What is important in Fecal Microbiota Transplantation; Practical aspects

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All there is to it?

1: donor:

2:

3: duodenal tube/colonoscopy

Background

- *Clostridium difficile* is ubiquitous
- High percentage of antibodies against toxin A/B in normal population
- Children high rate of asymptomatic carriers
- Change in microbiota predispose for CDI:

Depletion Bacteroides

Increase Enterobacteriaceae

Disturbance..

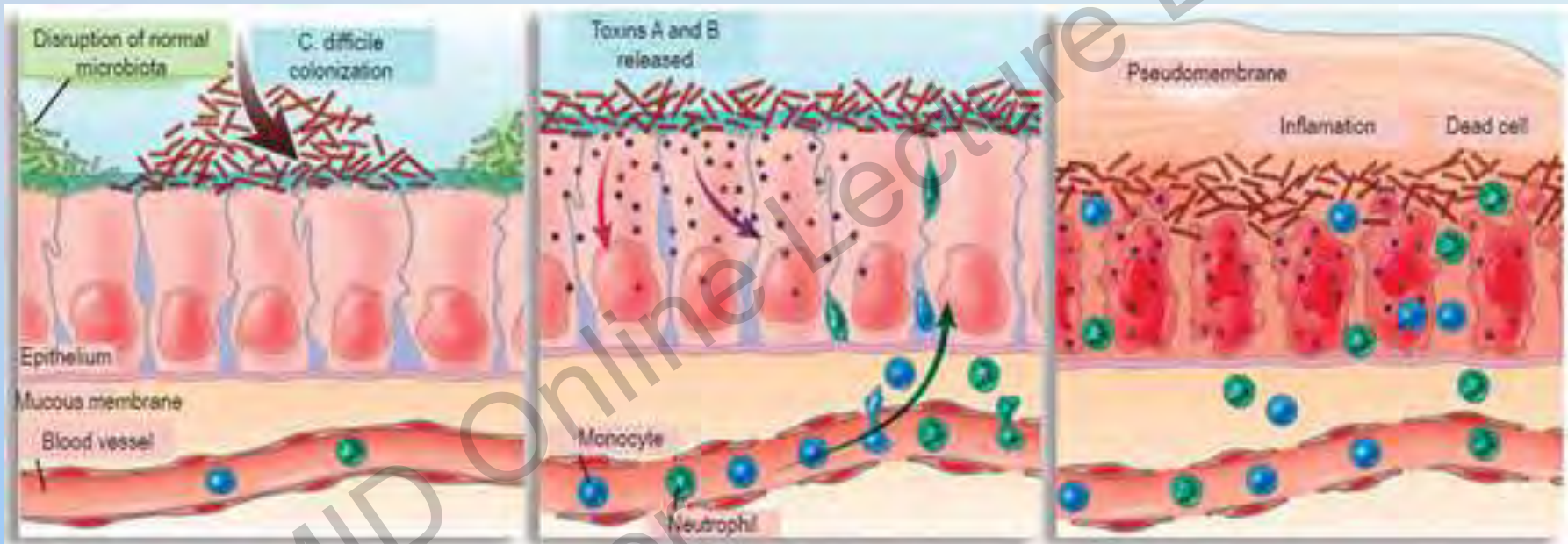
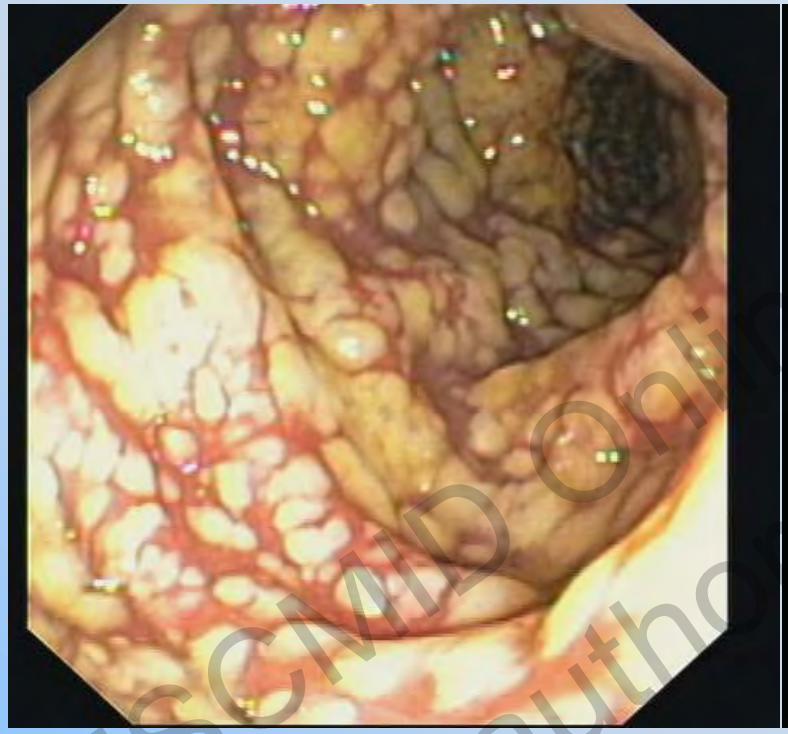
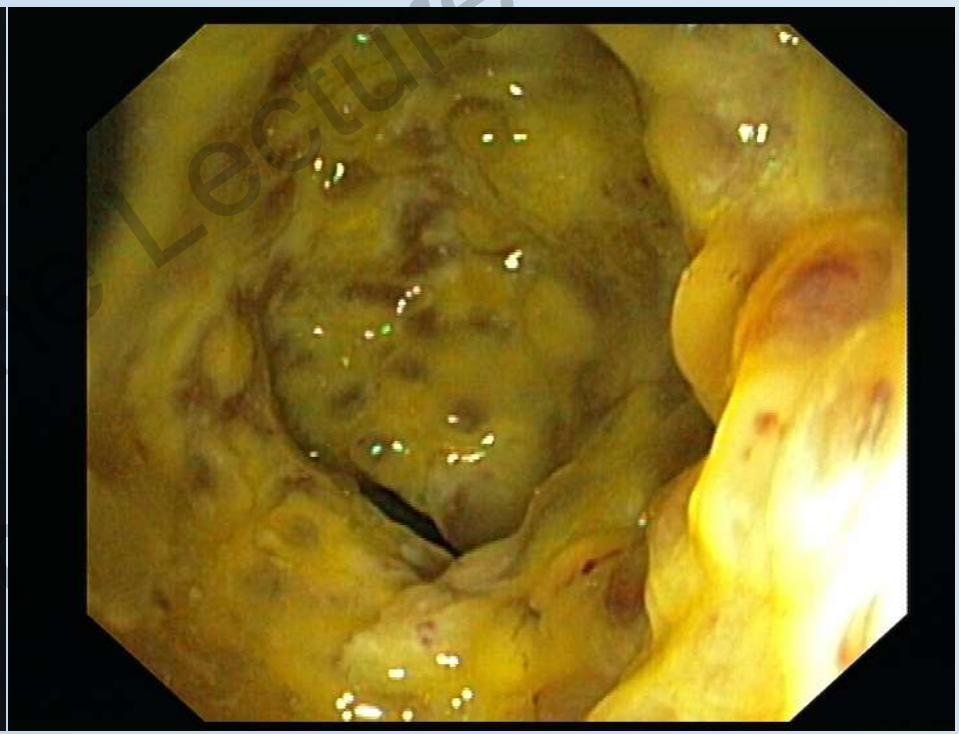


Figure 1. Pathogenesis of C. difficile infections. Taken and modified from Reference 2.

Rev Col Gastroenterol vol.28 no.1 Bogotá Jan./Mar. 2013

Leads to *Clostridium difficile* infection

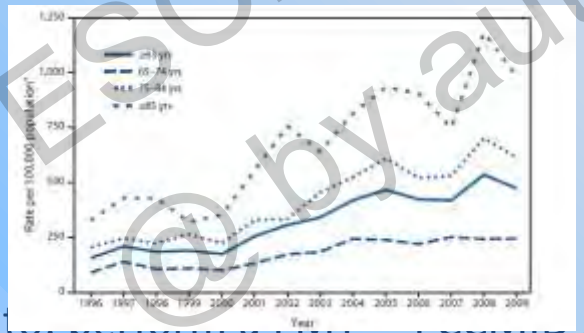


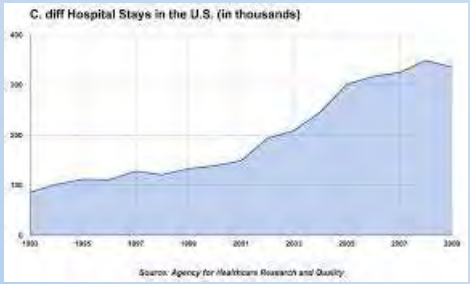


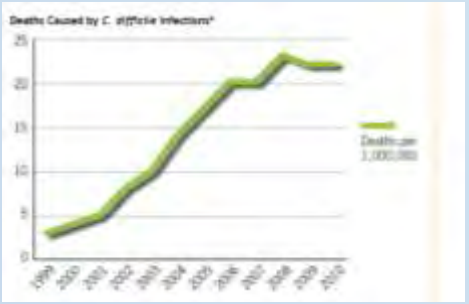
And sometimes to recurrent CDI

- Strains with higher associated morbidity and recurrence rate
- More disturbed microbiota compared to single CDI
- Continuous use of antibiotics
- Age, renal failure, operations

- Increase in prevalence and attention







Treatment of recurrent CDI

- Vancomycin/Taper schedules/Fidaxomicin
- Neurotoxicity of metronidazole
- ~ 80/60/40/20% success rate for 1st, 2nd, 3rd CDI
- Vancomycin = the drug of choice= limited success

- Restoration of microbiota: curation
- Probiotics > additional treatment of CDI with mixed results
- Normal bowel flora> logical step for restoration

Not very new?

FECAL ENEMA AS AN ADJUNCT IN THE TREATMENT OF PSEUDOMEMBRANOUS ENTEROCOLITIS

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THE apparent increased incidence of pseudomembranous enterocolitis has renewed interest in the pathogenesis and clinical management of this disease.[2, 6, 10, 14] Even with the aid of modern supportive measures, a mean mortality of 74 per cent is found in 3 recently published series.[4, 8, 12] The purpose of this paper is to report the successful use of fecal enemas in the management of 4 such cases in the hope that more complete evaluation of this simple therapeutic measure can be given further clinical trial by others.

Finney[3] in 1893 reported a case of necrotizing enterocolitis following gastroenterostomy for pyloric ulcer and since that time many reviews of this subject have been published. There appear to be 2 general types of the disease: the one precipitated by intestinal obstruction, shock, or impairment of intestinal vascular supply[9] and the other caused purely by an overwhelming *Micrococcus pyogenes* (staphylococcus) enteritis. A number of these cases bear no relationship to surgical procedures. Although pure cultures of *Micrococcus pyogenes* (staphylococcus) are found in the stools in many of these cases, this is not an invariable finding.[12] Faulty bacteriologic isolation techniques have been suggested to account for this discrepancy.[5, 11] Most of the recently reported cases have followed the use of oral broad-spectrum antibiotics,[4, 8, 13, 15, 16] suggesting that the intestinal flora was thus altered to permit an overgrowth of antibiotic-resistant *Micrococcus pyogenes* (staphylococcus) within the gut. The relationship of these drugs to the disease is debatable inasmuch as the incidence of the disease may not have increased since their use.[11]

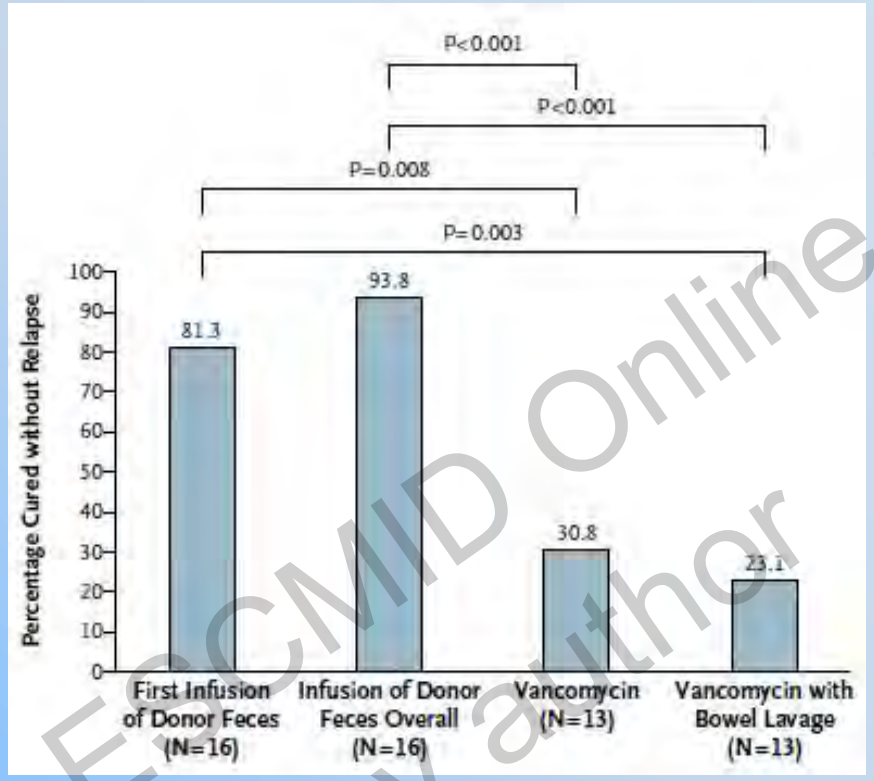
Because the mortality rate from pseudomembranous enterocolitis remains distressingly high despite the use of modern supportive measures and antibiotics

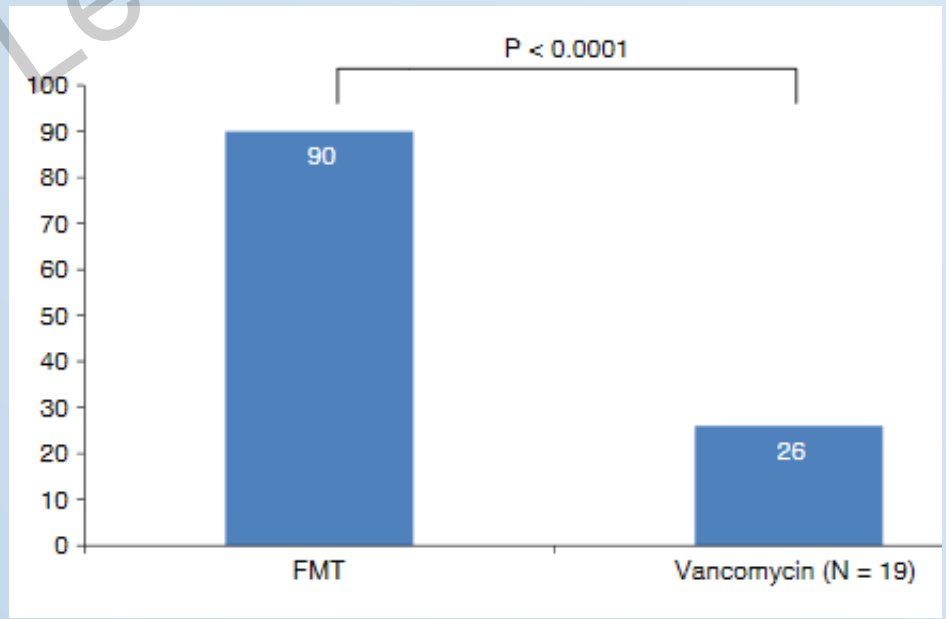
Fecal Microbiota Transplantation has been given for:

- Antibiotic associated diarrhea (historically)
- *Clostridium difficile* infection

- IBD (experimentally)
- Metabolic syndrome (experimentally)
- IBS? Pancreatitis? Depression?

RCTs for recurrent CDI





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Mechanism?

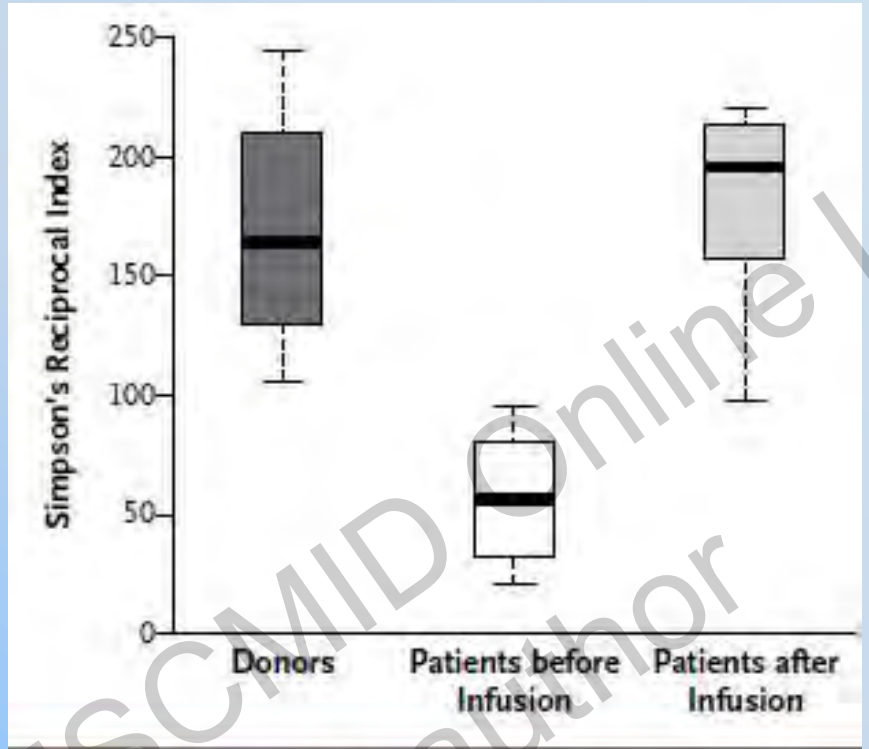
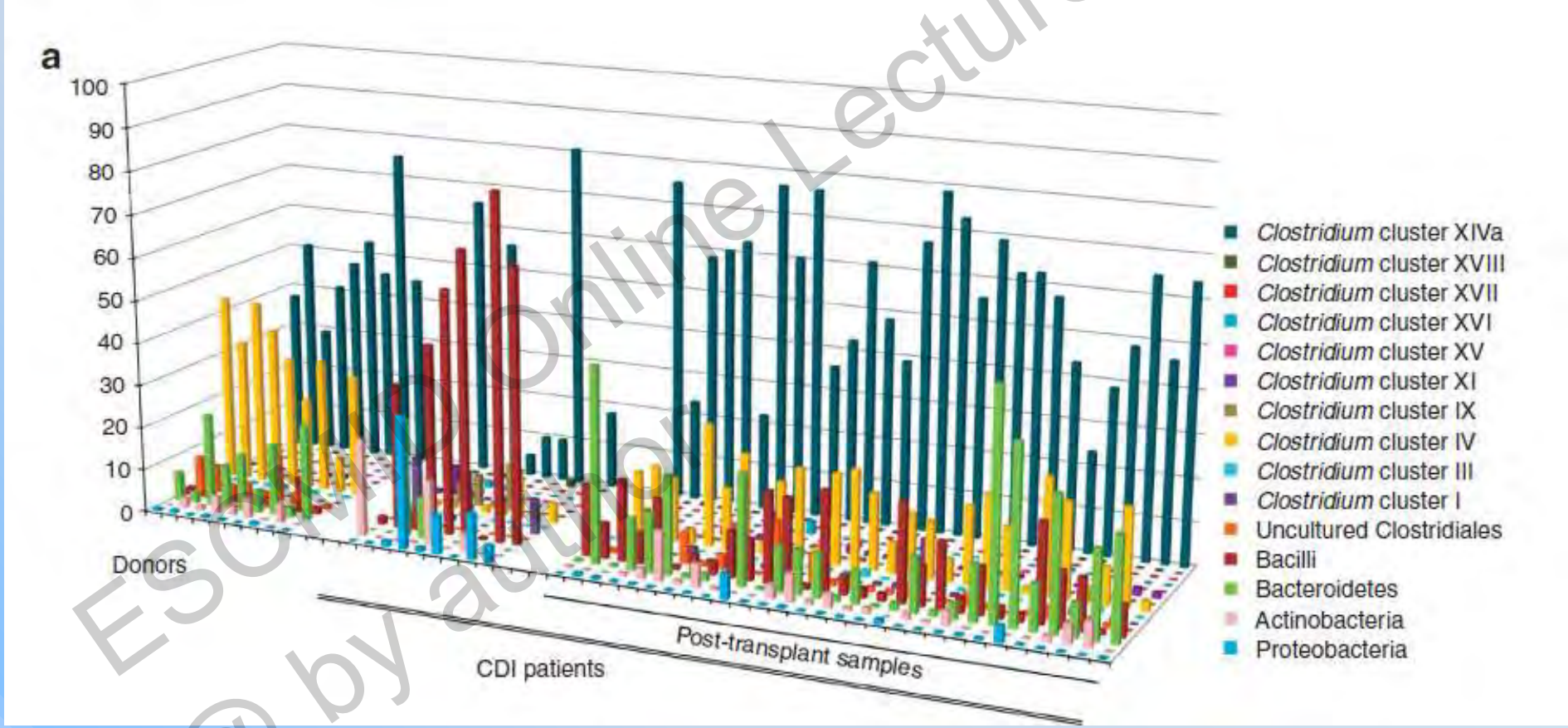


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

- Diversity:
- Richness and evenness
- Simpsons reciprocal index: the higher the more diversity
- Patient's feces resembles donor feces

Restoration of microbiota



Fuentes, ISMEJ 2014

April 2015:

67 studies found for: fecal microbiota transplantation

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Rank	Status	Study
1	Recruiting	**Standardized Fecal Microbiota Transplantation for Ulcerative Colitis** **Conditions:** Bacteria; Microbiota; Fecal Microbiota Transplantation; Inflammatory Bo Ulcerative Colitis **Interventions:** Procedure: Standardized Fecal Microbiota Transplantation; Drug: Tradition according to associated guidelines
2	Completed	**Fecal Microbiota Transplantation by Colonoscopy for Recurrent C. Difficile Infection** **Condition:** Recurrent C. Difficile Infection. **Interventions:** Other: Fecal Microbiota Transplantation; Drug: Standard Antibiotic Therapy Drug: Vancomycin (before randomization)
3	Recruiting	**Fecal Microbiota Transplantation in Irritable Bowel Syndrome With Bloating** **Condition:** Irritable Bowel Syndrome **Interventions:** Procedure: FMT with donor stool; Procedure: FMT with own stool
4	Not yet recruiting	**Fecal Microbiota Transplantation for Pancreatitis** **Conditions:** Acute Pancreatitis; Intestinal Bacteria Flora Disturbance; Intestinal Dysfur

Source: Clinicaltrials.gov

FMT for recurrent CDI

- > 800 patients described

- But: Still a nuisance
- “the aesthetics suck”
- Very effective, approximately 90% cured

Cammarota; Gough, CID ;Bartlett

Most important questions to ask:

Preparation:

- Does my patient really has CDI?
- Are there contraindications for FMT?

Implementation:

- How can I minimize the risk for transmission of diseases?

Evaluation:

- Is one treatment sufficient?

This means:

- Select the right patient, optimize success
- Select the right donor, minimize risk
- Choose the right route
- Prepare the feces
- Perform a FMT
- Clinical follow up

1 Select the right patient:

>> Patient with proven recurrent CDI> be careful not to treat patients for the wrong diagnosis

Obstacles:

- Immunodeficient patient?
- ICU patient or refractory disease?
- Patient with hampered bowel passage?
- Children?
- Food allergies?

Select the right patient
FMT for immunodeficient patient?

- Higher risk of developing CDI
- Higher risk of developing recurrent CDI

- Excluded in trial, less experience
- Retrospective series: 80 patients> 89% cured
- 12 SAE (15%) 10 hospitalized
- 1 †; aspiration for sedation

Kelly AJG 2014

Select the right patient Intensive Care/refractory disease

- Case reports successful
- Limited data
- Poor prognosis
- Results of the PROPATRIA trial warrant caution

(patients with severe pancreatitis receiving probiotics duodenally had higher mortality than those who didn't): rectally preferable?

Select the right patient: Hampered bowel passage

- Do not choose duodenal route
- Only rectal infusion
- Whole bowel lavage tests passage prior to FMT if in doubt?

Select the right patient Children?

- Role of CDI in children evolving
- Role of FMT not clear

No of children	Age	Success
1	13 months	FMT succesful
10	variable	90% cured
2	< 3	cured
6	21 months-21 yrs	100%
5	6.5-16	Overall 89%
10	1-19	90%

Wang 2015, Kronman 2015, Walia 2014
Pierog 2014, Kelly 2014

Lack of Evidence for an Unmet Need to Treat *Clostridium difficile* Infection in Infants Aged <2 Years: Expert Recommendations on How to Address This Issue

Saul N. Faust,[1] Mark H. Wilcox,[2] Aleksandra Banaszkiewicz,[3] Emilio Bouza,[4] Josette Raymond,[5] and Dale N. Gerding[6]

[1]National Institute for Health Research Wellcome Trust Clinical Research Facility, University Hospital Southampton NHS Foundation Trust and Academic Unit of Clinical and Experimental Sciences, University of Southampton, and [2]Leeds Teaching Hospitals and Leeds Institute of Biomedical and Clinical Sciences, Faculty of Medicine and Health, University of Leeds, United Kingdom; [3]Department of Paediatric Gastroenterology and Nutrition, Medical University of Warsaw, Poland; [4]Microbiology and Infectious Diseases Division, Department of Medicine, Universidad Complutense Madrid, Gregorio Maranon Hospital, Spain; [5]Université René Descartes-Bacteriology, Paris, France; and [6]Stritch School of Medicine, Loyola University Chicago, and Hines Veterans Affairs Hospital, Chicago, Illinois

The role of *Clostridium difficile* in causing disease in infants is unclear, and the existence of *C. difficile* infection (CDI) in this population is controversial. As part of the drug licensing process for new CDI therapies, a pediatric investigation plan is required to define studies in infants aged <2 years. This assumes an unmet medical need, even though clinical trials in this age group may not be feasible. Three pharmaceutical companies developing CDI treatments came together to seek advice from a panel of experts. Our unanimous opinion is that the existence of CDI is questionable in infants, and if it exists, is rare. There is therefore no unmet need for CDI treatment in this population. Interventional studies are not feasible with the current level of knowledge, and studies should be limited to noninterventional studies or open-label pharmacokinetic and safety studies to better define CDI in infants.

Keywords. *C. difficile* infection; diarrhea; infants; pediatrics; clinical trial.

Faust, CID 2015

2 Donor screening:

- Questionnaire AND Screening
- Important to minimize any risk for transmitting an (infectious) disease
- Always exclude:
- Riskful behavior
- Travel history with window period
- Potential transmittable diseases (IBD, cancer)
- Medication that can be excreted in bowel

Donor screening

Table 1. Screening of donors	
1. Initial screening	Questionnaire addressing risk factors for potentially transmittable disorders
2. Donor screening	Blood
	Cytomegalovirus (IgG and IgM)
	Epstein–Barr virus (VCA IgM, VCA IgG, VCA, anti-EBNA)
	Hepatitis A (total antibodies, if positive and not vaccinated also hepatitis A IgM)
	Hepatitis B (HbsAg, anti-HbsAg, anti-HBcore)
	Hepatitis C (anti-HCV)
	HIV types 1 and 2
	Human T-lymphotropic virus type I and II
	Treponema pallidum (TPHA)
	Entamoeba histolytica (agglutination and dipstick test)
	Strongyloides stercoralis (ELISA)
	Feces
	Bacteriological evaluation by local standards
	Parasitological evaluation by local standards (triple feces test or PCR)
	Test for *Clostridium difficile* (toxin ELISA and culture or PCR)
3. One day before donation of feces	Questionnaire addressing current stool frequency and pattern, general health, use of antibiotics, travel history and (recent) sexual behavior since initial screening

Donor

Issues to be addressed:

- EBV/CMV
- ESBL, HEV, viral pathogens, HTLV
- Obese donors allowed?
- Other diseases excluded?
- Adapted screening when patient is immunocompromised?

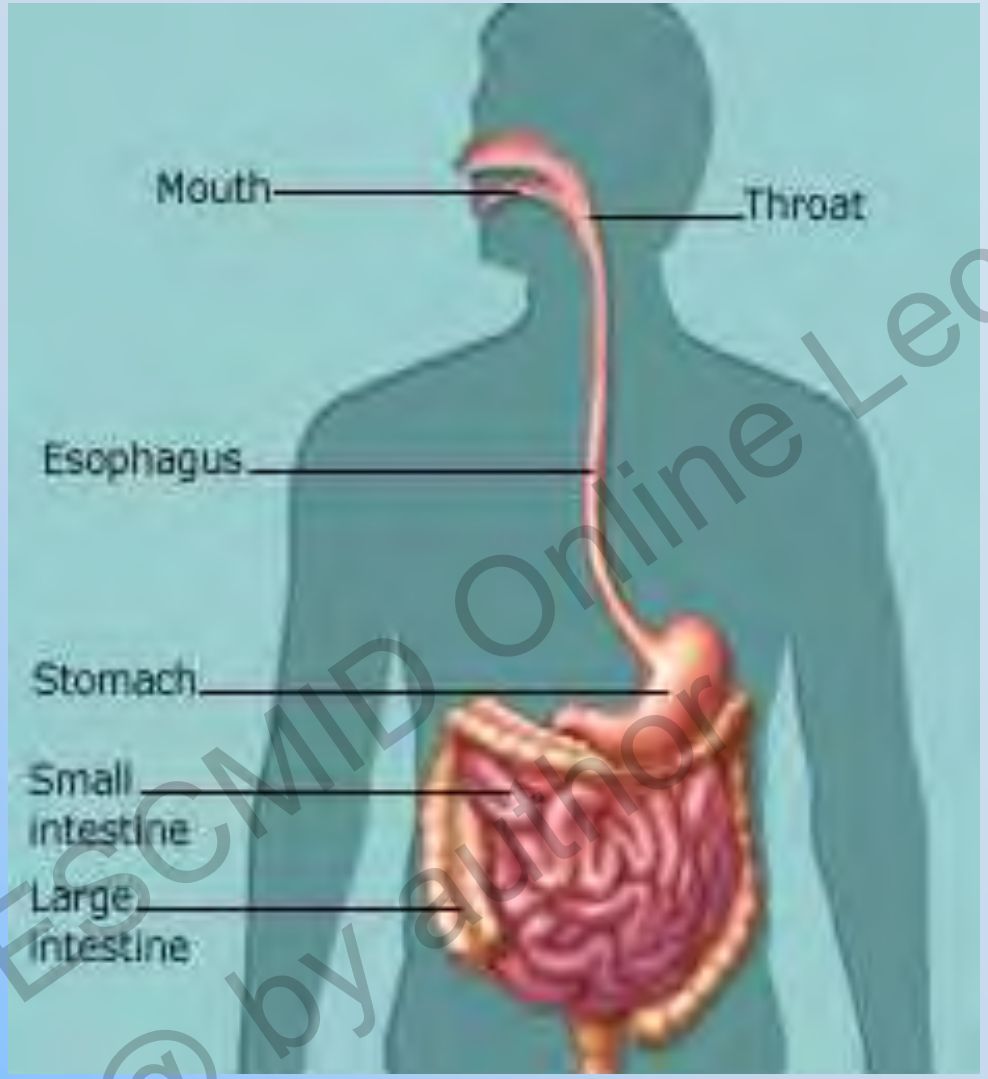
3 How to prepare a FMT?

How to prepare the feces

- See: You tube “fecal microbiota transplantation”
- Freshly produced is probably helpful
- Diluting the feces with saline, more than 50 gr
- Stirring/blending
- Freezing probably as effective
- Freezing/donor bank
- Capsules

Hamilton, Youngster

Which route?



Gastroscopy 81%

Duodenoscopy 86%

Colonoscopy 93%

Enema 84%

Protocol FMT

- Choose upper or lower GE route
- Whole bowel lavage & Vancomycin before FMT: logistically easy, uncertain if necessary
- Prepare feces
- Infuse slowly
- Clinical follow up
- Repeat if necessary

All there is to it?

1: donor:

2:

3: duodenal tube/colonoscopy

Conclusion

- FMT works for recurrent CDI
- Protocol and donor screening varies
- Selection of patient, route and donor increases chance of success
- Near future: alternative treatment: donor bank, capsules or bacterial preparations