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# Fecal Microbiota Transplantation in C. diff. colitis – Benefits and Limitations

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# Case

28 year old mother of a two year old daughter

4/2013 Cystitis: Therapy with Amoxicillin/Clavulanic acid

- 5/2013 Diarrhea; Clostridium difficile toxin positive;  
Therapy with metronidazole for 2 weeks
- 6/2013 again diarrhea; Clostridium difficile toxin positive;  
Therapy with vancomycine orally
- 7/2013 again Diarrhea; C. diff toxin negative  
weight loss of 10 kg; unable to work; unable to care for the  
daughter

# Is administration of probiotics useful when giving antibiotics?

antibiotics-associated diarrhea

	Probiotic	Control	P value*
<b>Diarrhoea</b>			
Yes	7 (12%)	19 (34%)	0.007
No	50 (88%)	37 (66%)	
No of patients	57 <sup>†</sup>	56 <sup>†</sup>	
<b><i>C difficile</i> toxin</b>			
Positive	0	9 (17%)	0.001
Negative	56 (100%)	44 (83%)	
No of patients	56 <sup>‡</sup>	53 <sup>‡</sup>	

\*Fisher's exact test.

<sup>†</sup>22/135 patients lost to follow-up or withdrew.

<sup>‡</sup> 4/113 patients not tested for *C difficile*.

## C. diff colitis – clinical impact

- most frequent form of hospital-acquired diarrhea<sup>1</sup>
- costs: > 1.000.000.000 \$ per year in the US<sup>2</sup>
- toxin A: enterotoxin; permeability, secretion ↑
- toxin B: cytotoxin; inflammation
- new, more virulent strains (BI/NAP1/027 & Co.), quinolon-resistance, gene-deletion: toxin-production ↑<sup>3</sup>
- US numbers 2008 – mortality:
  - 6x more deaths as compared to all other enteropathogens together
- increasing number of cases without antibiotic pre-treatment
- risk factors: age, co-morbidity, immunosuppression.....

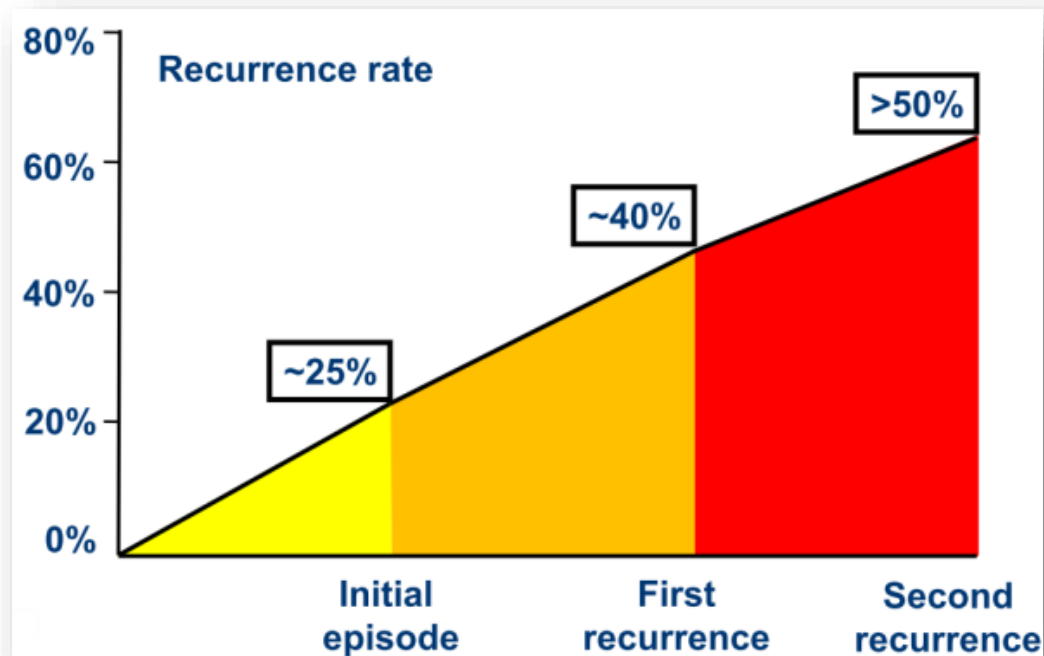
1. Lipp MJ, J Gastroenterol Hep. 2012

2. Lipp MJ, J Clin Gastroentol. Hepatol. 2012

3. O'Connor JR; Gastroenterology 2009

# Relapsing C. diff. Infection (rCDI)

- suggested **definition**: recurrence of symptoms within 8 weeks after successful antibiotic therapie<sup>1</sup>
- clinical definition: no repeated C. diff. Assay necessary
- recurrence – how frequent?
  - „only“ around 10-30%...
  - ...BUT if 1x relapse  
40-60% (up to 65%) further relapses <sup>2,3</sup>



# Therapy Recommendations - C. diff Colitis

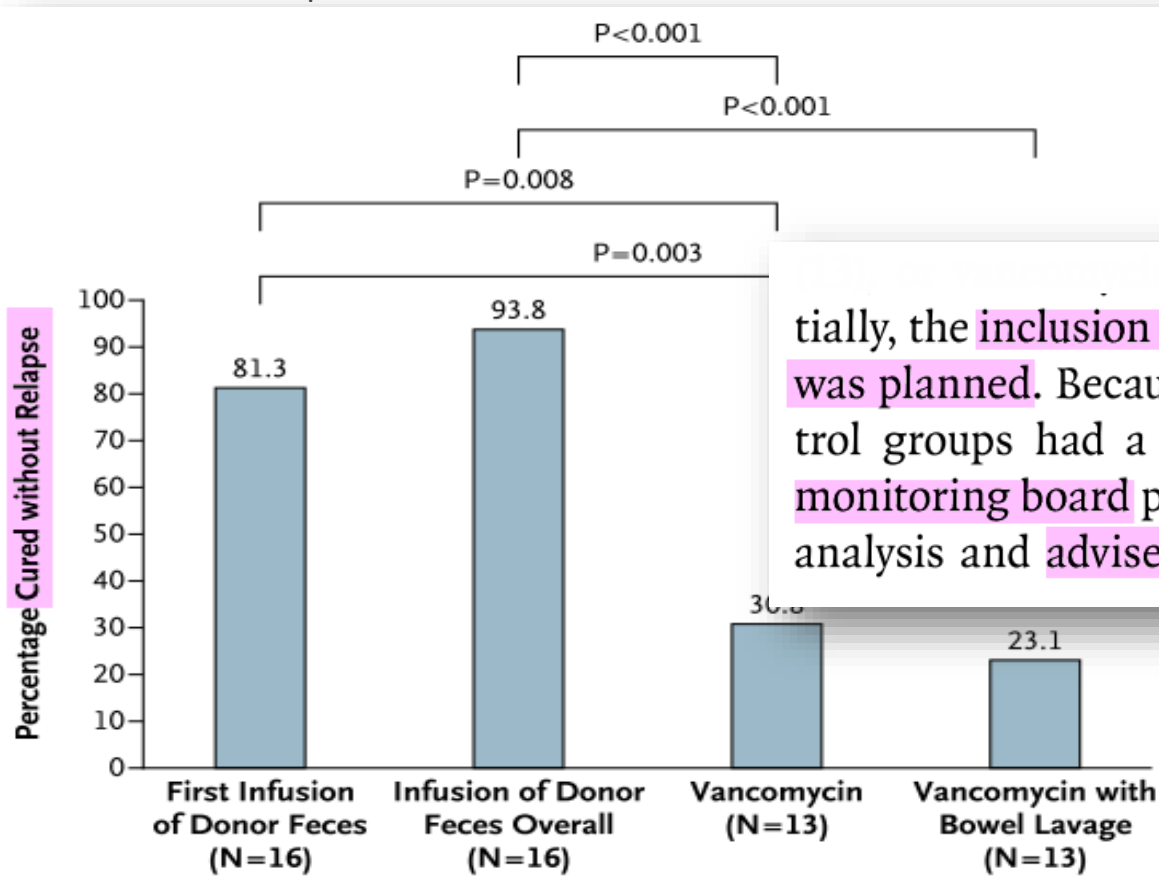
## CDC practice guidelines for treating *Clostridium difficile* infection

CLINICAL DEFINITION	SUPPORTIVE CLINICAL DATA	RECOMMENDED TREATMENT
<b>Initial episode, mild or moderate</b>	White blood cell (WBC) count $\leq 15,000$ cells/mL	Metronidazole 500 mg three times per day by mouth for 10–14 days
<b>Initial episode, severe</b>	WBC count $\geq 15,000$ cells/mL Serum creatinine $\geq 1.5$ times baseline	<u>Vancomycin 125 mg four times per day by mouth for 10–14 days</u>
<b>Initial episode, severe, complicated, or fulminant</b>	Severe <i>C difficile</i> infection complicated with hypotension, shock, ileus, or megacolon	Vancomycin 500 mg four times per day by mouth or nasogastric tube, <b>plus</b> metronidazole 500 mg every 8 hours intravenously If complete ileus, consider adding rectal instillation of vancomycin
<b>First recurrence</b>		<u>Same as for initial episode</u>
<b>Second recurrence</b>		<u>Vancomycin in a tapered and/or pulsed regimen</u>

ADAPTED FROM COHEN SH, GERDING DN, JOHNSON S, ET AL; SOCIETY FOR HEALTHCARE EPIDEMIOLOGY OF AMERICA; INFECTIOUS DISEASES SOCIETY OF AMERICA. CLINICAL PRACTICE GUIDELINES FOR *CLOSTRIDIUM DIFFICILE* INFECTION IN ADULTS: 2010 UPDATE BY THE SOCIETY FOR HEALTHCARE EPIDEMIOLOGY OF AMERICA (SHEA) AND THE INFECTIOUS DISEASES SOCIETY OF AMERICA (IDSA). INFECT CONTROL HOSP EPIDEMIOL 2010; 31:431–455. COPYRIGHT 2010, UNIVERSITY OF CHICAGO PRESS.

# FMT in C. diff. colitis - Evidence

- Power calculation: randomisation of **at least 118 Pat.**
- **Inclusion criteria:**
- - a relapse after at least one course of adequate antibiotic therapy ( $\geq 10$  days of vancomycin at a dose of  $\geq 125$  mg four times per day or  $\geq 10$  days of metronidazole at a dose of 500 mg three times per day).
- - diarrhea and a positive stool test for C. difficile toxin.



Initially, the inclusion of 40 patients per study group was planned. Because most patients in both control groups had a relapse, the data and safety monitoring board performed the interim efficacy analysis and advised termination of the trial, as

2. Van Nood E; NEJM 2013

# FMT - Procedure

- 30g of feces are sufficient!





# FMT - Procedure

- and then....?



VS.

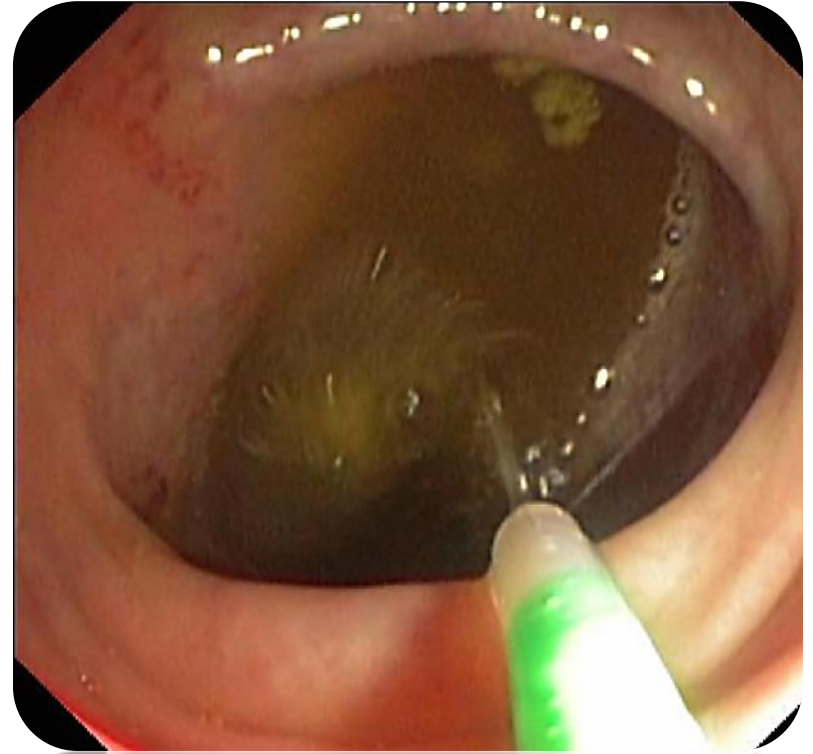


VS.



Trend in favor for lower GI route? – success 91.4% vs. 82.3%<sup>1</sup>

# FMT - Procedure



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- weight loss of 10 kg; unable to work; unable to care for the daughter

**8/2013; FMT regained 8 kg of weight, fully working**

**(writes nice e-mails every Christmas)**

# Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent *Clostridium difficile* Infection

## A Randomized Clinical Trial

Christine H. Lee, MD; Theodore Steiner, MD; Elaine O. Petrof, MD; Marek Smieja, MD, PhD; Diane Roscoe, MD; Anouf Nematallah, MD; J. Scott Weese, DVM; Stephen Collins, MBBS; Paul Moayyedi, MB; Mark Crowther, MD; Mark J. Ropeleski, MD; Padman Jayaratne, PhD; David Higgins, MB; Yingfu Li, PhD; Neil V. Rau, MD; Peter T. Kim, PhD

**OBJECTIVE** To determine whether frozen-and-thawed (frozen, experimental) FMT is noninferior to fresh (standard) FMT in terms of clinical efficacy among patients with recurrent or refractory CDI and to assess the safety of both types of FMT.

Comparable success rates (~85%)

**MAIN OUTCOMES AND MEASURES** The primary outcome measures were clinical resolution of diarrhea without relapse at 13 weeks and adverse events. Noninferiority margin was set at 15%.

**RESULTS** A total of 219 patients (n = 108 in the frozen FMT group and n = 111 in the fresh FMT group) were included in the modified intention-to-treat (mITT) population and 178 (frozen FMT: n = 91, fresh FMT: n = 87) in the per-protocol population. In the per-protocol population, the proportion of patients with clinical resolution was 83.5% for the frozen FMT group and 85.1% for the fresh FMT group (difference, -1.6% [95% CI, -10.5% to  $\infty$ ];  $P = .01$  for noninferiority). In the mITT population the clinical resolution was 75.0% for the frozen FMT group and 70.3% for the fresh FMT group (difference, 4.7% [95% CI, -5.2% to  $\infty$ ];  $P < .001$  for noninferiority). There were no differences in the proportion of adverse or serious adverse events between the treatment groups.

# FMT: Adverse events

## AGA SECTION

### Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook



**Table 2.** Adverse Events in Published Series of More Than 5 Patients Receiving FMT for CDI

bin,<sup>2</sup> Ashish Atreja,<sup>6</sup>

Authors	No.	Method of delivery	Follow-up	Adverse events
Van Nood et al <sup>4</sup>	16	Duodenal infusion	70 days	Diarrhea, 5; abdominal cramps, 5; belching, 3; nausea, 1; symptoms resolved in all within 3 hours
Youngster et al <sup>43</sup>	20	Nasogastric tube or colonoscopy	6 mo	Mild abdominal discomfort/bloating, 4; transient fever (day 2), 1
Rubin et al <sup>26</sup>	75	Nasogastric tube	60 days	No adverse events or deaths
MacConnachie et al <sup>27</sup>	15	Nasogastric tube	4–24 wk	No adverse events “related to transplant”; upper GI bleeding during the first month after FMT
Aas et al <sup>24</sup>	18	Nasogastric tube	90 days	Peritonitis in patient on peritoneal dialysis on day 3 (died “shortly thereafter”); pneumonia in patient with chronic obstructive
Mattila Hamilton				irregular first
Patel et al				sy that
Yoon et al				
Pathak et al	12	Colonoscopy, 11; nasoduodenal, 1	2–23 mo	No complications or FMT
Dutta et al <sup>40</sup>	27	Enteroscopy plus colonoscopy	10–34 mo	Low-grade fever, 5; bloating, 3; resolved within 12–24 h
Lee et al <sup>39</sup>	94	Enema	6–24 mo	No significant adverse events; 10% experienced transient constipation and excessive flatulence
Emanuelsson et al <sup>98</sup>	23	Rectal catheter	23	“A few” patients experienced temporary constipation (apparently soon after FMT)
Silverman et al <sup>37</sup>	7	Enema	4–14 mo	No adverse events but reported 1 patient with “postinfectious” IBS (mixed pattern)
Schwartz et al <sup>99</sup>	13	Colonoscopy	Not stated	Norovirus, 2 (2 days and 12 days after FMT); investigators speculated person-to-person rather than FMT transmission
Kelly et al <sup>42,a</sup>	80	Mixed	12 wk	Potentially related adverse events: Death: aspiration during colonoscopy with respiratory failure Hospitalizations: IBD flares, 4; postcolonoscopy abdominal pain, 1; fever, diarrhea, encephalopathy, pancytopenia in patient with lymphoma, 1 Nonserious adverse events: abdominal pain/bloating immediately after FMT, 3; “mucosal tear” at colonoscopy, 1; self-limited diarrhea, 3; fever, 1; IBD flare, 1

FMT associated SAE are rare



# FMT: open questions

## AGA SECTION

Update on Fecal Microbiota Transplantation 2015: Indications, Methodologies, Mechanisms, and Outlook



- Standardization
- Inclusion criteria for recipient and donor
- Costs
- Patient acceptance
- Risks (disease transmission, long-term effects)
- Fresh stool/frozen stool (open biome)
- Filtered supernatant may do it

Table 1. Suggested Donor Testing

Serological	Stool	Consider	Possibly
Hepatitis A virus/immunoglobulin M	<i>C difficile</i> toxin B (preferably by polymerase chain reaction)	<i>Giardia</i>	Cytomegalovirus
Hepatitis B surface antigen	Culture for enteric pathogens	<i>Cryptosporidium</i>	Human T-cell lymphoma virus
Antibody to hepatitis C virus	Ova and parasite examination, if travel history suggests	<i>Isospora</i> and <i>Cyclospora</i>	Epstein-Barr virus
Human immunodeficiency virus 1 and 2 enzyme immunoassay		<i>E coli</i> O157	<i>Dientamoeba fragilis</i>
Rapid plasma reagin (RPR)		Rotavirus	<i>Blastocystis hominis</i>
		Listeria	<i>Strongyloides stercoralis</i>
		Vibrio	<i>Entamoeba histolytica</i>
		Norovirus	<i>H pylori</i>
			<i>Schistosoma</i>
			JC virus
			Vancomycin-resistant enterococci
			Methicillin-resistant
			<i>Staphylococcus aureus</i>

# FMT: open questions

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Gastroenterology. 2016 Nov 17. pii: S0016-5085(16)35354-9. doi: 10.1053/j.gastro.2016.11.010. [Epub ahead of print]

## **Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With *Clostridium difficile* Infection.**

Ott SJ<sup>1</sup>, Waetzig GH<sup>2</sup>, Rehman A<sup>3</sup>, Moltzau-Anderson J<sup>4</sup>, Bharti R<sup>3</sup>, Grasis JA<sup>5</sup>, Cassidy L<sup>6</sup>, Tholey A<sup>6</sup>, Fickenscher H<sup>7</sup>, Seegert D<sup>2</sup>, Rosenstiel P<sup>3</sup>, Schreiber S<sup>8</sup>.

*“Stool was sterile-filtered to remove small particles and bacteria; the filtrate was transferred to patients in a single administration via nasojejun tube. .... A preliminary investigation of 5 patients with CDI shows that transfer of sterile filtrates from donor stool (FFT), rather than fecal microbiota, can be sufficient to restore normal stool habits and eliminate symptoms.”*

# FMT: - messages



- In relapsing C. diff. Infections FMT with very high success rates around 90%
- Patient acceptance is high (many requests in other indications such as IBS, multiple sclerosis, depression....but we only do rCDI!!)
- Many open questions with respect to practical application, however, all application forms seem to work (even sterile filtration)
- At present no conclusive data for other indications



# What's coming next?



**PharmaBiome will make microbiota therapy the new standard for the treatment of intestinal diseases.**

.....maybe.....



An aerial photograph of Zurich, Switzerland, showing the city's dense architecture, the Limmat river, and Lake Zurich. In the background, the Swiss Alps are visible with significant snow cover under a clear blue sky. The text "Thank you for your attention" is overlaid in the center of the image.

**Thank you for your attention**