Fecal Microbiota Transplantation in 2017

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Ancient History

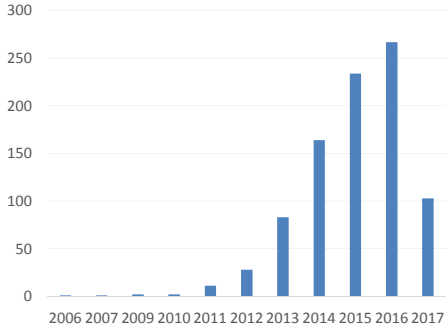
- FMT is NOT a new concept
- Don-jin dynasty (4th century)
- Ming dynasty (16th century)
- Veterinary medicine (17th century) – "transfaunation"
- 1958 – 4 patients treated for enterocolitis with fecal enemas

Am J Gastroenterol 2012;107:1755
Surgery 1958;44(5):854–9.

Outline

- Background
- FMT for treatment of rCDI
  - Non-IBD
  - IBD
- FMT for treatment of IBD
- Unanswered questions, future research

PubMed Results "Fecal Microbiota Transplant"



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Modern History

- 2013 – landmark study – 1st RCT

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 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. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

Evidence: FMT for Recurrent C diff

- Systematic Review
  - 2 RCTs
  - 21 case-series
  - 5 case reports

FMT Method	Patients With Resolution of Symptoms Without Recurrence, %*	Studies/Total Studies Analyzed, n/N
Upper GI tract	77	7/187†
Colonoscopy	90	11/257†
Enema	78	5/45
Upper GI tract and colonoscopy	100	1/27
All methods	85	23/516‡

Ann Intern Med. 2015;162:630-638.

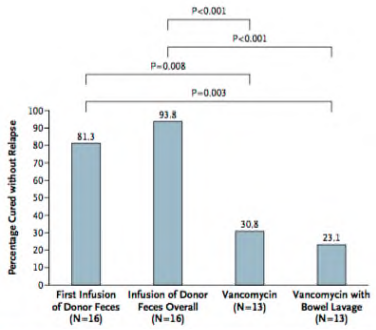


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.
Shown are the proportions of patients who were cured by the infusion of donor feces (first infusion and overall results), by standard vancomycin therapy, and by standard vancomycin therapy plus bowel lavage.

Evidence: FMT for C diff

- 3rd RCT – 2015
- 39 patients
- FMT versus vanco taper

AP&T Alimentary Pharmacology and Therapeutics

Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent *Clostridium difficile* infection

G. Cammarota*, L. Masucci†, G. Ianiro*, S. Bibbò*, G. Dinoi*, G. Costamagna‡, M. Sanguinetti† & A. Gasbarrini*

2nd RCT - 2014

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

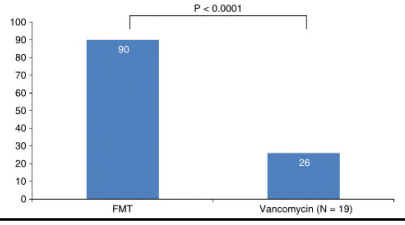
Ilan Youngster,[1,2,3] Jenny Sauk,[2,4] Christina Pindar,[1] Robin G. Wilson,[4] Jess L. Kaplan,[2,5] Mark B. Smith,[6] Eric J. Alm,[5] Dirk Gevers,[7] George H. Russell,[2,5] and Elizabeth L. Hohmann[1,2]

- 20 patients randomized to FMT via colonoscopy or NGT
- 70% cure rate

Clin Infect Dis. 2014;58: 1515-22.

Evidence: FMT for C diff

- 3rd RCT – 2015
- 39 patients
- FMT versus vanco taper



Conclusion #1

- For recurrent C diff in non-IBD patients:
  - FMT is superior to antibiotic treatment (overall cure rate 85%)
  - Colonoscopic delivery slightly superior to upper tract

FMT for C diff in IBD

Fecal Microbiota Transplantation is Safe and Efficacious for Recurrent or Refractory *Clostridium difficile* Infection in Patients with Inflammatory Bowel Disease

Monika Fischer, MD, Dina Kao, MD,† Colleen Kelly, MD,‡ Aishwarya Kuchipudi, MD,§ Syed-Mohammed Jafri, MD,¶ Mark Blumenkehl, MD, MS,# Douglas Rex, MD,* Mark Mellow, MD,‖ Nirmal Kaur, MD,# Harry Sokol, MD, PhD,¶ Gwen Cook, MS,* Matthew J. Hamilton, MD,** Emmalee Phelps, BS,* Brian Sipe, MD,†† Huiping Xu, PhD,* and Jessica R. Allegretti, MD, MPH***

- Cohort study – 67 patients from 8 centers in US and Canada
- IBD patients with rCDI, underwent FMT
- Primary outcome: recurrence at 3 months
- Secondary outcomes: IBD activity and safety

Inflamm Bowel Dis 2016;22:2402–2409

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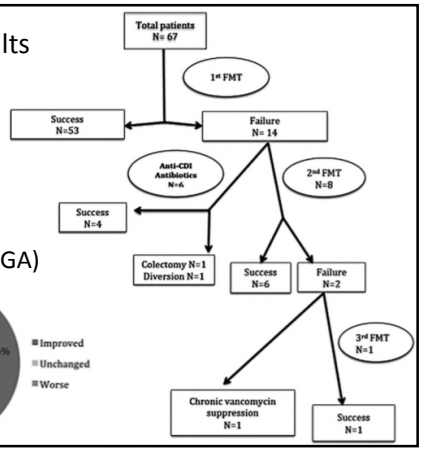
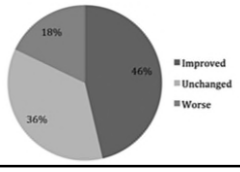
Results



IBD activity (PGA)



C diff in IBD patients

- Prevalence of CDI: 2.5-8 fold higher in IBD
- 10% lifetime risk
- Since 1998: CDI-related hospitalizations for IBD patients has doubled
- In-hospital death rate for IBD – 5X higher when complicated by C diff
- Is FMT effective and safe for treatment of C diff in IBD patients?

Inflamm Bowel Dis 2016;22:2402–2409

C diff 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‡

*Division of Gastroenterology, Department of Medicine, University of Minnesota, Minneapolis, Minnesota; and ‡BioTechnology Institute, University of Minnesota, Minneapolis, Minnesota

- 272 patients who underwent FMT for rCDI
- Cure rate for 1st FMT:
  - IBD patients: 74.4%
  - Non-IBD: 92.1%
- 25% of IBD patients experienced flare after FMT

Clinical Gastroenterology and Hepatology 2016;14:1433–1438

Conclusion #2

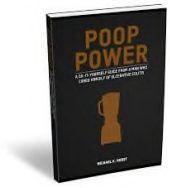
- For IBD patients with rCDI:
  - FMT is effective (maybe less so than non-IBD?)
  - FMT may induce flares of IBD (18-25%?)

FMT for treatment of IBD (not C diff)

- Also not a new concept…
- 1989 paper published in Lancet
- Physician self-treated UC (steroid dependent) with fecal retention enemas
- Steroid free remission for 6 months

Lancet; 1989:164

Outline



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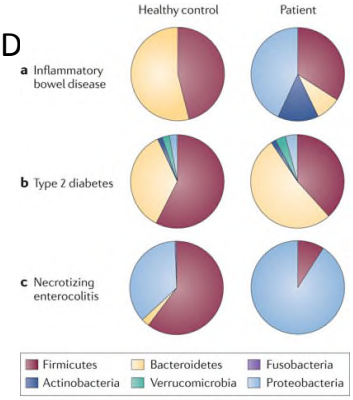
Dysbiosis in IBD



Nature Reviews Microbiology **9**, 279-290

Nature Reviews | Microbiology

FMT for treatment of IBD (not C diff)

- Also not a new concept…

FMT for treatment of UC

Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial

Paul Moayyedi,[1] Michael G. Surette,[1] Peter T. Kim,[2,3] Josie Libertucci,[1] Melanie Wolfe,[1] Catherine Onischi,[3] David Armstrong,[1] John K. Marshall,[1] Zain Kassam,[4] Walter Reinisch,[1] and Christine H. Lee[3]

[1]Farncombe Family Digestive Health Research Institute, Department of Medicine, McMaster University, Hamilton, Ontario, Canada; [2]Department of Mathematics and Statistics, University of Guelph, Guelph, Ontario, Canada; [3]Department of Pathology and Molecular Medicine, St Joseph's Healthcare, McMaster University, Hamilton, Ontario, Canada; and [4]Department of Biological Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts

- Canadian study 70 patients with active UC
- FMT via retention enema weekly x 6 wks
- Placebo controlled (water enemas)
- Clinical and endoscopic data

Gastroenterology 2015;149:102–109

FMT for treatment of UC

Table 2. Outcome Measures Comparing Fecal Microbial Transplantation With Placebo

Outcome	Placebo (n = 37)	FMT (n = 38)	*P* value
Clinical remission,* n (%)	2 (5)	9 (24)	.03
Clinical response,* n (%)	9 (24)	15 (39)	.16
Full Mayo score	6.34	6.00	.42
IBDQ score	149.38	152.13	.44
EQ-5D score	70.07	68.52	.99
CRP, *mg/L* (n = 17 placebo, n = 15 FMT)	3.3 ± 3.4	4.9 ± 5.9	.38
ESR, *mm/h* (n = 17 placebo, n = 15 FMT)	13.1 ± 11.2	15.9 ± 17.0	.59
Proportion with high ESR, n (%)	4 (24)	3 (20)	1.0
Proportion with high CRP, n (%)	5 (29)	2 (13)	.40
Patients with serious adverse events n (%)	2[a] (5)	3[a] (8)	1.0

Gastroenterology 2015;149:102–109

FMT for Crohn's

- No RCTs
- Only small case series and uncontrolled studies
- Pediatric study in China
  - 30 patients
  - midgut FMT
  - Clinical response and remission 86.7% and 76.7%
- More studies needed

J. Gastroenterol. Hepatol. 30, 51–58 (2015)

"TURN" trial

Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis

Noortje G. Rossen,[1] Susana Fuentes,[2] Mirjam J. van der Spek,[1] Jan G. Tijssen,[3] Jorn H. A. Hartman,[2] Ann Duflou,[1] Mark Löwenberg,[1] Gijs R. van den Brink,[1] Elisabeth M. H. Mathus-Vliegen,[1] Willem M. de Vos,[2,4] Erwin G. Zoetendal,[2] Geert R. D'Haens,[1] and Cyriel Y. Ponsioen[1]

[1]Department of Gastroenterology and Hepatology, Academic Medical Center, Amsterdam, The Netherlands; [2]Laboratory of Microbiology, Wageningen University, Wageningen, The Netherlands; [3]Department of Cardiology, Academic Medical Center, Amsterdam, The Netherlands; and [4]Departments of Bacteriology and Immunology and Veterinary Biosciences, University of Helsinki, Finland

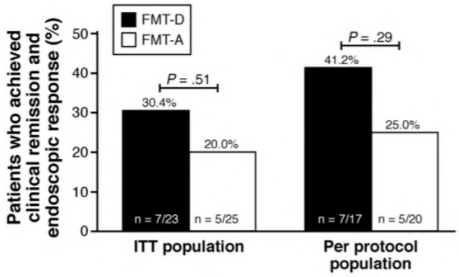
- 48 patients in the Netherlands
- Placebo controlled (autologous transplant)
- FMT via nasoduodenal tube 0 and 3 wks

Gastroenterology 2015;149:110–118

Conclusion #3

- FMT for treatment of IBD:
  - Preliminary results are mixed; more RCT data is needed

"TURN" trial



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Unknowns

- Long-term adverse effects of FMT?
- Role for FMT in non-C diff disorders
  - IBD, DM, obesity, NAFLD, alcoholic hepatitis, etc.
- Optimal route of administration
  - Upper tract, lower tract, capsulized stool
- Donor factors
- Isolation of most beneficial bacterial strains

Summary

- FMT is treatment of choice for recurrent/refractory C diff infection
- FMT is safe and effective for treatment of C diff in IBD patients
- FMT may have a role in treatment of IBD

Thank you