Fecal Microbiota Transplantation

CDDW Small Group Session
March 5, 2017 (11:50-12:30)

Nikhil Pai, MD FAAP FRCPC
Assistant Professor, Division of Pediatric GI & Nutrition
McMaster Children's Hospital, McMaster University

Karen Wong, MD FRCPC
Clinical Assistant Professor, Division of GI
University of Alberta

McMaster University HEALTH SCIENCES

UNIVERSITY OF ALBERTA
FACULTY OF MEDICINE & DENTISTRY
Department of Medicine

Name: Dr. Nikhil Pai

Financial Interest Disclosure

(over the past 24 months)

Commercial Interest	**Relationship**
Abbvie	Consultant
Janssen	Consultant
Rebiotix	Research materials

Name: Dr. Karen Wong

Financial Interest Disclosure

(over the past 24 months)

No relevant financial relationships with any commercial interests

CanMEDS Roles Covered

Medical Expert (as *Medical Experts*, physicians integrate all of the CanMEDS Roles, applying medical knowledge, clinical skills, and professional values in their provision of high-quality and safe patient-centered care. *Medical Expert* is the central physician Role in the CanMEDS Framework and defines the physician's clinical scope of practice.)
Communicator (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
Collaborator (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
Leader (as *Leaders*, physicians engage with others to contribute to a vision of a high-quality health care system and take responsibility for the delivery of excellent patient care through their activities as clinicians, administrators, scholars, or teachers.)
Health Advocate (as *Health Advocates*, physicians contribute their expertise and influence as they work with communities or patient populations to improve health. They work with those they serve to determine and understand needs, speak on behalf of others when required, and support the mobilization of resources to effect change.)
Scholar (as *Scholars*, physicians demonstrate a lifelong commitment to excellence in practice through continuous learning and by teaching others, evaluating evidence, and contributing to scholarship.)
Professional (as *Professionals,* physicians are committed to the health and well-being of individual patients and society through ethical practice, high personal standards of behaviour, accountability to the profession and society, physician-led regulation, and maintenance of personal health.)

Objectives

1. How is fecal microbial transplant (FMT) done and advantages/disadvantages of different FMT delivery modalities?

2. Describe indications for fecal microbial transplant (FMT) in Clostridium difficile infection in adult and pediatric patients

3. What is the approach to treatment of patients with concomitant IBD and recurrent C. difficile?

*4. Discuss short and long-term safety profile of FMT

Case Presentation

Patient with 12 Year History of Ulcerative Colitis

- 61 yo male
- History of ulcerative pancolitis
- Diagnosed 2004, maintained on Asacol
  - 2006 – flare up – treated with steroids
  - 2011 – flare up – treated with steroids
- CABG in July 2015 for triple vessel disease

Recurrent Episodes of C. Difficile Colitis

Date	Symptoms	C. Difficile Test	Treatment
Sept 14	Watery diarrhea	PCR +ve	Flagyl x 14 days
Oct 23	Watery diarrhea	Toxin +ve	Vancomycin x 14 days
Nov 23	Watery diarrhea	PCR +ve	Vancomycin x 7 week taper
Feb 11	Watery diarrhea*	PCR +ve	Vancomycin

*Partial response only:
8-10 BM/d with 20% blood
30 pound weight loss
No abdominal pain or fevers

Referred for FMT

Colonoscopy Performed for IBD Disease Staging

- Feb 24, 2016: colonoscopy performed
  - Persistent blood in stools after vancomycin taper
  - Scope showed moderately active pancolitis

How would you manage this patient?

Corticosteroid Treatment Initiated

- Hb 122, MCV 81, CRP 57
- C. difficile – negative

- Treated with IV solumedrol → oral prednisone
- Vancomycin continued, ↓125mg bid until FMT
- CRP normalized

Repeat Colonoscopy Performed and $\alpha_4\beta_7$ Started

- June 10, 2016: colonoscopy for FMT
  - Mild MAYO 1 disease

- July 1, 2016:
  - Started vedolizumab
  - Healthy in followup
  - No further episodes of *C. difficile*

Objective 1: How is fecal microbial transplant done?

Advantages/disadvantages of different FMT delivery modalities

No Standardized Methodology for FMT

- Several different methods published
- Little variation in clinical effectiveness across techniques of delivery

Step 1: Universal Donor Screening (UAH Model)

- Initial
  - Detailed history and physical exam
  - Donor questionnaire (to identify high risk behaviors)
  - Test negative for infections

- Subsequent
  - Rescreened every 4 months

Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A. Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. Am J Gastroenterol. 2012;107(5):761-7.

UAH Donor Questionnaire

Donor Questionnaire for human biotherapy/fecal microbiota transplantation

	Yes	No
e You		
1. Feeling healthy and well today?	☐	☐
2. Currently taking an antibiotic?	☐	☐
3. Currently taking any other medication for an infection?	☐	☐
4. Currently taking any immunosuppressant medication by mouth or injection?	☐	☐
you have		
5. History of chronic diarrhea persisting > 10 days?	☐	☐
6. History of blood in stool not related to hemorrhoid?	☐	☐
7. History of change in bowel habit, alternating from constipation to diarrhea?	☐	☐
8. Any type of active cancer that is not cured?	☐	☐
9. Any active autoimmune diseases?	☐	☐
the past **12 weeks** have you		
10. Had any vaccinations? If yes, please indicate which one(s)	☐	☐
11. Had contact with someone who had a smallpox vaccination?	☐	☐
12. taken antibiotics, systemic immunosuppressive or biological agents, systemic antineoplastic agents and exogenous glucocorticoids? If you have, you should not be a stool donor.	☐	☐
the past **16 weeks** have you		
13. Lived with a person who has hepatitis A?	☐	☐
14. If yes, have you received vaccine against hepatitis A?	☐	☐
the past **12 months** have you		
15. Had a blood transfusion?	☐	☐
16. Had a transplant such as organ, tissue or bone marrow?	☐	☐
17. Had a graft such as bone or skin?	☐	☐
18. Come into contact with someone else's blood?	☐	☐
19. Had an accidental needle-stick?	☐	☐
20. Had sexual contact with anyone who has HIV/AIDS or has had a positive test for the HIV/AIDS virus?	☐	☐
21. Had sexual contact with a prostitute or anyone else who takes money or drugs or other payment for sex?	☐	☐
22. Had sexual contact with anyone who has ever used needles to take drugs or steroids, or anything not prescribed by their doctor?	☐	☐
23. Had sexual contact with anyone who has hemophilia or has used clotting factor concentrates?	☐	☐

1. Female donors: Had sexual contact with a male who has ever had sexual contact with another male? (Males: check "I am male")	☐	☐	☐ I am male
2. Had sexual contact with a person who has hepatitis?	☐	☐	
3. Had a tattoo?	☐	☐	
4. Had ear or body piercing?	☐	☐	
5. Had or been treated for syphilis, gonorrhea or Chlamydia?	☐	☐	
6. Been in juvenile detention, lockup, jail, or prison for more than 72 hours?	☐	☐	
the past **three years** have you			
7. Been outside the United States or Canada? If yes, list the places(s)	☐	☐	
om **1980 to the present,** have you			
8. Receive a blood transfusion in the United Kingdom or France? (Review list of countries in UK.)	☐	☐	
om **1977 to the present,** have you			
9. Receive money, drugs, or other payment for sex?	☐	☐	
10. Male donors: had sexual contact with another male, even once? (Females: check "I am female")	☐	☐	☐ I am female
ive you **EVER**			
11. Had a positive test for the HIV/AIDS virus?	☐	☐	
12. Used needles to take drugs, steroids, or anything not prescribed by your doctor?	☐	☐	
13. Used clotting factor concentrates?	☐	☐	
14. Had hepatitis?	☐	☐	
15. Had malaria?	☐	☐	
16. Had Chagas' disease?	☐	☐	
17. Had babesiosis?	☐	☐	
18. Received a dura mater (or brain covering) graft?	☐	☐	
19. Had sexual contact with anyone who was born in or lived in Africa?	☐	☐	
20. Have any of your relatives had Creutzfeldt-Jakob disease?	☐	☐	

This information will remain strictly confidential

To the best of my knowledge, the above information is accurate and true.

Donor's Signature: **Date:**

Objective 1

Donor Screening Methods Also Show Variation

- Other models:
  - OpenBiome (publically funded stool bank) publishes screening protocol *(appendix)*
  - Rebiotix (private biotech, supporting several Canadian RCTs) publishes screening protocol
- Donor interval retesting standards common

Health Canada Offers "Guidance Document" Only

- Health Canada Guidance Document:
  - Single donor
  - Known to physician or patient
  - Screening (infections, "cancer," medications, health/lifestyle questionnaires)
  - Record-keeping of donor ID
- No allowance for public stool banks outside of research/special exemption

Regulation of Fecal Microbiota Therapy for the Treatment of C. difficile Infections. (2015, March).
Retrieved November 06, 2016, from http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/fecal_microbiota-bacterio_fecale-eng.php

Sample Published Methods for FMT Delivery

METHOD A

Blend 50g of stool
Dilute mixture with saline to 250mL
Filter down to 0.25mm with sieves
Administer 250mL

METHOD B

Blend 100g of stool
Emulsify with wooden spatula
Add drinking water to 300mL
Filter with gauze
Administer only 50mL

METHOD C (UAH)

Blend 100g in 400mL (colonoscopy)
Blend 50g in 200mL (EGD)

Hamilton M. et al. (2012) Standardized frozen preparation for transplantation of fecal microbiota for rCDI.Am J Gastroenterol 107(5): 761–767
Kassam Z. et al. (2012) Fecal transplant via retention enema for refractory or rCDI. Arch Intern Med 172: 191–193

Methodological Questions Have Been Addressed

- Fresh versus frozen FMT
  - (2016, JAMA) Frozen product equally effective for treatment of rCDI
  - n=219 (mITT population); 75.0% vs. 70.3% ($p<0.001$ for noninferiority)
- UGI versus LGI FMT administration
  - UGI associated with rare cases of aspiration pneumonia
  - Trend towards higher resolution with LGI route
    - n=273
    - 91.2% (95% CI: 86-95%) versus 82.3% (95% CI 69–90%)
- Oral microbial capsules versus colonoscopy similar efficacy

Lee CH, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection. JAMA. 2016;315(2):142-9.
Kassam Z, Lee CH, Yuan Y, Hunt RH. Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol. 2013;108(4):500-8.

RCT of Oral Microbial Capsules versus Colonoscopy for rCDI

	Oral Microbial Capsule (n=56)	Colonoscopy (n=59)
Cure rate after 1 FMT	98%	95%
Cure rate after 2 FMT	100%	98%
Serious adverse events	**0**	**1**
• FMT related infection	0	0
• Death	0	1
• Colonic perforation	-	0
Adverse events	**4**	**7**
• Nausea	3	2
• Vomiting	1	2
• Transient fever	0	1
• IBD flare	0	2

Kao D, Wong K *et al.* 2017. Unpublished data

FMT Has Several Key Practical Considerations

- Setup: supplies, handling of biohazards, cleaning precautions
- Method of delivery
  - Challenges of endoscopic administration particularly in pediatrics
- No evidence that pediatric protocols need be different than adult

Objective 2: Describe indications for fecal microbial transplant (FMT) in *Clostridium difficile* infection

In adult and pediatric patients

FMT for rCDI is Only Health Canada Approved Indications

- Recurrent *Clostridium difficile* colitis
- Research Trials:
  - Inflammatory bowel disease (UC/CD; adult, pediatric)
  - Metabolic syndrome (obesity, diabetes)
  - Hepatic encephalopathy
  - Multidrug resistant organism eradication
  - Chronic intestinal pseudoobstruction
  - Chronic constipation
  - Liver cirrhosis
  - NASH
  - Irritable bowel syndrome

Definition of *Recurrence* in rCDI

1. Recurrent or relapsing CDI:
   a) Three or more episodes of mild-moderate CDI and failure of 6-8wk taper with vancomycin with or without alternative antibiotic (ie. Rifaximin, nitazoxanide, fidaxomicin)
   b) At least two episodes of CDI resulting in hospitalizatoin and associated with significant morbidity
2. Moderate CDI not responding to standard therapy (vancomycin or fidaxomicin) for at least a week
3. Severe (even fulminant CDI) with no response to standard therapy after 48 hours

Kelly CR, Kim AM, Laine LA, Wu GD. The AGA's Fecal Microbiota Transplantation National Registry: An Important Step Toward Understanding Risks and Benefits of Microbiota Therapeutics. Gastroenterology. 2017;

FMT is Effective for rCDI

- 3 randomized-controlled trials, 29 case series

Fecal Microbiota Transplantation for *Clostridium difficile* Infection: Systematic Review and Meta-Analysis

Table 3. Subgroup analysis for fecal microbiota transplantation in *Clostridium difficile*

Subgroups	Unweighted rate *n/N* (percentage)	Weighted rate (95% CI)	Proportion difference of unweighted rate (95% CI, *P* value)	Proportion difference of weighted rate (95% CI, *P* value)
Delivery modality				
Lower gastrointestinal delivery (colonoscopy, enema)	203/222 (91.4%)	91.2 % (86.0%, 95.2%)	9.1% (−0.1%, 22.1%), *P*=0.046	10.6% (−0.6%, 21.8%), NS
Upper gastrointestinal delivery (nasogastric/nasojejunal tube, gastroscopy, gastrostomy tube)	42/51 (82.3%)	80.6% (69.3%, 89.8%)		
Donor type				
Patients selected (related family member, partner, spouse, close friend)	196/219 (89.5%)	89.2% (83.2%, 94.0%)	−1.2% (−8.5%, 9.9%), NS	−0.7% (−10.5%, 9.1%), NS
Anonymous	49/54 (90.7%)	89.9% (80.3%, 96.6%)		

Lee CH, Belanger JE, Kassam Z, et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory Clostridium difficile infection using single to multiple fecal microbiota transplantation via retention enema. Eur J Clin Microbiol Infect Dis 2014;33(8):1425-8.

FMT is Similarly Effective for rCDI in Pediatric Patients

- Pediatric data for FMT in rCDI limited
- 9 case series (n=45) show similar efficacy as adult trials
- No significant differences in technique

Ref	AGE (yr)	*n*	FMT route	Response rate
Hourigan *et al*[22], 2015	6-17	8	Colonoscopy	100%
Kronman *et al*[55], 2015	6-17	10	NG	90%
Wang *et al*[58], 2015	1	1	NJ	100%
Kelly *et al*[10], 2014	6-16	5	Not specified	89% (whole series)
Pierog *et al*[56], 2014	1-21	6	Colonoscopy	100%
Russell *et al*[57], 2014	1-21	10	NG (2); Colonoscopy (8)	90%
Walia *et al*[59], 2014	1-2	2	Colonoscopy	100%
Rubin *et al*[60], 2013	6-8	2	NG (64); EGD (7); Gastrostomy (previously placed) (4)	50%
Kahn *et al*[44], 2012	1	1	Colonoscopy	100%

Wang AY, Popov J, Pai N. Fecal microbial transplant for the treatment of pediatric inflammatory bowel disease. World J Gastroenterol. 2016;22(47):10304-10315.

Objective 3: Approach to patients with concomitant IBD and recurrent *Clostridium difficile* infection

Patients with IBD Have Unique Bacterial Signatures

- High proportion of patients with concurrent IBD and rCDI
- Unique intestinal microbial signatures in Crohn's and ulcerative colitis patients
- Reduced FMT treatment effectiveness for rCDI in IBD patients

Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent *Clostridium difficile* Infection

Alexander Khoruts,[*,‡] Kevin M. Rank,[*] Krista M. Newman,[*] Kimberly Viskocil,[*] Byron P. Vaughn,[*] Matthew J. Hamilton,[‡] and Michael J. Sadowsky[‡]

	rCDI alone (n=229)	rCDI + IBD (n=43)	*p value*
Age (mean ± SD)	60.8 ± 17.3	38.8 ± 17.9	<0.0001
Female gender	73%	51%	0.0065
IBD		UC: 21 CD: 22	
BM 24hrs pre FMT	5.2 ± 4.6	8.3 ± 7.2	0.0044
Success after 1 FMT	92%	75%	0.0018
Success after ≥2 FMT	98.7%	82.9%	
IBD flare post FMT		11 (25%) *4/11 had left sided colitis at time of FMT	

Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. Clin Gastroenterol Hepatol. 2016;14(10):1433-8.

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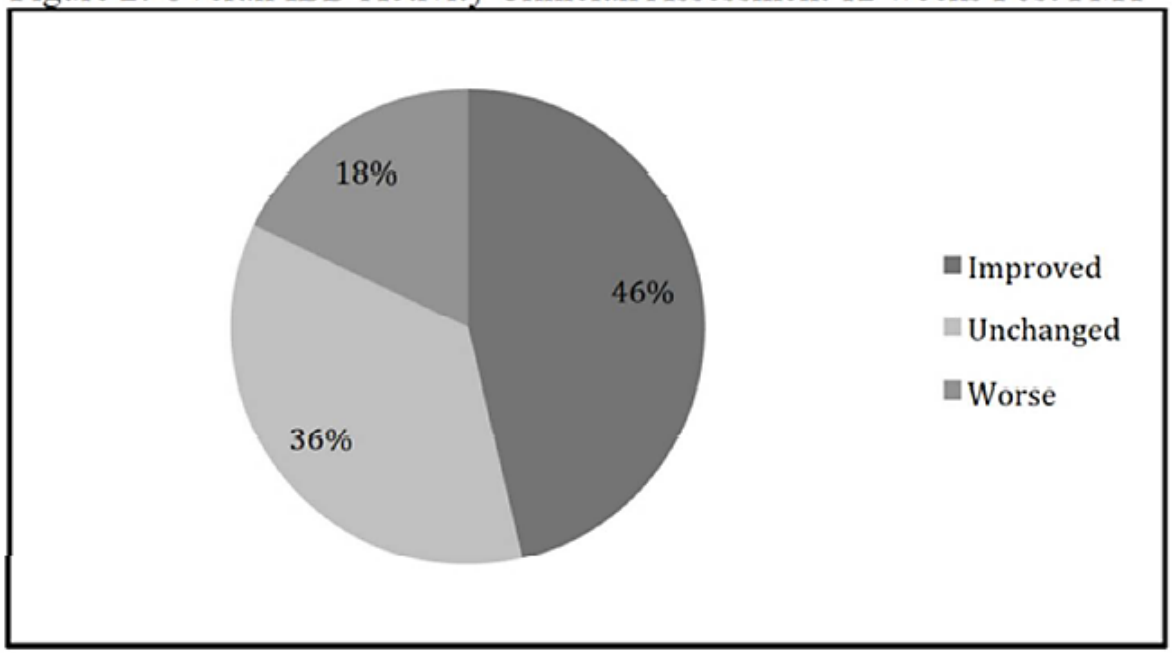
Table 4. Multivariate Analysis for Clinical Factors Associated With Failure of Initial FMT to Clear CDI

Variable	aOR (95% CI)	*P* value
Age	1.01 (0.99–1.04)	.2
Gender	0.9 (0.4–2.1)	.8
Immunosuppression	0.4 (0.1–1.2)	.08
IBD	8.7 (2.4–30.8)	.0008

Khoruts A, Rank KM, Newman KM, et al. Inflammatory Bowel Disease Affects the Outcome of Fecal Microbiota Transplantation for Recurrent Clostridium difficile Infection. Clin Gastroenterol Hepatol. 2016;14(10):1433-8.

Fecal microbiota transplantation is safe and efficacious for recurrent or refractory *Clostridium difficile* infection in patients with inflammatory bowel disease

Figure 2: Overall IBD Activity Clinician Assessment 12 weeks Post FMT



Fischer M, Kao D, Kelly C, et al. Fecal Microbiota Transplantation is Safe and Efficacious for Recurrent or Refractory Clostridium difficile Infection in Patients with Inflammatory Bowel Disease. Inflamm Bowel Dis. 2016;22(10):2402-9.

FMT for Crohn's Disease, Ulcerative Colitis Less Studied

- Systematic review of FMT in IBD (2014 JCC): 18 studies, n=122 (79 UC; 39 CD; 4 IBD-U)
  - Median f/u: 6wk (range: 1wk – 13yrs)
  - 37% clinical response for CD (I^2=37%; moderate heterogeneity in results)
  - 22% clinical response for UC (I^2=0%; little heterogeneity in results)

- Meta-analysis (2016 Mucos Immun): 9 UC publications, n=118
  - 30.3% clinical response for UC (95% CI: 19.3-44.2%)

Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. J Crohns Colitis 2014;8(12):1569-81.
Keshteli AH, Millan B, Madsen KL. Pretreatment with antibiotics may enhance the efficacy of fecal microbiota transplantation in ulcerative colitis. Mucosal Immunol. 2016 Dec

3 Adult RCTs of FMT for IBD with Differing Results

- 3 RCTs have been performed in adults
- 2017: Borody *et al.*
  - Colonoscopic FMT/placebo + 8wk serial enema infusion
  - Clinical + endoscopic remission/response 26.8% vs. 7.5% **(p=0.021)**
- 2015: Moayyedi *et al.*
  - Enemas from anonymous healthy donors vs. normal saline placebo
  - Clinical + endoscopic remission in 23.7% vs. 5.4% **(p=0.03)**
- 2015: Rossen *et al.*
  - Enemas from anonymous versus autologous
  - Clinical + endoscopic remission in 30.4% vs. 20.0% (p=0.29)

Moayyedi P, Surette MG, Kim PT, et al. Fecal microbiota transplantation induces remission in patients with active ulcerative colitis in a RCT. Gastroenterol 2015;149(1):102-109.e6.
Rossen NG, Fuentes S, Van der Spek MJ, et al. Findings from a randomized controlled trial of fecal transplantation for patients with Ulcerative Colitis. Gastroenterol 2015;149(1):110-118.e4.

Pediatric FMT for IBD Data Limited; 1 Canadian RCT

- No RCTs, 4 pediatric case series:
  - n=25 patients total
  - Different protocols
  - 56% unweight pooled response (combined clinical/endoscopic outcomes)

- McMaster Children's Hospital: 1st RCT of FMT for children
  - London Children's Hospital (PI: Dr. Ashok Dhandapani)
  - Sainte Justine's Children's Hospital (PI: Dr. Kelly Grzywacz)

Objective 3

Popov J, Wang AY, Pai N. Fecal Microbial Transplant for the Treatment of Pediatric Inflammatory Bowel Disease. World J Gastroenterol. 2016;22(47):10304-10315.
https://clinicaltrials.gov/ct2/show/NCT02487238; ClinicalTrials Identifier: NCT02487238

FMT for Patients with IBD + rCDI Involves Similar Approach

- Higher rates of 1st FMT failure for rCDI treatment in patients with IBD
  - Irrespective of whether patient is on immunosuppression
- FMT-specific adverse events does not appear to be increased with immunosuppression
  - ~ 20 % risk of IBD flare
- IBD may concurrently improve after FMT
  - Best evidence for FMT in IBD involves multiple FMT administrations
  - Treatment of rCDI involves different goals than treatment of IBD
- Best order of treatment (treat IBD first or rCDI first)?
  - Not known

Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol. 2014;109(7):1065-71.

Objective 4: Short & Long-Term Safety Profile of FMT

Safety Data for FMT Very Good, but Limited

- Limited data
- Short-term adverse outcomes described
  - Long-term risks remain speculative, largely based on (germ-free) animal data
- Differentiate endoscopic-related adverse outcomes from those of FMT

Agrawal M, et al. The Long-term Efficacy and Safety of Fecal Microbiota Transplant for Recurrent, Severe, and Complicated Clostridium difficile Infection in 146 Elderly Individuals. J Clin Gastroenterol. 2016;50(5):403-7.
Cammarota G, Ianiro G, Tilg H, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017;

Short-term Adverse Outcomes

- Minor
  - Abdominal discomfort, bloating, flatulence, diarrhea, constipation, borborygmia, vomiting
  - Transient fevers

- Serious
  - Transmission of enteric pathogens (rare)
    - Norovirus (endoscopy staff, community acquired?)
    - 2 cases *C. difficile* colitis (not found in donor, activation in recipient?)
    - Peritonitis in patient on peritoneal dialysis
  - IBD flares
  - Aspiration pneumonia

Agrawal M, et al. The Long-term Efficacy and Safety of Fecal Microbiota Transplant for Recurrent, Severe, and Complicated Clostridium difficile Infection in 146 Elderly Individuals. J Clin Gastroenterol. 2016;50(5):403-7.
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FMT for rCDI Safe in Immunocompromised Patients

- Patients with rCDI often immunocompromised
- 15% had significant adverse event within 12 weeks
  - 1 death (aspiration)
  - 14% IBD patients flared

Total number of study patients	**80**
Mean adult age (years)	53 (range 20–88)
Mean pediatric age (years)	10.9 (range 6.5–16)
Mean follow-up (months)	11 (range 3–46)
Reason for immunocompromised state:	
Immunosuppressive agents for IBD	36
Solid organ transplant recipients	19
HIV/AIDS	3
Treatment with antineoplastics	7
Other chronic medical conditions	15

Adverse event	N	IC Reason	Day Post FMT
Deaths			
Pneumonia	1	SOT	13
Aspiration	1	SOT	1
Hospitalizations			
Fever, diarrhea, encephalopathy	1	Cirrhosis	4
Abdominal pain	1	SOT	0
IBD flare	3	IBD	<84
Cerebrovascular accident	1	ESRD	21
Colectomy	1	IBD	<28
Hip fracture	1	End-stage COPD	84
Influenza B	1	SOT	3
Catheter inf'n	1	Cancer	14

Adverse event	N	IC Reason	Day Post FMT
Other adverse events			
Diarrhea	3	ESRD; SOT	≤84
Fever	1	SOT	1
Bloating, Abdominal Pain	3	HIV; ESRD; IBD	1–2
Hip pain	1	IBD	≤84
Crohn's flare	1	IBD	≤84
Pertussis	1	IBD	≤30
Nausea	1	IBD	30
Mucosal tear	1	SOT	0

Kelly CR, Ihunnah C, Fischer M, et al. Fecal microbiota transplant for treatment of Clostridium difficile infection in immunocompromised patients. Am J Gastroenterol. 2014;109(7):1065-71.

Long-term Adverse Outcomes

- Concerns largely speculative
  - Adult to pediatric FMT: age-related taxonomy
  - Transmission of infectious agents
  - Development of chronic diseases/conditions related to changes in gut microbiota
    - Obesity, diabetes, atherosclerosis, IBD, colon cancer, NAFLD, IBS, asthma, autism, neuropsychiatric conditions
    - Transmissibility of chronic conditions largely shown in *germ-free* animal models

Final Thoughts

Mechanism Behind FMT for rCDI Remains Unknown

- Significant efforts to optimize FMT for rCDI + extrapolation to other indications
- Persistent question: *what are we doing?*
  - rCDI FMT: recipient microbiome resembles donor microbiome initially
    - recipient microbiome reverts to baseline, CDI does not recur
    - CD/UC: no sustained microbiome difference among patients who respond to FMT, versus those who do not

Therapeutic Changes May Not be Mediated by Bacteria

- Role of bacteriophages in the intestinal microbiome
  - Bacteriophages = bacterial pathogens; modified by diet, antibiotics
  - *Promote* bacterial diversity by adapting, targeting abundant species
- Fungal diversity described in IBD
  - *Aspergillus* negatively correlated with bacterial SCFA production
  - *Candida albicans* promote inflammatory cytokine production
- Primary, secondary bile acids
  - 1° bile acids may promote germination of C. difficile spores
  - 2° bile acids may inhibit germination of C. difficile spores (2016 PLoS ONE)

Schirmer M, Smeekens SP, Vlamakis H, et al. Cell. 2016;167(7):1897.
Sheehan D, Moran C, Shanahan F. J Gastroenterol. 2015;50(5):495-507.
Theriot CM, Bowman AA, Young VB. mSphere. 2016;1(1)
Weingarden AR, Dosa PI, Dewinter E, et al. PLoS ONE. 2016;11(1):e0147210.

Therapeutic Changes May Not be Mediated by Bacteria

- Role of bacteriophages in the intestinal microbiome
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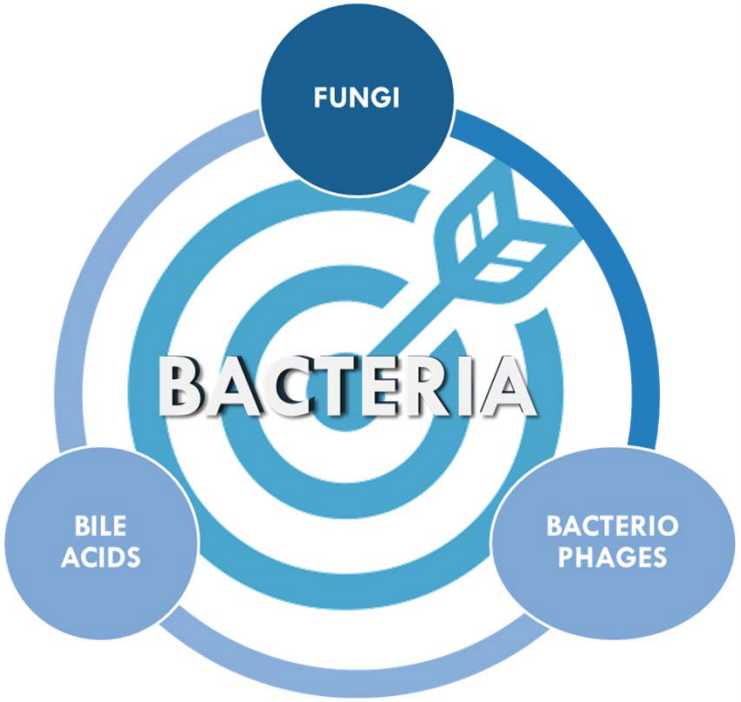
Theriot CM, Bowman AA, Young VB. mSphere. 2016;1(1)
Weingarden AR, Dosa PI, Dewinter E, et al. PLoS ONE. 2016;11(1):e0147210.

Efficacy of Sterile Fecal Filtrates in Treating rCDI

- (2016 Gastro) Sterile fecal filtrates (devoid of fecal residue, bacteria)
  - 5 immunocompromised rCDI patients
  - Response in all 5 patients
  - Bacterial DNA stimulating host responses via PRRs



Ott SJ, Waetzig GH, Rehman A, et al. Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With Clostridium difficile Infection. Gastroenterology. 2016

Useful Materials for Your Reference

This presentation will be available through CAG/CDDW for your reference

- Health Canada Guidance Document
  http://www.hc-sc.gc.ca/dhp-mps/consultation/biolog/fecal_microbiota-bacterio_fecale-eng.php
- NASPGHAN Draft Pediatric Consent
- UAH Adult Consent
- UAH FMT Delivery Protocol
- UAH FMT Screening Protocol

pain@mcmaster.ca
Nikhil Pai, MD FAAP FRCPC
DIVISION OF PEDIATRIC GASTROENTEROLOGY & NUTRITION
ASSISTANT PROFESSOR OF PEDIATRICS, MCMASTER CHILDREN'S HOSPITAL

karen.wong@ualberta.ca
Karen Wong, MD FRCPC
DIVISION OF GASTROENTEROLOGY
ASSISTANT PROFESSOR OF MEDICINE, ALBERTA HEALTH SERVICES

Appendix

FMT Case Presentation: Details

- PMHx:
  - CABG July 2015
  - COPD
  - HTN
- Meds:
  - ASA
  - Plavix
  - HCTZ
  - Olmesartan
- Referred for FMT

Donor Exclusion Criteria (UAH)

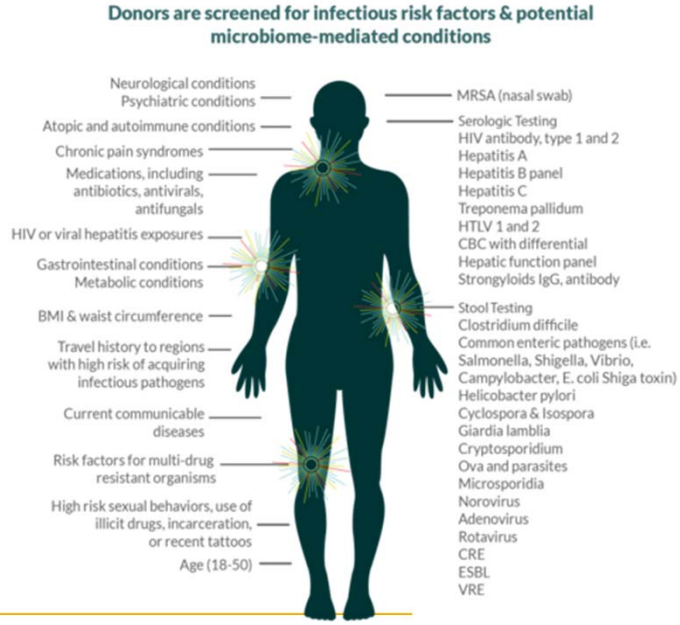
- Active cancer
- Autoimmune disease (eg multiple sclerosis, connective tissue disease)
- Metabolic syndrome
- Chronic pain syndrome
- Atopic diseases
- Risk factors for acquisition of HIV, syphilis, Hepatitis B, Hepatitis C, prion or any neurological disease
- Gastrointestinal comorbidities (IBD, IBS, chronic constipation or diarrhea, GI malignancy, known polyposis)
- Tattoo or body piercing within 6 months
- History of incarceration
- Blood transfusion from a country other than Canada within 6 months
- Antibiotic, immunosuppressive, biological, antineoplastic, exogenous glucocorticoids within 3 months
- Live vaccine within 3 months
- Ingestion of nut or shellfish within 3 days if recipient has known allergies to these foods
- Any current or previous medical/psychosocial condition which, in the opinion of the investigator, may pose risk to the recipients
- Travel to areas where diarrheal illnesses or BSE/TSE are endemic within 6 months

Donor Investigations

- Blood
  - CBC, electrolytes, creatinine, AST, ALT, ALP
  - HIV 1/2
  - Hepatitis A: IgM Ab
  - Hepatitis B: HBVsAg, HBVsAb, HBVc Ab (IgM and IgG)
  - Hepatitis C: antibody
  - RPR
  - HTLV I/II
- Stool
  - *Salmonella*, *Shigella*, *E.coli* O157 H7, *Yersinia*, *Campylobacter*
  - *C. difficile* toxin by EIA
  - Ova and parasites
  - Fecal *Giardia* and *Cryptosporidium* antigen
  - *H. pylori* fecal antigen for UGI FMT

University of Alberta Hospital

OpenBiome



OpenBiome Quality & Safety Program (Accessed Feb 26, 2017; https://tinyurl.com/jahk858)

Appendix