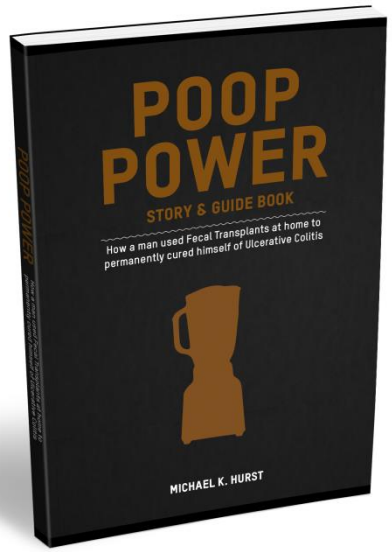
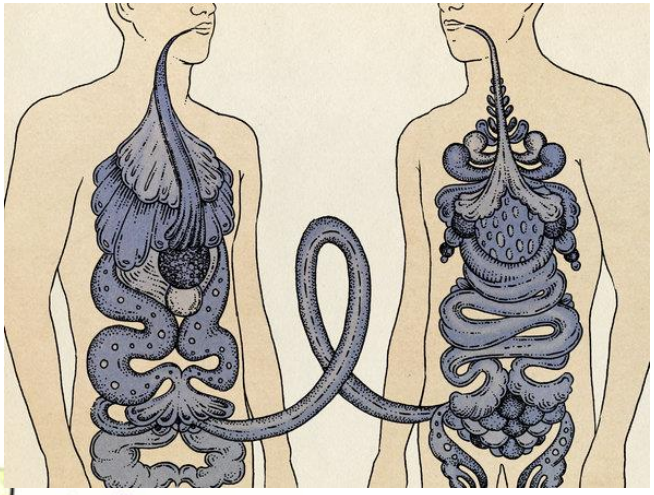
香港中文大學
The Chinese University of Hong Kong

Fecal Microbiota Transplantation — The Promise of an Old Therapy

Department of Microbiology, CUHK
PhD student: Luo Mingjing
Supervisor: Professor Margaret IP
03 Dec 2013

Fecal Microbiota Transplantation





http://fecaltransplant.org/poop-power-do-it-yourself-guide- from-a-man-who-cured-himself-of-ulcerative-colitis/
http://pregnantwithibd.blogspot.hk/2013/07/stool-transplantnot-looking-so-gross.html
http://cprgi.org/blog/fecal-microbiota-transplantation
http://anguishedrepose.com/2012/03/15/news-mash-when-its-evil-c-diff-vs-super-poo-who-will-win/

History of Fecal Microbiota Transplantation(FMT)

4th century

- Oral administration of “yellow soup” for treatment of food poisoning and severe diarrhea

16th century

- Oral administration of fresh or fermented fecal solution, dry feces, or infant feces for treatment of abdominal diseases with severe diarrhea, fever, pain, vomiting, and constipation

In 1958

- Used for the treatment of pseudomembranous colitis in four patients

Now

- Moving into the mainstream in treating recurrent *Clostridium difficile* infection(CDI)

Moving FMT to the mainstream

Major issues impeded the wide-scale acceptance of FMT

- Attitudes toward the unappealing nature of feces
- Efficiency, safety and mechanism

Reasons drive public's attention to the use of FMT

- Available knowledge about the importance of gut microbiota in human health and disease.
- High cure rates of FMT for the treatment of relapsing CDI patients in whom standard therapy with vancomycin has failed

Gut microbiota

Feces is a biologically active, complex mixture of a variety of microbes

Gut microbiota

- $>10^{14}$ bacteria (thousands of different species)
- >70% of all the microbes in the human body
- Critical to immune function, nutrient processing, and maintain host physiology
- Diet, antibiotics, stress, and host genome can influence the structure and function of human microbiota

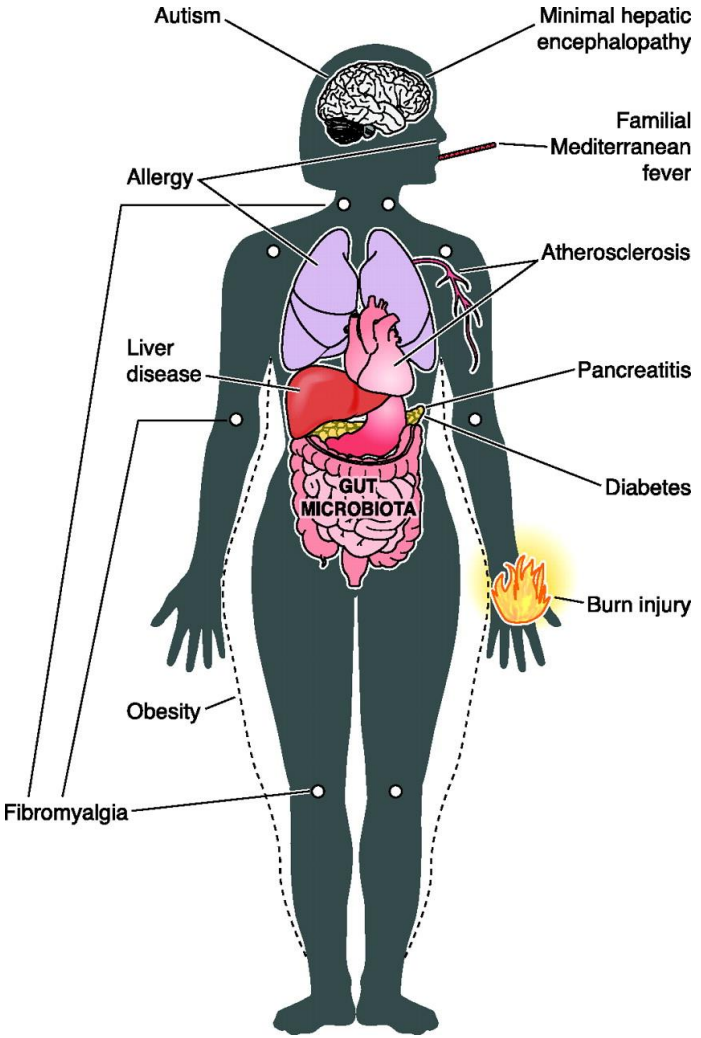
Dysbiosis of gut microbiota lead to choas

Gtu microbiota with disease inside gastrointesinal tract

- Recurrent CDI
- Inflammatory bowel disease (IBD)
- Irritable bowel syndrome(IBS)
- Idiopathic constipation
- Familial mediterrean fever
- Cholelithiasis
- Colorectal cancer
- Hepatic encephalopathy
- Gastric carcinoma and lymphoma

--- J. Brandt, et al *Gastrointestinal Endoscopy.*78(2), 240–249

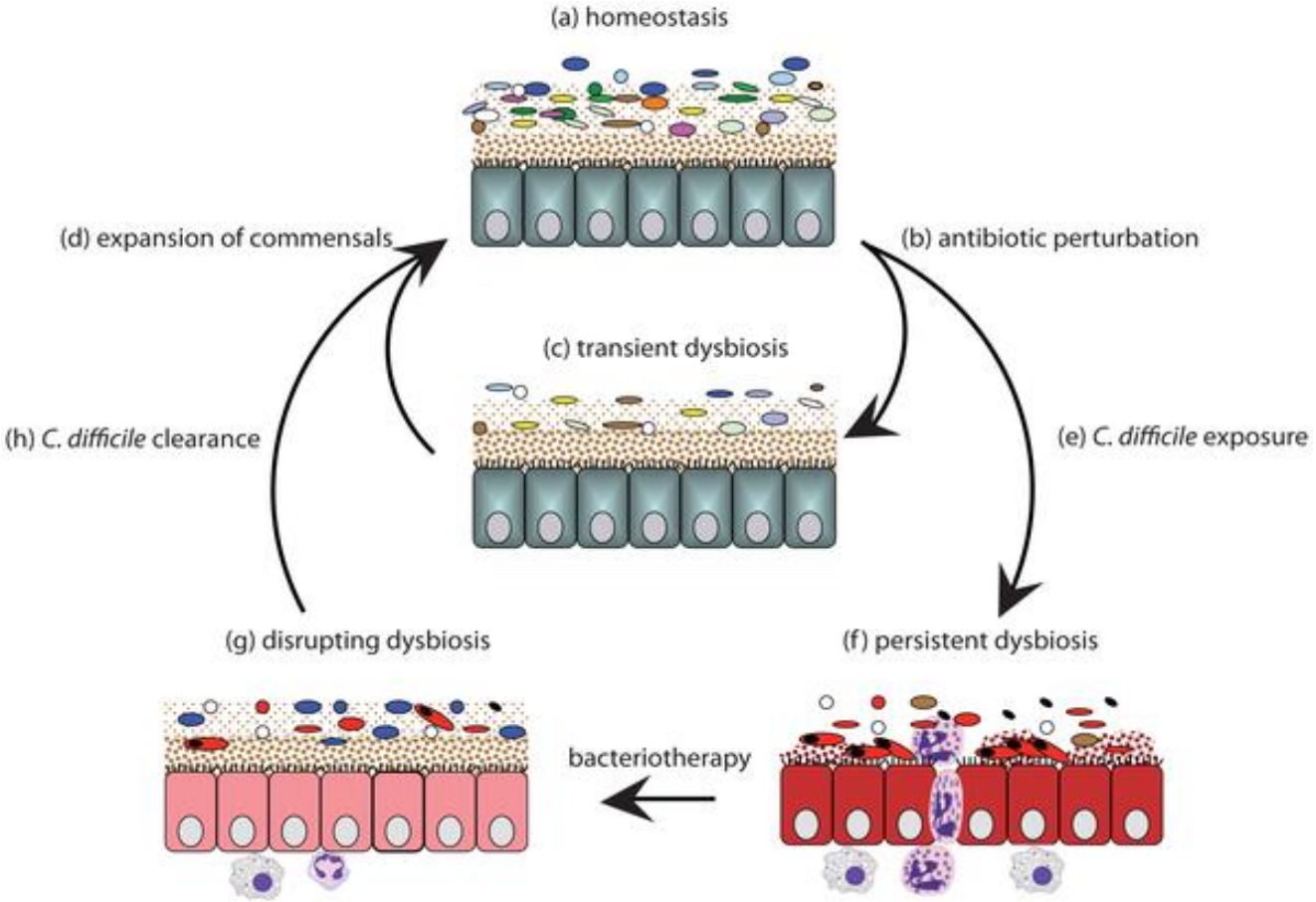
Gut microbiota with diseases outside of the gastrointestinal tract.



Sekirov I et al. Physiol Rev 2010;90:859-904

Recurrent CDI

- Infection incidence has doubled in last decade
- Antibiotic therapy is associated with high relapsing rates



Proposed model for establishment of C. difficile-mediated dysbiosis and successful FMT therapy

Lawley TD, Clare S, Walker AW, Stares MD, et al. (2012). PLoS Pathog 8(10): e1002995. doi:10.1371/journal.ppat.1002995

Systematic Review of Intestinal Microbiota Transplantation (Fecal Bacteriotherapy) for Recurrent *Clostridium difficile* Infection

Ethan Gough,[1] Henna Shaikh,[2] and Amee R. Manges[1,3]

Departments of [1]Epidemiology Biostatistics and Occupational Health, and [2]Biology, McGill University, and [3]Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

Clostridium difficile **infection (CDI) is a gastrointestinal disease believed to be causally related to perturbations to the intestinal microbiota. When standard treatment has failed, intestinal microbiota transplantation (IMT) is an alternative therapy for patients with CDI. IMT involves infusing intestinal microorganisms (in a suspension of healthy donor stool) into the intestine of a sick patient to restore the microbiota. However, protocols and reported efficacy for IMT vary. We conducted a systematic literature review of IMT treatment for recurrent CDI and pseudomembranous colitis. In 317 patients treated across 27 case series and reports, IMT was highly effective, showing disease resolution in 92% of cases. Effectiveness varied by route of instillation, relationship to stool donor, volume of IMT given, and treatment before infusion. Death and adverse events were uncommon. These findings can guide physicians interested in implementing the procedure until better designed studies are conducted to confirm best practices.**

The NEW ENGLAND JOURNAL of MEDICINE

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.

Fecal trial

- Oral vancomycin 500mg 4times/ day,14 days
- Oral vancomycin 500mg 4 times/ day, 14 days; Bowel lavage 1x
- Oral vancomycin 500 mg 4times/ day, 4 days; Bowel lavage 1x; Donor faeces 1x

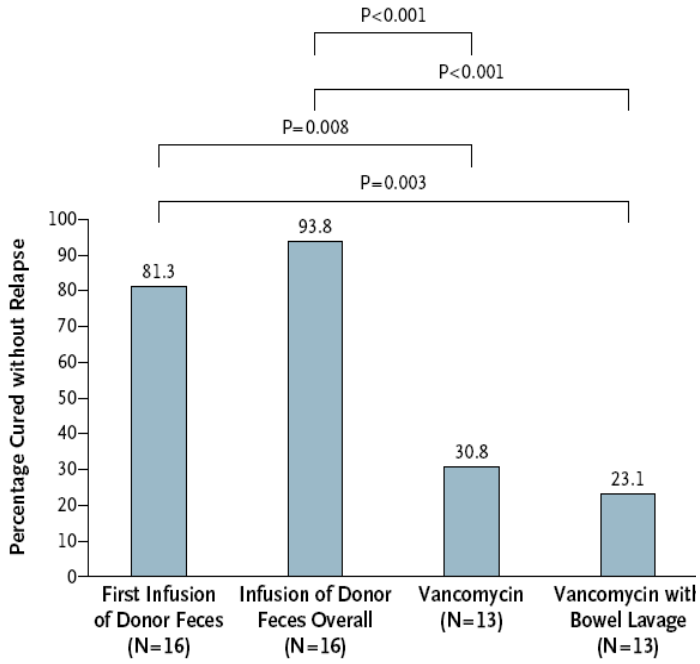


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

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.

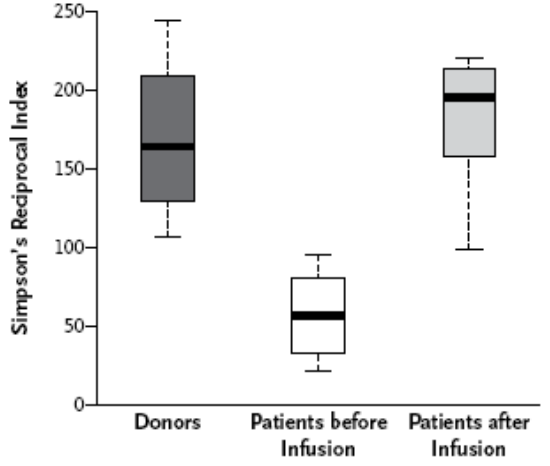


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

Microbiota diversity is expressed as Simpson's Reciprocal Index of diversity in fecal samples obtained from nine patients before and 14 days after the first infusion of donor feces, as compared with their donors. The index ranges from 1 to 250, with higher values indicating more diversity. The box-and-whisker plots indicate interquartile ranges (boxes), medians (dark horizontal lines in the boxes), and highest and lowest values (whiskers above and below the boxes).

Microbiome

METHODOLOGY Open Access

Stool substitute transplant therapy for the eradication of *Clostridium difficile* infection: 'RePOOPulating' the gut

Elaine O Petrof[1*†], Gregory B Gloor[2†], Stephen J Vanner[1], Scott J Weese[3], David Carter[4], Michelle C Daigneault[5], Eric M Brown[5], Kathleen Schroeter[5] and Emma Allen-Vercoe[5]

Abstract

Background: Fecal bacteriotherapy ('stool transplant') can be effective in treating recurrent *Clostridium difficile* infection, but concerns of donor infection transmission and patient acceptance limit its use. Here we describe the use of a stool substitute preparation, made from purified intestinal bacterial cultures derived from a single healthy donor, to treat recurrent *C. difficile* infection that had failed repeated standard antibiotics. Thirty-three isolates were recovered from a healthy donor stool sample. Two patients who had failed at least three courses of metronidazole or vancomycin underwent colonoscopy and the mixture was infused throughout the right and mid colon. Pre-treatment and post-treatment stool samples were analyzed by 16 S rRNA gene sequencing using the Ion Torrent platform.

Results: Both patients were infected with the hyper virulent *C. difficile* strain, ribotype 078. Following stool substitute treatment, each patient reverted to their normal bowel pattern within 2 to 3 days and remained symptom-free at 6 months. The analysis demonstrated that rRNA sequences found in the stool substitute were rare in the pre-treatment stool samples but constituted over 25% of the sequences up to 6 months after treatment.

Conclusion: This proof-of-principle study demonstrates that a stool substitute mixture comprising a multi-species community of bacteria is capable of curing antibiotic-resistant *C. difficile* colitis. This benefit correlates with major changes in stool microbial profile and these changes reflect isolates from the synthetic mixture.

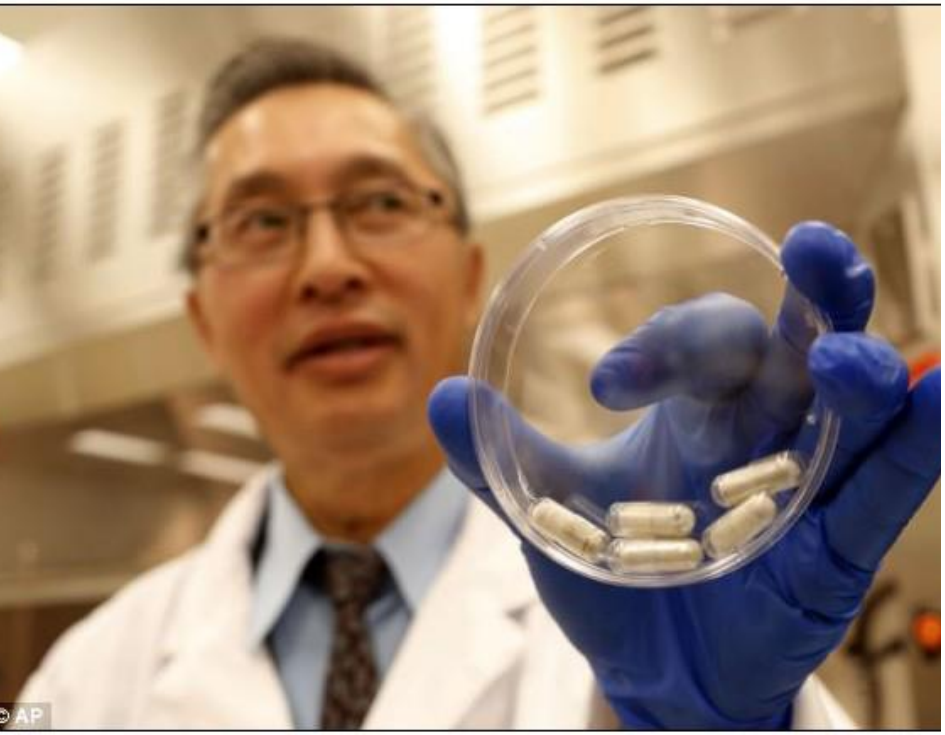
Trial registration: Clinical trial registration number: CinicalTrials.gov NCT01372943

Doctors create 'poop pills' that transfer feces from healthy people into guts of patients with infections

- **Stool samples taken from healthy relatives processed and packed into pill cases that dissolve when they reach the intestines**
- **Used to treat Clostridium difficile, which kills 14,000 Americans a year**
- **Canadian researchers tried pills on 27 patients and cured them all**

By ASSOCIATED PRESS and DAILY MAIL REPORTER

PUBLISHED: 20:26 GMT, 3 October 2013 | **UPDATED:** 20:48 GMT, 3 October 2013



FMT treatment for recurrent CDI

- >500 cases reported
- Resolution rate: 92%
- Adverse effects or death and relapsing are uncommon

FMT has moved into the mainstream in treating recurrent CDI

CME

Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections

Christina M. Surawicz, MD[1], Lawrence J. Brandt, MD[2], David G. Binion, MD[3], Ashwin N. Ananthakrishnan, MD, MPH[4], Scott R. Curry, MD[5], Peter H. Gilligan, PhD[6], Lynne V. McFarland, PhD[7,8], Mark Mellow, MD[9] and Brian S. Zuckerbraun, MD[10]

Management of recurrent CDI (RCDI)

19. The first recurrence of CDI can be treated with the same regimen that was used for the initial episode. If severe, however vancomycin should be used. The second recurrence should be treated with a pulsed vancomycin regimen. (Conditional recommendation, low-quality evidence)
20. If there is a third recurrence after a pulsed vancomycin regimen, fecal microbiota transplant (FMT) should be considered. (Conditional recommendation, moderate-quality evidence)
21. There is limited evidence for the use of adjunct probiotics to decrease recurrences in patients with RCDI. (Moderate recommendation, moderate-quality evidence)
22. No effective immunotherapy is currently available. Intravenous immune globulin (IVIG) does not have a role as sole therapy in treatment of RCDI. However, it may be helpful in patients with hypogammaglobulinemia. (Strong recommendation, low-quality evidence)

FMT for the treatment of IBD

AP&T Alimentary Pharmacology and Therapeutics

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

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

Results

Of the 5320 articles identified, 17 fulfilled the inclusion criteria, none of which were controlled trials. There were nine case series/case reports of patients receiving FMT for management of their IBD, and eight where FMT was for the treatment of infectious diarrhoea in IBD. These 17 articles reported on 41 patients with IBD (27 UC, 12 Crohn's, 2 unclassified) with a follow-up period of between 2 weeks and 13 years. Where reported, FMT was administered via colonoscopy/enema (26/33) or via enteral tube (7/33). In patients treated for their IBD, the majority experienced a reduction of symptoms (19/25), cessation of IBD medications (13/17) and disease remission (15/24). There was resolution of *C. difficile* infection in all those treated for such (15/15).

76% of patients with IBD experienced a reduction in symptoms

77% were able to stop taking medications for IBD

63% entered remission

Fecal Microbiota Transplantation in Ulcerative Colitis: Review of 24 Years Experience

Thomas Borody, MD, PhD, FACG, Antony Wettstein, MBBS(Hons), Jordana Campbell, BSc, Sharyn Leis, B Nursing, Margaux Torres, BSc, Sarah Finlayson, BScAdv (Hons), Anna Nowak, BMedSc. Centre for Digestive Diseases, Five Dock, NSW, Australia.

Methods: A review of all UC patients who underwent FMT at our centre was conducted. UC diagnosis was confirmed clinically, endoscopically, and histologically. Patients with indeterminate colitis or Crohn's Disease were excluded from the analysis. Sixty-two patients (40M; m 42.3 +/- 11.5y: 22F m 48.45 +/- 16.49y) with active UC and follow-up results were included in the analysis. Clinical remission was defined as a 0-1 modified Powell-Tuck index and partial remission as a ≥2 point decrease. Non-response was defined as ≤2 point decrease, unchanged score, increase in score over two consecutive visits, surgical intervention, or FMT-related adverse event requiring treatment cessation.

Results: Overall, 91.9% of patients responded to FMT. Of these, 67.7% of patients (42/62) achieved complete clinical remission, and 24.2% of patients (15/62) achieved partial response. The remaining 8% (5/62) were treatment failures. Improvement in CRP and ESR correlated with clinical response observed in FMT patients. Twenty-one patients underwent repeat colonoscopy with a mean time to follow-up of 33 mths (range 1-198 mths). Of these 12/21 (57.1%) were found to have profound mucosal healing with a normal mucosal appearance, return of vascular pattern and no histological inflammation, but in one patient scarring was seen in areas of previously severe inflammation. A further eight patients (8/21, 38.1%) achieved normalisation of mucosa but had some isolated areas of patchy, mild inflammation. One patient (1/21, 4.8%) had remaining active colitis. FMT was well tolerated and produced no significant adverse events.

FMT for the treatment of IBS

- Diarrhea-predominant IBS

55 cases reported

- Cure rate : 36%
- Decrease symptoms: 16%

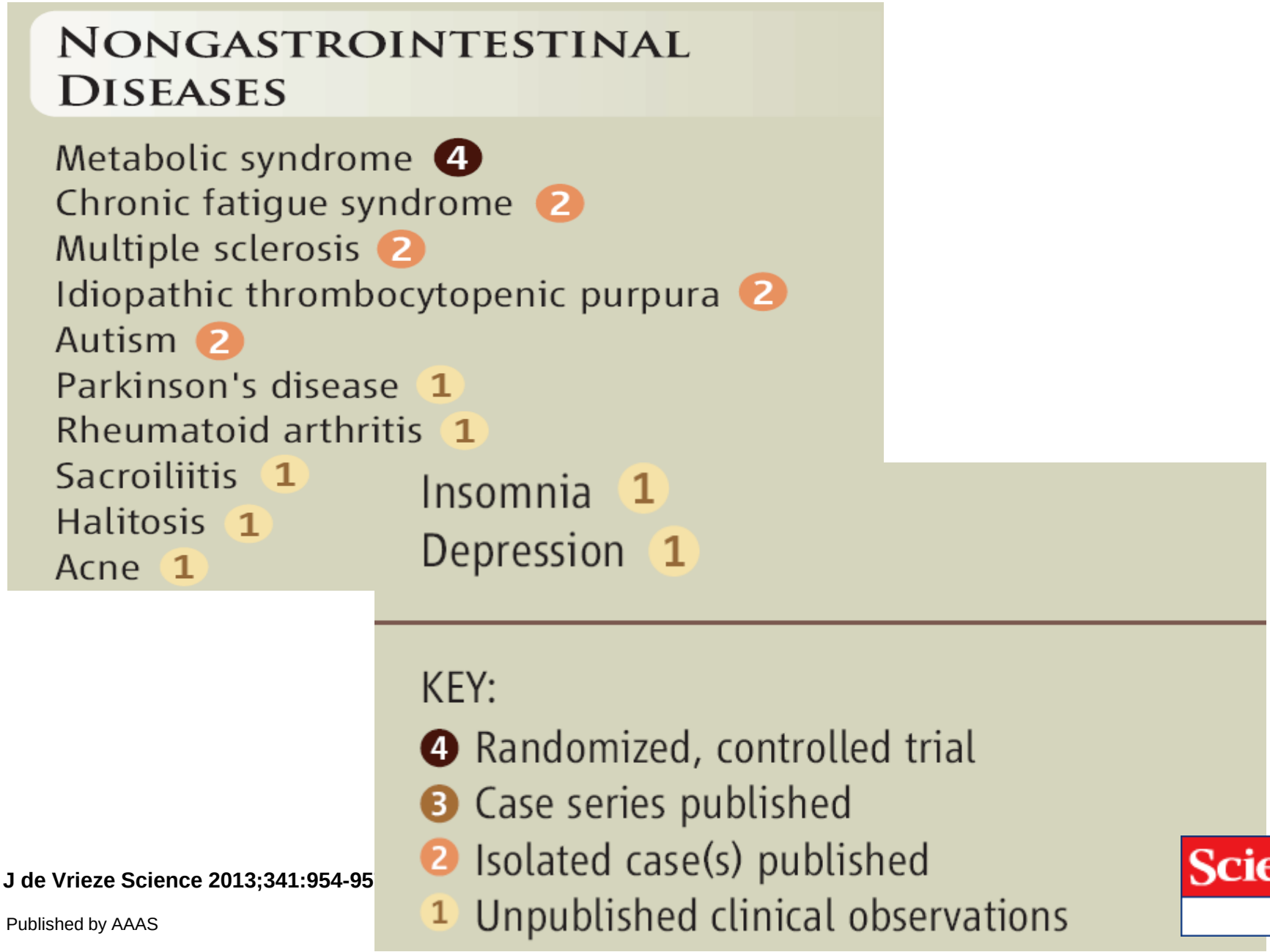
FMT was applied for the treatment of more than 300 patients with D-IBS

- Constipation-predominant IBS

45 cases reported

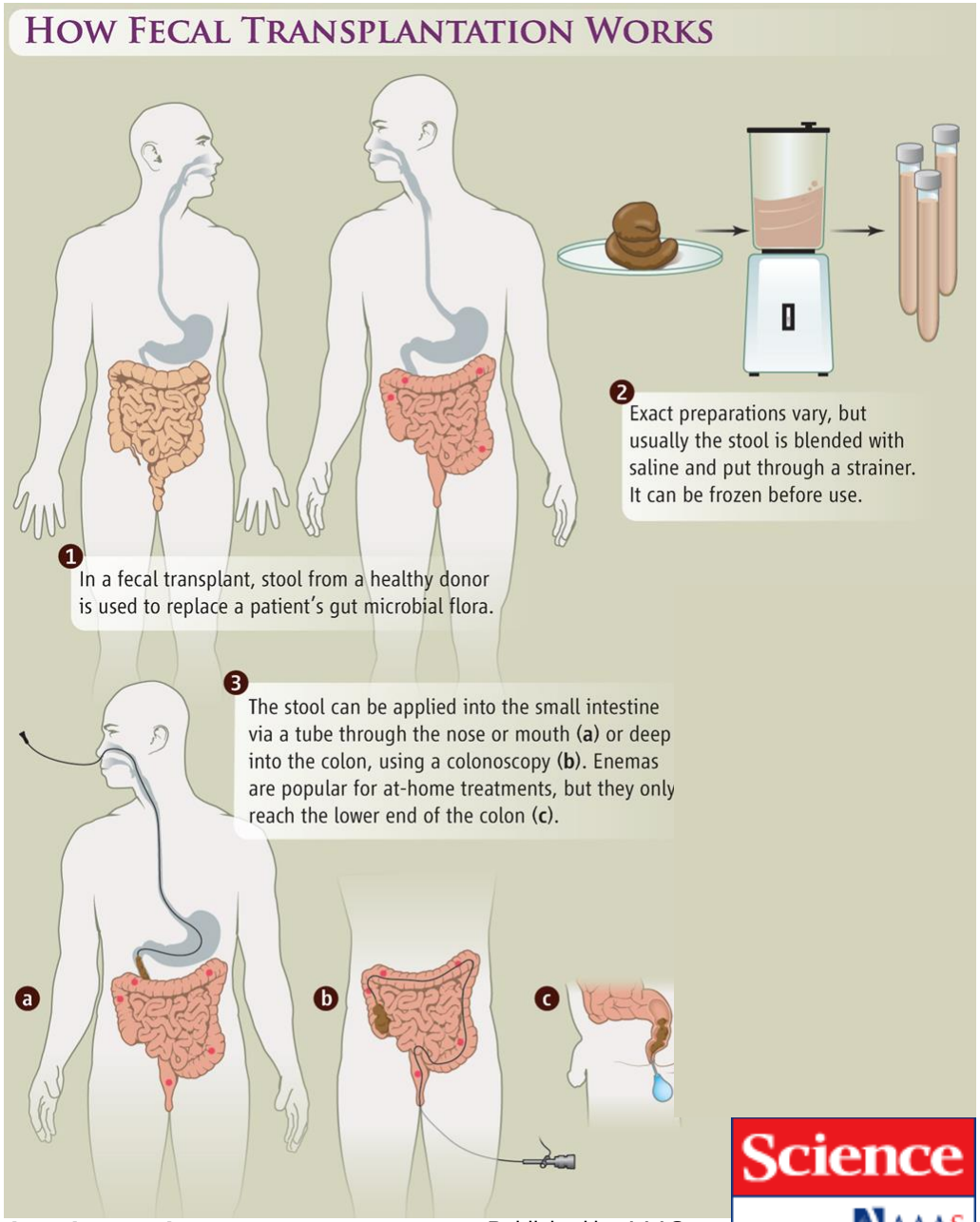
- 89% experience symptoms relief immediately after FMT
- 60% claim the improvement last for months

FMT for the treatment of Non-gastrointesitinal disease



J de Vrieze Science 2013;341:954-95

Current Methodology



J de Vrieze Science 2013;341:954-957 Published by AAAS

1 How to screen donor ?

2 How to process feces ?

Which diluent should be used?

3 How to perform?

How much stool is needed?

Which route of administration is best?

Fecal microbiota transplantation and donor standardization

Casey Owens, Elizabeth Broussard, and Christina Surawicz

Table 1. Infectious disease screening for FMT

Test	Pathogen(s) screened for
Blood	
Serology	Hepatitis A virus IgM, hepatitis B core IgM and IgG, hepatitis B surface antigen, hepatitis B surface antibody IgM, hepatitis C virus IgG
Serology	HIV type 1 and 2
Serology	Fluorescent treponemal antibody – absorption (syphilis)
Stool	
PCR (preferred to enzyme immunoassay)	*C. difficile* toxin B
Antigen	*Giardia*, rotavirus, *Cryptosporidium*
Microscopic exam	*Cyclospora*, *Cryptosporidium*, *Isospora* (acid-fast stain), and ova and parasites
Culture	Shiga toxin-producing *Escherichia coli*, *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, non-cholera *Vibrio*, *Plesiomonas*, *Aeromonas*

Box 1. Criteria for selecting a donor for FMT

Donors should meet the following criteria:

- No known communicable disease.
- No recent (3 months) antibiotic use.
- No history of diarrhea.
- No history of an immune disorder.
- No concurrent immunosuppressive agents.
- No history of inflammatory bowel disease, chronic constipation, or irritable bowel syndrome.
- No history of malignancy – non-melanoma skin cancer excluded.
- No recent (6 months) travel to endemic diarrhea areas.
- No current antineoplastic agent therapy.
- No current gastrointestinal symptoms.
- No risk factors – intravenous drug abuse, high-risk sexual behaviors, tattoos, current or historical incarceration, or body piercing (6 months).

Although not strict contraindications to donor eligibility, the following items are appropriate to consider with regard to excluding a donor:

- Diabetes mellitus type II or metabolic syndrome.
- History of major gastrointestinal surgery.
- Chronic pain syndromes.
- Systemic autoimmune disorders.
- Atopic diseases including eczema, asthma, or eosinophilic disorders of the gastrointestinal tract.

Outcomes Achieved in Patients Treated With Intestinal Microbiota Transplantation for *Clostridium difficile* Infection and Related Conditions, Excluding Retreatments After Treatment Failure, by Characteristics of the Procedure

Procedure characteristics	Studies, no.	Patients with outcome/patients in sample (%)			
		Resolution[a]	Relapse[b]	Deaths due to treated condition	Deaths due to any cause
Diluent					
Normal saline	20	169/196 (86.2)	5/169 (3.0)	4/196 (2.0)	11/196 (5.6)
Water	1	64/65 (98.5)	5/64 (7.8)	0/65 (0.0)	1/65 (1.5)
Other[e]	3	31/35 (88.6)	1/31 (3.2)	0/35 (0.0)	1/35 (2.9)
NR	4	20/21 (95.2)	0/20 (0.0)	0/21 (0.0)	0/21 (0.0)
Stool weight, g					
<50	9	53/64 (82.8)	2/53 (3.8)	0/64 (0.0)	2/64 (3.1)
≥50	7	100/116 (86.2)	1/100 (1.0)	3/116 (2.6)	6/116 (5.2)
NR	12	131/137 (95.6)	8/131 (6.1)	1/137 (0.7)	5/137 (3.6)
IMT suspension volume, mL					
<200	5	32/40 (80.0)	2/32 (6.2)	0/40 (0.0)	3/40 (7.5)
200–500	13	98/114 (86.0)	4/98 (4.1)	3/114 (2.6)	5/114 (4.4)
>500	2	107/110 (97.3)	5/107 (4.7)	0/110 (0.0)	1/110 (0.9)
NR	8	47/53 (88.7)	0/47 (0.0)	1/53 (1.9)	4/53 (7.5)
Instillation method[c]					
Colonoscope	9	55/62 (88.7)	3/55 (5.4)	0/62 (0.0)	0/62 (0.0)
Enema	11	105/110 (95.4)	5/105 (4.8)	1/110 (0.9)	5/110 (4.5)
Gastroscope or NJ tube	4	55/72 (76.4)	2/55 (3.6)	3/72 (4.2)	7/72 (9.7)
Rectal catheter	2	44/46 (95.6)	0/44 (0.0)	0/46 (0.0)	1/46 (2.2)
>1 method	2	19/21 (90.5)	1/19 (5.3)	0/21 (0.0)	0/21 (0.0)
NR	1	6/6 (100.0)	0/6 (0.0)	0/6 (0.0)	0/6 (0.0)
Pre-IMT treatment					
Vancomycin or metronidazole[f]	6	150/164 (91.5)	5/150 (3.3)	3/164 (1.8)	6/164 (3.7)
Antibiotics[g] and bowel lavage	2	33/35 (94.3)	4/33 (12.1	0/35 (0.0)	0/35 (0.0)
Other[h]	8	43/50 (86.0)	2/43 (4.6)	0/50 (0.0)	3/50 (6.0)
NR	12	58/68 (85.3)	0/58 (0.0)	1/68 (1.5)	4/68 (5.9)

Abbreviations: CDI, Clostridium difficile infection; IMT, intestinal microbiota transplantation; NR, not reported

E Gough, H Shaikh, AR Manges - Clinical infectious diseases, 2011.

Future direction

- Controlled studies to evaluate the best methodology for FMT
- Long –term studies to assess of risks of manipulation of gut microbiota of patients
- Identified the key microbes in feces contribute to the beneficial effects
- Adequate and well-controlled studies to evaluate the therapeutic potential of FMT for treatment of other diseases

Conclusion

- Feces is a biologically active, complex mixture of gut microbes.
- FMT is highly effective for recurrent CDI(92%)
- FMT show potential for the treatment for IBD and IBS. However, there is no randomized control trial and long-term outcomes are needed
- Gut microbiota associated with a variety of non-gastrointenisal disease, including Pakinson's disease, diabetes, liver cancer and so on. Further validated studies are needed before the used of FMT

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Thanks for your attention