Impact of *Clostridium difficile* Infection (CDI) on US Health Care

- CDI hospitalizations increased almost 3-fold from 2000-2008
- CDI Estimated case burden 2011 ~ 483,120
- ~29,000 estimated deaths 2011 linked to CDI
- $4.8 billion in excess Health care cost in US facilities 2008
- CDI most common US nosocomial infection

CDI Risk Factors

- Antibiotic usage
- Recent or ongoing hospitalization
- H₂ blocking agents and proton pump inhibitors
- Recent or ongoing chemotherapy
- Chronic renal disease
- Feeding tube

Objectives

- Impact of CDI on US Health care
- Initial CDI: US treatment proposals 2016
- Recurrent CDI: US treatment proposals 2016
- Treatment considerations when standard therapy fails
- Fecal microbiota treatment (FMT) strategies
- “How to” do FMT
- Obstacles to FMT
- Conclusions

References:

4. Lessa FC et al. NEJM 2015;372:825
5. Miller BA et al. ICHE 2011;32:387
Model for C. difficile-mediated dysbiosis

http://www.plospathogens.org/article/info:doi/10.1371/journal.ppat.1002995

Colonization resistance

- Obligate anaerobic bacteria belonging to the phyla Bacteroidetes (class Bacteroidia) and Firmicutes (class Clostridia) offer benefit by conferring niche protection against invading microbes, a property known as "colonization resistance".
- Secondary bile acid metabolites are inhibitory to C. difficile proliferation
- *Clostridium scindens* express enzymes crucial for secondary bile acid synthesis
- Other important species include:
  - *Pseudoflavonitractor capillosis*
  - *Barnesiella intestihominis*
  - *Blautia hansenii*

Buffie CG et al. Nature 2015; 517:205

Risk factors for CDI recurrence

- Concurrent antibiotic treatment during initial treatment of CDI
- Defective humeral immune response against *C. difficile* toxins
- Advanced age
- Underlying co-morbid medical conditions
- Continuous PPI therapy

Hu et al. Gastroenteral 2009;136:1206
Leffler et al. NEJM 2015;372:1539
McDonald EG et al. JAMA Int Med 2015;175(5):784

IDSA/SHEA 2016 proposed treatment
CDI Initial episode

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Supportive Clinical data</th>
<th>Recommended treatment</th>
<th>GRADE Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild-Moderate</td>
<td>WBC &lt; 15.0 x 10^9/L, S-Cr &lt; 1.5 mg/dL</td>
<td>Vancomycin 125 mg QID x 10 days, Fidaxomicin 200 mg BID x 10 days* or Metronidazole 500 mg TID x 10 days if above agents are unavailable</td>
<td>Strong, High</td>
</tr>
<tr>
<td>Severe(§)</td>
<td>WBC ≥ 15.0 x 10^9/L, S-Cr ≥ 1.5 mg/dL</td>
<td>Vancomycin 125 mg QID x 10 days, Fidaxomicin 200 mg BID x 10 days*</td>
<td>Strong, High</td>
</tr>
<tr>
<td>Fulminant(§)</td>
<td>WBC ≥ 15.0 x 10^9/L, S-Cr ≥ 1.5 mg/dL, Hypotension/shock</td>
<td>Vancomycin 500 mg QID, if ileus instill per rectum Metronidazole 500 mg IV Q 8h and oral or rectal vancomycin</td>
<td>Strong, Low</td>
</tr>
</tbody>
</table>

* The criteria proposed for defining severe CDI are based on expert opinion
* Fidaxomicin use for non-NAP1/027 *C. difficile* infection

IDSA/SHEA 2016 proposed treatment
CDI  Recurrent infection

<table>
<thead>
<tr>
<th>Clinical definition</th>
<th>Recommended treatment</th>
<th>GRADE Score</th>
</tr>
</thead>
</table>
| First recurrence    | - Fidaxomicin 200 mg BID x 10 days  
-Fidaxomicin 200 mg BID x 10 days  
-Vancomycin 125 mg QID x 10 days  
-Vancomycin Pulsed regimen §  
-Avoid metronidazole | Strong, Moderate  
Strong, Low  
Strong, Low |
| Second recurrence   | - Vancomycin tapered and/or pulsed regimen §  
-Vancomycin 125 mg QID x 10 days followed by rifaximin 400 mg TID x 20 days  
-Fidaxomicin 200 mg BID x 10 days | Strong, Low  
Weak, Low  
Weak, Low |
| Third recurrence    | - Fecal microbiota transplantation ¶ | Strong, Moderate |

§ If a standard vancomycin regimen was used for the initial episode

New US Antimicrobials for CDI

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>FDA Approval for CDI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dificid® (Fidaxomicin)</td>
<td>Yes</td>
</tr>
<tr>
<td>Xifaxan® (Rifaximin)</td>
<td>No</td>
</tr>
<tr>
<td>Alinia® (Nitazoxanide)</td>
<td>No</td>
</tr>
<tr>
<td>Tygacil® (Tigecycline)</td>
<td>No</td>
</tr>
<tr>
<td>Surotomycin</td>
<td>No</td>
</tr>
<tr>
<td>Cadazolid</td>
<td>No</td>
</tr>
</tbody>
</table>

Fidaxomicin compared to vancomycin

- Rates of clinical cure non-inferior
- Rates of recurrence with NAP-1/BI/027 strains similar
- Rates of first and second recurrence with non-PF type 1/027 strains significantly lower
- Rates of recurrence with concomitant antibiotic therapy significantly lower
- Rates of adverse events mild and similar
- Price for 10 day treatment course markedly higher
- Reimbursement of cost by US third party payers requires failed treatment with vancomycin

Louie et al. NEJM 2011;364:422

CDI: Antibiotic Agents US cost

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Dosing</th>
<th>Duration of treatment</th>
<th>AWP (USD)/Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vancomycin liquid</td>
<td>125 mg QID</td>
<td>10 days</td>
<td>4.25</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>500 mg TID</td>
<td>10 days</td>
<td>15.35</td>
</tr>
<tr>
<td>Vancomycin capsule</td>
<td>125 mg QID</td>
<td>10 days</td>
<td>45.00</td>
</tr>
<tr>
<td>Fidaxomicin</td>
<td>200 mg BID</td>
<td>10 days</td>
<td>329.70</td>
</tr>
</tbody>
</table>

www.goodrx.com
Jan 2016. Walgreen’s Pharmacy, Duluth, MN
Treatment of RCDI: An uphill struggle......

Theoretical benefits of FMT instillation

- Reintroduction of important commensal bacterial organisms
  - Competition for epithelial cell binding sites
  - Competition for food resources
  - Restoration of bacterial-endothelial cell trafficking
  - Production of bacteriocins
  - Enhanced innate immunologic function (T helper cells)
  - Eradication of MDROs

- Restoration of metabolic processes
  - Up-regulation of amino acid synthesis
  - Production of SCFAs and peptides
  - Recovery of active bile salt metabolism

Therapies to consider

- Another course of a recommended oral antibiotic
- Tapered withdrawal of recommended antibiotic
- Probiotic therapy
- Toxin-negative *C. difficile* administration
- Vaccination/immunoglobulin therapy
- Fecal microbiota therapy (FMT)*

* Faecal transplantation is strongly recommended for multiple recurrent CDI (A-1).


FMT: Unlimited supply. Treatment of choice for RCDI?

Courtesy Professor Arnold Berstad, Dept. Gastroenterology, University of Bergen, Norway
Recurrent *Clostridium difficile* Colitis: Case Series Involving 18 Patients Treated with Donor Stool Administered via a Nasogastric Tube

Johannes Aas 1, Charles E. Gessert 2, and Johan S. Bakken 3

1Department of Gastroenterology, 2Division of Education and Research, and 3Department of Infectious Diseases, St. Mary/Duluth Clinic Health System, Duluth, Minnesota

*Clostridium difficile*-associated diarrhea and colitis have emerged as major complications associated with use of systemic antimicrobials. In this study, the medical records for 18 subjects who received donor stool by nasogastric tube for recurrent *C. difficile* infection during a 9-year period at a single institution were retrospectively reviewed. During the period between the initial diagnosis of *C. difficile* colitis and the stool treatments, the 18 subjects received a total of 64 courses of antimicrobials (range, 2–7 courses; median, 3 courses). During the 90 days after receipt of treatment with stool, 2 patients died of unrelated illnesses. One of the 16 survivors experienced a single recurrence of *C. difficile* colitis during 90-day follow-up. No adverse effects associated with stool treatment were observed. Patients with recurrent *C. difficile* colitis may benefit from the introduction of stool from healthy donors via a nasogastric tube.


---

### FMT: Major Milestones

<table>
<thead>
<tr>
<th>Time</th>
<th>Researcher</th>
<th>Location</th>
<th>Product/discovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>4th Century BC</td>
<td>Ge Hong</td>
<td>China</td>
<td>“Yellow soup”</td>
</tr>
<tr>
<td>17th Century AD</td>
<td>Aquapendente</td>
<td>Italy</td>
<td>Manure/Transfaunation</td>
</tr>
<tr>
<td>1958</td>
<td>Eiseman</td>
<td>Denver, CO</td>
<td>Human stool</td>
</tr>
<tr>
<td>1989</td>
<td>Tvede</td>
<td>Copenhagen, DK</td>
<td>Feces substitute</td>
</tr>
<tr>
<td>2003</td>
<td>Aas</td>
<td>Duluth, MN</td>
<td>Human stool/FMT</td>
</tr>
<tr>
<td>2012</td>
<td>Silverman</td>
<td>Toronto, CA</td>
<td>FMT/DIY</td>
</tr>
<tr>
<td>2013</td>
<td>Van Nood</td>
<td>Amsterdam, NL</td>
<td>Human stool RCT</td>
</tr>
<tr>
<td>2013</td>
<td>Smith</td>
<td>Cambridge, MA</td>
<td>Commercial stool bank</td>
</tr>
<tr>
<td>2014</td>
<td>Jones</td>
<td>Minneapolis, MN</td>
<td>Commercial stool PRCTs</td>
</tr>
</tbody>
</table>

---

### FMT: Published cases

<table>
<thead>
<tr>
<th>Cases (n)</th>
<th>Cases treated</th>
<th>Cases cured</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004</td>
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</tr>
<tr>
<td>2030</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

### FMT administration strategies

<table>
<thead>
<tr>
<th>Route of instillation</th>
<th>Procedure</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric cavity</td>
<td>Feces loaded gel capsules</td>
<td>Louie 2013</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Youngster 2014</td>
</tr>
<tr>
<td>Proximal duodenum</td>
<td>Nasoduodenal tube</td>
<td>Aas 2003</td>
</tr>
<tr>
<td>Proximal jejunum</td>
<td>Gastroscopy</td>
<td>Lund Tønnesen 1998</td>
</tr>
<tr>
<td>Cecum</td>
<td>Colonoscopy</td>
<td>Brandt 2012</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hamilton 2012</td>
</tr>
<tr>
<td>Rectum</td>
<td>Retention enema tube</td>
<td>Jorup Rönström 2006</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Silverman 2010*</td>
</tr>
</tbody>
</table>

* DIY Instructions
### FMT 1958-2016 Instillation route

<table>
<thead>
<tr>
<th>Method</th>
<th>Reports</th>
<th>Cases</th>
<th>Success (%)</th>
<th>Range %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enema</td>
<td>22</td>
<td>601</td>
<td>535 (90)</td>
<td>69-100</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>34</td>
<td>681</td>
<td>600 (88)</td>
<td>78-100</td>
</tr>
<tr>
<td>NGT /NDT/Gastroscope</td>
<td>16</td>
<td>331</td>
<td>267 (81)</td>
<td>73-100</td>
</tr>
<tr>
<td>Mixed route</td>
<td>7</td>
<td>169</td>
<td>142 (84)</td>
<td>73-100</td>
</tr>
<tr>
<td>Oral capsules</td>
<td>5</td>
<td>48</td>
<td>37 (77)</td>
<td>50-100</td>
</tr>
<tr>
<td>Synthetic stool</td>
<td>4</td>
<td>71</td>
<td>51 (72)</td>
<td>64-100</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>87</strong></td>
<td><strong>1901</strong></td>
<td><strong>1632 (86)</strong></td>
<td></td>
</tr>
</tbody>
</table>

### North American FMT Provider sites 2016

- www.idsociety.org
- Guidelines/Patient Care/Emerging Clinical Issues/Clostridium difficile infection

### Timing of FMT vs. recurrences of CDI

- IDWeek 2013, Bakken et al. Poster Session 178, #1403
- Bakken JS et al. Anaerobe 2013;24:20. PMID: 24012687
OpenBiome

As of April 14, 2016

11,114 samples dispensed
>600 US hospitals
50 US states
6 countries
Success rate 86%

www.openbiome.org
Personal communication, Mark Smith PhD
P/

OpenBiome

FMT LOWER DELIVERY
microbiota preparation
FMP250
$385

FMT UPPER DELIVERY
microbiota preparation
FMP30
$385

FMT CAPSULE G3
microbiota preparation
with MEM technology
$535

http://www.openbiome.org/safety/

OpenBiome

FMT: Is donor screening necessary?

<table>
<thead>
<tr>
<th>Country</th>
<th>Population* (millions)</th>
<th>FMT treatment centers</th>
<th>Routine donor screening</th>
<th>Best donor candidate</th>
<th>Stool preparation</th>
<th>Approx. historical cases §</th>
<th>Any reported adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norway</td>
<td>5.0</td>
<td>&gt; 20</td>
<td>No</td>
<td>“Healthy”</td>
<td>Fresh or frozen</td>
<td>&gt;250</td>
<td>None</td>
</tr>
<tr>
<td>Sweden</td>
<td>9.4</td>
<td>&gt; 15</td>
<td>No</td>
<td>“Family”</td>
<td>Fresh or frozen</td>
<td>&gt;150</td>
<td>None</td>
</tr>
<tr>
<td>Denmark</td>
<td>5.6</td>
<td>10</td>
<td>No</td>
<td>NA</td>
<td>Fresh synthetic</td>
<td>&gt;200</td>
<td>None</td>
</tr>
<tr>
<td>Finland</td>
<td>5.4</td>
<td>10</td>
<td>Yes¶</td>
<td>“Family”</td>
<td>Fresh or frozen</td>
<td>&gt;150</td>
<td>None</td>
</tr>
<tr>
<td>Holland</td>
<td>6.5</td>
<td>8</td>
<td>Yes¶</td>
<td>“Family”</td>
<td>Fresh</td>
<td>&gt;150</td>
<td>None</td>
</tr>
</tbody>
</table>

* Wikipedia 2013
¶ Screening for HIV, viral hepatitis, entero-pathogenic bacteria
§ Personal communication Winter 2013

Open label RCT: Vancomycin vs. FMT (1)

Three arms: Vanco 500 mg QID x 4 days, then

a. Vanco QID x 14 days
b. Bowel lavage; vancomycin QID x 14 days
c. FMT via ND infusion

Interim analysis after 2 years:
Study interrupted

Van Nood et al. NEJM 2013;368:407-415
Open label RCT: Vancomycin vs. FMT (2)

39 patients enrolled into two arms
All received Vanco 125 mg QID x 3 days, then
a. Vanco QID x 10 days, the pulsed dosing Q 2-3 days for “at least 3 weeks”
b. FMT 1 or 2 infusions via colonoscopy
Interim analysis after 1 year: study interrupted

Cammarota et al. Aliment Pharmacol Ther 2015;41:835-43

Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection
A randomized Clinical Trial

• To determine if the efficacy of frozen-and-thawed FMT is noninferior to fresh FMT
• 26 month double-blinded RCT conducted at 6 academic centers in Canada
• Total of 219 patients enrolled to receive the FMT product by rectal enema
• Primary outcome: Resolution of diarrhea/no relapse and ADRs at 13 weeks
• 35/219 (16%) evaluable patients had severe CDI
• 80/219 (37%) received ≥ 2 fecal enema instillations
• Successful treatment outcomes (per protocol):
  Frozen FMT group: 76/91 (83.5%)
  Fresh FMT group: 74/87 (85.1%)
• No observed differences in proportions of adverse events
• 19 patients died (8.7%). None of the deaths were directly related to FMT

Lee CH et al. JAMA 2016;315;142-9

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

• Open-label two arm RTC: 10 patients each arm
• Healthy volunteer stool donors
• Donor screening per AABB recommendations
• Stool frozen and stored until time of instillation
• FMT administration: NGT or colonoscopy (Col)
• Instillation volume 90 ml each arm
• Cure: Col 8/10, NGT 6/10, p= 0.628
• Microbiota study (Shannon Diversity Index): 16 S gene, Illumina MiSeq


Oral, Capsulized, Frozen Fecal Microbiota Transplantation for Relapsing Clostridium difficile Infection

• Open label, single group feasibility study
• Twenty patients with at least 3 episodes of CDI
• Healthy volunteer stool donors screened per published guidelines
• Stool packed into multilayer gel capsules and stored at -80C
• 15 capsules administered on 2 consecutive days
• Resolution of diarrhea 14 patients (70%)
• 6 patients retreated: 4 were cured: Secondary cure rate 90%

A Novel Microbiome Therapeutic Increases Gut Microbial Diversity and Prevents Recurrent *Clostridium difficile* Infection

Sahil Khanna,1 Darrell S. Pardi,2 Colleen R. Kelly,2 Tanvi Dhere,3 Matthew R. Henn,4 Mary-Jane Lombardo,4 Marin Vulic,4 Toshiro Ohsumi,4 Jonathan Winkler,4 Christina Pindar,5 Barbara H. McGovern,4 Roger J. Pomerantz,4 John G. Aunins,4 David N. Cook,4 and Elizabeth L. Hohmann

1Mayo Clinic, Rochester, Minnesota; 2Miriam Hospital, Women’s Medicine Collaborative, Providence, Rhode Island; 3Emory University School of Medicine, Atlanta, Georgia; 4Seres Therapeutics, Cambridge, and 5Massachusetts General Hospital, Boston, Massachusetts

- Multicenter study with Ser-109
- Firmicute spores extracted from ethanol-treated stool, filled in hypromellose capsules
- Two study arms, each with 15 patients
- Cohort 1: Two doses, higher spore count
- Cohort 2: Single dose, lower spore count
- No diarrhea for 13/15 patients each arm at 8 weeks (primary end point)
- 4 patients had diarrhea at ≤ 9 days and stool was *C. difficile* positive
- 1 patient withdrew, 1 patient was retreated
- 29/30 (97%) had achieved cure at 8 weeks

Khanna S et al. *J Infect Dis* February 8, 2016. ePUB DOI: 10.1093/infdis/jiv766

---

FMT for severe or complicated CDI?

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>Route administration</th>
<th>Patients (n)</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yu</td>
<td>2014</td>
<td>Colonoscopy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Zainah</td>
<td>2014</td>
<td>NGT</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Crum-Cianflo</td>
<td>2014</td>
<td>Colonoscopy</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Agrawal</td>
<td>2015</td>
<td>Colonoscopy</td>
<td>57</td>
<td>45</td>
</tr>
<tr>
<td>Aroniadis</td>
<td>2015</td>
<td>Colonoscopy</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Fischer</td>
<td>2015</td>
<td>Colonoscopy</td>
<td>29</td>
<td>27</td>
</tr>
<tr>
<td>Lagier</td>
<td>2015</td>
<td>NGT</td>
<td>16</td>
<td>13</td>
</tr>
<tr>
<td>Costello</td>
<td>2015</td>
<td>NJT</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lee</td>
<td>2016</td>
<td>Rectal enema</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

171 147 (86%)

---

Billing for upper tract FMT

<table>
<thead>
<tr>
<th>Work process</th>
<th>E&amp;M/CPT code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial consultation</td>
<td>99223/99245</td>
<td>High complexity</td>
</tr>
<tr>
<td>Screening of donor</td>
<td>44705/G0455</td>
<td>Incident to pt. w/u</td>
</tr>
<tr>
<td>Radiograph abdomen</td>
<td>74000</td>
<td>Single AP view</td>
</tr>
<tr>
<td>Stool sample preparation</td>
<td>87999¶</td>
<td>Unlisted (microbiology)</td>
</tr>
<tr>
<td>FMT instillation</td>
<td>43999¶</td>
<td>Unlisted (stomach)</td>
</tr>
<tr>
<td>&quot;</td>
<td>44799¶</td>
<td>Unlisted (intestine)</td>
</tr>
</tbody>
</table>

¶ Bill for technologist or provider time

---

Billing for donor screening using ICD10 CPT Z-codes*

<table>
<thead>
<tr>
<th>Screening test</th>
<th>ICD 10 code</th>
<th>CPT Code</th>
<th>Charge ($)¶</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV- IgM</td>
<td>Z22.50</td>
<td>86709</td>
<td>76.66</td>
</tr>
<tr>
<td>HBsAg</td>
<td>Z22.51</td>
<td>87340</td>
<td>105.63</td>
</tr>
<tr>
<td>HCV-Ab</td>
<td>Z22.52</td>
<td>86803</td>
<td>169.10</td>
</tr>
<tr>
<td>HIV 1 EIA</td>
<td>Z11.4</td>
<td>87899</td>
<td>389.75</td>
</tr>
<tr>
<td>Norovirus (PCR)</td>
<td>Z11.59</td>
<td>87798</td>
<td>504.59</td>
</tr>
<tr>
<td>Enteric pathogen culture</td>
<td>Z22.1</td>
<td>87015,45,46</td>
<td>389.75</td>
</tr>
<tr>
<td>RPR</td>
<td>Z11.3</td>
<td>87680</td>
<td>50.63</td>
</tr>
<tr>
<td><em>C. difficile</em> PCR</td>
<td>Z22.1</td>
<td>87177</td>
<td>150.56</td>
</tr>
<tr>
<td>O + P (travel history)</td>
<td>Z11.0</td>
<td>87328, 9</td>
<td>353.36</td>
</tr>
</tbody>
</table>

Sum 1,921.04

* Excludes donors covered by Medicare only  ¶ St. Luke’s Hospital, Duluth, MN
Charges for FMT

<table>
<thead>
<tr>
<th>Route/product</th>
<th>Duluth MN</th>
<th>Lima OH</th>
<th>Boston MA</th>
<th>Wichita KS</th>
<th>S California</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donor screening</td>
<td>$1,000</td>
<td>$1,276</td>
<td>$507</td>
<td>$360</td>
<td>-</td>
</tr>
<tr>
<td>Sample preparation</td>
<td>$200</td>
<td>$200</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Purchase of capsules</td>
<td>-</td>
<td>Home made</td>
<td>-</td>
<td>$885</td>
<td>-</td>
</tr>
<tr>
<td>MD evaluation</td>
<td>Variable</td>
<td>Variable</td>
<td>$257</td>
<td>$365</td>
<td>-</td>
</tr>
<tr>
<td>NDT placement</td>
<td>$1,300</td>
<td>$257</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Instillation</td>
<td>-</td>
<td>$386</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>SUM</td>
<td>$2,500</td>
<td>$1,533</td>
<td>$1,200</td>
<td>$1,003</td>
<td>$1,250</td>
</tr>
</tbody>
</table>

Fecal bacteriotherapy
Obstacles and potential risks in the USA

- Appropriate donor of fecal sample may not be readily available
- FMT may not be offered in the patient’s geographical area
- Occult pathogens may be introduced with the donor stool sample
- Potential for physical complications from the instillation procedure
  - Perforation of hollow viscus
  - Aspiration of instilled feces content
- Perceived medico-legal limitations may be imposed by the local IRB
- Inadequate Medicare reimbursement of donor stool screening costs
- Fecal bacteriotherapy may appear esthetically unappealing
- FDA ruled February 2013 that all FMT providers must hold an approved Investigational New Drug (IND) permit
- IND requirement changed to "discretionary enforcement" in July 2013 provided informed consent given and donor known to patient/provider*

*http://www.regulations.gov/?docid=FDA-2013-D-0811-0002

FMT and the FDA March 1, 2016

FDA has issued new guidance and welcomes comment on its intention to "exercise enforcement discretion under limited conditions, regarding the IND requirements for the use of FMT to treat C. difficile infection not responding to standard therapies. FDA intends to exercise this discretion, provided that:

1. The licensed health care provider treating the patient obtains adequate consent from the patient or his or her legally authorized representative for the use of FMT products. The consent should include, at a minimum, a statement that the use of FMT products to treat C. difficile is investigational and a discussion of its reasonably foreseeable risks
2. The FMT product is not obtained from a stool bank
3. The stool donor and stool are qualified by screening and testing performed under the direction of the licensed health care provider for the purpose of providing the FMT product for treatment of the patient.*

An establishment that collects or prepares FMT products "solely under the direction of licensed health care providers for the purpose of treating their patients (e.g., a hospital laboratory) is not considered to be a stool bank under this guidance."

Send comments on this FDA guidance via the federal register docket by May 31

https://www.federalregister.gov/articles/2016/03/01/2016-04372/enforcement-policy-regarding-investigational-new-drug-requirements-for-use-of-fecal-microbiota-for...

Reported possible adverse events from FMT

- Peritonitis after colonoscopy: 2 patients
- Irritable bowel syndrome: 1 patient
- "Mild transient enteritis": 3 patients
- Upper GI bleeding: 1 patient
- Norovirus transmission: 2 patients
- "Autoimmune" phenomena: 4 patients
- Possible CMV infection: 1 patient with IBD
- Post-transplant weight gain: Daughter-to-mother
- Fatal fecal aspiration pneumonia: 1 patient

*Sofi. Scand J Gastroenterol 2012; van Nood. NEJM 2013;368:474
FMT is not a treatment option when

- The patient is not receptive to FMT ("yuk-factor")
- The treating physician is not receptive to FMT
- A suitable stool donor or commercial stool sample cannot be located
- Lack of FMT treatment facility in the geographical region
- Third party payer will not reimburse the cost of FMT
- The patient cannot afford the costs of FMT (donor screening)


US “recommendations” for FMT administration 2015

- FMT may be administered in the US without an IND when the indication is for treatment of RCDI. All other indications require an approved IND
- Patients must be informed about possible risks and consent to the procedure in writing
- “Best” stool donor resource remains undefined
- Commercial pre-screened stool samples are increasingly being utilized
- Immunosuppressed patients have tolerated FMT without reports of increased adverse effects
- IDSA/SHEA treatment guidelines are currently being updated. The new guideline will endorse FMT for treatment of RCDI (GRADE Strong, Moderate)
- A stool biorepository bank is currently in the planning stages and will be housed at the CDC, funded by the NIH

Conclusions I

- Vancomycin or fidaxomicin are preferred agents for treatment of initial episode of mild to severe CDI
- Metronidazole should used to treat mild to moderate CDI only if standard drugs are not available, and should not be used repeatedly
- High dose vancomycin is regimen of choice for fulminant CDI, but increasing evidence for successful outcomes with FMT
- CDI recurrence rate is lower after fidaxomicin than vancomycin therapy
- CDI first recurrence should be treated with vancomycin or fidaxomicin
- Pulsed vancomycin regimen is preferred for patients who have received prior treatment with standard vancomycin regimen
Conclusions II

- FMT is more effective at resolving multiple RCDI than alternative therapies
- FMT raw material supply is inexpensive but cost of screening is expensive
- FMT is easy to perform and can be performed anywhere
- The need for and extent of screening of a close family member fecal donor remains poorly defined
- Published literature to date strongly suggests that FMT is safe
- FMT may no longer be cost effective compared to standard treatment alternatives, but prescreened commercial stool may help reduce the cost
- Patient satisfaction after FMT is very high, but some object....
- For patients (and physicians) who object to FMT:
  - Similar success rate may be achieved with vancomycin STAW and kefir

Drekonja D. Ann Int Med 2015;162:630 (Systematic review)
¶ Bakken. Clin Infect Dis 2014;59:858 (STAW and kefir)

FMT: Remaining issues/needs

- Additional RTCs to confirm efficacy of FMT
- Additional experience with vancomycin STAW/Kefir
- Well defined indications for FMT beyond RCDI
- Standardized protocols for FMT administration
- Donor screening guidelines
- FMT registry for long term patient safety follow-up

Malani and Rao. JAMA 2016;315:137

UGI Tract FMT: Published Protocols

- Russell G. Pediatrics 2010;126:e239-42. PMID: 20547640
- Youngster I et al. JAMA 2014;312:1772-8. PMID: 25322359
Probiotics for treatment/secondary prevention of recurrent CDI

Clinical Infect Dis Advance Access published June 27, 2014

Staggered and Tapered Antibiotic Withdrawal With Administration of Kefir for Recurrent Clostridium difficile Infection

John S. Bakken
Section of Infectious Diseases, St Luke’s Hospital, Duluth, Minnesota

Daily administration of the probiotic kefir given in combination with a staggered and tapered antibiotic withdrawal regimen may resolve recurrent Clostridium difficile infection as effectively as fecal microbiota transplantation.

Keywords: antibiotic withdrawal; Clostridium difficile; diarrhea; kefir; recurrent.

with STAW between 2003 and 2009, and all successfully resolved their recurrent diarrhea [7]. This article reports the long-term follow-up of the initial 8 patients and 17 subsequent patients with recurrent CDI who were treated with STAW between 1 January 2009 and 31 October 2013. Each CDI recurrence was verified by ≥1 positive stool enzyme immunoassay test results for toxin A and B or polymerase chain reaction for the rfbB locus. At the initial evaluation, each patient was asked whether they preferred to be treated with FMT or with an oral antibiotic agent (metronidazole prior to 2007, vancomycin from 2007 onward) administered as STAW combined with regular intake of kefir (Lifeway kefir, Lifeway Foods, Morton Grove, Illinois) (Table 1). All 26 patients opted not to be treated with FMT, either because they were unable to afford the costs associated with FMT (in large part due to the cost of laboratory screening of the potential stool donor), or they preferred to take EMF until their last failed FMT. Those four patients received kefir.

Lifeway Kefir for treatment of CDI recurrence

www.lifeway.net

Bifidobacterium breve
B. lactis
B. longum
Lactobacillus acidophilus
L. casei
L. lactis
L. plantarum
L. reuteri
L. rhamnosus
Leuconostoc cremoris
Streptococcus diacetylactis
Saccaromyces florentinus

All Lifeway products contain 7-10 billion CFU's of the 12 live & active Kefir cultures per 8oz (~240 ml)

Disclaimer: I have no financial or formal relationship with Lifeway