Fecal Microbiota Transplant for *C. difficile Infection* ...and other diseases (whatever else ails you?)

L. Campbell Levy, MD
Co-Director IBD Center, DHMC
Director Year 4 Education, Geisel School of Medicine
NH ACP Annual Scientific Meeting
Friday, October 25, 2019
Disclosures... By way of a quiz

• No financial disclosures

• Five drugs for *C. difficile*. Can you name them?

1. Three are FDA-approved?
   • Vancomycin (Firvanq™, Vancocin), fidaxomicin (Dificid®), bezlotoxumab (Zinplava™)

2. One is used “off label”?
   • metronidazole

3. One is an investigational drug?
   • Stool!
Objectives

• Understand the circumstances surrounding the adoption of FMT – especially as it relates to the *C. difficile* epidemic and the limitations of antibiotic therapies

• Defend the rationale for FMT for the treatment of *C. difficile*

• Summarize several main mechanisms for FMT effectiveness in treatment of *C. difficile*

• Introduce emerging areas of investigation of dysbiosis, impacts on other organ systems, and potential areas for treatment
68 yo high school secretary

• Abscessed tooth treated with amoxicillin 2006
• Diagnosed with *C. difficile* infection 3 weeks later
• Recurrences off of antibiotics
• 2006-2010
  – 5 courses of metronidazole
  – Cholestyramine
  – 3 different probiotics
  – Rifampin
  – 6 courses of oral vancomycin... 125 mg bid for 14 months
Fecal Flora Reconstitution for Recurrent
*Clostridium difficile* Infection: Results and Methodology

Faith Rohlke, BA,* Christina M. Surawicz, MD, MACG,†

PMID: 11095355
Issn Print: 0002-9270
Publication Date: November 2000

Treatment of Recurrent*Clostridium Difficile*–Associated Diarrhea by Administration of Donated Stool Directly Through A Colonoscope

Seth Persky, Lawrence Brandt;

Review articles

Struggling with recurrent *Clostridium difficile* infections: is donor faeces the solution?

E van Nood¹, P Speelman¹, E J Kuijper², J J Keller³
FMT Efficacy in Case Series
Meta-analysis of FMT for RCDI

Pooled Resolution Rate 89.7% (95% CI 84-93%)

N=273

Garborg et al., 2000  0.83 (0.67, 0.93)
MacConnachie et al., 2009  0.73 (0.45, 0.92)
Polak et al., 2011  0.87 (0.60, 0.98)
Lund-Tonnesen et al., 1998  0.83 (0.59, 0.96)
Kassam et al., 2010  0.93 (0.76, 0.99)
Kelly et al., 2012  0.92 (0.75, 0.99)
Mellow and Kanatzar, 2011  0.92 (0.64, 1.00)
Mattila et al., 2012  0.94 (0.86, 0.98)
Rohlke et al., 2010  1.00 (0.82, 1.00)
Yoon and Brandt, 2010  1.00 (0.74, 1.00)
Aas et al., 2003  0.83 (0.59, 0.96)
Combined  0.89 (0.84, 0.93)

In 2010, DHMC assembles our Transplant team...
You are only \textit{half} human

\textbf{Distribution of cell number and mass for cell types in the human body}

\begin{itemize}
\item \textbf{human cells}:
  \begin{itemize}
  \item cells $[\times 10^{12}]$: 25 (erythrocytes), 5 (others)
  \end{itemize}
\item \textbf{bacteria}:
  \begin{itemize}
  \item cells $[\times 10^{12}]$: 38
  \end{itemize}
\item \textbf{mass [kg]}:
  \begin{itemize}
  \item 3 (erythrocytes), 13 (adipocytes), 10 (muscle cells), 20 (bacteria)
  \item 0.2 (others)
  \end{itemize}
\end{itemize}

\begin{flushleft}
\end{flushleft}
Microbiome, *Clostridioides difficile*, and Colonization Resistance

• A diverse, healthy microbiota can prevent colonization by pathogens, like *C. diff*, or at least control population (limit germination and vegetation).

• Perturbation of the microbiome (e.g. antibiotics) allows for colonization, germination, and toxin production.
Cycle of recurrent *C. difficile* infection (CDI)

- Normal microbiota
- Establishment of susceptibility
- Susceptible microbiota
- C difficile spores
- Germination
- Vegetative C difficile
- Disease initiation
- Toxin production
- Clearance/asymptomatic colonization
- Recurrence cycle
- Recurrent disease
- CDI treatment (antibiotics)
- CDI treatment (fecal transplant)
- Recovery
- Restoration of colonization resistance
- Loss of colonization resistance
- Britton and Young. Gastroenterology 2014;146:1547–1553
Fecal Transplant... Not that new

• “Medical miracle back from the brink of death” – 4th Century China

• “Yellow soup”
  Compendium of Materia Medica – 16th Century

• Fabricius Aquapendente – 17th Century Italy

"Toxins produced by putrefactive microbes in the colon accelerate senescence"
E. coli Nissle 1917 inhibits pathogenic bacteria

- German soldier stubbornly resistant to dysentery
- Isolated E. coli strain
- Antagonized shigella and salmonella strains
• Four cases of pseudomembranous colitis associated with antibiotic treatment successfully treated with fecal enema

• Thought to be S. aureus isolated from feces
**Clostridium difficile... Not that old**

- 1930’s – *B. difficillis* described in normal flora of neonates

- Post-operative pseudomembranous colitis (PMC) 1950s

- 1974 – “Clindamycin colitis” caused PMC

- 1978 - antibiotic associated pseudomembranous colitis (PMC) caused by *C. difficile toxin*
Epidemic strain of *C. difficile* 2003-04

700 *C. difficile* related deaths in Quebec, Canada in one year (2003-4)
Incidence of *C. difficile* infection in Quebec

400% increase 2002-03

>80% NAP1

BI/NAP1/027 Epidemic in the US

BI/NAP1 C. difficile in U.S. Nov. 2007 (n = 38)

www.cdc.gov/ncidod/dhqp/id_cdiff_data.html
Slide courtesy of Dr. David Binoin
Past vs. present of *C. difficile*

**Pre-NAP**
- Antibiotic assoc disease
- Metronidazole 90% effective

**Post-NAP**
- Doubling CDAD 1996-2003
- Diminished response to metronidazole
- Rise in mortality

**Annual CDI Mortality per 10^6**

Public enemy #1!
State of CDI since the 2000s

- >500,000 cases/yr

- ~29,000 related deaths/yr
  - 4X MRSA deaths
  - 6X all other enteric pathogens combined

- $3.2 billion/yr

- Cephalosporins and fluoroquinolones (OR 3.8 and 3.9)

1. www.cdc.gov/ncidod/dhqp/id_cdiff_data.html
Antibiotics work
Initial Treatment: Stratification by severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-Severe</td>
<td>VAN 125 mg PO qid X 10 d</td>
</tr>
<tr>
<td></td>
<td>FDX 200 mg PO bid x 10 d</td>
</tr>
<tr>
<td></td>
<td>If unavailable, could use MTZ</td>
</tr>
<tr>
<td>WBC &lt; 15K and Cr &lt; 1.5</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Vanco 125 mg PO qid X 10 d</td>
</tr>
<tr>
<td></td>
<td>FDX 200 mg PO bid x 10 d</td>
</tr>
<tr>
<td>WBC &gt; 15K or Cr &gt; 1.5</td>
<td></td>
</tr>
<tr>
<td>Fulminant</td>
<td>Vanco 500 mg PO/NGT qid AND MTZ 500 mg IV q8</td>
</tr>
<tr>
<td>Hypotension, shock, ileus, toxic megacolon</td>
<td></td>
</tr>
</tbody>
</table>

Achilles Heel Is Recurrence!

Recurrence rate

- Initial episode: ~25%
- First recurrence: ~40%
- Second recurrence: >50%

Obstacles to FMT for Recurrent C. difficile infection (rCDI) *circa* 2012

- Acceptance
- High quality data
- Regulation
- Applicability/Logistics
- Safety
“We believe [FMT]... can re-establish a “healthy” functional microbiota in the recipient. However, we think that the efficacy and willingness of patients are not enough to invite wider practice unless there is a standardized methodology for fecal preparation and administration.”

- American Journal of Gastroenterology, Nov 2012
What about acceptance?

The **PATIENTS’** Yuck Factor

Pt preferences for abx alone vs. abx with FMT

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Antibiotics + FR, No. (%)</th>
<th>Antibiotics Alone, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>After reading scenario 1</td>
<td>162 (85%)</td>
<td>29 (15%)</td>
</tr>
<tr>
<td>After reading scenario 2</td>
<td>154 (81%)</td>
<td>37 (19%)</td>
</tr>
<tr>
<td>(disclosure of FR specifics)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• If FR provided as colorless, odorless liquid given by NGT, enema, or colonoscopy</td>
<td>158 (83%)</td>
<td>33 (17%)</td>
</tr>
<tr>
<td>• If FR provided as colorless, odorless pill</td>
<td>171 (90%)</td>
<td>20 (10%)</td>
</tr>
<tr>
<td>• If FR (in any form) recommended by doctor</td>
<td>179 (94%)</td>
<td>12 (6%)</td>
</tr>
</tbody>
</table>

Abbreviations: FR, floral restoration; NGT, nasogastric tube.

...And the **Doctor’s Yuck Factor?**
Reasons physicians gave for not offering FMT

<table>
<thead>
<tr>
<th>Reasons for not offering FMT</th>
<th>Physicians reporting this reason, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Have not had the right clinical situation†</td>
<td>27 (33)</td>
</tr>
<tr>
<td>Believe that patients will find the concept too unappealing</td>
<td>20 (24)</td>
</tr>
<tr>
<td>Institutional barriers (eg, IRB) make it difficult</td>
<td>19 (23)</td>
</tr>
<tr>
<td>I (physicians) find the concept too unappealing</td>
<td>15 (18)</td>
</tr>
<tr>
<td>Do not know enough about it†</td>
<td>10 (12)</td>
</tr>
<tr>
<td>Do not know whom to refer to†</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Have concerns about the safety of the treatment</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Do not believe it is effective based on data</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Do not believe that I will receive reimbursement</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Other</td>
<td>10 (12)</td>
</tr>
</tbody>
</table>

Nasoduodenal FMT for Recurrent CDI

Cure rates at 10 wks w/o relapse

FMT, vanco, or fidaxomicin for rCDI

- Primary outcome: clinical cure + neg PCR at 8 wks
- Median previous CDI’s - 4
- Failed pts rescue FMT: 83% (20/24) cure + neg PCR
- FMT via NGT (4) or colo (19)
How effective is FMT compared to other options?

- Fecal Microbiota Transplant ~80-92%
- Fidaxomicin ~30-40%
- Vancomycin ~20-25%

Cammarota, et al APT 2015
Gastroenterology 2019;156:1324-1332
APT 2017;46:479-493
FDA Classification as an Investigational Biologic Drug/Product

• Spring 2013
  – “...intended to affect the structure of any function of the body of a man.”
  – Requires Investigation New Drug Application
Reconsideration by the FDA

Guidance for Industry

Enforcement Policy Regarding Investigational New Drug Requirements for Use of Fecal Microbiota for Transplantation to Treat *Clostridium difficile* Infection Not Responsive to Standard Therapies

...Intends to exercise enforcement discretion... provided that the treating physician obtains adequate informed consent

# Recurrent CDI

<table>
<thead>
<tr>
<th># of Recurrence</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Recurrence</td>
<td>• VAN 125 mg PO qid X 10 d (if MTZ was used 1st line</td>
</tr>
<tr>
<td></td>
<td>• <strong>VAN pulsed taper ~6-8 wks</strong></td>
</tr>
<tr>
<td></td>
<td>• FDX if vanco was used 1st line</td>
</tr>
<tr>
<td>Second Recurrence</td>
<td>• VAN pulsed taper ~6-8 wks</td>
</tr>
<tr>
<td></td>
<td>• VAN X 10 days with rifaximin 20 day “chaser”</td>
</tr>
<tr>
<td></td>
<td>• FDX 200 mg bid x 10 d</td>
</tr>
<tr>
<td></td>
<td>• <strong>FMT</strong>*</td>
</tr>
</tbody>
</table>

*“Opinion of the panel... 2 recurrences should be tried [with abx] prior to offering FMT”*
“Friends and Family Plan”

Tests Required of Donor Prior to Fecal Transplant

<table>
<thead>
<tr>
<th>Test</th>
<th>CPT code</th>
<th>eDH No</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syphilis IgG</td>
<td>86592</td>
<td>LAB1197</td>
<td>Reflexive specific RPR sent</td>
</tr>
<tr>
<td>HIV Ab, type 1&amp;2</td>
<td>86701</td>
<td>LAB473</td>
<td>Reflexive W. Blot</td>
</tr>
<tr>
<td>HepB s AB</td>
<td>86706</td>
<td>LAB472</td>
<td></td>
</tr>
<tr>
<td>HepB cAb, total</td>
<td>86704</td>
<td>LAB1242</td>
<td></td>
</tr>
<tr>
<td>HepB sAg</td>
<td>87340</td>
<td>LAB471</td>
<td></td>
</tr>
<tr>
<td>Hep A Ab IgM</td>
<td>86709</td>
<td>LAB798</td>
<td></td>
</tr>
<tr>
<td>HCV Ab</td>
<td>86803</td>
<td>LAB868</td>
<td></td>
</tr>
<tr>
<td>Stool culture</td>
<td>87145</td>
<td>LAB3711</td>
<td>Salm, shig, campy, yers, aero, plesio, vibrio</td>
</tr>
<tr>
<td>Giardia/Crypto</td>
<td>87272</td>
<td>LAB1319</td>
<td></td>
</tr>
<tr>
<td>C. Difficile screen (EIA)</td>
<td>87803</td>
<td>LAB3617</td>
<td></td>
</tr>
<tr>
<td>Cyclo/Iso stain</td>
<td>87207</td>
<td>LAB3145</td>
<td></td>
</tr>
</tbody>
</table>

Costs to the donor potentially ~$1200
OpenBiome
“Crapsules”

Open-label, feasibility
20 pts, at least 3 recurrences
15 capsules over 2 days
14/20 without relapse at 8 weeks.

How safe is FMT?

• No SAEs in 7 RCTS
  – Long-term constipation (15-20%), mild diarrhea (80-90%), bloating, cramping, belching

• Systemic Review of 50 publications
  – Adverse event rate (28.5%)
  – SAE 5.1% (44/855) – 2 definitely assoc with FMT (aspiration and perforation)
Two UC patients with CDI

Both treated with FMT

Toxin producing *Clostridium perfringens* isolated from stool only after FMT, when presented with diarrhea 2 mos later
Important Safety Alert Regarding Use of Fecal Microbiota for Transplantation and Risk of Serious Adverse Reactions Due to Transmission of Multi-Drug Resistant Organisms

- ESBL-producing *E. coli* in two immunocompromised pts
- One died
- Stool from same donor
- Stool bank did not test for the pathogen
- New FDA guidance re MDROs

Brave New World of the Microbiome

The Gut Microbiome & Digestive Health
A New Frontier

The Human Intestinal Microbiome in Health and Disease

Gut Microbiota Functions
- Influences
- Immune maturation and homeostasis
- Host cell proliferation
- Vascularization
- Neurologic signaling
- Pathogen burden
- Intestinal endocrine functions
- Bone density
- Energy biogenesis

Disease Indications
- Neurologic
- Psychiatric
- Respiratory
- Cardiovascular
- Gastrointestinal
- Hepatic
- Autoimmune
- Metabolic
- Oncologic

Biosynthesis
- Vitamins
- Steroid hormones
- Neurotransmitters

Metabolism
- Branched-chain and aromatic amino acids
- Dietary components
- Bile salts
- Drugs
- Xenobiotics
Solving the “Great Plate Count Anomaly”
The era of ‘omics and Next Gen Sequencing

• 16S rRNA sequencing
  – Highly conserved among bacteria
  – Composition of microbial community (taxa)

• Shotgun sequencing
  – Entire nucleotide pool
  – Accounts for virome, mycobiome
  – Higher resolution (species)
  – Functional capabilities of communities
10^6 Drop in sequencing costs
Human microbiome sample

- Extract DNA
  - 16S rRNA gene sequencing
    - Compare sequences to ribosomal databases
      - Bacteria and Archaea
  - 16S rRNA gene sequencing
    - Compare sequences to reference genomes
      - Fungus/Yeast
  - Total DNA sequencing (shotgun metagenomics)
    - Compare sequences to genomic databases
      - Viruses

- Extract RNA
  - RNA expression profiling (transcriptomics)
    - Gene expression
      - Metabolite characterization
      - What are the functions of the community?

- Extract small molecules
  - Mass spectroscopy (metabolomics)
    - Gene content
      - Identify relative frequencies and pathways
      - What organisms are present and what is their relative abundance?
Microbial diversity decreases in rCDI

FMT restores “normal” anaerobes quickly and durably
Mechanisms of FMT Transplantation

• Competition with indigenous bacteria
  – Accessing nutrition
  – Production of bacteriocins

• Secondary bile acid metabolism
  – Cholic class germinate spores
  – Chenodeoxycholic inhibit spores
  – rCDI lack secondary bile acids

• Immune-mediated colonization resistance
  – Neutrophil recruitment enzymes correlate with clinical severity whereas bacterial burden does NOT.
Dysbiosis in IBD

- Higher concentrations of bacteria that are proportion to disease severity
- Lower bacterial diversity
FMT for IBD Review and Meta-Analysis

- 18 studies (9 cohort, 8 case reports, 1 RCT), 122 patients (79 UC, 39 Crohn’s, 4 IBDU)

- Overall response rate, 45%
  - 22% UC
  - 61% Crohn’s

- Conclusion: safe, but effectiveness highly variable

Overall response in cohort studies, 36.2%

Colman RJ & Rubin DT, J CrohnsColitis 2014 online early.
Fecal Microbiota Therapy (FMT) Induces Remission in Pts with UC: RCT

- Randomized DB RCT
  - 70 pts with active UC
  - 6 wks of weekly FMT (n=38) via retention enemas vs placebo (water) (n=37)

- Results
  - 24% (9/38) FMT vs 5% (2/37) placebo in remission
  - 7/9 pts with FMT in histologic remission
  - 8/9 in remission at 52 weeks.
  - 7 of 9 pts in remission from single donor

FMT Induces Remission in Pts with UC: RCT
Germ Free Animal Models

- Exaggerated stress response of HPA axis
- Decreased cardiac output
- Decreased intestinal surface area
- Increased adiposity in atypical distributions
Microbiome affecting Obesity

- Obese littermates of lean mice have a relative abundance of *Bacteroidetes* and *Firmicutes*.

- Colonization of a germ-free mouse with an “obese microbiota” induces ~60% increase in total body fat as compared to a “lean microbiota.”
Metabolic phenotype is transmissible via microbiota transplant.
FMT for Metabolic Syndrome

- 9 FMT via NGT vs. autologous infusion via NGT
- Peripheral but not insulin sensitivity improved at 6 weeks but not maintained.
- 2018 RCT with no change

Vrieze et al. Gastroenterol 2012;143:913-16
Dysbiosis in NASH differs from Obese and is Reversible with Treatment

- 16S on 16 NASH pts and 22 controls from a prior probiotic trial
- Pts at month 6 of probiotics with lower intrahepatic triglycerides are distinguished by bacterial phyla

FMT in IBS

- Post-infectious IBS is common (30%)
- Increased sulfate-reducing bacteria in IBS-C
- Association between decrease numbers and diversity of *Bacteroidetes* in subsets of IBS

- 45 patients with IBS-C following bacteriotherapy
- 30/45 (60%) with improvement of bloating and abd pain over 9-19 months.
- No randomized trials

Bacteria control everything!
Conclusion

• Theories of colonization resistance have laid the groundwork for FMT

• FMT is effective for recurrent CDI

• Coinciding epidemic and technological advances have allowed for a deeper investigation into the potential role of the gut microbiota in disease
“The greatest poet placed himself where the future becomes present. Past and present and future are disjoined but joined.”

- Walt Whitman