Updates in Fecal Microbial Transplant

Dina Kao, MD FRCPC
Associate Professor, Gastroenterology
University of Alberta

Nikhil Pai, MD FAAP FRCPC
Assistant Professor, Ped Gastroenterology
McMaster University

UNIVERSITY OF ALBERTA

McMaster University

Financial Interest Disclosure

over previous 24 months

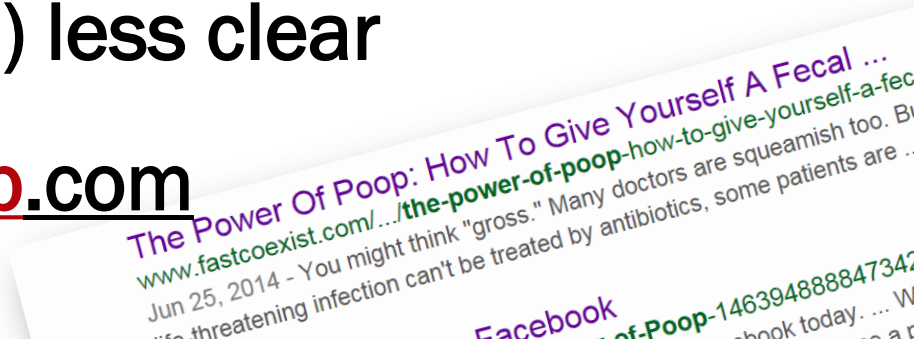
Commercial Interest	**Relationship**
Abbvie	Advisory board (Nikhil Pai)
Rebiotix	Research materials (Nikhil Pai, Dina Kao)
Rebiotix	Consultant (Dina Kao)
Acteion	Investigator (Dina Kao)

CanMEDS Roles Covered

X	**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.)
X	**Communicator** (as Communicators, physicians form relationships with patients and their families that facilitate the gathering and sharing of essential information for effective health care.)
X	**Collaborator** (as *Collaborators*, physicians work effectively with other health care professionals to provide safe, high-quality, patient-centred care.)
X	**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.)
X	**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.)
X	**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.)
X	**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.)

Current Evidence Supports FMT for Limited Indications

- Fecal Microbial Transplant (FMT) popular with clinicians, researchers, lay public
- Strongest evidence for treatment of recurrent *Clostridium difficile* colitis
- IBD (+obesity, diabetes, IBS…) less clear
- Extreme DIY: ThePowerofPoop.com



Objectives

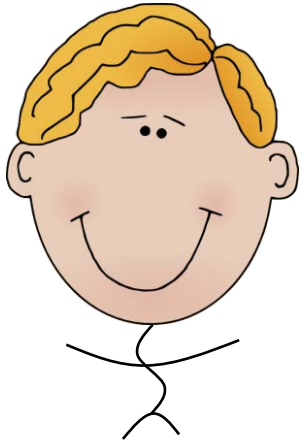
At the end of this session participants will be able to...

1. Describe current pediatric and adult evidence for fecal microbial transplantation (FMT) in the management of recurrent *Clostridium difficile* infection
2. Assess patient eligibility for FMT, and identify potential risks
3. Describe Health Canada regulations concerning FMT
4. BRIEFLY Discuss current pediatric and adult evidence for the role of FMT in the management of Crohn's Disease and Ulcerative Colitis

2 Cases

FMT in CDI, and FMT in IBD

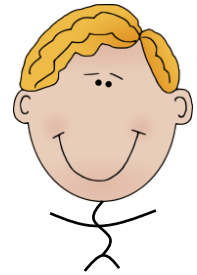
- 55 year old male with recurrent C. difficile infection (CDI)



- 8 year old female with inflammatory bowel disease (IBD)

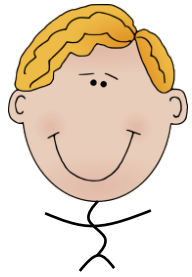
1. Describe current pediatric and adult evidence for fecal microbial transplantation (FMT) in the management of recurrent *Clostridium difficile* infection
2. Assess patient eligibility for FMT, and identify potential risks
3. Describe Health Canada regulations concerning FMT
4. Discuss current pediatric and adult evidence for the role of FMT in the management of Crohn's Disease and Ulcerative Colitis

FMT for CDI



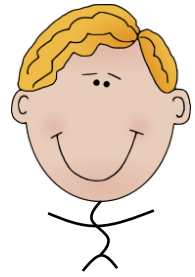
- 55 yo male
- Liver transplant for NASH cirrhosis Dec 13, 2012
  - 1 episode of CDI post op, responded well to metronidazole (finished on Dec 27)
  - Discharged home Jan 8, 2013
- Presented with profuse diarrhea Jan 18
  - Abdominal tenderness and distension
  - WBC=35,000, Creatinine=345 (75 on Jan 8)
  - Ascites WBC 600 (74% neutrophils)
  - C diff toxin positive Jan 19
  - AXR thumbprinting
  - CT abdomen showed pan-colitis and ascites

FMT for CDI



- IV fluids
- Tacrolimus stopped
- Pip-tazo, metronidazole IV 500 mg q8h, vancomycin PO 500 mg qid
- Hypotension requiring transfer to ICU
  - Pressor
  - Dialysis
- CMV in blood: 2565 copies/ml
  - Gancyclovir

FMT for CDI



- **Persistent diarrhea**
  - 5 to >10 watery BMs per day
  - WBC=13
  - Repeat C diff toxin negative Jan 30 (12 days of CDI Rx)
- **Sigmoidoscopy showed pseudomembranes in rectosigmoid colon**
- **Surgical consult**
  - Surgeons reluctant to operate
    - Suboptimal surgical candidate
- **What can we do to help him?**

FMT in CDI

Discussion & Evidence

- **Is FMT appropriate for this patient at this point?**
  - Evidence?
- **Is it safe in immunosuppressed patients ?**
  - Evidence?
- **How?**
  - Who should be his donor?
  - How do we screen a donor?
  - Route of delivery?
  - Fresh or frozen?

3 systematic reviews, 2 RCT

- 3 systematic reviews (2011, 2013, 2014)
  - Gough et al. (N=317): 89.0% 1 FMT, 92% ≥1 FMT
  - Kassam et al. (N=273): 89.1% 1 FMT
    - Lower GI delivery (91%) vs upper GI delivery (81%)
    - Patient directed donors= anonymous donors
  - Giovanni et al. (N= 536): 87% 1 FMT
    - Stomach (81%), duodenum/juejunum (86%), cecum/asc (93%), distal colon (84%)
    - ?site vs dose dependent?

- 2 RCTs
  - van Nood et al. 2013
    - VANC + lavage + FMT via ND tube, VANC, VANC + lavage
    - n=60: 94% vs. 31%, 23%
  - Kelly et al. 2015 (abstract)
    - Donor FMT vs sham (patient's own) FMT by colonoscopy
    - N=46: 91% vs 63% (p=0.024)
  - No significant adverse events reported

Fecal Microbiota Transplant for Treatment of *Clostridium difficile* Infection in Immunocompromised Patients

- **Retrospective, multi-center (17) (FMT working group)**
- **75 adults and 5 pediatric patients**
  - HIV/AIDS (3)
  - Solid organ transplant (19)
  - Oncologic condition (7)
  - IBD (36)
  - Others (15)
- **Recurrent (55%), refractory (11%) or overlap (34%)**
- **Mean F/U 12 months (3-51 months)**
- **Cure rate with 1 single infusion 78%**
  - 2nd infusion 89%
- **AE:**
  - 2 deaths (unrelated to FMT)
  - 1 unrelated infection
  - 2 self limited diarrhea
  - 3 IBD patients had flares
  - 1 superficial mucosal tear from colonoscopy

The American Journal of GASTROENTEROLOGY Received 6 January 2014; accepted 21 April 2014

Original Investigation

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

A Randomized Clinical Trial

- **108 in frozen FMT group vs 111 fresh FMT group**
  - 50 mL by enema (~17g donor stool)
  - 51% inpatients, 66% mod-severe CDI, 42% NAP1 strain, 24 immunosuppressed
  - No bowel preparation
- **83.5% vs 85.1% (P=0.01 for non-inferiority)**
  - ~50% cured with 1 FMT, ~70% with 2 FMT, ~80% with 3-5 FMT, ~85% with >5 FMT
- **No serious adverse events**

JAMA. 2016;315(2):142-149. doi:10.1001/jama.2015.18098

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

- **N=20**
  - 14/20 (70%) achieved cure after 1 single capsule-based FMT
    - 15 capsules/d x 2 days
  - 18/20 (90%) after 2 FMT
    - Same donor

JAMA. doi:10.1001/jama.2014.13875
Published online October 11, 2014.

Predictors of FMT failure

Predictors	Points
Inpatient FMT (OR 7.6)	6
Immunosuppression (OR 3.4)	3
Hospital admission for CDI (each) (OR 1.4)	1

Risk category (score)	FMT failure rate
Low (0)	~<10%
Moderate (1-3)	~11-17%
High (4+)	~45%

Fischer et al. Abstract ACG 2015. Accepted AJG 2016

FMT for CDI in Pediatrics

Evidence suggests safety, efficacy

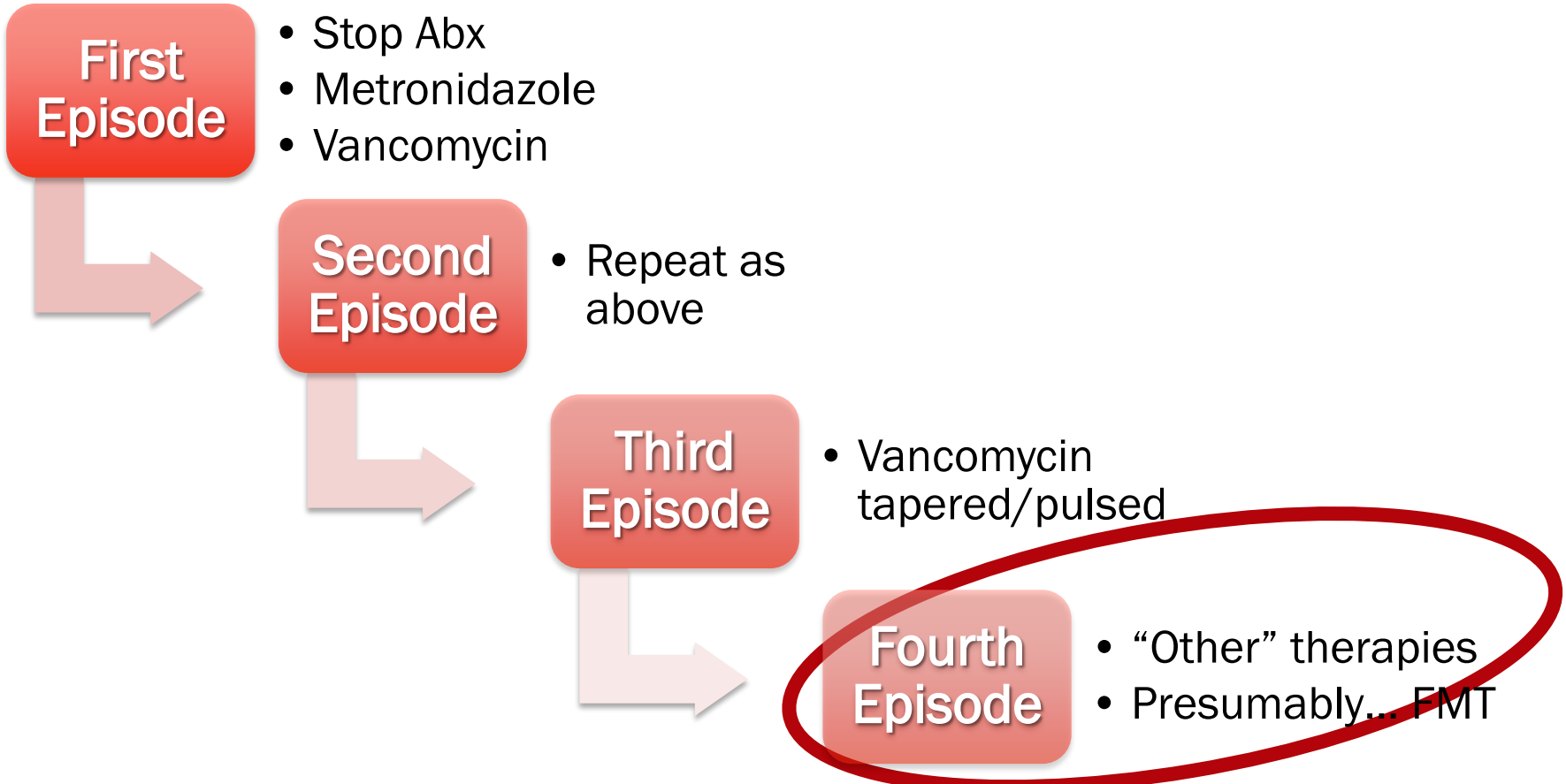
- Mostly case reports; effective for multiple indications
- N=10 patients, FMT via NG tube
- Median age 5.4 years, 30% IC: 90% remission
- No significant adverse events

Gough et al. (N=317): 89.0% 1 FMT, 92% ≥1 FMT
Kassam et al. (N=273): 89.1% 1 FMT
Lower GI delivery (91%) vs upper GI delivery (81%)
Giovanni et al. (N= 536): 87% 1 FMT

doi: 10.1097/MPG.0000000000000545

FMT for CDI in Pediatrics

Canadian Pediatric Society Position Statement



PMID: 24627655

FMT for CDI in Pediatrics

Loose “protocols” have been proposed

TABLE 1. Example of an empiric protocol for FMT (as used in the Department of Pediatrics of the Universitair Ziekenhuis Brussel)

1. Discuss the option in children with recurrent *Clostridium difficile* disease or severe ulcerative colitis not responding to classic treatment, in w
   colectomy is considered
2. Obtain informed consent from caregivers (both parents and the patients, if old enough)
3. Screen the donor and receiver for HIV, HBV, HCV, and HTLV
4. Refuse the following donors
   - Known contact with HIV and hepatitis B during the last 12 months
   - Known sexual behavior ‘‘at risk’’
   - Known use of drugs
   - Piercing and tattooing in the last 6 months
   - Known incarceration
   - Known transmittable disease
   - Known recent trip to an at-risk region
   - Autoimmune disease (multiple sclerosis, etc)
   - Atopy (eczema, asthma)
   - Obesity, metabolic syndrome
   - Chronic GI disease such as inflammatory disease, chronic constipation, chronic d… irriti…
     family members), and colon polyp
   - Presence of (occult) blood in the stools
   - Antibiotic intake during the last 3 months
   - Any known immunosuppressive therapy or chemotherapy
   - Check for dietary intake if receiver has severe food allergy
   - Check for recent viral diseases that could be harmful to a fetus if the recei…
5. Screen anyway the donor and the recipient for *Treponema pallidum*, HIV, HT… , EB…
   pylori (if administration via upper GI tract).
6. Screen the stools of the donor for *Salmonella*, *Shigella*, *Campylobacte… …fficile*, adeno… …trovirus, calici…
   A and E, presence of any parasite
7. Discuss the controversies
   - On the relevance of having feces from age-matched donors
   - Anonymous donors or family members
   - Fresh stools or frozen
   - Way of administration
8. Prepare the receptor in accordance with the chosen way of administration of the fecal material
   - Fasting if via upper GI tract
   - Colon cleaning if via colonoscopy
   - Antibiotic administration in case of *C difficile* can be considered
9. Obtain the stools and administer them in adequate amounts
   - A 50% diluted freshly suspended fecal slurry (1 g volume feces suspended in 1 mL of a water a…
     and filtered through gauze; the suspension is further gently stirred until administration as soon as …
     room temperature 10 mL/kg if administered in the colon, and half of this volume is administered duodena…
10. Observe the patient for a couple of hours and keep in bed if colonic administration to delay defecation
11. Conserve a sample of the stools for ≥30 years

CMV = cytomegalovirus; EBV = Epstein-Barr virus; FMT = fecal microbiota transplantation; GI = gastrointestinal; HBV = hepatitis B; HCV = hepatitis C virus; HIV = human immunodeficiency virus; HTLV = human T-lymphotropic virus.

TABLE 1. Exclusion criteria and screening for potential donors

1. Chronic systemic infections or risks for infection
   - Serological testing for:
     a. HIV, type 1 and 2 (HIV-1 p24 antigen and HIV-1 and HIV-2 antibody screening), performed and reviewed no more than 14 days before donation
     b. Hepatitis A virus IgM
     c. Hepatitis B virus surface antigen, core antibody (IgG and IgM), surface antibody
     d. Hepatitis C virus IgG
     e. RPR and fluorescent treponemal antibody-absorbed
   - Known HIV, hepatitis B or C infections
   - Known exposure to HIV or viral hepatitis (within the previous 12 mo)
   - High-risk sexual behaviors (eg, sexual contact with anyone with HIV/acquired immunodeficiency syndrome or hepatitis, men who have sex with men, sex for drugs or money)
   - …e of illicit drugs
   - …body piercing within 6 mo
   - …istory of incarceration
   - …icable disease (eg, upper respiratory tract infection)
   - …utzfeldt-Jakob disease
   - …ms identified through screening studies

Gastro…
- St…
  a…

…*C difficile* antigen and toxins A&B; *C difficile* toxin B PCR is used in cases of antigen-positive but toxin-negative

…creening for protozoa, trophozoites and cysts, helminths and ova including *Entamoeba histolytica*, *Microsporidia* …*Blastocystis hominis*, *Giardia lamblia*, *Ascaris lumbricoides*, trematodes, and tapeworms. Acid-fast staining for …, and *Isospora*

…ic pathogens (includes *Salmonella* species, *Shigella* species, *Campylobacter* species, *Staphylococcus aureus*, *Aeromonas* …*sinia*, *Vibrio parahaemolyticus*, *Vibrio cholerae*, *E coli* 0157, and *Listeria* species).

…bidities

…atory bowel disease

… bowel syndrome, idiopathic chronic constipation, or chronic diarrhea

…testinal malignancy or known polyposis

… affect the composition of the intestinal microbiota

… the preceding 3 mo

…ppressive medications, for example, calcineurin inhibitors, exogenous glucocorticoids, biological agents, and so on

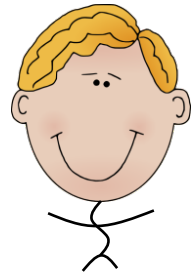
…plastic agents

…er testing of donor stool and blood was performed and reviewed no more than 30 days before donation, except as otherwise mentioned.
…assay; HIV = human immunodeficiency virus; Ig = immunoglobulin; PCR = polymerase chain reaction; RPR = rapid plasma reagin.

doi: 10.1097/MPG.0000000000000816

doi: 10.1097/MPG.0000000000000545

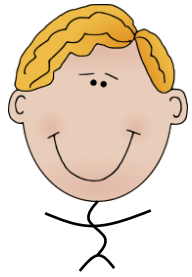
Back to the Case



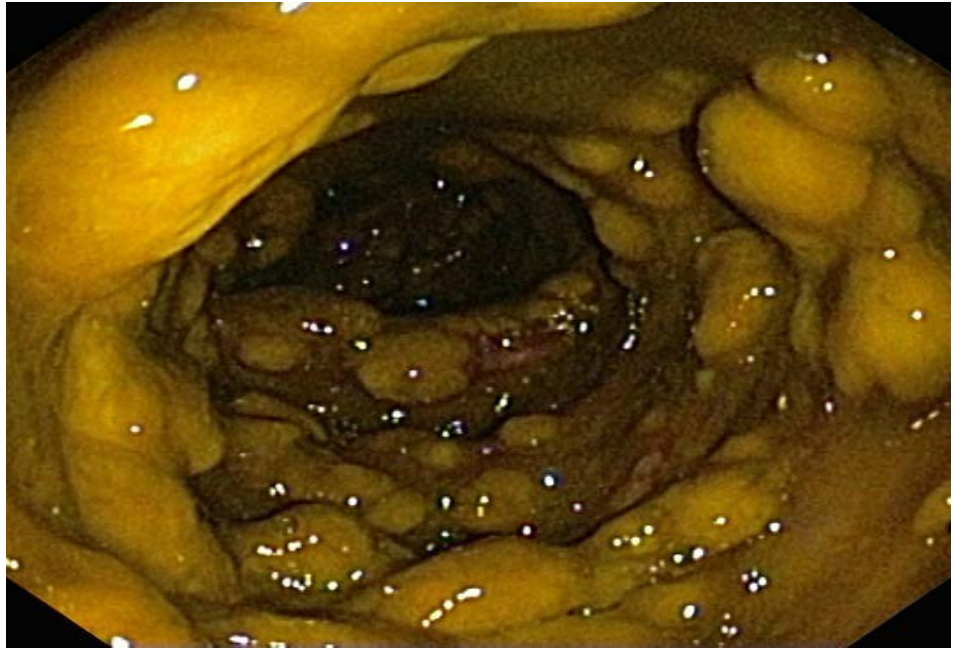
- **1st FMT by NJ infusion**
  - 60 cc fresh fecal suspension
  - Low grade fever the following day
  - Back on flagyl and vancomycin

- **2nd FMT by colonoscopy 6 days after 1st FMT**
  - 450 cc frozen-and-thawed fecal suspension
  - +++Pseudomembranes

Back to the Case



PMC on colonoscopy



3 days later...

1. Describe current pediatric and adult evidence for fecal microbial transplantation (FMT) in the management of recurrent Clostridium difficile infection
2. Assess patient eligibility for FMT, and identify potential risks
3. Describe Health Canada regulations concerning FMT
4. Discuss current pediatric and adult evidence for the role of FMT in the management of Crohn's Disease and Ulcerative Colitis

Indications for FMT

- ≥ 3 episodes of mild-moderate CDI and failure to respond to therapy
- ≥ 2 episodes of CDI resulting in hospitalization and associated with significant morbidity
- Moderated CDI not responding to ≥ 7 days of therapy
- Severe/fulminant CDI not responding ≥ 48 hours of therapy

Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook. Kelly et al. Gastroenterology 2015 Jul; 149 (1): 223-37

Adverse Events/Potential Risks Associated with FMT

- Overall safe
- Reported
  - Aspiration pneumonia
  - CMV, B. homonis, norovirus
  - IBD flare
  - Weight gain
- Theoretical
  - Infections
  - Donor phenotype?
- Reported risks same in pediatrics
  - Theoretical risk of early life FMT

Describe current pediatric and adult evidence for fecal microbial transplantation (FMT) in the management of recurrent Clostridium difficile infection 1

Assess patient eligibility for FMT, and identify potential risks 2

Describe Health Canada regulations concerning FMT 3

Describe Health Canada regulations concerning FMT 4

Health Canada Regulatory Issues re FMT

- HC regard FMT as
  - Investigational
  - a biologic “drug”
- HC guidance document Mar 2015
- “Classical FMT (fresh or frozen) used in the treatment of patients with CDI not responsive to conventional therapies”
- Informed consent
- FMT produced from a single donor known to either patient or health care practitioner
- Donor screening
- Record keeping of donor-recipient as part of a lookback/traceback program

Health Canada Regulatory Issues re FMT

- ***"HC inspectors have the authority to carry out inspections in order to assess a site's compliance with guidance documents or legislative requirements"***

Describe current pediatric and adult evidence for fecal microbial transplantation (FMT) in the management of recurrent Clostridium difficile infection 1

Assess patient eligibility for FMT, and identify potential risks 2

Describe Health Canada regulations concerning FMT 3

Discuss current pediatric and adult evidence for the role of FMT in the management of Crohn's Disease and Ulcerative Colitis 4

FMT for IBD versus CDI

Varied results likely reflect differences in pathophysiology between infectious colitis and chronic autoimmune colitis

- Reduction in “alpha diversity” in IBD
- Changes in bacterial abundance, metabolites
- Varied protocols, extrapolation from CDI trials
- Studies: few RCTs, case series, concomitant CDI

doi: 10.1016/j.pharmthera.2014.12.006
doi:10.1038/ajg.2014.133

FMT IBD Treatment Response Varies

Heterogenous results may reflect significant differences in protocols between studies

- Variability in parameters measured, protocols
- 2014 systematic review: clinical improvement 71%, UC/CD
  - 69% improvement in IBD patients without CDI
  - 62% improvement with objective scoring measure
- Endoscopic improvement 57%
  - 20% improvement with objective scoring measure
- No improvement in pouchitis

doi: 10.1097/MD.0000000000000097

2 RCTs of FMT in UC

- Moayyedi *et al* (2013) n=75 with active UC
  - Fecal enema vs Saline enema qWeekly x 6 weeks
  - 23.7% remission vs. 5.2% (2/26) (FMT vs placebo)
- Rossen *et al* (2015) n=37 with active UC
  - Fecal enema vs autologous FMT via ND tube
  - 30.4% remission vs. 20.0% (FMT vs autologous)
- Adverse events equivalent between both groups

2 FMT Randomized Controlled Trials

group	Rossen *et al*	Moayyedi *et al*
N (ACTIVE/PLACEBO)	48 (23/25)	75 (38/37)
POPULATION	Mild-moderate UC	Mild-moderate UC
ACTIVE ARM	500 cc ND infusion (120 g healthy donor stool) @ wk 0,3	50 cc enema (8g healthy donor stool) qWk x 6
CONTROL ARM	Autologous FMT (patient's stool)	Normal Saline
INCLUSION OF PATIENTS ON A BIOLOGIC AGENT	No	Yes
PRIMARY OUTCOME	Remission (SCCAI $\leq$2 & $\geq$1pt reduction in Mayo endo score) @ wk12	Remission (partial Mayo score <3 and Mayo endo score =0) @ wk7
RESULTS	7/23 (30%) vs 5/25 (20%); p=0.51	*9/38 (24%) vs 2/37 (5%); p=0.03*
SECONDARY OUTCOMES	Safety Microbial composition	Microbial composition IBDQ, EQ-5D

doi:10.1053/j.gastro.2015.03.045
doi: http://dx.doi.org/10.1053/j.gastro.2015.04.001

FMT for IBD in Pediatrics

Few small case series; within household, family donors

- **Mostly case series**
- **Suskind *et al* (n=9), 12-19yo CD patients, PCDAI mild-moderate score**
  - 1x NG tube FMT; 56% remission at 12 wks
- **Suskind et al. (n=4), 13-16yo UC patients, PUCAI moderate score**
  - 1x NG tube FMT; 0% remission at 12 wks

doi: 10.1097/MIB.0000000000000307

FMT in Pediatric IBD

8 year old female with IBD Unclassified

- Diagnosed in 2013 with IBD-U
- Patchy disease through colon; normal EGD, TI, MRE
- Prednisone; Maintenance: AZA + IFX 10mg/kg q4wk
  → AZA + Adalimumab q2wk
- FCal 1024, albumin 35, Hgb 112, CRP <0.2, PUCAI 10
- Family interested in fecal transplant

FMT in Pediatric IBD

8 year old female with IBD Unclassified

- FMT for IBD: Investigational trial only
- Entered first pediatric RCT of FMT in IBD (PediFETCh)
- Anonymous donor fecal enemas x 6 weeks (biweekly)

outcome	BASELINE	WEEK 4	*pre* WEEK 5
PUCAI	10	25	↑ 45
HGB	112	114	113
CRP	<0.2	0.5	↑ 60.0
ALB	35	37	35
FCAL	1024	1013	↓ 578

https://clinicaltrials.gov/ct2/show/NCT02487238

FMT in Pediatric IBD

8 year old female with IBD Unclassified

- c/o sore throat + household flulike symptoms
- Infectious workup: negative
- Empiric flagyl + qHS cortenema + scheduled Humira
- Returned to baseline over 1 month

FMT in Pediatric IBD

- Does evidence support FMT for IBD?
  - Pediatric data?
- What are the risks?
- Optimal mode of delivery?
  - Frequency?
- How does it work?

FMT in Pediatric IBD

8 year old female with IBD Unclassified

outcome	BASELINE	WEEK 4	*pre* WEEK 5	Followup
PUCAI	10	25	↑ 45	40
HGB	112	114	113	↓ 93
CRP	<0.2	0.5	↑ 60.0	↓ 3.8
ALB	35	37	35	↓ 28
FCAL	1024	1013	↓ 578	↑ 728

Trial recruitment ongoing

Microbiome analyses pending

Conclusions

FMT

- Current indications:
  - RCDI
  - Possibly refractory CDI
- Highly effective and safe
- Cost effective
- Many unanswered questions

Questions, Discussion

thank you for your attendance and participation

Dina Kao: dkao@ualberta.ca

Nikhil Pai: pain@mcmaster.ca