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	
MT in recurrent Clostridium	
difficile infection	

The NEW ENGLAND JOURNAL of MEDICINE

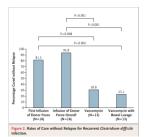
ESTABLISHED IN 1

JANUARY 31, 2013

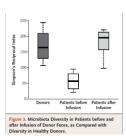
NOT THE NO. 5

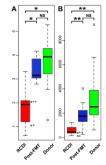
Duodenal Infusion of Donor Feces for Recurrent Clostridium difficile

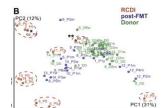
Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D. Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G. P. Jissen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf,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

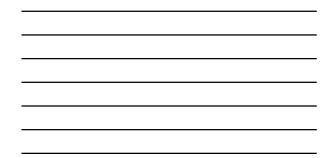


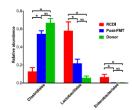


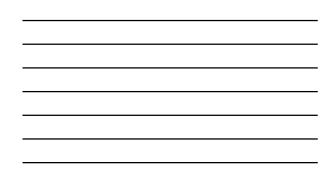


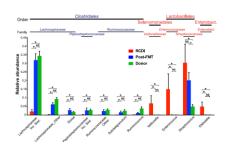














Fecal Microbiota Transplantation for Clostridium	
difficile Infection: Systematic Review and Meta-Analysis	
Zain Kassam, MD, FRCPC', Christine H. Lee, MD, FRCPC, FIDSA ^{3,4} , Yuhoong Yuan, MD, PhD ^{1,5} and Richard H. Hunt, MB, FRCP, FRCPC,	
MACG, AGAP ¹⁵ Am J Gastroenterol 2013; 108-500-508; doi:10.1038/ajg.2013.59; published online 19 March 2013 AP _S T Alimentary Pharmacology and Therapeutics	
Argi Alimentaly Filalinacology and Therapeutics	
Systematic review: faecal transplantation for the treatment of	
Clostridium difficile-associated disease	
B. Guo", C. Harstall", T. Louie [†] , S. Veldhuyzen van Zanten [‡] & L. A. Dieleman [‡] 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	
Ban Youngdow, MD, MMSC, George H, Bansel, M., MSC, Christians Prinder, BA, Tomer 27th Battan, PRID, Jerny Stak, LMD, Elackhell, L. Hohmann, 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.	
Tablisted Offine October 11, 2011.	
Facel Migrapiota Transplant for Palancing	
Fecal Microbiota Transplant for Relapsing Clostridium difficile Infection Using a Frozen	
Inoculum From Unrelated Donors: A	
Randomized, Open-Label, Controlled Pilot Study	
llan Youngster, ^{1,23} Jenny Saok, ²⁴ Christina Pindar, ² Robin G. Wilson, ⁵ Jess L. Kaplan, ^{1,5} Mark B. Smith, ⁶ Eric J. Alm, ⁶ Dirk Gevery R. Bassell, ²³ and Einzbeth L. Hohmann, ^{2,7}	
*Bivision of Infactions Eleasons Massachusatts General Homital *Hannert Marlind School *Bivision of Infactions Diseasons Reston (Nikhan's Homital	
*Division of Gastoemschop, Masschusetts General Hespital, vord *Department of Prédants Gasteensteelogy and Nachton, Masschusetts General Hespital for Children, Batter, and *Dispartment of Bedged Englishering, and *Board Institute, Masschusetts Institute of Technology, Carloidge, Masschusetts Masschusetts Mas	
Clinical Infectious Diseases Received 20 December 2013; accepted 20 February 2014.	

Colonoscopy vs NG FMT	
41g donor stool/dose20 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 adminstration 	
Impact of Route on Change in Community Diversity 2.5	
IGSL 1.5 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0 1.0	
80 0.5 8 0.0	
0 -0.5 -1.0 p481	
-1.5 Colonoscopic Nasogastric	
FMT in IBD	

2 DCT ucin	a FNAT to troot IIC	
Z KCI USINĮ	g FMT to treat UC	
Group Total N (active/placebo)	Dutch	McMaster 75 (38/37)
Total N (active/placebo) Patient population	48 (23/25) Mild-mod UC	75 (38/37) 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
Secondary	Safety	Reduction of >3 points Mayo score
	Changes in microbial composition	Changes in microbial composition IBDQ, EQ-5D
Primary outcome	7/23 (30%) vs 5/25 (20%) p=0.51 early by DSMB due to futility	9/38 (24%) vs 2/37 (5%) p=0.03
managemer J. L. Anderson, R. J. E REVIEW ARTICLE Fecal microbiota tr	ransplantation as therapy weel disease: A systematic nalysis	
Edmont	on FMT prog	ram
	5.11 1111 P10B	

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
 Overlite account and American Management
- Quality assurance: Andy Mason
 - The Applied Genomic Center (TAGC)

FMT is an investigation	nal therapy		
RCT for recurrent Clostridium diff Colonoscopy vs capsule delivery Open label trials: Ulcerative colitis			
Crohn's colitis Hepatic encephalopathy			
(Obesity and metabolic syndrome)			
35.4 (5.6) (1.5) (4.5) (1.5) (Page 1 of 2	
Findings and Security Designed Contents	Approved Form		
amount informer or time than the following t	Principal Come August ES, 2014 Principal Come Name Starty To Principal Come Name A presention, multi-record continuous double folial focus in the sales appropriate to	COS Existing County County of Marie	
The criticals in Fair Implicates IA. If an all controlles the insight into the place Similary in Control of March 1997, and the control of th	Approved Exprise August In. 1995 Open of 160 man August In. 1995 August In.		
Filtrament for this intergenetic research. 1. Illingui, the contribution and including provinging on classed with his interface and district, it is a suggested than defined contribution and all the real processing in soft or excluding in the last and of the contribution of the all all the contributions of the contribution o	For the place are in the state of the state	- Trained dust Facel, which have, an expedition to be less than a repulsable to be less to be less to repulsable to be less to be less to repulsable to be less than a repulsable to be less to be less than a repulsable	
integral in the first which it towed of colonies." In temporal C and CC, and CC, and CC, and CC and	this work "Received Citiva East Comment of interior thap text by exciton the first find of the comment of a contact to terminate track extremely and offers approximate and approximate promite the second contact the companies for the comment of the comment of the comment of the comment of the comment of the describe advantage and drough Contragations.	Media Accordinate Control (a) of the related his designation (b) of the related his designation (c) of the related his designation (d) of the related his designation (d) of the related his designation (d) of the related his designation (e) of the relative his his designation (e) of the relative his his designation (e) of the relative	
specification after given the facts to med. Framework of the off-cheeded despisability of cheese, you must about a complical Chinele Profiles appropriately may go at a consistency and of the other. — Significant control of the other cheese of t	A School Restricted Set Later Set and a later have been seen of the secretary of the secret	in the fact or motion of the control	
Canadi	https://ecom.suburu.co/EEM/dibuvil/2/ft/a/EH/dibpsEP/dib/ts/cross-	6/07/develop, 85/3(i)	
Ball or fra			
■ □ Cut 2. Come Come Come Come Come Come Come Come	Madagion and Genetic Theorytic Directivate 200 Theoryte French Chicaropy		
/gr 1 28, 2014 20, Disa Kao	Chern, Coloris XI A ICS Fit in 1927 OREWIGSIC Controller 173-06 December 19-1755		
Assisted Practices Chemics of Undersonated The Greeness of the Directory of Alberta on Variously of Alberta Collection and Alberta Chemics Collection and Chemics Collection and Chemics Collection of The Alberta Tax 100-08 3200 Tax 100-08 3200			
Dentile Kon:	sine Transplantin (DMI) filmen herbanyy 3,384 concerns Theoret 6,092 in differ 'A 1 standard complaints (FMI) in the mesignace of		
to a constance with Part C, Thirkian S of the Roc initialing files that,	I and Drug Applications, there is no objection to		
Area of the Inglementato Farm, gette as indicating of You are constanted of the prosperimental conduction and in the marging this ingression and does are agreed and in the marging the ingression and does not the following and a Constante in Engineeric Engineeric (Intellection and According Linguise). Elimental in the following and a Constante in Engineeric Elimental (Intellection and According Linguise).	ushi in Cris Fell you meet rubeit a completed Chinon's with dishest etc. Chinon's Timi Para-Best Franchise mish felt of drags to be you Chinon's Liquid Para-Best Franchise mish felt of drags to be you Chinon's Approved drags of chinon's desirably from the stress and composition of short and days are drawn from the joy more shown with Timin's TES of Timin's Canada's Cold Approved to the China Cold Approved to the Cold Approved to the Cold Approved to the Cold Approved to the cold Approved to the Cold		
China This Sis Information Forms and David Drug Rennico (ADE) reports stanish to firm in	Coll Approximate. 3th Terms Alexandr Institute 135-941-1788. Althouse 603-957-0364. antice and Deciment of Chester's First Engineering to the Chester's regions that collect that is offered to the Chester's Chester'		
ormal, wings a publishy modelsh angiety fish on Glainsteink gav (www. drainsteinst. ga Central Controlled Telesh (www. controlled Central Controlled Telesh (www. controlled	namme was in kinnel outel distribution the stiglised to mich are: *) Led thinks meal)		

To Disc. Con. C	
(sp. 15, 20.4) To Banker The Marker The Command of The Command	
Constitution of the Consti	
No combination with Dark CE Provision of the Revel and Darp Apparlments, there for endphrisen to biological bands. Never with the December Dark Service Service Service Service Service states a compared Chicano' (mail the December Dark Service	
The me manifold of the representation when of 2 most find of the first behavior shell for the gas behavior and the control of	
Condesses of A facility Condesses of Condess	
faceally.	
Randomized Controlled Trial (RCT) for RCDI	
Collaboration with Calgary	
Tom Louie & Paul Beck Comparing Colonoscopy vs oral capsule delivered FMT	
• 1º outcome: Efficacy • 2º outcomes: • Safety	
Keystone species associated with cure Bile acid metabolism and bacterial species responsible Durability	
Quality of life Patient preference Cost effectiveness	
RCT for RCDI	
 At least 3 episodes of CDI Stratified by age (<65 vs ≥ 65) and immune status (normal vs 	
immuncompromised) • N=200	
Recruitment began in Oct 2014	

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 Steroid use Immunosuppressant Biologic	2 (UC) 0 1 1	1 (Crohn's) 0 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 very good good fair poor	1 (7.7%) 4 (30.8%) 2 (15.4%) 2 (15.4%) 4 (30.8%)	0 4 (28.6%) 3 (21.4%) 4 (28.6%) 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	-	1
hr		

RCDI in Crohn's colitis 11/27/13 5/16/14 RCDI and UC 5/16/14

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 PMT
 FM | S | O | O | O | O | O | O |
 S | O | O | O | O | O | O |
 S | O | O | O | O | O |
 S | O | O | O | O | O |
 S | O | O | O | O | O |
 S | O | O | O | O | O |
 S | O | O | O | O | O |
 S | O | O | O | O | O |
 S | O | O | O | O |
 S | O | O | O | O |
 S | O | O | O | O |
 S | O | O | O | O |
 S | O | O | O | O |
 S | O | O | O | O |
 S | O | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O | O |
 S | O | O |

- Payer perspective
 Nospital admissions and ER visits due to CDI
 Schopktal admissions and ER visits due to CDI
 Schopktal Admission in hospital * \$2300 (not including cost of isolation or ICU admission if required)
 Schopktal * 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

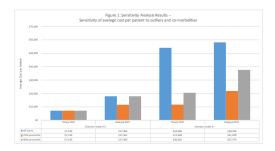
	All patient	Timely FMT	Delayed FMT
Total patient	71	31	40
F/M	39/32	17/11	22/19
Age (mean)	65.5	62	68
Charlson comorbidity index 0-2 3+	24 47	15 16	9 31
Duration of RCDI (d) (mean)	203.8	102.3	282.5
CDI episodes	3.94	2.9	4.8
Hospital admission due to CDI (d) (mean)	17.2	13	20.5
# ER visit due to CDI (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 familial	58 (77%) 13 (23%)	24 (75%) 7 (25%)	34 (78%) 6 (22%)
FMT prep type fresh Frozen	21 (56%) 50 (44%)	9 (30%) 19 (71%)	12 (30%) 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=71)	Timely FMT (N=31)	Delayed FMT (N=40)
eatment Costs			
Total	\$2,918,266	\$972,173	\$1,966,093
Mean (CI)	\$41,384 (\$26,555-556,213)	\$31,360 (\$7,015.52-\$55,705)	\$49,152 (30,192-\$68,112)
Median (Range)	\$19,434 (\$795-\$329,730)	\$1,933 (\$795-\$329,730)	\$30,815 (\$795-\$250,065)
atment Costs Post- 1 rd unsuccessful FMT			
	Total Patients (N=3)	Timely FMT (N=1)	Delayed FMT (N=2)
Total	\$66,069	\$417	965,652
Mean	\$22,023	\$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 immunosupressant ≥ 3 mo
- Active colonic inflammation (2/3)
 CRP >8 mg/L
 FC >250 ug/g
 SES-CD 4-19

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

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

4 weeks post FMT



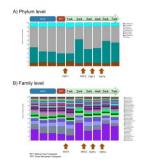


Ileocolonic Crohn's

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

TI		
8/8/14 10/3/14	1	
12		
FMT in hepatic ence	ohalopathy	
Background		
 Patients with liver cirrhosis and hepatic en 	cephalopathy (HE) have	
intestinal dysbiosis • Urease producing bacteria • Pathogenesis of HE not clear		
 Bacterial urease converts host derived urea to Ammonia is excreted by liver and kidney 		
In liver cirrhosis ammonia excretion is impaire associated neurotoxicity and HE Rx: rifaximine +/- lactulose		
FMT represents a novel approach to treat	HE	

		lwk	2wk	3wk	4wk	7wk	10wk	14wl
	Before FMT	FMT #1 (by colonoscopy)		FMT #2 (by enema)	FMT # 3 (by enema)	FMT#4 (by enema)		
Inhibitory control test (lures) (Normal <5)	17	19	A*	15	5	8	В*	17
Stroop test (sec) (Normal<200 sec)	250.9	203.4	270	190.6	183.5	213.4	В*	312.9
Serum NH3 level	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