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Fecal Microbiota Transplantation as Therapy for Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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Abstract

Background and aims—Fecal microbiota transplantation (FMT) has gained interest as a novel treatment option for inflammatory bowel diseases (IBD). While publications describing FMT as therapy for IBD have more than doubled since 2012, research that investigates FMT treatment efficacy has been scarce. We conducted a systematic review and meta-analysis to evaluate the efficacy of FMT as treatment for patients with IBD.

Methods—A systematic literature search was performed through May 2014. Inclusion criteria required FMT as primary therapeutic agent. Clinical remission (CR) and/or mucosal healing were defined as primary outcomes. Studies were excluded if they did not report clinical outcomes or included patients with infections.

Results—Eighteen studies (9 cohort studies, 8 case studies and 1 randomized controlled trial) were included in the analysis. 122 patients were described (79 ulcerative colitis (UC); 39 Crohn's disease (CD); 4 IBD unclassified). Overall, 45% (54/119) of patients achieved CR during follow up. Among cohort studies, the pooled proportion of patients that achieved CR was 36.2% (95% CI 17.4%-60.4%), with a moderate risk of heterogeneity (Cochran's Q, $P=0.011$; $I^2 = 37\%$). Subgroup analyses demonstrated a pooled estimate of clinical remission of 22% (95% CI 10.4%-40.8%) for UC (Cochran's Q, $P=0.37$; $I^2 = 0\%$) and 60.5% (95% CI 28.4%-85.6%) for CD (Cochran's Q, $P=0.05$; $I^2 = 37\%$). Six studies performed microbiota analysis.

Conclusions—This analysis suggests that FMT is a safe, but variably efficacious treatment for IBD. More randomized controlled trials are needed and should investigate frequency of FMT administration, donor selection and standardization of microbiome analysis.

Keywords

Fecal microbiota transplantation; inflammatory bowel disease; microbiome; systematic review; meta-analysis; mucosal healing

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1. Introduction

Fecal microbiota transplantation (FMT) has become an increasingly popular avenue of inquiry for patients with inflammatory bowel disease (IBD). Prior to 2013, research that explored the treatment efficacy of FMT was generally limited to patients with *Clostridium difficile* infections (CDI). Data from this body of research demonstrated excellent results within this patient population.¹ FMT research has been sparse outside of the context of CDI and is limited to case reports alone for the IBD patient population.²⁻⁹ As a result, the two systematic reviews of this topic were completed in 2012 and 2013 and were predominantly comprised of case reports.^{10, 11} These studies included IBD patients both with and without co-morbid CDI and were limited in quantitative analysis due to the statistical limitations of existing publications.

In this updated systematic review and meta-analysis, we investigate the efficacy of FMT as therapy for IBD. We performed a pooled analysis and meta-analysis with data from the first published cohort studies on this topic. Secondly, we examined the safety of FMT among the IBD population and treatment efficacy associated with microbiota analysis.

2. Methods

2.1. Search strategy and study selection

A systematic literature search was performed and used MOOSE, PRISMA and Cochrane guidelines.¹²⁻¹⁴ The MOOSE checklist was followed accordingly.^{12, 14} The systematic literature search was conducted using EMBASE (1947 - May 2014), MEDLINE (1950-May 2014), the Cochrane library and Biomed central Cases Database. Proceedings from annual meetings of national and international gastroenterology conferences (American College of Gastroenterology (ACG), Digestive Diseases Week (DDW), Advances in IBD (AIBD), European Crohn's and Colitis Organization (ECCO), North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN), European Society for Pediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) and the British Society of Gastroenterology annual meeting were searched manually from 2010 up to and including May 2014.

A Population, Intervention, Comparison, Outcomes, Study design (PICOS) question was designed to determine inclusion and exclusion criteria. Databases were searched with the following alternatives for fecal microbiota transplant: "fecal", "faecal", "microbiota", "microflora", "feces", "faeces", "stool", "fecal flora", "faecal flora"; individually with each of the following variations on transplant: "transplant", "transfusion", "implantation", "implant", "instillation", "microbiota", "donor", "enema", "reconstitution", "infusion", "therapy", "bacteriotherapy", as earlier identified by Anderson et al.¹⁰ These terms were searched alone and in combination. The results were combined with varied IBD descriptor terms ("Crohn disease", "Crohn's disease", "inflammatory bowel disease", "colitis", "ileitis", "regional enteritis", "ulcerative colitis", "IBD", "CD", or "UC") and combined by the Boolean term "AND". This strategy was used both as Medical Subject Headings (MeSH) terms if available and as free text. Searching was limited to publications with human subjects. No language limits were used.

Two authors independently reviewed all articles. Inclusion criteria for publications required inclusion of IBD patient sample and clearly described clinical treatment outcomes. Studies were excluded if clinical endpoints were not reported or if the study included only patients with co-morbid infections.

Studies that included patients with concomitant infections (eg. CDI) were considered only if there were clear descriptions of clinical outcomes and patient characteristics of the remaining patients without co-morbid infection.

Data was extracted using preset criteria into a Microsoft Excel Office Professional Plus 2010 (Microsoft, Redmont, WA) spread sheet. Study characteristics and outcomes were reported and a separate spread sheet was used to record individual patient characteristics and outcomes.

2.2. Risk of bias

Quality and bias of cohort studies was assessed by an adjusted version of the Newcastle-Ottawa Scale for cohort studies.¹³ The scale was adjusted for use in cohort studies without control group (**Table 1**). The Newcastle-Ottawa Scale is used to assess quality and biases of studies that assigns points for specific biases on a nine-point scale. This was adjusted to a six-point scale after the questions that assess for control groups were removed. The first 3 points assessed for cohort selection and included representativeness of the IBD cohort (for age, sex and disease severity), ascertainment of FMT exposure, and evidence that there was no prior exposure to FMT. The remaining 3 points were awarded for outcome quality (that utilized predefined disease activity scores or mucosal evaluation), longevity follow-up (at least 3 months), and bias due to drop-out or incomplete follow up. A follow-up of 3 months was chosen due to case reports that demonstrated improvement after 1 month.¹⁵

2.3. Data analysis

Data from all included publications were extracted into IBM SPSS Statistics (Version 20.0. Armonk, NY: IBM Corp.). Descriptive statistics were completed. A clinical remission rate of all known studies and patients was calculated. To minimize risk of publication bias, a secondary analysis was performed using cohort studies only and included only full publications or abstracts with clearly described selection and outcome criteria. A meta-analysis was performed with the pooled estimate proportion of patients that achieved clinical remission. This data was pooled using a random effects model with the DerSimonian-Laird method calculated with Meta-Analyst software (version Beta 3.13; Tufts Medical Center, Boston, MA).^{16, 17} Statistical heterogeneity was assessed using the Cochran's Q test (χ^2) and I^2 method. In the Q test a p value of <0.1 was deemed statistically significant. The I^2 method was used to assess for degree of heterogeneity, with a score discrimination of 0-40%, 30-60%, 50-90% and 75-100% consistent with low, moderate, substantial and considerable heterogeneity, respectively.¹⁸

3. Results

3.1. Study characteristics

Eight-hundred-seventeen studies were identified (**Figure 1**). After review of the titles and abstracts, 795 papers were excluded based on the criteria determined by the PICOS question. Of those that remained, another 3 studies were excluded because they included data previously reported in other publications. One additional study did not provide clear clinical outcome measures and was subsequently excluded as well.¹⁹ Eighteen studies were included in the final review. This included 9 prospective uncontrolled cohort studies and 8 retrospective case series and case reports (5 case series and 3 case reports).^{2-9, 20-28} In addition, one randomized controlled trial (RCT) was identified and included in this review.²⁹ Disease subtypes were distributed as follows among the publications: 11 UC, 4 CD, 2 ‘IBD unspecified colitis’, and 1 publication included more than one disease subtype. One systematic review of IBD patients both with and without co-morbid CDI was found.¹⁰ No meta-analyses were identified. **Table 2-1 and 2-2** present the characteristics of each original study.

3.2. Risk of bias of individual studies

All cohort studies exhibited ascertainment of FMT exposure, assessment of outcome and adequacy of follow-up. However, only 4 studies met length of follow-up requirements and documented no prior FMT exposure.^{21-23, 26} With the exception of two studies, all publications included cohorts with either severe disease or disease refractory to standard therapy.

Publication dates ranged from 1989 (case studies) to 2014. Over 60% of studies were published in 2013 or 2014. The earliest two case reports were published in 1989 and the first abstract of a cohort study in 2012.^{2, 4, 27} Each case study included 1-6 patients. Cohort studies ranged from 4-16 patients. The RCT included 31 patients that underwent FMT and 30 that received placebo treatment.

3.3. Patient demographics

Eighteen publications yielded discrete 122 patients (79 Ulcerative Colitis (UC) (5 of which had a status of post-colectomy pouchitis), 39 Crohn's disease (CD), and 4 IBD unclassified). Studies included both pediatric and/or adult patients. The age range of participants extended from 7 years to 64 years. Clinical follow-up of patients ranged from 1 week to 13 years with median 1.5 months.

3.4. Disease severity and Efficacy of FMT

Of the 122 patients included in this review, 3 patients were excluded from the analysis due to FMT enema intolerance. Of the remaining 119 patients in the cumulative analysis, 27 (23%) were described as having mild or mild/moderate disease, 16 (13%) as having moderate/severe, and 19 (16%) as having severe disease. Other disease descriptors included “therapy refractory” 10 (8%), “active disease” 44 (37%), and 5 (4%) “refractory pouchitis”. Overall, 45% (54/119) of patients achieved clinical remission during follow up. Mucosal healing, was achieved in 12 of the 16 (75%) of case study patients. In cohort studies,

mucosal healing was observed in 1 of 36 (3%) patients and not described the remaining patients (n=34) (**Table 3**). Four of the 70 (6%) patients in the cohort studies deteriorated after FMT administration. However 2 of these improved and recovered to baseline by week 8 of follow-up.

Moayyedi et al., completed an RCT that compared FMT of 31 patients receiving fecal enemas to 30 patients receiving water enemas.²⁹ Patients with active UC (as defined by a mayo score of ≥ 4 and an endoscopic sub score of ≥ 1) received FMT or placebo weekly for 6 weeks. At week 7, 7 patients (23%) who received FMT achieved remission (as defined by a mayo score < 2 and an endoscopic sub score of 0) compared with 2 patients (7%) who received placebo ($P=0.15$). Absolute mayo scores and health-related quality of life (HRQoL) (measured by the general EQ-5D or IBD specific IBDQ) did not significantly vary between groups at 6 weeks.

3.5. Meta-analysis of cohort studies

The cohort studies included in this meta-analysis were awarded at least a score of 3/6 on the Newcastle-Ottawa Scale (**Table 1**). Among the 9 cohort studies included, the pooled proportion of patients who achieved clinical remission was 36.2% (95% CI 17.4%-60.4%) (**Figure 2**), with a median effect size of 0.29. This was consistent with moderate heterogeneity (Cochran's Q, $P=0.011$; $I^2 = 37\%$).

3.6. Subgroup analyses

Among studies that included UC patients only, the proportion of patients achieving clinical remission was 22% (95% CI 10.4%-40.8%) (**Figure 3a**). This was a statistically homogenous meta-analysis (Cochran's Q, $P=0.37$; $I^2 = 0\%$). After excluding a single pouchitis study, the subgroup analysis (which now comprised almost only left-sided and extensive/pancolitis patients) demonstrated a pooled estimate of achieved clinical remission of 24.1% (95% CI 11.1%-44.9%), with a low risk for heterogeneity (Cochran's Q, $P=0.35$; $I^2 = 0\%$) (**Figure 3b**). The subgroup analysis for CD consisted of 4 studies and demonstrated moderate heterogeneity (Cochran's Q, $P=0.05$; $I^2 = 37\%$). Due to the relatively larger sample size and magnitude of response in Zhang's and Suskind's study, the pooled estimate for clinical remission was 60.5% (95% CI 28.4%-85.6%) (**Figure 3c**).^{25, 28}

3.7. Studies focusing on younger populations

Two studies focused exclusively on young patients (age 7 to 20 years).^{23, 25} The pooled estimate for clinical remission among patients included in these studies (1 with UC patients and 1 CD patients) was 64.1% (95% CI 10.6%-96.4%, Cochran's Q, $P=0.029$; $I^2 = 44\%$) (**Figure 3d**) and is consistent with moderate heterogeneity. In line with the results of other studies that utilized an older patient population, mucosal healing was not reported.

3.8. Donor selection

Donor descriptors were reported in 105 of 122 patients receiving FMT. Forty-seven of these 105 patients (45%) were involved in the donor selection process. Twenty-three patients received their fecal material from a first degree relative. In 3 of the 5 cohort studies that contained patients who achieved remission, included donors that were first-degree

relatives.^{21, 23, 25, 28} One of these 5 studies (Zhang et al.) did not report any donor source, and the other study (Vaughn et al.) used healthy anonymous donors.^{26, 28}

3.9. Preparation

Preparation methods of cohort studies included both fresh (n=5) and frozen (n=2) protocols. Of those studies that demonstrated clinical remission, 60% (3/5) used a fresh feces protocol, 20% (1/5) the frozen protocol, and the other did not report this.^{21, 23, 25, 26, 28}

3.10. FMT delivery and frequency

FMT delivery methodology included enema administration (n=7), nasogastric/nasojejunal (n=4), colonoscopic instillation (n=5) and gastroscopic instillation (n=1). At least 41% (n=34) of patients in case and cohort studies received FMT more than once (some studies did not clarify).^{3, 4} In one case study, administration was reported as high as 70 times in a single patient.⁶ There was no correlation between efficacy and number of FMT sessions performed. The majority of the case series reported multiple FMT sessions. Of the 5 cohort studies that demonstrated clinical remission, 1 study (Kunde et al.) administered enemas for 5 consecutive days while the other 4 studies (Damman et al., Suskind et al., Vaughn et al., and Zhang et al.) performed either a single nasogastric, single gastroscopic or colonoscopic administration.^{21, 23, 25, 26, 28} The RCT conducted weekly single enema administrations for 6 weeks during the blinded phase.²⁹

3.11. Safety and Adverse events

Adverse events were monitored and reported in most cohort studies (except Damman et al. and Landy et al.) but in none of the case studies. Overall, FMT was well tolerated. No serious adverse events were reported by any study. **Table 4** provides an overview of all adverse events reported during FMT follow-up. Other specifications included administration routes, duration and if medical treatment was required. Fever in varying degrees, with or without chills, abdominal tenderness, and CRP elevation after FMT were reported in 11 patients (15%) from 4 studies.^{20, 22, 23, 27} Fever severity and duration ranged from self-limiting to requiring acetaminophen treatment and was present from several hours up to two days after FMT administration. Almost all other reported events included the gastrointestinal (GI) tract and were thought to be directly related to the administration procedure (such as NJ tube irritation).²⁰ One study reported a patient with pancreatitis of unknown origin during follow-up.²⁰ In the RCT no major adverse events were observed although two of the (UC) patients receiving FMT were diagnosed with Crohn's disease after receiving FMT and one patient in the placebo group.²⁹

3.12. Microbiota and histological analysis

Microbiota analysis was reported in six studies. Four of these examined FMT efficacy among UC patients and 2 among CD patients. All 6 six studies analyzed the microbiome of fecal samples but only Kump and colleagues analyzed the microbiome of mucosal samples.²² In the UC studies, Angelberger et al. demonstrated that recipient microbiota acquired, and subsequently maintained, donor microbiota similarity in 1 of 5 patients for at least 12 weeks.²⁰ Of interest, change in microbiota occurred in the only patient that had

symptomatic response to FMT (after a transient increase of CRP). Data from Angelberger et al. also suggests a correlation between Mayo scores and an overrepresentation of *Enterobacteriaceae* and an underrepresentation of *Lachnospiraceae* at the family level.²⁰ Kump et al. found no long-term difference in bacterial richness or diversity. However, an analysis at phylum level demonstrated a significant reduction seen in *Proteobacteria* and an increase in *Bacteroidetes* after FMT.²² Colonic microbiota of recipients became more similar to the donor microbiota in 50% (3 of 6) of patients. These changes were not associated with clinical response.²² Two other UC studies also included metagenomic analyses.^{21, 30} Damman et al. found a positive correlation of FMT, including *Gordonibacter pamelaea* and improved UCDAI scores.²¹ The group that conducted the RCT found an increase in butyrate producing groups in responders versus non-responders.³⁰ These groups included *Ruminococcus*, *Blautia* and *Lachnospiraceae* (*Roseburia* and *Faecalibacterium*). In addition, the microbiome diversity was not altered post-FMT in either the responders or the non-responders. However, feces of responders demonstrated several functional metagenomic differences including butanoate metabolism, biosynthesis, and degradation of secondary metabolites and bacterial toxins compared to non-responders.

Vermeire et al. analyzed both donor and recipient stool pre-FMT administration among patients with Crohn's disease.²⁷ Results suggested that microbiota of donor stool appeared clustered on a phylogenetic level. In contrast, recipients' stool did not reveal coherent clustering and returned to their baseline composition at week 8. When Vaughn et al. investigated the microbiome by 16S rRNA sequencing as well as deep shotgun metagenomic sequencing, they found that the microbiome had shifted towards less disease associated (donor) taxa.²⁶ In addition, deep shotgun metagenomics of one donor-recipient pair found that only 10% of recipient organisms of the pre-FMT analysis were left.

Cellular changes from mucosal biopsies were examined in only one study.²⁴ Landy et al. monitored tight junction alteration and immunological parameters pre-FMT and 4 weeks post-FMT in 5 patients with pouchitis. None of these parameters changed post-FMT and no patients within this study demonstrated improvement.

4. Discussion

To date, this is the largest systematic review and first meta-analysis of FMT in IBD. The results of these analyses reveal additional insights into the promise and limitations of this novel therapy. We identified 18 (1 RCT, 9 cohort studies and 8 case studies) studies that examined FMT as primary or adjunctive therapy for IBD. Clinical remission was achieved in 54 of 119 (45%) of patients. Notably, the inclusion of case studies in this analysis elevates the risk of publication bias. A meta-analysis of cohort studies was performed to minimize this bias, and demonstrated a pooled estimate for achieving short-term clinical remission after FMT of 36.2%. A subgroup meta-analysis including only UC patients of cohort studies showed a pooled estimate for achieving remission of 22%. This rate appears similar to the remission rate suggested by the RCT by Moayyedi et al. among UC patients, approximately 23%. In examining subgroup meta-analyses alone, it might appear that FMT is more efficacious in a younger population. However, the results are significantly heterogeneous, which considerably limits the applicability of the conclusions. In addition, factors such as

duration of disease or differences in environmental triggers cannot be adequately accounted for with a sample size this small. A limited number of cohort studies described and/or observed mucosal healing, an endpoint that would have increased the objectivity of the authors' findings. These findings are corroborated by Moayyedi et al, who demonstrated no difference between the two groups when the endoscopic Mayo score or HRQoL scores were used as endpoints.²⁹ While it would be of great interest to further analyze factors such as disease severity and location or extent of disease, the total number of patients used to calculate the rate of patients achieving clinical remission was too small to draw statistically meaningful conclusions.

This review has several methodological and theoretical limitations. First, the applicability of the results from this review and meta-analysis are constrained by the lack of published research and the methodological quality of research that has been published so far. All eligible studies were included in the initial pooled analysis systematic review. While this increases the risk for heterogeneity and biases, these studies were included to provide a general updated overview of data available and to provide comparison with the 2 previously published systematic reviews. To minimize these risks, an additional meta-analysis was performed and only included cohort studies. Additionally, meta-analysis and subgroup meta-analyses were completed to further address concern for bias. These analyses attempt to control for study variation and limit the undue influence of cohort studies, the heterogeneity of study populations, and FMT methodology (e.g. administration type and frequency). The limited research within this field precluded the analysis of specific FMT delivery protocols. As such, the variability in methodology may have diluted the effect or efficacy of a particular treatment paradigm. It is also possible that the inclusion of case studies within this review inadvertently inflated the reported effect size and cumulative results.

There are 2 published systematic reviews of FMT among IBD patients that were completed prior to this publication.^{10, 11} While results from the systematic review by Anderson and colleagues demonstrated endoscopic and histologic disease remission in 15 of 24 patients (63%)¹⁰, the validity of the data was limited by significant methodological concerns. The authors did not include a complete clinical overview of patients achieving clinical remission. Therefore, the high rates of remission in that review can likely be attributed to publication bias; at that time, there were only 2 cohort studies in press, both of which did not report or demonstrate any endoscopic or histologic remission. In addition, the authors designated 'symptom-free' as a categorical endpoint but included no pre-defined criteria. A second systematic review by Sha and colleagues included outcomes of FMT for IBD treatment and was published in the same journal. The review contained mostly case reports and calculated a 'success rate' of 77.8% for adult IBD patients.¹¹ However, this review also contained several methodological limitations, most notably that FMT outcomes were measured by treatment 'success rates' and not any other more validated measures. In addition, one of the studies that was included in the overall success rate was a case report that did not assess clinical outcome, but investigated microbiota modification only.³¹ Two other studies that are included in this review appear to overlap with earlier studies published by the same group, and one of these included *Clostridium difficile* eradication in its success rate.^{32, 33}

The etiology of IBD is complex, multifactorial and incompletely understood. Throughout the past century many theories have proposed and/or implicated the role of different bacteria.³⁴ In particular, microbial dysbiosis has been hypothesized as a key player in disease development.³⁵ Studies that have examined the role of altered microbiota in IBD demonstrate reduced gut microbiome richness and biodiversity, such as a decrease in *Feacalibacteria* with *feacalibacterium prausnitzii* in mucosa-associated microbiota or feces.^{36, 37} In contrast to what might be then expected, probiotics have demonstrated mixed results as treatment for ulcerative colitis.³⁸⁻⁴⁰ A definite causal relationship between bacteria and the pathogenesis of IBD has not yet been identified. As a result, proof of Koch's postulates for IBD is elusive and it remains possible that all observations about the microbiome and attempts to modify it are simple associations rather causal relationships.^{41, 42}

A strength of our review is that it provides a comprehensive overview and that it excluded studies that included co-morbid IBD and GI infections. FMT has strong empirical support for CDI. As such, symptomatic improvement of symptoms after transplantation in an individual with co-morbid diagnosis cannot be attributed to improvement in IBD directly. In addition, this is the first systematic review to include a complete meta-analysis of cohort studies alone. As meta-analyses allow for a more objective evaluation of FMT efficacy in IBD patients, its inclusion within the greater systematic review provides a more comprehensive view of treatment success.

4.1. Safety

Results from these analyses suggest that FMT is generally tolerable and safe. Although multiple studies report fever (predominantly self-limiting) post-FMT, most conceptualize post-administration symptoms as a consequence of the administration procedures themselves. Long-term immunologic effects or onset of latent infections cannot be assessed in these studies due to relative short follow-up. Thus, rigorous screening of the donor and donor stool remains particularly important. To this end, both the infectious and gastroenterological societies recommend the utilization of the patient's partner, family or family friend for feces donation.⁴³ Given the heritability of both IBD and the gut microbiome itself, the role of donor selection should be investigated further.

Due to the emerging nature of FMT in IBD, this review is limited both by the quality and number of studies and published RCTs available (although we did include the one RCT of FMT in IBD that is currently available). As a result, our meta-analysis of cohort studies had small subgroup analyses with a heterogeneous population among most subgroups. Due to the experimental nature of this therapy and myriad of variables in study design (such as donor choice, preparation of feces and substance delivery) it is not possible to compare all of these individual factors yet. Two recent systematic reviews of FMT in patients with CDI, (one of which included a meta-analysis) did not find significant differences in clinical outcomes for studies that differed in donor selection or FMT delivery.^{44, 45} This said, as IBD is a more complicated and heterogeneous pathology than CDI, it may be likely that these results will vary among the IBD patient population. Other factors may have influenced these outcomes, including: differences in preparation of recipients and donor stool,

administration of antibiotics to the recipient pre-FMT, and lavage of the donor before feces collection.^{20, 22} In addition, follow-up varied as well and protocols differed in both duration and methods. Mucosal assessment was not always performed prior to FMT administration and, as a result, clinical information about disease severity and location were not consistently documented.

In these, the early days of attempting microbiota modification as treatment for IBD, it is important to recognize the strengths and range of documented research while being mindful of its limitations and the pressing need for ongoing, thoughtful study. More research from randomized controlled trials that evaluate endoscopic appearance pre-FMT and mucosal healing post-FMT and that allow for sufficient follow-up clearly are needed. Future work should also assess the role of the different FMT delivery modalities and frequencies, and continue to assess the microbiome in both recipient and donor. Only through such careful study will we be able to determine the true utility of FMT in IBD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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(Non-standardized) abbreviations

FMT	Fecal Microbiota Transplantation
CR	Clinical Remission
IBD	Inflammatory Bowel Disease
CD	Crohn's Disease
UC	Ulcerative Colitis
CDI	Clostridium difficile Infection
PICOS Population	Intervention Control Outcomes Study design
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
ACG	American College of Gastroenterology
DDW	Digestive Diseases Week
AIBD	Advances in IBD
ECCO	European Crohn's and Colitis Organization
NASPGHAN	North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

ESPGHAN

European Society for Pediatric Gastroenterology, Hepatology and Nutrition

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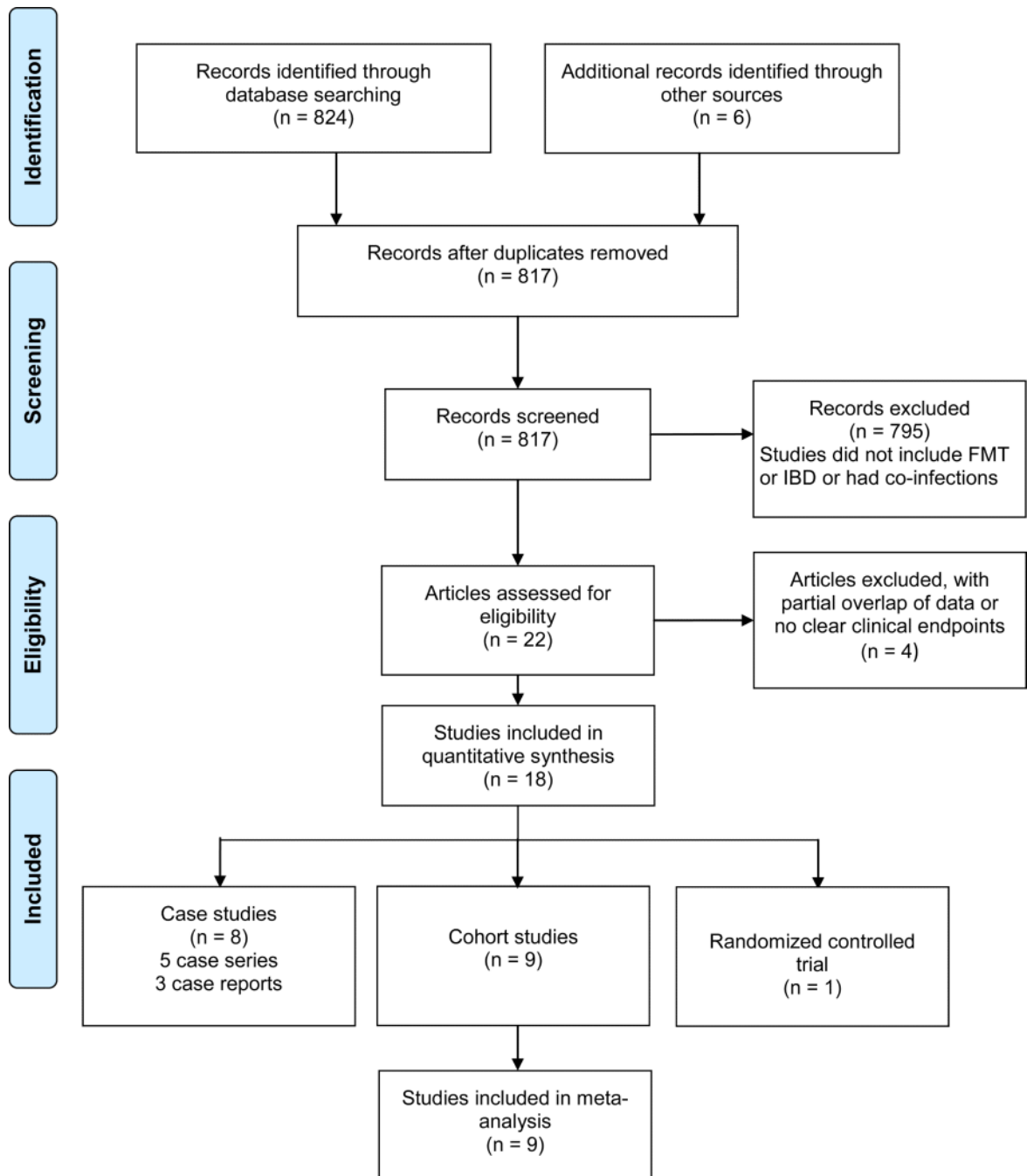


Figure 1.
Flow-diagram of identified studies.

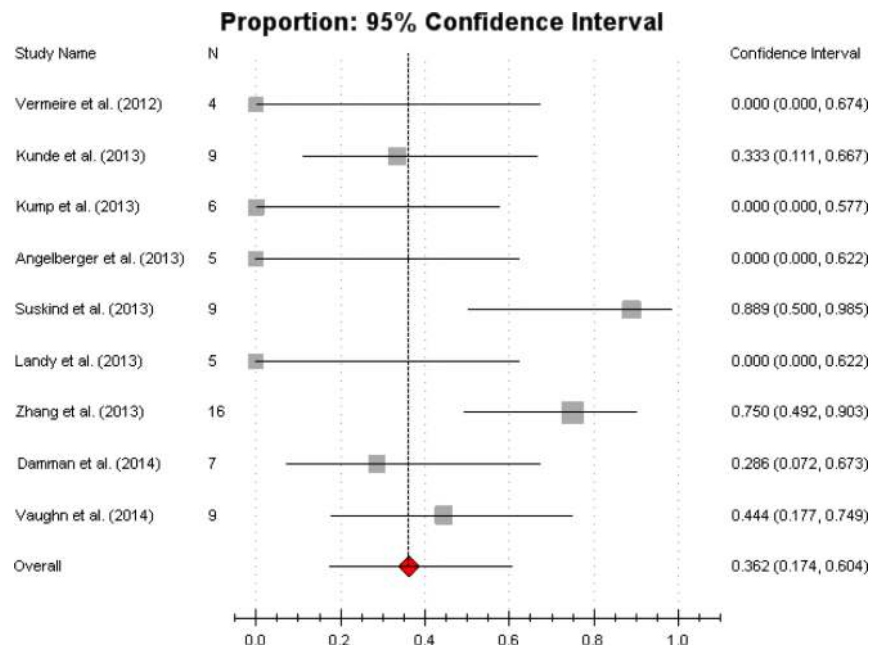
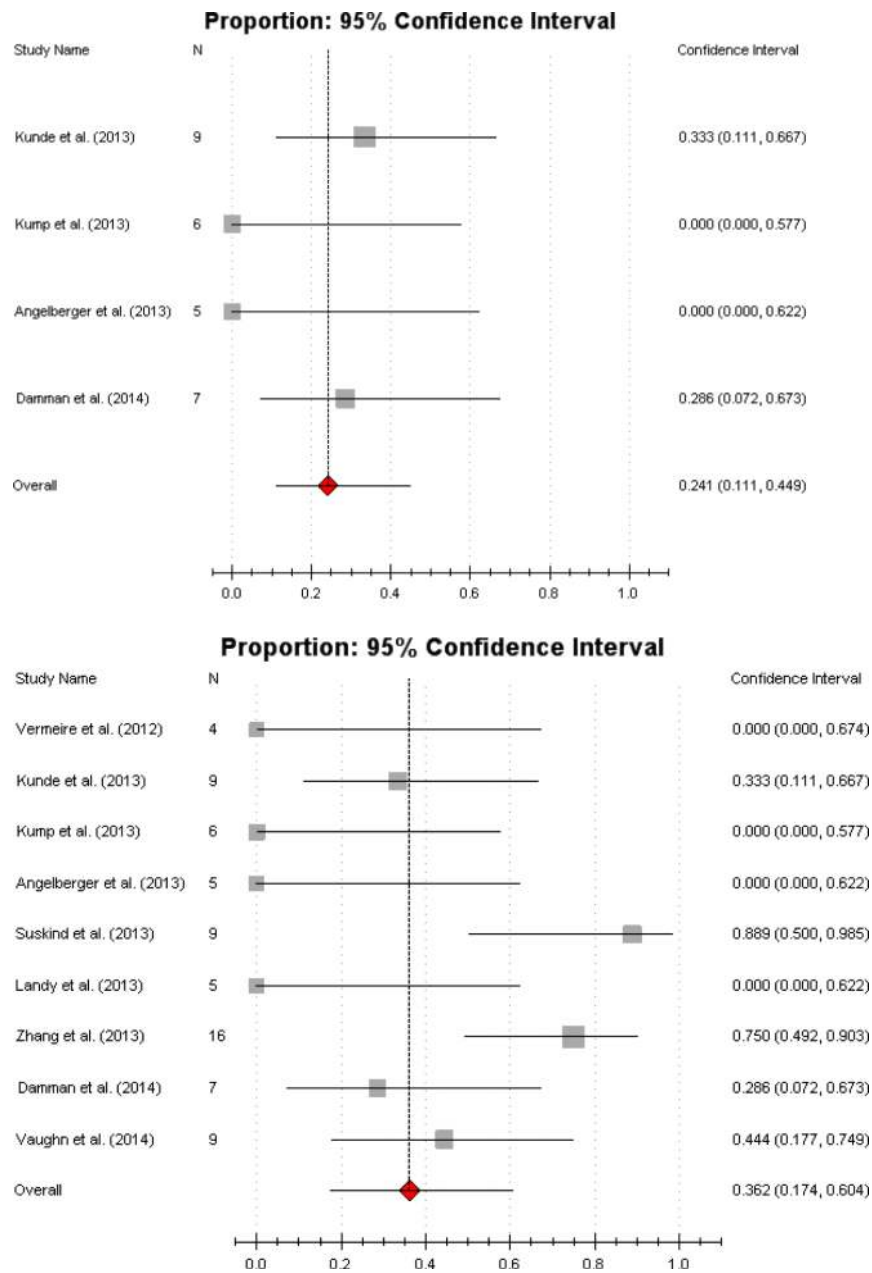


Figure 2. Forest plot of all cohort studies overall Pooled estimate of clinical remission (CR) of 36.2% (95% CI 17.4%-60.4%).

**Figure 3.**

Individual forest plots of subgroups:

Figure 3a Forest plot of UC only. Pooled estimate of CR 22% (95% CI 10.4%-40.8%).

Figure 3b UC without pouchitis. Pooled estimate of CR 24.1% (95% CI 11.1%-44.9%).

Figure 3c CD only Pooled estimate of CR 60.5% (95% CI 28.4%-85.6%).;

Figure 3d Young population (age 7-20yrs) studies only. Pooled estimate of CR 64.1% (95% CI 10.6%-96.4%).

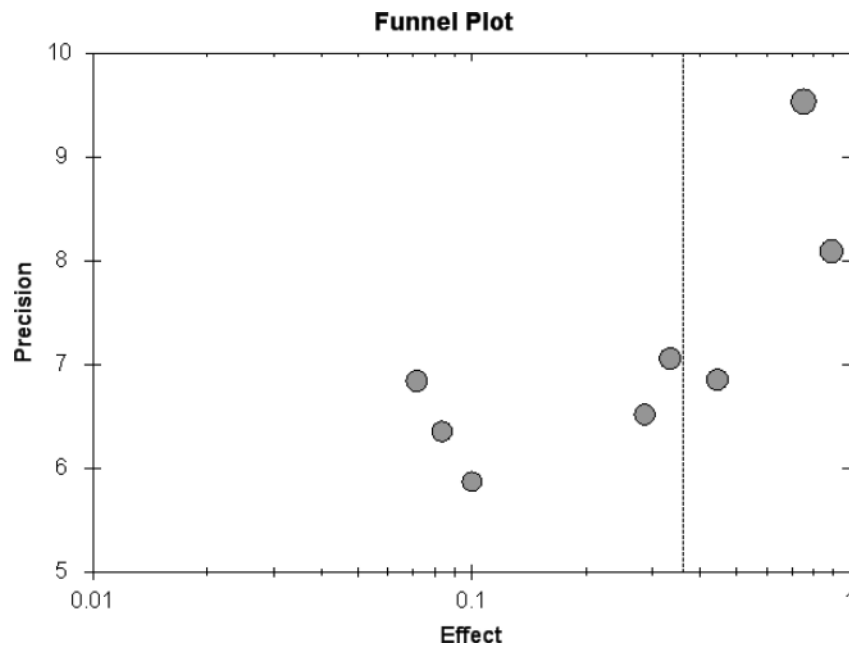


Figure 4.
Funnel plot of main meta-analysis (all cohort studies).

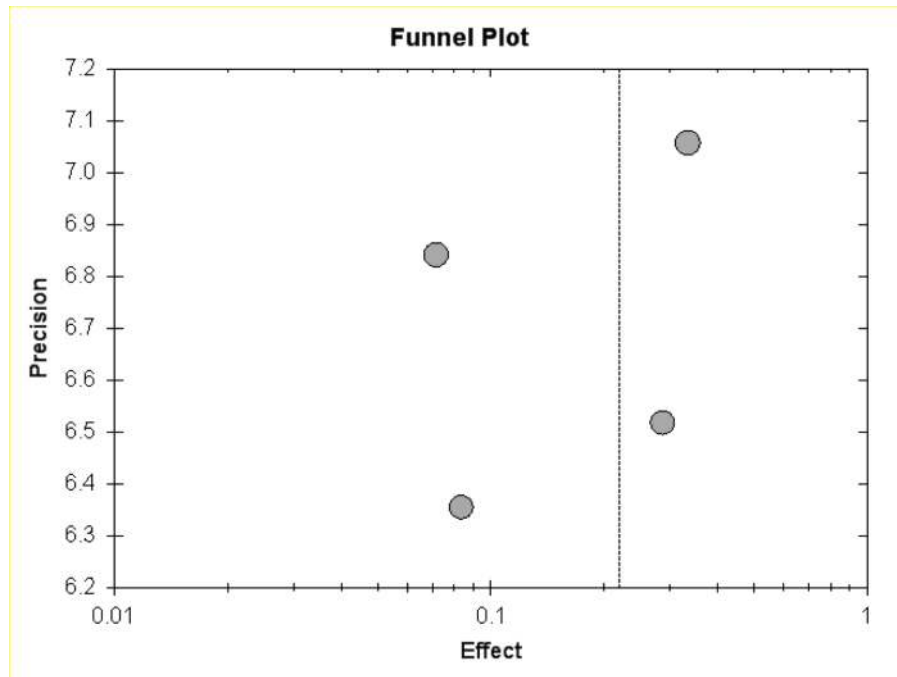


Figure 5a.
Funnel plot of UC meta-analysis.

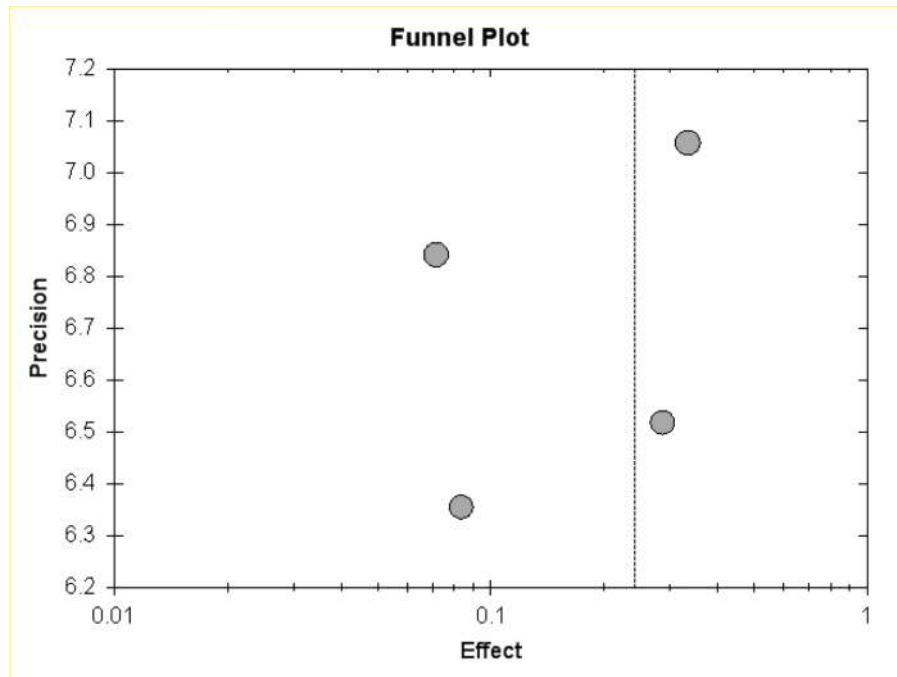


Figure 5b.
Funnel plot of UC meta-analysis, but pouchitis excluded.

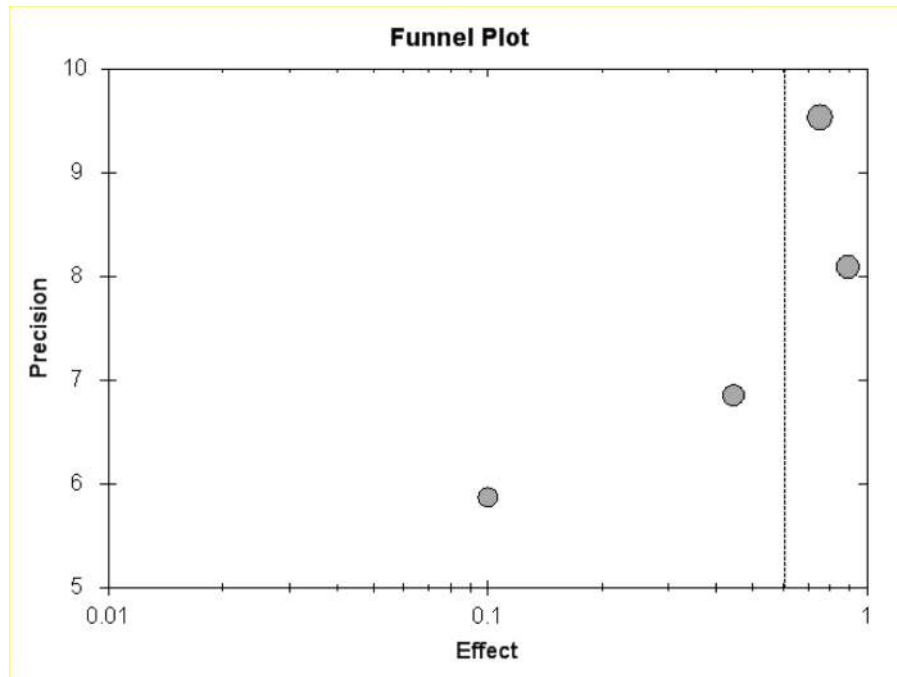


Figure 5c.
Funnel plot of CD meta-analysis, but pouchitis excluded.

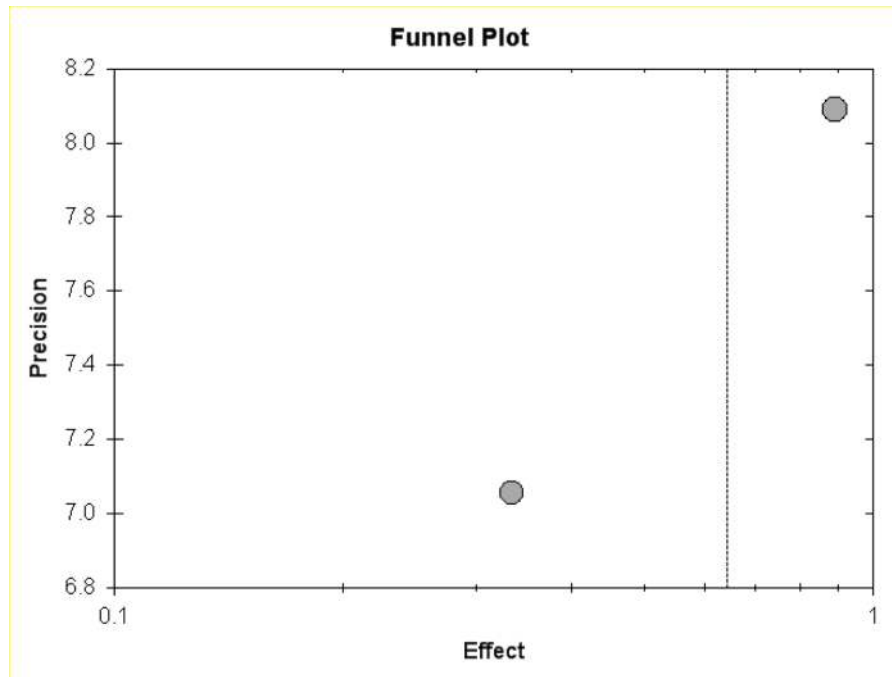


Figure 5d.
Funnel plot of meta-analysis of young-populations (age 7-20) only.

Table 1

Newcastle-Ottawa Scale for assessing quality of cohort studies.

Quality assessment Scale	Accepted Criteria	Vermeire <i>et al.</i> (2012), ²⁷	Kunde <i>et al.</i> (2012), ²³	Kump <i>et al.</i> (2013), ²²	Angelberger <i>et al.</i> (2013), ²⁰	Suskind <i>et al.</i> (2013), ²⁵	Landy <i>et al.</i> (2013), ²⁴	Zhang <i>et al.</i> (2013), ²⁸	Damman <i>et al.</i> (2014), ²¹	Vaughn <i>et al.</i> (2014), ²⁶
Selection										
Representativeness of the exposed cohort	Representative of average child/adult with IBD Sex, Age and disease severity	-	*	-	-	*	-	-	*	*
Ascertainment of FMT exposure	Secure records, structured interview	*	*	*	*	*	*	*	*	*
Demonstration that outcome of interest was not present at start of study	Evidence of no prior FMT exposure	-	-	*	* ^a	-	-	-	*	*
Outcome										
Assessment of outcome	Utilization of predefined disease activity scores or mucosal evaluation?	*	*	*	*	*	*	*	*	*
Follow-up enough for outcome to occur?	Follow-up for at least 3 months	-	-	*	*	-	-	-	*	*
Adequacy of follow up of cohorts	Follow-up of complete cohort or unlikely to introduce bias?	*	*	*	*	*	*	*	*	*
Total	(max=6)	3	4	5	5	4	3	3	6	6

^a (4/5 pts no prior FMT)

Table 2-1

Case Study Characteristics.

Nr	Study	#IBD pts	IBD Type	IBD Severity	FMT dosage	FMT delivery	Pre-Abs / lavage	Frequency	Donor	Follow-up
1	Bennet <i>et al.</i> (1989). ²	1	UC	Severe	NR	Large volume enema's	NR	multiple x1	NR	6 months
2	Borody <i>et al.</i> (1989). ⁴	2	UC,CD	Active	NR	NR	NR	NR	NR	1-12months
3	Borody <i>et al.</i> (2001). ⁵	3	UC	Quiescent	Suspended in 200ml saline+table spoon psyllium	Enema	NR	daily x 5days	Healthy adults	8-28 months
4	Borody <i>et al.</i> (2003). ⁷	6	UC	Severe	200-300g(diluted to 200-300ml)	Enema	Vancomycin, Metronidazole and rifampicin for 7-10 days +3L oral PEG solution	daily x 5days	Family or close relation	1-13 years
5	Borody <i>et al.</i> (2011). ⁶	3	IBD	IM/anti-TNF refractory-severe	NR	Enema (Self)	NR	daily&weekly X34-70	Clinic donor, family, partner	1-4 years
6	Borody <i>et al.</i> (2011). ³	1	UC+ITP	Chronic-relapsing UC	NR	NR	NR	NR	NR	NR
7	Kao <i>et al.</i> (2014). ⁹	1	IBD	Moderate-Severe	400cc fresh fecal suspension	Colonoscopy	NR	x3 (0.4, 10 wks)	universal donor	2 months
8	Kellermayer <i>et al.</i> (2013). ⁸	4 (-1) ^a	UC	IM/anti-TNF dependent	NR	Colonoscopy	NR	Serial	?	>5 months

NR=Not Reported

^aExcluded from final analysis due to enema intolerance.

Table 2-2

Cohort Study Characteristics.

Nr	Study	#IBD pts	IBD Type	IBD Severity	FMT dosage	FMT delivery	Pre-Abs / lavage	Frequency	Donor	Follow-up
1	Vermeire <i>et al.</i> (2012), ²⁷	4	CD	Medically-refractory	200g feces	NJ infusion	NR	3x in 36 hrs	Healthy donor	2 months
2	Kunde <i>et al.</i> (2013), ²³	10 (-1 ^a)	UC	mild-moderate	90-113g/250ml	Enema up to (4x60ml) /day	NR	x5 days	Parents	6 wks
3	Kump <i>et al.</i> (2013), ²²	6	UC	therapy-refractory	100-150g/200-350ml saline - >total 300-500mL	Colonoscopy	Lavage of donor pre collection	x1	Nonrelatives, different household	1 yr
4	Angelberger <i>et al.</i> (2013), ²⁰	5	UC	Severe	Initially 60g/250mL NJ 17-25g/250mL, Enema 6-22g/100mL	NJ + enema	Metronidazole for 5-10days	x3 consecutive days	No family/hospital staff	>1 yr
5	Suskind <i>et al.</i> (2014), ²⁵	9	CD	mild-moderate	NR	NG	NR	x1	parent	6 weeks
6	Landy <i>et al.</i> (2013), ²⁴	5	UC	chronic refractory pouchitis	30g / 250ml saline	Nasogastric	NR	x1	nominated by participating pts	4 weeks
7	Zhang <i>et al.</i> (2013), ²⁸	16	CD	refractory (HBI ⚡)	NR	gastroscopic	NR	x1	NR	1 month
8	Damman <i>et al.</i> (2014), ²¹	8 (-1 ^a)	UC	Mild-moderate (UCDAI 3-10)	NR	Colonoscopic	Standard colonoscopy prep	x1	Chosen by recipient	12 wks
9	Vaughn <i>et al.</i> (2014), ²⁶	9	CD	Active CD (HBI ⚡)	50g in 250ml saline	Colonoscopic	Standard colonoscopy prep	x1	Healthy unrelated	12 wks

NR=Not Reported; NJ= Nasojejunal tube; NG= Nasogastric tube; Abs= antibiotics

^aExcluded from final analysis due to enema intolerance.

Table 3

Clinical outcomes of cohort studies & protocol type.

Nr.	Study	Deterioration	No improvement	Improvement	No remission	CR	ER/HR	Protocol type
1	Vermeire <i>et al.</i> (2012). ²⁷ (n=4)	-	4	-	-	-	-	NR
2	Kunde <i>et al.</i> (2013). ²³ (n=9)		3 ^g	3 ^d		3	NR	Fresh
3	Kump <i>et al.</i> (2013). ²² (n=6)	1 ^b	3	2 ^e		-	-	Frozen
4	Angelberger <i>et al.</i> (2013). ²⁰ (n=5)	2 ^c	2	1 ^f		-	-	Fresh
5	Suskind <i>et al.</i> (2014). ²⁵ (n=9)	-	-	1		8	NR	NR
6	Landy <i>et al.</i> (2013). ²⁴ (n=5)	NR	NR	NR		-	-	Fresh
7	Zhang <i>et al.</i> (2013). ²⁸ (n=16)	-	1	3		12	NR	Fresh
8	Damman <i>et al.</i> (2014). ²¹ (n=7)	1	4	-		2	1	Fresh
9	Vaughn <i>et al.</i> (2014). ²⁶ (n=9)	-	3	2		4	-	Frozen

CR= Clinical remission; ER/HR =Endoscopic or Histologic Remission; NR=Not (exactly) Reported; PUCAI=Pediatric Ulcerative Colitis Activity Index; MCID=Minimal Clinically Important Difference

^b (initial improve then relapse+ colectomy)

^c partial deterioration after 4 wks w/ returning to baseline

^d Improvement >20 PUCAI MCID

^e Additional reduction of (3and 4 pts of mayo score)

^f Reduction by 4 points on Mayo score

^g within PUCAI <20 MCID.

Table 4

Adverse events reported during FMT & follow-up (n=7/9 cohort studies).

	FMT administration	Adverse events per patient	Time span & Action
Vermeire <i>et al.</i> (2012). ²⁷	Single NJ tube	• 3/4 patients High fever and abdominal tenderness (n=3)	• Start at day of FMT and Disappeared after 2 days
Kunde <i>et al.</i> (2013). ²³	Daily enemas x5 consec days	• Moderate Fever&chills 3 hrs after FMT (n=1) • Single episode low grade fever no Rx necessary (n=1) • Other GI symptoms (n=9) • Fatigue (n=3)	• All self-limiting except 1 fever. (n=1) Required acetaminophen and diphenhydramine.
Kump <i>et al.</i> (2013). ²²	Single Colonoscopy	Self-limiting fever up to T 39C + incr stool frequency (+ temp, CRP, and IL6 elevation) (n=1)	Day1 post-FMT- day 3 (self-limiting).
Angelberger <i>et al.</i> (2013). ²⁰	NJ +enema (both on 3 consec days)	• Fever+CRP elevation (n=5) • NJ tube irritation (n=5) • Flatulence (n=2) • Vomiting (n=1)	After fever in subject 1, all patients received metronidazole pre-FMT and some received probiotics.
Suskind <i>et al.</i> (2014). ²⁵	Single NG	Mild gassiness and bloating (n=3)	Day after FMT no intervention.
Zhang <i>et al.</i> (2013). ²⁸	Single gastroscopic	Increased diarrhea (n=5)	Onset within 3 hrs (self-limiting)
Vaughn <i>et al.</i> (2014). ²⁶	Single colonoscopic	No immediate complications or adverse events in the first 4 weeks post-FMT.	

NJ= Nasojejunal tube. NG=nasogastric tube