difficile* infection:
- Infectious disease of a bowel with disturbed flora
- Lack of effective antibiotics

→ Model for the study of normal and disturbed microbiome

*Donor feces infusion*:
- High cure rate for recurrent *C. difficile*
- Safe and well tolerated (but unappealing)
- Restores healthy microbiome
Further research

*Clostridium difficile* infection:

- Prevention - powerful probiotics?

Donor feces infusion:

- Infusion of selected bacteria
• 2 patients with multiple relapses *C. difficile*
• Stop AB, bowel lavage
• age
• Mixture of 33 bacteria cultured from 1 donor
  – Cultured anaerobic conditions from stool (100 cc; 3.5 x 10^9/cc)
  – No resistance AB (33/62)
  – Infused by colonoscope
• Both cured
• 2 patients with multiple relapses *Clostridium difficile*
• Stop AB, bowel lavage
• age
• Mixture of 33 bacteria cultured from 1 donor
  – Cultured anaerobic conditions from stool (100 cc; 3.5 x 10^9/cc)
  – No resistance AB (33/62)
  – Infused by colonoscope
• Both cured

• Tvede, Lancet 1989: 4 patients cured with mixture of bacteria
Other potential applications

- IBD
- Obesity and insulin resistance
- Constipation, MS, ……
Well controlled trial navy recruits
Prophylactic aureomycin or penicillin or placebo
Weight gain in antibiotic group after 4 and 7 weeks
Insulin resistance and obesity

• Obesity: disturbed microbiota

• Germ free mice:
  colonization with “lean microbiota”
  colonization with “obese microbiota” →more ↑weight

Turnbaugh et al 2006
Bowel lavage
Allogenic gut microbiota infusion (n=9)

Bowel lavage
Autologous gut microbiota infusion (n=9)

Randomisation

- Hyperinsulinemic clamp
- Small intestinal biopsies
- Fecal gut microbiota composition

Baseline

6 weeks

Exposes both small and large intestine!
## Results

**Supplementary Table 1.** Characteristics of Study Subjects at Baseline and After 6 Weeks

<table>
<thead>
<tr>
<th></th>
<th>Allogenic group (N = 9)</th>
<th></th>
<th>Autologic group (N = 9)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>6 weeks</td>
<td>Baseline</td>
<td>6 weeks</td>
</tr>
<tr>
<td>Age, y</td>
<td>47 ± 4</td>
<td></td>
<td>53 ± 3</td>
<td></td>
</tr>
<tr>
<td>Length, cm</td>
<td>185 ± 2</td>
<td></td>
<td>178 ± 2</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td>123 ± 6</td>
<td>122 ± 6</td>
<td>113 ± 7</td>
<td>113 ± 7</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>35.7 ± 1.5</td>
<td>35.6 ± 1.4</td>
<td>35.6 ± 1.5</td>
<td>35.7 ± 1.6</td>
</tr>
<tr>
<td>Body fat mass, %</td>
<td>40 ± 1</td>
<td>40 ± 1</td>
<td>39 ± 2</td>
<td>39 ± 1</td>
</tr>
<tr>
<td>Fasting plasma glucose, mmol/L</td>
<td>5.7 ± 0.2</td>
<td></td>
<td>4.8 ± 0.3</td>
<td></td>
</tr>
<tr>
<td>Glycated hemoglobin, mmol/mol</td>
<td>39 ± 1.1</td>
<td></td>
<td>40 ± 1.5</td>
<td></td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>4.5 ± 0.4</td>
<td>4.6 ± 0.4</td>
<td>4.0 ± 0.1</td>
<td>4.0 ± 0.1</td>
</tr>
<tr>
<td>HDLc</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>0.9 ± 0.1</td>
</tr>
<tr>
<td>LDLc</td>
<td>3.1 ± 0.4</td>
<td>3.0 ± 0.3</td>
<td>2.9 ± 0.2</td>
<td>2.9 ± 0.2</td>
</tr>
<tr>
<td>TG</td>
<td>1.4 ± 0.3</td>
<td>1.5 ± 0.4</td>
<td>1.6 ± 0.3</td>
<td>1.8 ± 0.4</td>
</tr>
<tr>
<td>Plasma free fatty acid, mmol/L</td>
<td>0.5 ± 0.1</td>
<td></td>
<td>0.7 ± 0.2</td>
<td>0.5 ± 0.1</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>138 ± 3</td>
<td></td>
<td>140 ± 2</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85 ± 2</td>
<td></td>
<td>84 ± 2</td>
<td></td>
</tr>
</tbody>
</table>

NOTE. Values are expressed as mean ± standard error of the mean. The body mass index is the weight in kilograms divided by the square of the height in meters. No significant differences in clinical variables were found between baseline and 6 weeks in both treatment groups. HDLc, high-density lipoprotein cholesterol; LDLc, low-density lipoprotein cholesterol; TG, triglycerides.
Effect donor feces on peripheral insulin sensitivity

A.Vrieze, Gastroenterology 2012
Changes in microbiota

• Before transplantation
  – Obese microbiota less diverse
    more *Bacteroides*
    less *Clostridium* cluster XIVa

  – After transplantation increased diversity
    increase of 2 butyrate producers:
    *roseburia intestinalis*
    *eubacterium hallii*
Conclusions

- Promising approach (?) but experimental
- Effect on insulin resistance: proof of principle
- Mechanism: via butyrate producing bacteria?
Els van Nood
Peter Speelman
Joep Bartelsman
Caroline Visser
Marcel Dijkgraaf
Max Nieuwdorp
Anne Vrieze
Hans Zaaijer
Tom van Gool

Ed Kuijper

Willem de Vos
Erwin Zoetendal
BACTERIOTHERAPY FOR CHRONIC RELAPSING CLOSTRIDIUM DIFFICILE DIARRHOEA IN SIX PATIENTS
Tvede, Lancet 1989

• Enemas
  • 10 bacteria, healthy volunteers
  • 180 cc; 10^8-10^9 bacteria/cc
• 4 patients cured
• Increase of bacteroides after treatment
FATLOSE trial
Faecal Administration To LOSE metabolic syndrome

• Study design: double blind RCT
  - allogenic FT (from lean male volunteers, n=9)
  - autologic FT (own faeces) n= 9

• Inclusion criteria:
  – male subjects
    • BMI ≥ 30 kg/m²
    • FPG ≥ 5.6 mmol/l
    • Age 21-65 years
    • No medication use!
Outcome measures

- **Insulin sensitivity**
  - Hyperinsulinemic euglycemic clamp at T=0 and T=6wks

- **Gut microbiota composition**
  - HITChip: phylogenetic microarray analysis (HITchip) on faeces samples in small and large intestinal samples
  - T=0 and 6wks