Fecal transplant: when and how?

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The challenge of MDR & XDR infections

1. Basic concepts in gut microbiota

2. Current use of FMT

3. Potential future use of FMT

Human microbiota

- **Microbiota –** The community of microorganisms present in a defined environment
- **Microbiome -** The sum of microbial genes in a microbiota
- **Bacterial classification -** All organisms are classified in a hierarchical manner.
- **Adult gut microbiota:** ~10^{14} microorganism (95% bacteria); ~1000 bacterial species, dominant phyla:

Phylum	Characteristics	Examples
Firmicutes (50%)	Gram-positive; diverse in their morphology (rod, coccoid, spiral), physiology (anaerobic, aerobic); include commensal and beneficial bacteria	*Lactobacillus*; *Ruminococcus*; *Clostridium*; *Staphylococcus*; *Enterococcus*; *Faecalibacterium*
Bacteroidetes (40%)	Gram-negative; composed of 3 large classes widely distributed in the environment, including soil, seawater, and guts of animals	*Bacteroides*; *Prevotella*
Proteobacteria	Gram-negative; include a wide variety of pathogens	*Escherichia*; *Pseudomonas*
Actinobacteria	Gram-positive; diverse morphology; major antibiotic producers in the pharmaceutical industry	*Bifidobacterium*; *Streptomyces*; *Nocardia*

What are the functions of gut microbiota ?

- **Metabolism**
  - Fatty acids, glucose and bile acids
  - Liberating nutrients and/or energy from otherwise inaccesible dietary substrates
  - Production of vitamines and co-factors

- **Stimulating the immune system**
  - Priming of systemic immune cells

- **Host defense against pathogens**
  - Production of bacteriocins
  - Stimulation of production of antimicrobial peptides and mucus by intestinal cells
  - Competition for space and nutrients - Colonization resistance

Fecal microbiota transplantation in clinical practice

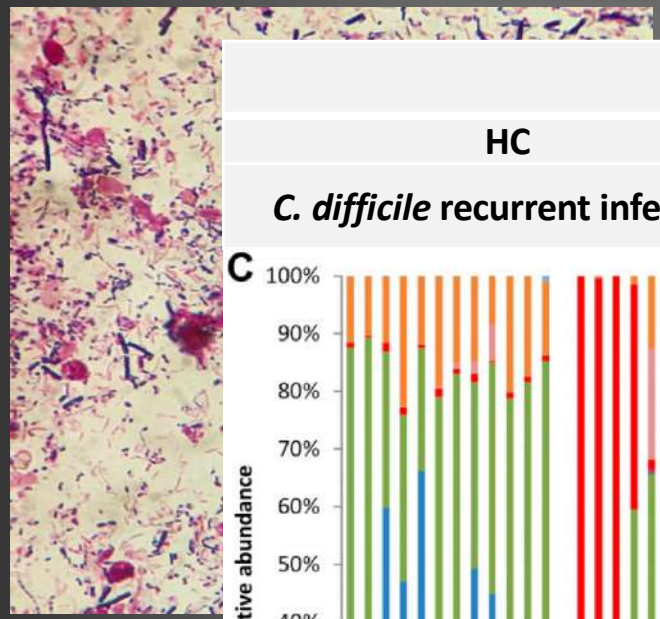
Fecal microbiota transplantation (FMT) or (IMT) is the transfer of stool samples from healthy donors to a patients's gastrointestinal tract using different routes

1. Treatment of infections caused by *C. difficile*

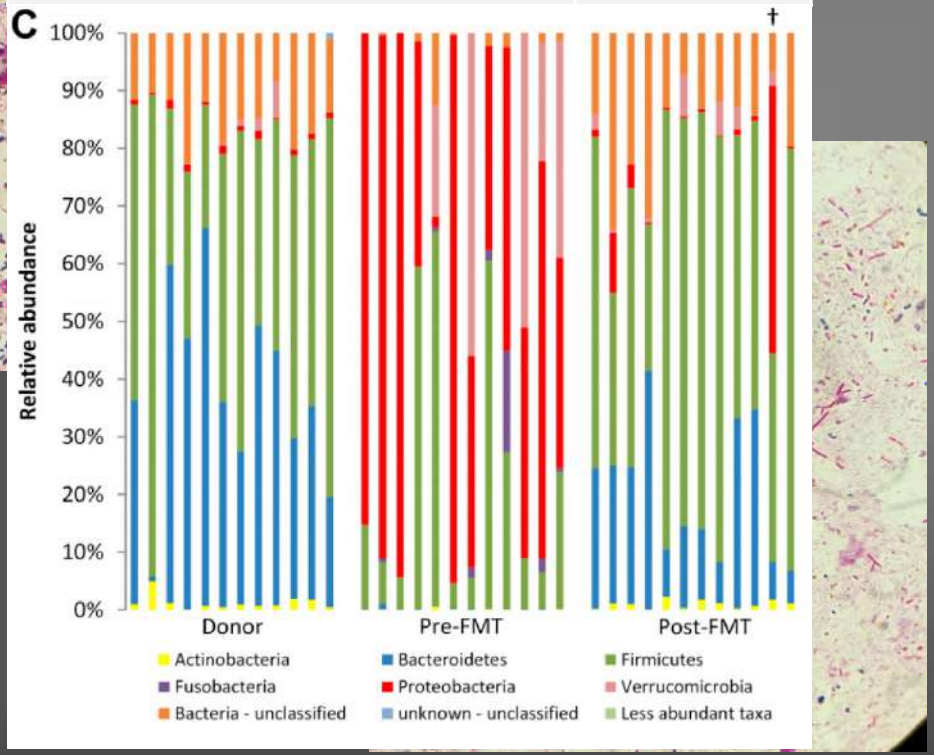
2. Treatment of recurrent urinary tract infections

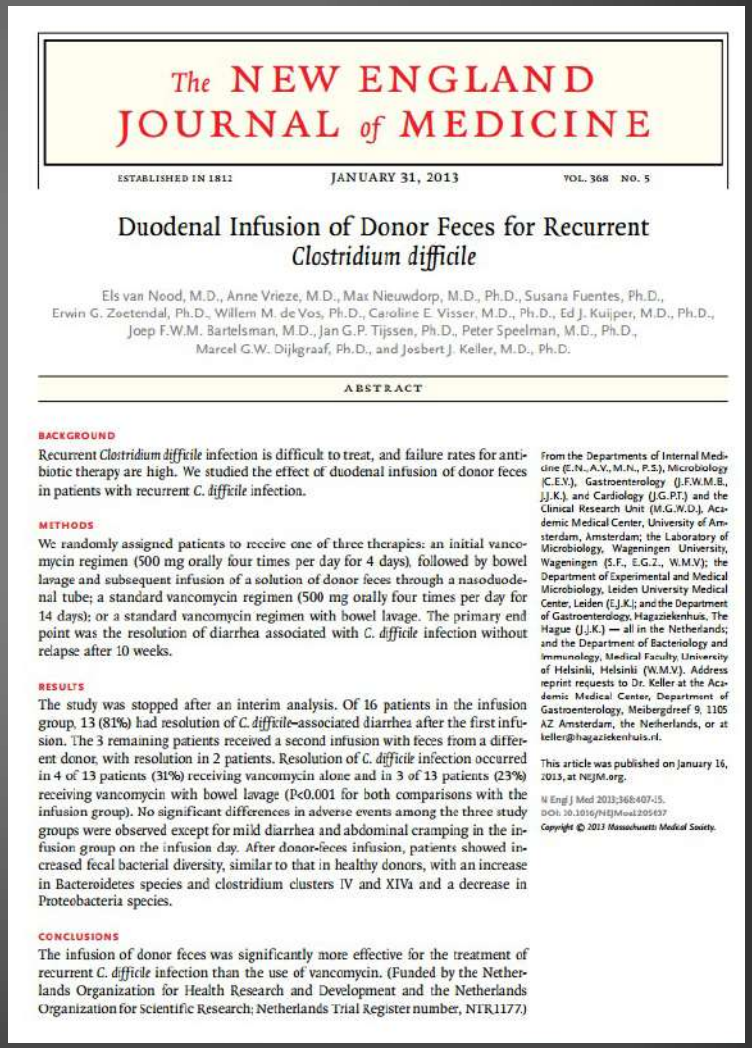
3. Removal of MDR bacteria from the gut

Treatment of infections caused by *C. difficile*



	n
HC	12
***C. difficile* recurrent infection**	12





The NEW ENGLAND JOURNAL of MEDICINE

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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., 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.

ABSTRACT

BACKGROUND

Recurrent *Clostridium difficile* infection is difficult to treat, and failure rates for antibiotic therapy are high. We studied the effect of duodenal infusion of donor feces in patients with recurrent *C. difficile* infection.

METHODS

We randomly assigned patients to receive one of three therapies: an initial vancomycin regimen (500 mg orally four times per day for 4 days), followed by bowel lavage and subsequent infusion of a solution of donor feces through a nasoduodenal tube; a standard vancomycin regimen (500 mg orally four times per day for 14 days); or a standard vancomycin regimen with bowel lavage. The primary end point was the resolution of diarrhea associated with *C. difficile* infection without relapse after 10 weeks.

RESULTS

The study was stopped after an interim analysis. Of 16 patients in the infusion group, 13 (81%) had resolution of *C. difficile*–associated diarrhea after the first infusion. The 3 remaining patients received a second infusion with feces from a different donor, with resolution in 2 patients. Resolution of *C. difficile* infection occurred in 4 of 13 patients (31%) receiving vancomycin alone and in 3 of 13 patients (23%) receiving vancomycin with bowel lavage ($P<0.001$ for both comparisons with the infusion group). No significant differences in adverse events among the three study groups were observed except for mild diarrhea and abdominal cramping in the infusion group on the infusion day. After donor-feces infusion, patients showed increased fecal bacterial diversity, similar to that in healthy donors, with an increase in Bacteroidetes species and clostridium clusters IV and XIVa and a decrease in Proteobacteria species.

CONCLUSIONS

The infusion of donor feces was significantly more effective for the treatment of recurrent *C. difficile* infection than the use of vancomycin. (Funded by the Netherlands Organization for Health Research and Development and the Netherlands Organization for Scientific Research; Netherlands Trial Register number, NTR1177.)

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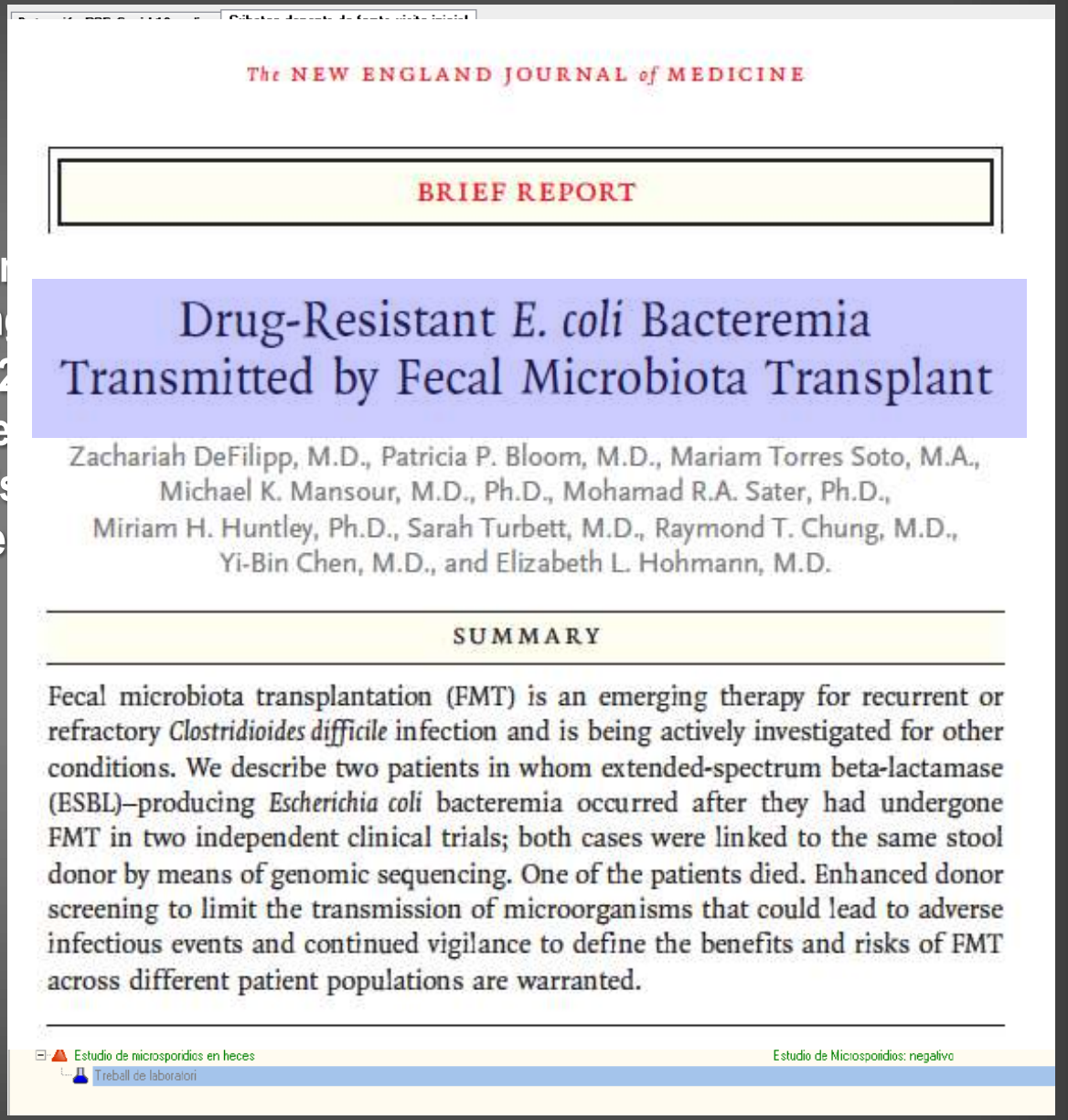
N Engl J Med 2013;368:407-15.
DOI: 10.1056/NEJMoa1205037

Weingarden AR et al. (2014) Am J Physiol Gastrointest Liver Physiol 306; G310

Circuit to follow:

1. Donor recruitment
2. Face-to-face visit: physical exa
   followed by analytical screenin
3. Start the donation process for 2
4. Second donor screening to rule
   intercurrent process during thi
5. Release of samples for therape

Initial screening of the stool donor



The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Drug-Resistant *E. coli* Bacteremia Transmitted by Fecal Microbiota Transplant

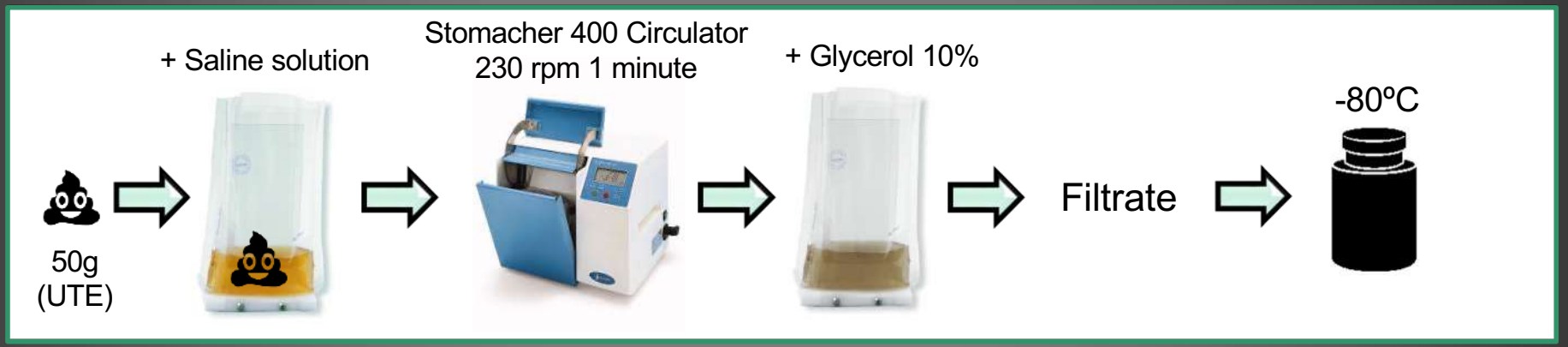
Zachariah DeFilipp, M.D., Patricia P. Bloom, M.D., Mariam Torres Soto, M.A., Michael K. Mansour, M.D., Ph.D., Mohamad R.A. Sater, Ph.D., Miriam H. Huntley, Ph.D., Sarah Turbett, M.D., Raymond T. Chung, M.D., Yi-Bin Chen, M.D., and Elizabeth L. Hohmann, M.D.

SUMMARY

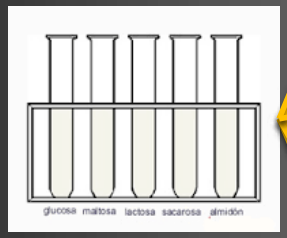
Fecal microbiota transplantation (FMT) is an emerging therapy for recurrent or refractory *Clostridioides difficile* infection and is being actively investigated for other conditions. We describe two patients in whom extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* bacteremia occurred after they had undergone FMT in two independent clinical trials; both cases were linked to the same stool donor by means of genomic sequencing. One of the patients died. Enhanced donor screening to limit the transmission of microorganisms that could lead to adverse infectious events and continued vigilance to define the benefits and risks of FMT across different patient populations are warranted.

Estudio de microsporidios en heces — Estudio de Microsporidios: negativo
Treball de laboratori

From the donor to the FMT



Efficacy rates in "recurrent" *Clostridium difficile* infection treated with different FM preparations



Fresh feaces filtered

	1 infus	>1 infus
NG tube vs vanco vs vanco*[1]	81% vs 31% vs 23%	93%
Colon vs NG tube[2]	80% vs 60%	
Enema vs vanco tapered[7]	43.8% vs 58.3%	
Colonoscopy[8] vs vanco tap	90% vs 26%	
Frozen vs fresh[3]	83.5% vs 85.1%	
Frozen capsulized[4] (15/2 days)	70%	90%
Frozen capsulized (40) vs. Frozen colonoscopy[5]	96.2% vs 96.2%	
Freeze dried[6]	88%	

* vanco + bowel lavage

[1] Van Nood , et al. *N Engl J Med 2013; 368: 407* (RCT)
[2] *Youngster I, et al. Clin Infect Dis 2014; 58: 1515* (RCT)
[3] Lee Ch, et al. *JAMA 2016; 315: 142* (RCT)
[4] Youngster I, et al. *JAMA 2014; 312: 1772*
[5] Kao D, et al. *JAMA 2017; 318: 1985* (RCT)
[6] Staley Ch, et al. *Am J Gastroenterol 2017;112: 940*
[7] Hota SS, et al. *CID 2017; 64: 265* (RCT), [8] Cammarota G, et al. *Aliment Ph Th 2015; 41: 835* (RCT)

Treatment of CDI – Phase 3

Antibacterial agent	"Route of administration"	Pharma. Indust.
RBX2660*	Enema	Ferring
Drugs (2022) 82: 1527	262 patients enrolled (one o more episodes after primary episode)	
one administration by enema	Treatment success	70.4% in RBX2660 group
	"	57.5% in placebo group
SER-109**	Oral	Seres Therapeutics
NEJM (2022) 386: 220.	182 patients enrolled (3 o more episodes of CDI in 12 months)	
4 capsules once daily for 3 days	Recurrent CDI.	12% in SER-109 group
	"	40% in placebo group
BB128	Colonoscopy	BiomeBank

* Accepted by FDA Nov. 30th, 2022; **Highly purified Firmicutes spores

Overall considerations about the FMT

- Amount of fecal material
  - <50 g 71% s.i. / 88% m.i.; 51-100 g 81% s.i / 97% m.i.
- Single versus multiple infusions
  - 76% vs 93%
- Route of delivery of fecal material (single vs multiple infusions)
  - Duodenal, 73% vs 81%
  - Capsule, 80% vs 92%
  - Colonoscopy, 78% vs 98%
  - Enema, 56% vs 92%

Ianiro et al. (2018) UEG Journal 6: 1232

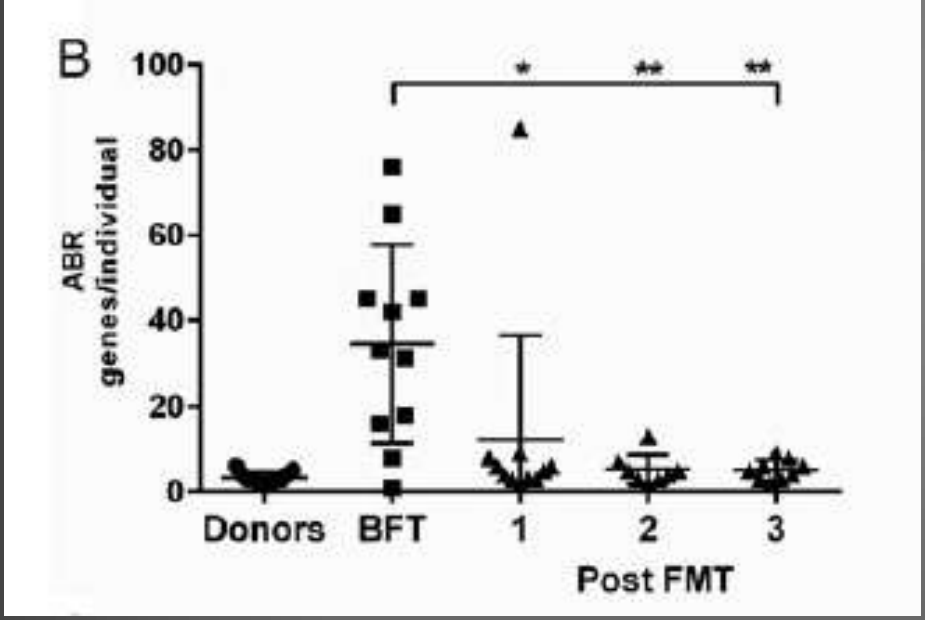
Treatment of recurrent urinary tract infections

- Increase abundance of uropathogenic organisms in the gut is a direct factor for ocurrence of rUTIs with the same microorganism
- Several studies showed that patients with rUTI who were treated with FMT to rCDI had a reduction in their ocurrence of rUTI

- Tariq R (2017) CID 65: 1745; Aira A et al. (2021) Infect Dis Ther 10: 1065; Wang et al. (2018) OFID 5: ofy016; Biehl LM (2018) Infection 46: 871, Bier N (2020) OFID 7: 830; Jeney S (2020) Obstet Gynecol 136: 771

Millan B et al: Fecal Microbial Transplants Reduce Antibiotic-resistant Genes in Patients With Recurrent *Clostridium difficile* Infection

Clinical Infectious Diseases 2016; 62: 1479



1 = 1-4 weeks
2 = 4-8 weeks
3 = 8-22 weeks

FMT is effective in the eradication of pathogenic antibiotic-resistant organisms and elimination of ABR genes.

Removal of MDR bacteria from the gut

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journal homepage: www.elsevier.com/locate/jinf

Review

Fecal microbiota transplantation for Carbapenem-Resistant Enterobacteriaceae: A systematic review

Jordán Macareño-Castro[a], Adán Solano-Salazar[a], Le Thanh Dong[b], Md Mohiuddin[c], J. Luis Espinoza[d,*]

10 studies (209 patients)

3 st. (53 pts.). Retrospective

7 st. (156 pts.) Prospective

55/90 cases at one month after FMT

74/94 cases at the end of the follow up (6-12 month)

underlying conditions. In conclusion, FMT appears to be safe and effective in eradicating CRE colonization, however, more studies, especially randomized trials, are needed to validate the safety and clinical utility of FMT for CRE eradication.

Other potential future applications

1. **FMT ameliorates intestinal GvHD in allogeneic hematopoietic cell transplant recipients (AutoBanking)**

   van Lier YF (2020) Science Translational Medicine 12: eaaz8926; Zhao et al. (2021) 12: 678476

2. **FMT and sepsis (Treatment)**

   Wey Y (2016) Critical Care 20: 332; Li Q et al. (2014) Am J Gastroenter 109: 1832

3. **Treatment of IBD (Chron diseases and ulcerative colitis)**

   It seems that there is a strong donor effect (superdonor) on IBD

Conclusions

1. The gut microbiota can be seen as a separate organ with both local and systemic function.
2. FMT was more effective than vancomycin (RR: 0.23, 95%CI: 0.07-080) to treat CDI
3. Clinical resolution was 92% (95%CI 89-94)
4. Lower delivery of FMT was superior to upper (95% vs 88%)
5. No differences between fresh and frozen preparations
6. Consecutive courses increase the effectiveness
7. In the future we will probably see more applications (397 studies on clinicaltrials.gov related to FMT)

Thanks