Fecal Microbiota Transplant: Past, Present and Future

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Financial Interest Disclosure
(over the past 24 months)

No relevant financial relationships with any commercial interests
**CanMEDS Roles Covered in this Session:**

<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
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<tr>
<td>Medical Expert</td>
<td>(as Medical Experts, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional attitudes in their provision of patient-centered care. Medical Expert is the central physician Role in the CanMEDS framework.)</td>
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<tr>
<td>Communicator</td>
<td>(as Communicators, physicians effectively facilitate the doctor-patient relationship and the dynamic exchanges that occur before, during, and after the medical encounter.)</td>
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<tr>
<td>Collaborator</td>
<td>(as Collaborators, physicians effectively work within a healthcare team to achieve optimal patient care.)</td>
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<td>Manager</td>
<td>(as Managers, physicians are integral participants in healthcare organizations, organizing sustainable practices, making decisions about allocating resources, and contributing to the effectiveness of the healthcare system.)</td>
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<td>Health Advocate</td>
<td>(as Health Advocates, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.)</td>
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<tr>
<td>Scholar</td>
<td>(as Scholars, physicians demonstrate a lifelong commitment to reflective learning, as well as the creation, dissemination, application and translation of medical knowledge.)</td>
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<tr>
<td>Professional</td>
<td>(as Professionals, physicians are committed to the health and well-being of individuals and society through ethical practice, profession-led regulation, and high personal standards of behaviour.)</td>
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1. What is the history of FMT?
2. What is current status and how did we get here?
3. What might the future hold?
Fecal Microbiota Transplant

- Healthy donor stool to colon via enema, colonoscopy or upper-tract
- Rationale: restore normal microbiome
- Other terms: stool transplant; fecal flora reconstitution; fecal bacteriotherapy
Ancient History

1700 years ago in China,
- 4th Century used human feces to treat severe diarrhea
- 16th century used infant feces, called it “yellow soup”, to treat diarrheal illnesses

Zhang et al, Am J Gastroenterol 2012; 107:1755 (letter)
Surgical patients

- Fecal enema as adjunct in the treatment of pseudomembranous enterocolitis – 4 patients - 1958
  
- Fecal enemas to treat 16 patients with severe Clostridium difficile disease - 1981

Eiseman et al, Surgery 1958; 44:854-9
Bowden, Amer Surgeon, 1981; 47:178-83
History

• 1983: first case using fecal enema to treat RCDI, Schwan et al
• 1989 Tvede et al: mixture of aerobes and anaerobes to treat RCDI cases
• 1998 – Lund-Tonnesen: colonoscopy to deliver stool to treat RCDI, Norwegian paper
History

- 2000- Persky and Brandt: case report of colonoscopy to treat RCDI patient
- 2002 Faust et al, 6 patients, Canadian series – Abstract only
- 2003 Aas et al, per NG tube; 18 pts
- 2010 Silverman et al, home administered enemas
Epidemic of C difficile

• Around the Year 2000- 2002
  – Many more cases, severe, deaths, surgeries
  – Associated with hypervirulent strain and quinolone use
  – Thus more cases of RCDI
  – Nothing else was working
  – So some of us started doing this
  – It was really effective!
Fecal Microbiota Transplant

- Lots of case reports and small series
- Routes: enema, NG tube, colonoscopy
- Multiple systematic and meta analyses show 90% efficacy in treatment of RCDI
  - (Guo et al APT 2012; Sofi et al Scand J Gastro 2013; Kassam et al Am J Gastroenterol 2013)
Duodenal Infusion of Donor Feces for RCDI

RCT from Netherlands showed efficacy in RCDI pts. given donor stool via nasoduodenal route

Cure rates for RCDI.

- First Infusion of Donor Feces (N=16): 81.3%
- Infusion of Donor Feces Overall (N=16): 93.8%
- Vancomycin (N=13): 30.8%
- Vancomycin with Bowel Lavage (N=13): 23.1%

Significance levels:
- P<0.001
- P<0.001
- P=0.008
- P=0.003
The Present

- Methods
- Safety- short term
- Long term follow up
Patient Selection

• Recurrent C difficile infection
  – 3 or more recurrences with adequate treatment
    • Vanco pulse regimen 125 mg qid x 10 d, then one pill every 3 days for 10 more doses
    – I make sure it is RCDI and post infectious IBS
• Recommended by ACG guidelines for 3d recurrence (2013) and strongly recommended for multiple recurrences by European Society Clinical Microbiology and Infectious Diseases (2014)

Surawicz et al, Am J Gastroentero2013:108;478-498; Debast et al Clin Infect 2014: 20(suppl 2); 1-26
Donor Selection

• Usually family or friend
• If no suitable donor, we schedule on same day and divide stool or ask donor to deliver again another day, plan for stool bank product
• Extensive initial questionnaire, like for blood donation, including
  – Cancer
  – Autoimmune disorders
  – Metabolic syndrome
  – GI disease or GI symptoms
Did fecal transplant make woman obese?

Woman gained 40 lbs and rising after FMT (32 yo, 16 yo daughter, BMI 26, but wt went from 140 lb to 170 lb)

Her BMI: 26 to 33

Not able to lose weight

Alang and Kelly, Open forum infectious diseases November 2014
Donor Screening- Blood

Hepatitis A, B,C
  Hep A IgM
  Hep B surface antigen and
  core antibody
  Hep C antibody
HIV 1 and 2
Syphilis
CONSIDER: CMV, EBV, Strongyloides, Ameba
Donor Screening- Stool

- Enteric pathogens, expanded, includes Yersinia
- C difficile PCR
- O&P (one)
- Acid fast stain: cyclospora and isospora (sp)
- Giardia antigen
- Rotavirus EIA
- CONSIDER Listeria, Vibrio, MRSA, VRE
Donor Preparation- Stool

• Take a laxative the night before and inform us if any change in health
• Avoid allergens like nuts if pt has allergies, i.e. Put sample in disposable container
• Prefer fresh, 6 hrs., ice not needed
• We weigh (200 gm or more best), mix by hand, filter thru gauze. 6 fifty cc syringes full into colon
Patient Preparation

- Baseline blood work for Hep A,B,C, HIV and syphilis
- Prep for colonoscopy—want excellent
- Consent: not guaranteed to work, could have risks of unknown infection or short or long-term consequences
- After procedure get loperamide and stay for 2 hours
- Follow up phone calls at 24 hr., 2 wks. and clinic visit at 3 months
Results

90% effective
Intermittent diarrhea common, usually resolves
Significant diarrhea, test for C diff and treat if positive-
   Use vanco pulse regimen
If fails, repeat FMT with another donor
I have only 2 pts. on long term vanco
   frail elderly women
# Risks of FMT

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<th>Real</th>
<th>Theoretical</th>
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<td>1. Transmit infection</td>
<td>1. Alter microbiome</td>
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<td>2. Risks of procedure to administer</td>
<td>2. ↑ obesity</td>
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<tr>
<td>3. Risks of anesthesia for procedure</td>
<td>3. Autoimmune disorders</td>
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FMT- Adverse Events

• Symptoms - common
  – Diarrhea
  – Constipation
  – Change in flatus
  – Transient fevers

• Infections - uncommon
  – Proteus bacteremia, one case
  – Norovirus, one case
Flares in IBD- several cases

High fevers and abdominal tenderness post-FMT
78 y/o M with relapsing CDI
- UC quiescent >20 years (off meds)
- FMT (wife donor)
- Transient UC flare 9 days after FMT

deLeon L. et al. Clin Gastroenterol and Hepatol 2013
FMT in Immunocompromised Hosts

• Multicenter (16) series; 80 IC patients treated with FMT

• IBD, solid organ transplant, oncologic condition, HIV/AIDS, other condition

• 78% cure after single FMT, 89 % overall cured
Immune compromised series: adverse events

• 12 (15%) Serious
• 4 related, 5 possibly related, 3 unrelated
  – 10 hospitalizations
    • Abdominal pain
    • Transient diarrhea
    • Unrelated infection (IV catheter)
  – 5 IBD flares (14%)

No infections related to FMT
Immune compromised series

2 deaths (1 related to FMT procedure)

• Aspiration during sedation for colonoscopy, pt had advanced esophageal cancer
• The other pt had pneumonia before and after FMT
Short term follow up- 1 year

70 patients with RCDI treated with FMT
No immediate complications
Success rate 89%
10 pts. died within a year, all of unrelated causes

Mattila et al, Gastroenterology 2012: 132:490
Long-Term Follow-Up Study: FMT

- 77 patients—5 centers in US
- Follow-Up: 3 months to 5 ½ years
- Success rate: 82% $\rightarrow$ 98% (second infusion)
- New conditions: 4 patients
  - Rheumatoid Arthritis
  - Sjogren’s Syndrome
  - ITP (Idiopathic Thrombocytopenic Purpura)
  - Peripheral Neuropathy

Brandt, et al. Amer J Gastroenterol 2012; 107
The future

- Regulation
- Registry
- Research
Regulation: US

- May use to treat *C. difficile* not responding to standard therapy
- Informed consent
  - State it is investigational
  - Discuss potential risks
- Suggest donor known to patient or provider
  - Public comments are being considered

www.fda.gov
Health Canada

• **Stool—”New Biologic Drug”**
  – Investigational only
  – Clinical trial requirement
    • Review
    • Evaluate production process on-site
    • Good manufacturing processes
    • Lot—release information
    “No objection letter”

Regulatory Status—FDA

• Stool—characterized as a drug, not a tissue (a biologic property)
• But stool is not really a drug!
• FDA regulates tissues: blood, cartilage, bone, skin, and egg cells
Regulation as a drug-problems

- Stool is highly variable and complex, more similar to tissue
- This would restrict FMT to companies that can fund large clinical trials
- Restrictive rules would limit access,
- Patients will self treat
Regulation as tissue- benefits

Patient safety and promotes access to FMT
Need to require establishment of a registry
screen and test donors
prepare and follow written protocols
maintain records
Facilitates research
Registry for tracking AEs and long term outcomes
supply material for clinical trials
human studies need monitoring by local IRBs
Defined synthetic microbial communities would be
regulated as drugs

Smith et al Nature 2014
Regulation will maximize access and safety

- Require specific screening, follow-up, records
- Facilitate research
- Track adverse outcomes
- Track long-term outcomes
- Need for a registry
A National FMT Registry

• AGA Microbiome Center Scientific Advisory Board
  • Infectious Disease Society of America (IDSA)
    • NASPGHAN
    • CCFA

AGA
Registry expertise with a CRO (ACI Clinical)

FMT Registry
NIH NIAID Application for a R24 (resource related research project)

Penn-CHOP Microbiome Initiative

Biobank
Stool/microbial products

FDA
Oversight of FMT, Stool-based products, and “next generation” probiotics

Professional Societies
Clinical practice standards (efficacy/safety), liability, reimbursement

Academia, CDC, NIH and Other (i.e. Industry)
Basic and clinical investigation, product development
Research: other products, other uses and mechanisms

• Oral capsules of stool effective
  – Tom Louie; Dina Kao study in progress
• Oral capsules of frozen stool- 20 pts
  – Youngster et al, JAMA 2014
• Frozen stool from universal donors
  – OpenBiome stool bank, Massachusetts (MIT).
  – $250 per dose
Stool Substitute for RCDI – “RePOOPulating” the Gut

- Isolated 33 strains of bacteria from a healthy 41 y.o. female donor
- Synthetic stool given via colonoscopy
- Successful treatment of 2 RCDI patients
  - 6 month follow up

Petrof et al, Microbiome 2013; 1:3
Research

• Understanding the microbiome
• Severe “refractory” CDI—RCT needed
• IBD therapy
  – Adults with Active UC—2 RCT, no benefit
    • 2 trials, Netherlands, Canada (?) Some benefit in final study
  – Children with Active Crohn’s, open trial, n=9, safe, clinical and lab improvement
    – Suskind et al; IBD 2015
Optimizing Safety

- Balance risk/benefit
- Consider individual patient
- Mitigate risk through careful donor selection and screening
- Care in choosing method of administration
- Clinical trials will provide more robust safety data
Summary

1. For recurrent *C difficile* infection, FMT is very effective
2. Nothing else is nearly as effective!
3. Short term it appear safe
4. Long term data are needed
5. We must standardize indication, methodology, and many other factors to ensure patient safety
6. We must be clear about the appropriate indication (*C difficile* infection) and do research on other indications