Systematic Review and Meta-analysis: Fecal Microbiota Transplantation for Treatment of Active Ulcerative Colitis

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Background: Changes in the colonic microbiota may play a role in the pathogenesis of ulcerative colitis (UC) and restoration of healthy gut microbiota may ameliorate disease. A systematic review and meta-analysis was conducted to assess fecal microbiota transplantation (FMT) as a treatment for active UC.

Methods: A literature search was conducted to identify high-quality studies of FMT as a treatment for patients with UC. The primary outcome was combined clinical remission and endoscopic remission or response. Secondary outcomes included clinical remission, endoscopic remission, and serious adverse events. Odds ratios with 95% confidence intervals (CIs) are reported.

Results: Overall, 4 studies with 277 participants were eligible for inclusion. Among 4 randomized controlled trials, FMT was associated with higher combined clinical and endoscopic remission compared with placebo (risk ratio UC not in remission was 0.80; 95% CI: 0.71–0.89) with a number needed to treat of 5 (95% CI: 4–10). There was no statistically significant increase in serious adverse events with FMT compared with controls (risk ratio adverse event was 1.4; 95% CI: 0.55–3.58).

Conclusions: Among randomized controlled trials, short-term use of FMT shows promise as a treatment to induce remission in active UC based on the efficacy and safety observed. However, there remain many unanswered questions that require further research before FMT can be considered for use in clinical practice.

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Key Words: ulcerative colitis, fecal transplant, fecal microbiota transplant, inflammatory bowel disease

Ulcerative colitis (UC) is a chronic disease characterized by inflammation of the colon mucosal layer. The precise etiology of UC is unclear, with interaction of genetic, environmental, and microbiological factors likely playing a role.[1] Dysbiosis in the gastrointestinal tract is thought to be a contributing factor in the development of UC. However, treatment aimed at alteration of the microbiota in UC, such as probiotics and antibiotics, has limited clinical success.[2,3]

Over the last several years, fecal microbiota transplantation (FMT) has been successfully used as a treatment for recurrent *Clostridium difficile* infection (CDI).[4] Given the potential role of the microbiome in inflammatory bowel disease (IBD), there has been much interest in FMT for IBD.[5] Initial case reports and non-controlled case series of FMT in IBD were promising. A meta-analysis of 119 patients with IBD who received FMT (predominantly for CDI) found that 45% (54 of 119) of patients achieved clinical remission of their IBD during follow-up.[6] Delivery of FMT in these cases was quite heterogeneous, including a variety of delivery modalities and dosing regimens. Three other meta-analyses have since been published, but are limited by heavy reliance on observational data and heterogeneous inclusion criteria.[7–9] Two randomized controlled trials (RCTs) for FMT in UC have been published since the most recent meta-analysis.[10,11] Furthermore, no meta-analysis to date has focused on randomized trials or examined endoscopic healing from FMT, an outcome which is felt to be a key endpoint of clinical trials in UC given the long-term outcomes associated with it.[12]

To update and improve on the previous systematic reviews, we conducted a systematic review and meta-analysis to evaluate the efficacy and safety of FMT in UC using only high-quality evidence.

METHODS

Study Selection

A systematic literature search was conducted to identify studies that investigated treatment with fecal microbiota

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TABLE 1. Definition of Outcomes from Trials Included

First Author	Year	Inclusion Eligibility for Trial	Combined Clinical and Endoscopic Improvement	Definition of Clinical Remission	Definition of Clinical Response	Definition of Endoscopic Remission
Costello	2017	Mild-to-moderate UC (Mayo score 3–10, with endoscopic subscore ≥2)	Mayo score <3 and endoscopic Mayo score ≤1	SCCAI ≤2	≥3 point reduction in Mayo score	Mayo endoscopic score ≤1
Moayyedi	2015	Mild-to-moderate UC (Mayo score ≥4, with endoscopic subscore ≥1)	Mayo score <3 and endoscopic Mayo score = 0	Mayo score <3	≥3 point reduction in Mayo score	Mayo endoscopic score = 0
Paramsothy	2017	Mild-to-moderate UC (Mayo score 4–10, with endoscopic subscore ≥1)	Mayo score <3 and ≥1 reduction in endoscopic Mayo score	Mayo score <3	≥3 point reduction in Mayo score, or 50% or greater reduction from baseline in combined rectal bleeding plus stool frequency subscores, or both	Mayo endoscopic score = 0
Rossen	2015	Mild-to-moderate UC (SCCAI 4–11, with endoscopic subscore ≥1)	SCCAI ≤2 and ≥1 reduction in endoscopic Mayo subscore	SCCAI ≤2	≥1.5 point reduction in SCCAI	Mayo endoscopic score = 0

SCCAI, simple clinical colitis activity index.

transplantation in UC. We identified sources from the MEDLINE, Embase, and PubMed databases from the years 1950 to February 2017. There were no language restrictions. Keywords used were {FMT or ([faecal or fecal or feces or faeces or stool] and [transplant* or microbiota or transfusion or implant* or instillation or donor* or enema or reconstitution or infusion* or transfer*]) or bacteriotherapy} and (UC or ulcerative colitis). Both free-text words and subject headings were searched. Variations of root words were searched alone or in combination. High sensitivity filter was used to limit studies to RCTs. The reference lists of any studies meeting inclusion criteria were reviewed manually to identify additional relevant publications. We adhered to PRISMA (preferred reporting items for systematic reviews and meta-analyses) recommendations where possible.[13]

Inclusion/Exclusion Criteria

For inclusion in the meta-analysis, studies were required to meet the following criteria: (1) prospective randomized controlled design; (2) enrolled adult subjects with endoscopically and clinically active UC based on clinical assessment scores commonly used for UC; (3) fecal transplantation offered in the interventional arm; and (4) control group receives a placebo consisting of only the FMT excipient (no microbiota) or an autologous FMT. Patients receiving FMT through different modalities (i.e., colonoscopy, enteric tube, or enemas) were all permitted, as were studies that used either single or pooled donor FMT. Where studies did not provide sufficient information, authors were contacted to obtain additional data.

Outcomes of Interest

The primary outcome was short-term combined clinical remission with endoscopic remission or response, assessed after 6 to 12 weeks of therapy. Secondary outcomes included clinical remission, endoscopic remission, and serious adverse events during the intervention period. Adverse events were considered serious if they were infections requiring treatment, hospitalization, surgery, malignancy or death, and occurred during the interventional period. Table 1 reports inclusion criteria and definitions of these outcomes for each study included in the meta-analysis.

Data Extraction and Quality Assessment

Study selection and data extraction was carried out independently by 4 investigators (P.M., Y.Y., N.N. and Z.K.) with discrepancies resolved by consensus in consultation with the senior authors (J.-F.C., C.P. and W.R.). Risk of bias tables were used to assess the quality of randomized studies, as recommended by the Cochrane Collaboration.[13] The risk of bias is assessed in 7 different domains using this tool, including sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other sources of bias. This was done independently by N.N., Y.Y., and P.M., and differences were resolved by discussion. The overall bias for a study is determined to be low if the risk of bias is low in all domains, high if the risk of bias is high in at least one domain, or unclear if the risk of bias is unclear in at least one domain (with no domains having a high risk of bias). We subsequently used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to determine the overall quality of evidence. GRADE assesses the overall quality of the evidence within many domains, including design, consistency, precision, directness, and publication bias, to determine if further research would lead to changes in the estimate

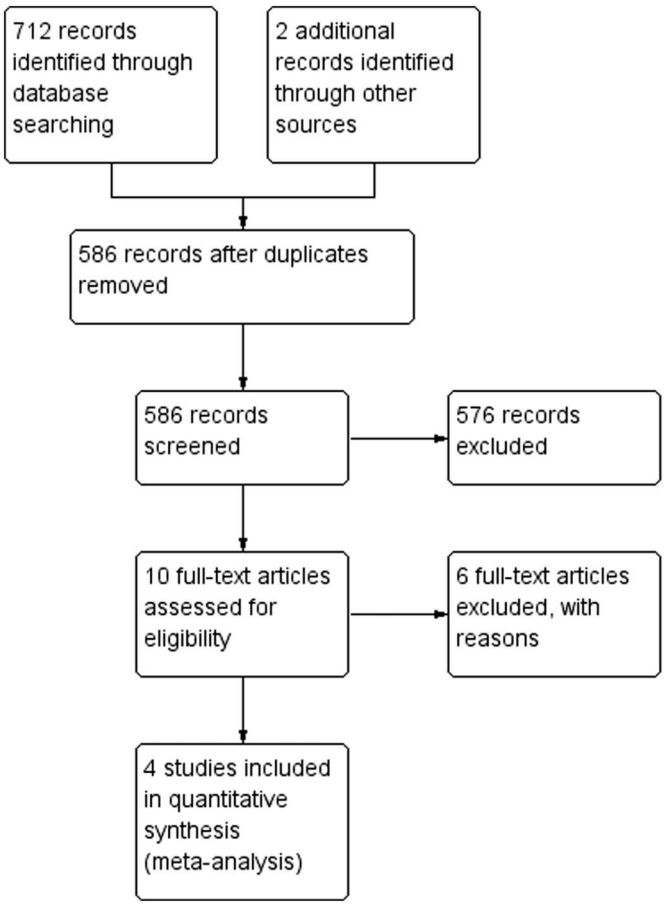


FIGURE 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowsheet.

of effect.[14] Quality assessment details are available in Supplemental Digital Content 1, http://links.lww.com/IBD/B615.

Statistical Analysis

Meta-analyses were conducted by combining individual study data into a pooled risk ratio (RR) using a random-effects model. Intention-to-treat data were extracted from all studies. We tested for heterogeneity using the χ^2 test and the I^2 test. The χ^2 test suggests heterogeneity between studies when the P-value is less than 0.15. The I^2 test describes the percentage of variability in effect estimates that is due to heterogeneity rather than chance, wherein an I^2 test greater than 50% suggests substantial heterogeneity. A random-effects model was used because this provides a more conservative estimate than a fixed effects model when heterogeneity is present. For assessment of publication bias, we planned to perform funnel plots and calculated Egger's regression intercept for studies that reported our primary outcome, provided we identified at least 10 trials.[15] Analyses were performed with RevMan 5.1 (Review Manager [RevMan] [Computer program] Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011).

RESULTS

Search Results

The literature search identified 714 citations, of which 118 were removed due to duplicates. Additionally, 586 were excluded on review of the title and abstracts (Fig. 1). A further 6 studies were excluded after careful review of the full text; 5 were cohort studies[14–18] and 1 was a pediatric RCT.[19] Overall, 4 studies (including 1 abstract) with 277 participants were eligible for meta-analysis.[10,11,20,21]

Characteristics of Included Studies

Characteristics of studies included are outlined in Tables 1 and 2. All 4 studies were prospective RCTs.[10,11,20,21] One study administered FMT through the upper gastrointestinal tract (through nasoduodenal infusion)[21] and the other studies used the lower gastrointestinal tract for administration.[11,20,21] Two studies used low frequency of administration (2–3 doses total)[11,21] and 2 studies used higher frequency of administration (6–41 doses total).[10,20] Two studies used single donor for FMT[20,21] and 2 studies used pooled donors for FMT preparation.[10,11] One study ensured all FMT samples were anaerobically prepared.[11] Duration of the studies was between 7 and 12 weeks. All 4 studies reported on all the outcomes of interest. These 4 studies included 140 participants who received donor FMT and 137 subjects received placebo or autologous FMT.

Combined Clincial Remission and Endoscopic Remission/Response

The pooled RR for combined clinical remission with endoscopic remission or response not being achieved in the FMT arm compared with placebo was 0.8 (95% confidence interval [CI]: 0.71–0.89) ($P < 0.0001$) with an $I^2 = 0\%$ and $\chi^2 = 0.55$ (df = 3), $P = 0.91$ (Fig. 2). The pooled rate for achieving the combined outcome in these studies is 27.9% for those receiving donor FMT and 9.5% for those receiving the control interventions, for a number needed to treat of 5 (95% CI: 4–10).

Clinical Remission

Significantly more patients receiving donor FMT achieved clinical remission compared with those receiving control interventions, with a pooled RR of not achieving remission was 0.76 (95% CI: 0.62–0.93) ($P = 0.01$) with an $I^2 = 31\%$ and $\chi^2 = 4.36$ (df = 3), $P = 0.23$ (Fig. 3). The heterogeneity was driven by the trial that delivered FMT by the nasoduodenal route,[21] and when this was excluded, the RR was 0.70 (95% CI: 0.58–0.85) with no significant heterogeneity ($I^2 = 0\%$ and $\chi^2 = 1.37$ [df = 2], $P = 0.50$). The pooled rate of clinical remission in all 4 trials was 42.1% in the group receiving donor FMT and 22.6% in those receiving control interventions with an number needed to treat equal to 5 (95% CI: 3–17).

Endoscopic Remission

All studies required the presence of endoscopic inflammation at baseline and assessed for endoscopic improvement at the

TABLE 2. Characteristics of Included Studies and Data Extracted for Measured Outcomes

First Author and Year	Country	Intervention FMT	Placebo	No. Patients FMT	No. Patients Placebo	Concomitant Medication	Time of Evaluation of Treatment Response	Combined Clinical Remission and Endoscopic Remission/ Response FMT	Combined Clinical Remission and Endoscopic Remission/ Response Placebo	Clinical Remission FMT	Clinical Remission Placebo	Endoscopic Remission FMT	Endoscopic Remission Placebo	Serious Adverse Events FMT	Serious Adverse Events Placebo
Costello 2017	Australia	Anaerobically prepared, pooled donor stool (3–4 donors); administered by means of colonoscopy at time 0, then 2 enemas at day 7	Aerobically prepared, autologous stool; administered by means of colonoscopy at time 0, then 2 enemas at day 7	38	35	Stable maintenance medication (5-ASA, thiopurines, MTX, anti-TNF, vedolizumab), prednisolone ≤20 mg/d with mandatory wean	Week 8	12	3	19	6	21	6	3	2
Moayyedi 2015	Canada	Single donor FMT; administered through weekly enema	Water retention enema	38	37	Stable maintenance medication (5-ASA, thiopurines, MTX, anti-TNF, steroids)	Week 7	9	2	15	9	9	3	3	2
Paramsothy 2017	Australia	Pooled donor stool (3–7 donors); administered by means of colonoscopy at time 0, then 5 enemas per wk for 8 weeks	Saline + odorant + food colouring in enema	41	40	Stable maintenance medication (5-ASA, thiopurines, MTX), prednisolone ≤20 mg/d with mandatory wean	Week 8	11	3	18	8	5	3	2	1
Rossen 2015	The Netherlands	Fresh single-donor FMT, administered through nasoduodenal tube at time 0 then at week 3	Autologous stool administered through nasoduodenal tube	23	25	Stable maintenance medication (5-ASA, thiopurines), prednisolone ≤10 mg/d	Week 12	7	5	7	8	2	2	2	2

5-ASA, 5-aminosalicylates; MTX, methotrexate; TNF, tumor necrosis factor.

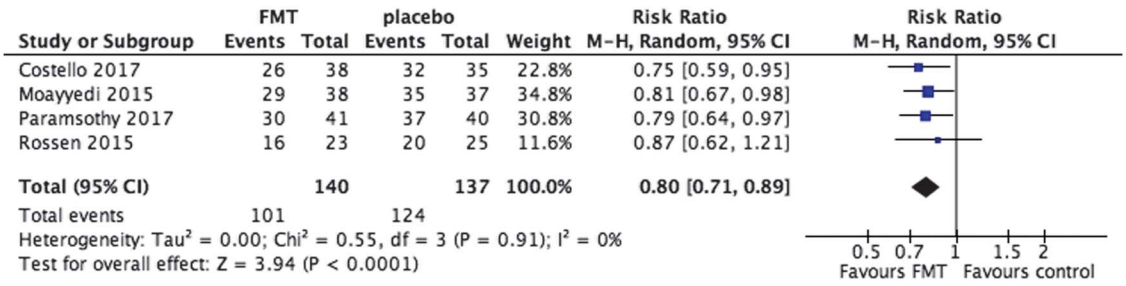


FIGURE 2. Forrest plot of all studies reporting combined clinical remission with endoscopic remission or response.

end of the study. The pooled RR for not achieving endoscopic remission with donor FMT compared with controls was 0.85 (95% CI: 0.69–1.05) ($P = 0.12$) with statistically significant heterogeneity ($I^2 = 77\%$ and $\chi^2 = 12.86$ [df = 3], $P = 0.0005$) (Fig. 4). The pooled rate of endoscopic remission for patients who received donor FMT was 26.4% compared with 10.2% for patients in the control arms.

Serious Adverse Events

Figure 5 demonstrates no significant difference between patients receiving donor FMT compared with control patients with regards to serious adverse events. The pooled RR among the randomized studies was 1.40 (95% CI: 0.55–3.58 [$P = 0.49$]) with no statistically significant heterogeneity ($I^2 = 0\%$ and $\chi^2 = 0.15$ [df = 3], $P = 0.99$). The pooled rate of serious adverse events in patients receiving FMT was 7.1% and 5.1% for those in the control group. Two of the patients who received FMT required colectomy, one for worsening of underlying colitis[10] and one for development of *C. difficile*–associated colitis.[11] There were no mortalities reported in any of the studies.

Quality Assessment and Publication Bias

Risk of bias tables are provided in Appendix 1, Supplemental Digital Content 1, http://links.lww.com/IBD/B615. Table 3 provides a summary of the risk of bias tables. According to the GRADE system for assessing quality, evidence from RCTs begins with a "high" rating. We downgraded the overall rating to low, mainly due to imprecision of treatment effect and because of heterogeneity in methodology of administering the FMT between studies. Details are available in Appendix 2, Supplemental Digital Content 1, http://links.lww.com/IBD/B615. There were too few studies to statistically assess for publication bias. Sensitivity analyses were performed for the primary outcome of combined clinical remission and endoscopic remission/response by removing the study with the largest treatment effect[11] and by removing the study with the largest number of participants,[10] and the significant treatment effect seen with FMT compared with placebo persisted.

DISCUSSION

Fecal microbiota transplantation seems beneficial and safe for treatment of active UC based on the results of this meta-analysis. There remain many questions to be addressed before it can be recommended as routine standard of care.

From a safety perspective, currently there is no long-term safety data for FMT in UC, although the reported long-term experience of FMT for patients with recurrent CDI seems reassuring.[22] However, there are theoretical concerns about conferring microbiome-associated diseases, such as autoimmune conditions, in FMT recipients. Ongoing prospective studies, including a recently funded American Gastroenterological Association (AGA) national FMT registry that aims to prospectively monitor 4000 patients for up to 10 years post-FMT, will help determine the short-term and long-term safety profile of FMT (Clinicaltrials.gov NCT02403622).[23]

Rigorous donor screening protocols were used for these studies and would need to be used if FMT were to become acceptable for clinical practice. FMT referral centers with training in FMT, which has been recommended at a European consensus conference, may be helpful in enhancing best practices in safety

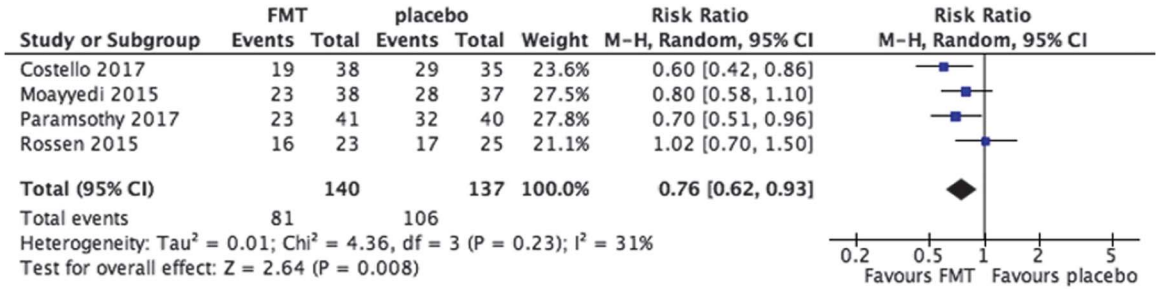


FIGURE 3. Forrest plot of all studies reporting clinical remission.

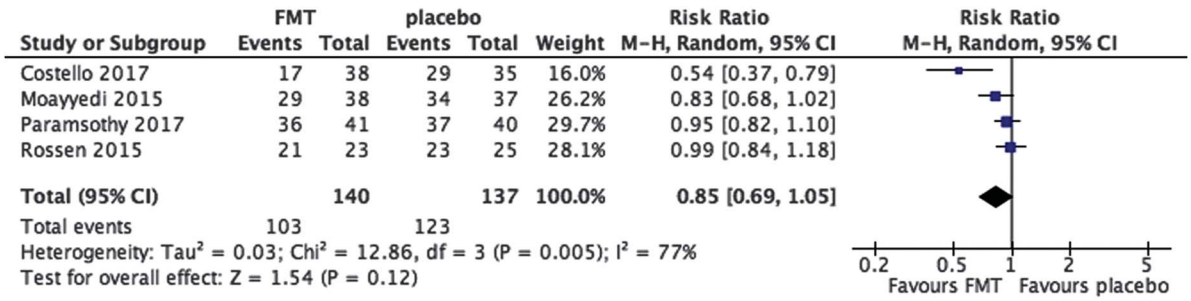


FIGURE 4. Forrest plot of all studies reporting endoscopic remission.

for FMT.[24] Additionally, the emergence of stool banks with robust screening of universal donors may help facilitate access to safe stool.[25–27]

There is also uncertainty about the most effective delivery modality of FMT. The study from the Netherlands evaluated FMT administered through nasoduodenal tubes and did not find a statistically significant improvement for outcomes such as clinical and endoscopic remission, although it may have been underpowered.[21] Additionally, both studies from Australia used colonoscopy for "induction dose," presumably to guarantee the administration of microbiota in the proximal colon, followed by enemas for maintenance therapy at different intervals. It is unclear if an initial colonoscopic administration is required given the use of enema only in the Canadian study. The use of colonoscopy to deliver FMT may help deliver a larger quantity of stool for induction than retention enemas; however, retention enemas are less expensive and safer to administer. FMT administered by means of oral capsules have been demonstrated to be efficacious for CDI and with a similar engraftment profile as colonoscopy but whether they can be used for UC remains unclear.[28,29] Overall, no studies of UC have compared the various FMT routes of administration, although an ongoing study (Clinicaltrials.gov NCT03006809) aims to add evidence to this unexplored research area.

Although the concept of adjunct interventions, such as bowel lavage or pretreatment antibiotics, to decrease the bacterial burden and enable healthy microbial engraftment in the host has been speculated upon, there is a paucity of data. In terms of bowel preparation, one study[21] intentionally used bowel lavage before administration of FMT by the upper gastrointestinal tract and results from 2 studies[10,11] may have been confounded by bowel preparation before colonoscopic administration of FMT. Overall, there are conflicting results on the impact of bowel lavage on a host's microbiome and it requires further examination, although positive results from an enema-based study suggests it may not be necessary.[17,30–32] Antibiotics are routinely administered before FMT when treating CDI.[33] However, none of the RCTs in this meta-analysis had antibiotic pretreatment as part of their methods. At this time, it is unclear if there is benefit to pretreatment with antibiotics before FMT; however, an ongoing study may clarify this (Clinicaltrials.gov NCT02606032).

The preparation of FMT material may have an impact on the microbiota. Specifically, data suggest oxygen exposure during fecal homogenization alters the composition of living fecal microbiota.[34] Interestingly, the study with the largest treatment benefit used anaerobic techniques for FMT preparation. Additionally, the ideal dosage (grams of stool) for both the induction and the maintenance doses remains uncertain. The fecal dosage was variable across the RCTs, and although there are some dose finding studies in CDI,[35] none have been conducted in UC. In addition to dosage, the frequency of administration also remains ambiguous, as the largest treatment effects were demonstrated in one study with very frequent administration (baseline colonoscopy infusion followed by 5 enemas weekly)[10] and another study with very low treatment burden (baseline colonoscopy infusion and 2 enemas at day 7).[11] Sustainability of FMT treatment effect also is unclear, as 2 studies measured their primary endpoint 6 weeks[11] and 9 weeks[21] after the last FMT treatment, respectively, and the other 2 measured outcomes just after the last administration.[10,20]

The most significant uncertainly in the role of FMT in UC is the impact of the donor. Among a 1999 patient cohort, the

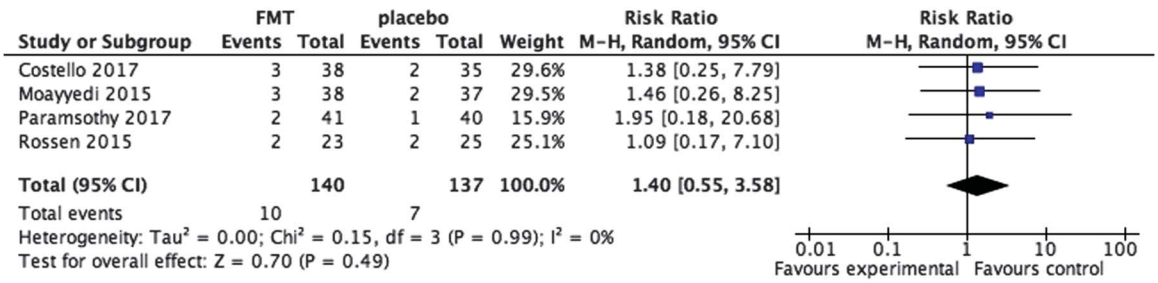
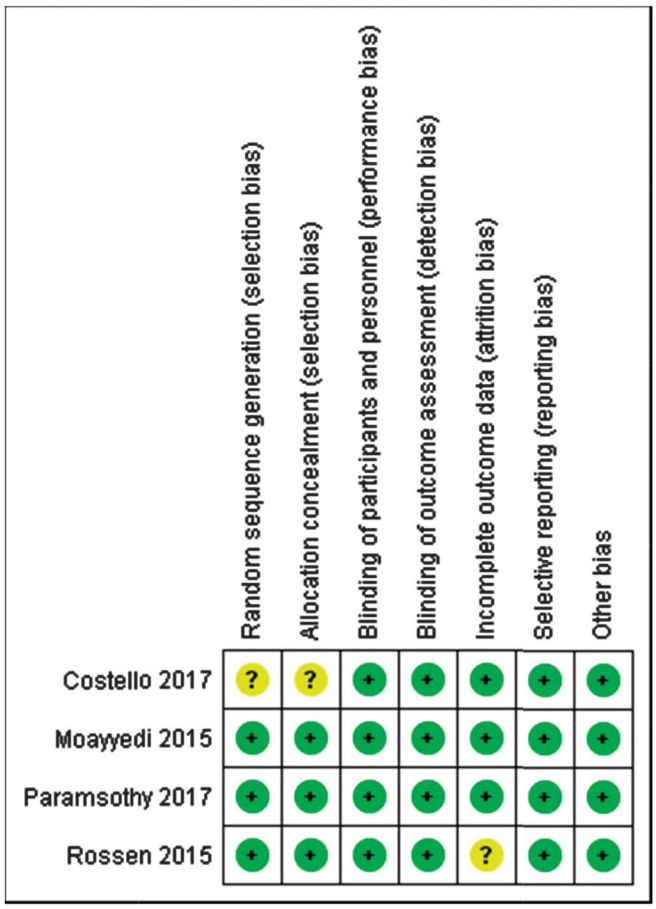


FIGURE 5. Forrest plot of all studies reporting serious adverse events.

TABLE 3. Risk of Bias Summary of Studies



"+" indicates study meets criteria. "?" indicates unclear if study meets criteria.

selection of donor did not seem to be important for the successful treatment of CDI.[36] The donor; however, seems to impact treatment outcomes when using FMT for UC. This was most evident in study by Moayyedi et al, where most treatment successes were driven by a single donor, "donor B." In this study, enrichment with Lachnospiraceae and *Ruminococcus* were notable in the stool of donor B and may be associated with treatment success.[20] Other studies have identified other bacterial targets. Rossen et al[21] reported that patients with UC have a lower prevalence of *Clostridium* clusters IV, XIVa, and XVIII at baseline. Vermeire et al[37] suggested that FMT responders were more likely to acquire the following phylotypes from donors: *Roseburia*, *Oscillibacter*, unclassified Lachnospiraceae, and unclassified Ruminococcaceae. Paramsothy et al reported that several microbial taxa were associated with remission, including *Barnesiella* spp., *Parabacteroides* spp., *Clostridium* cluster IV and XVIII, *Blautia* spp., Dorea spp., and *Ruminococcus* spp. They also found that *Fusobacterium* spp. and *Sutterella* spp. were frequently associated with no remission.[10] Furthermore, it is possible that undetected alterations in the virome and fungome are occurring in responders to treatment.[38,39] The bacterial, viral, or fungal profile necessary for successful treatment in UC is unclear and may require a "personalized microbial medicine" to identify the ideal patient with UC who will respond to microbial therapies. Overall, further work is required to determine whether deficiencies within the microbiota can be identified in certain patients with UC that would predict successful treatment with FMT.

This meta-analysis demonstrates that short-term use of FMT is beneficial for improvement in clinical symptoms and endoscopic healing of patients with UC. Despite this benefit, there are still unanswered questions that require further research. No controlled studies have yet reported outcomes of maintenance treatment with FMT. Additionally, questions remain regarding donor selection, identification of patients most likely to respond, ideal dosing regimen, and mode of delivery. Cost-effectiveness and need for long-term ongoing treatment is also unclear. Further RCTs and long-term observational registries to capture the safety profile are needed to help clarify some of these uncertainties. Until there is further clarification on some of these questions, FMT for UC should remain confined to clinical trials, but microbial therapies may offer a promising new treatment opportunity for patients suffering from IBD.

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