

Where are we going with FMT

Dina Kao
Karen Madsen
June 6, 2015

Objectives

- To review current evidence for FMT in recurrent *Clostridium difficile* infection
- To review current evidence for FMT in inflammatory bowel disease
- To discuss results from Edmonton FMT program

FMT in recurrent *Clostridium* *difficile* infection

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Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D.,
Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D.,
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Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

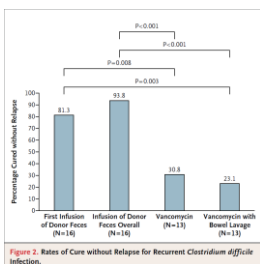


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* infection.

Table 2. Adverse Events in 16 Patients in the Infusion Group.^a

Adverse Event	On Day of Infusion of Donor Feces	During Follow-up
no. of events		
Belching	3	0
Nausea	1	0
Vomiting	0	0
Abdominal cramps	5	0
Diarrhea	15	0
Constipation	0	3
Abdominal pain	2 (associated with cramping)	0
Infection	0	2†
Hospital admission	NA	1‡
Death	0	0
Other adverse event	1§	1‡

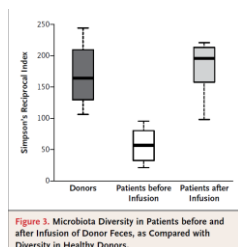
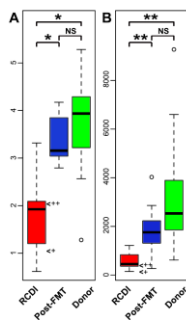
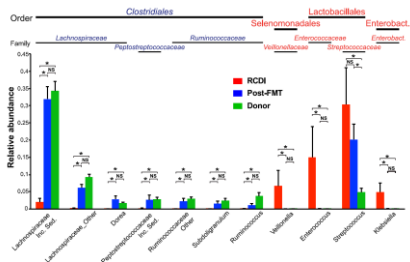
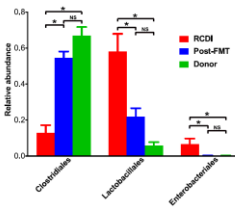
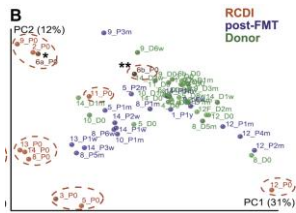


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.





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

Zain Kassam, MD, FRCPC¹; Christine H. Lee, MD, FRCPC¹; FIDSIA^{1,2,3}; Yuhong Yuan, MD, PhD^{1,2,3} and Richard H. Hunt, MB, FRCP, FRCPC¹, MACG, AGAP^{1,2}
Am J Gastroenterol 2013; 108:500–508; doi:10.1038/ajg.2013.59; published online 19 March 2013

AP₃T Alimentary Pharmacology and Therapeutics

Systematic review: faecal transplantation for the treatment of *Clostridium difficile*-associated disease

B. Guo¹, C. Harstall¹, T. Louie², S. Veldhuyzen van Zanten³ & L. A. Dieleman¹
Aliment Pharmacol Ther 2012; 35: 865–875

Fecal Microbiota Transplantation for the Treatment of *Clostridium difficile* Infection A Systematic Review

Giovanni Cammarota, MD, Gianluca Ianiro, MD, and Antonio Gasbarrini, MD
J Clin Gastroenterol • Volume 00, Number 00, ■■ 2014

Preliminary Communication

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

Ben Youngster, MD, MMSc, George H. Russell, MD, MSc, Christina Pender, BA, Torrey Ziv-Baran, PhD, Jenny Seok, MD, Elizabeth L. Helmsworth, MD

- Open label pilot study N= 20
- RCDI ≥ 3 episodes of mild-mod CDI or ≥ 2 episodes of severe CDI
- 15 capsules/d x 2 consecutive days
- Primary cure rate 14/20 (70%)
- Secondary cure rate 18/20 (90%)
- No serious adverse events attributed to FMT observed

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

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

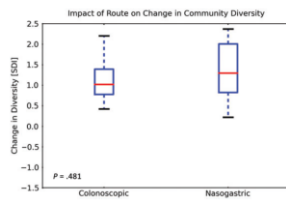
Ben Youngster,^{1,2,3} Jenny Seok,^{1,2} Christine Pinder,¹ Robin G. Wilson,⁴ Jess L. Kaplan,^{1,2} Mark B. Smith,⁵ Eric J. Alm,⁶ Dirk Giersen,⁷ George H. Russell,^{1,2} and Elizabeth L. Helmsworth^{1,2}

¹Division of Infectious Diseases, Massachusetts General Hospital, ²Harvard Medical School, ³Division of Infectious Diseases, Boston Children's Hospital, ⁴Division of Gastroenterology, Massachusetts General Hospital, and ⁵Department of Pediatric Gastroenterology and Nutrition, Massachusetts General Hospital for Children, Boston, and ⁶Department of Biological Engineering, and ⁷Truist Institute, Massachusetts Institute of Technology, Cambridge, Massachusetts

Clinical Infectious Diseases Received 20 December 2013; accepted 20 February 2014.

Colonoscopy vs NG FMT

- 41g donor stool/dose
- 20 mg losec daily x 2 days
- 4L golytely
- N= 20 colonoscopy group
 - Colonoscopy group= 10, NG group= 10
- Primary cure rate 14/20 (70%)
 - Colonoscopy group: 8/10 (80%) vs NG group: 6/10 (60%) (P= 0.628)
- Secondary cure rate 18/20 (90%)
 - 1 patient refused retreatment, 5 failed patients chose NG administration



FMT in IBD

2 RCT using FMT to treat UC

Group	Dutch	McMaster
Total N (active/placebo)	48 (23/25)	75 (38/37)
Patient population	Mild-mod UC	Mild-mod UC
Active arm (real FMT)	500 cc nasoduodenal infusion (120 g donor stool) at wk 0 and 3	50 cc enema (8g donor stool) weekly X6
Control	Sham FMT (patient stool)	Water
Outcomes		
Primary	Remission (SCCAI ≤ 2 + and ≥ 1 point reduction in Mayo endo score) @ wk 12	Remission (Mayo score < 3 and Mayo endo score=0) @ wk 7
Secondary	Safety Changes in microbial composition	Reduction of ≥ 3 points Mayo score Changes in microbial composition IBDQ, EQ-5D
Primary outcome	7/23 (30%) vs 5/25 (20%) p=0.51	9/38 (24%) vs 2/37 (5%) p=0.03

*Both trials were stopped early by DSMB due to futility

AP₃T Alimentary Pharmacology and Therapeutics

Systematic review: faecal microbiota transplantation in the management of inflammatory bowel disease

J. L. Anderson, R. J. Edey & K. Whelan

Aliment Pharmacol Ther 2012; 36: 503-516

REVIEW ARTICLE

Fecal microbiota transplantation as therapy for inflammatory bowel disease: A systematic review and meta-analysis

Ruben J. Colman¹, David T. Rubin²

DOI:10.1111/j.1365-2036.2011.04800.x

Edmonton FMT program

Edmonton FMT Program Statistics

- 149 patients treated Oct 2012- Mar 2015
- Patients are seen within 2 weeks of referral
- 4 universal stool donors
- Overall success rate

# of FMT required	Cumulative success rate
1 FMT	86%
2 FMT	95%
3 FMT	97%



Edmonton FMT Program

Clinical care

- Clinical lead: Dina Kao
- Nurse: Brandi Roach

Research

- Basic science lead: Karen Madsen
 - Lab manger: Naomi Hotte
 - Lab technician: Matt Emberg
 - Post doc fellow: Hee Kuk Park
 - Master's student: Braden Millan
- Quality assurance: Andy Mason
 - The Applied Genomic Center (TAGC)

FMT is an investigational therapy...

- RCT for recurrent Clostridium difficile infection
 - Colonoscopy vs capsule delivery
- Open label trials:
 - Ulcerative colitis
 - Crohn's colitis
 - Hepatic encephalopathy
 - (Obesity and metabolic syndrome)



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Patient baseline characteristics

	Capsule group (N= 13)	Colonoscopy group (14)
Age	69	67
Gender	F/M: 12/1	F/M: 10/4
BMI	22.7	27.5
Inpatient status at screening	1	1
Concurrent IBD	2 (UC)	1 (Crohn's)
Steroid use	0	0
Immunosuppressant	1	1
Biologic	1	1
PPI	3	4
# episodes of CDI (mean)	3.85	3.77
Regular bowel habit prior to RCDI (1-3 BMs/d)	8 (62%)	9 (64%)

Patient baseline characteristics

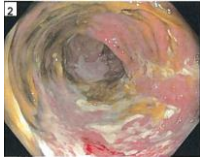
	Capsule group (N= 13)	Colonoscopy group (14)
Patient reported health status		
excellent	1 (7.7%)	0
very good	4 (30.8%)	4 (28.6%)
good	2 (15.4%)	3 (21.4%)
fair	2 (15.4%)	4 (28.6%)
poor	4 (30.8%)	3 (21.4%)
Charlson comorbidity index	3.7	3.4
Hb (g/L)	134.85	135.07
WBC	7.5	7.3
CRP	11.37	11.38
Creatinine (umol/L)	78.5	71.5

Results

	Capsule group (N= 13)	Colonoscopy group (14)
Cure rate after 1 FMT	12/13 (92%)	14/14 (100%)
Adverse events		
FMT related infection	0	0
Death	0	0
Nausea	2	0
Vomiting	1	0
Colonic perforation	-	0
Inability to retain transplant for 1 hr	-	1

RCDI in Crohn's colitis

11/27/13



5/16/14



RCDI and UC

5/16/14



9/4/14



RCDI in small bowel

- RCD enteritis is rare and more difficult to treat
- 1 patient with Crohn's disease
 - Colectomy for "UC" in Sept 2013 → ileostomy
 - Imuran and remicade for ileal Crohn's disease
 - Imodium 4 capsules/d
 - RCDI in small bowel since Jan 2014
 - Dec 2014: ileoscopy showed very mild TI inflammation
- Rx: 20 FMT capsules/d X 3
- Doing well so far

Cost averted with timely FMT for RCDI

- Cost per hospital admission for CDI \$8,911-\$30,049
- Ideal timing for FMT has not been determined
- Timely FMT (after 3 episodes) vs delayed FMT (≥ 4 episodes)
- Retrospective analysis of FMT program database Oct 2012- Aug 2013
 - Colonoscopy delivered FMT
 - F/U > 3 months post FMT
- Payer perspective
 - Hospital admissions and ER visits due to CDI
 - Each day admitted in hospital ~ \$2300 (not including cost of isolation or ICU admission if required)
 - Each ER visit ~ \$415
 - Cost of antibiotic for CDI not considered since it accounts for ~ 5% of total cost in previous analysis
 - Family MD visits, rehab costs not included
 - Indirect cost not included

Cost averted with timely FMT

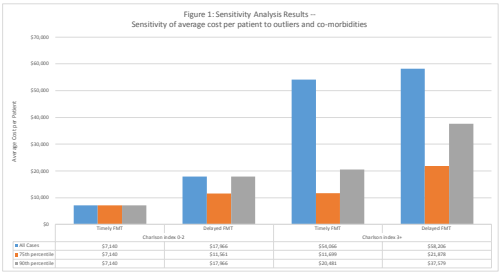
	All patient	Timely FMT	Delayed FMT
Total patient	71	31	40
F/M	39/32	17/11	22/19
Age (mean)	65.5	62	68
Charlson comorbidity index			
0-2	24	15	9
3+	47	16	31
Duration of RCDI (d) (mean)	203.8	102.3	282.5
CDI episodes	3.94	2.9	4.8
Hospital admission due to CDI (d) (mean)	17.2	13	20.5
# ER visit due to CDI (mean)	2	1.3	2.6

Cost averted with timely FMT

	All patients (N=71)	Timely FMT (N=31)	Delayed FMT (N=40)
Donor type			
universal	58 (77%)	24 (75%)	34 (78%)
familial	13 (23%)	7 (25%)	6 (22%)
FMT prep type			
fresh	21 (56%)	9 (30%)	12 (30%)
Frozen	50 (44%)	19 (71%)	30 (70%)
Primary cure rate	94.5%	93.5%	90%
Recurrence after 1 FMT	6	2	4
Secondary cure rate after 2 FMT	98.6%	96.7%	100%

Cost averted with timely FMT

	Total Patients (N=211)	Timely FMT (N=91)	Delayed FMT (N=120)
Treatment Costs			
Total	\$2,938,204	\$972,179	\$1,966,025
Mean (\$)	\$41,884 (\$26,555-\$58,213)	\$11,860 (\$7,015-\$2,555,705)	\$49,152 (\$0,192-\$58,112)
Median (Range)	\$18,406 (\$795-\$128,730)	\$1,813 (\$795-\$128,730)	\$10,819 (\$795-\$150,085)
Treatment Costs Post 1 st unsuccessful FMT			
	Total Patients (N=5)	Timely FMT (N=1)	Delayed FMT (N=2)
Total	\$65,089	\$417	\$65,652
Mean	\$12,023	\$417	\$33,034



Effects of Fecal Microbial Transplantation on the Gut Resistome in Patients with Recurrent Clostridium difficile infection

Open label FMT for Crohn's

Inclusion

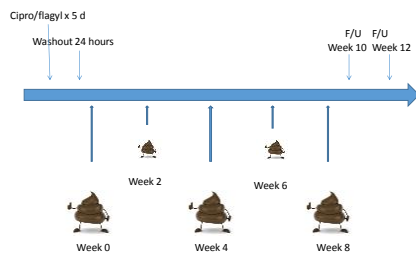
- Age >18 and < 65
- Dx colonic or ileocolonic Crohn's
- Mild to moderate HBI 5-16
- Failed 5 ASA or immunosuppressant ≥ 3 mo
- Active colonic inflammation (2/3)
 - CRP >8 mg/L
 - FC >250 ug/g
 - SES-CD 4-19

Exclusion

- Ileocecal resection
- Pregnancy/breastfeeding
- Exposure to a biologic
- Active perianal disease
- Active infection
- Allergy to cirpo and flagyl
- Dysplasia

FC= fecal calprotectin; SES-CD= simple endoscopic score for Crohn's disease

Trial design

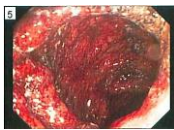


Outcomes of interest

- Clinical and endoscopic assessment
- Fecal and mucosa associated microbial analyses
- Cytokine profile in serum and mucosa
- Bile acid and short chain fatty acid composition
- Quality of life

FMT in Crohn's

Before FMT



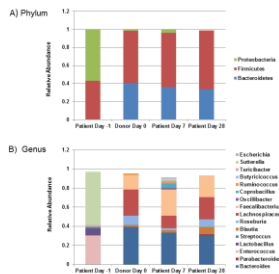
cecum

4 weeks post FMT



cecum

Kao D, Hotte N, & Madsen, K. JCG 2014



Kao D, Hotte N, & Madsen, K. JCG 2014

Ileocolonic Crohn's

	CRP	FC	endo score	HBI score
Screening	22.6	5235		5
Week 0 FMT #1 (colonoscopy)			23	
Day 1	14.9	no stool		
Week 1	11.1	1792		1
Week 2 FMT #2 (enema)	18.1	3815		0
Week 4 FMT #3 (colonoscopy)	12.2	1608	13	2
Week 6 FMT #4 (enema)	11.8	3090		0
Week 8 FMT #5 (colonoscopy)	18.4	8110	9	0
Week 10	8.7	2289		0
Week 12				

TI

8/8/14



10/3/14

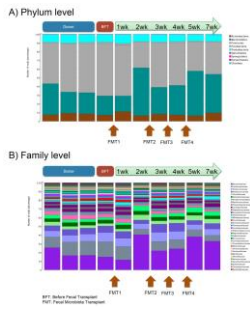


FMT in hepatic encephalopathy

Background

- Patients with liver cirrhosis and hepatic encephalopathy (HE) have intestinal dysbiosis
 - Urease producing bacteria
- Pathogenesis of HE not clear
 - Bacterial urease converts host derived urea to ammonia and carbon dioxide
 - Ammonia is excreted by liver and kidney
 - In liver cirrhosis ammonia excretion is impaired → hyperammonemia-associated neurotoxicity and HE
 - Rx: rifaximine +/- lactulose
- FMT represents a novel approach to treat HE

	Before FMT	1wk	2wk	3wk	4wk	7wk	10wk	14wk
		FMT #1 (by colonoscopy)		FMT #2 (by enema)	FMT #3 (by enema)	FMT#4 (by enema)		
Inhibitory control test (limes) (Normal <5)	17	19	A*	15	5	8	B*	17
Stroop test (sec) (Normal <200 sec)	250.9	203.4	270	190.6	183.5	213.4	B*	312.9
Serum NH3 level (Normal <55)	75	45	110	57	107	92	33	77



Conclusions

- FMT is highly effective and safe in RCDI
- FMT in IBD is investigational
- Potential for FMT in other indications
 - Obesity and metabolic syndrome
 - HE
 - Others