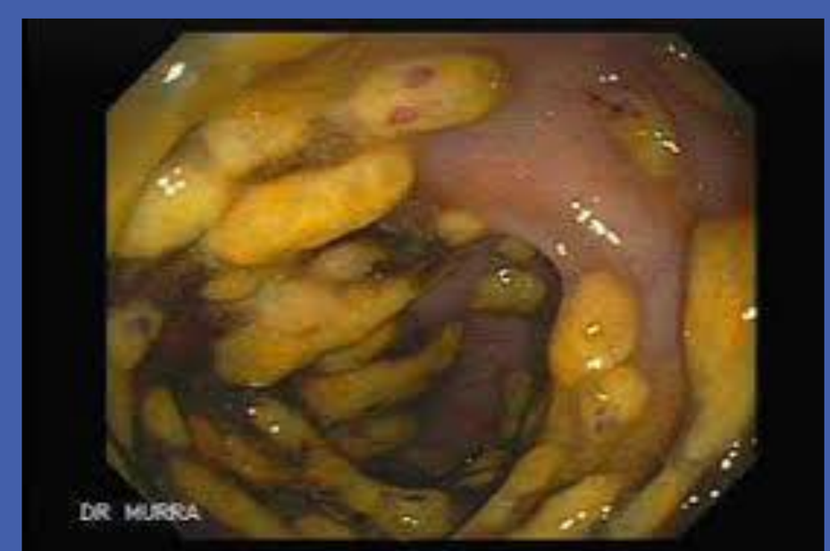
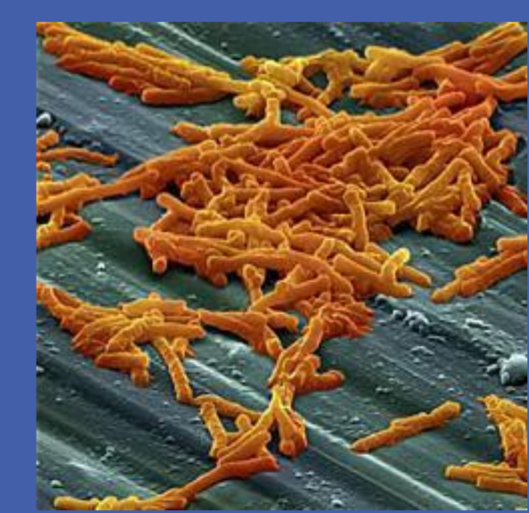
Efficacy of Fecal Microbiota Transplantation for Recurrent C. difficile Infection





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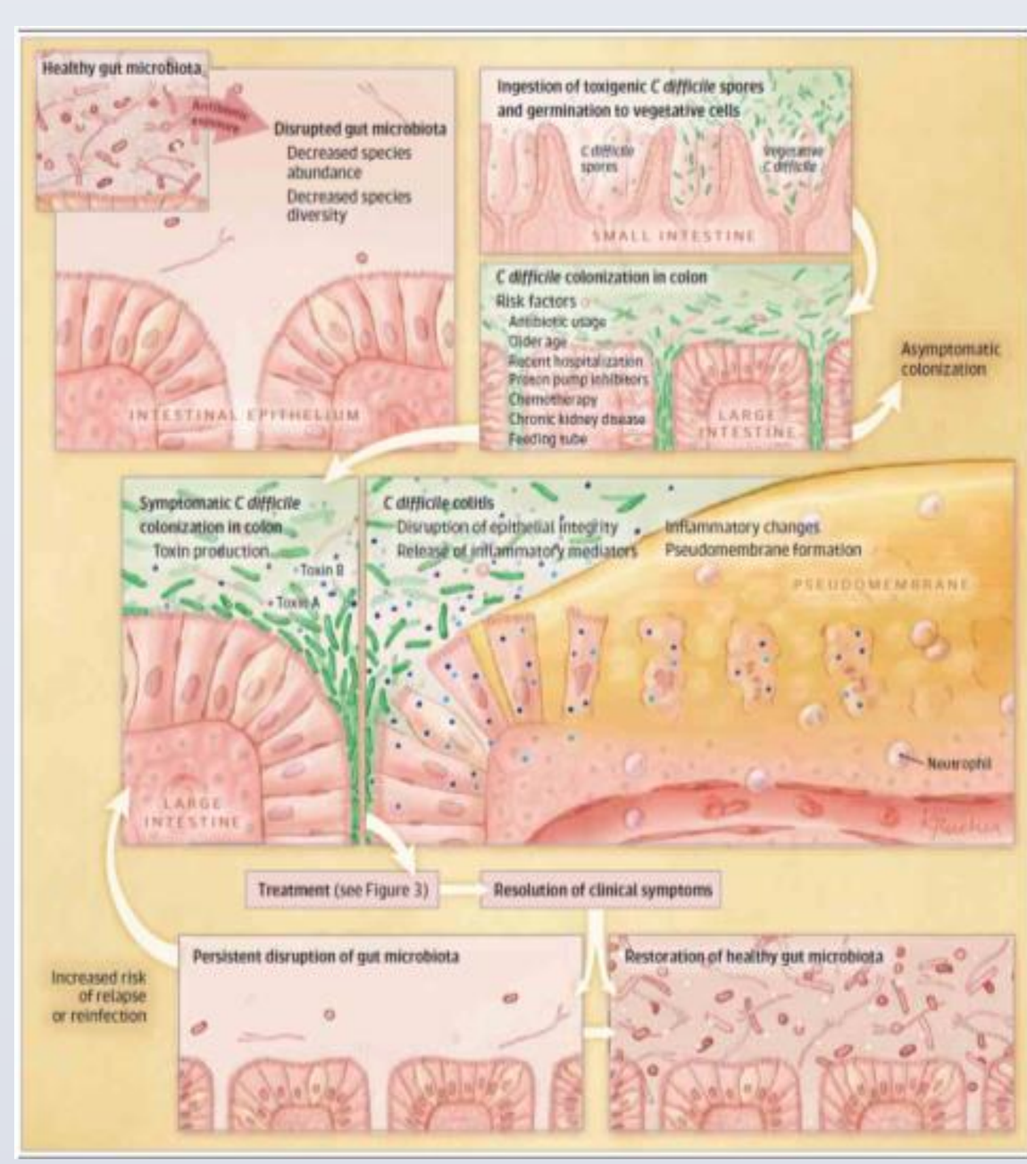
Introduction

Epidemiology of *C. Difficile*: *Clostridium difficile* is the leading cause of nosocomial infectious bacterial diarrhea in industrialized countries and is associated with significant morbidity including: severe diarrhea, pseudomembranous colitis, toxic megacolon, colonic perforation, and sepsis[1]. *C. Difficile* infections (CDI) cause 337,000 cases and 14,000 deaths annually, making it the leading cause of gastroenteritis-associated death in the U.S. The financial burden of CDI is also significant, resulting in excess healthcare costs of $4.8 billion in primary care alone[7]. Since the introduction of the highly virulent B1/NAP1/027 strain in 2000, the prevalence, severity, and recurrence of CDI has increased dramatically[2]. The ESCMID reported that recurrence is the most important issue in CDI management: 25 % of patients suffer a recurrence and secondary recurrence risk increases to 65 %[1]. The two major risk factors for primary and recurrent CDI are: age over 65 and antibiotic exposure. Individuals over 65 are considered to be at greater risk of developing CDI due to greater exposure (prolonged hospital stays and residence in long term care facilities), greater likelihood to receive antibiotic therapy, and less effective immune response to the *C. difficile* toxin. Malnutrition and medical comorbidities also contribute to poor immune responses to CDI in older adults[4]. The U.S. Census Bureau estimates that the adult population over 65 will increases from 13 % (2010) to an estimated 20 % by the year 2050, increasing the at risk population and likely amplifying the prevalence of CDI .

Pathogenesis of *C. Difficile* Infection (CDI): CDI requires both exposure and susceptibility to toxin producing microbe. The current hypothesis is that antibiotic therapy creates colonic dysbiosis, or an imbalance of the colonic microbiota: when sensitive microflora are killed, resistance to colonization by opportunistic organisms is impaired[10].



(Bagdasarian et al, 2015)

Current Treatment for CDI:
Current treatment guidelines for CDI are stratified based on severity and recurrence of infection:

- 1° CDI: stop offending antibiotic and establish contact precautions.
  - Non severe: Metronidazole (500 mg tid for 10-14 d).
  - Severe: Vancomycin (125 mg qid for 10-14 d)
- First recurrence: same antibiotic regimen as the first treatment
- 2 or more recurrences: tapered oral vancomycin regimen. For example, 125 mg qid for 7-14 d → 125 mg bid for 7 d → 125 mg od for 7 d → 125 mg eod for 7 d → 125 mg every 3 d for 7 d

Rationale for proposed use of Fecal Microbiota Transplantation (FMT): Treatment outcomes for recurrent CDI using standard antibiotic therapy is suboptimal as evidence by high recurrence rates. FMT is proposed as a therapy that uniquely targets the pathophysiology of the disease by correcting dysbiosis instead of merely eliminating the offending pathogen. Despite the theoretical validity of this treatment and reports of high safety and efficacy, FMT is considered an investigational therapy by the US FDA.

PICO

For an adult patient with recurrent *C. difficile* infection (CDI) is fecal microbiota transplantation more effective therapy than traditional antibiotic regimens in causing resolution of CDI in the hospital setting.

- P = hospitalized patients with RCDI
- I = FMT
- C = antibiotic therapy
- O = cure rate

METHODS

A PubMed literature search was performed for studies involving FMT treatment for recurrent CDI. The following key words were used: *Clostrium difficile*, *C. difficile*, fecal microbiota transplantation, fecal bacteriotherapy, and vancomycin. Results were limited to RCT and systematic reviews of human subject studies written in English and available in full text. Eight articles were reviewed. The data extracted from these are listed in the table below.

RESULTS

Source	Study Design (Level of Evidence)	Patients	Outcome	Conclusion	Limitations
Kassam Z, et al, 2013	Systematic Review (I) 11 studies; Evaluate evidence for the efficacy of FMT in treating CDI	N = 273 Mean age 65, 65 % female All had refractory or recurrent CDI	Overall resolution: 245/273 **UPR = 89.7 %** **WPR = 89.1 %** CI = 84=93 %	FMT is a promising therapy for CDI We need RCTs and long-term follow up studies to define efficacy and safety.	Systematic reviews can be impacted by selection and publication biases.
Van Nood E, et al, 2013	Prospective, open-label RCT (II) Compare the efficacy of FMT with thr conventional 14-day vancomycin regimen for *C. difficile* colitis	3 treatment groups: 1. FMT following abbreviated Vancomycin/bowel lavage (N=17, mean age 73) 2. Vancomycin only (N= 13, mean age 66) 3. Vancomycin + bowel lavage (N=13, mean age 69)	**Group 1- 94 % cure rate (p < 0.001)** Group 2- 31 % cure rate Group 3- 23 % cure rate (18 patients from Groups 2 & 3 relapsed and saw an 83 % cure rate with FMT) FMT increased diversity of intestinal microbiota	Infusion of donor feces for recurrent CDI results in better treatment outcomes than vancomycin alone.	Study terminated early because most patients in both control groups had a relapse. Small sample size, low power. Mean ages were > 65 making this study less generalizable. However, this age group is at high risk for CDI so its efficacy in this population is important
Matilla E, et al, 2012	Retrospective Chart Review (IV) Investigate the efficacy of FMT in the treatment of CDI	N=70 (36 with 027 ribotype) Mean age 73, 60% female, Mean of 4.5 failed antibiotic treatments 5 Medical Centers in Finland	**non-027 strain: 100% resolution** **027 strain: 89% resolution** Overall; 94 % resolution	FMT is an efficacious treatment for recurrent CDI including patients with the highly resistant 027 strain.	May have missed patients with an unfavorable outcome resulting in bias in favor of FMT Most patients were outpatients – not generalizable to hospital setting.
Brandt L, et al, 2012	Retrospective long-term follow-up (IV) Review efficacy of colonoscopic FMT for recurrent CDI	N=77 Mean age = 65; 73% female Mean # failed antibiotic treatment = 5 5 Medical Centers in US	**Primary cure rate 91 %** (resolution + no recurrence) **Secondary cure rate 98 %** (resolution after one further course of vancomycin ± FMT)	FMT is an efficacious treatment for long-term resolution of CDI	The retrospective nature of the study lends itself to the possibility of selection bias and information bias. Also present is the risk of recall bias.
Youngster I, Sauk J, et al, 2014	Open-label RCT (II) Compare efficacy of frozen FMT inoculum administered via colonoscopic vs. nasogastric tube	N=20 (N=10 in each treatment group) Age 7-90 All had refractory or recurrent CDI Study site: Massachusetts General	14/20 cure rate after 1st infusion (8/10 colonoscopy; 6/10 NGT) - 5/6 were given 2nd infusion, 4 of these obtained cure **Overall cure rate = 90 %** Both increased microbiota diversity	Infusion of unrelated frozen donor stool is efficacious in treating patients with relapsing/remitting CDI	Not generalizable (subjects all from one medical center). Not blinded. Resolution based on symptoms not presence of toxin. Small sample size
Gough E, et al, 2011	Systematic Review (I) Reviewed 27 unique studies to summarize the literature on the use of FMT in humans for CDI	N=317 Mean age 53 All had recurrent or relapsing CDI or PMC (pseudomembranous colitis)	**Over-all resolution rate = 92 %** (89 % after a single treatment)	FMT is a highly effective therapy for CDI and PMC when standard treatments fail.	Classification of variables associated with FMT not standard across studies. Heterogeneous sample (8 countries, 53 year period) makes it difficult to pool and analyze data. Unable to assess study quality and publication bias of case reports
Burke KE, et al, 2013	Systematic Review (I) Reviewed 10 studies to assess efficacy and safety of FMT for CDI in older adults	N=115 Age 60-101, mean age = 77 All had refractory or recurrent CDI	**Durable remission achieved in 89.6%** over a follow-up period of 2 mo to 5 yr. Relapse in the remaining 10.4 % was associated with antibiotic use for non-CDI. Durable change in colonic microbiome	FMT is a safe and durable 2nd-line therapy for recurrent CDI in older adults	Systematic reviews are subject to selection and publication bias. Many patients had various forms of treatment prior to FMT. Multiple donors from various sites. Baseline health status was not assessed.
Youngster I, Russell G et al, 2014	Open-label, single-group preliminary feasibility study Evaluate the safety and rate of diarrhea resolution following administration of frozen FMT capsules for CDI	N=20 All had refractory or recurrent CDI Study site: Massachusetts General	**Overall rate of resolution = 90 %** No serious adverse effects observed Patients who needed a 2nd FMT had lower pretreatment health scores Longer time to resolution (4 d vs 2 d)	Demonstrated the feasibility of oral administration of frozen encapsulated fecal material from unrelated donors to treat patients with recurrent CDI	Not generalizable – subjects all from one medical center Small sample size Lack of placebo or active comparator

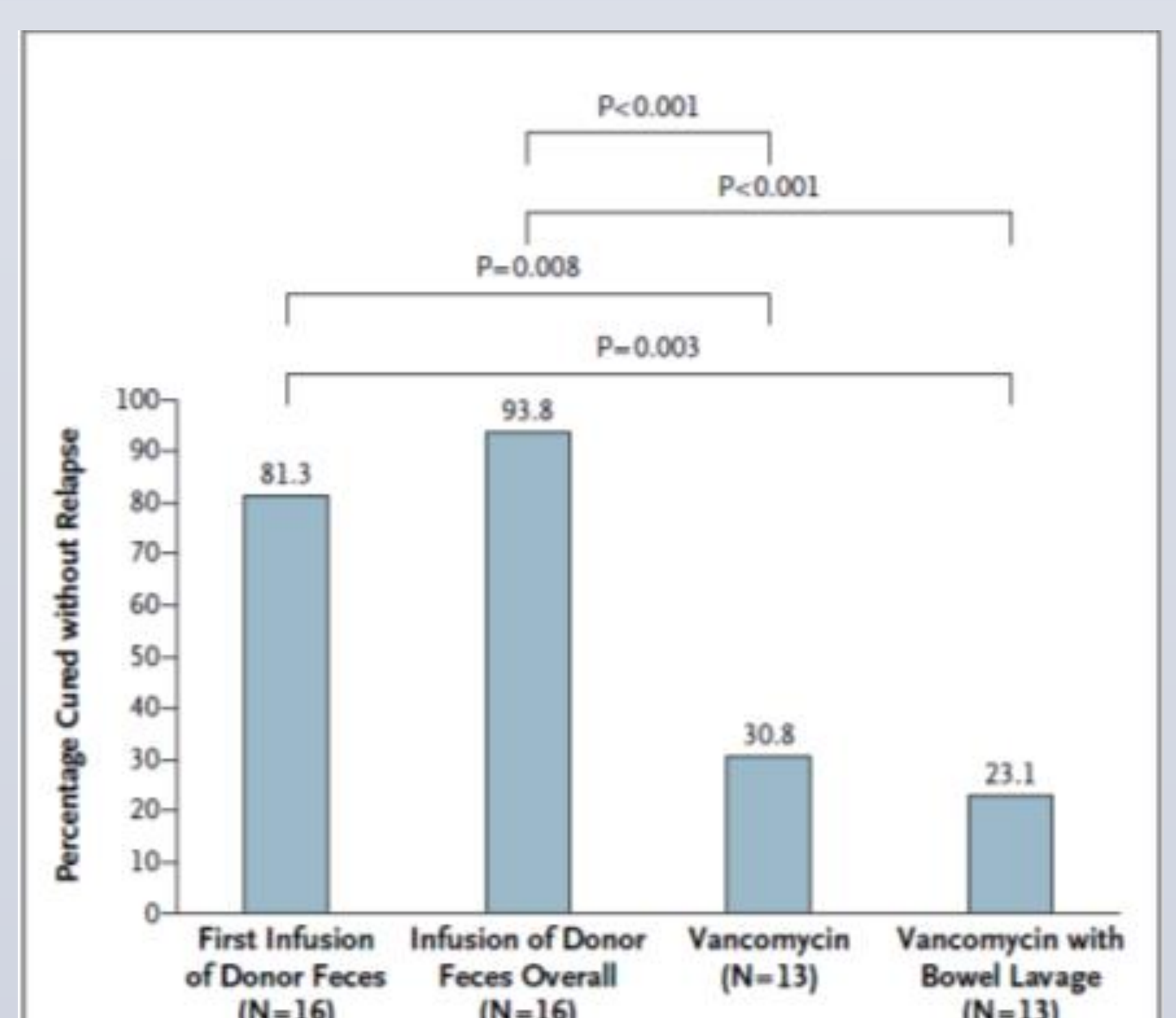


Figure 2. Rates of Cure without Relapse for Recurrent *Clostridium difficile* Infection.

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.

van Nood et al. 2013

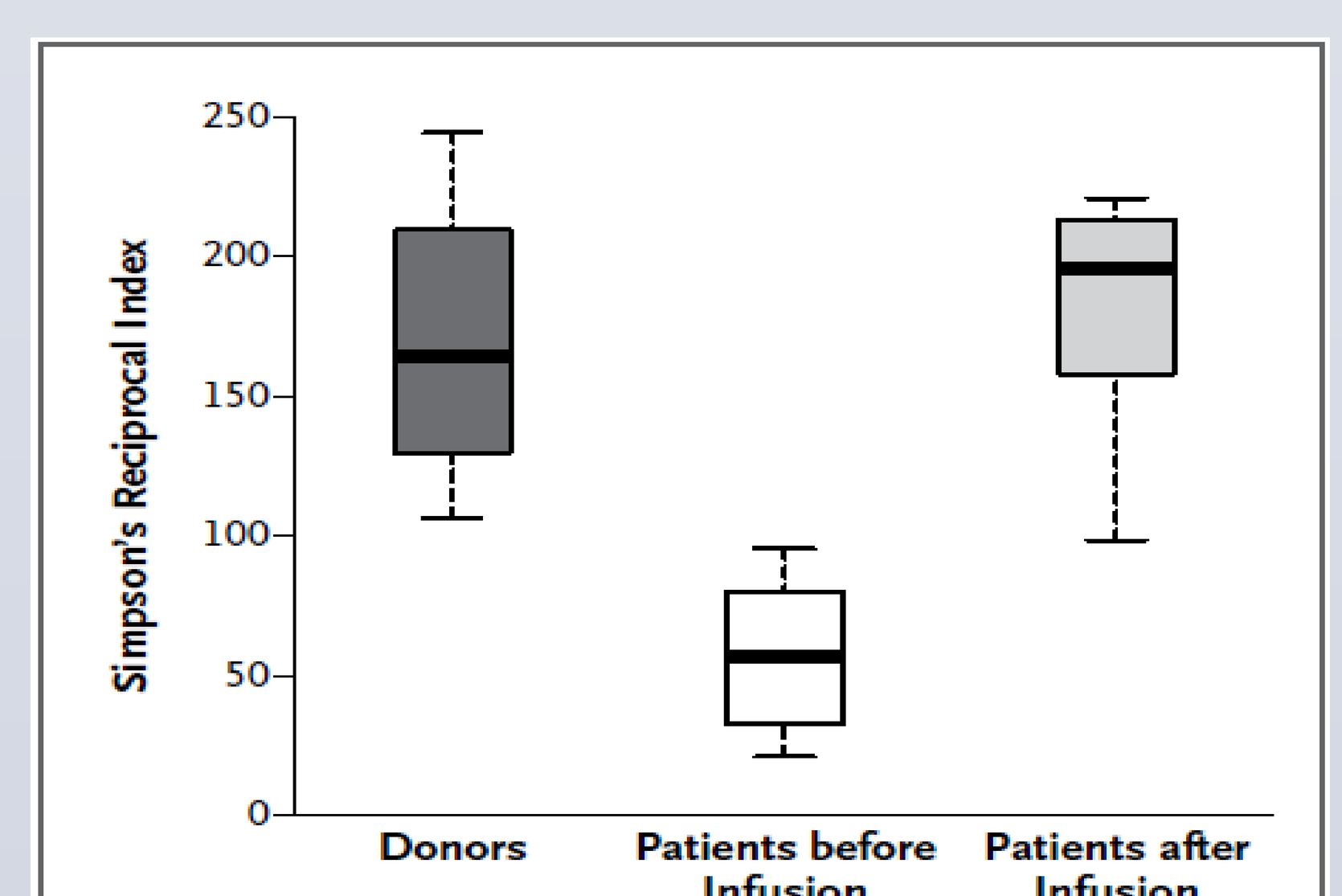


Figure 3. Microbiota Diversity in Patients before and after Infusion of Donor Feces, as Compared with Diversity in Healthy Donors.

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).

van Nood et al. 2013

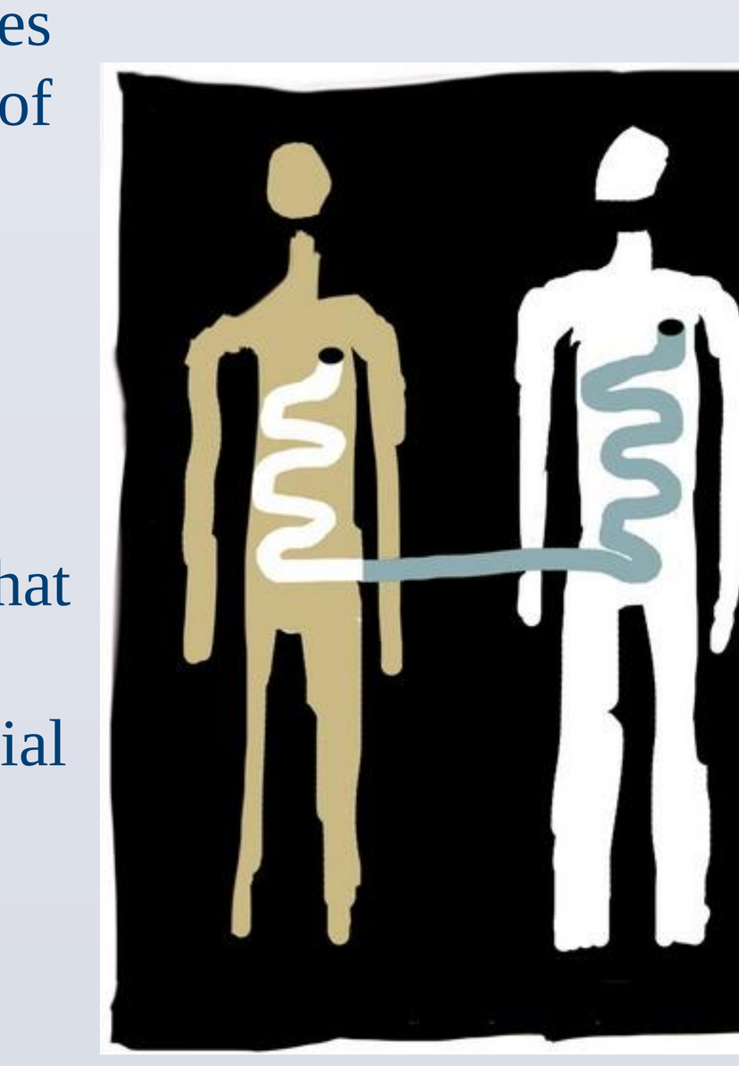
Conclusions

Fecal microbiota transplantation is an efficacious, durable, safe and cost-effective treatment for recurrent CDI. Resolution rates reported by the articles reviewed range from 89 % to 100 % for FMT, far superior to traditional antibiotic therapy. The RCT comparing FMT directly to Vancomycin showed that FMT resulted in statistically and clinically significant increases in resolution rate. The procedure caused resolution without recurrence in long term studies up to 5 years. This durable cure is thought to be due to the microbiota change cause by FMT. In addition, the procedure was effective in treating the hypervirulent B1/NAP1/027 strain. The procedure causes only mild side effects: cramping, belching, nausea, and diarrhea that resolve within 3 hr if the inoculum is administered via colonoscopy or nasogastric tube or within 72 hr via capsules[4,9,12]. A computer analysis conducted by Varier et al was used to predict cost for 90 days of treatment with FMT compared to vancomycin. They determined that FMT was less costly ($1,669 vs $3,788) and more effective than vanocmycin for recurrent CDI. FMT remained superior to vancomycin even when the clinical efficacy was reduced from 94 % to 53 % in the model.

Recommendations

FMT should be considered as first line therapy for RCDI. It is the only therapy to date that uniquely targets the pathophysiology of CDI and is an effective treatment for hypervirulent *C. difficile* strains. Despite cost and care benefits, the FDA views it as an investigational procedure. In order to elevate FMT to an FDA approved therapy for CDI, more data needs to be collected. More RCT need to be performed to further prove the effectiveness and safety of FMT for CDI. Available data are based on retrospective case series and include only a single, small size RCT[13]. In addition, RCT should be designed to answer the following questions:

1. What is the optimal protocol for donor-feces infusion: route of administration, volume of inoculum, and inoculum preparation?[9]
2. How should donors be screened and who should be selected to donate?[3,6]
3. What is the exact impact of FMT on hypervirulent strains?[6]
4. Is it possible to design synthetic stool? What bacterial strains are most effective in restoring a healthy, diverse colonic microbial flora?[6]
5. Should FMT be used after the first recurrence or even as first line treatment?
6. What are the long term adverse effects?



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